From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Monday, February 23, 2015 9:50 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Fwd: Celldex's Rindopepimut (Rintega(R)) Receives FDA Breakthrough Therapy Designation for the Treatment of Adult Patients with EGFRvIII-positive Glioblastoma - Yahoo Finance

FYI

Arie Belldegrun, MD FACS
President and CEO, Chairman
Kite Pharma

www.kitepharma.com

Begin forwarded message:

> **From:** Ran Nussbaum <ran@pontifax.com>
> **Date:** February 23, 2015 at 05:11:36 PST
> **To:** Rizwana Sproule <RSproule@kitepharma.com>, Cynthia Butitta <cbutitta@kitepharma.com>, Arie Belldegrun <Arie@kitepharma.com>, "Margo Roberts" <mroberts@kitepharma.com>
> **Cc:** Adrian Bot <abot@kitepharma.com>, David Chang <dchang@kitepharma.com>
> **Subject: Celldex's Rindopepimut (Rintega(R)) Receives FDA Breakthrough Therapy Designation for the Treatment of Adult Patients with EGFRvIII-positive Glioblastoma - Yahoo Finance**
>
> http://finance.yahoo.com/news/celldexs-rindopepimut-rintega-r-receives-130100842.html
>
>

From: Rosenberg, Steven A. (NIH/NCI) [E]
Sent: Thursday, February 26, 2015 10:07 AM
To: David Chang MD PhD (dchang@kitepharma.com); Jeff Wiezorek MD (JWiezorek@kitepharma.com)
Subject: cancel meeting today

My regrets for the late notice but I have been travelling and need to cancel our phone call for today.
Today I need to attend the Melanoma Research Alliance meeting here in DC that goes all day.

Steve

Steven A. Rosenberg M.D., Ph.D.
Chief, Surgery Branch
National Cancer Institute
10 Center Drive MSC 1201
CRC Room 3-3940
Bethesda, MD 20892
301-496-4164
sar@nih.gov

From: Rosenberg, Steven A. (NIH/NCI) [E]
Sent: Friday, February 27, 2015 11:07 AM
To: 'David Chang'
Subject: RE: cancel meeting today

I will be out of town on Thursday ad Friday March 6 and 7. Delighted to discuss this at any other time.

Steven A. Rosenberg M.D., Ph.D.
Chief, Surgery Branch
National Cancer Institute
10 Center Drive MSC 1201
CRC Room 3-3940
Bethesda, MD 20892
301-496-4164
sar@nih.gov

From: David Chang [mailto:dchang@kitepharma.com]
Sent: Thursday, February 26, 2015 10:29 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Cc: Jeff Wiezorek
Subject: Re: cancel meeting today

Dear Steve,

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Thanks,
David

David D. Chang, M.D., Ph.D.
Tel: (310) 622-9094
PERSONAL INFORMATION,REDACTED PER AGREEMENT
www. kitepharma.com

Sent from my iPad

On Feb 26, 2015, at 7:06 AM, Rosenberg, Steven A. (NIH/NCI) [E] <sar@mail.nih.gov> wrote:

> My regrets for the late notice but I have been travelling and need to cancel our phone call for today. Today I need to attend the Melanoma Research Alliance meeting here in DC that goes all day.
>
> Steve
>
> Steven A. Rosenberg M.D., Ph.D.
> Chief, Surgery Branch
> National Cancer Institute
> 10 Center Drive MSC 1201
> CRC Room 3-3940
> Bethesda, MD 20892
> 301-496-4164
> sar@nih.gov

From: Rosenberg, Steven A. (NIH/NCI) [E]
Sent: Sunday, March 08, 2015 11:54 AM
To: 'dchang@kitepharma.com'
CC: M. D. FACS Arie Belldegrun (arie@belldegrun.com)
Subject: FW: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

David

Paul Robbins forwarded your email to me.

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Steve

Steven A. Rosenberg M.D., Ph.D.
Chief, Surgery Branch
National Cancer Institute
10 Center Drive MSC 1201
CRC Room 3-3940
Bethesda, MD 20892
301-496-4164
sar@nih.gov

-----Original Message-----
From: Robbins, Paul (NIH/NCI) [E]
Sent: Friday, March 06, 2015 12:26 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]; Tran, Eric (NIH/NCI) [F]
Subject: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Paul

> From: David Chang [dchang@kitepharma.com]
> Sent: Thursday, March 05, 2015 10:19 AM
> To: Robbins, Paul (NIH/NCI) [E]
> Cc: Margo Roberts
> Subject: FW: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT
>
> Paul ,
>
> Just passing along. PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

> Thanks, David
>
> From: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT
> Sent: Wednesday, March 04, 2015 12:53 PM
> To: David Chang
> Subject: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT
>
> Dear David,
>

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

> Best regards,
>

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

>
>
> CONFIDENTIALITY NOTICE: This email is intended for the use of the person to whom it is addressed and may contain information that is privileged and confidential. If the receiver of thisemail is not the intended recipient, you are hereby notified that any dissemination, distribution or copying of this information is strictly prohibited. If you have received this email in error, please notify the sender immediately.
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[https://t.yesware.com/t/7f04a4f15b0084653516ce78d4f2afecbd6eace7/b31beaf6e5cc29faa2436e5f64ba1ad8/spacer.gif]
[http://t.yesware.com/t/7f04a4f15b0084653516ce78d4f2afecbd6eace7/b31beaf6e5cc29faa2436e5f64ba1ad8/spacer.gif]

From: Rosenberg, Steven A. (NIH/NCI) [E]
Sent: Sunday, March 08, 2015 3:23 PM
To: 'David Chang'
CC: 'Belldegrun, Arie M.D.'
Subject: RE: This Thursday (March 12)

David

I leave tomorrow (Monday) for Stockholm where I will give a lecture at the Karolinska Institute
PERSONAL INFORMATION,REDACTED PER AGREEMENT

I do not return until Friday evening and thus will not be able to join a Thursday meeting this week. Let's postpone the meeting for one week.

Steve

Steven A. Rosenberg M.D., Ph.D.
Chief, Surgery Branch
National Cancer Institute
10 Center Drive MSC 1201
CRC Room 3-3940
Bethesda, MD 20892
301-496-4164
sar@nih.gov

-----Original Message-----
From: David Chang [mailto:dchang@kitepharma.com]
Sent: Sunday, March 08, 2015 1:56 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Cc: Arie Belldegrun
Subject: This Thursday (March 12)

Steve,

I wanted to check to see if you will be in your office this Thursday. I have plans to be in Miami/Tampa Tuesday/Wednesday and can easily extend a trip by a day spend time to see you, Paul, Nick, and Jim, along with joining into the NCI-Kite call from NCI.

Thanks, David

David D. Chang, M.D., Ph.D.
Tel: (310) 622-9094
PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

www. kitepharma.com

Sent from my iPad

From: Rosenberg, Steven A. (NIH/NCI) [E]
Sent: Sunday, March 08, 2015 8:51 PM
To: 'David Chang'
Subject: RE: This Thursday (March 12)

yes

Steven A. Rosenberg M.D., Ph.D.
Chief, Surgery Branch
National Cancer Institute
10 Center Drive MSC 1201
CRC Room 3-3940
Bethesda, MD 20892
301-496-4164
sar@nih.gov

-----Original Message-----
From: David Chang [mailto:dchang@kitepharma.com]
Sent: Sunday, March 08, 2015 6:35 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Cc: Belldegrun, Arie M.D.
Subject: Re: This Thursday (March 12)

Steve,

We will take care of rescheduling the meeting. Safe travels!

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Thanks,

David

David D. Chang, M.D., Ph.D.
Tel: (310) 622-9094
PERSONAL INFORMATION,REDACTED PER AGREEMENT

www.kitepharma.com

Sent from my iPhone

> On Mar 8, 2015, at 12:23 PM, Rosenberg, Steven A. (NIH/NCI) [E] <sar@mail.nih.gov> wrote:
>
> David
>
> I leave tomorrow (Monday) for Stockholm where I will give a lecture at the Karolinska Institute
PERSONAL INFORMATION,REDACTED PER AGREEMENT
>
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> Steve
>
> Steven A. Rosenberg M.D., Ph.D.
> Chief, Surgery Branch
> National Cancer Institute
> 10 Center Drive MSC 1201
> CRC Room 3-3940
> Bethesda, MD 20892
> 301-496-4164
> sar@nih.gov
>
>
> -----Original Message-----
> From: David Chang [mailto:dchang@kitepharma.com]
> Sent: Sunday, March 08, 2015 1:56 PM
> To: Rosenberg, Steven A. (NIH/NCI) [E]
> Cc: Arie Belldegrun
> Subject: This Thursday (March 12)
>
> Steve,
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> I wanted to check to see if you will be in your office this Thursday. I have plans to be in Miami/Tampa Tuesday/Wednesday and can easily extend a trip by a day spend time to see you, Paul, Nick, and Jim, along with joining into the NCI-Kite call from NCI.
>
> Thanks, David
>
> David D. Chang, M.D., Ph.D.
> Tel: (310) 622-9094
> PERSONAL INFORMATION,REDACTED PER AGREEMENT
>
> www. kitepharma.com
>
> Sent from my iPad

From: Rosenberg, Steven A. (NIH/NCI) [E]
Sent: Sunday, March 08, 2015 8:57 PM
To: 'David Chang'
CC: M. D. FACS Arie Belldegrun (arie@belldegrun.com)
Subject: RE: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

David

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Steve

Steven A. Rosenberg M.D., Ph.D.
Chief, Surgery Branch
National Cancer Institute
10 Center Drive MSC 1201
CRC Room 3-3940
Bethesda, MD 20892
301-496-4164
sar@nih.gov

-----Original Message-----
From: David Chang [mailto:dchang@kitepharma.com]
Sent: Sunday, March 08, 2015 1:06 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Cc: M. D. FACS Arie Belldegrun (arie@belldegrun.com)
Subject: Re: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Dear Steve,

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Thank. We appreciate the support we are getting from you and your team.

David

David D. Chang, M.D., Ph.D.
Tel: (310) 622-9094
PERSONAL INFORMATION,REDACTED PER AGREEMENT

www. kitepharma.com

Sent from my iPad

> On Mar 8, 2015, at 8:53 AM, Rosenberg, Steven A. (NIH/NCI) [E] <sar@mail.nih.gov> wrote:
>
> David
>
> Paul Robbins forwarded your email to me.

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

> Steve
>
> Steven A. Rosenberg M.D., Ph.D.
> Chief, Surgery Branch
> National Cancer Institute
> 10 Center Drive MSC 1201
> CRC Room 3-3940
> Bethesda, MD 20892
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> sar@nih.gov
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>
>
> -----Original Message-----
> From: Robbins, Paul (NIH/NCI) [E]
> Sent: Friday, March 06, 2015 12:26 PM
> To: Rosenberg, Steven A. (NIH/NCI) [E]; Tran, Eric (NIH/NCI) [F]
> Subject: FW: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT
>

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

> Paul
>
>> From: David Chang [dchang@kitepharma.com]
>> Sent: Thursday, March 05, 2015 10:19 AM
>> To: Robbins, Paul (NIH/NCI) [E]
>> Cc: Margo Roberts
>> Subject: FW: Neo-antigen prediction using whole-exome sequencing
>>
>> Paul ,
>>

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

>> Thanks, David
>>
>> PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

>> Sent: Wednesday, March 04, 2015 12:53 PM
>> To: David Chang
>> Subject: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT
>>
>> Dear David,
>>

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

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[https://t.yesware.com/t/7f04a4f15b00846535 16ce78d4f2afecbd6eace7/b31beaf6e5cc29faa2436e5f64ba1ad8/spacer.gif]
[http://t.yesware.com/t/7f04a4f15b00846535 16ce78d4f2afecbd6eace7/b31beaf6e5cc29faa2436e5f64ba1ad8/spacer.gif]

From: Rosenberg, Steven A. (NIH/NCI) [E]
Sent: Tuesday, March 17, 2015 5:16 PM
To: 'David Chang'
Subject: RE PROPRIETARY INFORMATION 2nd Annual Lymphoid Malignancies & Multiple Myeloma Summit

David

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Steve

Steven A. Rosenberg M.D., Ph.D.
Chief, Surgery Branch
National Cancer Institute
10 Center Drive MSC 1201
CRC Room 3-3940
Bethesda, MD 20892
301-496-4164
sar@nih.gov

From: David Chang [mailto:dchang@kitepharma.com]
Sent: Tuesday, March 17, 2015 3:48 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: PROPRIETA RY INFORMA 2nd Annual Lymphoid Malignancies & Multiple Myeloma Summit

Steve,

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conveyed.

Thanks, David

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

All the best,
David

David D. Chang, MD, PhD
Executive Vice President of R&D
and Chief Medical Officer
Kite Pharma, Inc
office: 310-622-9094

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PER AGREEMENT

www.kitepharma.com

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Thursday, March 26, 2015 5:32 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Neoantigen Science paper
Attachments: Pages from Schumacher_galley.pdf

Hi Steve ,

Thanks for the excellent discussion today. You are not only writing the future of Immunotherapy, but now also rewiring the T-cell Immunology text books... fascinating! .

I learned that the Science online will be published ahead of the AACR meeting and ahead of the printed addition. Will have the exact day earlier next week.

All the best,

Arie Belldegrun, M.D.,FACS
President and CEO
Chairman, Board of Directors; Founder
Kite Pharma Inc.

2225 Colorado Avenue
Santa Monica, CA 90404
Tel: 310-622-9093
PERSONAL INFORMATION,REDACTED PER AGREEMENT
arie@kitepharma.com

www.kitepharma.com

REVIEW

Neoantigens in cancer immunotherapy

Ton N. Schumacher[1]* and Robert D. Schreiber[2]*

The clinical relevance of T cells in the control of a diverse set of human cancers is now beyond doubt. However, the nature of the antigens that allow the immune system to distinguish cancer cells from noncancer cells has long remained obscure. Recent technological innovations have made it possible to dissect the immune response to patient-specific neoantigens that arise as a consequence of tumor-specific mutations, and emerging data suggest that recognition of such neoantigens is a major factor in the activity of clinical immunotherapies. These observations indicate that neoantigen load may form a biomarker in cancer immunotherapy and provide an incentive for the development of novel therapeutic approaches that selectively enhance T cell reactivity against this class of antigens.

Immunotherapies that boost the ability of endogenous T cells to destroy cancer cells have demonstrated therapeutic efficacy in a variety of human malignancies. Until recently, evidence that the endogenous T cell compartment could help control tumor growth was in large part restricted to preclinical mouse tumor models and to human melanoma. Specifically, mice lacking an intact immune system were shown to be more susceptible to carcinogen-induced and spontaneous cancers compared with their immunocompetent counterparts (*1*). With respect to human studies, the effects of the T cell cytokine interleukin-2 in a small subset of melanoma patients provided early clinical evidence of the potential of immunotherapy in this disease. In 2010, the field was revitalized by a landmark randomized clinical trial that demonstrated that treatment with ipilimumab, an antibody that targets the T cell checkpoint protein CTLA-4, improved overall survival of patients with metastatic melanoma (*2*). As a direct test of the tumoricidal potential of the endogenous T cell compartment, work by Rosenberg and colleagues demonstrated that infusion of autologous ex vivo expanded tumor-infiltrating lymphocytes can induce objective clinical responses in metastatic melanoma (*3*), and at least part of this clinical activity is due to cytotoxic T cells (*4*). Importantly, recent studies demonstrate that T cell–based immunotherapies are also effective in a range of other human malignancies. In particular, early phase trials of antibodies that interfere with the T cell checkpoint molecule PD-1 have shown clinical activity in tumor types as diverse as melanoma, lung cancer, bladder cancer, stomach cancer, renal cell cancer, head and neck cancer, and Hodgkin's lymphoma (*5*). Based on the relationship between pretherapy CD8+ T cell infiltrates and response to PD-1 blockade in melanoma, cytotoxic T cell activity also appears to play a central role in this form of cancer immunotherapy (*6*).

An implicit conclusion from these clinical data is that in a substantial fraction of patients, the endogenous T cell compartment is able to recognize peptide epitopes that are displayed on major histocompatibility complexes (MHCs) on the surface of the malignant cells. On theoretical grounds, such cancer rejection epitopes may be derived from two classes of antigens. A first class of potential cancer rejection antigens is formed by nonmutated proteins to which T cell tolerance is incomplete—for instance, because of their restricted tissue expression pattern. A second class of potential cancer rejection antigens is formed by peptides that are entirely absent from the normal human genome, so-called neoantigens. For the large group of human tumors without a viral etiology, such neo-epitopes are solely created by tumor-specific DNA alterations that result in the formation of novel protein sequences. For virus-associated tumors, such as cervical cancer and a subset of head and neck cancers, epitopes derived from viral open reading frames also contribute to the pool of neoantigens.

As compared with nonmutated self-antigens, neoantigens have been postulated to be of particular relevance to tumor control, as the quality of the T cell pool that is available for these antigens is not affected by central T cell tolerance (*7*). Although a number of heroic studies provided early evidence for the immunogenicity of mutation-derived neoantigens [reviewed in (*8*)], technology to systemically analyze T cell reactivity against these antigens only became available recently. Here, we review our emerging understanding of the role of patient-specific neoantigens in current cancer immunotherapies and the implications of these data for the development of next generation immunotherapies.

Exome-guided neoantigen identification—process considerations

A large fraction of the mutations in human tumors is not shared between patients at

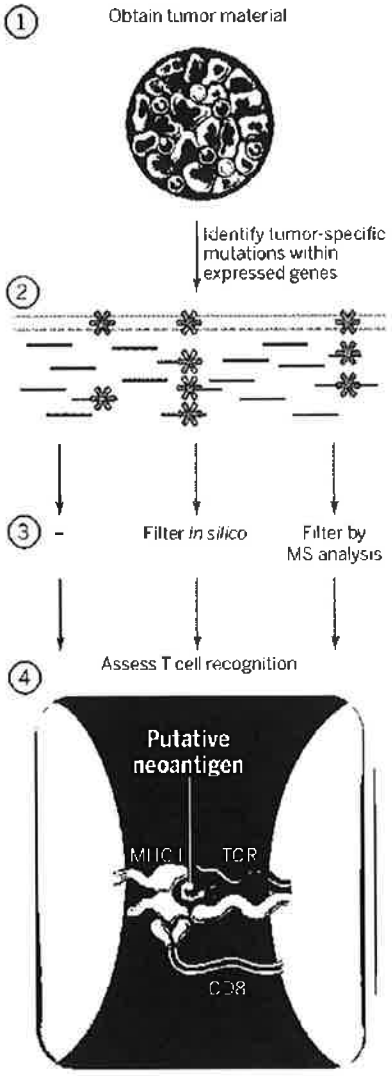

Fig. 1. Cancer exome-based identification of neoantigens. (**1**) Tumor material is analyzed for nonsynonymous somatic mutations. When available, RNA sequencing data are used to focus on mutations in expressed genes. (**2**) Peptide stretches containing any of the identified nonsynonymous mutations are generated in silico and are either left unfiltered (*16, 17*), filtered through the use of prediction algorithms [e.g., (*10–13*)], or used to identify MHC-associated neoantigens in mass spectrometry data (*15, 20*). Modeling of the effect of mutations on the resulting peptide-MHC complex may be used as an additional filter (*20*). Resulting epitope sets are used to identify physiologically occurring neoantigen-specific T cell responses by MHC multimer–based screens (*13, 22*) or functional assays [e.g., (*11, 12*)], within both CD8+ [e.g., (*11–13, 19, 39*)] and CD4+ (*16, 18*) T cell populations. Alternatively, T cell induction strategies are used to validate predicted neoantigens [e.g., (*10, 20*)].

[1]Division of Immunology, Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX, Amsterdam, Netherlands. [2]Department of Pathology and Immunology, Washington University School of Medicine, 660 South Euclid Avenue, St. Louis, MO 63110, USA.
*Corresponding author. E-mail: t.schumacher@nki.nl (T.N.S.); schreiber@immunology.wustl.edu (R.D.S.)

meaningful frequencies and may therefore be considered patient-specific. Because of this, technologies to interrogate T cell reactivity against putative mutation-derived neoantigens need to be based on the genome of an individual tumor. With the development of deep-sequencing technologies, it has become feasible to identify the mutations present within the protein-encoding part of the genome (the exome) of an individual tumor with relative ease and thereby predict potential neoantigens (*9*). Two studies in mouse models provided the first direct evidence that such a cancer exome-based approach can be used to identify neoantigens that can be recognized by T cells (*10*, *11*). In brief, for all mutations that resulted in the formation of novel protein sequence, potential MHC binding peptides were predicted, and the resulting set of potential neoantigens was used to query T cell reactivity. Subsequent studies have demonstrated that cancer exome-based analyses can also be exploited in a clinical setting, to dissect T cell reactivity in patients that are treated by either tumor-infiltrating lymphocyte (TIL) cell therapy or checkpoint blockade (*12*, *13*). Furthermore, following this early work, the identification of neoantigens on the basis of cancer exome data has been documented in a variety of experimental model systems and human malignancies (*10*–*22*).

The technological pipeline used to identify neoantigens in these different studies has varied substantially, and further optimization is likely possible (Fig. 1). Accepting the limitations of probing the mutational profile of a tumor in single biopsy (*23*), the genetic analysis of the tumor itself can be considered a robust process. Specifically, based on the analysis of neoantigens previously identified by other means, the false-negative rate of cancer exome sequencing is low—i.e., the vast majority of neoantigens occur within exonic sequence for which coverage is sufficient (*24*). At the same time, it is apparent from unbiased screening efforts—in which the entire collection of identified mutations was used to query T cell reactivity—that the vast majority of mutations within expressed genes do not lead to the formation of neoantigens that are recognized by autologous T cells (*16*, *17*). Because of this, a robust pipeline that can be used for the filtering of cancer exome data is essential, in particular for tumors with high mutational loads.

How can such filtering be performed? With the set of mutations within expressed genes as a starting point, two additional requirements can be formulated. First, a mutated protein needs to be processed and then presented as a mutant peptide by MHC molecules. Second, T cells need to be present that can recognize this peptide-MHC complex. In two recent preclinical studies, presentation of a handful of predicted neoantigens by MHC molecules was experimentally demonstrated by mass spectrometry (*15*, *20*), and this approach may form a valuable strategy to further optimize MHC presentation algorithms. At the same time, the sensitivity of mass spectrometry is presently still limited, thereby likely resulting in a substantial fraction of false negatives. For this reason, but also because of logistical issues, implementation of this approach in a clinical setting is unlikely to happen soon. Lacking direct evidence for MHC presentation, as can be provided by mass spectrometry, presentation of neoantigens by MHC class I molecules may be predicted using previously established algorithms that analyze aspects such as the likelihood of proteasomal processing, transport into the endoplasmic reticulum, and affinity for the relevant MHC class I alleles. In addition, gene expression levels (or perhaps preferably protein translation levels) may potentially also be used to help predict epitope abundance (*25*).

Although most neoantigen identification studies have successfully used criteria for epitope prediction that are similar to those previously established for the identification of pathogen-derived epitopes [e.g., (*12*, *13*)], Srivastava and colleagues have argued that neoantigens in a transplantable mouse tumor model display very different properties from viral antigens and generally have a very low affinity for MHC class I (*14*). Although lacking a satisfactory explanation to reconcile these findings, we do note that the vast majority of human neoantigens that have been identified in unbiased screens do display a high predicted MHC binding affinity (*24*, *26*). Likewise, minor histocompatibility antigens, an antigen class that is conceptually similar to neoantigens, are correctly identified by classical MHC binding algorithms (*27*). Moreover, the mutations that were identified in a recent preclinical study as forming tumor-specific mutant antigens that could induce therapeutic tumor rejection when used in tumor vaccines (*15*) were not predicted to be significant using the Srivastava approach. Another potential filter step that has been suggested examines whether the mutation is expected to improve MHC binding, rather than solely alter the T cell receptor (TCR)–exposed surface of the mutant peptide. However, with examples of both categories in both mouse models and human data, the added value of such a filter may be relatively modest (*11*, *15*, *20*, *26*). For MHC class I restricted neoantigens, conceivably the biggest gain in prediction algorithms can be made with respect to identification of the subset of MHC binding peptides that can successfully be recognized

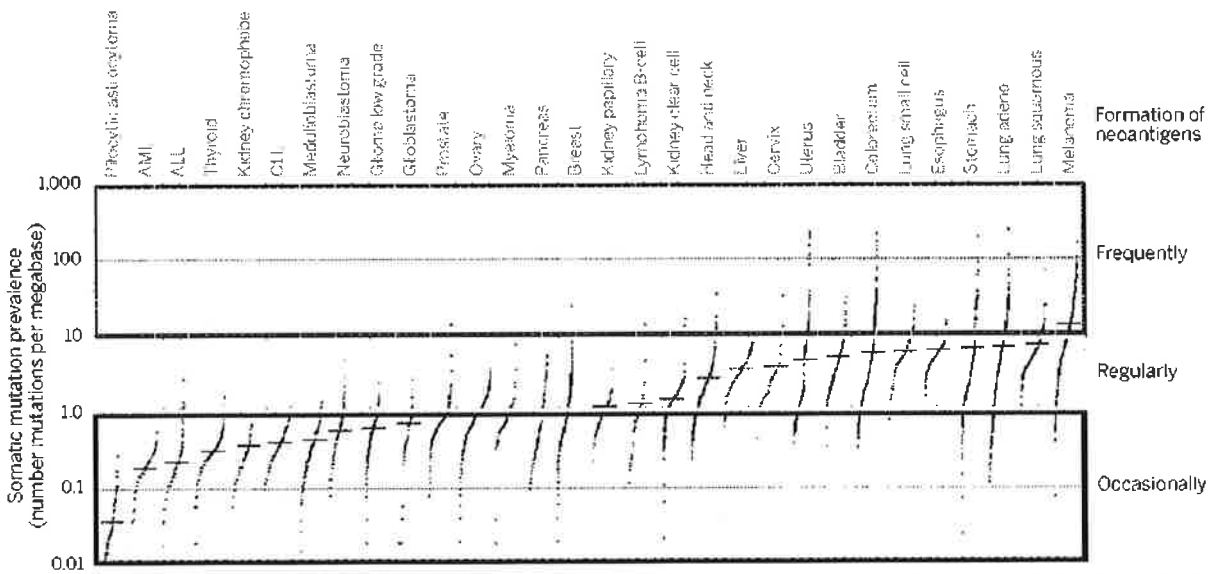

Fig. 2. Estimate of the neoantigen repertoire in human cancer. Data depict the number of somatic mutations in individual tumors. Categories on the right indicate current estimates of the likelihood of neoantigen formation in different tumor types. Adapted from (*50*). It is possible that the immune system in melanoma patients picks up on only a fraction of the available neoantigen repertoire, in which case the current analysis will be an underestimate. A value of 10 somatic mutations per Mb of coding DNA corresponds to ~150 nonsynonymous mutations within expressed genes.

by the TCR repertoire. With respect to this, the nature of the central TCR-exposed residues of MHC-bound peptides has been shown to be associated with peptide immunogenicity (*28*). By the same token, alterations at these sites may potentially be picked up by the immune system more readily (*20*). However, a substantial further experimental effort is required to evaluate to what extent algorithms that predict immunogenicity can facilitate the identification of MHC class I-restricted neoantigens. For MHC class II-restricted neoantigens, it will be important to obtain a better understanding not only of peptide immunogenicity but also of the basic factors that determine the efficiency of epitope presentation.

Size and nature of the neoantigen repertoire

Large-scale analyses of neoantigen-specific T cell reactivity have now been carried out for a substantial number of patients, mostly in melanoma (*12, 13, 16, 17*). With the caveat of a potential selection bias toward patients with a clinical benefit upon immunotherapeutic intervention, these analyses provide a first estimate of the frequency with which the immune system recognizes the neoantigens that are formed as a consequence of mutations. The first and arguably most important conclusion that can be drawn from these analyses is that the T cell-based immune system reacts to both MHC class I-restricted (*12, 13, 17*) and MHC class II-restricted neoantigens (*16*) in a large fraction of melanoma patients. The second conclusion that can be drawn from these analyses is that only a very small fraction of the nonsynonymous mutations in expressed genes in these tumors leads to the formation of a neoantigen for which CD4+ or CD8+ T cell reactivity can be detected within tumor-infiltrating lymphocytes.

What do these observations mean for the potential formation of neoantigen repertoires in other human malignancies? Most human melanomas have a mutational load above 10 somatic mutations per megabase (Mb) of coding DNA, and this is apparently sufficient to lead to the frequent formation of neoantigens that can be seen by T cells. Based on these data, formation of neoantigens that can potentially be recognized by autologous T cells is expected to also be common for other tumors with a mutational load above 10 somatic mutations per Mb (corresponding to approximately 150 nonsynonymous mutations within expressed genes) (Fig. 2). This group contains a sizable fraction of high-prevalence tumor types such as lung cancer and colorectal cancer. If formation of neoantigens is a frequent event in tumors with mutational loads above 10 somatic mutations per Mb, many tumors with a mutational load of 1 to 10 per Mb may still be expected to carry neoantigens that can be recognized by T cells. However, as based on the fact that even for melanomas with a mutational load around 10 mutations per Mb, T cell reactivity is not always observed (*16*), tumor types with a mutational load below 1 mutation per Mb appear less likely to commonly express neoantigens that can be recognized by autologous T cells.

Although this analysis provides a useful first sketch of the expected relevance of neoantigens in different tumor types, three important factors should be taken into account. First, by relying on the presence of preexisting T cell reactivity as a readout, the human studies carried out to date will only detect neoantigens that were immunogenic during in vivo tumor outgrowth (either spontaneously or boosted by therapy). It is conceivable that not all tumor-expressed neoantigens induce an autologous T cell response—for instance, because they are not efficiently cross presented. In addition, at least in preclinical models, there is evidence for immunodominance of tumor antigens, where the immune system becomes so fixated on particular antigens that it ignores other antigens that are both present and detectable in the tumor (*29*). If only a fraction of the available neoantigens would normally elicit T cell reactivity, the analyses carried out to date may underestimate the actual neoantigen repertoire. As a second consideration, it is important to realize that the formation of neoantigens is a probabilistic process in which each additional mutation increases the odds that a relevant neoantigen is created. Thus, in this "neoantigen lottery," there will be cases in which despite a high mutational load, neoantigen-specific T cell reactivity is lacking or, vice versa, in which a tumor with only a handful of mutations will express an MHC class I- or class II-restricted neoantigen. Third, although we here make a prediction with regard to the frequency with which neoantigens that can potentially be recognized by the TCR repertoire are formed, it should be kept in mind that the presence of a neoantigen does not equal the induction of T cell reactivity. Human tumors vary substantially in the composition of their microenvironment, and this is likely to influence the ability of the T cell pool to respond to mutated antigens. Related to this, from a conceptual point of view, therapeutic manipulation of T cell reactivity would seem particularly attractive for tumor types that do express large numbers of antigens but in which the tumor microenvironment hinders the activation of the T cells that recognize them.

What are the characteristics of mutation-derived neoantigens in human cancer, both with respect to the genes from which they are derived and the frequency with which they occur within the patient population? In an ideal world, neoantigens would be derived from essential oncogenes and occur in large patient groups, to both reduce the likelihood of escape and facilitate clinical interventions that enhance T cell reactivity against them. Clearly, T cell responses do sometimes occur against MHC class I-restricted (*30*) and MHC class II-restricted neoantigens in validated oncogenes that are shared between subgroups of patients (*31*). At the same time, it is apparent that, at least in melanoma, the bulk of the neoantigen-specific T cell response is directed toward mutated proteins that are essentially unique to that tumor and that are unlikely to play a key role in cellular transformation (Fig. 3, top and bottom) (*16*). A direct implication of this bias in neoantigen-specific T cell reactivity toward patient-specific passenger mutations is that the targeting of defined neoantigens will likely require the development of personalized immunotherapies.

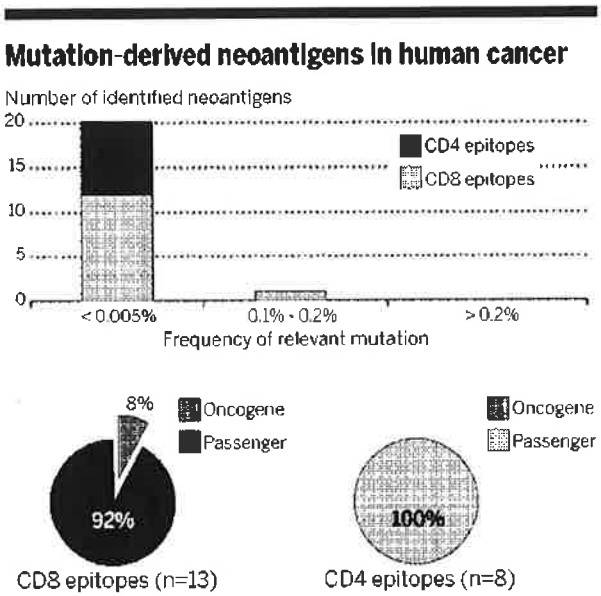

Fig. 3. Characteristics of melanoma neoantigens. (Top) For a group of CD4+ T cell neoantigens (8 epitopes) and CD8+ T cell neoantigens (13 epitopes) identified by cancer exome based screens, the frequency of mutation of that residue in a cohort of ~20,000 human tumor samples (*51*) is depicted. **(Bottom)** For the same group of CD4+ T cell and CD8+ T cell neoantigens, the fraction of encoding mutations that occurs within known oncogenes (*52*) is depicted.

Extrinsic influences on the tumor antigenic landscape

The neoantigen repertoire expressed in a clinically apparent cancer may have been substantially influenced by the developing tumor's interaction with the immune system that occurs even before it becomes clinically apparent. This is the process of "cancer immunoediting" that has been well documented in preclinical cancer models (*1, 32, 33*). In its most complex form, cancer immunoediting may occur in three phases: elimination, in which the innate and adaptive immune systems work together to recognize a developing tumor and

destroy it before it becomes clinically apparent; equilibrium, in which residual occult tumor cells not destroyed in the elimination phase are held in a state of tumor dormancy as a consequence of adaptive immune system activity and undergo "editing"; and escape, in which edited tumor cells are no longer recognized or controlled by immune processes, begin to grow progressively, induce an immunosuppressive tumor microenvironment, and then emerge as clinically apparent cancers. Recent work has demonstrated that T cells play a major role in shaping the immunogenicity of developing cancers—i.e., "edit" tumor immunogenicity—and exert this effect by at least two mechanisms. First, T cells can shape tumor antigenicity/immunogenicity through an immunoselection process by destroying tumor cells that express strong tumor-specific mutant antigens, leaving behind tumor cells that either express weaker antigens (some of which may still be mutant tumor antigens) or are incapable of expressing antigens (e.g., those that have developed mutations in antigen processing or presentation) (*11*). Second, chronic T cell attack on a tumor has been shown to silence expression of certain tumor-specific antigens through epigenetic mechanisms in a preclinical model (*34*). Strikingly, a recent study, based on analysis of thousands of Cancer Genome Atlas solid tumor samples, showed that, in particular in colorectal cancer, mutated peptides predicted to bind to autologous MHC class I molecules are less frequent than expected by chance, an observation that is consistent with immune-based selection (*35*). By extension, the combination of cell extrinsic forces such as cancer immunoediting and the stochastic nature of epitopes arising from tumor-specific mutations, may help drive the heterogeneous mutational—and by inference, antigenic—landscapes that have been noted in certain tumors (*23*). As such, the antigenic heterogeneity of tumors might explain some of the differences in response that individual patients display to checkpoint blockade therapy. Individuals who develop durable responses to checkpoint blockade may be those whose tumors retain sufficient antigenicity to render them sensitive to the heightened immune function that accompanies cancer immunotherapy, despite not being controlled by naturally occurring antitumor immune responses.

Role of neoantigens in cancer immunotherapy

On theoretical grounds, two factors should determine the relative importance of neoantigens and nonmutated self-antigens in the effects of cancer immunotherapies such as checkpoint blockade and TIL therapy: first, the frequency with which T cell responses against the two antigen classes occur; second, the relative potency of T cell responses specific for the two antigen classes. Recent work in mouse models using transplantable carcinogen-induced cancers has demonstrated that checkpoint blockade alters both the quality of the neoantigen-specific intratumoral T cell response [as reflected by common- and treatment-specific changes in gene expression in CD8+ TILs isolated from tumor-bearing mice treated with antibodies to CTLA-4 (anti–CTLA-4) and/or antibodies to PD-1 (anti–PD-1)] and the magnitude of this T cell response (seen with CTLA-4 or combined CTLA-4/PD-1 blockade but not with PD-1 blockade only) (*15*). Because the neoantigens identified in this model serve as cancer rejection antigens, these data provide compelling evidence that checkpoint blockade acts at least in part through neoantigen-specific T cell reactivity in this setting. However, in the case of human melanoma, where autochthonous tumors may be in contact with the immune system for years, the situation is more complicated. As discussed above, T cell reactivity against neoantigens is common in melanoma. Furthermore, a case report has shown that such reactivity can be enhanced by anti–CTLA-4 treatment (*13*). However, T cell reactivity against nonmutated shared antigens is also observed in the majority of melanoma patients, and broadening of this T cell response has been documented following both TIL therapy and anti–CTLA-4 treatment (*36*, *37*). Thus, although the murine data show that neoantigen-specific T cell reactivity can be critical to the effects of checkpoint blockade, the human data are presently only consistent with this possibility.

What other data are available with respect to this issue? If recognition of neoantigens is an important component of cancer immunotherapy, one would expect tumor types with high numbers of mutations to be characterized by strong T cell responses and to be particularly sensitive to immunotherapy. Furthermore, also within a given tumor type, response rate should correlate with mutational load. Evidence for a role of neoantigens in driving the strength of the intratumoral T cell response is provided by the observation that the presence of CD8+ T cells in cancer lesions, as read out using RNA sequencing data, is higher in tumors with a high mutational burden (*38*). Furthermore, an extensive analysis by Hacohen and colleagues has demonstrated that the level of transcripts associated with cytolytic activity of natural killer cells and T cells correlates with mutational load in a large series of human tumors (*35*). With respect to the effects of immunotherapy in tumors with different mutational loads, in non–small cell lung cancer patients treated with anti–PD-1, mutational load shows a strong correlation with clinical response (*22*). Likewise, in melanoma patients treated with ipilimumab, an antibody to CTLA-4, long-term benefit is also associated with a higher mutational load, although the effect appears less profound in this setting (*39*). A striking observation in the latter study has been that the predicted MHC-binding neoantigens in patients with a long-term clinical benefit were enriched for a large series of tetrapeptide motifs that were not found in tumors of patients with no or minimal clinical benefit. An appealing interpretation of these data is that the neoantigen-specific T cell response is preferentially directed toward a subset of mutant sequences, something that could facilitate bioinformatic identification of neoantigens for therapeutic targeting. However, analysis of the sequence properties of human neoantigens identified in other studies does not show the profound bias toward these tetrapeptide signatures that would be predicted if their role were central in the tumor-specific T cell response (*40*), and conceivably the identified tetrapeptide motifs play a different role.

The genetic damage that on the one hand leads to oncogenic outgrowth can also be targeted by the immune system to control malignancies.

It will be valuable to extend the analysis of genomic determinants of tumor cell sensitivity to cancer immunotherapeutics to other malignancies. However, because of the probabilistic nature of neoantigen generation, mutational load will by itself always remain an imperfect biomarker, even in a situation in which neoantigen reactivity is the sole tumor-specific T cell reactivity that is relevant to tumor control. Furthermore, the formation of tumor-specific antigens is only one of a number of essential conditions for a successful immune attack on cancer cells, a concept that is well described by the cancer-immunity cycle introduced by Chen and Mellman (*41*). As an example, genetic inactivation of the β_2-microglobulin subunit of MHC class I molecules is a relatively frequent event in some tumor types (*42*). In addition, a recent analysis of genetic alterations that are present in tumors with high immune activity provides evidence for a series of other escape mechanisms (*35*). In such cases, in which the cancer-immunity cycle is disrupted at another site, the number of neoantigens produced is unlikely to still be of much relevance. Because of this interdependence of different phases of the cancer-immunity cycle, the combined use of assay systems that report on these different phases appears warranted.

Arguably the most direct data on the relevance of neoantigen-specific T cells in human tumor control comes from a small number of clinical studies that involve infusion of defined T cell populations or infusion of TCR-transduced T cells. Encouragingly, a recent case report demonstrated regression of a metastatic cholangiocarcinoma by infusion of a CD4+ T cell product that was highly enriched for reactivity against an MHC class II–restricted neoantigen (*18*). Combined with the observation that, at least in melanoma, CD4+ T cell recognition of neoantigens is a frequent event (*16*), these data underscore the potential clinical relevance of MHC class II–restricted neoantigens. Comparison of the clinical effects of TIL therapy with that of T cells modified with TCRs recognizing different shared antigens can also be considered informative. Infusion of T cells modified with TCRs directed against the gp100 and MART-1

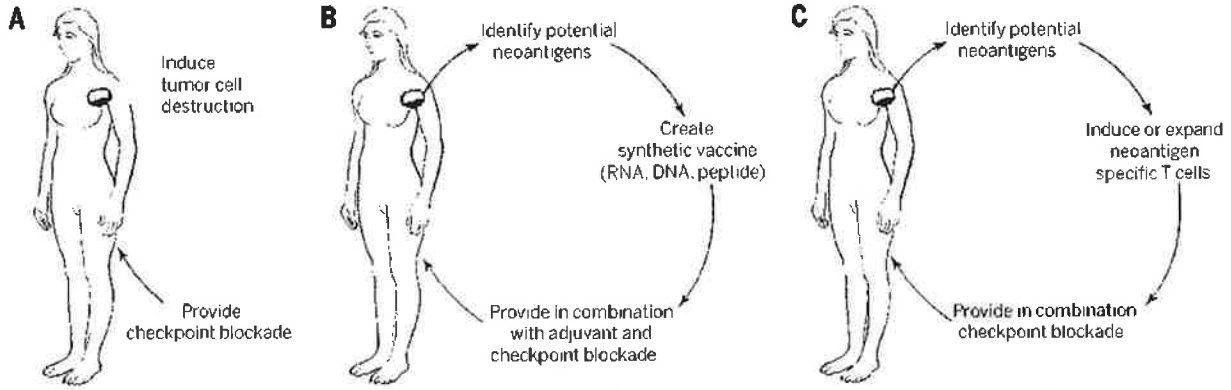

Fig. 4. Strategies to target the patient-specific neoantigen repertoire. (**A**) Immunotherapy is given in combination with interventions such as radiotherapy that enhance exposure to autologous neoantigens. (**B**) Potential neoantigens are identified as in Fig. 1 steps 1 to 3, a patient-specific vaccine is produced, and this vaccine is given together with adjuvant and T cell checkpoint-blocking antibodies. (**C**) Potential neoantigens are identified as in Fig. 1 steps 1 to 3, T cells that are specific for these neoantigens are induced or expanded in vitro, and the resulting T cell product is given together with T cell checkpoint-blocking antibodies.

melanocyte differentiation antigens, a prominent class of self-antigens in melanoma, shows a relatively modest clinical effect that is accompanied by substantial on-target toxicity against healthy melanocytes (*43*). Because this toxicity is relatively infrequent in TIL therapy, these data strongly suggest that T cell reactivity against the melanocyte differentiation antigens is not a major driver of the antitumor activity of this therapy. At the same time, there is data showing that T cell products directed against NY-eso-1, one of the nonmutant self-antigens from the family of cancer/germline antigens that show very limited expression in healthy tissue, can display substantial antitumor activity (*44*, *45*). Thus, although the available data support the notion that T cell recognition of neoantigens contributes substantially to the effects of the currently used immunotherapies, it would not be justified to dismiss a potential contribution of T cell responses against a subset of nonmutant antigens. A direct comparison of the antitumor activity of neoantigen-specific and self-antigen–specific T cells obtained from individual patients would be useful to further address this issue.

Therapeutic use of the patient-specific neoantigen repertoire

Based on the fact that, at least in tumors with high mutational loads, the amount of DNA damage is sufficient for the immune system to see one or multiple epitopes as foreign, it becomes of interest to stimulate neoantigen-specific T cell responses in cancer patients. Such stimulation can obviously only be of value if the strength of the neoantigen-specific T cell response is otherwise a limiting factor in tumor control. Human data on this important issue are lacking. However, in mouse models, vaccination with defined neoantigens has been show to result in increased tumor control (*10*, *14*, *15*, *20*), providing sufficient rationale for the clinical development of neoantigen-directed therapeutics. Because the majority of possible neoantigens are specific to the individual being treated (Fig. 3), such therapeutic approaches will in most cases entail personalized immunotherapies that either exploit the antigen repertoire in the tumor cells themselves, or information on that repertoire, as obtained by tumor sequencing (Fig. 4). As a first approach, a combination of checkpoint-blocking antibodies with therapeutic interventions—such as tumor radiotherapy, oncolytic viruses, or autologous tumor cell vaccines—that can increase neoantigen exposure to the T cell–based immune system may be synergistic (Fig. 4A). As a downside, as compared to molecularly defined vaccines, the neoantigens released by such strategies will be diluted by the large amount of nonmutant peptides that are also present. In addition, control over the maturation signals received by antigen-presenting cells is relatively limited. Nevertheless, because of the relative ease of clinical development of some of these combination therapies, extensive testing of such therapies is warranted.

To allow a more defined targeting of the neoantigen repertoire in human tumors, two alternative approaches should be considered, in both cases relying on sets of potential neoantigens as identified by sequencing of tumor material (Fig. 4, B and C). First, synthetic vaccines may be produced that contain or encode a set of predicted neoantigens. Although still a substantial departure from the classical pharmaceutical model, clinical development of such personalized vaccines is within reach (*46*–*48*). Mouse model data support the clinical translation of this approach, and the two most pressing questions appear to be (i) whether our ability to predict the most relevant neoantigens is already sufficiently advanced and (ii) how such vaccines may best be administered. Second, the information obtained from tumor sequencing may be used to create neoantigen-specific T cell products in vitro. This may either involve the expansion of neoantigen-specific T cell populations that can already be detected within tumor tissue or in blood or the de novo induction of such cells.

Regardless of the strategy used to enhance neoantigen-specific T cell reactivity, it will likely prove important to target multiple neoantigens simultaneously in order to prevent tumor escape by editing of the mutated epitope concerned (*1*). In addition, it may be prudent to avoid the targeting of mutations in gene products that are seen by the immune system in autoimmune disease to avoid induction of or exacerbation of cancer-associated autoimmune disease (*49*).

Concluding remarks

Based on data obtained over the past few years, it is plausible that neoantigen-specific T cell reactivity forms a major "active ingredient" of successful cancer immunotherapies. In other words, the genetic damage that on the one hand leads to oncogenic outgrowth can also be targeted by the immune system to control malignancies. Based on this finding, it will be important to engineer therapeutic interventions by which neoantigen-specific T cell reactivity is selectively enhanced. Because of the tumor-restricted expression of the antigens that are being targeted, these personalized cancer immunotherapies offer the promise of high specificity and safety. Conceivably, the boosting of neoantigen-specific T cell reactivity that can be achieved with such personalized immunotherapies will further increase the spectrum of human malignancies that respond to cancer immunotherapy.

REFERENCES AND NOTES

1. R. D. Schreiber, L. J. Old, M. J. Smyth, *Science* **331**, 1565–1570 (2011).
2. F. S. Hodi *et al.*, *N. Engl. J. Med.* **363**, 711–723 (2010).
3. C. S. Hinrichs, S. A. Rosenberg, *Immunol. Rev.* **257**, 56–71 (2014).
4. M. E. Dudley *et al.*, *J. Clin. Oncol.* **31**, 2152–2159 (2013).
5. P. Sharma, J. P. Allison, *Science* **347**, xxx–xxx (2015).
6. P. C. Tumeh *et al.*, *Nature* **515**, 568–571 (2014).
7. E. Gilboa, *Immunity* **11**, 263–270 (1999).
8. B. Heemskerk, P. Kvistborg, T. N. Schumacher, *EMBO J.* **32**, 194–203 (2013).

9. N. H. Segal *et al.*, *Cancer Res.* **68**, 889–892 (2008).
10. J. C. Castle *et al.*, *Cancer Res.* **72**, 1081–1091 (2012).
11. H. Matsushita *et al.*, *Nature* **482**, 400–404 (2012).
12. P. F. Robbins *et al.*, *Nat. Med.* **19**, 747–752 (2013).
13. N. van Rooij *et al.*, *J. Clin. Oncol.* **31**, e439–e442 (2013).
14. F. Duan *et al.*, *J. Exp. Med.* **211**, 2231–2248 (2014).
15. M. M. Gubin *et al.*, *Nature* **515**, 577–581 (2014).
16. C. Linnemann *et al.*, *Nat. Med.* **21**, 81–85 (2015).
17. Y. C. Lu *et al.*, *Clin. Cancer Res.* **20**, 3401–3410 (2014).
18. E. Tran *et al.*, *Science* **344**, 641–645 (2014).
19. D. A. Wick *et al.*, *Clin. Cancer Res.* **20**, 1125–1134 (2014).
20. M. Yadav *et al.*, *Nature* **515**, 572–576 (2014).
21. M. Rajasagi *et al.*, *Blood* **124**, 453–462 (2014).
22. N. A. Rizvi *et al.*, *Science* **347**, xxx–xxx (2015).
23. M. Gerlinger *et al.*, *N. Engl. J. Med.* **366**, 883–892 (2012).
24. M. M. van Buuren, J. J. Calis, T. N. Schumacher, *Oncoimmunology* **3**, e28836 (2014).
25. M. H. Forbes *et al.*, *J. Exp. Med.* **208**, 595–610 (2008).
26. E. F. Fritsch *et al.*, *Cancer Immunol. Res.* **2**, 522–529 (2014).
27. C. A. Van Bergen *et al.*, *Cancer Res.* **70**, 9073–9083 (2010).
28. J. J. A. Calis *et al.*, *PLOS Comput. Biol.* **9**, e1003266 (2013).
29. M. E. Dudley, D. C. Roopenian, *J. Exp. Med.* **184**, 441–447 (1996).
30. T. Wölfel *et al.*, *Science* **269**, 1281–1284 (1995).
31. T. Schumacher *et al.*, *Nature* **512**, 324–327 (2014).
32. C. M. Koebel *et al.*, *Nature* **450**, 903–907 (2007).
33. V. Shankaran *et al.*, *Nature* **410**, 1107–1111 (2001).
34. M. DuPage, C. Mazumdar, L. M. Schmidt, A. F. Cheung, T. Jacks, *Nature* **482**, 405–409 (2012).
35. M. S. Rooney, S. A. Shukla, C. J. Wu, G. Getz, N. Hacohen, *Cell* **160**, 48–61 (2015).
36. P. Kvistborg *et al.*, *Sci. Transl. Med.* **6**, 254ra128 (2014).
37. P. Kvistborg *et al.*, *Oncoimmunology* **1**, 409–418 (2012).
38. S. D. Brown *et al.*, *Genome Res.* **24**, 743–750 (2014).
39. A. Snyder *et al.*, *N. Engl. J. Med.* **371**, 2189–2199 (2014).
40. T. N. Schumacher, C. Kesmir, M. M. van Buuren, *Cancer Cell* **27**, 12–14 (2015).
41. D. S. Chen, I. Mellman, *Immunity* **39**, 1–10 (2013).
42. C. M. Cabrera *et al.*, *Tissue Antigens* **61**, 211–219 (2003).
43. L. A. Johnsen *et al.*, *Blood* **114**, 535–546 (2009).
44. N. N. Hunder *et al.*, *N. Engl. J. Med.* **358**, 2698–2703 (2008).
45. P. F. Robbins *et al.*, *Clin. Cancer Res.* **21**, 1019–1027 (2015).
46. V. Boisguérin *et al.*, *Br. J. Cancer* **111**, 1469–1475 (2014).
47. E. F. Fritsch, N. Hacohen, C. J. Wu, *Oncoimmunology* **3**, e29311 (2014).
48. R. H. Vonderheide, K. L. Nathanson, *Nat. Med.* **19**, 1098–1100 (2013).
49. C. G. Joseph *et al.*, *Science* **343**, 152–157 (2014).
50. L. B. Alexandrov *et al.*, *Nature* **500**, 415–421 (2013).
51. S. A. Forbes *et al.*, *Nucleic Acids Res.* **43**, D805–D811 (2015).
52. P. A. Futreal *et al.*, *Nature Rev. Cancer* **4**, 177 (2004).

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10.1126/science.aaa4971

From: Aric Belldegrun [Aric@kitepharma.com]
Sent: Friday, March 27, 2015 2:28 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Fwd: Immunogenomics meeting

FYI

Arie Belldegrun, MD FACS
President and CEO, Chairman
Kite Pharma

www.kitepharma.com

Begin forwarded message:

> **From:** <t.schumacher@nki.nl>
> **Date:** March 26, 2015 at 23:24:04 PDT
> **To:** <JJackson@burnsmc.com>
> **Cc:** <Arie@kitepharma.com>
> **Subject: Fwd: Immunogenomics meeting**
>
> Hi Justin, pls see below. Ton
>
> Sent from mobile
>
> Begin forwarded message:
>
> From: Kristen Mueller <kmueller@aaas.org<mailto:kmueller@aaas.org>>
> Date: 27 maart 2015 01:12:48 CET
> To: Ton Schumacher <t.schumacher@nki.nl<mailto:t.schumacher@nki.nl>>
> Cc: Natasha Pinol <npinol@aaas.org<mailto:npinol@aaas.org>>
> Subject: Re: Immunogenomics meeting
>
> Dear Ton.
> The special issue review will be published at 2pm ET Apr 2, so is under embargo until then. If they do want to publish something then, it would best if they got in touch with our press office for any coordination. I'm cc'ing Natasha Pinol here. She would be the best person to contact.
>
> I think the pages went to the printer today so it may be too late to add this disclosure, but I will see.
> Best.
> Kristen
>
> Sent from my iPad
>
> On Mar 26, 2015, at 17:49, "t.schumacher@nki.nl<mailto:t.schumacher@nki.nl>" <t.schumacher@nki.nl<mailto:t.schumacher@nki.nl>> wrote:
>
> Hi Kristen,
>
> Two quick notes: in the past week, a small biotech that I founded last year was taken over by Kite Pharma. As Kite Pharma has an interest in developing adoptive cellular therapies that target neo-antigens, I would also list Kite Pharma in my disclosures if I would write the review right now, will leave it up to you whether you still want to include.
>
> On a related note, I know through some people at Kite that, because of the recent work on neo-antigens by us and others, Reuters is potentially interested in doing a report on the topic. If this would indeed be the case, would seem very nice if this would coincide with your AACR review series. Do you already know when the pieces will come online (if you can share that info)? Best, Ton

From: Kristen Mueller <kmueller@aaas.org<mailto:kmueller@aaas.org><mailto:kmueller@aaas.org>>
Date: Thursday 26 March 2015 01:27
To: t Schumacher <t.schumacher@nki.nl<mailto:t.schumacher@nki.nl><mailto:t.schumacher@nki.nl>>
Subject: Re: Immunogenomics meeting

Thanks for getting back to me. I'll look forward to your response.

Kristen L Mueller, PhD
Senior Editor, Science

Sent from Outlook<http://taps.io/outlookmobile>

On Wed, Mar 25, 2015 at 2:04 PM -0700,
"t.schumacher@nki.nl<mailto:t.schumacher@nki.nl><mailto:t.schumacher@nki.nl>"
<t.schumacher@nki.nl<mailto:t.schumacher@nki.nl><mailto:t.schumacher@nki.nl>> wrote:

Dear Kristen, I hadn't yet decided, the topic is of clear interest to me, but my agenda is just way too full these days. Will think it over and get back to the organizers in the coming days, all the best, Ton

---

Sent from mobile

From: Kristen Mueller
<kmueller@aaas.org<mailto:kmueller@aaas.org><mailto:kmueller@aaas.org><mailto:kmueller@aaas.org>>
Date: Wednesday 25 March 2015 20:38
To: t Schumacher
<t.schumacher@nki.nl<mailto:t.schumacher@nki.nl><mailto:t.schumacher@nki.nl><mailto:t.schumacher@nki.nl>>
Subject: Immunogenomics meeting

Dear Ton,
Last week you should have received an email inviting you to the Immunogenomics 2015 conference, which is being held at the HudsonAlpha Institute of Biotechnology in Huntsville, AL Sept 28-30, 2015. Science is working with HudsonAlpha to organize the meeting and I wanted to follow-up with you to encourage you to accept our invitation. One of the most exciting applications of immunogenomics is in the cancer immunotherapy arena, so we would be delighted to have you speak.
All the best,
Kristen

Kristen L Mueller, PhD
Senior Editor, Science

Sent from Outlook<http://taps.io/outlookmobile>

Tel: 310-622-9093
PERSONAL INFORMATION,REDACTED PER AGREEMENT
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From: Rosenberg, Steven A. (NIH/NCI) [E]
Sent: Friday, March 27, 2015 11:19 AM
To: 'Arie Belldegrun'
Subject: RE: Neoantigen Science paper
Attachments: Galleys - Review in Science April 2015.pdf; neoantigens.ppt

Arie

Attached are the galleys from our review, a good portion of this refers to the targeting of mutated antigens. See especially the "blueprint" for treatment in Figure 3.

I will be giving a one hour talk at AACR on April 18 at 430 pm and will present much new unpublished information on the targeting of neoantigens in common epithelial cancers in humans as well as update prior information (the cholangiocarcinoma patient we reported in Science is still experiencing regression over 16 months after treatment see attached slide)). Perhaps the Reuter's journalist would like to attend the lecture.

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Steve

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From: Arie Belldegrun [mailto:Arie@kitepharma.com]
Sent: Thursday, March 26, 2015 5:32 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Neoantigen Science paper

Hi Steve ,

Thanks for the excellent discussion today. You are not only writing the future of Immunotherapy, but now also rewiring the T-cell Immunology text books... fascinating! .

I learned that the Science online will be published ahead of the AACR meeting and ahead of the printed addition. Will have the exact day earlier next week.

All the best,

Arie Belldegrun, M.D.,FACS
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REVIEW

Adoptive cell transfer as personalized immunotherapy for human cancer

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Adoptive cell therapy (ACT) is a highly personalized cancer therapy that involves administration to the cancer bearing host of immune cells with direct anticancer activity. ACT using naturally occurring tumor-reactive lymphocytes has mediated durable, complete regressions in patients with melanoma, probably by targeting somatic mutations exclusive to each cancer. These results have expanded the reach of ACT to the treatment of common epithelial cancers. In addition, the ability to genetically engineer lymphocytes to express conventional T cell receptors or chimeric antigen receptors has further extended the successful application of ACT for cancer treatment.

Adoptive cell therapy (ACT) has multiple advantages compared with other forms of cancer immunotherapy that rely on the active in vivo development of sufficient numbers of antitumor T cells with the functions necessary to mediate cancer regression. For use in ACT, large numbers of antitumor lymphocytes (up to 10^{11}) can be readily grown in vitro and selected for high-avidity recognition of the tumor, as well as for the effector functions required to mediate cancer regression. In vitro activation allows such cells to be released from the inhibitory factors that exist in vivo. Perhaps most importantly, ACT enables the manipulation of the host before cell transfer to provide a favorable microenvironment that better supports antitumor immunity. ACT is a "living" treatment because the administered cells can proliferate in vivo and maintain their antitumor effector functions.

A major factor limiting the successful use of ACT in humans is the identification of cells that can target antigens selectively expressed on the cancer and not on essential normal tissues. ACT has used either natural host cells that exhibit antitumor reactivity or host cells that have been genetically engineered with antitumor T cell receptors (TCRs) or chimeric antigen receptors (CARs). With the use of these approaches, ACT has mediated dramatic regressions in a variety of cancer histologies, including melanoma, cervical cancer, lymphoma, leukemia, bile duct cancer, and neuroblastoma. This Review will discuss the current state of ACT for the treatment of human cancer, as well as the principles of effective treatment that point toward improvements in this approach.

A brief history of ACT

Very little was known about the function of T lymphocytes until the 1960s, when it was shown that lymphocytes were the mediators of allograft rejection in experimental animals. Attempts to use T cells to treat transplanted murine tumors were limited by the inability to expand and manipulate T cells in culture. Thus, ACT used transfer of syngeneic lymphocytes from rodents heavily immunized against the tumor, and modest growth inhibition of small established tumors was observed (*1*, *2*). In early preclinical studies, the importance of host inhibitory factors was suggested by findings that lymphodepletion using either chemotherapy or radiation before cell transfer enhanced the ability of transferred lymphocytes to treat established tumors (*3*, *4*).

The ability to use ACT was facilitated by the description of T cell growth factor [interleukin-2 (IL-2)] in 1976, which provided a means to grow T lymphocytes ex vivo, often without loss of effector functions (*5*). The direct administration of high doses of IL-2 could inhibit tumor growth in mice (*6*), and studies in 1982 demonstrated that the intravenous injection of immune lymphocytes expanded in IL-2 could effectively treat bulky subcutaneous FBL3 lymphomas (*7*). In addition, administration of IL-2 after cell transfer could enhance the therapeutic potential of these adoptively transferred lymphocytes (*8*). The demonstration in 1985 that IL-2 administration could result in complete durable tumor regressions in some patients with metastatic melanoma (*9*) provided a stimulus to identify the specific T cells and their cognate antigens involved in this cancer immunotherapy. Lymphocytes infiltrating into the stroma of growing, transplantable tumors were shown to represent a concentrated source of lymphocytes capable of recognizing tumor in vitro, and studies in murine tumor models demonstrated that the adoptive transfer of these syngeneic tumor-infiltrating lymphocytes (TILs) expanded in IL-2 could mediate regression of established lung and liver tumors (*10*). In vitro studies in 1986 showed that human TILs obtained from resected melanomas contained cells capable of specific recognition of autologous tumors (*11*), and these studies led in 1988 to the first demonstration that ACT using autologous TILs could mediate objective regression of cancer in patients with metastatic melanoma (*12*).

Populations of TILs that grow from tumors are generally mixtures of $CD8^+$ and $CD4^+$ T cells with few if any major contaminating cells in mature cultures. The ability of pure populations of T lymphocytes to mediate cancer regression in patients provided the first direct evidence that T cells played a vital role in human cancer immunotherapy. However, responses were often of short

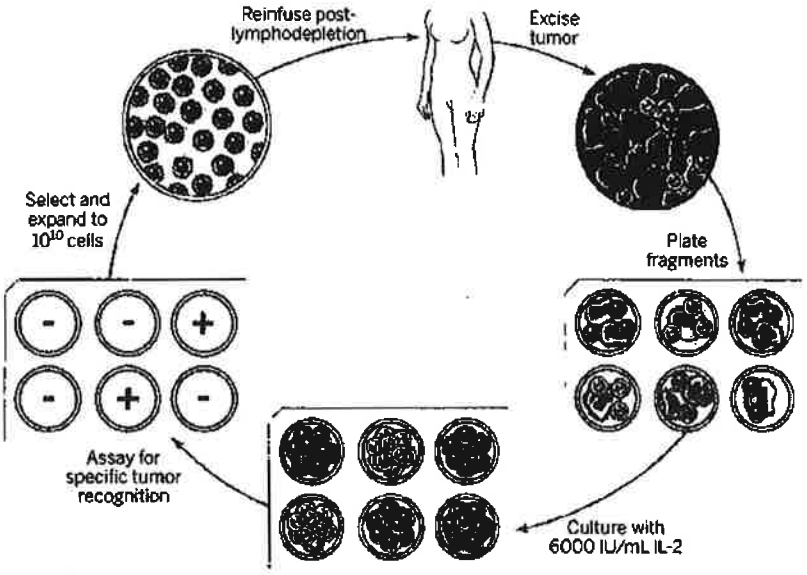

Fig. 1. General schema for using the adoptive cell transfer of naturally occurring autologous TILs. The resected melanoma specimen is digested into a single-cell suspension or divided into multiple tumor fragments that are individually grown in IL-2. Lymphocytes overgrow, destroy tumors within 2 to 3 weeks, and generate pure cultures of lymphocytes that can be tested for reactivity in coculture assays. Individual cultures are then rapidly expanded in the presence of excess irradiated feeder lymphocytes, OKT3, and IL-2. By approximately 5 to 6 weeks after resecting the tumor, up to 10^{11} lymphocytes can be obtained for infusion into patients.

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duration, and the transferred cells could rarely be found in the circulation just days after administration. A critical improvement in the application of ACT to the treatment of human cancer was reported in 2002 when it was shown that lymphodepletion using a nonmyeloablative chemotherapy regimen administered immediately before TIL transfer could lead to increased cancer regression, as well as the persistent oligoclonal repopulation of the host with the transferred antitumor lymphocytes (*13*). In some patients, the administered antitumor cells represented up to 80% of the $CD8^+$ T cells in the circulation months after the infusion.

Lymphocyte cultures can be grown from many tumor histologies; however, melanoma appeared to be the only cancer that reproducibly gave rise to TIL cultures capable of specific antitumor recognition. The stimulus to more widely apply ACT to treat multiple human cancers led to studies of the genetic engineering of lymphocytes to express antitumor receptors. Following mouse models (*14*), it was shown for the first time in humans in 2006 that administration of normal circulating lymphocytes transduced with a retrovirus encoding a TCR that recognized the MART-1 melanoma-melanocyte antigen could mediate tumor regression (*15*). Administration of lymphocytes genetically engineered to express a chimeric antigen receptor (CAR) against the B cell antigen CD19 was shown in 2010 to mediate regression of an advanced B cell lymphoma (*16*). These findings of the use of either naturally occurring or genetically engineered antitumor T cells set the stage for the extended development of ACT for the treatment of human cancer.

ACT using TILs is an effective immunotherapy for patients with metastatic melanoma

Adoptive cell therapy using autologous TILs is the most effective approach to induce complete durable regressions in patients with metastatic melanoma (Table 1). The general approach for growing and administering human TILs is shown in Fig. 1. The resected melanoma specimen is digested into a single-cell suspension or divided into multiple tumor fragments that are individually grown in IL-2. Lymphocytes overgrow, destroy tumors within 2 to 3 weeks, and give rise to pure cultures of lymphocytes that can be tested for reactivity against tumors, if available, in coculture assays. Individual cultures are then rapidly expanded in the presence of excess irradiated feeder lymphocytes, an antibody targeting the epsilon subunit within the human CD3 complex of the TCR, and IL-2. By ~5 to 6 weeks after resecting the tumor, up to 10^{11} lymphocytes can be obtained for infusion into patients. A substantial increase in cell persistence and the incidence and duration of clinical responses was seen when patients received a lymphodepleting preparative regimen before the cell infusion (*13*). It might be possible to optimize the intensity or duration of the lymphodepletion that is employed, but the most frequently used lymphodepleting preparative regimen consists of 60 mg/kg cyclophosphamide and 25 mg/m^2 fludarabine administered over 5 days followed by cells and IL-2 given at 720,000 IU/kg to tolerance (Fig. 2). In a pilot study in the Surgery Branch, National Cancer Institute (NCI), objective cancer regressions by RECIST criteria (Response Evaluation Criteria in Solid Tumors) were seen in 21 of 43 patients (49%), including 5 patients (12%) who underwent complete cancer regression (*13*). When 200 or 1200 centigray (cGy; 1 Gy = 100 rads) total-body irradiation (TBI) was added to the preparative regimen in pilot trials of 25 patients each, objective response (OR) rates of 52 and 72% were seen, including 20 and 40% complete regressions. However, there were no statistically significant differences in the OR rates between preparative regimens (*13*, *17*). Twenty of the 93 patients (22%) in these trials had complete regressions, and 19 (20%) have not experienced recurrences at follow-up times of 5 to 10 years and are probably cured. A prospective randomized study comparing the chemotherapy preparative regimen alone versus chemotherapy plus the addition of 1200 cGy TBI in 101 patients was recently concluded at the NCI, National Institutes of Health (NIH), and results are pending.

In the combined experience of the treatment of 194 patients using TILs grown from individual melanoma fragments at the NCI (Bethesda, Maryland), 107 patients (55%) have shown ORs. Similar OR rates to TIL therapy have been reported by multiple groups, including those from the Moffitt Cancer Center (Tampa, Florida) (38% OR rate) (*18*), the MD Anderson Cancer Center (Houston, Texas) (48% OR rate) (*19*), and the Ella Cancer Institute (Ramat Gan, Israel) (40% OR rate) (*20*) (Table 1).

There is no relation between the bulk of disease or the site of metastases and the likelihood of achieving a complete cancer regression (*17*). Of the 34 complete responders thus far seen in the two trials at the NCI, only one has recurred, and only one patient with complete regression received more than one treatment. The brain is not a sanctuary site, and regression of brain metastases has been observed (*21*). Prior treatment with targeted therapy using the Braf inhibitor vemurafenib (Zelboraf) does not appear to affect the likelihood of having an OR to ACT treatment in patients with melanoma.

Lymphodepletion prior to T cell transfer is followed by immune reconstitution

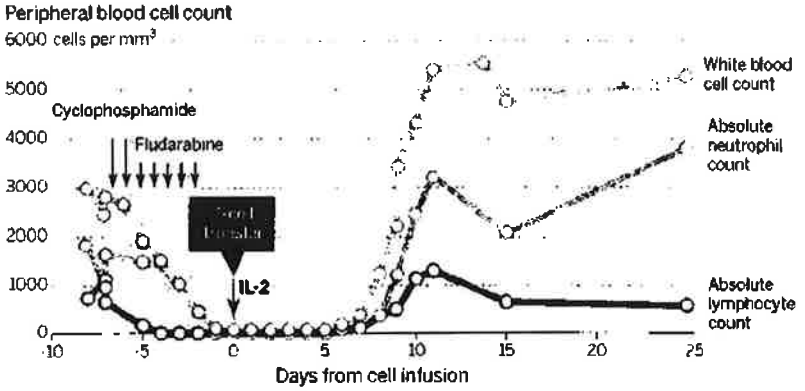

Fig. 2. A substantial increase in cell persistence and the incidence and duration of clinical responses is observed when patients received a lymphodepleting preparative regimen before the cell infusion. The most frequently used lymphodepleting preparative regimen consists of 60 mg/kg cyclophosphamide given for 2 days and 25 mg/m^2 fludarabine administered over 5 days, followed by [illegible] cells and IL-2 administration.

The ACT ... ACT can also be effective after other immunotherapies have failed. Of the 194 patients treated in the NCI trials, OR rates in patients who had no prior therapy or who progressed through IL-2, antibody to cytotoxic T lymphocyte–associated protein 4 (anti-CTLA-4), anti-PD1, or Braf inhibitors were 48, 63, 42, 50, and 43%, respectively.

Lymphodepletion appears to be an important component of ACT, and mouse models have shown that lymphodepletion given before cell transfer can increase the effectiveness of treatment more than 10-fold. In the clinic, the persistence of T cells was once a rarity (*22*), but in trials conducted after the initiation of lymphodepleting therapy, adoptively transferred T cells could comprise the majority of the peripheral blood $CD8^+$ cells 1 month after transfer (*13*). The cellular basis of the effect of lymphodepletion is complex and is still not completely understood. In mouse models, myeloid-derived suppressor cells and $CD4^+$ FoxP3 regulatory T cells can be found at high levels in tumors in vivo and can depress immune responses in the mouse tumor microenvironment (*23*). In accord with these preclinical findings, preparative chemotherapy in humans severely depletes lymphocytes and myeloid cells

Table 1. Selected clinical trials of ACT for the treatment of human cancer. CLL, xxxxxxxxxxxxxxxx; ALL, xxxxxxxxxxxxxxxx; CR, xxxxxxxxxxxxxx; HPC, human papillomavirus; allo-HSCT, allogeneic hematopoietic stem cell transplantation; DLBCL, xxxxxxxxxxxxxxxxxxxxxxxxxxxx; EBV, Epstein-Barr virus.

CELLS USED FOR ACT	YEAR	CANCER HISTOLOGY	MOLECULAR TARGET	PATIENTS	NUMBER OF ORS	COMMENTS
Tumor-infiltrating lymphocytes*	1998	Melanoma (*12*)		20	55%	Original use TIL ACT
	1994	Melanoma (*88*)		86	34%	
	2002	Melanoma (*13*)		13	46%	Lymphodepletion before cell transfer
	2011	Melanoma (*17*)		93	56%	20% CR beyond 5 years
	2012	Melanoma (*19*)		31	48%	
	2012	Melanoma (*18*)		13	38%	Intention to treat: 26% OR rate
	2013	Melanoma (*20*)		57	40%	Intention to treat: 29% OR rate
	2014	Cervical cancer (*89*)		9	33%	Probably targeting HPV antigens
	2014	Bile duct (*44*)	Mutated ERB2	1	–	Selected to target a somatic mutation
In vitro sensitization	2008	Melanoma (*90*)	NY-ESO-1	9	33%	Clones reactive against cancer-testes antigens
	2014	Leukemia (*91*)	WT-1	11	–	Many treated at high risk for relapse
Genetically engineered with CARs	2010	Lymphoma (*16*)	CD19	1	100%	First use of anti-CD19 CAR
	2011	CLL (*68*)	CD19	3	100%	Lentivirus used for transduction
	2013	ALL (*70*)	CD19	5	100%	Four of five then underwent allo-HSCT
	2014	ALL (*92*)	CD19	30	90%	CR in 90%
	2014	Lymphoma (*71*)	CD19	15	80%	Four of seven CR in DLBCL
	2014	ALL (*93*)	CD19	16	88%	Many moved to allo-HSCT
	2014	ALL (*94*)	CD19	21	67%	Dose-escalation study
	2011	Neuroblastoma (*78*)	GD2	11	27%	CR2 CARs into EBV-reactive cells
Genetically engineered with TCRs	2011	Synovial sarcoma (*81*)	NY-ESO-1	6	67%	First report targeting nonmelanoma solid tumor
		Melanoma		11	45%	

*Molecular targets of TIL in melanoma appear to be exomic mutations expressed by the cancer. (*39, 40, 44*)

from the circulation at the time of cell infusion, although the rate of reappearance of FoxP3 inhibitory T cells after lymphodepletion was inversely correlated with clinical response (*24*). Levels of homeostatic cytokines, which promote T cell proliferation and survival, are dramatically induced upon lymphodepletion (*25*) in mouse models. In humans, lymphodepletion leads to the appearance in the circulation of the T cell growth factor IL-15, which serves to promote the expansion of the transferred cells in the absence of competing endogenous lymphocytes (*26*). Further, lymphodepletion can enhance the translocation of commensal microflora across mucosal barriers in the mouse, and this can enhance the effect of ACT by stimulating Toll-like receptors (*27*) to activate antigen-presenting cells (APCs). These preclinical results have highly affected clinical translation, and it seems likely that immune ablation will be a part of future cell-based treatments in patients with cancer.

Adoptive cell therapy is a "living" treatment, and administered lymphocytes can expand more than 1000-fold after administration. Studies in mouse models, including those involving the injection of human cells into immunodeficient animals, have emphasized the importance of the differentiation state of the infused cells (*28, 29*). The phenotypic and functional status of less differentiated murine cells is highly positively correlated with their ability to eliminate vascularized tumor in vivo. These findings are in accordance with the high positive correlation between the persistence of the transferred TILs in the circulation of patients at 1 month and with the induction of partial and complete clinical responses (*17*). Further, one clinical study showed a strong correlation between expression of the phenotypic marker CD27, which is associated with cells early in their differentiation pathway, and clinical response (*17*). The presence of longer telomeres as a correlate of clinical response was seen in one study (*17*) but not in another (*18*).

The observation that melanoma TILs can mediate durable, complete, and probably curative cancer regression in patients with metastatic melanoma has raised considerable interest in the possible use of TILs for the treatment of multiple cancer types. Although TILs can be grown in vitro from virtually all tumors, only melanomas consistently give rise to TILs with antitumor reactivity. In an attempt to gain insight into the possible extension of ACT to the treatment of other common cancers, extensive studies of the antigens recognized by TILs have been pursued.

Melanoma TILs recognize the products of cancer mutations

Early studies identified two nonmutated melanoma-melanocyte differentiation proteins, MART-1 and gp100, that were often recognized by melanoma TILs (*30, 31*). Melanocytes in the skin, eye, and ear express the MART-1 and gp100 proteins, and yet toxicity targeting these proteins was not seen in the majority of patients treated with TILs who underwent complete cancer regression. In contrast, when a high-affinity TCR against MART-1 or gp100 was inserted into lymphocytes used for ACT, profound eye and ear toxicity was often seen in the absence of antitumor activity, which suggests that the reactivity against melanoma-melanocyte antigens was not the decisive target resulting in the in vivo antitumor activity of melanoma TILs (*32*).

A study of exomic mutation rates in more than 3000 tumor-normal pairs revealed that the frequency of nonsynonymous mutations varied more than 1000-fold across different cancer types (*33*). Pediatric cancers exhibited mutation frequencies as low as 0.1/Mb, whereas melanomas and lung cancers often exceeded 100 mutations/Mb. The suggestion that mutations might be targets of

immune recognition of tumor cells has been around for some time (*34*). The responsiveness of melanoma to a variety of immunotherapy approaches such as ACT, IL-2, anti–CTLA-4, and anti–PD-1 suggested that peptide epitopes encoded by the large number of mutations in melanoma might be the targets of TIL therapy (*35*). Support for this hypothesis comes from recent observations that anti–PD-1 can mediate ORs not only in patients with melanoma but also in patients with lung and bladder cancer, the two tumor types closest to melanoma with a high frequency of mutations (*36*). A patient successfully treated with anti–CTLA-4 generated circulating T cells that recognized a distinct mutation in the melanoma (*37*). Another study suggested that increased numbers of exonic mutations in a cancer correlated with better outcomes (*38*).

New approaches using whole-exonic sequencing of tumor-normal pairs in patients with melanoma have consistently identified nonsynonymous cancer mutations recognized by autologous TILs that mediated complete cancer regressions (*39*, *40*). However, not all expressed mutations can be recognized by T cells. Proteins incorporating the mutations must be processed to short peptides of ~9 amino acids for major histocompatibility complex (MHC) class 1 and a bit longer for MHC class 2; these peptides are then presented on the cell surface. One approach to identify the immunogenic mutations that we have taken is to identify 21- to 25-amino acid polypeptides, each one containing a mutated amino acid flanked by 10 to 12 normal residues. Using peptide-MHC binding algorithms, these polypeptides can then be scanned to identify peptides with high binding to individual MHC molecules of the patient. The top-predicted binding peptides are then synthesized and tested for recognition by coculture with TILs that mediated cancer regression. This method depends on the accuracy of peptide-MHC binding algorithms, which are often inadequate for many of the less frequent MHC molecules (*39*).

An alternate method eliminates the need for predicted peptide binding to MHC and enables the screening of all candidate peptides on all MHC loci in a single test (*40*) (Fig. 3). As above, minigenes, rather than polypeptides, are constructed that encode each mutated amino acid flanked by 10 to 12 amino acids. Strings of 6 to 20 minigenes are then linked into tandem minigenes, and these DNA constructs are subsequently cloned into an expression plasmid and in vitro transcribed to RNA, which is electroporated into the patient's autologous APCs. These APCs present all mutated peptides capable of being processed and binding to any of the patient's class 1 or class 2 MHC molecules. Culture of the patient's TILs with these APCs can identify the tandem minigene as well as the individual minigene responsible for tumor recognition. Using these approaches, TILs from 21 patients with melanoma that responded to ACT identified 45 mutations presented on a variety of class 1 and class 2 MHC molecules. Thus far, every mutation recognized by TILs was distinct (i.e., each from a different expressed protein), with none shared by another melanoma in the set studied. These findings provide suggestive evidence that melanoma TILs capable of mediating antitumor responses were recognizing random somatic mutations in the cancer. In many cases, multiple mutations were recognized by an individual TIL population. The concept that cancer regressions after immunotherapy are the result of targeting mutations explains why patients can experience tumor regression without autoimmune sequelae. Conversely, the ineffectiveness of the vast number of therapeutic cancer vaccines that targeted nonmutated self-proteins can also be explained (*41*, *42*). Whereas strong reactivity to self-antigens causes autoimmune toxicity, vaccines against self-antigens trigger the expansion of low-affinity TCRs against self-proteins that escaped negative selection in the thymus. This raises the possibility that vaccines targeting mutated immunogenic epitopes may be much more effective. The specific targeting of individual mutated antigens in a patient's cancer presents a daunting problem for widespread therapeutic application of ACT but also presents an opportunity to develop treatments for multiple cancer types. Schumacher and Schreiber discuss additional aspects for targeting mutated antigens in this issue (*43*).

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TILs from common epithelial cancers can also recognize cancer mutations

A recent report has shown that the mutated antigens in a nonmelanoma epithelial cancer

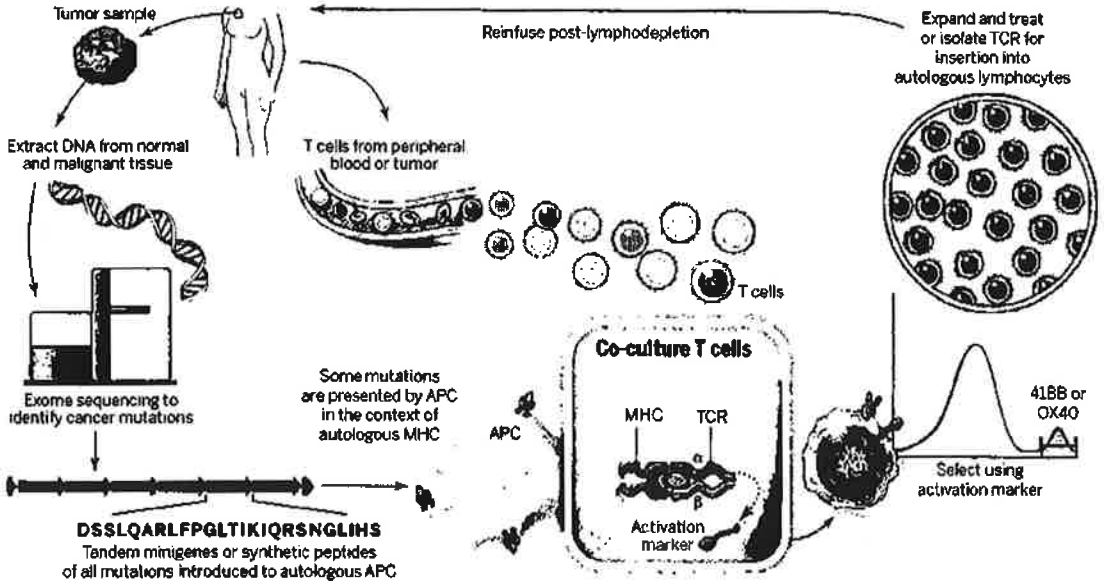

Fig. 3. A "blueprint" for the treatment of patients with T cells recognizing tumor-specific mutations. The sequences of exonic DNA from tumor cells and normal cells from the same patient are compared to identify tumor-specific mutations. Knowledge of these mutations can then be used to synthesize either minigenes or polypeptides encoding each mutated amino acid flanked by 10 to 12 amino acids. These peptides or minigenes can be expressed by a patient's autologous APCs, where they are processed and presented in the context of a patient's MHC. Coculture of the patient's T cells with these APCs can be used to identify all mutations processed and presented in the context of all of a patient's MHC class I and class II molecules. The identification of individual mutations responsible for tumor recognition is possible because T cells express activation markers, such as 41BB ($CD8^+$ T cells) and OX40 ($CD4^+$ T cells), when they recognize their cognate target antigen. T cells expressing the activation marker can then by purified using flow cytometry before their expansion and reinfusion into the tumor-bearing patient.

can give rise to immune responses, despite the low number of mutations in these cancers (*44*). Exomic sequencing of a metastatic cholangiocarcinoma in a patient who had progressed through multiple chemotherapies revealed 26 nonsynonymous mutations. Tandem minigenes that encoded each mutated amino acid and its flanking sequences were constructed and electroporated into the patient's APCs. CD4 cells from TIL cultures from this patient's tumor recognized the ERBB2IP mutation restricted by the MHC class 2 antigen HLA-DQ 06. ERBB2IP is a tumor suppressor that binds to ERBB2 and attenuates downstream RAS/ERK signaling. Despite the lack of an objective clinical response to the administration of bulk autologous TILs in this patient, administration of TILs that were selected to contain more than 95% ERBB2IP mutation-reactive TILs mediated a dramatic regression of liver and lung metastases ongoing beyond 1 year. This result provides compelling evidence that mutation-reactive T cells are capable of mediating in vivo tumor regression in patients with this epithelial cancer. Further, the findings suggest that this treatment approach may be suitable for patients with other common epithelial cancers that are not normally considered to be immunogenic.

Mutations that are targeted may be driver mutations essential for the malignant phenotype of the cell, or alternatively, the TILs may contain reactivity against multiple immunogenic passenger mutations, which would decrease the likelihood that the loss of any individual antigen would subvert the clinical antitumor response. TIL populations can be highly polyclonal and thus are likely to be capable of potentially recognizing multiple antigens simultaneously. Given their curative potential, it seems likely that TILs are able to recognize antigens expressed by cancer stem cells. Although some of the mutations are probably driver mutations because they are found in expressed genes associated with known oncogenic pathways (e.g., mutated β-catenin), many of the targets of TILs may well be passenger mutations.

Genetic engineering of lymphocytes for use in ACT

In an attempt to broaden the reach of ACT to other cancers, techniques were developed to introduce antitumor receptors into normal T cells that could be used for therapy. The specificity of T cells can be redirected by the integration of genes encoding either conventional alpha-beta TCRs or CARs. CARs were pioneered by Gross and colleagues in the late 1980s (*45*) and can be constructed by linking the variable regions of the antibody heavy and light chains to intracellular signaling chains such as CD3-zeta, often including costimulatory domains encoding CD28 (*46*) or CD137 to fully activate T cells (*47, 48*). CARs can provide non-MHC-restricted recognition of cell surface components and can be introduced into T cells with high efficiency using viral vectors.

An important question confronting the use of genetically engineered cells in the ACT of cancer involves selection of the ideal human T cell subpopulation into which the gene should be introduced, as well as the selection of appropriate antigenic targets of the introduced TCRs or CARs. Preclinical studies in mouse models strongly suggest that improved antitumor responses are seen when T cells in early stages of differentiation (such as naïve or central memory cells) are transduced (*49*), a result supported by studies in monkeys showing improved in vivo persistence of infused central memory compared with effector memory cells (*50*). $CD8^+$ T cells can be categorized into distinct memory subsets based on their differentiation states. We and others have found that $CD8^+$ T cells follow a progressive pathway of differentiation from naïve T cells into central memory and effector memory T cell populations [summarized in (*51*)]. $CD8^+$ T cells paradoxically lose antitumor T cell functionality as they acquire the ability to lyse target cells and to produce the cytokine interferon-γ, qualities thought to be important in their antitumor efficacy (*52*). The differentiation state of $CD8^+$ T cells is inversely related to their capacity to proliferate and persist (*52–54*). These findings may be clinically relevant, and younger T cells are statistically positively correlated with clinical effectiveness in ACT trials (*17*). It seems clear that, like many organ systems in the body, $CD8^+$ T cells can exist in a stem cell–like state, capable of clonal repopulation. Human T memory

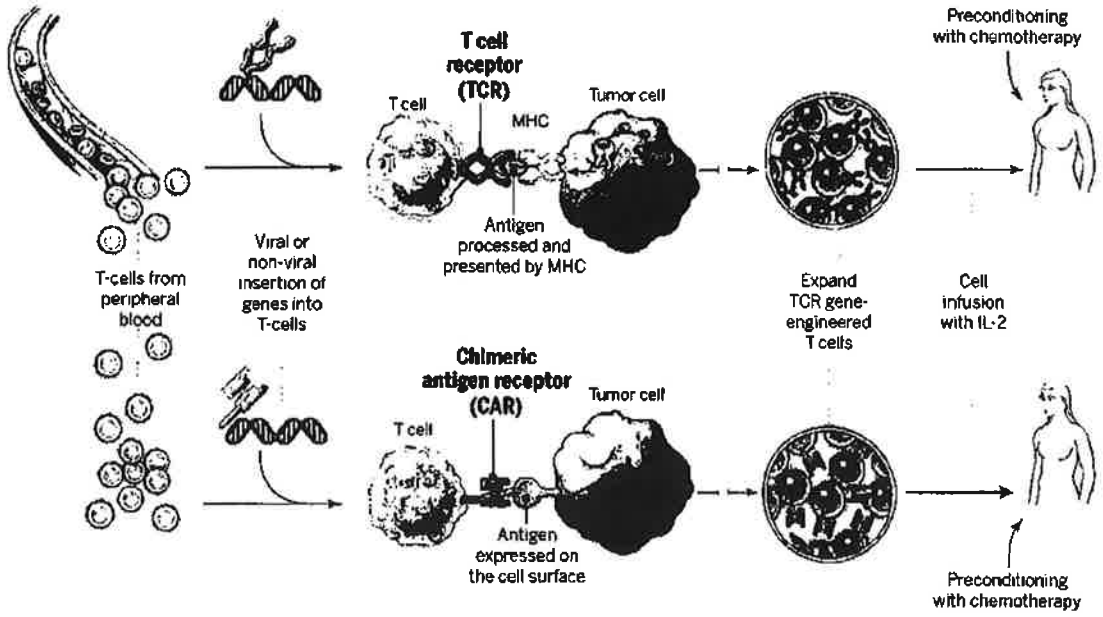

Fig. 4. Gene-modification of peripheral blood lymphocytes. In an attempt to broaden the reach of ACT to other cancers, techniques are being developed to introduce antitumor receptors into normal T cells that could be used for therapy. The top panel shows the insertion of a conventional TCR into a patient's T lymphocytes, followed by the expansion and infusion back into the patient. The bottom panel shows the insertion of a CAR into a patient's T cell, followed by the expansion of these cells and their re-infusion. TCRs and CARs are fundamentally different in their structures and in the structures that they recognize. TCRs are composed of one α chain and one β chain, and they recognize antigens that have been processed and presented by one of the patient's own MHC molecules. CARs are artificial receptors that can be constructed by linking the variable regions of the antibody heavy and light chains to intracellular signaling chains (such as CD3-zeta, CD28, 41BB) alone or in combination with other signaling moieties. CARs recognize antigens that do not need to be MHC-restricted, but they must be presented on the tumor cell surface.

stem cells express a gene program that enables them to proliferate extensively and can further differentiate into other T cell populations (29).

Much of the existing work in cancer immunotherapy has focused on $CD8^+$ T cells. However, $CD4^+$ T cells can also efficiently promote tumor rejection. $CD4^+$ T cells do not merely enhance $CD8^+$ T cell function, but they also play a more direct role in tumor elimination. This notion has been validated recently in humans (44). The roles that $CD4^+$ T cells play in the antitumor immune response crucially depend on their polarization, which is determined by their expression of key transcription factors. $CD4^+$ cells can destroy tumor cells, and recent evidence suggests that adoptively transferred T helper 17 cells can promote long-lived antitumor immunity (55).

Toxicity of ACT when targeting antigens shared by tumors and normal tissue

The marked potency of T cells enables the recognition of minute levels of antigen expressed on normal cells. Thus, targeting normal, nonmutated antigenic targets that are expressed on normal tissues but overexpressed on tumors has led to severe on-target, off-tumor toxicity in patients. Suitable antigens to target are those presented exclusively on the cancer or, alternatively, on normal cells that are not essential for survival.

The first successful application of ACT using genetically engineered lymphocytes treated 17 patients with metastatic melanoma using autologous T cells transduced with a weakly avid human TCR recognizing the MART-1 melanoma-melanocyte differentiation antigen (15). Two patients experienced objective partial regressions of metastatic melanoma, and in both patients the transferred cells could be found in the peripheral blood 1 year after cell infusion. This approach was expanded to 36 patients with metastatic melanoma who received high-avidity TCRs that recognized either the MART-1 or gp100 melanoma-melanocyte antigens (32). Although objective cancer regressions were observed in 30 and 19% of patients who received the MART-1 or gp100 TCR, respectively, severe off-tumor, on-target toxicity was seen in the skin, eyes, and ears of patients due to the expression of melanocytes in these organs. These findings coincided with severe eye toxicity seen in mice when targeting melanocyte antigens and provided an early demonstration of the power of T cell therapy (56). The treatment of patients with renal cancer using T cells encoding a CAR against carbonic anhydrase 9, which is overexpressed in renal cancer, led to severe liver toxicity due to expression of this antigen in biliary duct epithelium (57). A high-affinity TCR against the carcinoembryonic antigen was used to treat patients with metastatic colorectal cancer that expressed high levels of this antigen (58). All three patients experienced life-threatening colitis and colonic hemorrhage that precluded further use of this TCR, even though one patient exhibited a partial response of liver metastases. Unexpected toxicities can also result when previously unknown cross-reactivities are seen that target normal self-proteins expressed in vital organs. MAGE-A3, a cancer-testes antigen to be discussed in more detail below, is not known to be expressed in any normal tissues. However, targeting an HLA-A*0201–restricted peptide in MAGE-A3 caused severe damage to gray matter in the brain, resulting in two deaths because this TCR recognized a different but related epitope expressed by MAGE-A12, expressed at very low levels in the brain (59). It should also be noted that CARs are capable of toxicity against self-antigens as well. Acute pulmonary toxicity resulting in death was observed after infusion of CAR T cells specific for ERBB2, which seemed likely due to the recognition of low levels of this antigen on pulmonary epithelium (60).

Several groups have attempted to affinity-enhance TCRs by altering amino acids in the antigen-combining sites of the TCR (61, 62). By removing the protective effects of negative thymic selection that eliminate high-affinity TCRs against normal proteins, these modified TCRs could potentially recognize new and unrelated determinants. Two patients (one with multiple myeloma and one with melanoma) were treated with an HLA-A1–restricted MAGE-A3–specific TCR whose affinity was enhanced by this site-specific mutagenesis, and both experienced fatal cardiogenic shock due to the recognition of an HLA-A1–restricted peptide derived from an unrelated protein, titin, present in cardiac muscle (63). Thus, methods aimed at enhancing the affinities of TCRs can be fraught with problems of unexpected toxicities, which remain difficult to predict. Of course, the same pitfalls of unexpected toxicities may apply to the use of novel CARs.

Targeting antigens expressed on cancers and nonessential human tissues

Cancers that express target molecules shared with nonessential normal organs represent potential targets for human cancer immunotherapy using ACT. A prominent example of such an antigen is the CD19 molecule expressed on more than 90% of B cell malignancies and on B cells at all stages of differentiation, excluding plasma cells. Following preclinical work by many groups [summarized in (64–67)], the first successful clinical application of anti-CD19 CAR gene therapy in humans was reported in 2010 (16). Administration of autologous cells expressing the anti-CD19 CAR to a patient with refractory lymphoma resulted in cancer regression in a patient who remains progression free after two cycles of treatment ongoing 4 years after treatment. Multiple groups have now shown the effectiveness of ACT targeting CD19 in patients with follicular lymphoma, large-cell lymphomas, chronic lymphocytic leukemia, and acute lymphocytic leukemia (68–77). On-target toxicity against CD19 results in B cell loss in the circulation and in the bone marrow and can be overcome by the periodic administration of immunoglobulin infusions. Substantial toxicity can be seen by the excessive release of cytokines by CAR-expressing cells and, thus, careful selection of the lymphodepleting preparative regimen and the cell dose is required to safely apply ACT targeting CD19, as well as many other antigens now under experimental study (72).

Dramatic regressions of lymphomas and leukemias with ACT have elicited considerable enthusiasm, although most reports contain fewer than 20 patients, and fewer than 200 patients have been treated worldwide. The introduction of CARs into lymphocytes have mainly used gammaretroviruses and lentiviruses, although nonviral approaches such as transposon-transposase systems (73) and CRISPR-cas (CRISPR, clustered regularly interspaced palindromic repeat) technology to introduce genes are also being explored (74). The single-chain antibody governs recognition of the antigen to be targeted, although the T cell is activated via the CD3-zeta chain signaling domain. In addition to the zeta chain, a variety of costimulatory molecules have been employed in retroviral constructs such as CD27, CD28, CD134, CD137, or ICOS that can profoundly influence the function of the CAR [reviewed in (64–66)]. Optimization of these costimulatory domains is a subject of active study. The results of CAR therapy for B cell malignancies might be confounded by the sensitivity of lymphomas and leukemias to the preparative chemotherapy regimen. Thus, delineation between the effects of the preparative therapy and those of the CAR T cells needs to be considered.

Multiple other B cell antigens are being studied as targets, including CD22, CD23, ROR-1, and the immunoglobulin light-chain idiotype expressed by the individual cancer (65). CARs targeting either CD33 or CD123 have been studied as a therapy for patients with acute myeloid leukemia, though the expression of these molecules on normal precursors can lead to prolonged myeloablation (75). BCMA is a tumor necrosis factor receptor family protein expressed on mature B cells and plasma cells and can be targeted on multiple myeloma (65). The Reed-Sternberg cell expresses CD30, and this target is being explored as a treatment for patients with refractory Hodgkin lymphoma (75–77).

Although CARs are being successfully applied to the treatment of hematologic malignancies, the lack of shared antigens on the surface of solid tumors that are not also expressed on essential normal tissues has severely limited the application of CARs to the treatment of solid tumors. Thyroglobulin is a potential target for some patients with thyroid cancers because thyroglobulin is present only in the thyroid gland and not on solid tissues. Neuroblastomas express GD2, which has been targeted by CARs (75). Mesothelin has also been forwarded as a potential target, although it is also expressed on normal tissues, including cells in the pericardium and pleural and peritoneal linings (79). A search is ongoing for other tissue-specific surface antigens expressed on tissues that are not essential for survival.

Cancer-testis antigens are a family of intracellular proteins that are expressed during fetal development but have highly restricted expression in adult normal tissues (80). There are more than 100 different members of this family of molecules whose expression is epigenetically up-regulated from 10 to 80% of cancer types using highly

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MS no: RVaaa4967/LK/IMMUNOLOGY

sensitive techniques. However, initial enthusiasm for targeting cancer-testes antigens has been tempered by the lack of high levels of protein expression of these antigens. Approximately 10% of common cancers appear to express enough protein to be suitable targets for antitumor T cells. There are low levels of some cancer-testes antigens expressed on normal tissues, and this can lead to untoward toxicities. The NYESO-1 cancer-testes antigen has been targeted via a human TCR transduced into autologous cells (*81*). ORs were seen in 5 of 11 patients with metastatic melanoma and 4 of 6 patients with highly refractory synovial cell sarcoma.

Looking to the future of ACT for the treatment of cancer

The continued development of ACT, as well as other immunologic approaches to the treatment of cancer, depends on the identification of suitable targets for immunologic attack. Although CARs have been successful in the treatment of hematologic malignancies and are likely to soon join the mainstream of oncologic treatment, the ability to treat common epithelial solid cancers, which account for ~90% of all cancer fatalities, is severely limited by the lack of suitable targets exclusive to cancer. Extensive searches for monoclonal antibodies that can recognize distinct determinants on the surface of solid cancers but not normal tissues have been in progress for more than 30 years, but few suitable determinants have been found. The EGFRvIII mutation on ~40% of high-grade glioblastomas is a rare example of a shared-surface mutation, and attempts to target this molecule using CARs are in progress (*82*). Shared mutations in intracellular proteins involved in oncogenesis—such as Braf in melanomas and Kras in pancreatic and other solid cancers—would be ideal ACT targets using conventional alpha-beta TCRs, though immunogenic epitopes have not yet been identified in these molecules. Driver and random somatic mutations occurring in many solid cancers may represent excellent targets for the treatment of solid tumors.

Opportunities to improve ACT involve the identification and development of specific antitumor T cells with the functional properties optimal for tumor destruction (*83*). One approach under active evaluation is the growth of cells under conditions that enable in vitro proliferation while limiting differentiation, such as the use of IL-21 or inhibitors that target the kinase AKT (*84*, *85*). Improved specific lymphodepleting preparative regimens and better design of the transducing vectors, including the incorporation of optimal costimulatory molecules, are likely to improve clinical results. Introduction of genes encoding other molecules such as the cytokine IL-12, which can profoundly alter the tumor microenvironment to favor antitumor immunity, has shown substantial promise in animal models (*86*). Enhanced methods for regulating the expression of these highly potent cytokine genes would be an important part of incorporating them into clinical treatment. The incorporation of "suicide" genes that can enable destruction of the transferred cells could add an extra level of safety when exploring genetic changes in lymphocytes (*87*).

Adoptive cell therapy is a more complex approach to the delivery of cancer treatment than many other types of immunotherapy and has often been criticized as impractical and too costly for widespread application. The need to develop highly personalized treatments for each patient does not fit into the paradigm of major pharmaceutical companies that depend on "off-the-shelf" reagents that can be widely distributed. However, curative immunotherapies for patients with common epithelial cancers will probably dictate the need for more personalized approaches. Several new biotechnology companies have arisen to meet the need to expand a patient's lymphocytes, and detailed genetic analysis of individual tumors is already commonplace at large academically affiliated medical centers. Although multiple commercial models have been proposed, widespread application of ACT will probably depend on the development of centralized facilities for producing tumor-reactive TILs or genetically modified lymphocytes that can then be delivered to the treating institution. The effectiveness of treatment will need to trump convenience of administration in the application of new effective approaches to cancer immunotherapy.

REFERENCES AND NOTES

1. E. J. Delorme, P. Alexander, *Lancet* **284**, 117–120 (1964).
2. A. Feler, *Cancer Res.* **29**, 2177–2183 (1969).
3. E. Fernandez-Cruz, B. A. Woda, J. D. Feldman, *J. Exp. Med.* **152**, 823–841 (1980).
4. M. J. Berendt, R. J. North, *J. Exp. Med.* **151**, 69–80 (1980).
5. D. A. Morgan, F. W. Ruscetti, R. Gallo, *Science* **193**, 1007–1008 (1976).
6. S. A. Rosenberg, J. J. Mulé, P. J. Spiess, C. M. Reichert, S. L. Schwarz, *J. Exp. Med.* **161**, 1169–1188 (1985).
7. T. J. Eberlein, M. Rosenstein, S. A. Rosenberg, *J. Exp. Med.* **156**, 385–397 (1982).
8. J. M. Donohue *et al.*, *J. Immunol.* **132**, 2123–2128 (1984).
9. S. A. Rosenberg *et al.*, *N. Engl. J. Med.* **313**, 1485–1492 (1985).
10. S. A. Rosenberg, P. Spiess, R. Lafreniere, *Science* **233**, 1318–1321 (1986).
11. L. M. Muul, P. J. Spiess, E. P. Director, S. A. Rosenberg, *J. Immunol.* **138**, 989–995 (1987).
12. S. A. Rosenberg *et al.*, *N. Engl. J. Med.* **319**, 1676–1680 (1988).
13. M. E. Dudley *et al.*, *Science* **298**, 850–854 (2002).
14. H. W. H. G. Kessels, M. C. Wolkers, M. D. van den Boom, M. A. van der Valk, T. N. M. Schumacher, *Nat. Immunol.* **2**, 957–961 (2001).
15. R. A. Morgan *et al.*, *Science* **314**, 126–129 (2006).
16. J. N. Kochenderfer *et al.*, *Blood* **116**, 4099–4102 (2010).
17. S. A. Rosenberg *et al.*, *Clin. Cancer Res.* **17**, 4550–4557 (2011).
18. S. Pilon-Thomas *et al.*, *J. Immunother.* **35**, 615–620 (2012).
19. L. G. Radvanyi *et al.*, *Clin. Cancer Res.* **18**, 6758–6770 (2012).
20. M. J. Besser *et al.*, *Clin. Cancer Res.* **19**, 4792–4800 (2013).
21. J. J. Hong *et al.*, *Clin. Cancer Res.* **16**, 4892–4898 (2010).
22. S. A. Rosenberg *et al.*, *N. Engl. J. Med.* **323**, 570–578 (1990).
23. V. Bronte *et al.*, *J. Immunol.* **161**, 5313–5320 (1998).
24. X. Yao *et al.*, *Blood* **119**, 5688–5696 (2012).
25. L. Gattinoni *et al.*, *J. Exp. Med.* **202**, 907–912 (2005).
26. M. E. Dudley *et al.*, *J. Clin. Oncol.* **26**, 5233–5239 (2008).
27. C. M. Paulos *et al.*, *J. Clin. Invest.* **117**, 2197–2204 (2007).
28. N. P. Restifo, M. E. Dudley, S. A. Rosenberg, *Nat. Rev. Immunol.* **12**, 269–281 (2012).
29. L. Gattinoni *et al.*, *Nat. Med.* **17**, 1290–1297 (2011).
30. Y. Kawakami *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **91**, 6458–6462 (1994).
31. Y. Kawakami *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **91**, 3515–3519 (1994).
32. L. A. Johnson *et al.*, *Blood* **114**, 535–546 (2009).
33. M. S. Lawrence *et al.*, *Nature* **499**, 214–218 (2013).
34. T. Wölfel *et al.*, *Science* **269**, 1281–1284 (1995).
35. M. M. Gubin *et al.*, *Nature* **515**, 577–581 (2014).
36. S. L. Topalian *et al.*, *N. Engl. J. Med.* **366**, 2443–2454 (2012).
37. R. N. van Rooij *et al.*, *J. Clin. Oncol.* **31**, e439–e442 (2013).
38. S. D. Brown *et al.*, *Genome Res.* **24**, 743–750 (2014).
39. P. F. Robbins *et al.*, *Nat. Med.* **19**, 747–752 (2013).
40. Y. C. Lu *et al.*, *Clin. Cancer Res.* **20**, 3401–3410 (2014).
41. S. A. Rosenberg, J. C. Yang, N. P. Restifo, *Nat. Med.* **10**, 909–915 (2004).
42. C. A. Klebanoff, N. Acquavella, Z. Yu, N. P. Restifo, *Immunol. Rev.* **239**, 27–44 (2011).
43. T. N. Schumacher, R. D. Schreiber, *Science* **348**, xxx–xxx [this issue] (2015).
44. E. Tran *et al.*, *Science* **344**, 641–645 (2014).
45. G. Gross, T. Waks, Z. Eshhar, *Proc. Natl. Acad. Sci. U.S.A.* **86**, 10024–10028 (1989).
46. J. Maher, R. J. Brentjens, G. Gunset, I. Rivière, M. Sadelain, *Nat. Biotechnol.* **20**, 70–75 (2002).
47. C. Imai *et al.*, *Leukemia* **18**, 676–684 (2004).
48. D. G. Song *et al.*, *Cancer Res.* **71**, 4617–4627 (2011).
49. C. A. Klebanoff *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **102**, 9571–9576 (2005).
50. C. Berger *et al.*, *J. Clin. Invest.* **118**, 294–305 (2008).
51. L. Gattinoni, D. J. Powell Jr., S. A. Rosenberg, N. P. Restifo, *Nat. Rev. Immunol.* **6**, 383–393 (2006).
52. L. Gattinoni *et al.*, *J. Clin. Invest.* **115**, 1616–1626 (2005).
53. V. R. Buchholz *et al.*, *Science* **340**, 630–635 (2013).
54. C. Gerlach *et al.*, *Science* **340**, 635–639 (2013).
55. P. Muranski *et al.*, *Immunity* **35**, 972–985 (2011).
56. D. C. Palmer *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **105**, 8061–8066 (2008).
57. C. H. Lamers *et al.*, *Mol. Ther.* **21**, 904–912 (2013).
58. M. R. Parkhurst *et al.*, *Mol. Ther.* **19**, 620–626 (2011).
59. R. A. Morgan *et al.*, *J. Immunother.* **36**, 133–151 (2013).
60. R. A. Morgan *et al.*, *Mol. Ther.* **18**, 843–851 (2010).
61. Y. Li *et al.*, *Nat. Biotechnol.* **23**, 349–354 (2005).
62. P. F. Robbins *et al.*, *J. Immunol.* **180**, 6116–6131 (2008).
63. G. P. Linette *et al.*, *Blood* **122**, 863–871 (2013).
64. R. A. Gardner, M. C. Jensen, *Cancer J.* **20**, 107–111 (2014).
65. S. Gill, C. H. June, *Immunol. Rev.* **263**, 68–89 (2015).
66. M. Sadelain, R. Brentjens, I. Rivière, *Cancer Discov.* **3**, 388–398 (2013).
67. J. N. Kochenderfer, S. A. Rosenberg, *Nat. Rev. Clin. Oncol.* **10**, 267–276 (2013).
68. M. Kalos *et al.*, *Sci. Transl. Med.* **3**, 95ra73 (2011).
69. S. A. Grupp *et al.*, *N. Engl. J. Med.* **368**, 1509–1518 (2013).
70. R. J. Brentjens *et al.*, *Sci. Transl. Med.* **5**, 177ra38 (2013).
71. J. N. Kochenderfer *et al.*, *J. Clin. Oncol.* **33**, 540–549 (2015).
72. D. W. Lee *et al.*, *Blood* **124**, 188–195 (2014).
73. H. Singh, H. Huls, P. Kebriaei, L. J. Cooper, *Immunol. Rev.* **257**, 181–190 (2014).
74. J. A. Doudna, E. Charpentier, *Science* **346**, 1258096 (2014).
75. I. Pizzitola *et al.*, *Leukemia* **28**, 1596–1605 (2014).
76. B. Savoldo *et al.*, *Blood* **110**, 2620–2630 (2007).
77. A. K. Gopal *et al.*, *Blood* **125**, 1236–1243 (2015).
78. C. U. Louis *et al.*, *Blood* **118**, 6050–6056 (2011).
79. Y. Zhao *et al.*, *Cancer Res.* **70**, 9053–9061 (2010).
80. M. J. Scanlan, A. O. Gure, A. A. Jungbluth, L. J. Old, Y. T. Chen, *Immunol. Rev.* **188**, 22–32 (2002).
81. P. F. Robbins *et al.*, *J. Clin. Oncol.* **29**, 917–924 (2011).
82. R. A. Morgan *et al.*, *Hum. Gene Ther.* **23**, 1043–1053 (2012).
83. A. Gros *et al.*, *J. Clin. Invest.* **124**, 2246–2259 (2014).
84. Y. Li, M. Bleakley, C. Yee, *J. Immunol.* **175**, 2261–2269 (2005).
85. J. G. Crompton *et al.*, *Cancer Res.* **75**, 296–305 (2015).
86. S. P. Kerkar *et al.*, *J. Clin. Invest.* **121**, 4746–4757 (2011).
87. A. Di Stasi *et al.*, *N. Engl. J. Med.* **365**, 1673–1683 (2011).
88. S. A. Rosenberg *et al.*, *J. Natl. Cancer Inst.* **86**, 1159–1166 (1994).
89. C. S. Hinrichs *et al.*, 2014 American Society of Clinical Oncology (ASCO) Annual Meeting, Chicago, IL, 30 May to 3 June 2014 (ASCO, Alexandria, VA, 2014), abstract LBA3008; http://meetinglibrary.asco.org/content/129263-144.
90. N. N. Hunder *et al.*, *N. Engl. J. Med.* **358**, 2698–2703 (2008).
91. A. G. Chapuis *et al.*, *Sci. Transl. Med.* **5**, 174ra27 (2013).
92. S. L. Maude *et al.*, *N. Engl. J. Med.* **371**, 1507–1517 (2014).
93. M. L. Davila *et al.*, *Sci. Transl. Med.* **6**, 224ra25 (2014).
94. D. W. Lee *et al.*, *Lancet* **385**, 517–528 (2015).

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Attachment

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From: Dr. Arie Belldegrun [arie@belldegrun.com]
Sent: Monday, March 30, 2015 4:27 PM
To: 'Justin Jackson'; Rosenberg, Steven A. (NIH/NCI) [E]; David Chang; Jeff Wiezorek
Subject: FW: ACT review article
Attachments: June et al. Adoptive cellular therapy.pdf

FYI, "joint" Kite, Novartis Juno paper.....

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IMMUNOTHERAPY

Adoptive cellular therapy: A race to the finish line

Carl H. June,[1]* Stanley R. Riddell,[2]* Ton N. Schumacher[3]*

Adoptive T cell transfer for cancer, chronic infection, and autoimmunity is an emerging field that shows promise in recent trials. Using the principles of synthetic biology, advances in cell culture and genetic engineering have made it possible to generate human T cells that display desired specificities and enhanced functionalities compared with the natural immune system. The prospects for widespread availability of engineered T cells have changed dramatically, given the recent entry of the pharmaceutical industry to this arena. Here, we discuss some of the challenges—such as regulatory, cost, and manufacturing—and opportunities, including personalized gene-modified T cells, that face the field of adoptive cellular therapy.

INTRODUCTION

Adoptive cell transfer (ACT) is a term coined by Billingham and colleagues to describe the transfer of lymphocytes to mediate an effector function (*1*). Presently, there are three types of therapies that are advancing on a path toward regulatory approval (Fig. 1): tumor-infiltrating lymphocytes (TILs) as well as chimeric antigen receptor (CAR) and T cell receptor (TCR) engineered T cells. TILs have been developed with slow but continuing progress over several decades, primarily at the National Cancer Institute. Recently, an international phase 3 randomized trial began for treating patients with metastatic melanoma with TILs (NCT02278887). A number of pharmaceutical and newly formed biotechnology companies are now commercializing various forms of ACT, including TIL therapies (Table 1).

In contrast to TILs, gene-transfer–based strategies have been developed to overcome the consequences of immune tolerance on the tumor-specific T cell repertoire. These approaches redirect T cells to tissues by the transfer of CARs composed of antibody-binding domains fused to T cell signaling domains, or transfer of TCR α/β heterodimers. The infusion of gene-modified T cells directed to specific targets offers the possibility to endow the immune system with reactivities that are not naturally present and has the added benefit of the rapid onset of action that is usually seen with cytotoxic chemotherapy or with targeted therapies, contrasting to delayed effects observed with vaccines and some of the T cell checkpoint therapies.

Currently, most trials are using α/β T cells for ACT. However, investigators are exploring the use of numerous lymphocyte subsets—including γ/δ T cells, invariant natural killer (NK) T cells, NK cells, and T helper 17—for their specialized functions in various clinical settings of cancer and chronic infection. For indications involving autoimmunity, tolerance induction, prevention of organ graft rejection, and treatment of graft-versus-host disease (GVHD), regulatory T cells (T_{reg} cells), including natural and induced T_{reg} cells, are being tested. Myeloid-derived suppressor cells and regulatory B cells, which have anti-inflammatory properties involving mechanisms distinct from T_{reg} cells, have also been proposed as novel forms of ACT (*2*, *3*). In this Perspective, we review the status of ACT and the rapidly emerging role of the biotechnology industry in the race to accelerate the development and promote the widespread availability of this new form of cellular therapy that has demonstrated efficacy treating patients with refractory life-threatening cancers.

ACT is generally considered in the context of cancer, typically leukemias and melanoma (Table 1). It is interesting to note from a historical perspective that some of the first forms of ACT involving gene-modified T cells were conducted two decades previously in patients with advanced HIV-1/AIDS (*4*). Many of the results from trials conducted in patients with AIDS have informed current concepts in the field of cancer, as exemplified by the demonstration that CAR T cells could survive for more than a decade in HIV/AIDS patients (*5*). These initial trials were done in order to control drug-resistant forms of HIV-1 infection. However, the current challenge in the field is to develop cellular therapies with the potential to eliminate the reservoir of HIV-1 that is resistant to current antiviral therapies (*6*). The field has been energized by an extraordinary experiment conducted by Gero Hütter and colleagues in Berlin in a patient who has apparently been cured of HIV infection after an allogeneic hematopoietic stem cell transplant and ACT from a homozygous C-C chemokine receptor type 5 (CCR5) Δ32 donor (*7*). There are several approaches to induce a cell-intrinsic resistance to HIV-1 infection and to target the reservoir of HIV-1 by gene-modified ACT and cytotoxic T lymphocytes (CTL) (*8*, *9*).

Cancer immunotherapies that target T cell checkpoints, such as cytotoxic T lymphocyte–associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) (*10*), rely on the ability of the endogenous T cell compartment to recognize the tumor as foreign because of the epitopes it carries. TIL therapy likewise relies on an intrinsic tumor recognition capacity of the T cell compartment, and checkpoint therapies and TIL therapy may therefore be assumed to have potential for a similar set of human cancers. Notably, recent work suggests that T cell recognition of neoantigens that are created as a consequence of tumor-specific mutations forms a major component of the clinical activity of checkpoint therapies (*11*, *12*), and clinical activity of these therapies may therefore be highest in tumors with a high mutational load. Adoptive therapy with gene-modified T cells has the potential to address an entirely different need by creating a tumor-specific T cell compartment that is otherwise lacking in patients (Fig. 1). As such, gene-modified ACT has potential for tumor types that may not be responsive to T cell checkpoint or TIL therapies, such as most cancers occurring in children and many of the hematological malignancies. In addition, gene-modified ACT addresses a different critical node in the "cancer–immunity cycle," the series of stepwise events required for an anticancer immune response to lead to cancer cell eradication (*13*). Furthermore, T cell checkpoint therapies and gene-modified ACT have the potential to work synergistically.

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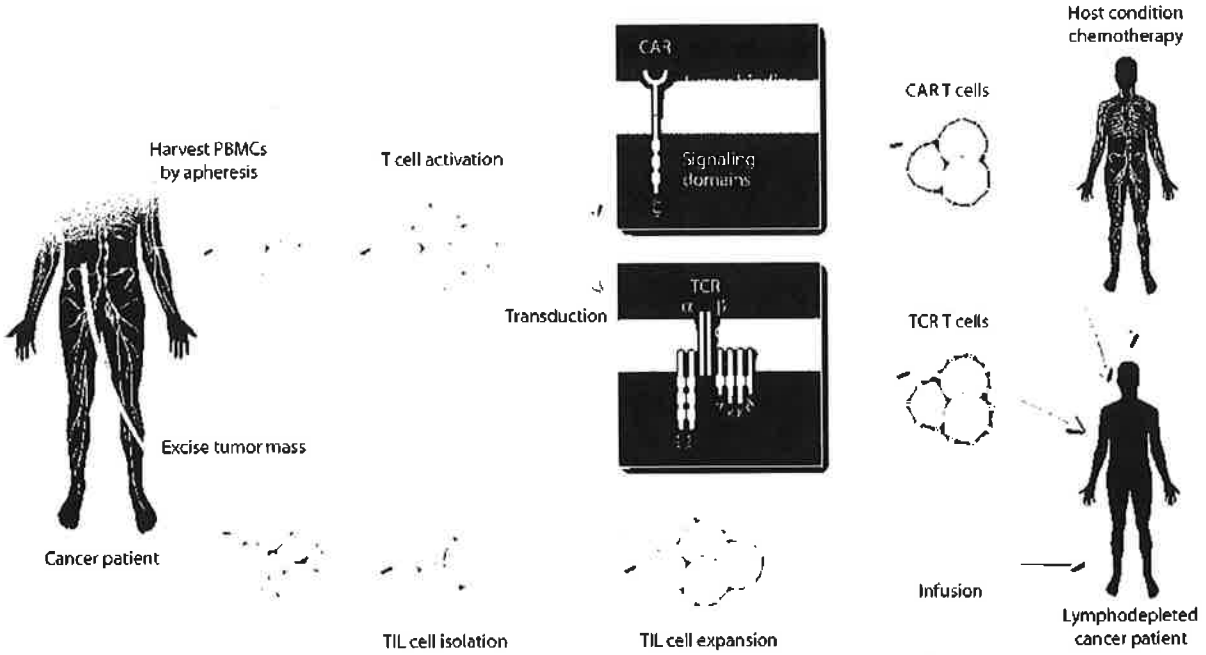

Fig. 1. Adoptive cell therapy is currently represented by three general approaches. TILs are produced after surgical excision of tumor and enrichment and expansion of TILs from a disaggregated tumor biopsy sample. TCR- and CAR-modified T cells are produced from peripheral blood lymphocytes in a manufacturing step that includes introduction of the desired receptor through viral or nonviral methods in order to engineer cells. Patients often receive a lymphodepleting chemotherapy regimen before infusion. PBMC, peripheral blood mononuclear cell.

SOURCE OF CARS AND TCRS

Most of the chimeric antigen receptors currently used to create gene-modified T cells are derived from mouse antibodies, and both antibody and T cell responses against CARs have been observed in clinical trials (*14*, *15*). Furthermore, the extent of this problem may presently be underestimated because the most visible trials in the area have involved the targeting of the B cell compartment—a clinical setting in which transgene-specific humoral immunity will be less of an issue than in settings in which the humoral immune system is left intact. To minimize the impact of transgene-specific immune responses on the activity of introduced cells, the use of humanized or fully human antibodies obtained from mice transgenic for the human immunoglobulin (Ig) loci forms an obvious solution. Clinical trials with fully human CARs have only recently opened (NCT02209376 and NCT01837602). In addition, it may be beneficial to engineer the CAR format so that the formation of nonhuman sequences at the domain fusion sites is also avoided.

By the same token, immunogenicity of nonhuman TCR sequences has been described in a subset of patients treated with TCR-modified T cells—in this case, involving antibody recognition of mouse TCR variable domains (*16*). Here again, the isolation of receptors from the human T cell repertoire or from mice that carry a humanized TCR repertoire is likely to be an effective solution (*17*). In the case of TCRs, the source from which the receptor is obtained will also influence the likelihood of off-target toxicity: the recognition and destruction of normal tissues that express a different epitope from that of the targeting agent. From a conceptual point of view, the T cell pool from a human lymphocyte antigen (HLA)–matched individual should be considered the safest source of TCRs, but the quality of the available TCR pool is likely capped by T cell tolerance for many antigens. The breadth of the available repertoire will be—roughly in order—greater in HLA-transgenic mice, in T cell pools from HLA-mismatched individuals, and in the in vitro TCR display systems that avoid T cell tolerance altogether. However, the safe use of the latter type of technologies is only feasible when rigorous assay systems are in place that can screen against unwanted cross-reactivity.

TOXICITY FROM ACT

In accord with expectations, toxicities from ACT have increased as the therapies have become more potent. Although TILs have generally been safe (as with other forms of autologous cellular therapy), both on-target and off-target recognition of normal tissue can occur with engineered T cells. For instance, on-target toxicity has been reported in patients treated with T cells engineered with a TCR that is specific for the carcinoembryonic antigen, resulting in severe inflammatory colitis developed from expression of target antigen in normal colon (*18*). With B cell–directed forms of ACT with CARs, commonly observed on-target toxicities have been B cell aplasia and cytokine release syndrome (*19*). Severe cardiac toxicity was reported owing to off-tumor and off-target recognition of titin after ACT with T cells expressing an affinity-engineered TCR that was originally specific for melanoma-associated antigen 3 (MAGE A3) (*20*). Methods involving computational and bio-

Table 1. Pharmaceutical and biotechnology companies in the ACT space. ACT applications are shown for cancers, infections, and GVHD.

Company	Technology/cell type	Indication
	Cancer	
Lion Biotechnologies	TIL (autologous)	Metastatic melanoma
Autolus	CAR (autologous)	Unspecified
Novartis	CAR (autologous) targeting CD19	Pediatric and adult ALL, diffuse large B cell lymphoma, non-Hodgkin's lymphoma (NHL)
Juno Therapeutics	CAR (autologous) targeting CD19, TCR (autologous) targeting Wilms tumor protein (WT-1)	Adult and pediatric ALL, NHL, adult acute myeloid leukemia (AML), non–small cell lung cancer (NSCLC)
Cardio3 Biosciences	CARs targeting NK cell p30-related protein (NKp30); NK group 2, member D (NKG2D); B7 homolog 6 (B7H6)	Range of hematological malignancies and solid tumors
Cellular Biomedicine Group	CARs targeting CD19, CD20, CD30, and EGFR	Range of hematological malignancies and solid tumors
CARsgen	CARs targeting glypican-3 (GPC-3)	Hepatocellular carcinoma
Celgene/Bluebird	CAR (autologous)	Range of hematological malignancies and solid tumors
Kite Pharma/Amgen	CAR (autologous) targeting CD19, TCR	Relapsed or refractory ALL
Cellectis/Servier/Pfizer	CAR (allogeneic, UCART 19)	CLL, ALL, and AML in preclinical stage, phase 1 for B cell leukemia to be initiated in 2015
GSK/Adaptimmune	TCR (autologous) targeting the cancer testis antigen NY-ESO-1 and other targets	Trials in multiple myeloma (MM), melanoma, sarcoma, and ovarian cancer
Janssen/Transposagen	CAR (allogeneic)	Unspecified
Unum Therapeutics/Sanofi-Genzyme	Antibody-coupled TCR (autologous)	Unspecified
Ziopharm Oncology/Intrexon	CAR	Unspecified
Opus Bio	CAR (autologous) targeting CD22	Pediatric and adult ALL and NHL. CD22 licensed to Juno
Takara Bio (Japan)	CAR (autologous) targeting CD19, TCR, MAGE-A4	NHL, esophageal cancer
Bellicum Pharmaceuticals	CAR (autologous) targeting CD19 with a proprietary safety switch to mute unwanted adverse events, such as cytokine release syndrome	Potential hematological malignancies and solid tumors
Cellular Therapeutics Ltd (UK)	CAR (autologous)	Metastatic melanoma, esophago-gastric cancer
Cell Medica (UK)	Virus-specific T cells (allogeneic) targeting Epstein-Barr virus antigen	Advanced NK/T cell lymphoma
Celdara Medical	CAR (autologous) targeting NKG2D	AML, advanced myelodysplastic syndrome (MDS), MM
Catapult Cell Therapy (UK)	TCR (autologous) targeting WT-1–overexpressing cells	AML, MDS
Medigene (Germany)	TCR (autologous)	Hematological malignancies
TheraVectys (France)	CARs (autologous) targeting CD19, CD33, and CD123	ALL, CLL, AML
BioNTech AG (Germany)	TCR, CAR (autologous)	Solid tumors (ovarian, endometrial, lung)
CARsgen (China)	CAR (autologous) targeting GPC-3 expressed in hepatocellular carcinoma; other CARs	Liver, lung, and brain cancers
FF CanVac	Virus-specific T cells (autologous)	Head and neck cancer
Apceth	Genetically engineered mesenchymal stem cells (MSC) (autologous)	Advanced, recurrent, or metastatic gastrointestinal cancer
Pocastem	Genetically engineered MSCs	Solid tumors (head and neck, brain)
TVAX Biomedical	Antigen-specific T cells (autologous)	Solid tumors (brain, kidney)
TC Biopharm (Scotland)	γ/δ T cells (autologous)	Melanoma
Immunovative Therapies (Israel)	Activated T cells (allogeneic)	Hematological malignancy, prostate cancer, breast cancer, glioblastoma, colorectal cancer with liver metastases, kidney cancer, NSCLC
CytoVac (Denmark)	Activated T cells/NK cells (autologous)	Glioblastoma, prostate cancer, pancreatic cancer
Conkwest	CAR NK cell line	AML
Coronado Biosciences	Activated NK cells (autologous)	AML
	HIV/Infection	
Calimmune	CCR5 knockdown $CD4^+$ T cells and stem cells	HIV
Cell Medica (UK)	Cytomegalovirus (CMV) infection after allogeneic hematopoietic stem cell transplant (HSCT)	CMV infection
Sangamo Biosciences	CCR5-mutated $CD4^+$ T cells and stem cells	HIV
Stage Therapeutics (Germany)	CMV-specific donor lymphocytes	CMV infection
Takara Bio (Japan)	mRNA interferase MazF (autologous) endoribonuclease–modified $CD4^+$ T cells	HIV
	GVHD	
Kiadis Pharma (Netherlands)	Allo-depleted T cells (allogeneic)	Facilitate early immune reconstitution without life-threatening (acute) GVHD in leukemia patients (ALL, AML, MDS) undergoing HSCT
Miltenyi Biotec GmbH/Prometheus Laboratories (Germany)	T_{reg}-enriched infusion (allogeneic) + low-dose IL2	Steroid-refractory chronic GVHD

logical approaches are being developed to predict off-target recognition by engineered TCRs (*21*).

Apart from toxicity consequent to the reactivity pattern of the introduced CAR or TCR itself, it is expected that autoimmunity and inflammation will sometimes result from the infusion of ex vivo–activated autologous lymphocytes. Current experimental trials exclude patients with active autoimmune disorders, so the incidence of immunopathology may rise when ACT achieves broad usage in the community. Severe side effects from CTLA-4 and PD-1 antagonism occur with relatively high frequency, especially upon combined checkpoint blockade (*22*, *23*), and we expect that this will occur with ACT unless, for example, steps are taken to edit out endogenous TCRs. In mice, the inflammatory consequences of immunotherapy are more severe in aged mice than in young mice and in obese rather than in thin mice (*24*). This may also happen in humans, and relevant to this is the observation that GVHD occurs more frequently and is more severe in aged rather than young patients (*25*).

A potential safety concern related to ACT with engineered T cells is integration-related insertional mutagenesis and cellular transformation—events previously demonstrated with engineered hematopoietic stem cells. To date, transformation of human lymphocytes has not been reported after ACT (*5*, *19*), and the incidence can be calculated to be less than one event per 1000 patient years of exposure to engineered T cells, an event rate that is lower than that reported for cytotoxic chemotherapy (*26*). The low genotoxicity with ACT may be due to cell-extrinsic mechanisms that control T cell homeostasis (*27*).

THE EXPANDING TOOLBOX FOR GENETIC ENGINEERING

Novel technologies that enable targeted alterations of the genome to modify or regulate cellular functions provide an opportunity for improving both the efficacy and safety of ACT. Zinc-finger nucleases (ZFNs) and transcription activator–like effector nucleases (TALENS) that rely on customized DNA binding proteins, and the natural bacterial CRISPR-Cas9 system of RNA-guided nucleases, can introduce DNA double-strand breaks at specific sites and lead to disruption of a gene sequence or provide a site for targeted gene insertion (*28*, *29*). ZFNs and TALENS have been used to disrupt endogenous TCR genes, and the first clinical application of ZFNs to disrupt expression of the HIV co-receptor CCR5 in $CD4^+$ T cells was reported recently (*30*–*33*).

Efficient genome editing paves the way for additional applications in ACT. The importance of T cell–intrinsic regulatory molecules such as CTLA-4 and PD-1 in suppressing beneficial tumor-reactive T cell responses has been established by using antibodies targeting these pathways (*34*–*36*). Selective editing of PD-1 or CTLA-4 genes in adoptively transferred T cells might similarly enhance efficacy without the side effects of systemic antibody blockade. Other regulatory pathways that inhibit T cell function locally in the tumor microenvironment have been revealed by introducing pooled short hairpin RNA (shRNA) libraries into tumor-specific T cells used in ACT, and this provides previously unidentified targets for gene editing, including intracellular targets that are not amenable to antibody-mediated blockade (*37*). A potential caveat of editing regulatory genes in T cells is that these molecules serve context-dependent roles in normal physiology, and permanent disruption, even in a subset of T cells, may have unforeseen consequences.

Genes can also be introduced into T cells in order to enhance their ability to localize at tumor sites and to function in the immunosuppressive tumor microenvironment. The introduction of chemokine receptor genes in T cells that bind chemokines produced by tumors can enhance T cell migration into tumors (*38*), and expression of dominant-negative transforming growth factor–β (TGF-β) receptors renders T cells resistant to the local inhibitory effects of TGF-β (*39*). Engineering T cells to secrete interleukin-12 (IL-12) induces a programmatic change in myeloid cells in the tumor microenvironment to promote tumor destruction, while avoiding the systemic toxicity of IL-12 (*40*).

Modifying T cells by means of gene editing or insertion to enhance therapeutic potency should coincide with attention to the safety of transferred T cells. Transgenes that provide for conditional cell suicide have been developed and can rapidly reverse acute or long-term toxicities of ACT. These include cell-surface molecules, such as CD20 or truncated epidermal growth factor receptor (EGFR), that are recognized by clinically approved monoclonal antibodies that mediate antibody-dependent cellular cytotoxicity (*41*, *42*). Herpes simplex virus thymidine kinase (HSV-TK) confers sensitivity of dividing T cells to ganciclovir and has been used effectively to eliminate transferred T cells that cause GVHD after allogeneic hematopoietic stem cell transplantation, although this approach is limited in immunocompetent hosts by immune responses to the viral TK (*43*). A nonimmunogenic suicide construct that consists of human caspase-9 fused to a modified domain of the human FK506-binding protein can induce cell death through exposure to a synthetic dimerizing drug, AP1903. The administration of AP1903 rapidly and completely reversed clinical manifestations of GVHD that occurred after T cell administration (*44*), suggesting that this "safety switch" approach may be sufficiently rapid to abrogate unexpected immediate toxicities of ACT.

FROM UNIVERSAL T CELLS TO PERSONALIZED ACT

Current approaches to gene-modified T cell therapy are personalized in the sense that a patient-specific cell product is created but generic in the sense that the same receptor is used for larger patient groups. As extensions to this, strategies to develop universal T cell products and to develop patient-specific receptors have recently been proposed.

Approaches toward universal T cell therapy aim to allow the widespread application of gene-modified T cell therapy at a lower cost (Fig. 2A). With respect to the creation of such universal T cells, several substantial barriers need to be overcome. First, alloreactivity within the endogenous TCR pool leads to GVHD when HLA-mismatched donor-derived T cells are used for therapy. By the same token, recognition of donor-cell allo-determinants by the patient's T cell pool leads to rapid rejection of infused cells unless additional measures are taken. Genome engineering technologies make it feasible to create T cell products in which one or both of the endogenous TCR chains have been inactivated, allowing a more comprehensive editing of T cell specificity and consequent avoidance of allo-reactivity (*30*, *31*, *33*). In addition, such inactivation of both the endogenous TCR α and β chains avoids the formation of the mixed TCR dimers that have been shown to cause GVHD in mouse models (*45*). With respect to technologies to suppress rejection of the infused cells, inactivation of donor major histocompatibility complex genes could potentially be used to prevent T cell–mediated rejection (*46*) but may at the same time trigger NK

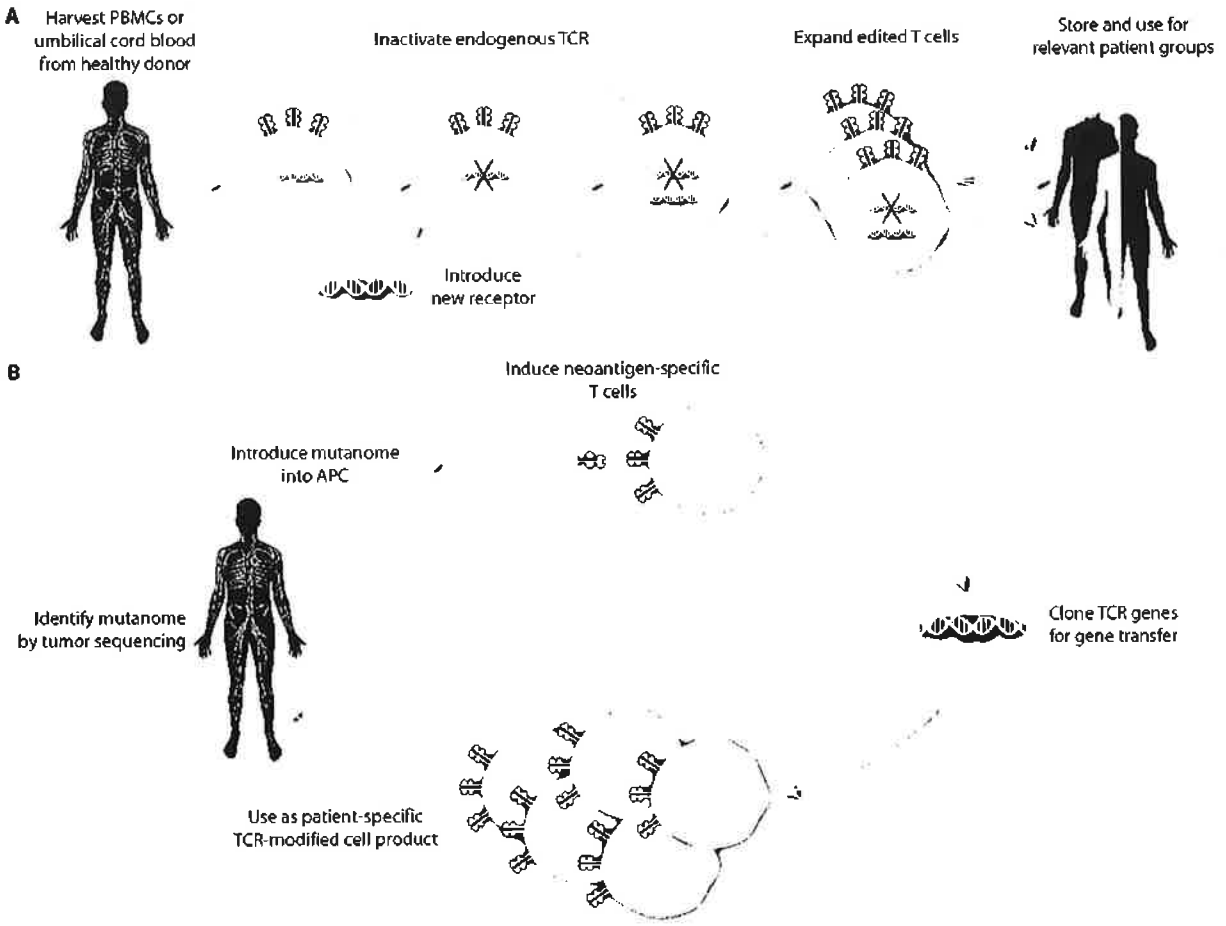

Fig. 2. From universal to highly personalized gene-modified ACT. (**A**) Universal T cells in which the endogenous TCR has been replaced by a CAR or TCR as "off-the-shelf" ACT products. Expression of the endogenous TCR can be eliminated through genetic editing. (**B**) Targeting the patient-specific mutanome by gene-modified ACT. Tumor-specific mutations are expressed in antigen-presenting cells (APCs), and the TCR repertoire is isolated from the responding T cells. The desired tumor-specific TCRs can be isolated and introduced into T cells for later ACT.

cell recognition. Conceivably, development of approaches that render infused cells selectively insensitive to immunosuppressive drugs may form a superior alternative.

At present, the number of antigens that can safely be targeted by TCRs or CARs is still limited to a handful. To increase the antigenic targets that are available to gene-modified T cell therapy, approaches to obtain receptors that are reactive against patient-specific neoantigens may be of interest (Fig. 2B). Recent work has shown that in human melanoma, both $CD8^+$ and $CD4^+$ T cell recognition of neoantigens occurs frequently (*11*, *47*, *48*). And based on overlap in mutational loads, formation of neoantigens that can be recognized by T cells can be expected in several other high-prevalence human tumors (*47*). In case the endogenous T cell pool generally "picks up" on the majority of neoantigens presented by an individual tumor, isolation of the relevant TCRs from the autologous T cell pool may be a way to boost immune reactivity against this class of antigens. Alternatively, it seems possible that in some human tumor types, priming of an endogenous T cell response may be inefficient. In such cases, it may be attractive to exploit antigen-presenting cells that express the patient-specific mutanome so as to induce such reactivities.

From a safety perspective, the targeting of the patient-specific neoantigen repertoire is highly appealing. However, it remains to be established for which tumor types neoantigen-specific TCRs can readily be obtained, and the logistic hurdles—with respect to regulation, timelines, and projected costs—are substantial.

TRANSLATIONAL BOTTLENECKS AND CHALLENGES

Therapeutically effective T cells can be derived from tumor infiltrates in melanoma patients; however, the peripheral blood is the preferable site for obtaining T cells for genetic modification for ACT because of the ease of procurement. To date, the focus has been on genetically modifying α/β T cells without regard to subset or differentiation status. However, α/β T cells are present in

functionally heterogeneous $CD4^+$ and $CD8^+$ subsets that differ in frequency, phenotype, transcriptional profile, and effector function. Current models suggests progressive differentiation from antigen-inexperienced naïve cells (T_N) to $CD62L^+$ central memory (T_{CM}), $CD62L^-$ effector memory (T_{EM}), and effector (T_E) T cell subsets, with loss of proliferative capacity and acquisition of effector function (*49*–*51*). Treatment efficacy after adoptive transfer of endogenous or genetically redirected tumor-reactive T cells correlates best with the ability of transferred T cells to proliferate and persist in vivo, suggesting that selection of T_N and/or T_{CM} may provide greater therapeutic potency. The optimal composition of $CD4^+$ and $CD8^+$ subsets for ACT may also differ depending on the malignancy being treated. Unfortunately, the lack of rapid, cost-effective, and efficient clinical-grade cell-selection devices and procedures currently impedes the evaluation of therapeutic T cell products derived from distinct T cell subsets.

A challenge for all cell therapies, including T cell therapy, is the need to develop cost-effective and efficient manufacturing and delivery capabilities. The sipuleucel-T (Provenge®) dendritic cell vaccine for prostate cancer developed by Dendreon demonstrated that cell therapies could be manufactured and delivered to physicians but illustrated that efficacy needed to be high to justify the cost and complexity and to compete with more easily administered pharmaceuticals. ACT has been pioneered in academic laboratories for which the resources to develop closed robotic automated systems for cell selections, genetic modification, and expansion are not readily available. The recent influx of biotechnology and pharmaceutical companies into cell-based therapeutics should accelerate automation to reduce cost and improve feasibility and delivery (Table 1). Off-the-shelf genetically modified tumor-specific T cells from allogeneic donors could further diminish the manufacturing burden for ACT, in case the immunologic barriers to this approach can be overcome.

The ability to redirect T cells with previously unidentified TCRs and CARs is increasing the types of malignancies that can be targeted with ACT. In the case of CARs, few targets that are exclusively expressed by tumor cells have been identified. The potential for—and consequences of—on-target recognition of normal cells can be evaluated in animal models, providing that the expression patterns are identical to humans (*52*). Logic gates, such as dual targeting with split receptor systems, may be used to improve the selectivity of tumor cell recognition by CAR-T cells for targets expressed on tumor and a subset of normal cells (*53*).

As the clinical applications of ACT expand, it will be important to identify biomarkers that predict success. Analysis of tumor biopsies before therapy might identify signatures that predict susceptibility to ACT or define interventions that may be necessary to improve therapeutic efficacy. The ability of T cells to proliferate and/or persist in vivo has correlated with therapeutic efficacy after ACT for viral diseases and cancer. Thus, analysis of the functional properties of engineered T cells before transfer and their fate and function after transfer could provide insights into optimal compositions of ACT for therapeutic efficacy. Combining ACT with checkpoint-blocking antibodies, vaccines, and targeted drug therapies is supported by studies in animal models (*54*, *55*) and is beginning to be investigated in clinical trials.

The development of ACT, particularly with genetically modified T cells, has occurred predominantly in the United States. ACT with TILs for melanoma, CARs targeting CD19, TCRs for cancer, and gene-edited T cells for HIV have advanced to phase 2 clinical trials (NCT02228096, NCT01567891, NCT02348216, and NCT02225665), and it is likely that one or more of these T cell therapies will obtain eventual U.S. Food and Drug Administration (FDA) approval (Table 1). Regulatory agencies in Europe have not had the same experience in this field, and given the early success of this approach, these agencies are likely to be inundated with new applications and challenged by patient demand. The complexity of ACT makes it vital to educate patients and physicians regarding the appropriate indications and the particular toxicities and their management so as to avoid preventable adverse outcomes. New therapeutic technologies including ACT are expensive, and this will present additional challenges regarding reimbursement that are best overcome by clearly demonstrating therapeutic value and cost-effective outcome as compared with those of alternative therapies.

SUMMARY

Advances in genetic engineering have reinvigorated efforts to engineer T cells to be tumor-reactive to treat advanced human malignancies through adoptive transfer. Remarkable success in patients treated on trials at academic centers has enticed unprecedented interest from the biotechnology and pharmaceutical industry (Table 1), which is now rapidly advancing these approaches for FDA approval and accelerating research and development to safely apply ACT to a broad range of human diseases, from acute lymphoblastic leukemia (ALL) to glioblastoma to HIV. The field faces numerous scientific, regulatory, and economic obstacles and challenges in educating clinicians in the use of ACT. Surmounting these obstacles will require collaboration between academia and biotechnology in order to ensure that therapy with engineered T cells is established as a viable approach for common human malignancies. Results in cancer are likely to pave the way to ACT as a new approach for infections and autoimmunity.

REFERENCES AND NOTES

1. R. E. Billingham, L. Brent, P. B. Medawar, Quantitative studies on tissue transplantation immunity. II. The origin, strength and duration of actively and adoptively acquired immunity. *Proc. R. Soc. London Ser. B* **143**, 58–80 (1954).
2. L. Drujont, L. Carretero-Iglesia, L. Bouchet-Delbos, G. Berlou, E. Merleau, M. Hill, Y. Delneste, M. C. Cuturi, C. Louvet, Evaluation of the therapeutic potential of bone marrow-derived myeloid suppressor cell (MDSC) adoptive transfer in mouse models of autoimmunity and allograft rejection. *PLOS ONE* **9**, e100013 (2014).
3. S. Sattler, G.-S. Ling, D. Xu, L. Hussaarts, A. Romaine, H. Zhao, L. Fossati-Jimack, T. Malik, H. T. Cook, M. Botto, Y. L. Lau, H. H. Smits, F. Y. Liew, F. P. Huang, IL-10-producing regulatory B cells induced by IL-33 (Breg(IL-33)) effectively attenuate mucosal inflammatory responses in the gut. *J. Autoimmun.* **50**, 107–122 (2014).
4. S. R. Riddell, M. Elliott, D. A. Lewinsohn, M. J. Gilbert, L. Wilson, S. A. Manley, S. D. Lupton, R. W. Overell, T. C. Reynolds, L. Corey, P. D. Greenberg, T-cell mediated rejection of gene-modified HIV-specific cytotoxic T lymphocytes in HIV-infected patients. *Nat. Med.* **2**, 216–223 (1996).
5. J. Scholler, T. Brady, G. Binder-Scholl, W.-T. Hwang, G. Plesa, K. Hege, A. Vogel, M. Kalos, J. Riley, S. Deeks, R. Mitsuyasu, W. Bernstein, N. Aronson, B. Levine, F. Bushman, C. June, Decade-long safety and function of retroviral-modified chimeric antigen receptor T cells. *Sci. Transl. Med.* **4**, 132Ra153 (2012).
6. Y. C. Ho, L. Shan, N. N. Hosmane, J. Wang, S. B. Laskey, D. I. Rosenbloom, J. Lai, J. N. Blankson, J. D. Siliciano, R. F. Siliciano, Replication-competent noninduced proviruses in the latent reservoir increase barrier to HIV-1 cure. *Cell* **155**, 540–551 (2013).
7. G. Hütter, D. Nowak, M. Mossner, S. Ganepola, A. Müssig, K. Allers, T. Schneider, J. Hofmann, C. Kücherer, O. Blau, I. W. Blau, W. K. Hofmann, E. Thiel, Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. *N. Engl. J. Med.* **360**, 692–698 (2009).
8. J. J. Rossi, C. H. June, D. B. Kohn, Genetic therapies against HIV. *Nat. Biotechnol.* **25**, 1444–1454 (2007).
9. K. Deng, M. Pertea, A. Rongvaux, L. Wang, C. M. Durand, G. Ghiaur, J. Lai, H. L. McHugh, H. Hao, H. Zhang, J. B. Margolick, C. Gurer, A. J. Murphy, D. M. Valenzuela, G. D. Yancopoulos, S. G. Deeks, T. Strowig, P. Kumar, J. D. Sili-

ciano, S. L. Salzberg, R. A. Flavell, L. Shan, R. F. Siliciano, Broad CTL response is required to clear latent HIV-1 due to dominance of escape mutations. *Nature* **517**, 381–385 (2015).
10. A. M. Lesokhin, M. R. Callahan, M. A. Postow, J. D. Wolchok, On being less tolerant: Enhanced cancer immunosurveillance enabled by targeting checkpoints and agonists of T cell activation. *Sci. Transl. Med.* **7**, 280sr1 (2015).
11. N. van Rooij, M. M. van Buuren, D. Philips, A. Velds, M. Toebes, B. Heemskerk, L. J. van Dijk, S. Behjati, H. Hilkmann, D. El Atmioui, M. Nieuwland, M. R. Stratton, R. M. Kerkhoven, C. Kesmir, J. B. Haanen, P. Kvistborg, T. N. Schumacher, Tumor exome analysis reveals neoantigen-specific T-cell reactivity in an ipilimumab-responsive melanoma. *J. Clin. Oncol.* **31**, e439–e442 (2013).
12. M. M. Gubin, X. Zhang, H. Schuster, E. Caron, J. P. Ward, T. Noguchi, Y. Ivanova, J. Hundal, C. D. Arthur, W. J. Krebber, G. E. Mulder, M. Toebes, M. D. Vesely, S. S. Lam, A. J. Korman, J. P. Allison, G. J. Freeman, A. H. Sharpe, E. L. Pearce, T. N. Schumacher, R. Aebersold, H. G. Rammensee, C. J. Melief, E. R. Mardis, W. E. Gillanders, M. N. Artyomov, R. D. Schreiber, Checkpoint blockade cancer immunotherapy targets tumour-specific mutant antigens. *Nature* **515**, 577–581 (2014).
13. D. S. Chen, I. Mellman, Oncology meets immunology: The cancer-immunity cycle. *Immunity* **39**, 1–10 (2013).
14. C. H. Lamers, R. Willemsen, P. van Elzakker, S. van Steenbergen-Langeveld, M. Broertjes, J. Oosterwijk-Wakka, E. Oosterwijk, S. Sleijfer, R. Debets, J. W. Gratama, Immune responses to transgene and retroviral vector in patients treated with ex vivo-engineered T cells. *Blood* **117**, 72–82 (2011).
15. M. H. Kershaw, J. A. Westwood, L. L. Parker, G. Wang, Z. Eshhar, S. A. Mavroukakis, D. E. White, J. R. Wunderlich, S. Canevari, L. Rogers-Freezer, C. C. Chen, J. C. Yang, S. A. Rosenberg, P. Hwu, A phase I study on adoptive immunotherapy using gene-modified T cells for ovarian cancer. *Clin. Cancer Res.* **12**, 6106–6115 (2006).
16. J. L. Davis, M. R. Theoret, Z. Zheng, C. H. Lamers, S. A. Rosenberg, R. A. Morgan, Development of human anti-murine T-cell receptor antibodies in both responding and nonresponding patients enrolled in TCR gene therapy trials. *Clin. Cancer Res.* **16**, 5852–5861 (2010).
17. L. P. Li, J. C. Lampert, X. Chen, C. Leitao, J. Popović, W. Müller, T. Blankenstein, Transgenic mice with a diverse human T cell antigen receptor repertoire. *Nat. Med.* **16**, 1029–1034 (2010).
18. M. R. Parkhurst, J. C. Yang, R. C. Langan, M. E. Dudley, D. A. Nathan, S. A. Feldman, J. L. Davis, R. A. Morgan, M. J. Merino, R. M. Sherry, M. S. Hughes, U. S. Kammula, G. Q. Phan, R. M. Lim, S. A. Wank, N. P. Restifo, P. F. Robbins, C. M. Laurencot, S. A. Rosenberg, T cells targeting carcinoembryonic antigen can mediate regression of metastatic colorectal cancer but induce severe transient colitis. *Mol. Ther.* **19**, 620–626 (2011).
19. J. Corrigan-Curay, H. P. Kiem, D. Baltimore, M. O'Reilly, R. J. Brentjens, L. Cooper, S. Forman, S. Gottschalk, P. Greenberg, R. Junghans, H. Heslop, M. Jensen, C. Mackall, C. June, O. Press, D. Powell, A. Ribas, S. Rosenberg, M. Sadelain, B. Till, A. P. Patterson, R. C. Jambou, E. Rosenthal, L. Garglulo, M. Montgomery, D. B. Kohn, T-cell immunotherapy: Looking forward. *Mol. Ther.* **22**, 1564–1574 (2014).
20. B. J. Cameron, A. B. Gerry, J. Dukes, J. V. Harper, V. Kannan, F. C. Bianchi, F. Grand, J. E. Brewer, M. Gupta, G. Plesa, G. Bossi, A. Vuidepot, A. S. Powlesland, A. Legg, K. J. Adams, A. D. Bennett, N. J. Pumphrey, D. D. Williams, G. Binder-Scholl, I. Kulikovskaya, B. L. Levine, J. L. Riley, A. Varela-Rohena, E. A. Stadtmauer, A. P. Rapoport, G. P. Linette, C. H. June, N. J. Hassan, M. Kalos, B. K. Jakobsen, Identification of a Titin-derived HLA-A1-presented peptide as a cross-reactive target for engineered MAGE A3-directed T cells. *Sci. Transl. Med.* **5**, 197ra103 (2013).
21. M. E. Birnbaum, J. L. Mendoza, D. K. Sethi, S. Dong, J. Glanville, J. Dobbins, E. Ozkan, M. M. Davis, K. W. Wucherpfennig, K. C. Garcia, Deconstructing the peptide-MHC specificity of T cell recognition. *Cell* **157**, 1073–1087 (2014).
22. C. J. Voskens, S. M. Goldinger, C. Loquai, C. Robert, K. C. Kaehler, C. Berking, T. Bergmann, C. L. Bockmeyer, T. Eigentler, M. Fluck, C. Garbe, R. Gutzmer, S. Grabbe, A. Hauschild, R. Hein, G. Hundorfean, A. Justich, U. Keller, C. Klein, C. Mateus, P. Mohr, S. Paetzold, I. Satzger, D. Schadendorf, M. Schlaeppi, G. Schuler, B. Schuler-Thurner, U. Trefzer, J. Ulrich, J. Vaubel, R. von Moos, P. Weder, T. Wilhelm, D. Göppner, R. Dummer, L. M. Heinzerling, The price of tumor control: An analysis of rare side effects of anti-CTLA-4 therapy in metastatic melanoma from the ipilimumab network. *PLOS ONE* **8**, e53745 (2013).
23. J. D. Wolchok, H. Kluger, M. K. Callahan, M. A. Postow, N. A. Rizvi, A. M. Lesokhin, N. H. Segal, C. E. Ariyan, R. A. Gordon, K. Reed, M. M. Burke, A. Caldwell, S. A. Kronenberg, B. U. Agunwamba, X. Zhang, I. Lowy, H. D. Inzunza, W. Feely, C. E. Horak, Q. Hong, A. J. Korman, J. M. Wigginton, A. Gupta, M. Sznol, Nivolumab plus ipilimumab in advanced melanoma. *N. Engl. J. Med.* **369**, 122–133 (2013).
24. A. Mirsoian, M. N. Bouchlaka, G. D. Sckisel, M. Chen, C. C. Pai, E. Maverakis, R. G. Spencer, K. W. Fishbein, S. Siddiqui, A. M. Monjazeb, B. Martin, S. Maudsley, C. Hesdorffer, L. Ferrucci, D. L. Longo, B. R. Blazar, R. H. Wiltrout, D. D. Taub, W. J. Murphy, Adiposity induces lethal cytokine storm after systemic administration of stimulatory immunotherapy regimens in aged mice. *J. Exp. Med.* **211**, 2373–2383 (2014).
25. P. A. McSweeney, D. Niederwieser, J. A. Shizuru, B. M. Sandmaier, A. J. Molina, D. G. Maloney, T. R. Chauncey, T. A. Gooley, U. Hegenbart, R. A. Nash, J. Radich, J. L. Wagner, S. Minor, F. R. Appelbaum, W. I. Bensinger, E. Bryant, M. E. Flowers, G. E. Georges, F. C. Grumet, H. P. Kiem, B. Torok-Storb, C. Yu, K. G. Blume, R. F. Storb, Hematopoietic cell transplantation in older patients with hematologic malignancies: Replacing high-dose cytotoxic therapy with graft-versus-tumor effects. *Blood* **97**, 3390–3400 (2001).
26. J. M. Kaldor, N. E. Day, F. Pettersson, E. A. Clarke, D. Pedersen, W. Mehnert, J. Bell, H. Hast, P. Prior, S. Karjalainen, F. Neal, M. Koch, P. Band, W. Choi, V. P. Kirn, A. Arslan, B. Zarén, A. R. Belch, H. Storm, B. Kittelmann, P. Fraser, M. Stovall, Leukemia following chemotherapy for ovarian cancer. *N. Engl. J. Med.* **322**, 1–6 (1990).
27. J. Hataye, J. J. Moon, A. Khoruts, C. Reilly, M. K. Jenkins, Naive and memory CD4+ T cell survival controlled by clonal abundance. *Science* **312**, 114–116 (2006).
28. J. A. Doudna, E. Charpentier, Genome editing. The new frontier of genome engineering with CRISPR-Cas9. *Science* **346**, 1258096 (2014).
29. H. Kim, J. S. Kim, A guide to genome engineering with programmable nucleases. *Nat. Rev. Genet.* **15**, 321–334 (2014).
30. E. Provasi, P. Genovese, A. Lombardo, Z. Magnani, P. Q. Liu, A. Reik, V. Chu, D. E. Paschon, L. Zhang, J. Kuball, B. Camisa, A. Bondanza, G. Casorati, M. Ponzoni, F. Ciceri, C. Bordignon, P. D. Greenberg, M. C. Holmes, P. D. Gregory, L. Naldini, C. Bonini, Editing T cell specificity towards leukemia by zinc finger nucleases and lentiviral gene transfer. *Nat. Med.* **18**, 807–815 (2012).
31. B. Berdien, U. Mock, D. Atanackovic, B. Fehse, TALEN-mediated editing of endogenous T-cell receptors facilitates efficient reprogramming of T lymphocytes by lentiviral gene transfer. *Gene Ther.* **21**, 539–548 (2014).
32. P. Tebas, D. Stein, W. W. Tang, I. Frank, S. Q. Wang, G. Lee, S. K. Spratt, R. T. Surosky, M. A. Giedlin, G. Nichol, M. C. Holmes, P. D. Gregory, D. G. Ando, M. Kalos, R. G. Collman, G. Binder-Scholl, G. Plesa, W. T. Hwang, B. L. Levine, C. H. June, Gene editing of CCR5 in autologous CD4 T cells of persons infected with HIV. *N. Engl. J. Med.* **370**, 901–910 (2014).
33. H. Torikai, A. Reik, P. Q. Liu, Y. Zhou, L. Zhang, S. Maiti, H. Huls, J. C. Miller, P. Kebriaei, B. Rabinovitch, D. A. Lee, R. E. Champlin, C. Bonini, L. Naldini, E. J. Rebar, P. D. Gregory, M. C. Holmes, L. J. Cooper, A foundation for universal T-cell based immunotherapy: T cells engineered to express a CD19-specific chimeric-antigen-receptor and eliminate expression of endogenous TCR. *Blood* **119**, 5697–5705 (2012).
34. F. S. Hodi, S. J. O'Day, D. F. McDermott, R. W. Weber, J. A. Sosman, J. B. Haanen, R. Gonzalez, C. Robert, D. Schadendorf, J. C. Hassel, W. Akerley, A. J. van den Eertwegh, J. Lutzky, P. Lorigan, J. M. Vaubel, G. P. Linette, D. Hogg, C. H. Ottensmeier, C. Lebbé, C. Peschel, I. Quirt, J. I. Clark, J. D. Wolchok, J. S. Weber, J. Tian, M. J. Yellin, G. M. Nichol, A. Hoos, W. J. Urba, Improved survival with ipilimumab in patients with metastatic melanoma. *N. Engl. J. Med.* **363**, 711–723 (2010).
35. S. L. Topalian, F. S. Hodi, J. R. Brahmer, S. N. Gettinger, D. C. Smith, D. F. McDermott, J. D. Powderly, R. D. Carvajal, J. A. Sosman, M. B. Atkins, P. D. Leming, D. R. Spigel, S. J. Antonia, L. Horn, C. G. Drake, D. M. Pardoll, L. Chen, W. H. Sharfman, R. A. Anders, J. M. Taube, T. L. McMiller, H. Xu, A. J. Korman, M. Jure-Kunkel, S. Agrawal, D. McDonald, G. D. Kollia, A. Gupta, J. M. Wigginton, M. Sznol, Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N. Engl. J. Med.* **366**, 2443–2454 (2012).
36. J. R. Brahmer, S. S. Tykodi, L. Q. Chow, W. J. Hwu, S. L. Topalian, P. Hwu, C. G. Drake, L. H. Camacho, J. Kauh, K. Odunsi, H. C. Pitot, O. Hamid, S. Bhatia, R. Martins, K. Eaton, S. Chen, T. M. Salay, S. Alaparthy, J. F. Grosso, A. J. Korman, S. M. Parker, S. Agrawal, S. M. Goldberg, D. M. Pardoll, A. Gupta, J. M. Wigginton, Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N. Engl. J. Med.* **366**, 2455–2465 (2012).
37. P. Zhou, D. R. Shaffer, D. A. Alvarez Arias, Y. Nakazaki, W. Pos, A. J. Torres, V. Cremasco, S. K. Dougan, G. S. Cowley, K. Elpek, J. Brogdon, J. Lamb, S. J. Turley, H. L. Ploegh, D. E. Root, J. C. Love, G. Dranoff, N. Hacohen, H. Cantor, K. W. Wucherpfennig, In vivo discovery of immunotherapy targets in the tumour microenvironment. *Nature* **506**, 52–57 (2014).
38. A. Di Stasi, B. De Angelis, C. M. Rooney, L. Zhang, A. Mahendravada, A. E. Foster, H. E. Heslop, M. K. Brenner, G. Dotti, B. Savoldo, T lymphocytes coexpressing CCR4 and a chimeric antigen receptor targeting CD30 have improved homing and antitumor activity in a Hodgkin tumor model. *Blood* **113**, 6392–6402 (2009).
39. G. M. Bendle, C. Linnemann, L. Bies, J. Y. Song, T. N. Schumacher, Blockade of TGF-β signaling greatly enhances the efficacy of TCR gene therapy of cancer. *J. Immunol.* **191**, 3232–3239 (2013).
40. S. P. Kerkar, R. S. Goldszmid, P. Muranski, D. Chinnasamy, Z. Yu, R. N. Reger, A. J. Leonardi, R. A. Morgan, E. Wang, F. M. Marincola, G. Trinchieri, S. A. Rosenberg, N. P. Restifo, IL-12 triggers a programmatic change in dysfunctional myeloid-derived cells within mouse tumors. *J. Clin. Invest.* **121**, 4746–4757 (2011).
41. X. Wang, W. C. Chang, C. W. Wong, D. Colcher, M. Sherman, J. R. Ostberg, S. J. Forman, S. R. Riddell, M. C. Jensen, A transgene-encoded cell surface polypeptide for selection, in vivo tracking, and ablation of engineered cells. *Blood* **118**, 1255–1263 (2011).
42. B. Philip, E. Kokalaki, L. Mekkaoui, S. Thomas, K. Straathof, B. Flutter, V. Marin, T. Marafioti, R. Chakraverty, D. Linch, S. A. Quezada, K. S. Peggs, M. Pule, A highly compact epitope-based marker/suicide gene for easier and safer T-cell therapy. *Blood* **124**, 1277–1287 (2014).
43. C. Berger, M. E. Flowers, E. H. Warren, S. R. Riddell, Analysis of transgene-specific immune responses that limit

the in vivo persistence of adoptively transferred HSV-TK-modified donor T cells after allogeneic hematopoietic cell transplantation. *Blood* **107**, 2294–2302 (2006).
44. A. Di Stasi, S. K. Tey, G. Dotti, Y. Fujita, A. Kennedy-Nasser, C. Martinez, K. Straathof, E. Liu, A. G. Durett, B. Grilley, H. Liu, C. R. Cruz, B. Savoldo, A. P. Gee, J. Schindler, R. A. Krance, H. E. Heslop, D. M. Spencer, C. M. Rooney, M. K. Brenner, Inducible apoptosis as a safety switch for adoptive cell therapy. *N. Engl. J. Med.* **365**, 1673–1683 (2011).
45. G. M. Bendle, C. Linnemann, A. I. Hooijkaas, L. Bies, M. A. de Witte, A. Jorritsma, A. D. Kaiser, N. Pouw, R. Debets, E. Kieback, W. Uckert, J. Y. Song, J. B. Haanen, T. N. Schumacher, Lethal graft-versus-host disease in mouse models of T cell receptor gene therapy. *Nat. Med.* **16**, 565–570, 1p. 570 (2010).
46. H. Torikai, A. Reik, F. Soldner, E. H. Warren, C. Yuen, Y. Zhou, D. L. Crossland, H. Huls, N. Littman, Z. Zhang, S. S. Tykodi, P. Kebriaei, D. A. Lee, J. C. Miller, E. J. Rebar, M. C. Holmes, R. Jaenisch, R. E. Champlin, P. D. Gregory, L. J. Cooper, Toward eliminating HLA class I expression to generate universal cells from allogeneic donors. *Blood* **122**, 1341–1349 (2013).
47. C. Linnemann, M. M. van Buuren, L. Bies, E. M. Verdegaal, R. Schotte, J. J. Calis, S. Behjati, A. Velds, H. Hilkmann, D. E. Atmioui, M. Visser, M. R. Stratton, J. B. Haanen, H. Spits, S. H. van der Burg, T. N. Schumacher, High-throughput epitope discovery reveals frequent recognition of neo-antigens by CD4$^+$ T cells in human melanoma. *Nat. Med.* **21**, 81–85 (2015).
48. P. F. Robbins, Y. C. Lu, M. El-Gamil, Y. F. Li, C. Gross, J. Gartner, J. C. Lin, J. K. Teer, P. Cliften, E. Tycksen, Y. Samuels, S. A. Rosenberg, Mining exomic sequencing data to identify mutated antigens recognized by adoptively transferred tumor-reactive T cells. *Nat. Med.* **19**, 747–752 (2013).
49. N. P. Restifo, L. Gattinoni, Lineage relationship of effector and memory T cells. *Curr. Opin. Immunol.* **25**, 556–563 (2013).
50. C. Gerlach, J. C. Rohr, L. Perié, N. van Rooij, J. W. van Heijst, A. Velds, J. Urbanus, S. H. Naik, H. Jacobs, J. B. Beltman, R. J. de Boer, T. N. Schumacher, Heterogeneous differentiation patterns of individual CD8$^+$ T cells. *Science* **340**, 635–639 (2013).
51. V. R. Buchholz, M. Flossdorf, I. Hensel, L. Kretschmer, B. Weissbrich, P. Gräf, A. Verschoor, M. Schiemann, T. Höfer, D. H. Busch, Disparate individual fates compose robust CD8$^+$ T cell immunity. *Science* **340**, 630–635 (2013).
52. C. Berger, D. Sommermeyer, M. Hudecek, M. Berger, A. Balakrishnan, P. J. Paszkiewicz, P. L. Kosasih, C. Rader, S. R. Riddell, Safety of targeting ROR1 in primates with chimeric antigen receptor-modified T cells. *Cancer Immunol. Res.* **3**, 206–216 (2015).
53. C. C. Kloss, M. Condomines, M. Cartellieri, M. Bachmann, M. Sadelain, Combinatorial antigen recognition with balanced signaling promotes selective tumor eradication by engineered T cells. *Nat. Biotechnol.* **31**, 71–75 (2013).
54. W. Peng, G. Lizée, P. Hwu, Blockade of the PD-1 pathway enhances the efficacy of adoptive cell therapy against cancer. *Oncoimmunology* **2**, e22691 (2013).
55. R. C. Koya, S. Mok, N. Otte, K. J. Blacketor, B. Comin-Anduix, P. C. Tumeh, A. Minasyan, N. A. Graham, T. G. Graeber, T. Chodon, A. Ribas, BRAF inhibitor vemurafenib improves the antitumor activity of adoptive cell immunotherapy. *Cancer Res.* **72**, 3928–3937 (2012).

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Citation: C. H. June, S. R. Riddell, T. N. Schumacher, Adoptive cellular therapy: A race to the finish line. *Sci. Transl. Med.* **7**, 280ps7 (2015).

From: David Chang [DChang@KitePharma.com]
Sent: Thursday, April 02, 2015 4:33 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: FW: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT
Attachments:

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

From: David Chang
Sent: Monday, March 16, 2015 5:13 PM
To: Steve Rosenberg (SAR@nih.gov)
Cc: Arie Belldegrun
Subject: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Steve,

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Thanks,

David

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Steve,

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All the best,
David

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To: Rosenberg, Steven A. (NIH/NCI) [E]
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FYI

Presentation Abstract

Abstract Number:	CT105
Presentation Title:	PROPRIETARY INFORMATION,REDACTED PER AGREEMENT
Presentation Time:	Sunday, Apr 19, 2015, 1:35 PM - 1:55 PM
Location:	Terrace Ballroom I (400 Level), Pennsylvania Convention Center
Author Block:	Janos L. Tanyi, Andrew R. Haas, Gregory L. Beatty, Mark A. Morgan, Caitlin J. Stashwick, Mark H. O'Hara, David L. Porter, Marcela V. Maus, Bruce L. Levine, Simon F. Lacey, Anne Marie Nelson, Maureen McGarvey, Naseem DS Kerr, Gabriela Plesa, Carl H. June. Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

All the best,
David

David D. Chang, MD, PhD
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From: David Chang [DChang@KitePharma.com]
Sent: Thursday, April 02, 2015 5:06 PM
To: Feldman, Steven (NIH/NCI) [E]; Scott Bernstein
CC: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: RE: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Steve F,

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Thanks, David

From: Feldman, Steven (NIH/NCI) [E] [mailto:feldmanst@mail.nih.gov]
Sent: Thursday, April 02, 2015 1:41 PM
To: David Chang
Cc: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

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Steve

Steven A. Feldman, Ph.D.
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Sent: Thursday, April 02, 2015 5:06 PM
To: Feldman, Steven (NIH/NCI) [E]; Scott Bernstein
CC: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: RE: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Steve F,

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Thanks, David

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Sent: Thursday, April 02, 2015 1:41 PM
To: David Chang
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Subject: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Hello David,

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

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From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Monday, April 06, 2015 10:28 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Fwd: Kite Pharma Announces Publication in Science of Cancer Immunotherapy Articles Authored by Lead Collaborators at the National Cancer Institute and the Netherlands Cancer Institute

FYI

Thank you for everything,

Arie Belldegrun, MD FACS
President and CEO, Chairman
Kite Pharma

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Begin forwarded message:

> **From:** "Kite Pharma, Inc." <jjackson@burnsmc.com>
> **Date:** April 6, 2015 at 05:04:01 PDT
> **To:** <Arie@kitepharma.com>
> **Subject: Kite Pharma Announces Publication in Science of Cancer Immunotherapy Articles Authored by Lead Collaborators at the National Cancer Institute and the Netherlands Cancer Institute**

Logo

Kite Pharma Announces Publication in Science of Cancer Immunotherapy Articles Authored by Lead Collaborators at the National Cancer Institute and the Netherlands Cancer Institute

SANTA MONICA, Calif., April 6, 2015 (GLOBE NEWSWIRE) -- Kite Pharma, Inc. (Kite) (Nasdaq:KITE), a clinical-stage biopharmaceutical company focused on developing engineered autologous T cell therapy (eACT™) products for the treatment of cancer, today announced articles being published in the current issue of *Science*, one article by the Company's Cooperative Research and Development Agreement (CRADA) collaborators at the National Cancer Institute (NCI) and the second article by the Netherlands Cancer Institute (NKI). The first article, "Adoptive Cell Transfer as personalized immunotherapy for human cancer," was authored by Steven A. Rosenberg, M.D., Ph.D., Chief of Surgery at the NCI, and his colleague Nicholas P. Restifo, M.D., Senior Investigator at NCI's Surgery Branch. The second article, "Neoantigens in cancer immunotherapy," was written by Professor Dr. Ton N. M. Schumacher, Ph.D., Deputy Director of NKI, and Robert D. Schreiber, Ph.D., Director, Center for Human Immunology and Immunotherapy Programs, at Washington University School of Medicine. Professor Schumacher also serves as Chief Scientific Officer of Kite Pharma EU.

In their article, Drs. Rosenberg and Restifo reviewed the development of adoptive cell therapy, including the advent of genetically modified T cells and their promising results in patients with multiple tumor types. Last month, Kite announced an expansion of its CRADA with the Surgery Branch at the NCI, led by Dr. Rosenberg. The amendment encompasses emerging areas of research in

From: David Chang [DChang@KitePharma.com]
Sent: Monday, April 06, 2015 12:45 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
CC: Feldman, Steven (NIH/NCI) [E]; Scott Bernstein
Subject: RE: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Steve,

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Thanks,

David

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Sent: Friday, April 03, 2015 11:31 AM
To: David Chang; Scott Bernstein
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From: David Chang [mailto:DChang@KitePharma.com]
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To: Feldman, Steven (NIH/NCI) [E]; Scott Bernstein
Cc: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: RE: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Steve F,

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Thanks, David

From: Feldman, Steven (NIH/NCI) [E] [mailto:feldmanst@mail.nih.gov]
Sent: Thursday, April 02, 2015 1:41 PM
To: David Chang
Cc: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Hello David,

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Subject: FW: Science
Attachments: Sharma and Allison Science 2015.full.pdf; Garrett Science 2015.pdf; Joyce and Fearon Science 2015.pdf; Rizvi Mutational Burden in PD1 response Science 2015.pdf; Rosenberg & Restifo Science 2015.full.pdf; Schumacher and Schreiber Science 2015.pdf

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Sent: Monday, April 6, 2015 12:12 PM
To: Arie Belldegrun
Subject: fyi

http://cancerresearch.org/news-publications/our-blog/april-2015/special-issue-of-science-devoted-to-cancer-immunotherapy

Best,
Gregory Zuckerman
Special Writer, Wall Street Journal
212-416-3614; @GZuckerman
(Shameless Plug To Follow):
Author, ***The Frackers: The Outrageous Inside Story of the New Billionaire Wildcatters*** (Penguin, Nov.2013)
http://www.amazon.com/The-Frackers-Outrageous-Billionaire-Wildcatters/dp/1591846455

REVIEWS

The future of immune checkpoint therapy

Padmanee Sharma[1,2]* and James P. Allison[1]*

Immune checkpoint therapy, which targets regulatory pathways in T cells to enhance antitumor immune responses, has led to important clinical advances and provided a new weapon against cancer. This therapy has elicited durable clinical responses and, in a fraction of patients, long-term remissions where patients exhibit no clinical signs of cancer for many years. The way forward for this class of novel agents lies in our ability to understand human immune responses in the tumor microenvironment. This will provide valuable information regarding the dynamic nature of the immune response and regulation of additional pathways that will need to be targeted through combination therapies to provide survival benefit for greater numbers of patients.

The field of immune checkpoint therapy has joined the ranks of surgery, radiation, chemotherapy, and targeted therapy as a pillar of cancer therapy. Three new immune checkpoint agents have now been approved by the U.S. Food and Drug Administration (FDA) for the treatment of melanoma, and there is a high expectation that these agents, and others in this class, will also be approved over the next several years for treatment of patients with lung cancer, kidney cancer, bladder cancer, prostate cancer, lymphoma, and many other tumor types. The antibody against CTLA-4 ipilimumab was approved in 2011, and two antibodies against PD-1 (pembrolizumab and nivolumab) were approved in 2014. These drugs represent a radical and disruptive change in cancer therapy in two ways. First, they do not target the tumor cell, but target molecules involved in regulation of T cells, the soldiers of the immune system. And, perhaps in a more radical shift, the goal of the therapy is not to activate the immune system to attack particular targets on tumor cells, but rather to remove inhibitory pathways that block effective antitumor T cell responses. Immune checkpoint therapy, with anti-CTLA-4 having longer follow-up than other agents, leads to durable clinical responses that can last a decade and more, but only in a fraction of patients. There are ongoing studies to identify predictive biomarkers with which to select patients for treatment with a particular agent, but the complexity of the immune response has made this difficult.

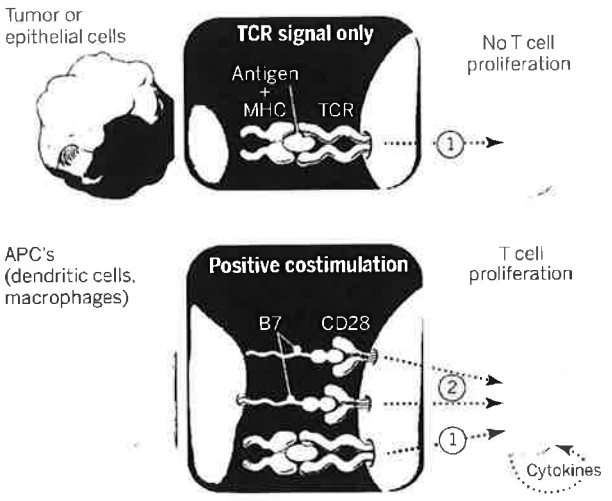

Fig. 1. Activation of T cells requires two signals. T cell activation occurs only after interaction between T cell receptor (TCR) and antigen in the context of MHC (signal 1) plus CD28 costimulation (signal 2).

In the past two decades, remarkable advances in basic science have led to new strategies for the treatment of cancer, which are justifiably generating optimism that it may soon be possible to cure a subset of patients with some types of cancer. We now have detailed knowledge of the molecular basis of cancer to allow a more "personalized" treatment based on genomic sequencing of an individual's cancer cells to identify specific mutations in genes. These mutations can then be targeted with compounds to block the downstream pathways that drive cancer development and progression. Therefore, each specific mutation serves as the predictive biomarker for selecting patients for treatment with a given agent. For example, patients with melanoma whose tumors harbor the BRAFV600E mutation, which enables constitutive activation of the BRAF signaling pathway, would be selected to receive treatment with an agent that inhibits BRAF (*1*, *2*). These targeted therapies have led to promising clinical responses, albeit generally of short duration, in patients whose tumors express the appropriate target biomarker.

The clinical success of genomically targeted agents laid the foundation for other cancer therapies, including the prerequisite to identify predictive biomarkers for selection of patients for treatment. Eventually, as the field of cancer immunotherapy found clinical success with agents based on a greater understanding of how to unleash T cell responses by targeting immune checkpoints, it became clear that the framework used for identification of predictive biomarkers for genomically targeted agents would present a challenge. As opposed to mutated genes in tumors that permanently mark a tumor, the immune response is dynamic and changes rapidly. Therefore, the issue facing the field of cancer immunotherapy may not be the identification of a single biomarker to select a subset of patients for treatment. Instead, we must assess the effectiveness of an evolving immune response, define the immune response that contributes to clinical benefit, and then, hopefully, drive every patient's immune response in that direction through combination therapies.

Tumor microenvironment: Cancer cells and host immune responses

Tumors are composed of many cell types, including the cell of origin with genetic alterations and a myriad of other cells, such as fibroblasts, endothelial cells, and eventually, perhaps, a variety of immune cells. Initially the immune infiltrates may be scarce, but eventually may contain natural killer (NK) cells and macrophages with lytic capacity and, perhaps most importantly, T cells. T cells attack tumor cells that express tumor-specific antigens in the form of complexes of tumor-derived peptides bound to major histocompatibility complex (MHC) molecules on the cell. The tumor antigens can be derived from oncogenic viruses, differentiation antigens, epigenetically regulated molecules such as cancer testes antigens, or neoantigens derived from mutations associated with the process of carcinogenesis (*3*). T cells survey the microenvironment and become activated when tumor antigens are recognized. They then proliferate and differentiate, ultimately leading to the T cell's ability to attack and destroy cells that express relevant antigens. However, regulation of T cell responses is an extremely complex process consisting of both stimulatory and inhibitory cell intrinsic signaling pathways, which limit T cell responses against cancer and prevent eradication of tumors.

Recognition of antigen-MHC complexes by the T cell antigen receptor is not sufficient for

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activation of naïve T cells—additional costimulatory signals (*4*, *5*) are required that are provided by the engagement of CD28 on the T cell surface with B7 molecules (CD80 and CD86) on the antigen-presenting cell (APC) (Fig. 1). Expression of B7 molecules is limited to subsets of hematopoietic cells, especially dendritic cells, which have specialized processes for efficient antigen presentation. With the exception of certain lymphomas, cancer cells do not express B7 molecules, and hence are largely invisible to the immune system. This can be overcome by an inflammatory response, such as the killing of tumor cells, which permits APCs, such as dendritic cells, to take up antigen and present antigen bound to MHC along with B7 molecules for effective activation of T cells.

After encountering tumor antigen in the context of B7 costimulation, initially in tumor-draining lymph nodes, tumor-specific T cells may acquire effector function and traffic to the tumor site to mount an attack on the tumor. Infiltration of T cells into the tumor microenvironment is a critical hurdle that must be overcome for an effective antitumor immune response to occur. However, once T cells are in the tumor microenvironment, the success of the assault is determined by their ability to overcome additional barriers and counter-defenses they encounter from the tumor cells, stroma, regulatory T cells, myeloid-derived suppressor cells, inhibitory cytokines, and other cells in the complex tumor microenvironment that act to mitigate antitumor immune responses.

In the 1980s, tumor antigens from human melanomas were found to elicit T cell responses (*6*), which drove efforts to use vaccination strategies to mobilize the immune system to attack cancer. The vaccines generally consisted of some form of the antigen (for example, peptide or DNA vaccines), as well as additional components to enhance responses (for example, cytokines). While there were anecdotal successes, in hundreds of trials there was scant evidence of reproducible clinical responses (*7*). This failure to induce effective immune responses by attempting to turn T cell response "on" with antigenic vaccines led many to become skeptical of the potential of immunotherapy as a strategy for cancer treatment.

Regulation of T cell responses

Further insights into the fundamental mechanisms that regulate early aspects of T cell activation may provide one of many possible explanations for the limited effectiveness of these early vaccine trials. By the mid-1990s, it was becoming clear that T cell activation was even more complex, and in addition to initiating proliferation and functional differentiation, T cell activation also induced an inhibitory pathway that could eventually attenuate and terminate T cell responses. Expression of *ctla-4*, a gene with very high homology to CD28, is initiated by T cell activation, and, like CD28, CTLA-4 binds B7 molecules, albeit with much higher affinity. Although CTLA-4 was first thought to be another costimulatory molecule (*8*), two laboratories independently showed that it opposed CD28 costimulation and down-regulated T cell responses (*9*, *10*). Thus, activation of T cells results in induction of expression of CTLA-4, which accumulates in the T cell at the T cell–APC interface, reaching a level where it eventually blocks costimulation and abrogates an activated T cell response (Fig. 2).

Based on knowledge of the function of CTLA-4, we proposed that blocking its interaction with the B7 molecules might allow T cell responses to persist sufficiently to achieve tumor eradication. We hypothesized that this could be achieved by releasing the endogenous immune responses, perhaps even without specific knowledge of the antigenic targets of those responses or even the type of cancer. We also proposed that combination treatment with an antibody against CTLA-4 and agents that directly killed tumor cells to release antigens for presentation by APCs to T cells would improve antitumor responses. Our hypotheses were tested in many different experiments in mice (*11*–*15*), with data generated to support the concept, leading to the development of ipilimumab, an antibody against human CTLA-4 for clinical testing. Ipilimumab led to considerable improvement in overall survival for patients with metastatic melanoma (*16*, *17*), which led to FDA approval in 2011.

The preclinical successes of anti-CTLA-4 in achieving tumor rejection in animal models and the ultimate clinical success opened a new field of immune checkpoint therapy (*18*, *19*). It is now known that there are many additional immune checkpoints. Programmed cell death-1 (PD-1) was shown in 2000 to be another immune checkpoint that limits the responses of activated T cells (*20*). PD-1, like CTLA-4, has two ligands, PD-L1 and PD-L2, which are expressed on many cell types. The function of PD-1 is completely distinct from CTLA-4 in that PD-1 does not interfere with costimulation, but interferes with signaling mediated by the T cell antigen receptor (*4*). Also, one of its ligands, PD-L1 (B7-H1), can be expressed on many cell types (Fig. 2), including T cells, epithelial cells, endothelial cells, and tumor cells after exposure to the cytokine interferon-γ (IFN-γ), produced by activated T cells (*21*). This has led to the notion that rather than functioning early in T cell activation, the PD-1/PD-L1 pathway acts to protect cells from T cell attack.

Immune checkpoint therapy in the clinic

Ipilimumab, a fully human antibody to human CTLA-4, entered clinical trials in the late 1990s and early 2000s. As predicted, tumor regression was observed in patients with a variety of tumor types. Phase I/II trials showed clinical responses in

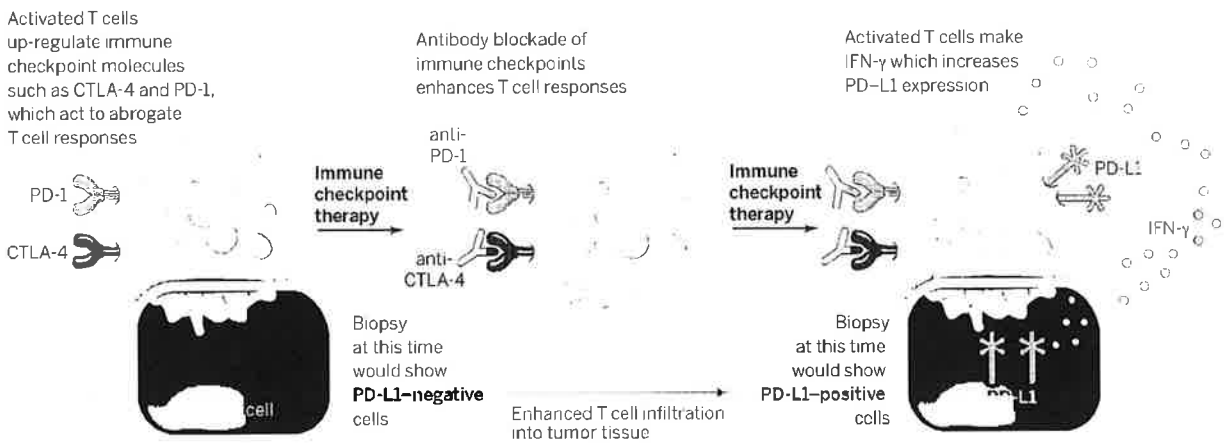

Fig. 2. Blockade of immune checkpoints to enhance T cell responses. After T cell activation, T cells express immune checkpoints such as CTLA-4 and PD-1. A biopsy of tumors taken from patients before treatment with immune checkpoint therapy (so prior to infiltration of activated T cells into tumor tissues) may indicate lack of PD-L1 expression. However, upon T cell activation, T cells can traffic to tumors, up-regulate expression of immune checkpoints such as CTLA 4 and PD 1, and produce cytokines such as IFN-γ, which leads to expression of PD-L1 on tumor cells and other cells, including T cells, within the tumor tissues.

patients with melanoma (22), renal cell carcinoma (23), prostate cancer (24), urothelial carcinoma (25), and ovarian cancer (26). Two phase III clinical trials with anti-CTLA-4 (ipilimumab) were conducted in patients with advanced melanoma and demonstrated improved overall survival for patients treated with ipilimumab (16, 17). Importantly, durable responses were observed in about 20% of patients living for more than 4 years, including a recent analysis indicating survival of 10 years or more for a subset of patients (27).

Antibodies targeting the PD-1/PD-L1 axis have also shown clinical responses in multiple tumor types. Anti-PD-L1 antibodies led to tumor regression in patients with melanoma, renal cell carcinoma, non-small cell lung cancer (28), and bladder cancer (29). Phase I clinical trials with anti-PD-1 (nivolumab) demonstrated similar clinical responses (30). Recently, a large phase I clinical trial with the anti-PD-1 antibody MK-3475 was shown to lead to response rates of ~37 to 38% in patients with advanced melanoma (31), with a subsequent study reporting an overall response rate of 26% in patients who had progressive disease after prior ipilimumab treatment (32), which led to FDA approval of MK-3475 (pembroluzimab) in September 2014. A phase III trial of a different anti-PD-1 antibody (nivolumab) also showed clinical benefit in patients with metastatic melanoma. In this trial, the objective response rate was 40% and overall survival rate was 72.9% for patients treated with nivolumab as compared to an objective response rate of 13.9% and overall survival rate of 42.1% for patients treated with dacrabazine chemotherapy (33). Nivolumab received FDA approval in December 2014 as a treatment for patients with metastatic melanoma. In addition, nivolumab was FDA-approved in March 2015 for patients with previously treated advanced or metastatic non-small cell lung cancer based on a phase III clinical trial, which reported an improvement in overall survival for patients treated with nivolumab as compared to patients treated with docetaxel chemotherapy.

That CTLA-4 and PD-1 regulate distinct inhibitory pathways and have nonoverlapping mechanisms of action suggested that concurrent combination therapy with both might be more efficacious than either alone. This was indeed shown to be the case in preclinical studies in murine models (34). In 2013, a phase I clinical trial with anti-CTLA-4 (ipilimumab) in combination with anti-PD-1 (nivolumab) demonstrated tumor regression in ~50% of treated patients with advanced melanoma, most with tumor regression of 80% or more (35). There are ongoing clinical trials with anti-CTLA-4 plus anti-PD-1, or anti-PD-L1, in other tumor types, with preliminary data indicating promising results, which highlight this novel combination as an effective immunotherapy strategy for cancer patients.

Tissue-based immune monitoring: Anti-CTLA-4 therapy

Properly designed presurgical or tissue-based trials, where treatment is administered before surgical resection of tumors, can provide valuable insight into the cellular and molecular mechanisms of immune checkpoint therapy by providing sufficient tissues to conduct a battery of analyses. Data gathered from analysis of tumor tissue can then guide rational searches for relevant markers in the blood. We designed the first presurgical clinical trial with anti-CTLA-4 (ipilimumab), which was administered to 12 patients with localized bladder cancer prior to radical cystectomy (36). The endpoints of this study were safety and access to samples for immune monitoring. We did not view this trial as a neoadjuvant study, which administers therapy prior to surgery for clinical benefit, but as a presurgical study to provide mechanistic insights regarding the impact of anti-CTLA-4 therapy on the tumor microenvironment. Unexpectedly, the trial enabled us to detect a clinical signal for anti-CTLA-4 as a therapeutic agent for patients with bladder cancer since three patients had no residual tumors identified within the cystectomy samples. This trial was also successful in establishing the safety of anti-CTLA-4 in the presurgical setting, which would be important for future trials, and obtaining patients' matched tumor and blood samples for immune monitoring. This work laid the foundation for using presurgical trials as an important tool to evaluate human immune responses in the tumor microenvironment, which should be included in the current paradigm of phase I, II, and III clinical trials.

"Because of the very nature of immune checkpoint therapy, the development of pharmacodynamic, predictive, or prognostic biomarkers faces unique challenges."

The collection of fresh tumor samples at the time of surgery can provide sufficient tissue for genetic, phenotypic, and functional studies, as well as material for immunohistochemical (IHC) analyses, which can provide extensive insight into the biologic impact of the immunotherapy agent on the tumor microenvironment. For example, high-quality mRNA can be obtained for gene expression studies comparing posttreatment tumor tissues to pretreatment tumor tissues or untreated samples obtained from a stage-matched control group of patients. These types of studies allow unbiased analyses of the samples to identify novel genes and pathways that are affected by therapy. In our ipilimumab trial, gene array data revealed that most of the differences between treated and untreated samples could be attributed to pathways involved in T cell signaling, which is not surprising given the large increases in T cell infiltrates in tumor tissues after CTLA-4 blockade (25, 26). The most pronounced difference was an increase in T cells that express inducible costimulator (ICOS), a T cell surface molecule that is a closely related member of the extended CD28/CTLA-4 family. We confirmed our gene expression studies by flow cytometry. $ICOS^+$ T cells were increased in tumor tissues from patients treated with ipilimumab (36). The increase in the frequency of $ICOS^+$ T cells in tumor infiltrates was accompanied by similar increases in the blood. These data, coupled with other studies, showed that an increase in the frequency of $ICOS^+$ CD4 T cells served as a pharmacodynamic biomarker of anti-CTLA-4 treatment (37).

To test our hypothesis that $ICOS^+$ CD4 T cells might play a role in the therapeutic effect of CTLA-4 blockade, we conducted studies in mice. In wild-type C57BL/6 mice, anti-CTLA-4 treatment resulted in tumor rejection in 80 to 90% of mice, but in gene-targeted mice that were deficient for either ICOS or its ligand, the efficacy was less than 50% (38). The loss of efficacy of CTLA-4 blockade in the absence of an intact ICOS pathway indicates the critical importance of ICOS to the therapeutic effects of treatment with anti-CTLA-4 antibodies. The important role played by ICOS in the effectiveness of CLTA-4 blockade suggested that providing an agonistic stimulus for the ICOS pathway during anti-CTLA-4 therapy might increase its effectiveness. To test this notion, we conducted studies in mice to provide an agonistic signal through ICOS in combination with CTLA-4 blockade. We found that combination therapy resulted in an increase in efficacy that was about four to five times as large as that of control treatments (39). Thus, ICOS is a stimulatory checkpoint that provides a novel target for combination immunotherapy strategies. Antibodies for ICOS are being developed for clinical testing, which are expected to start within the next year.

Whereas some presurgical and tissue-based trials are focused on evaluating human immune responses in the tumor microenvironment, other studies have focused on evaluating components of the cancer cells that may contribute to clinical benefit with anti-CTLA-4. Genetic analyses of melanoma tumors revealed that higher numbers of mutations, termed "mutational load," and creation of new antigens that can be recognized by T cells as a result of these mutations, termed "neoantigens," correlated with clinical responses to anti-CTLA-4 therapy (3, 40). These studies provide a strong rationale to integrate genetic analyses of the tumor with immune profiling of the tumor microenvironment for a more comprehensive evaluation of mechanisms that contribute to clinical responses with anti-CTLA-4 therapy.

Tissue-based immune monitoring: Anti-PD-1/PD-L1 therapy

Given that immune checkpoint therapy only benefits a fraction of patients, there are ongoing efforts to identify predictive biomarkers that could be used to select patients for treatment.

Because the PD-1 ligand PD-L1 (and sometimes PD-L2) can be expressed on tumor cells and immune cells in the tumor microenvironment, there have been efforts to use expression of PD-L1 as a criterion for selecting patients for treatments with antibodies targeting the PD-1/PD-L1 pathway.

The initial phase I trial with anti-PD-1 therapy (nivolumab) reported that PD-L1 expression on tumor cells, measured on pretreatment archival samples by immunohistochemical (IHC) methods, may potentially serve as a predictive marker to indicate which patients would benefit from treatment (*30*). Patients with PD-L1–positive tumors (≥5% staining for PD-L1 on tumor cells) had an objective response rate of 36% (9 of 25 patients) whereas patients with PD-L1–negative tumors did not show any objective clinical responses (0 of 17 patients). However, in subsequent trials, some patients whose tumors were deemed to be PD-L1–negative had clinical responses to anti-PD-1 and anti-PD-L1 treatments with either tumor regression or stabilization of disease. For example, on a phase I trial with anti-PD-1 (nivolumab), patients with PD-L1–positive tumors had an objective response rate of 44% (7 of 16) and patients with PD-L1–negative tumors had an objective response rate of 17% (3 of 18) (*41*). Although PD-L1 expression in tumor tissues does correlate with higher response rates, it is not predictive for clinical benefit. Furthermore, current data indicate that the differences in response rates do not translate to differences in survival benefit. For patients with metastatic melanoma who received treatment with nivolumab on a phase III trial, the median overall survival had not been reached for either PD-L1 subgroup, and both subgroups had improved overall survival as compared to patients who received dacarbazine chemotherapy (*33*).

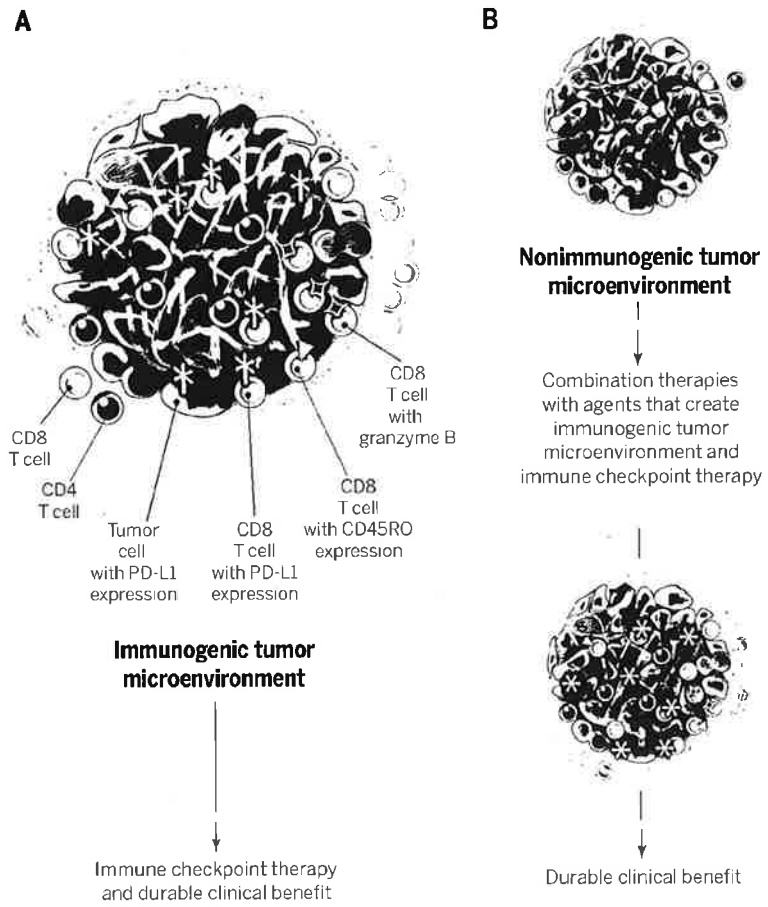

Fig. 3. Potential characteristics of immunogenic and nonimmunogenic tumors. (**A**) Tumor tissue depiction indicating tumor cells and an invasive margin (dotted line), which may delineate separation of tumor cells from stromal components. Evaluation of tumor tissues may reveal an immunogenic tumor microenvironment consisting of many immunologic markers, including CD8 T cells, CD4 T cells, PD-L1, granzyme B, and CD45RO, which may be effectively treated with immune checkpoint therapy to elicit clinical benefit. (**B**) Tumor tissues that lack expression of many immunologic markers may indicate a nonimmunogenic tumor microenvironment, which may require combination therapies consisting of an agent to create an immunogenic tumor microenvironment plus an immune checkpoint agent to further enhance the immune response for clinical benefit.

In a phase I study of anti-PD-L1 (MPDL3280A), patients with bladder cancer were considered to have PD-L1–positive tumors if their pretreatment archival tumor samples contained ≥5% PD-L1–positive tumor-infiltrating immune cells (*29*). Twenty-one patients with PD-L1–positive tumors were enrolled onto the trial prior to enrollment of patients with PD-L1–negative tumor samples. Data were reported after a minimum of 6 weeks of follow-up. An objective response rate of 43.3% (13 out of 30 patients) and stable disease rate of 26.7% (8 of 30) was reported for patients with PD-L1–positive tumors, which was compared to an objective response rate of 11.4% (4 of 35 patients) and stable disease rate of 37.1% (13 of 35) for patients with PD-L1–negative tumors. Because the patients with PD-L1–positive tumors received treatment for a longer period of time as compared to patients with PD-L1–negative tumors, it is unclear if the difference in response rates in this study was due to PD-L1 expression or time on treatment. However, for patients with metastatic bladder cancer whose disease had progressed after first-line chemotherapy and in a setting where there are no approved second-line treatments, an objective response rate of 11% and stable disease rate of 37.1% are clinically relevant.

Similarly, in another phase I study of anti-PD-L1 (MPDL3280A) in multiple tumor types, objective response rates were reported as 46% in the cohort of patients whose tumors had the highest PD-L1–expression, 17% in the cohort of patients whose tumors had moderate expression of PD-L1, 21% in the cohort of patients whose tumors had minimal PD-L1 expression, and 13% in the cohort of patients whose tumors had no detectable level of PD-L1 expression (*42*). Thus, this trial also showed that patients whose tumors were deemed as PD-L1–negative can have objective responses. Interestingly, the cohort of patients whose tumors were categorized as moderate expression of PD-L1, which correlates with PD-L1–positive status, had objective responses (17%) and median progression-free survival (18 weeks) that were similar to the objective responses (21%) and median progression-free survival (17 weeks) of the cohort of patients whose tumors had minimal expression of PD-L1, which correlates with PD-L1–negative status. Additional studies will be needed to determine whether PD-L1 expression in the tumor microenvironment affects survival outcomes for patients treated with anti-PD-L1.

On the basis of data reported thus far, it seems fair to conclude that expression of PD-L1 in tumor tissues should not be used as a predictive biomarker for selection or exclusion of patients for treatment with either anti-PD-1 or anti-PD-L1 antibodies. In a study of primary and

metastatic melanoma samples, many taken from the same patient, it was shown that PD-L1 expression was discordant between primary tumors and metastases and between intrapatient metastases. In addition, patients whose tumor tissues were positive for both PD-L1 expression and infiltration of T cells were found to have improved overall disease-specific survival as compared to patients who had only one of the two features or lacked both features (*43*). Similarly, in a study with anti-PD-1 (pembrolizumab), it was reported that while expression of PD-L1 in pretreatment tumor tissues correlated with clinical outcomes, the preexisting density of CD8 T cells in the invasive margin of the tumor was more predictive of clinical response to anti-PD-1 (*44*). These data suggest that PD-L1 expression in the tumor is most compelling when it is observed in the context of an active T cell response, and that the ongoing T cell response itself, not PD-L1 expression, is the key factor.

Taken together, these data indicate the complexity of determining the PD-L1 status of a patient's tumor by examination of a single pretreatment tumor sample (Fig. 2). It also raises questions as to whether clinical decisions regarding treatment of patients who have failed conventional therapies and for whom no other treatments are available should be based on static assessment of PD-L1 expression in pretreatment tumor samples.

However, in some settings, expression of PD-L1 in tumors is constitutive and is neither associated with T cell infiltration nor induced by IFN-γ. In these settings, assessment of PD-L1 expression in tumor tissues may be very useful in guiding treatment. In Hodgkin's lymphoma, Reed-Sternberg cells are known to harbor amplification of chromosome 9p24.1, which encodes PD-L1 and PD-L2 and leads to their constitutive expression. Anti-PD-1 (nivolumab) was shown to elicit an objective response rate of 87% in a cohort of 20 patients with Hodgkin's lymphoma (*45*). Therefore, in the setting of Hodgkin's lymphoma, and possibly other malignancies that harbor amplification of chromosome 9p24 or up-regulate PD-L1 or PD-L2 in response to an oncogenic signal, the expression of these ligands may indeed serve as a predictive biomarker.

In addition to evaluation of PD-L1 expression, tumor tissues can also be studied to identify patterns of expression of multiple immunologic components, including other checkpoints and their ligands. T cells that coexpress PD-1 together with other inhibitory molecules such as LAG-3 or Tim-3 may be even more profoundly hyporesponsive than those expressing PD-1 alone and indicate the need for the blockade of multiple checkpoints (*46*, *47*). Given the complexity of regulation of T cell responses by multiple signaling pathways, both negative and positive, it will be necessary to determine the patterns of expression of the receptors, as well as the ligands on T cells, tumor cells, myeloid cells, and other components of the tumor microenvironment, for development of combination strategies with greater clinical benefit.

Additional biomarkers that play a role in antitumor responses elicited by anti-PD-1 therapy and anti-PD-L1 therapies may also be identified through genetic analyses of tumor cells. Similar to previous reports with anti-CTLA-4 therapy, higher numbers of mutations, including mutations in DNA repair pathways, with subsequent increase in numbers of neoantigens, was found to correlate with clinical responses in patients with non–small cell lung cancer who received treatment with anti-PD-1 (pembrolizumab) (*48*). These data highlight the complex interplay between cancer cells and the immune system, which will need further elucidation, to guide rational development of combination therapies.

Combination therapy to increase clinical benefit

Given the dynamic nature of immune responses to tumors and the complexity of regulation of expression of multiple immune checkpoints and their ligands, it may be difficult to rely on any single immunologic biomarker to select patients for treatment. It may be necessary to evaluate multiple components within the tumor microenvironment, which may enable us to distinguish between an immunogenic (hot) tumor microenvironment (Fig. 3A) that is comprised of infiltrating T cells, cytokines such as granzyme B, memory T cell markers such as CD45RO and PD-L1 expression versus a non-immunogenic (cold) tumor microenvironment that lacks these components (Fig. 3B). Patients whose tumors are immunogenic would be treated with immune checkpoint therapy to elicit durable clinical benefit but, patients whose tumors are non-immunogenic would receive combination therapies designed to create an immunogenic tumor microenvironment that would respond to treatment with subsequent durable clinical benefit (Fig. 3).

Substantial data already exist to indicate that certain combination therapies may overcome the limitations of anti-CTLA-4 and anti-PD-1/PD-L1 monotherapies. For example, anti-CTLA-4 seems to drive T cells into tumors, resulting in an increase in the number of T cells and a concomitant increase in IFN-γ. This, in turn, can induce expression of PD-L1 in the tumor microenvironment, with subsequent inhibition of antitumor T cell responses, but also increase the chance of benefit from anti-PD-1 and anti-PD-L1 therapies. Therefore, combination treatment with anti-CTLA-4 plus anti-PD-1 or anti-PD-L1 should enable the creation of an immunogenic tumor microenvironment with subsequent clinical benefit for patients regardless of whether their pretreatment tumor tissues have infiltrating T cells or express PD-L1. Data from a recent phase I clinical trial with anti-CTLA-4 (ipilimumab) plus anti-PD-1 (nivolumab) demonstrated that patients with metastatic melanoma had similar response rates in the setting of concurrent therapy regardless of PD-L1 expression in pretreatment tumor tissues (*35*). For patients with PD-L1–positive tumors, the objective response rate was 46% (6 of 13 patients), which was similar to the objective response rate of 41% (9 of 22 patients) for those patients with PD-L1–negative tumors. Similar data were reported for a combination study with anti-PD-1 (nivolumab) plus anti-CTLA-4 (ipilimumab) in patients with metastatic renal cell carcinoma (mRCC) (*49*).

Conventional cancer therapies (Table 1) may also lead to tumor cell death and release of antigens to initiate activation of T cells, which may then migrate into tumor tissues. Therefore, combination studies with these conventional agents and immune checkpoint therapies should create an "immunogenic" tumor microenvironment with subsequent clinical benefit for patients. There are multiple ongoing trials with radiation therapy in combination with anti-CTLA-4 or anti-PD-1/PD-L1 antibodies, which will provide valuable information regarding schedule, safety, and efficacy of these combinations for future studies (*50*, *51*). In addition, combination treatment with anti-PD-1 (nivolumab) plus pazopanib or sunitib in patients with mRCC resulted in promising clinical responses, with response rates that were similar across all patients regardless of PD-L1 expression in pretreatment tumor tissues (*52*).

Other combination strategies, such as vaccines plus anti-CTLA-4 (ipilimumab), are also being developed and have shown promising results in patients with pancreatic cancer, which has

Table 1. Potential agents for combination therapy. List of some conventional cancer therapies, inhibitory immune signals and stimulatory immune signals that can be considered for combination strategies to improve antitumor responses and durable clinical benefit.

CONVENTIONAL THERAPIES	INHIBITORY IMMUNE SIGNALS	STIMULATORY IMMUNE SIGNALS
Chemotherapy	CTLA-4	ICOS
Radiation	PD-1/PD-L1	OX40
Surgery	LAG-3	41BB
Genomically targeted	TIM-3	Vaccines
Anti-angiogenic	VISTA	Cytokines
Hormonal	BTLA	Oncolytic virus

been consistently viewed as a nonimmunogenic tumor type (*53*). Combination treatments are also being developed to enable blockade of multiple inhibitory pathways, such as LAG-3 (*54*, *55*), TIM-3 (*56*, *57*), VISTA (*58*, *59*), and BTLA (*60*, *61*), or blockade of an inhibitory pathway while providing an agonistic signal through a stimulatory pathway, such as ICOS (*39*), OX40 (*62*), 41BB (*63*), vaccines (*24*, *53*), cytokines (*64*), and oncolytic virus (*65*). The development of these combinations and others are critical for driving antitumor immune responses in many cancer patients, even those who are deemed to have nonimmunogenic or PD-L1–negative tumors.

Discussion

Because of the very nature of immune checkpoint therapy, the development of pharmacodynamic, predictive, or prognostic biomarkers faces unique challenges. Agents that block immune checkpoints unleash dynamic and complex immune responses. Anti-CTLA-4 antibody overcomes a block in essential costimulatory signals that are required for activation of both naïve T cells and resting clones, whereas PD-1/PD-L1 blockade seems to remove a barrier to the function of T cells later in the response and in the tumor tissue. Therefore, there is a fundamental difference in the predictive value of preexisting tumor inflammation for PD-1/PD-L1 and CTLA-4 blockade. The existence of a T cell infiltrate and select biomarkers, such as expression of PD-L1, which indicate a "hot" tumor microenvironment, does correlate with clinical benefit for patients treated with anti-PD-1 or anti-PD-L1. However, in the setting of a "cold" tumor microenvironment, it seems that anti-CTLA-4 therapy can drive T cells into the tumor and induce expression of PD-L1, thus creating a tumor microenvironment that may be responsive to anti-PD-1 or anti-PD-L1 therapy, which provides a strong rationale for combination therapy.

There are many ongoing efforts to identify predictive biomarkers of immune checkpoint therapy. It may be that germline differences in immune genes and pathways or host microbiome may affect host immune responses and clinical outcomes in the setting of immune checkpoint therapy. Also, the nature of the tumor itself can also affect the outcome of immune checkpoint therapy. Tumor types differ considerably in their mutational load, which may affect the number of neoantigens that can serve as targets of antitumor T cell responses (*66*). Patients with tumors at the high end of the mutational spectrum may be more likely to respond to immune checkpoint therapy. For example, anti-PD-1 therapy was thought to be ineffective against colon cancer, but it appears that colon cancer with microsatellite instability, and consequently a higher overall mutational load, may be responsive to treatment with anti-PD-1 (*67*). However, this concept may not hold true for all tumor types, because patients with kidney cancer, which has relatively low numbers of mutations, have had notable clinical responses to immune checkpoint therapy (*28*, *30*).

There are multiple immunologic pathways, both positive and negative, with new checkpoints and ligands that emerge as an immune response develops. Because of the constant evolution of an immune response, it is unlikely that a single immunologic biomarker can be identified at baseline that can predict responses to any agent. It will probably be necessary to develop panels of markers based on patterns of expression of relevant markers, and use these to guide development of combination therapies that will increase the response rate. These combinations will not be limited to agents that target immune checkpoints, because it is apparent that small molecules that target signaling pathways involved in cancer can affect antitumor immune responses (*68*). This can occur at the level of the T cells by enhancing activation signals, but also at the level of the tumor by inducing tumor antigen expression and presentation, thus making the tumors more susceptible to T cell killing. The goal then should be to use panels of markers to guide development of combination therapies, and then examine tumor tissues for changes in markers elicited by the combinations to guide decisions about additional treatment to further increase efficacy, and, hopefully, durable clinical responses.

Immune checkpoint therapies and combination strategies with immunotherapy have provided cancer patients with novel treatments that have the potential to elicit durable control of disease and even cures. The specificity, adaptability, and memory response that are inherent to the immune system give us the opportunity to measure multiple components, not just a single biomarker, that can be targeted over time to provide curative treatments for many patients. The ability of an activated immune response to generate a diverse T cell repertoire that adapts to heterogeneous and genetically unstable tumors and the persistence of memory T cells with specificity for tumor antigens, which provide efficient recall responses against recurrent disease, make it absolutely essential to expand our efforts to find rational combinations to unleash antitumor immune responses for the benefit of cancer patients. Properly done, it seems likely that cures for many types of cancer will soon become reality.

REFERENCES AND NOTES

1. J. A. Curtin *et al.*, *N. Engl. J. Med.* **353**, 2135–2147 (2005).
2. H. Davies *et al.*, *Nature* **417**, 949–954 (2002).
3. T. Schumacher, R. Schreiber, *Science* **348**, 69–74 (2015).
4. R. J. Greenwald, G. J. Freeman, A. H. Sharpe, *Annu. Rev. Immunol.* **23**, 515–548 (2005).
5. S. E. Townsend, J. P. Allison, *Science* **259**, 368–370 (1993).
6. P. van der Bruggen *et al.*, *Science* **254**, 1643–1647 (1991).
7. S. A. Rosenberg, J. C. Yang, N. P. Restifo, *Nat. Med.* **10**, 909–915 (2004).
8. P. S. Linsley *et al.*, *J. Exp. Med.* **176**, 1595–1604 (1992).
9. T. L. Walunas *et al.*, *Immunity* **1**, 405–413 (1994).
10. M. F. Krummel, J. P. Allison, *J. Exp. Med.* **182**, 459–465 (1995).
11. D. R. Leach, M. F. Krummel, J. P. Allison, *Science* **271**, 1734–1736 (1996).
12. A. A. Hurwitz, T. F. Yu, D. R. Leach, J. P. Allison, *Proc. Natl. Acad. Sci. U.S.A.* **95**, 10067–10071 (1998).
13. A. van Elsas, A. A. Hurwitz, J. P. Allison, *J. Exp. Med.* **190**, 355–366 (1999).
14. R. Waitz, M. Fassò, J. P. Allison, *Oncoimmunology* **1**, 544–545 (2012).
15. D. Zamarin *et al.*, *Sci. Transl. Med.* **6**, 226ra32 (2014).
16. F. S. Hodi *et al.*, *N. Engl. J. Med.* **363**, 711–723 (2010).
17. C. Robert *et al.*, *N. Engl. J. Med.* **364**, 2517–2526 (2011).
18. P. Sharma, K. Wagner, J. D. Wolchok, J. P. Allison, *Nat. Rev. Cancer* **11**, 805–812 (2011).
19. D. M. Pardoll, *Nat. Rev. Cancer* **12**, 252–264 (2012).
20. G. J. Freeman *et al.*, *J. Exp. Med.* **192**, 1027–1034 (2000).
21. H. Dong *et al.*, *Nat. Med.* **8**, 793–800 (2002).
22. J. S. Weber *et al.*, *J. Clin. Oncol.* **26**, 5950–5956 (2008).
23. J. C. Yang *et al.*, *J. Immunother.* **30**, 825–830 (2007).
24. A. J. van den Eertwegh *et al.*, *Lancet Oncol.* **13**, 509–517 (2012).
25. B. C. Carthon *et al.*, *Clin. Cancer Res.* **16**, 2861–2871 (2010).
26. F. S. Hodi *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **105**, 3005–3010 (2008).
27. D. Schadendorf *et al.*, *J. Clin. Oncol.* 10.1200/JCO.2014.56.2736 (2015).
28. J. R. Brahmer *et al.*, *N. Engl. J. Med.* **366**, 2455–2465 (2012).
29. T. Powles *et al.*, *Nature* **515**, 558–562 (2014).
30. S. L. Topalian *et al.*, *N. Engl. J. Med.* **366**, 2443–2454 (2012).
31. O. Hamid *et al.*, *N. Engl. J. Med.* **369**, 134–144 (2013).
32. C. Robert *et al.*, *Lancet* **384**, 1109–1117 (2014).
33. C. Robert *et al.*, *N. Engl. J. Med.* **372**, 320–330 (2015).
34. M. A. Curran, W. Montalvo, H. Yagita, J. P. Allison, *Proc. Natl. Acad. Sci. U.S.A.* **107**, 4275–4280 (2010).
35. J. D. Wolchok *et al.*, *N. Engl. J. Med.* **369**, 122–133 (2013).
36. C. I. Liakou *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **105**, 14987–14992 (2008).
37. D. Ng Tang *et al.*, *Cancer Immunol. Res.* **1**, 229–234 (2013).
38. T. Fu, Q. He, P. Sharma, *Cancer Res.* **71**, 5445–5454 (2011).
39. X. Fan, S. A. Quezada, M. A. Sepulveda, P. Sharma, J. P. Allison, *J. Exp. Med.* **211**, 715–725 (2014).
40. A. Snyder *et al.*, *N. Engl. J. Med.* **371**, 2189–2199 (2014).
41. J. Grosso *et al.*, *J. Clin. Oncol.* **31** (suppl.), 3016 (2013).
42. R. S. Herbst *et al.*, *Nature* **515**, 563–567 (2014).
43. J. Madore *et al.*, *Pigment Cell Melanoma Res.* 10.1111/pcmr.12340 (2014).
44. P. C. Tumeh *et al.*, *Nature* **515**, 568–571 (2014).
45. S. M. Ansell *et al.*, *N. Engl. J. Med.* **372**, 311–319 (2015).
46. S. R. Woo *et al.*, *Cancer Res.* **72**, 917–927 (2012).
47. K. Sakuishi *et al.*, *J. Exp. Med.* **207**, 2187–2194 (2010).
48. N. Rizvi *et al.*, *Science* **348**, 124–128 (2015).
49. J. H. Hammers *et al.*, *J. Clin. Oncol.* **32** (suppl.), 4504 (2014).
50. M. Crittenden *et al.*, *Semin. Radiat. Oncol.* **25**, 54–64 (2015).
51. C. Tang *et al.*, *Cancer Immunol Res* **2**, 831–838 (2014).
52. A. Amin *et al.*, *J. Clin. Oncol.* **32** (suppl.), 4010 (2014).
53. D. T. Le *et al.*, *J. Immunother.* **36**, 382–389 (2013).
54. F. Triebel *et al.*, *J. Exp. Med.* **171**, 1393–1405 (1990).
55. M. V. Goldberg, C. G. Drake, *Curr. Top Microbiol Immunol* **344**, 269–278 (2011).
56. J. Fourcade *et al.*, *J. Exp. Med.* **207**, 2175–2186 (2010).
57. V. K. Kuchroo, D. T. Umetsu, R. H. DeKruyff, G. J. Freeman, *Nat. Rev. Immunol.* **3**, 454–462 (2003).
58. L. Wang *et al.*, *J. Exp. Med.* **208**, 577–592 (2011).
59. L. Le Mercier *et al.*, *Cancer Res.* **74**, 1933–1944 (2014).
60. L. Derré *et al.*, *J. Clin. Invest.* **120**, 157–167 (2010).
61. J. Fourcade *et al.*, *Cancer Res.* **72**, 887–896 (2012).
62. W. L. Redmond, S. N. Linch, M. J. Kasiewicz, *Cancer Immunol Res* **2**, 142–153 (2014).
63. H. E. Kohrt *et al.*, *J. Clin. Invest.* **124**, 2668–2682 (2014).
64. F. S. Hodi *et al.*, *J. Am. Med. Assoc.* **312**, 1744–1753 (2014).
65. C. E. Engeland *et al.*, *Mol. Ther.* **22**, 1949–1959 (2014).
66. L. B. Alexandrov *et al.*, *Nature* **500**, 415–421 (2013).
67. N. J. Llosa *et al.*, *Cancer Discov.* **5**, 43–51 (2015).
68. D. T. Frederick *et al.*, *Clin. Cancer Res.* **19**, 1225–1231 (2013).

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31. L. J. Bayne *et al.*, *Cancer Cell* **21**, 822–835 (2012).
32. Y. Pylayeva-Gupta, K. E. Lee, C. H. Hajdu, G. Miller, D. Bar-Sagi, *Cancer Cell* **21**, 836–847 (2012).
33. D. C. Strachan *et al.*, *OncoImmunology* **2**, e26968 (2013).
34. Y. Zhu *et al.*, *Cancer Res.* **74**, 5057–5069 (2014).
35. A. J. Garcia *et al.*, *Mol. Cell. Biol.* **34**, 2017–2028 (2014).
36. D. G. DeNardo *et al.*, *Cancer Discov.* **1**, 54–67 (2011).
37. B. Molon *et al.*, *J. Exp. Med.* **208**, 1949–1962 (2011).
38. G. T. Motz *et al.*, *Nat. Med.* **20**, 607–615 (2014).
39. X. Zang *et al.*, *Mod. Pathol.* **23**, 1104–1112 (2010).
40. R. J. Buckanovich *et al.*, *Nat. Med.* **14**, 28–36 (2008).
41. Y. Huang, S. Goel, D. G. Duda, D. Fukumura, R. K. Jain, *Cancer Res.* **73**, 2943–2948 (2013).
42. G. C. Jayson, D. J. Hicklin, L. M. Ellis, *Nat. Rev. Clin. Oncol.* **9**, 297–303 (2012).
43. R. K. Shrimali *et al.*, *Cancer Res.* **70**, 6171–6180 (2010).
44. Y. Huang *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **109**, 17561–17566 (2012).
45. D. I. Gabrilovich *et al.*, *Nat. Med.* **2**, 1096–1103 (1996).
46. J. Hamzah *et al.*, *Nature* **453**, 410–414 (2008).
47. A. Johansson, J. Hamzah, C. J. Payne, R. Garss, *Proc. Natl. Acad. Sci. U.S.A.* **109**, 7841–7846 (2012).
48. A. Calcinotto *et al.*, *J. Immunol.* **188**, 2687–2694 (2012).
49. E. D. Thompson, H. L. Enriquez, Y. X. Fu, V. H. Engelhard, *J. Exp. Med.* **207**, 1791–1804 (2010).
50. Y. Ma *et al.*, *Cancer Res.* **74**, 436–445 (2014).
51. M. L. Broz *et al.*, *Cancer Cell* **26**, 638–652 (2014).
52. K. Hildner *et al.*, *Science* **322**, 1097–1100 (2008).
53. B. Ruffell *et al.*, *Cancer Cell* **26**, 623–637 (2014).
54. X. Yang *et al.*, *Cancer Cell* **25**, 37–48 (2014).
55. M. Z. Noman *et al.*, *J. Exp. Med.* **211**, 781–790 (2014).
56. O. R. Colegio *et al.*, *Nature* **513**, 559–563 (2014).
57. M. J. Cavnar *et al.*, *J. Exp. Med.* **210**, 2873–2886 (2013).
58. P. J. Murray *et al.*, *Immunity* **41**, 14–20 (2014).
59. B. Z. Qian, J. W. Pollard, *Cell* **141**, 39–51 (2010).
60. D. H. Munn, A. L. Mellor, *Trends Immunol.* **34**, 137–143 (2013).
61. M. Platten, W. Wick, B. J. Van den Eynde, *Cancer Res.* **72**, 5435–5440 (2012).
62. C. Smith *et al.*, *Cancer Discov.* **2**, 722–735 (2012).
63. R. B. Holmgaard, D. Zamarin, D. H. Munn, J. D. Wolchok, J. P. Allison, *J. Exp. Med.* **210**, 1389–1402 (2013).
64. M. D. Sharma *et al.*, *Immunity* **38**, 998–1012 (2013).
65. P. Zhou *et al.*, *Nature* **506**, 52–57 (2014).
66. S. M. Pyonteck *et al.*, *Nat. Med.* **19**, 1264–1272 (2013).
67. G. L. Beatty *et al.*, *Science* **331**, 1612–1616 (2011).
68. N. I. Affara *et al.*, *Cancer Cell* **25**, 809–821 (2014).
69. A. Pommier *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **110**, 13085–13090 (2013).
70. Y. Murata, T. Kotani, H. Ohnishi, T. Matozaki, *J. Biochem.* **155**, 335–344 (2014).
71. K. Weiskopf *et al.*, *Science* **341**, 88–91 (2013).
72. H. Salmon *et al.*, *J. Clin. Invest.* **122**, 899–910 (2012).
73. M. Kraman *et al.*, *Science* **330**, 827–830 (2010).
74. E. W. Roberts *et al.*, *J. Exp. Med.* **210**, 1137–1151 (2013).
75. M. H. Sherman *et al.*, *Cell* **159**, 80–93 (2014).
76. C. J. Scotton *et al.*, *Cancer Res.* **62**, 5930–5938 (2002).
77. J. J. Liang *et al.*, *Cancer Epidemiol. Biomarkers Prev.* **19**, 2598–2604 (2010).
78. Y. Akishima-Fukasawa *et al.*, *Am. J. Clin. Pathol.* **132**, 202–210; quiz 307 (2009).
79. M. C. Poznansky *et al.*, *Nat. Med.* **6**, 543–548 (2000).
80. I. Eyles *et al.*, *J. Clin. Invest.* **120**, 2030–2039 (2010).
81. J. Predina *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **110**, E415–E424 (2013).
82. T. Chiba *et al.*, *Br. J. Cancer* **91**, 1711–1717 (2004).

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REVIEWS

Cancer and the microbiota

Wendy S. Garrett[1,2,3,4]

A host's microbiota may increase, diminish, or have no effect at all on cancer susceptibility. Assigning causal roles in cancer to specific microbes and microbiotas, unraveling host-microbiota interactions with environmental factors in carcinogenesis, and exploiting such knowledge for cancer diagnosis and treatment are areas of intensive interest. This Review considers how microbes and the microbiota may amplify or mitigate carcinogenesis, responsiveness to cancer therapeutics, and cancer-associated complications.

The relationship between cancer and microbes is complex. Although cancer is generally considered to be a disease of host genetics and environmental factors, microorganisms are implicated in ~20% of human malignancies (*1*). Microbes present at mucosal sites can become part of the tumor microenvironment of aerodigestive tract malignancies, and intratumoral microbes can affect cancer growth and spread in many ways (*2*–*6*). In counterpoise, the gut microbiota also functions in detoxification of dietary components, reducing inflammation, and maintaining a balance in host cell growth and proliferation. The possibility of microbe-based cancer therapeutics has attracted interest for more than 100 years, from Coley's toxins (one of the earliest forms of cancer bacteriotherapy) to the current era of synthetic biology's designer microbes and microbiota transplants. Thus, interrogation of the roles of microbes and the microbiota in cancer requires a holistic perspective.

The ways in which microbes and the microbiota contribute to carcinogenesis, whether by enhancing or diminishing a host's risk, fall into three broad categories: (i) altering the balance of host cell proliferation and death, (ii) guiding immune system function, and (iii) influencing metabolism of host-produced factors, ingested foodstuffs, and pharmaceuticals (Fig. 1). Assigning microbial communities, their members, and aggregate biomolecular activities into these categories will require a substantial research commitment. This Review discusses how microbes and the microbiota may contribute to cancer development and progression, responsiveness to cancer therapeutics, and cancer-associated complications.

Microbial contributions to carcinogenesis

Of the estimated 3.7×10^{30} microbes living on Earth (*7*), only 10 are designated by the International Agency for Cancer Research (IACR) as carcinogenic to humans (*1*). Although most of these carcinogenic microbes colonize large percentages of the human population, only a subset of affected individuals develop cancer, because host and microbial genotypes influence cancer susceptibility.

Tumors arising at boundary surfaces, such as the skin, oropharynx, and respiratory, digestive, and urogenital tracts, harbor a microbiota, which complicates cancer-microbe causality. Enrichment of a microbe at a tumor site does not connote that a microbe is directly associated, let alone causal, in disease. Rather, microbes may find a tumor's oxygen tension or carbon sources permissive and take advantage of an underused nutritional niche. Decreased abundances of specific microbes may also place a host at enhanced risk for cancer development at sites local or distant from this microbial shift. Thus, rigorous frameworks for interpreting tumor-associated microbiota data are essential (*2*).

Oncomicrobes, shifting the balance of when to die and when to grow

Bona fide oncomicrobes—microbes that trigger transformation events in host cells—are rare. Beyond the 10 IACR-designated microbes, there are a handful of other microorganisms with robust but fewer aggregate data supporting their role in human carcinogenesis. As many of these and their carcinogenic mechanisms have been recently reviewed (*2*–*6*, *8*), select activities representing common pathways by which microbes influence cancer will be highlighted.

Human oncoviruses can drive carcinogenesis by integrating oncogenes into host genomes. Human papillomaviruses (HPV) express oncoproteins such as E6 and E7. Data from recent genomic analyses of HPV$^+$ cervical cancers suggest that viral integration also selectively triggers amplification of host genes in pathways with established roles in cancer (*9*).

Microbes also drive transformation by affecting genomic stability, resistance to cell death, and proliferative signaling. Many bacteria have evolved mechanisms to damage DNA, so as to kill competitors and survive in the microbial world. Unfortunately, these bacterial defensive factors can lead to mutational events that contribute to carcinogenesis (Fig. 2). Examples include colibactin encoded by the *pks* locus [expressed by B2

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group *Escherichia coli* (*10*) as well as by other Enterobacteriaceae (*11*)], *Bacteroides fragilis* toxin (Bft) produced by enterotoxigenic *B. fragilis*, and cytolethal distending toxin (CDT) produced by several ε- and γ-proteobacteria. Colibactin has emerged as a molecule of interest in colorectal carcinogenesis, given the detection of pks$^+$ *E. coli* in human colorectal cancers and the ability of colibactin-expressing *E. coli* to potentiate intestinal tumorigenesis in mice (*12*, *13*). Accumulating data also support a role for enterotoxigenic *B. fragilis* in both human and animal models of colon tumors (*14*–*17*). Both colibactin and CDT can cause double-stranded DNA damage in mammalian cells (*18*). In contrast, Bft acts indirectly by eliciting high levels of reactive oxygen species (ROS), which in turn damage host DNA (*19*). Chronically high ROS levels can outpace a host's DNA repair mechanisms, leading to DNA damage and mutations (Fig. 2).

Beyond damaging DNA, several microbes possess proteins that engage host pathways involved in carcinogenesis. The Wnt/β-catenin signaling pathway, which regulates cell stemness, polarity, and growth (*20*), is one example and is altered in many malignancies. Several cancer-associated bacteria also can influence β-catenin signaling (Fig. 2). Oncogenic type 1 strains of *Helicobacter pylori* express a protein called CagA, which is injected directly into the cytoplasm of host cells and aberrantly modulates β-catenin to drive gastric cancer (*8*). CagA-mediated β-catenin activation leads to up-regulation of genes involved in cellular proliferation, survival, and migration, as well as angiogenesis—all processes central to carcinogenesis. *Fusobacterium nucleatum* is a member of the oral microbiota and is associated with human colorectal adenomas and adenocarcinomas and amplified intestinal tumorigenesis in mice (*21*–*24*). *F. nucleatum* expresses FadA, a bacterial cell surface adhesion component that binds host E-cadherin, leading to β-catenin activation (*25*). Enterotoxigenic *B. fragilis*, which is enriched in some human colorectal cancers (*14*), can stimulate E-cadherin cleavage via Btf, leading to β-catenin activation (*26*). *Salmonella typhi* strains that maintain chronic infections secrete AvrA, which can activate epithelial β-catenin signaling (*27*, *28*), and are associated with hepatobiliary cancers (*29*–*31*).

Fig. 1. The path from health to solid tumor malignancies at mucosal sites and the microbiota's contribution. Human body surfaces are subject to constant environmental insult and injury. Infections, trauma, dietary factors, and germline mutations can contribute to breach of the body's mucosal barriers. In most individuals, barrier breaches are rapidly repaired and tissue homeostasis is restored. Impaired host or microbial resiliency contributes to persistent barrier breach and a failure to restore homeostasis. In these settings, the microbiota may influence carcinogenesis by (i) altering host cell proliferation and death, (ii) perturbing immune system function, and (iii) influencing metabolism within a host.

This phenomenon of activating β-catenin signaling reflects an interesting convergence of evolution, as several of these bacteria are normal constituents of the human microbiota. Although microbial engagement of β-catenin signaling may reflect a drive to establish a niche in a new tissue site, the presence of these cancer-potentiating microbes and their access to E-cadherin in evolving tumors demonstrate that a loss of appropriate boundaries and barrier maintenance between host and microbe is a critical step in the development of some tumors (Figs. 1 and 2).

The immune system, microbes, microbiota, and cancer

Mucosal surface barriers permit host-microbial symbiosis (*32*); they are susceptible to constant environmental insult and must rapidly repair to reestablish homeostasis. Compromised resiliency of the host or microbiota can place tissues on a path to malignancy. Cancer and inflammatory disorders can arise when barriers break down and microbes and immune systems find themselves in geographies and assemblages for which they have not coevolved. Once barriers are breached, microbes can further influence immune responses in evolving tumor microenvironments by eliciting proinflammatory or immunosuppressive programs (Fig. 2).

Proinflammatory responses can be procarcinogenic

Both the chronic, high-grade inflammation of inflammatory disorders (e.g., inflammatory bowel disease) and the lower-grade smoldering inflammation of malignancies and obesity drive a tumor-permissive milieu. Inflammatory factors such as reactive oxygen and nitrogen species, cytokines, and chemokines can contribute to tumor growth and spread (Fig. 2). Data from human tissues and animal models show that tumors can up-regulate and activate many pattern recognition receptors, including Toll-like receptors (*3*, *8*). Activation of these receptors results in feedforward loops of activation of NF-κB, a master regulator of cancer-associated inflammation (*33*) (Fig. 2). Numerous cancer-associated microbes appear to activate NF-κB signaling within the tumor microenvironment [e.g., the colon cancer–associated *F. nucleatum* (*23*)]. The activation of NF-κB by *F. nucleatum* may be the result of pattern recognition receptor engagement (*10*, *34*–*37*) or FadA engagement of E-cadherin (*25*). Other pattern recognition receptors, such as the nucleotide-binding oligomerization domain–like receptor (NLR) family members NOD-2, NLRP3, NLRP6, and NLRP12, may play a role in mediating colorectal cancer; mice deficient in these NLRs display an enhanced susceptibility to colitis-associated colorectal cancer (caCRC) (*38*–*44*).

Engagement of the immune system within the tumor microenvironment is not restricted to the innate immune system. Once barriers are breached and the innate immune system is activated, subsequent adaptive immune responses ensue, often with deleterious consequence for

tumor progression. The interleukin-23 (IL-23)–IL-17 axis (*45*), tumor necrosis factor–α (TNF-α)–TNF receptor signaling (*3, 5, 6, 46*), IL-6–IL-6 family member signaling (*46, 47*), and STAT3 activation (*48, 49*)—an output of these cytokine-mediated signaling pathways—all represent innate and adaptive pathways contributing to tumor progression and growth (Fig. 2).

The microbiota is responsive and adapts to changes in its host, such as inflammation. Adaptation to new selective pressures may result in a microbiota at a tissue site that is not well suited for barrier repair, immune homeostasis, or maintenance of traditional host and microbe boundaries. Mouse models of caCRC furnish insight in this regard. One such model uses azoxymethane, a genotoxin, and dextran sodium sulfate, a colon barrier–disrupting agent. Either agent alone results in colon tumors in susceptible mouse strains; using them together accelerates tumorigenesis. Although this model does not recapitulate the molecular and environmental events that lead to caCRC, it provides an opportunity to study the convergence of an environmental genotoxin, barrier disruption, and severe chronic inflammation on cancer development.

Microbiota transfer studies in caCRC models support the idea that perturbations to a host immune system, either by genetic deletion or genotoxin coupled with inflammatory stimulus, may select for microbiotas enriched for bacterial clades adept at attaching to host surfaces, invading host tissue, or triggering host inflammatory mediators (*21, 22, 40, 50, 51*). Fecal microbiota from *Nod2*- or *Nlrp6*-deficient mice acquire features that enhance the susceptibility of wild-type mice to caCRC (*40, 44*). In mice, the gut microbiota modulate colon tumorigenesis, independent of genetic deficiencies. When germ-free mice were colonized with microbes

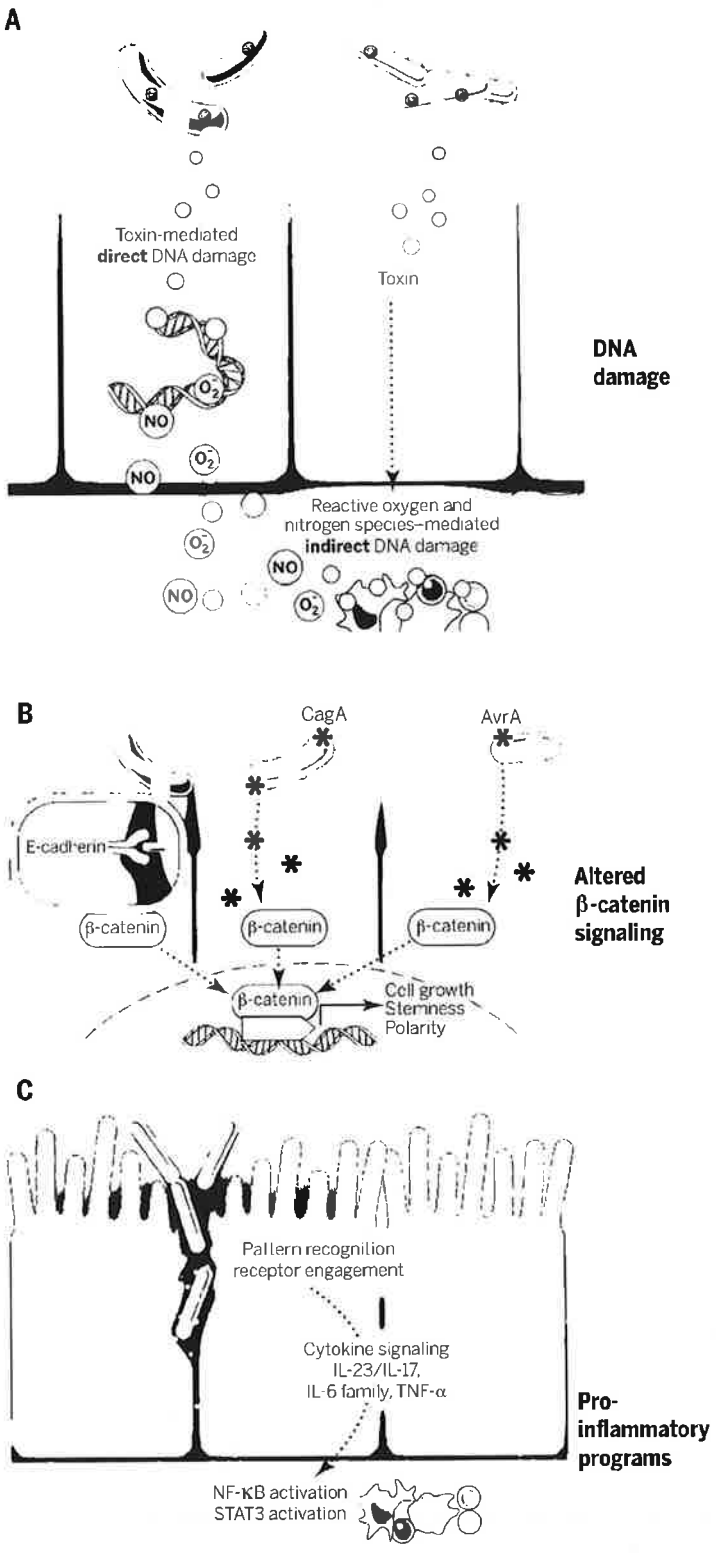

Fig. 2. Mechanisms by which microbes influence cancer development and progression. (**A**) Bacterial toxins can directly damage host DNA. Bacteria also damage DNA indirectly via host-produced reactive oxygen and nitrogen species. When DNA damage exceeds host cell repair capacity, cell death or cancer-enabling mutations occur. (**B**) β-Catenin signaling alterations are a frequent target of cancer-associated microbes. Some microbes bind E-cadherin on colonic epithelial cells, with altered polarity or within a disrupted barrier, and trigger β-catenin activation. Other microbes inject effectors (e.g., CagA or AvrA) that activate β-catenin signaling, resulting in dysregulated cell growth, acquisition of stem cell–like qualities, and loss of cell polarity. (**C**) Pro-inflammatory pathways are engaged upon mucosal barrier breach in an evolving tumor. Loss of boundaries between host and microbe engages pattern recognition receptors and their signaling cascades. Feedforward loops of chronic inflammation mediated by NF-κB and STAT3 signaling fuel carcinogenesis within both transforming and non-neoplastic cells within the tumors.

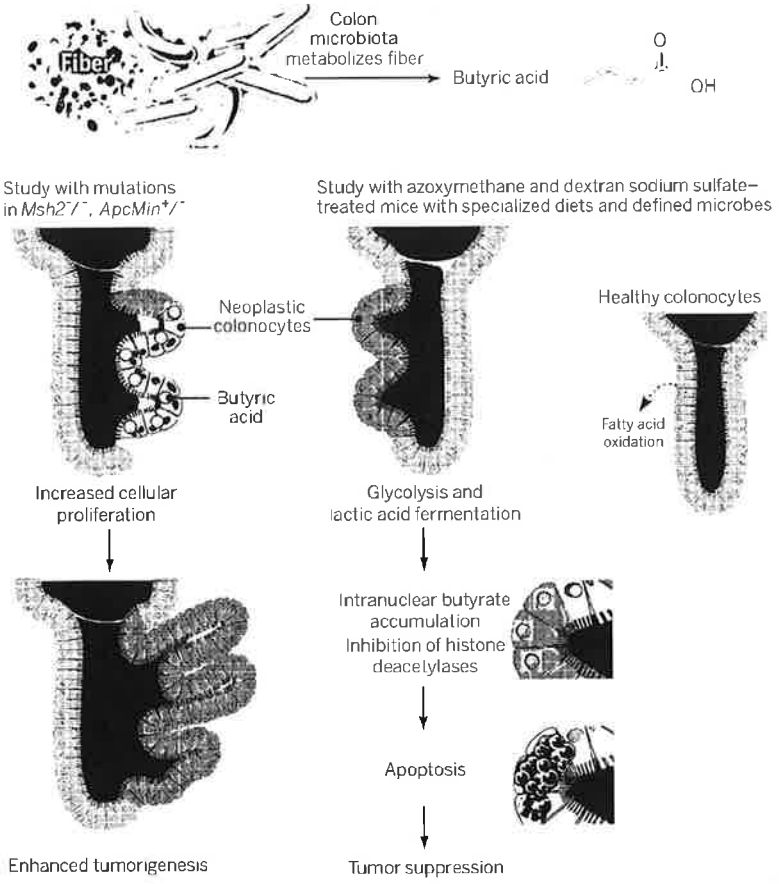

Fig. 3. Dietary fiber, microbiota, butyrate, and tumorigenesis. Metabolism of fiber by colonic microbes results in generation of butyric acid. When genetic mutations in *Msh2* and *Apc* are present, butyrate increases cell proliferation and enhances tumorigenesis. Data from another model of colorectal carcinogenesis indicate the opposite outcome: Neoplastic colonocytes engage in glycolysis for cellular energy, unlike healthy colonocytes (which favor fatty acid oxidation). As a result, butyrate accumulates in the nucleus of neoplastic cells, engaging tumor-suppressive pathways and apoptosis.

from donors with or without caCRC, followed by treatments that induced caCRC, those recipients that received gut microbiomes from caCRC-bearing mice developed more tumors (*51*). Similar mouse experiments using fecal transfers from humans with colon cancer suggest that there are microbiome structures, both protective and risk-elevating, that influence tumorigenesis (*52*).

Inflammation also results in the generation of respiratory electron acceptors such as nitrate, ethanolamine, and tetrathionate, which some bacterial clades can use for their own fitness advantage (*53*–*59*). Several bacteria (e.g., *E. coli* and *Salmonella* spp.) can use these electron acceptors and also possess the key features that reinforce the chronic inflammatory programs that can enhance cancer growth and spread. However, it remains to be determined whether bacterial use of these electron acceptors enhances cancer growth.

Immune-dampening responses can be cancer-permissive

Microbes not only trigger and reinforce proinflammatory immune circuits but also exploit or elicit immunosuppressive responses. A microbe may take advantage of preexisting immunosuppression or elicit immune-dampening responses to avoid destruction. Chronic systemic immunosuppression, as seen with advanced HIV infection, increases the risk for many cancers, especially virally associated malignancies. Microbial-elicited immunosuppression can also contribute to impaired antitumor immunity. Most current cancer-directed immunotherapies are focused on rousing immune responsiveness to tumors (*60*). The colon cancer–associated bacterium *F. nucleatum* may directly inhibit antitumor immunity by engaging TIGIT, a receptor with immunoglobulin and ITIM domains expressed on some T cells and natural killer cells, and blocking its ability to kill tumor cells (*61*). Whether microbes contribute to immunotherapeutic resistance in other cancers remains to be investigated.

Interrogating the role of microbes and microbiotas in cancer with new and old technologies

Microbiota studies in cancer remain at an early stage. Information gathering and descriptive studies are still necessary, and many critical questions remain. What other mechanisms might microbes use to influence tumorigenesis? If single microbes can compromise antitumor immunity or enhance susceptibility to oncomicrobes, are there configurations of the microbiota that do this, too (or are protective)? Are there microbes or microbiotas that enhance responsiveness to immunotherapies or other therapeutic interventions? To answer these questions, it is important to identify the key next steps in understanding how the human microbiota affects tumor growth and spread.

Sequencing-based technologies are a boon to both cancer biology and microbiology. Cancer genomes and their functional analyses have led to the implementation of precision medicine approaches to cancer care. Efforts to sequence individual microbes and human microbiomes are providing insight into how they influence human health and disease. Computational tools that identify microbial data within human sequencing data sets are welcome new additions to the armamentarium of cancer microbe hunters (*62*, *63*).

Despite the affordable price of sequencing, advances in culture techniques (*64*–*66*), and high-throughput analysis pipelines, the path of cancer microbiome discovery is fraught with pitfalls. Cancers may develop over decades, and different microbes and microbiotas may participate at distinct stages of the neoplastic process. For many malignancies, by the time a cancer is detected, the window of opportunity for identifying the inciting microbial agent(s) may have passed, allowing these organisms to remain elusive. However, the microbiota should remain a focus of study in locally advanced and metastatic cancer, as microbes may contribute to an established cancer's continued growth and spread.

Beyond sequencing, microscopy and flow cytometry–based approaches are useful tools to detect and study tumor-associated microbiotas. Human colon tumors may harbor specific consortia of bacteria that assemble themselves into biofilms (*17*). These biofilms appear to be specific to certain biogeographies within the gastrointestinal tract and have members that have been associated with colorectal adenomas and adenocarcinomas in human and mouse studies (e.g., enterotoxigenic *B. fragilis* and *F. nucleatum*). Microbiological studies of the oral cavity have shed light on microbial biofilms and their roles in human health and disease (*67*, *68*).

Within biofilms, microbial cross-feeding and co-metabolism occur (*69*). Consortia of tumor-associated microbes have the potential to generate metabolites that require collective microbial metabolism, and these co-metabolites may contribute to or halt carcinogenesis. The role of microbial metabolism in host physiology is an exciting area, with several recent studies re-examining the role of microbial metabolites in cancer (*4*, *70*).

Microbes, metabolism, and cancer

In 1956, Warburg put forth the hypothesis that altered cellular metabolism is the root cause of carcinogenesis (*71*), and cancer cell metabolism is currently a promising therapeutic target (*72*). Microbes participate in a range of host metabolic activities. Microbial metabolites or co-metabolites (generated with contributions from both host and microbe) can contribute to inflammatory tone and can influence the balance of proliferation and cell death in tissues (*4*). Consideration of the effects of a microbiota's metabolism, and specifically microbial metabolites generated within the tumor microenvironment, on cancer growth and spread adds another therapeutic and diagnostic angle for targeting cancers through metabolic alterations.

A meal fit/unfit for a tumor: Fiber and fats

What defines a microbial oncometabolite (*73*), and how are such metabolites generated? Both the host and its microbes affect the metabolism of dietary fiber, fats, ethanol, and phytoestrogens. As with microbes, metabolites can affect immune cell function, barrier function, and cell proliferation and death. Metabolites generated from dietary fiber and fats that have an established effect on cancer are considered below, along with recent insights.

Intestinal fermentation of dietary fiber by members of the colonic microbiota results in the generation of several short-chain fatty acids (SCFAs) including acetic, propionic, and butyric acids. These SCFAs have a range of effects on many cell types, including anti-inflammatory effects on myeloid cells (*74*) and colonic regulatory T cells (*75*–*77*), with consequences for intratumoral inflammation. SCFA's effects may be tuned by the receptors that they bind (e.g., Niacr1/Gpr109a, Gpr43, Gpr41, or Olfr78). Gpr109a is a receptor for niacin and butyrate. It plays an important role in mediating the effects of dietary fiber and the microbiota in the colon, where it is expressed by both colonic epithelial cells and intestinal myeloid cells. Activation of Gpr109a by butyrate results in anti-inflammatory host responses in myeloid cells that lead to regulatory T cell generation, and loss of *Gpr109a* increases susceptibility to caCRC (*78*).

SCFAs also affect host gene expression patterns, cell proliferation, and cell death via both receptor-mediated and receptor-independent mechanisms. SCFAs and their activation of Gpr43 reduce the proliferation rate of leukemia cells (*79*). In a study of ~70 human colon adenocarcinomas, *GPR43* expression was reduced in cancer versus healthy tissue; restoration of *GPR43* in a human colon cancer line increased apoptotic cell death upon SCFA exposure (*80*).

SCFAs' effects on host cellular processes vary according to concentration and host genotype. Two recent mouse studies, which arrived at different conclusions regarding the relationship of dietary fiber, the microbiota, and butyrate to colorectal tumorigenesis, reflect this heterogeneous response to SCFAs (Fig. 3). Dietary fiber and butyrate-producing bacteria suppressed tumors in mice that harbored strictly defined microbial communities, received specialized diets, and were treated with azoxymethane and dextran sodium sulfate (*81*). This study's data supported a model wherein the glycolytic metabolism of cancer cells resulted in reduced metabolism of butyrate and enhanced butyrate nuclear accumulation. High intranuclear butyrate levels increased histone acetylation and led to increased apoptosis and reduced cellular proliferation. In a mouse model of intestinal tumorigenesis driven by mutations in both the *Apc* gene and the mismatch repair gene *Msh2*, the microbiota and butyrate had tumor-promoting effects (*82*). Butyrate's principal effect in this model system was to drive a hyperproliferative response in *Msh2*-deficient epithelial cells. Cancer genetics and butyrate concentrations were critical factors in SCFAs' disparate effects on tumorigenesis between these studies. These studies underscore the challenges of translating microbiome, diet, and cancer basic science data into consensus guidelines for dietary interventions to reduce cancer risk. Given that a single microbial metabolite can mediate a range of effects in tumor models, investigators will require additional experimental systems to unravel the effects of the human-microbial meta-metabolome for health and cancer susceptibility.

In contrast with the conflicting basic science and epidemiological data surrounding dietary fiber (*83*), there is consensus that high saturated fat intake heightens cancer risk. Debate surrounding a high-fat diet (HFD) focuses on several mechanisms that may act alone or in combination, involving obesity, the microbiome, bile acids, and inflammation. There are a myriad of studies exploring the interconnection between obesity and malignancy (*84*–*86*). Obesity is now regarded as an inflammatory state (*87*), and we are learning more about the gut microbiome's contribution to obese and lean states (*88*, *89*). Data support the idea that inflammation, the microbiota, and obesity constitute an inseparable trio that fuels cancer. However, a recent study suggests otherwise. In a mouse model of duodenal hyperplasia, adenomas, and invasive cancer driven by *k-ras* mutation, HFD and microbial dysbiosis amplified tumor growth and spread in the absence of obesity or the development of a robust proinflammatory response (*90*); mutated *k-ras* modulated Paneth

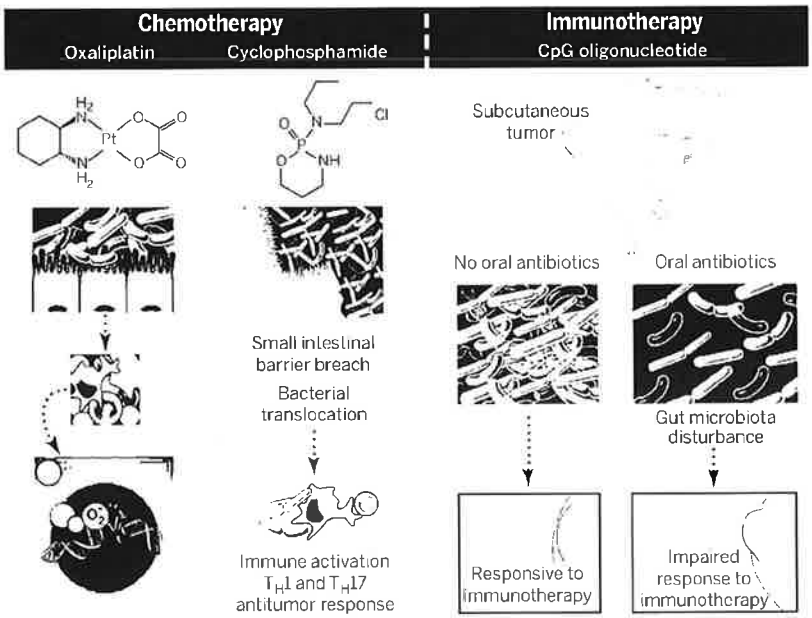

Fig. 4. How the microbiota modulate chemotherapy and immunotherapy efficacy in mouse models. The gut microbiota stimulate immune cells to produce reactive oxygen species (ROS). ROS enhance DNA damage caused by oxaliplatin, blocking DNA replication and transcription and resulting in cell death. Cyclophosphamide can cause small intestinal barrier breach. This barrier disruption results in bacterial translocation that potentiates antitumor T_H1 and T_H17 responses. CpG oligonucleotides are a microbial-associated molecular pattern and are used in immunotherapy. Antibiotic disruption of the gut microbiota in mice compromised the efficacy of CpG in a mouse subcutaneous tumor model.

cell antimicrobial expression and HFD affected intestinal mucin expression, thereby altering the intestinal microbiota. The fecal microbiota of HFD *k-ras* mutant mice was sufficient to transmit the cancer-potentiating effects of the HFD when transferred to antibiotic-treated *k-ras* mutant mice.

Another mechanism by which HFD influences cancer risk is via bile acids that are produced to solubilize and digest the consumed fats—specifically, the microbially generated secondary bile acids. The role of secondary bile acids in increased or decreased cancer risk has been studied for decades (*2*). One recent study provided new insight into deoxycholic acid's prooncogenic mechanisms in liver cancer: HFD or genetic susceptibility to obesity can increase deoxycholic acid–mediated activation of a mitogenic and proinflammatory response program in hepatic stellate cells, thereby potentiating liver cancer in mice (*91*). These studies reinforce the importance of gene-environment interactions in carcinogenesis and underscore the need to consider how dietary patterns influence the genomes and genomic outputs of both host and microbiome in mitigating or amplifying cancer risk.

Drugs, bugs, and cancer

The gut microbiota function in drug metabolism, influencing toxicity and efficacy (*92*, *93*). Because chemotherapeutic agents have a narrow therapeutic window, there is interest in the microbiota's modulation of chemotherapy toxicity and efficacy (Fig. 4). Irinotecan is a topoisomerase-1 inhibitor that is used in combination with other chemotherapies to treat several cancers. A common side effect is diarrhea. For some patients, the severity of the diarrhea requires hospitalization. Microbial-produced β-glucuronidases regulate levels of irinotecan's bioactive form within the intestinal lumen and thus influence irinotecan's toxicity (*94*). Oral bacterial β-glucuronidase inhibitors blunt the dose-limiting toxicities of irinotecan in mice and do not harm host cells or kill bacteria, which suggests that microbial metabolism is a plausible target in cancer care (*95*).

The gut microbiota also affect the efficacy of chemotherapy. Oxaliplatin is a platinum-based chemotherapy used to treat several gastrointestinal malignancies. Together, the microbiota and immune system contribute to oxaliplatin's efficacy (*96*). The gut microbiota prime myeloid cells for high-level ROS production. The resultant intratumoral oxidative stress augments oxaliplatin-associated DNA damage, triggering cancer cell death (*96*). Cyclophosphamide, an alkylating agent used in hematologic malignancies and solid tumors, can injure the small intestinal epithelium. The ensuing barrier breach results in gut microbiota–dependent, T helper (T_H) cell-mediated antitumor responses (*97*). Delineating the roles of gut microbiota in response to chemotherapy in model systems and undertaking epidemiologic studies with microbiome analysis in patients with and at risk for cancer will be critical for realizing the microbiota as an adjuvant therapy that enhances efficacy or attenuates toxicity of chemotherapies.

The microbiota and immunotherapy: Friend or foe?

The success of immunotherapy (in the form of cytokine therapy, targeting immune checkpoint blockade, and vaccine therapy) has been one of the most exciting developments in cancer care over the past decade (*98*). Given the intertwined nature of the microbiota and the immune system, it is plausible that the microbiota influence a host's responsiveness to immunotherapy. In support of this idea, antibiotic-mediated disruption of the microbiota in mice bearing subcutaneous tumors impaired the effectiveness of CpG oligonucleotide immunotherapy (Fig. 4) (*96*). Observations that immunotherapies are showing efficacy in melanoma and bladder, renal, and lung cancer but not in cancer of the colon (which is densely populated by bacteria) fuel interest in how the microbiota contributes to immunotherapy's efficacy. Furthermore, given the severe colitis observed in some patients receiving immunotherapies (*99*) (e.g., antibodies to CTLA4 and PD-L1) and the role of gut microbes in colitis, it is possible that the gut microbiota influences this toxicity. As patient populations expand, investigators will hopefully interrogate whether there are microbiota that are predictive for colitis and other toxicities. Examining the microbiota and its effects on immunotherapy efficacy and toxicity in preclinical models and patients is a critical next step.

Hematopoietic transplants, complications, and the microbiota

Allogeneic hematopoietic stem cell transplant (allo-HSCT), a mainstay in hematologic malignancy treatment, is a challenge to both host and microbiota. An individual's microbiota is confronted with a new host within its host as well as chemotherapy, radiation, oral and gastrointestinal barrier breach, and broad-spectrum antibiotics. Studies have begun to examine perturbations to the gut microbiota and clinical outcomes during allo-HSCT (*100*).

Bacteremia, *Clostridium difficile* infection, and graft-versus-host disease (GVHD) are common events in allo-HSCT patients. Bacteremias with vancomycin-resistant *Enterococcus* (VRE) are a grave concern. Two preclinical studies examining how antibiotics perturb the gut microbiota to enable VRE displacement of a healthy microbiota (*101*) and how the anaerobic bacteria *Barnesiella* spp. may confer resistance to VRE (*102*) have provided mechanistic insight into these bloodstream infections. These studies set the stage for a clinical study showing that enterococcal gut microbiota domination was associated with a factor of 9 higher risk of VRE bacteremia in allo-HSCT patients (*103*). Hospitalized patients and allo-HSCT patients both confront toxigenic *C. difficile* infection. Using mouse models, microbiome analysis, and allo-HSCT patient populations, researchers identified a microbe that can restore bile acid–mediated resistance to *C. difficile* (*104*). The workflows of this precision medicine–based study are applicable to many diseases associated with altered microbiotas.

Allo-HSCT patients can experience gastrointestinal, pulmonary, and skin complications after transplant; some of these are idiopathic clinical syndromes while others are GVHD manifestations. Using shotgun DNA sequencing of colon tissue and the PathSeq pipeline, investigators found that *Bradyrhizobium enterica* was enriched in affected colonic tissue from patients with idiopathic colitis after receiving a cord blood transplant (*105*), providing insight and a potential treatment. Using samples from mice and humans that had undergone allogeneic bone marrow transplants, investigators characterized the gut microbiota changes in active intestinal GVHD (*106*). In mice, depletion of lactobacilli exacerbated GVHD-associated intestinal inflammation and their reintroduction attenuated inflammation (*106*). The challenge intrinsic to these studies, and realized in (*104*), is to use our evolving knowledge of the microbiome and microbes to identify bacteriotherapy for cancer and its complications.

Back to the future: Perspectives and directions for cancer bacteriotherapy

The genesis of immunotherapy came from an appreciation for the co-adaptation between host and microbe. Exploiting this knowledge and using bacteria to trigger the immune system to attack and destroy cancers dates back to the 1850s, when several German physicians noticed that some cancer patients with active infections showed signs of tumor regression. This led Coley to test bacterial extracts in patients with bone cancers around 1900. Heat-killed cultures of *Streptococcus pyogenes* and *Serratia marcescens*, or Coley's toxins, were one of earliest forms of immunotherapy (*60*). Since this seminal work, one bacterium has entered the mainstream of cancer treatment. For the past three to four decades, Bacillus Calmette-Guerin (BCG) has been used to treat non–muscle-invasive bladder cancer. The live bacteria, which are delivered directly into the bladder, elicit inflammation that triggers an antitumor immune response (*107*). Much still remains to be learned about the immune response to BCG and antitumor immunity, and why BCG loses efficacy once the cancer is more invasive (*108*).

Over the past 30 years, several bacterial-based approaches to cancer therapy have emerged. Bacterial-based vaccines that express tumor antigens have shown efficacy in preclinical studies, and recombinant *Listeria monocytogenes*–based vaccines showed tremendous promise in mice (*109*). Interest remains in using bacteria as a delivery vehicle for plant toxins, such as ricin and saporin, or pseudomonal exotoxins that can block protein synthesis and induce apoptosis in cancer cells (*110*). Bacteria have evolved elegant systems to communicate with each other, to kill one another (*111*), and to deliver their

effectors into host cells (*112*). The extension and application of these secretion systems, which have been honed by millennia of evolution, seems like a therapeutic slam dunk but has been challenging in practice. A recent study in dogs (*113*) has breathed new life into the concept of bacteriotherapy with *Clostridium novyi*, which emerged as a promising concept in preclinical models almost 15 years ago (*114*); however, balancing toxicity with efficacy remains difficult.

Synthetic biology approaches to cancer care hold enormous potential, especially those that make use of bacteria. These efforts involve the reengineering of bacterial cells for the delivery of biomolecules under tunable networks and on/off toggle switches triggered by host responses (*115*). The goals are simple: to target cancers and minimize damage to healthy tissues via genetic network designs informed by engineering principles. Proof of concept that designer microbes can invade cancer cells (*116*) to target and perturb key cancer pathways has been established (*117*). Evaluation in robust preclinical models will be the next step. Application and design for cancer care will need to focus on maximizing anticancer responses while minimizing toxicities and infectious complications.

Like synthetic biology, microbiome studies have emerged as a promising area of investigation for cancer care over the past decade. The microbiome may afford many answers to several looming questions in cancer biology: What are the critical gene-environmental interactions in cancer susceptibility? Why do certain foods or dietary patterns confer increased or decreased risk in certain populations and individuals? Why do chemotherapies, immunotherapies, and preventive agents fail or succeed for patients, irrespective of host germline or cancer genotype? The microbiome seems to provide many potential answers in the forms of select clades, consortia, metabolites, and enzymatic activities, but it remains unclear whether and how these will translate from preclinical models to humans. One opportunity for the microbiota in the near term is as a biomarker for diagnosis (*118*), prognostication, or identifying those most at risk for treatment-related complications. Although there may be dissent about the best next steps, there is consensus that therapeutic consideration of cancer and the microbiota requires a multidisciplinary approach and more intensive investigation.

REFERENCES AND NOTES

1. C. de Martel *et al.*, *Lancet Oncol.* **13**, 607–615 (2012).
2. C. L. Sears, W. S. Garrett, *Cell Host Microbe* **15**, 317–328 (2014).
3. R. F. Schwabe, C. Jobin, *Nat. Rev. Cancer* **13**, 800–812 (2013).
4. P. Louis, G. L. Hold, H. J. Flint, *Nat. Rev. Microbiol.* **12**, 661–672 (2014).
5. E. Elinav *et al.*, *Nat. Rev. Cancer* **13**, 759–771 (2013).
6. T. Irrazábal, A. Belcheva, S. E. Girardin, A. Martin, D. J. Philpott, *Mol. Cell* **54**, 309–320 (2014).
7. J. Kallmeyer, R. Pockalny, R. R. Adhikari, D. C. Smith, S. D'Hondt, *Proc. Natl. Acad. Sci. U.S.A.* **109**, 16213–16216 (2012).
8. M. T. Agreu, R. M. Peek Jr., *Gastroenterology* **146**, 1534–1546.e3 (2014).
9. A. I. Ojesina *et al.*, *Nature* **506**, 371–375 (2014).
10. J.-P. Nougayrede *et al.*, *Science* **313**, 848–851 (2006).
11. J. Putze *et al.*, *Infect. Immun.* **77**, 4696–4703 (2009).
12. J. C. Arthur *et al.*, *Nat. Commun.* **5**, 4724 (2014).
13. J. C. Arthur *et al.*, *Science* **338**, 120–123 (2012).
14. A. Boleij *et al.*, *Clin. Infect. Dis.* **60**, 208–215 (2015).
15. C. L. Sears *et al.*, *Clin. Infect. Dis.* **47**, 797–803 (2008).
16. S. Wu *et al.*, *Nat. Med.* **15**, 1016–1022 (2009).
17. C. M. Dejea *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **111**, 18321–18326 (2014).
18. L. Guerra, R. Guidi, T. Frisan, *FEBS J.* **278**, 4577–4588 (2011).
19. A. C. Goodwin *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **108**, 15354–15359 (2011).
20. H. Clevers, R. Nusse, *Cell* **149**, 1192–1205 (2012).
21. M. Castellarin *et al.*, *Genome Res.* **22**, 299–306 (2012).
22. A. D. Kostic *et al.*, *Genome Res.* **22**, 292–298 (2012).
23. A. D. Kostic *et al.*, *Cell Host Microbe* **14**, 207–215 (2013).
24. A. N. McCoy *et al.*, *PLOS ONE* **8**, e53653 (2013).
25. M. R. Rubinstein *et al.*, *Cell Host Microbe* **14**, 195–206 (2013).
26. C. L. Sears, *Clin. Microbiol. Rev.* **22**, 349–369 (2009).
27. R. Lu *et al.*, *Oncogenesis* **3**, e105 (2014).
28. R. Lu *et al.*, *Am. J. Physiol. Gastrointest. Liver Physiol.* **303**, G1113–G1125 (2012).
29. U. Dutta, P. K. Garg, R. Kumar, R. K. Tandon, *Am. J. Gastroenterol.* **95**, 784–787 (2000).
30. E. C. Lazcano-Ponce *et al.*, *CA Cancer J. Clin.* **51**, 349–364 (2001).
31. I. I. Wistuba, A. F. Gazdar, *Nat. Rev. Cancer* **4**, 695–706 (2004).
32. L. V. Hooper, D. R. Littman, A. J. Macpherson, *Science* **336**, 1268–1273 (2012).
33. J. A. DiDonato, F. Mercurio, M. Karin, *Immunol. Rev.* **246**, 379–400 (2012).
34. G. Zhang, R. Chen, J. D. Rudney, *J. Periodontal Res.* **46**, 558–567 (2011).
35. M. R. Milward *et al.*, *Clin. Exp. Immunol.* **148**, 307–324 (2007).
36. E. Allen-Vercoe, J. Strauss, K. Chadee, *Gut Microbes* **2**, 294–298 (2011).
37. S.-R. Park *et al.*, *Infect. Immun.* **82**, 1914–1920 (2014).
38. I. C. Allen *et al.*, *J. Exp. Med.* **207**, 1045–1056 (2010).
39. G. Y. Chen, M. Liu, F. Wang, J. Bertin, G. Núñez, *J. Immunol.* **186**, 7187–7194 (2011).
40. B. Hu *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **110**, 9862–9867 (2013).
41. B. Hu *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **107**, 21635–21640 (2010).
42. M. H. Zaki, P. Vogel, M. Body-Malapel, M. Lamkanfi, T.-D. Kanneganti, *J. Immunol.* **185**, 4912–4920 (2010).
43. M. H. Zaki *et al.*, *Cancer Cell* **20**, 649–660 (2011).
44. A. Couturier-Maillard *et al.*, *J. Clin. Invest.* **123**, 700–711 (2013).
45. S. I. Grivennikov *et al.*, *Nature* **491**, 254–258 (2012).
46. S. I. Grivennikov, M. Karin, *Ann. Rheum. Dis.* **70** (suppl. 1), i104–i108 (2011).
47. S. I. Grivennikov, *Cancer Cell* **24**, 145–147 (2013).
48. H. Yu, D. Pardoll, R. Jove, *Nat. Rev. Cancer* **9**, 798–809 (2009).
49. N. Li, S. I. Grivennikov, M. Karin, *Cancer Cell* **19**, 429–431 (2011).
50. R. L. Warren *et al.*, *Microbiome* **1**, 16 (2013).
51. J. P. Zackular *et al.*, *MBio* **4**, e00692-13 (2013).
52. N. T. Baxter, J. P. Zackular, G. Y. Chen, P. D. Schloss, *Microbiome* **2**, 20 (2014).
53. F. Haber, A. J. Bäumler, *Immunol. Lett.* **162**, 48–53 (2014).
54. F. Rivera-Chávez *et al.*, *PLOS Pathog.* **9**, e1003267 (2013).
55. S. E. Winter, A. J. Bäumler, *Gut Microbes* **5**, 71–73 (2014).
56. S.-P. Nuccio, A. J. Bäumler, *MBio* **5**, e00929-14 (2014).
57. S. E. Winter *et al.*, *Science* **339**, 708–711 (2013).
58. P. Thiennimitr *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **108**, 17480–17485 (2011).
59. S. E. Winter *et al.*, *Nature* **467**, 426–429 (2010).
60. I. Mellman, G. Coukos, G. Dranoff, *Nature* **480**, 480–489 (2011).
61. C. Gur *et al.*, *Immunity* **42**, 344–355 (2015).
62. A. D. Kostic *et al.*, *Nat. Biotechnol.* **29**, 393–396 (2011).
63. D. R. Riley *et al.*, *PLOS Comput. Biol.* **9**, e1003107 (2013).
64. A. L. Goodman *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **108**, 6252–6257 (2011).
65. I. Vanwonterghem, P. D. Jensen, D. P. Ho, D. J. Batstone, G. W. Tyson, *Curr. Opin. Biotechnol.* **27**, 55–64 (2014).
66. M. V. Sizova *et al.*, *Appl. Environ. Microbiol.* **78**, 194–203 (2012).
67. C. J. Wright *et al.*, *Mol. Oral Microbiol.* **28**, 83–101 (2013).
68. M. A. Curtis, C. Zenobia, R. P. Darveau, *Cell Host Microbe* **10**, 302–306 (2011).
69. K. E. Boyle, S. Heilmann, D. van Ditmarsch, J. B. Xavier, *Curr. Opin. Microbiol.* **16**, 207–212 (2013).
70. R. Medzhitov, D. S. Schneider, M. P. Soares, *Science* **335**, 936–941 (2012).
71. O. Warburg, *Science* **123**, 309–314 (1956).
72. M. G. Vander Heiden, *Nat. Rev. Drug Discov.* **10**, 671–684 (2011).
73. S. J. Bultman, C. Jobin, *Cell Host Microbe* **16**, 143–145 (2014).
74. K. M. Maslowski *et al.*, *Nature* **461**, 1282–1286 (2009).
75. P. M. Smith *et al.*, *Science* **341**, 569–573 (2013).
76. N. Arpaia *et al.*, *Nature* **504**, 451–455 (2013).
77. Y. Furusawa *et al.*, *Nature* **504**, 446–450 (2013).
78. N. Singh *et al.*, *Immunity* **40**, 128–139 (2014).
79. L. B. Bindels *et al.*, *Br. J. Cancer* **107**, 1337–1344 (2012).
80. Y. Tang, Y. Chen, H. Jiang, G. T. Robbins, D. Nie, *Int. J. Cancer* **128**, 847–856 (2011).
81. D. R. Donohoe *et al.*, *Cancer Discov.* 10.1158/2159-8290.CD-14-0501 (2014).
82. A. Belcheva *et al.*, *Cell* **158**, 288–299 (2014).
83. M. Song, W. S. Garrett, A. T. Chan, *Gastroenterology* 10.1053/j.gastro.2014.12.035 (2015).
84. R. W. O'Rourke, *Surg. Obes. Relat. Dis.* **10**, 1208–1219 (2014).
85. J. Park, T. S. Morley, M. Kim, D. J. Clegg, P. E. Scherer, *Nat. Rev. Endocrinol.* **10**, 455–465 (2014).
86. N. A. Berger, *Ann. N.Y. Acad. Sci.* **1311**, 57–76 (2014).
87. M. F. Gregor, G. S. Hotamisligil, *Annu. Rev. Immunol.* **29**, 415–445 (2011).
88. R. E. Ley, *Curr. Opin. Gastroenterol.* **26**, 5–11 (2010).
89. P. J. Turnbaugh *et al.*, *Nature* **457**, 480–484 (2009).
90. M. D. Schulz *et al.*, *Nature* **514**, 508–512 (2014).
91. S. Yoshimoto *et al.*, *Nature* **499**, 97–101 (2013).
92. A. D. Patterson, P. J. Turnbaugh, *Cell Metab.* **20**, 761–768 (2014).
93. R. N. Carmody, P. J. Turnbaugh, *J. Clin. Invest.* **124**, 4173–4181 (2014).
94. A. B. Roberts, B. D. Wallace, M. K. Venkatesh, S. Mani, M. R. Redinbo, *Mol. Pharmacol.* **84**, 208–217 (2013).
95. B. D. Wallace *et al.*, *Science* **330**, 831–835 (2010).
96. N. Iida *et al.*, *Science* **342**, 967–970 (2013).
97. S. Viaud *et al.*, *Science* **342**, 971–976 (2013).
98. J. Couzin-Frankel, *Science* **342**, 1432–1433 (2013).
99. C. Gedye, A. van der Westhuizen, T. John, *Intern. Med. J.* 10.1111/imj.12653 (2014).
100. Y. Taur *et al.*, *Blood* **124**, 1174–1182 (2014).
101. C. Ubeda *et al.*, *J. Clin. Invest.* **120**, 4332–4341 (2010).
102. C. Ubeda *et al.*, *Infect. Immun.* **81**, 965–973 (2013).
103. Y. Taur *et al.*, *Clin. Infect. Dis.* **55**, 905–914 (2012).
104. C. G. Buffie *et al.*, *Nature* **517**, 205–208 (2015).
105. A. S. Bhatt *et al.*, *N. Engl. J. Med.* **369**, 517–528 (2013).
106. R. R. Jenq *et al.*, *J. Exp. Med.* **209**, 903–911 (2012).
107. M. A. Ingersoll, M. L. Albert, *Mucosal Immunol.* **6**, 1041–1053 (2013).
108. G. Rebeiman-Sidi, M. S. Glickman, B. H. Bochner *Nat. Rev. Urol.* **11**, 153–162 (2014).
109. Z. K. Pan, G. Ikonomicis, A. Lazenby, D. Pardoll, Y. Paterson, *Nat. Med.* **1**, 471–477 (1995).
110. N. Nair, T. Kasai, M. Seno, *Anticancer Res.* **34**, 6289–6296 (2014).
111. B. T. Ho, T. G. Dong, J. J. Mekalanos, *Cell Host Microbe* **15**, 9–21 (2014).
112. J. E. Galán, H. Wolf-Watz, *Nature* **444**, 567–573 (2006).
113. N. J. Roberts *et al.*, *Sci. Transl. Med.* **6**, 249ra111 (2014).
114. L. H. Dang, C. Bettegowda, D. L. Huso, K. W. Kinzler, B. Vogelstein, *Proc. Natl. Acad. Sci. U.S.A.* **98**, 15155–15160 (2001).
115. W. C. Ruder, T. Lu, J. J. Collins, *Science* **333**, 1248–1252 (2011).
116. J. C. Anderson, E. J. Clarke, A. P. Arkin, C. A. Voigt, *J. Mol. Biol.* **355**, 619–627 (2006).
117. S. Xiang, J. Fruehauf, C. J. Li, *Nat. Biotechnol.* **24**, 697–702 (2006).
118. J. P. Zackular, M. A. M. Rogers, M. T. Ruffin 4th, P. D. Schloss, *Cancer Prev. Res.* **7**, 1112–1121 (2014).

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10.1126/science.aaa4972

9. N. H. Segal *et al.*, *Cancer Res.* **68**, 889–892 (2008).
10. J. C. Castle *et al.*, *Cancer Res.* **72**, 1081–1091 (2012).
11. H. Matsushita *et al.*, *Nature* **482**, 400–404 (2012).
12. P. F. Robbins *et al.*, *Nat. Med.* **19**, 747–752 (2013).
13. N. van Rooij *et al.*, *J. Clin. Oncol.* **31**, e439–e442 (2013).
14. F. Duan *et al.*, *J. Exp. Med.* **211**, 2231–2248 (2014).
15. M. M. Gubin *et al.*, *Nature* **515**, 577–581 (2014).
16. C. Linnemann *et al.*, *Nat. Med.* **21**, 81–85 (2015).
17. Y. C. Lu *et al.*, *Clin. Cancer Res.* **20**, 3401–3410 (2014).
18. E. Tran *et al.*, *Science* **344**, 641–645 (2014).
19. D. A. Wick *et al.*, *Clin. Cancer Res.* **20**, 1125–1134 (2014).
20. M. Yadav *et al.*, *Nature* **515**, 572–576 (2014).
21. M. Rajasagi *et al.*, *Blood* **124**, 453–462 (2014).
22. N. A. Rizvi *et al.*, *Science* **348**, 124–128 (2015).
23. M. Gerlinger *et al.*, *N. Engl. J. Med.* **366**, 883–892 (2012).
24. M. M. van Buuren, J. J. Calis, T. N. Schumacher, *Oncoimmunology* **3**, e28836 (2014).
25. M. H. Fortier *et al.*, *J. Exp. Med.* **205**, 595–610 (2008).
26. E. F. Fritsch *et al.*, *Cancer Immunol. Res.* **2**, 522–529 (2014).
27. C. A. Van Bergen *et al.*, *Cancer Res.* **70**, 9073–9083 (2010).
28. J. J. A. Calis *et al.*, *PLOS Comput. Biol.* **9**, e1003266 (2013).
29. M. E. Dudley, D. C. Roopenian, *J. Exp. Med.* **184**, 441–447 (1996).
30. I. Wölfel *et al.*, *Science* **269**, 1281–1284 (1995).
31. T. Schumacher *et al.*, *Nature* **512**, 324–327 (2014).
32. C. M. Koebel *et al.*, *Nature* **450**, 903–907 (2007).
33. V. Shankaran *et al.*, *Nature* **410**, 1107–1111 (2001).
34. M. DuPage, C. Mazumdar, L. M. Schmidt, A. F. Cheung, T. Jacks, *Nature* **482**, 405–409 (2012).
35. M. S. Rooney, S. A. Shukla, C. J. Wu, G. Getz, N. Hacohen, *Cell* **160**, 48–61 (2015).
36. P. Kvistborg *et al.*, *Sci. Transl. Med.* **6**, 254ra128 (2014).
37. P. Kvistborg *et al.*, *Oncoimmunology* **1**, 409–418 (2012).
38. S. D. Brown *et al.*, *Genome Res.* **24**, 743–750 (2014).
39. A. Snyder *et al.*, *N. Engl. J. Med.* **371**, 2189–2199 (2014).
40. T. N. Schumacher, C. Kesmir, M. M. van Buuren, *Cancer Cell* **27**, 12–14 (2015).
41. D. S. Chen, I. Mellman, *Immunity* **39**, 1–10 (2013).
42. C. M. Cabrera *et al.*, *Tissue Antigens* **61**, 211–219 (2003).
43. L. A. Johnson *et al.*, *Blood* **114**, 535–546 (2009).
44. N. N. Hunder *et al.*, *N. Engl. J. Med.* **358**, 2698–2703 (2008).
45. P. F. Robbins *et al.*, *Clin. Cancer Res.* **21**, 1019–1027 (2015).
46. V. Boisgérin *et al.*, *Br. J. Cancer* **111**, 1469–1475 (2014).
47. E. F. Fritsch, N. Hacohen, C. J. Wu, *Oncoimmunology* **3**, e29311 (2014).
48. R. H. Vonderheide, K. L. Nathanson, *Nat. Med.* **19**, 1098–1100 (2013).
49. C. G. Joseph *et al.*, *Science* **343**, 152–157 (2014).
50. L. B. Alexandrov *et al.*, *Nature* **500**, 415–421 (2013).
51. S. A. Forbes *et al.*, *Nucleic Acids Res.* **43**, D805–D811 (2015).
52. P. A. Futreal *et al.*, *Nature Rev. Cancer* **4**, 177 (2004).

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REVIEWS

T cell exclusion, immune privilege, and the tumor microenvironment

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Effective immunotherapy promotes the killing of cancer cells by cytotoxic T cells. This requires not only that cancer-specific T cells be generated, but also that these T cells physically contact cancer cells. The coexistence in some patients of cancer cells and T cells that recognize them indicates that tumors may exhibit the phenomenon of immune privilege, in which immunogenic tissue is protected from immune attack. Here, we review the evidence that stromal cells of the tumor microenvironment mediate this restriction by excluding T cells from the vicinity of cancer cells. Overcoming this T cell checkpoint may thus enable optimal immunotherapy.

The microenvironment of tumors contains numerous cell types in addition to cancer cells, which include bone marrow–derived inflammatory cells, lymphocytes, blood vessels, fibroblastic cells, and the extracellular matrix composed of collagen and proteoglycans (*1*, *2*). The importance of a stromal microenvironment, especially one that has characteristics of a "wound" or regenerating tissue, has been recognized for at least a century (*3*), but its possible role in blunting an immune attack of cancer cells awaited the discovery of adaptive cellular immunity. In 1960, Klein and colleagues found that when mice developed primary methylcholanthrene-induced sarcomas, they also developed an antitumor immune response mediated by lymph node cells to a secondary challenge comprising cancer cells derived from the primary tumor (*4*). The paradoxical and critical finding of the study was that this anticancer immune response did not control the growth of the primary tumor, despite its ability to prevent the establishment of a secondary tumor comprising cancer cells derived from the primary tumor. In traditional immunological terminology, the primary tumor evaded immune control by establishing an immune-privileged microenvironment that is functionally analogous to that of certain normal tissues, such as the eye (*5*).

Unambiguous evidence for the inability in humans of a systemic immune response to eliminate immunogenic cancer cells was provided by Boon's studies 30 years later of the antigens that elicit specific $CD8^+$ T cell responses in melanoma patients (*6*). Cloned $CD8^-$ T cells from a melanoma patient were used to identify the antigen expressed by that patient's cancer: MAGE-A1. The explicit demonstration of the coexistence of a progressing melanoma with melanoma-specific T cells in this patient implicitly raised the question of why the T cells did not control the growth of the cancer. Immunoediting, or the elimination of immunogenic cancer cells (*7*), could be excluded, which left the possibility of immune suppression by the tumor microenvironment (TME). Despite this evidence that the presence of antigen-specific $CD8^-$ T cells alone may not be sufficient for the control of cancer, a major pharmaceutical company recently conducted phase III trials in patients with non–small cell lung cancer (NSCLC) of the clinical efficacy of vaccination with the MAGE-A3 antigen (MAGRIT, NCT00480025). The study did not meet its primary end point of extending disease-free survival and was discontinued in 2014. Moreover, Rosenberg and colleagues reported evidence of disease recurrence in melanoma patients despite very high levels of vaccine-induced circulating T cells and no evidence of antigen loss by the cancer cells (*8*).

The discovery of melanoma-specific T cells in patients led to another strategy to increase the frequency of cancer-specific T cells in patients, that of adoptively transferring large numbers of in vitro expanded tumor-infiltrating lymphocytes (TILs). As discussed elsewhere in this issue of *Science* (*9*), this approach has shown some efficacy, which has been of major importance to the field by serving as proof that the immune system has the potential to control cancer (*10*). However, adoptive T cell therapy (ACT) with TILs has not had the dramatic success of ACT with virus-specific $CD8^+$ T cells to immunodeficient bone marrow transplant recipients with cytomegalovirus infection (*11*) or Epstein-Barr virus–associated lymphoproliferative disorders (*12*). Differences in the microenvironments of virally infected tissues and cancers may account for these distinct outcomes, with the latter being immune-suppressive. Another important point of comparison is that the TME of solid cancers is likely to be fundamentally different to that of the leukemias, in which clinical trials of ACT with T cells expressing chimeric antigen receptors, so-called CAR T cells, have demonstrable efficacy (*9*). These findings raise the possibility that increasing the frequency of cancer-specific T cells, by whatever means, may be more effective if combined with an approach that alters the immune-suppressive TME.

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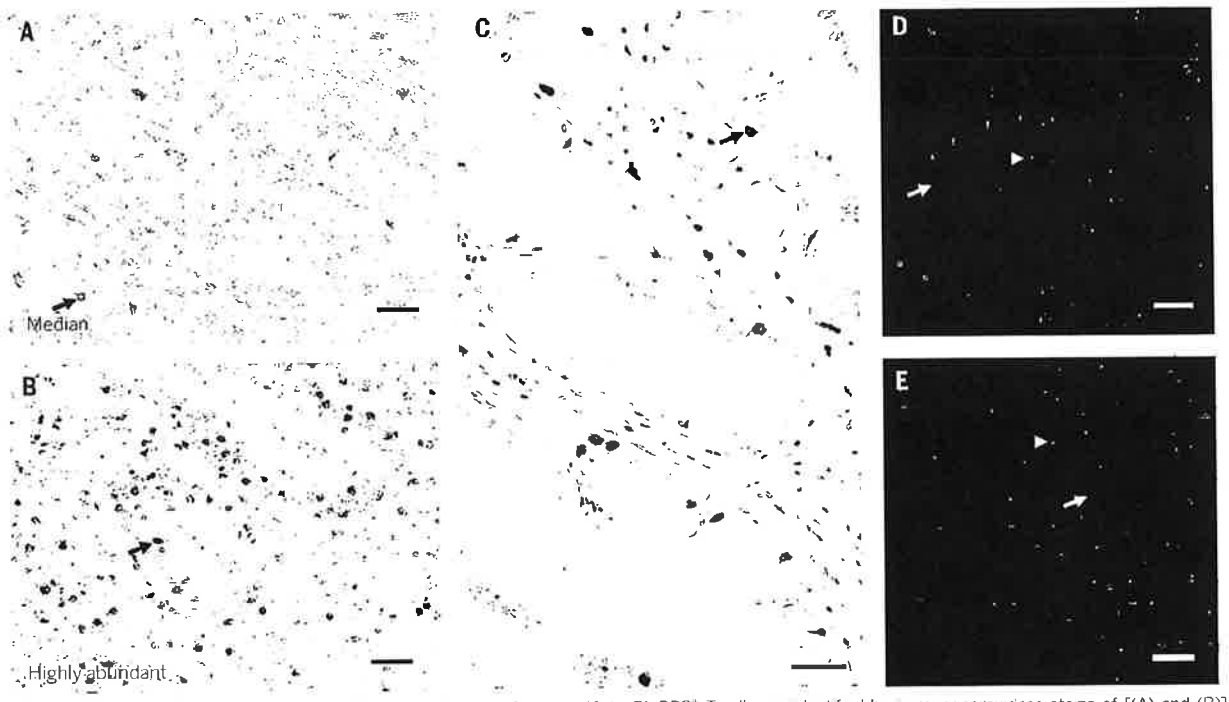

Fig. 1. Exclusion of T cells from human and mouse adenocarcinomas. (**A** to **C**) $CD3^+$ T cells are identified by immunoperoxidase stains of [(A) and (B)] human colorectal (*82*) and (C) human pancreatic ductal adenocarcinomas , demonstrating the presence of few [(A) and (C)] and many (B) intraductal T cells. (**D** and **E**) $CD3^+$ T cells and $p53^+$ cancer cells are identified by use of immunofluorescent stains of pancreatic ductal adenocarcinomas taken from (D) untreated mice and (E) mice that have been treated for 24 hours with the CXCR4 antagonist, AMD3100, demonstrating that T cell exclusion can be regulated by CXCR4 signaling (*29*). Scale bars, 50 μm. Arrows indicate examples of $CD3^+$ T cells, and arrowheads indicate examples of $p53^+$ cancer cells.

The more recent strategy of enhancing the function of effector T cells by targeting immunoregulatory membrane receptors has been successful in subsets of patients with melanoma, NSCLC, urothelial bladder cancer, and renal cell cancer (*13*–*18*). The therapeutic effect of blocking antibodies to the immune checkpoint regulators cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and the programmed cell death protein 1 (PD-1)/PD-L1 receptor-ligand pair is covered in detail elsewhere in this issue of *Science* (*19*), and we briefly discuss them here because these therapies relate to the TME. For example, in the mice, anti-CTLA-4 therapy leads to clearance from the tumor of $Foxp3^+$ regulatory T cells (T_{reg} cells) (*20*), which may impair the functions of effector T cells at that site (*21*). Cancer cells—as well as infiltrating monocytic cells, including dendritic cells (DCs) and macrophages—express PD-L1 (*16*, *17*, *22*, *23*), which suppresses the proliferative and effector responses of T cells by engaging the inhibitory PD-1 receptor on these cells. Nevertheless, it has become apparent that even if these T cell checkpoint antagonists overcome some of the immune-suppressive effects of the TME, there may be other, more fundamental inhibitory reactions in the TME to explain why most patients—especially those with microsatellite stable colorectal cancer (CRC), ovarian cancer, prostate cancer, and pancreatic ductal adenocarcinoma (PDA)—rarely exhibit objective responses to these therapies (*14*, *15*, *24*).

A clue to the nature of this dominant immune suppression mediated by the TME comes from studies that have examined the spatial relationship of $CD8^+$ effector T cells to cancer cells in three of the tumors that did not respond to anti-PD-1/anti-PD-L1: CRC, ovarian cancer, and PDA (Fig. 1). In 1998, the exclusion of $CD8^+$ T cells from the vicinity of cancer cells in CRC was shown to correlate with a poor long-term clinical outcome (*25*), an observation that was confirmed and extended by Galon and colleagues in 2006 (*26*). Exclusion of T cells from the vicinity of cancer cells was also found in ovarian cancer (*27*, *28*) and PDA (*29*). Thus, the tumor immunology field provided evidence more than 10 years ago that the TME can limit the capacity of T cells to accumulate among cancer cells. It is reasonable to conclude that until this problem is circumvented, the full potential of other approaches to T cell–mediated tumor immunotherapy, such as augmenting the numbers and function of cancer-specific T cells, may not be realized.

Fortunately, studies over the past several years have begun to explain how this form of immune suppression is mediated. Preclinical studies in mouse models of cancer now implicate the major stromal cell types of the TME, cancer-associated fibroblasts (CAFs) and myelomonocytic cells, including several subsets of cells within the general designation of myeloid-derived suppressor

Table 1. Myelomonocytic cells and CAFs control the accumulation of T cells.

TUMOR	TARGET	CELL TYPE AFFECTED BY THERAPEUTIC INTERVENTION	REFERENCE
B16 melanoma-GM-CSF	CCR2	Monocytes	(*30*)
PDA	GM-CSF	MDSCs	(*31*)
PDA	GM-CSF	MDSCs	(*32*)
Cervical, Breast	CSF-1R	Monocytes, TAMs	(*33*, *36*)
PDA	CXCR4	Likely T cells (CXCL12 is produced by CAFs)	(*29*)
PDA	CSF-1R	Monocytes, TAMs	(*34*)
Prostate	CSF-1R	Monocytes, TAMs	(*35*)

cells (MDSCs) and tumor-associated macrophages (TAMs), as being responsible for restricting the accumulation of T cells in the vicinity of cancer cells (*29*–*36*) (Table 1). As would be predicted, overcoming this restriction revealed the antitumor effects of a T cell checkpoint antagonist that had been ineffective when administered as monotherapy. Moreover, as will be discussed, the tumor vasculature also plays an active role in restricting T cell entry into the TME. Fortunately, for each immune suppressive element of the TME there are therapeutic entities that are potentially suitable for administration to patients.

Control by the TME of the extravasation of T cells from the circulatory system into tumors

After the priming of cancer-specific T cells in the lymph nodes that drain the tumor, these T cells traffic via the circulatory system to the tumor. Studies have shown that the TME may regulate the accumulation of T cells in tumors at the initial step of their interaction with local blood vessels. Given that many other immune cells that compose the TME are nonetheless able to extravasate from the circulation (*1*), there must be means by which these distinct cell types are differentially recruited into the tumor. One mechanism for cellular discrimination comes from the release of chemokines that preferentially recruit certain immune cell types over others. Another is the capacity of the TME to posttranslationally alter chemokines. For example, the production of reactive nitrogen species by MDSCs within the TME induces nitration of CCL2 (N-CCL2), which

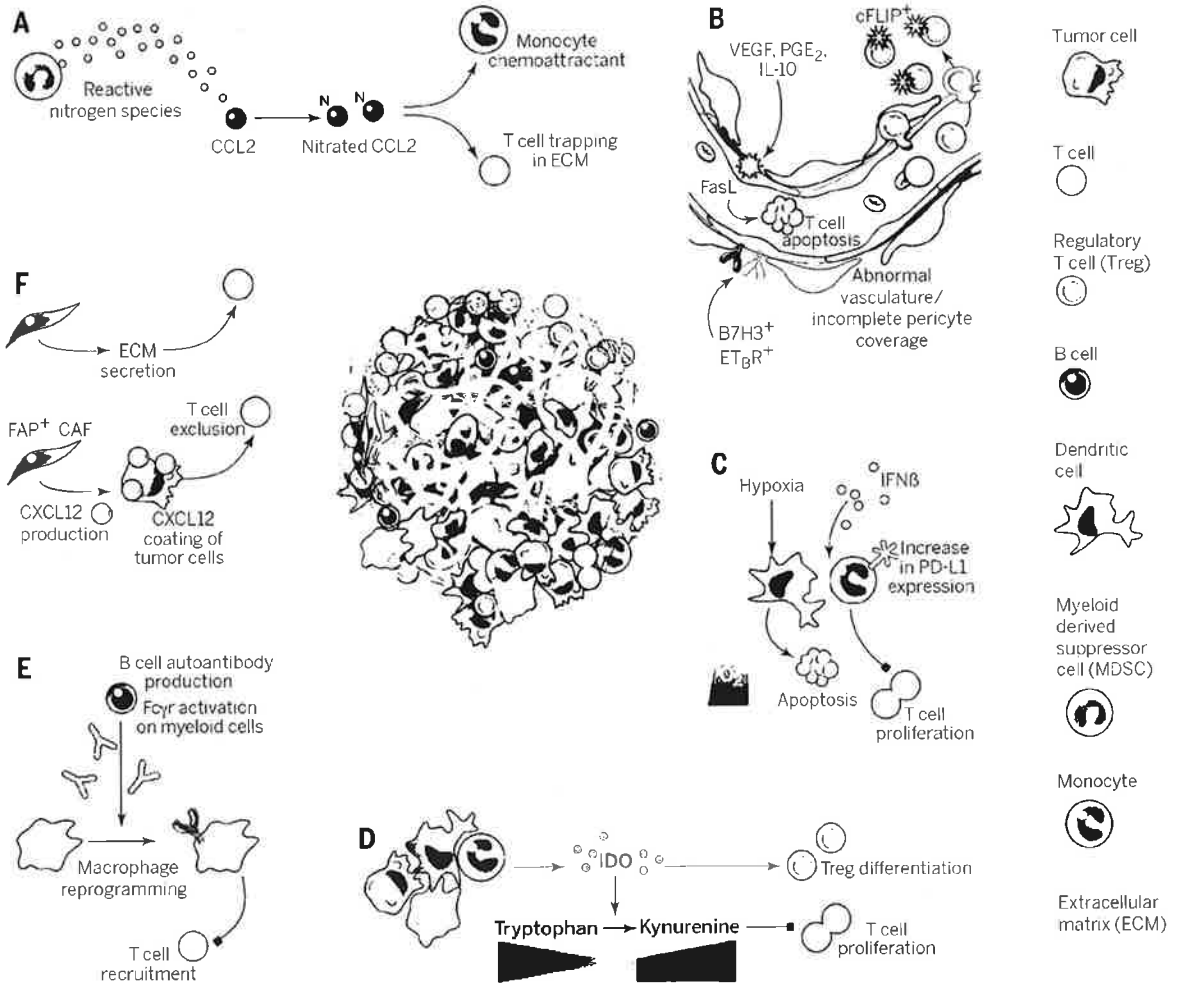

Fig. 2. Mechanisms of TME-driven immune suppression. A plethora of noncancerous cells in the TME regulate the infiltration, accumulation, and proliferation of T cells in tumors, with representative examples shown here. (**A**) T cell recruitment can be blocked by nitration of the chemokine CCL2, resulting in T cell trapping in the stroma. (**B**) The tumor vasculature plays a complex role in preferential recruitment of other immune cells over T cells, in part through endothelial cell (EC)–specific expression of FasL, ET_BR, and B7H3. (**C**) PD-L1 expression can be up-regulated in myelomonocytic cells, in addition to tumor cells, and is driven in part by hypoxic conditions in the TME and the production of cytokines, such as IFNβ. (**D**) The aberrant production of metabolites in the TME, such as the pathway regulated by IDO, can result in a multitude of effects directly on T cell functions and indirectly via other cells such as T_{reg} cells. (**E**) B cells can regulate the phenotype of TAMs resulting in suppression of CD8 cells. (**F**) Cancer-associated fibroblasts (CAFs) have multiple functions in the TME, in part through extracellular matrix (ECM)–mediated T cell trapping and CXCL12-regulated T cell exclusion.

results in the trapping of T cells in the stroma that surrounds tumor cells of human colon and prostate cancers (Fig. 2A) (*37*). In contrast, N-CCL2 still attracts monocytes, potentially contributing to the differential recruitment of these distinct immune cell types in vivo. Inhibitors of CCL2 nitration enhanced the accumulation of TILs in the corresponding animal models and resulted in improved efficacy of ACT.

Even if the appropriate chemotactic signals for the extravasation and recruitment to the tumor of T cells are present, the vasculature can override their effects and actively exclude T cells (Fig. 2B), a function that may distinguish between the effector T cells and other leukocyte populations, such as T_{reg} cells and myeloid cells. Insights into the mechanism of how this might occur have come from studies comparing T cell–rich and T cell–poor tumors. These studies revealed that the apoptosis inducer Fas ligand (FasL) is expressed in the tumor vasculature of multiple tumor types, including ovarian, colon, prostate, breast, bladder, and renal cancer (*38*). In tumors with high levels of endothelial FasL, there are few $CD8^+$ T cells but abundant T_{reg} cells, which may be protected against FasL-mediated killing by their relatively high expression of the apoptosis inhibitor, c-FLIP. Accordingly, in preclinical models FasL inhibition resulted in a substantial increase in the influx of tumor-rejecting T cells relative to T_{reg} cells, which led to T cell–dependent tumor suppression. FasL expression itself is induced by the TME-derived immunosuppressive factors vascular endothelial growth factor (VEGF), prostaglandin E_2 (PGE_2), and interleukin-10 (IL-10), suggesting that multiple

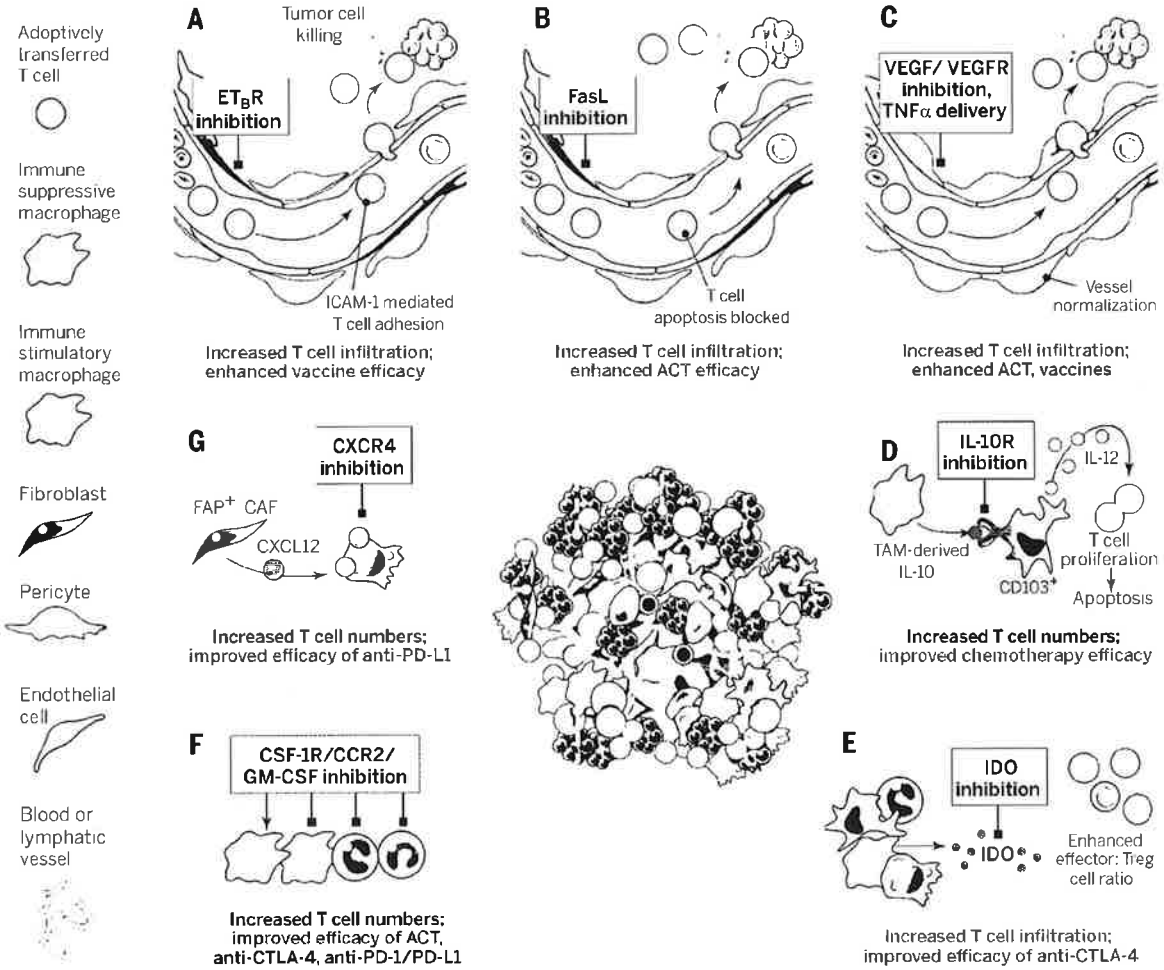

Fig. 3. Therapeutic strategies to overcome immune suppression in the TME. A number of vascular-targeted therapies result in increased T cell infiltration and improved efficacy of different immunotherapies such as adoptive cell therapy and anticancer vaccines. These include (**A**) ET_BR inhibition, (**B**) FasL inhibition, and (**C**) VEGF/VEGFR/TNFα inhibition. (**D**) Dendritic cells (DCs) can have opposing functions in the TME, either supporting or suppressing tumor development. $CD103^+$ DCs have an immune stimulatory function, resulting in IL-12 secretion and T cell replication when the immune-suppressive cytokine receptor IL-10R is inhibited. (**E**) IDO inhibition has multiple effects on TILs, including augmenting T cell expansion and preventing their differentiation into T_{reg} cells. (**F**) Various myelomonocytic cells suppress T cell numbers and/or functions; this suppression can be relieved by inhibition of a number of cytokine signaling pathways indicated here, resulting in depletion or reeducation of these cells in the TME. Further information is provided in Table 1. (**G**) Inhibition of CXCL12/ CXCR4 downstream of FAP^+ CAFs in the TME leads to T cell accumulation and increased efficacy of anti-PD-L1 therapy.

networks of cellular interactions may converge to establish immune tolerance. In ovarian cancer elevated VEGF levels, and expression of the immune regulatory ligand B7H3 (CD276), or the endothelin B receptor (ET_BR) on tumor vessels correlates with decreased T cell infiltration and worse clinical outcome (*27*, *39*, *40*). Pharmacological inhibition of ET_BR increased T cell adhesion to endothelial cells in an intercellular adhesion molecule-1 (ICAM-1)–dependent manner, resulting in significantly enhanced TIL numbers in mice and a corresponding tumor response to an otherwise ineffective anticancer vaccine (Fig. 3A) (*40*). Similarly, FasL inhibition also improves the efficacy of ACT (Fig. 3B) (*38*). The improved efficacy of these distinct TME-directed immunotherapies was not as a consequence of a more effective systemic antitumor immune response but could be attributed to increased effector T cell infiltration into tumors.

Attention has also been focused on anti-angiogenic therapies as a potential means to enhance the efficacy of immunotherapy (*41*). Anti-angiogenic inhibitors targeting VEGF and its receptor VEGFR2, which are approved for clinical use in multiple cancers (*42*), induce vascular normalization. This, in turn, increases TILs and improves the efficacy of ACT and cancer vaccines in preclinical models (Fig. 3C) (*43*, *44*). In relation to the next section of this Review, VEGF impairs the maturation of DCs (*45*), so that anti-VEGF therapy has an additional means by which it could enhance intratumoral immune responses. Further support for the importance of vascular normalization has come from the finding that deleting the regulator of G-protein signaling, Rgs5 (*46*), reduced vessel leakiness and hypoxia, enhanced T cell infiltration into mouse pancreatic neuroendocrine tumors, and prolonged animal survival. Therefore, from an immunotherapeutic perspective, vascular normalization is likely to be more efficacious than anti-angiogenic therapies that result in vessel destruction, as exemplified by the differential effects of delivering the pro-inflammatory cytokines interferon-γ (IFN-γ) versus tumor necrosis factor-α (TNF-α). Only targeted delivery of the latter, which was reported to normalize tumor blood vessels and increase $CD8^+$ T cell infiltration, enhanced vaccine and ACT therapies (Fig. 3C) (*47*, *48*).

TME-mediated regulation of the local replication of T cells within tumors

The extravasation of cancer-specific T cells into the tumor is a necessary, but not sufficient, step in the immune control of cancer. For effective immune killing of cancer cells, these T cells must also locally replicate to further increase their frequency, avoid being killed themselves by hostile elements of the TME, and overcome barriers that restrict their distribution to the stroma and away from cancer cells. The TME affects all three of these intratumoral T cell responses.

Although the site of the self-renewing T cells that are clonally expanding in response to cancer cell-associated antigens is likely to be the draining lymph nodes, the enrichment of cancer-specific effector T cells within the tumor relative to their frequency in the periphery indicates that replication of effector T cells within the tumor also occurs. Findings in preclinical models suggest that the TME may be the major site of clonal expansion of cancer-specific T cells (*49*, *50*), and that the $CD8^+$ T cell replicative response at this site is orchestrated by the $CD103^+$, Batf3-dependent DC, which can efficiently cross-present cancer cell antigens (*51*, *52*). The dependence of T cell–mediated tumor regression on the intratumoral presence of $CD103^+$ DCs suggests that therapeutic interventions that enhance their numbers or capacity for driving T cell replication in the TME may contribute to tumor control. Among such strategies are antibodies to the IL-10R, which in a mouse model of mammary carcinoma neutralized the effects of IL-10 produced by TAMs, relieved the suppression of IL-12 production by intratumoral DCs, and improved the $CD8^+$ T cell–dependent antitumor effects of chemotherapy (Fig. 3D) (*53*). A similar outcome was achieved by neutralizing CSF-1, which impaired the intratumoral accumulation of TAMs (*32*, *33*). Yet another strategy is the administration of antibody-IFN-β complexes, targeted against oncogenic receptors, such as EGFR, that activate intratumoral DCs for cross-presentation of antigen to $CD8^+$ T cells (*54*). Tumor eradication resulted when PD-L1, which also was induced by IFN-β acting on DCs, was neutralized, demonstrating the recurring theme in the immune system that activating stimuli prompt compensatory inhibitory responses. DC function also may be adversely affected by the hypoxic conditions characteristic of the TME, which induces PD-L1 expression on DCs and other myelomonocytic cells (Fig. 2C) as a result of HIF-1α binding directly to a hypoxia-responsive element in the PD-L1 promoter (*55*). Even the aerobic glycolysis of cancer cells may antagonize local immune reactions via its increased production of lactate, which induces the M2 polarization of TAMs (*56*). An M1 to M2 phenotypic transition of intratumoral macrophages has also been reported after the induction of cancer cell apoptosis in human and mouse gastrointestinal stromal tumors by the administration of the KIT oncoprotein inhibitor, imatinib (*57*). It should be noted that the designation of M1 and M2 polarization states undoubtedly represent an oversimplification of the complexity of macrophage biology (*58*) and that at least six different TAM subpopulations have been reported (*59*). Therefore, descriptors of TAM phenotypes in the TME are likely to be most informative in investigating and therapeutically targeting these cells.

In addition to altering T cell replication indirectly via effects on myeloid cells, the TME may directly impair intratumoral T cell proliferation. Indole 2,3-dioxygenase (IDO)—which can be expressed by DCs, MDSCs, and cancer cells—catabolizes tryptophan and generates kynurenine (Fig. 2D). Both the deprivation of tryptophan and the generation of its metabolic product inhibit clonal expansion (*60*, *61*). IDO also promotes the conversion of naïve T cells to T_{reg} cells and increases IL-6 expression, which augments MDSC functions (*62*). Accordingly, IDO1 genetic deficiency is associated with reduced tumor burden and metastasis and enhanced survival in mouse models of lung and breast cancer (*62*). The therapeutic potential of inhibiting IDO, in combination with the T cell checkpoint antagonist anti-CTLA-4, has been demonstrated in the B16 melanoma model and was associated with increased accumulation of intratumoral T cells (Fig. 3E) (*63*). Last, the capacity of IDO to block the reprogramming of T_{reg} cells to helperlike cells by suppressing the loss of the transcription factor Eos, and the corresponding transcriptional program it regulates, exemplifies another means by which this enzyme promotes immune suppression within the TME (*64*).

Control by the TME of the viability of T cells within tumors

The TME can also limit the viability of T cells. Both IDO and PD-L1 not only may impair the intratumoral proliferation of effector T cells but may also induce apoptosis of these cells. Products of myelomonocytic cells that cause the apoptosis of T cells include FasL, TNF-α, and TNF-related apoptosis inducing ligand (TRAIL). In addition to these known effectors of death, previously unidentified pathways that control the viability of intratumoral T cells may be discovered by innovative, unbiased approaches. For example, an in vivo, pooled short hairpin RNA screen identified Ppp2r2d as a key regulator promoting T cell apoptosis and suppressing T cell proliferation within the TME (*65*).

Interventions that target intratumoral TAMs and MDSCs can also lead to reduced tumor burdens in preclinical models, in both T cell–dependent and T cell–independent ways. For instance, inhibiting chemokine receptor type 2 (CCR2) (*30*), colony-stimulating factor-1 receptor (CSF-1R) (*33*, *34*, *36*), and granulocyte macrophage colony-stimulating factor (GM-CSF) (*31*, *32*) in preclinical models of melanoma, pancreatic, breast, and prostatic carcinoma increased intratumoral T cells and controlled tumor growth, especially when combined with anti-CTLA-4 or anti-PD-1/PD-L1 (Table 1 and Fig. 3F). Although these studies did not determine whether the increases in T cells were a consequence of enhanced viability or replication, they emphasize again how elements of the TME regulate the accumulation of effector T cells. Inhibition of CSF-1R in a preclinical model of proneural glioblastoma multiforme and in patient-derived glioma xenografts increased survival and caused regression of established tumors in an apparent T cell–independent manner that correlated with the reprogramming of macrophages away from an M2 phenotype (*66*). Similarly, an activator of TAMs, an agonistic antibody to CD40, when administered in combination with the chemotherapeutic drug gemcitabine, suppressed the growth of mouse PDA in a T cell–independent manner (*67*), suggesting that macrophages alone, when appropriately stimulated, may have potent anticancer functions. B cells have also been shown to regulate the phenotype of TAMs in the squamous cell carcinoma TME (Fig. 2E) (*68*). Correspondingly, B cell depletion reprogrammed TAMs, thus relieving their suppression of CD8 cells and enhancing chemotherapy efficacy. Another example

of how the antitumor effects of macrophages can be used therapeutically is an autochthonous mouse model of melanoma in which the melanoma-killing capability of these cells was revealed by depleting T_{reg} cells and neutralizing IL-10 (*69*). TAMs would also be the mediators of the antitumor effects of antibodies (*70*) and genetically engineered ligands (*71*) that interact with CD47 on cancer cells to prevent the CD47/signal regulatory protein-α (SIRPα) signaling system from suppressing the phagocytosis of antibody-coated cancer cells.

The TME regulates spatial distribution of T cells within tumors

Increased numbers of intratumoral, cancer-specific T cells will be of little import if T cells are restricted to the stroma and prevented from accumulating in the vicinity of cancer cells. CAFs, which may be identified by their expression of the membrane protein fibroblast activation protein-α (FAP), have been shown to have two means by which they can mediate this restriction, the first of which is a physical exclusion mediated by the extracellular matrix that they produce (Fig. 2F). Live cell imaging of lung tumor tissue slices from patients revealed active T cell motility in regions of loose fibronectin and collagen, whereas T cells migrated poorly in dense matrix areas surrounding tumor nests (*72*). When either collagenase was added to reduce matrix rigidity, or the chemokine CCL5 was experimentally produced by tumor cells, there was increased T cell movement out of the stromal regions and into contact with cancer cells.

The second means by which FAP^+ CAFs exclude T cells involves their biosynthesis of CXCL12 (Fig. 2F). Conditionally depleting these cells from the stroma of an ectopic, transplanted tumor (*73*) and of an autochthonous PDA (*29*) allowed preexisting cancer-specific T cells to rapidly control tumor growth and revealed the antitumor effects of anti-PD-L1. However, depleting FAP^+ stromal cells is not a reasonable therapeutic option unless the depletion can be limited to the TME because these cells carry out essential functions in several normal tissues (*74*). The recent report of "reprogramming" these cells in the TME by administration of a vitamin D analog (*75*) may be one means of circumventing this problem. Another may be to block their immune suppressive mechanism. In a preclinical mouse model of PDA, FAP^- CAFs produce the chemokine CXCL12, which is bound by the PDA cancer cells, which had been previously reported for cancer cells in human PDA, CRC, and ovarian cancer (*76*–*78*). Because FAP^- stromal cells also accumulate in nontransformed, inflammatory lesions, this "coating" of cancer cells may reflect a means by which "injured" epithelial cells protect themselves from adaptive immune attack. Administering an inhibitor of CXCR4, the receptor for CXCL12, to the PDA-bearing mice caused the rapid accumulation of T cells among cancer cells, arrest of tumor growth, and tumor sensitivity to anti-PD-L1 (Fig. 3G) (*29*). How the cancer cell–bound CXCL12 excludes T cells has not yet been shown, although the mechanism must involve either T cells or myelomonocytic cells because they, and not cancer cells or FAP^+ CAFs, express CXCR4 in this model.

Conceptual challenges and therapeutic opportunities

Among the challenges that remain for understanding the immune suppressive roles of the TME, three are foremost: comprehending the mechanisms by which the TME excludes T cells, determining whether the TME of primary and metastatic tumor sites differ, and assessing the potential clinical efficacy of interventions that affect the TME. The preclinical studies in mice that showed that inhibiting CCR2, CSF-1/CSF-1R, GM-CSF, or CXCR4 improved immune control of tumor growth also showed that these interventions shared a capacity for increasing the frequency of T cells among cancer cells (Fig. 3). Because targeting CCR2 and CSF-1/CSF-1R diminishes the accumulation of CCR2-expressing cell types, including bone marrow–derived TAMs and DCs, one must conclude that at least one function of these cells is to suppress the accumulation of intratumoral T cells. However, given that these cells are distributed in both the stromal and cancer cell regions of tumors, it is not readily apparent how they can selectively exclude T cells only from the vicinity of the cancer cells. On the other hand, the distribution of intratumoral CXCL12, which is associated with cancer cells, does correlate, albeit inversely, with that of T cells, so that the hypothesis that CXCL12 is involved with T cell exclusion would be reasonable and is supported by the antitumor outcome of inhibiting CXCR4. Even here a mechanism that may account for this effect of CXCR4, other than T cell "repulsion" (*79*), is not apparent. For the moment, then, one may only suggest that because CSF1R- and CCR2-dependent cells and CXCR4 signaling are both required for the exclusion of T cells, they are elements of a single pathway that mediates this dominant immune suppressive process.

Regarding the TME of metastatic sites, most preclinical and clinical analyses to date have been restricted to primary tumors. It has been noted earlier that mice in which an immune response has been induced by growth of a primary methycholanthrene-induced sarcoma prevent the establishment of a secondary tumor by these sarcoma cells (*4*). In a preclinical model of spontaneous melanoma, cancer cells were found to disseminate early but to remain in a dormant state that was mediated, at least in part, by $CD8^+$ T cells (*81*). Consistent with this report of immune-induced metastatic dormancy is a study that found metastases in another mouse model that grew rapidly in association with the exclusion of $CD8^+$ T cells (*81*). A challenge will be to determine whether the immune-suppressive intensity of the TMEs of metastatic lesions may vary, with dormant metastases being dominated by immune control and growing lesions exhibiting immune suppression.

With respect to clinically assessing the effects of altering the TME for the purpose of increasing the frequency of intratumoral effector T cells, the academic oncologist already has several agents available that are specific for the same targets in humans that have regulated this process in mouse cancers: IDO inhibitors, CSF-1R inhibitors, CCR2-specific antibodies, and an inhibitor of CXCR4. Examples of each are already in clinical trials in human cancer patients, usually as monotherapies. There is an obvious rationale to combine those agents that are found to augment the intratumoral accumulation of effector T cells with therapies that improve the response of T cells to TCR ligation, such as antibodies to PD-1 and PD-L1, or increase the overall frequency of cancer-specific T cells, such as vaccines and ACT.

Last, recognition of the function of the TME in excluding T cells prompts an interest in the identity of the normal biological circumstance that is responsible for the development of this phenomenon. Tumor immunologists currently consider mutated genes to be the major source of antigens in cancer cells that T cells respond to, but some cancers that have a low mutational burden may elicit cancer-specific $CD8^+$ T cells, as exemplified by the mouse model of PDA (*29*). Is it possible that nontransformed epithelial cells in regenerating tissues also express immunogenic neoantigens, a circumstance that would select for an immune suppressive microenvironment? The frequent occurrence of the immune suppressive elements of the TME, myelomonocytic cells, and FAP^+ stromal fibroblasts in regenerating tissues is consistent with this conjecture and merits further investigation.

REFERENCES AND NOTES

1. D. F. Quail, J. A. Joyce, *Nat. Med.* **19**, 1423–1437 (2013).
2. D. Hanahan, L. M. Coussens, *Cancer Cell* **21**, 309–322 (2012).
3. F. S. Jones, P. Rous, *J. Exp. Med.* **20**, 404–412 (1914).
4. G. Klein, H. O. Sjogren, E. Klein, K. E. Hellstrom, *Cancer Res.* **20**, 1561–1572 (1960).
5. P. B. Medawar, *Br. J. Exp. Pathol.* **29**, 58–69 (1948).
6. P. van der Bruggen *et al.*, *Science* **254**, 1643–1647 (1991).
7. R. D. Schreiber, L. J. Old, M. J. Smyth, *Science* **331**, 1565–1570 (2011).
8. S. A. Rosenberg *et al.*, *J. Immunol.* **175**, 6169–6176 (2005).
9. S. A. Rosenberg, N. P. Restifo, *Science* **348**, 62–68 (2015).
10. S. A. Rosenberg *et al.*, *Clin. Cancer Res.* **17**, 4550–4557 (2011).
11. S. R. Riddell *et al.*, *Science* **257**, 238–241 (1992).
12. E. B. Papadopoulos *et al.*, *N. Engl. J. Med.* **330**, 1185–1191 (1994).
13. F. S. Hodi *et al.*, *N. Engl. J. Med.* **363**, 711–723 (2010).
14. J. R. Brahmer *et al.*, *N. Engl. J. Med.* **366**, 2455–2465 (2012).
15. S. L. Topalian *et al.*, *N. Engl. J. Med.* **366**, 2443–2454 (2012).
16. T. Powles *et al.*, *Nature* **515**, 558–562 (2014).
17. R. S. Herbst *et al.*, *Nature* **515**, 563–567 (2014).
18. P. C. Tumeh *et al.*, *Nature* **515**, 568–571 (2014).
19. P. Sharma, J. P. Allison, *Science* **348**, 56–61 (2015).
20. T. R. Simpson *et al.*, *J. Exp. Med.* **210**, 1695–1710 (2013).
21. S. Z. Josefowicz, L. F. Lu, A. Y. Rudensky, *Annu. Rev. Immunol.* **30**, 531–564 (2012).
22. T. Okazaki, S. Chikuma, Y. Iwai, S. Fagarasan, T. Honjo, *Nat. Immunol.* **14**, 1212–1218 (2013).
23. F. Wei *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **110**, E2480–E2489 (2013).
24. R. E. Royal *et al.*, *J. Immunother.* **33**, 828–833 (2010).
25. Y. Naito *et al.*, *Cancer Res.* **58**, 3491–3494 (1998).
26. J. Galon *et al.*, *Science* **313**, 1960–1964 (2006).
27. L. Zhang *et al.*, *N. Engl. J. Med.* **348**, 203–213 (2003).
28. E. Sato *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **102**, 18538–18543 (2005).
29. C. Feig *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **110**, 20212–20217 (2013).
30. A. M. Lesokhin *et al.*, *Cancer Res.* **72**, 876–886 (2012).

31. L. J. Bayne *et al.*, *Cancer Cell* **21**, 822–835 (2012).
32. Y. Pylayeva-Gupta, K. E. Lee, C. H. Hajdu, G. Miller, D. Bar-Sagi, *Cancer Cell* **21**, 836–847 (2012).
33. D. C. Strachan *et al.*, *OncoImmunology* **2**, e26968 (2013).
34. Y. Zhu *et al.*, *Cancer Res.* **74**, 5057–5069 (2014).
35. A. J. Garcia *et al.*, *Mol. Cell. Biol.* **34**, 2017–2028 (2014).
36. D. G. DeNardo *et al.*, *Cancer Discov.* **1**, 54–67 (2011).
37. B. Molon *et al.*, *J. Exp. Med.* **208**, 1949–1962 (2011).
38. G. T. Motz *et al.*, *Nat. Med.* **20**, 607–615 (2014).
39. X. Zang *et al.*, *Mod. Pathol.* **23**, 1104–1112 (2010).
40. R. J. Buckanovich *et al.*, *Nat. Med.* **14**, 28–36 (2008).
41. Y. Huang, S. Goel, D. G. Duda, D. Fukumura, R. K. Jain, *Cancer Res.* **73**, 2943–2948 (2013).
42. G. C. Jayson, D. J. Hicklin, L. M. Ellis, *Nat. Rev. Clin. Oncol.* **9**, 297–303 (2012).
43. R. K. Shrimali *et al.*, *Cancer Res.* **70**, 6171–6180 (2010).
44. Y. Huang *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **109**, 17561–17566 (2012).
45. D. I. Gabrilovich *et al.*, *Nat. Med.* **2**, 1096–1103 (1996).
46. J. Hamzah *et al.*, *Nature* **453**, 410–414 (2008).
47. A. Johansson, J. Hamzah, C. J. Payne, R. Ganss, *Proc. Natl. Acad. Sci. U.S.A.* **109**, 7841–7846 (2012).
48. A. Calcinotto *et al.*, *J. Immunol.* **188**, 2687–2694 (2012).
49. E. D. Thompson, H. L. Enriquez, Y. X. Fu, V. H. Engelhard, *J. Exp. Med.* **207**, 1791–1804 (2010).
50. Y. Ma *et al.*, *Cancer Res.* **74**, 436–445 (2014).
51. M. L. Broz *et al.*, *Cancer Cell* **26**, 638–652 (2014).
52. K. Hildner *et al.*, *Science* **322**, 1097–1100 (2008).
53. B. Ruffell *et al.*, *Cancer Cell* **26**, 623–637 (2014).
54. X. Yang *et al.*, *Cancer Cell* **25**, 37–48 (2014).
55. M. Z. Noman *et al.*, *J. Exp. Med.* **211**, 781–790 (2014).
56. O. R. Colegio *et al.*, *Nature* **513**, 559–563 (2014).
57. M. J. Cavnar *et al.*, *J. Exp. Med.* **210**, 2873–2886 (2013).
58. P. J. Murray *et al.*, *Immunity* **41**, 14–20 (2014).
59. B. Z. Qian, J. W. Pollard, *Cell* **141**, 39–51 (2010).
60. D. H. Munn, A. L. Mellor, *Trends Immunol.* **34**, 137–143 (2013).
61. M. Platten, W. Wick, B. J. Van den Eynde, *Cancer Res.* **72**, 5435–5440 (2012).
62. C. Smith *et al.*, *Cancer Discov.* **2**, 722–735 (2012).
63. R. B. Holmgaard, D. Zamarin, D. H. Munn, J. D. Wolchok, J. P. Allison, *J. Exp. Med.* **210**, 1389–1402 (2013).
64. M. D. Sharma *et al.*, *Immunity* **38**, 998–1012 (2013).
65. P. Zhou *et al.*, *Nature* **506**, 52–57 (2014).
66. S. M. Pyonteck *et al.*, *Nat. Med.* **19**, 1264–1272 (2013).
67. G. L. Beatty *et al.*, *Science* **331**, 1612–1616 (2011).
68. N. I. Affara *et al.*, *Cancer Cell* **25**, 809–821 (2014).
69. A. Pommier *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **110**, 13085–13090 (2013).
70. Y. Murata, T. Kotani, H. Ohnishi, T. Matozaki, *J. Biochem.* **155**, 335–344 (2014).
71. K. Weiskopf *et al.*, *Science* **341**, 88–91 (2013).
72. H. Salmon *et al.*, *J. Clin. Invest.* **122**, 899–910 (2012).
73. M. Kraman *et al.*, *Science* **330**, 827–830 (2010).
74. E. W. Roberts *et al.*, *J. Exp. Med.* **210**, 1137–1151 (2013).
75. M. H. Sherman *et al.*, *Cell* **159**, 80–93 (2014).
76. C. J. Scotton *et al.*, *Cancer Res.* **62**, 5930–5938 (2002).
77. J. J. Liang *et al.*, *Cancer Epidemiol. Biomarkers Prev.* **19**, 2598–2604 (2010).
78. Y. Akishima-Fukasawa *et al.*, *Am. J. Clin. Pathol.* **132**, 202–210, quiz 307 (2009).
79. M. C. Poznansky *et al.*, *Nat. Med.* **6**, 543–548 (2000).
80. J. Eyles *et al.*, *J. Clin. Invest.* **120**, 2030–2039 (2010).
81. J. Predina *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **110**, E415–E424 (2013).
82. T. Chiba *et al.*, *Br. J. Cancer* **91**, 1711–1717 (2004).

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REVIEWS

Cancer and the microbiota

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A host's microbiota may increase, diminish, or have no effect at all on cancer susceptibility. Assigning causal roles in cancer to specific microbes and microbiotas, unraveling host-microbiota interactions with environmental factors in carcinogenesis, and exploiting such knowledge for cancer diagnosis and treatment are areas of intensive interest. This Review considers how microbes and the microbiota may amplify or mitigate carcinogenesis, responsiveness to cancer therapeutics, and cancer-associated complications.

The relationship between cancer and microbes is complex. Although cancer is generally considered to be a disease of host genetics and environmental factors, microorganisms are implicated in ~20% of human malignancies (*1*). Microbes present at mucosal sites can become part of the tumor microenvironment of aerodigestive tract malignancies, and intratumoral microbes can affect cancer growth and spread in many ways (*2*–*6*). In counterpoise, the gut microbiota also functions in detoxification of dietary components, reducing inflammation, and maintaining a balance in host cell growth and proliferation. The possibility of microbe-based cancer therapeutics has attracted interest for more than 100 years, from Coley's toxins (one of the earliest forms of cancer bacteriotherapy) to the current era of synthetic biology's designer microbes and microbiota transplants. Thus, interrogation of the roles of microbes and the microbiota in cancer requires a holistic perspective.

The ways in which microbes and the microbiota contribute to carcinogenesis, whether by enhancing or diminishing a host's risk, fall into three broad categories: (i) altering the balance of host cell proliferation and death, (ii) guiding immune system function, and (iii) influencing metabolism of host-produced factors, ingested foodstuffs, and pharmaceuticals (Fig. 1). Assigning microbial communities, their members, and aggregate biomolecular activities into these categories will require a substantial research commitment. This Review discusses how microbes and the microbiota may contribute to cancer development and progression, responsiveness to cancer therapeutics, and cancer-associated complications.

Microbial contributions to carcinogenesis

Of the estimated 3.7×10^{30} microbes living on Earth (*7*), only 10 are designated by the International Agency for Cancer Research (IACR) as carcinogenic to humans (*1*). Although most of these carcinogenic microbes colonize large percentages of the human population, only a subset of affected individuals develop cancer, because host and microbial genotypes influence cancer susceptibility.

Tumors arising at boundary surfaces, such as the skin, oropharynx, and respiratory, digestive, and urogenital tracts, harbor a microbiota, which complicates cancer-microbe causality. Enrichment of a microbe at a tumor site does not connote that a microbe is directly associated, let alone causal, in disease. Rather, microbes may find a tumor's oxygen tension or carbon sources permissive and take advantage of an underused nutritional niche. Decreased abundances of specific microbes may also place a host at enhanced risk for cancer development at sites local or distant from this microbial shift. Thus, rigorous frameworks for interpreting tumor-associated microbiota data are essential (*2*).

Oncomicrobes, shifting the balance of when to die and when to grow

Bona fide oncomicrobes—microbes that trigger transformation events in host cells—are rare. Beyond the 10 IACR-designated microbes, there are a handful of other microorganisms with robust but fewer aggregate data supporting their role in human carcinogenesis. As many of these and their carcinogenic mechanisms have been recently reviewed (*2*–*6*, *8*), select activities representing common pathways by which microbes influence cancer will be highlighted.

Human oncoviruses can drive carcinogenesis by integrating oncogenes into host genomes. Human papillomaviruses (HPV) express oncoproteins such as E6 and E7. Data from recent genomic analyses of HPV$^+$ cervical cancers suggest that viral integration also selectively triggers amplification of host genes in pathways with established roles in cancer (*9*).

Microbes also drive transformation by affecting genomic stability, resistance to cell death, and proliferative signaling. Many bacteria have evolved mechanisms to damage DNA, so as to kill competitors and survive in the microbial world. Unfortunately, these bacterial defensive factors can lead to mutational events that contribute to carcinogenesis (Fig. 2). Examples include colibactin encoded by the *pks* locus [expressed by B2

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CANCER IMMUNOLOGY

Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer

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Immune checkpoint inhibitors, which unleash a patient's own T cells to kill tumors, are revolutionizing cancer treatment. To unravel the genomic determinants of response to this therapy, we used whole-exome sequencing of non–small cell lung cancers treated with pembrolizumab, an antibody targeting programmed cell death-1 (PD-1). In two independent cohorts, higher nonsynonymous mutation burden in tumors was associated with improved objective response, durable clinical benefit, and progression-free survival. Efficacy also correlated with the molecular smoking signature, higher neoantigen burden, and DNA repair pathway mutations; each factor was also associated with mutation burden. In one responder, neoantigen-specific CD8+ T cell responses paralleled tumor regression, suggesting that anti–PD-1 therapy enhances neoantigen-specific T cell reactivity. Our results suggest that the genomic landscape of lung cancers shapes response to anti–PD-1 therapy.

Today, more than a century since the initial observation that the immune system can reject human cancers (*1*), immune checkpoint inhibitors are demonstrating that adaptive immunity can be harnessed for the treatment of cancer (*2*–*7*). In advanced non–small cell lung cancer (NSCLC), therapies with an antibody targeting programmed cell death-1 (anti–PD-1) demonstrated response rates of 17 to 21%, with some responses being remarkably durable (*3*, *8*).

Understanding the molecular determinants of response to immunotherapies such as anti–PD-1 therapy is one of the critical challenges in oncology. Among the best responses have been in melanomas and NSCLCs, cancers largely caused by chronic exposure to mutagens [ultraviolet light (*9*) and carcinogens in cigarette smoke (*10*), respectively]. However, there is a large variability in mutation burden within tumor types, ranging from 10s to 1000s of mutations (*11*–*13*). This range is particularly broad in NSCLCs because tumors in never-smokers generally have few somatic mutations compared with tumors in smokers (*14*). We hypothesized that the mutational landscape of NSCLCs may influence response to anti–PD-1 therapy. To examine this hypothesis, we sequenced the exomes of NSCLCs from two independent cohorts of patients treated with pembrolizumab, a humanized immunoglobulin G (IgG) 4-kappa isotype antibody to PD-1 (n = 16 and n = 18, respectively), and their matched normal DNA (fig. S1 and table S1) (*15*).

Overall, tumor DNA sequencing generated mean target coverage of 164x, and a mean of 94.5% of the target sequence was covered to a depth of at least 10x; coverage and depth were similar between cohorts, as well as between those with or without clinical benefit (fig. S2). We identified a median of 200 nonsynonymous mutations per sample (range 11 to 1192). The median number of exonic mutations per sample was 327 (range 45 to 1732). The quantity and range of mutations were similar to published series of NSCLCs (*16*, *17*) (fig. S3). The transition/transversion ratio (Ti/Tv) was 0.74 (fig. S4), also similar to previously described NSCLCs (*16*–*18*). To ensure accuracy of our sequencing data, targeted resequencing with an orthogonal method (Ampliseq) was performed using 376 randomly selected variants, and mutations were confirmed in 357 of those variants (95%).

Higher somatic nonsynonymous mutation burden was associated with clinical efficacy of pembrolizumab. In the discovery cohort (n = 16), the median number of nonsynonymous mutations was 302 in patients with durable clinical benefit (DCB) (partial or stable response lasting >6 months) versus 148 with no durable benefit (NDB) (Mann-Whitney P = 0.02) (Fig. 1A). Seventy-three percent of patients with high nonsynonymous burden (defined as above the median burden of the cohort, 209) experienced DCB, compared with 13% of those with low mutation burden (below median) (Fisher's exact P = 0.04). Both confirmed objective response rate (ORR) and progression-free survival (PFS) were higher in patients with high nonsynonymous burden [ORR 63% versus 0%, Fisher's exact P = 0.03; median PFS 14.5 versus 3.7 months, log-rank P = 0.01; hazard ratio (HR) 0.19, 95% confidence interval (CI) 0.05 to 0.70] (Fig. 1B and table S2).

The validation cohort included an independent set of 18 NSCLC samples from patients treated with pembrolizumab. The clinical characteristics were similar in both cohorts. The median nonsynonymous mutation burden was 244 in tumors from patients with DCB compared to 125 in those with NDB (Mann-Whitney P = 0.04) (Fig. 1C). The rates of DCB and PFS were again significantly greater in patients with a nonsynonymous mutation burden above 200, the median of the validation cohort (DCB 83% versus 22%, Fisher's exact P = 0.04; median PFS not reached versus 3.4 months, log-rank P = 0.006; HR 0.15, 95% CI 0.04 to 0.59) (Fig. 1D and table S2).

In the discovery cohort, there was high concordance between nonsynonymous mutation burden and DCB, with an area under the receiver operator characteristic (ROC) curve (AUC) of 87% (Fig. 1E). Patients with nonsynonymous mutation burden ≥178, the cut point that combined maximal sensitivity with best specificity, had a likelihood ratio for DCB of 3.0; the sensitivity and specificity of DCB using this cut point was 100% (95% CI 59 to 100%) and 67% (29 to 93%), respectively. Applying this cut point to the validation cohort, the rate of DCB in patients with tumors harboring ≥178 mutations was 75% compared to 14% in those with <178, corresponding to a sensitivity of 86% and a specificity of 75%.

There were few but important exceptions. Five of 18 tumors with ≥178 nonsynonymous mutations had NDB, and one tumor with a very low burden (56 nonsynonymous mutations) responded to pembrolizumab. However, this response was transient, lasting 8 months. Across both cohorts, this was the only patient with a tumor mutation burden <178 and confirmed objective response. Notably, although higher nonsynonymous mutation burden correlated with improved ORR, DCB, and PFS (Fig. 1, F and G), this correlation was less evident when examining total exonic mutation burden (table S2).

We next examined all 34 exomes collectively to determine how patterns of mutational changes were associated with clinical benefit to pembrolizumab (tables S4 and S5). C-to-A transversions were more frequent, and C-to-T transitions were less frequent, in patients with DCB compared to

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NDB (Mann-Whitney $P = 0.01$ for both) (fig. S5). A previously validated binary classifier to identify the molecular signature of smoking (*17*) was applied to differentiate transversion-high (TH, smoking signature) from transversion-low (TL, never-smoking signature) tumors. Efficacy was greatest in patients with tumors harboring the smoking signature. The ORR in TH tumors was 56% versus 17% in TL tumors (Fisher's exact $P = 0.03$); the rate of DCB was 77% versus 22% (Fisher's exact $P = 0.004$); the PFS was also significantly longer in TH tumors (median not reached versus 3.5 months, log-rank $P = 0.0001$) (Fig. 2A). Self-reported smoking history did not significantly discriminate those most likely to benefit from pembrolizumab. The rates of neither DCB nor PFS were significantly different in ever-smokers versus never-smokers (Fisher's exact $P = 0.66$ and log-rank $P = 0.29$, respectively) or heavy smokers (median pack-years >25) versus light/never smokers (pack-years ≤25) (Fisher's exact $P = 0.08$ and log-rank $P = 0.15$, respectively). The molecular smoking signature correlated more significantly with nonsynonymous mutation burden than smoking history (fig. S6, A and B).

Although carcinogens in tobacco smoke are largely responsible for the mutagenesis in lung cancers (*19*), the wide range of mutation burden within both smokers and never-smokers implicates additional pathways contributing to the accumulation of somatic mutations. We found deleterious mutations in a number of genes that are important in DNA repair and replication. For example, in three responders with the highest mutation burden, we identified deleterious mutations in *POLD1*, *POLE*, and *MSH2* (Fig. 3). Of particular interest, a *POLD1* E374K mutation was identified in a never-smoker with DCB whose tumor harbored the greatest nonsynonymous mutation burden ($n = 507$) of all never-smokers in our series. POLD1 Glu374 lies in the exonuclease proofreading domain of Pol δ (*20*), and mutation of this residue may contribute to low-fidelity replication of the lagging DNA strand. Consistent with this hypothesis, this tumor exome had a relatively low proportion of C-to-A transversions (20%) and predominance of C-to-T transitions (51%), similar to other *POLD1* mutant, hypermutated tumors (*21*) and distinct from smoking-related lung cancers. Another responder, with the greatest mutation burden in our series, had a C284Y mutation in *POLD1*, which is also located in the exonuclease proofreading domain. We observed nonsense mutations in *PRKDC*, the catalytic subunit of DNA-dependent protein kinase (DNA-PK), and *RAD17*. Both genes are required for proper DNA repair and maintenance of genomic integrity (*22*, *23*).

Genes harboring deleterious mutations common to four or more DCB patients and not present in NDB patients included *POLR2A*, *KEAP1*, *PAPPA2*, *PXDNL*, *RYR1*, *SCN8A*, and *SLIT3*. Mutations in *KRAS* were found in 7 of 14 tumors from patients with DCB compared to 1 of 17 in the NDB group, a finding that may be explained by the association between smoking and the presence of *KRAS* mutations in NSCLC (*24*). There were no mutations or copy-number alterations in antigen-presentation pathway–associated genes or *CD274*

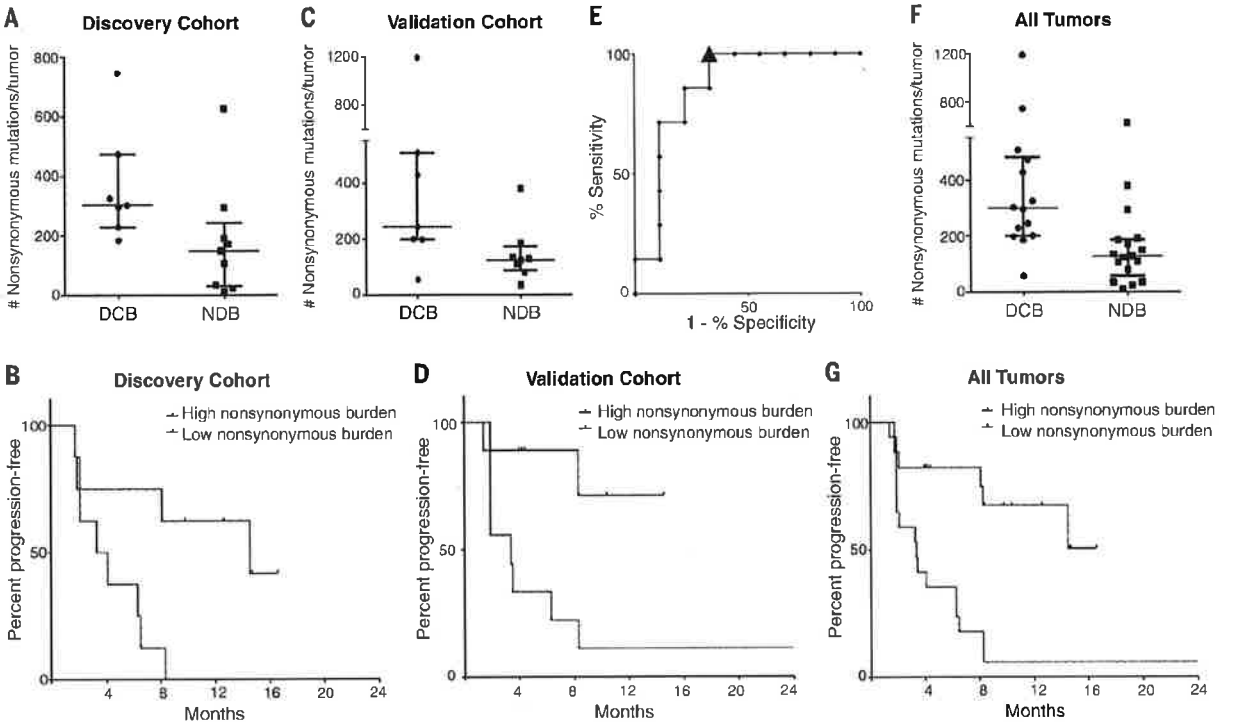

Fig. 1. Nonsynonymous mutation burden associated with clinical benefit of anti–PD-1 therapy. (**A**) Nonsynonymous mutation burden in tumors from patients with DCB ($n = 7$) or with NDB ($n = 9$) (median 302 versus 148, Mann-Whitney $P = 0.02$). (**B**) PFS in tumors with higher nonsynonymous mutation burden ($n = 8$) compared to tumors with lower nonsynonymous mutation burden ($n = 8$) in patients in the discovery cohort (HR 0.19, 95% CI 0.05 to 0.70, log-rank $P = 0.01$). (**C**) Nonsynonymous mutation burden in tumors with DCB ($n = 7$) compared to those with NDB ($n = 8$) in patients in the validation cohort (median 244 versus 125, Mann-Whitney $P = 0.04$). (**D**) PFS in tumors with higher nonsynonymous mutation burden ($n = 9$) compared to those with lower nonsynonymous mutation burden ($n = 9$) in patients in the validation cohort (HR 0.15, 95% CI 0.04 to 0.59, log-rank $P = 0.006$). (**E**) ROC curve for the correlation of nonsynonymous mutation burden with DCB in discovery cohort. AUC is 0.86 (95% CI 0.66 to 1.05, null hypothesis test $P = 0.02$). Cut-off of ≥178 nonsynonymous mutations is designated by triangle. (**F**) Nonsynonymous mutation burden in patients with DCB ($n = 14$) compared to those with NDB ($n = 17$) for the entire set of sequenced tumors (median 299 versus 127, Mann-Whitney $P = 0.0008$). (**G**) PFS in those with higher nonsynonymous mutation burden ($n = 17$) compared to those with lower nonsynonymous mutation burden ($n = 17$) in the entire set of sequenced tumors (HR 0.19, 95% CI 0.08-0.47, log-rank $P = 0.0004$). In (A), (C), and (F), median and interquartile ranges of total nonsynonymous mutations are shown, with individual values for each tumor shown with dots.

[encoding programmed cell death ligand-1 (PD-L1)] that were associated with response or resistance.

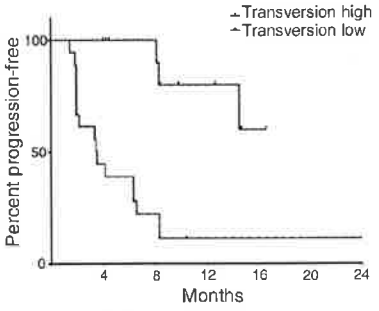

Fig. 2. Molecular smoking signature is significantly associated with improved PFS in NSCLC patients treated with pembrolizumab. PFS in tumors characterized as TH by molecular smoking signature classifier (n = 16) compared to TL tumors (n = 18) (HR 0.15, 95% 0.06 to 0.39, log-rank P = 0.0001).

How does increased mutation burden affect tumor immunogenicity? The observation that nonsynonymous mutation burden is associated with pembrolizumab efficacy is consistent with the hypothesis that recognition of neoantigens, formed as a consequence of somatic mutations, is important for the activity of anti-PD-1 therapy. We examined the landscape of neoantigens using our previously described methods (*25*) (fig. S7). Briefly, this approach identifies mutant nonamers with ≤500 nM binding affinity for patient-specific class I human lymphocyte antigen (HLA) alleles (*26*, *27*), which are considered candidate neoantigens (table S6). We identified a median of 112 candidate neoantigens per tumor (range 8 to 610), and the quantity of neoantigens per tumor correlated with mutation burden (Spearman ρ 0.91, P < 0.0001), similar to the correlation recently reported across cancers (*28*). Tumors from patients with DCB had significantly higher candidate neoantigen burden compared to those with NDB (Fig. 4A), and high candidate neoantigen burden was associated with improved PFS (median 14.5 versus 3.5 months, log-rank P = 0.002) (Fig. 4B). The presence of specific HLA alleles did not correlate with efficacy (fig. S8). The absolute burden of candidate neoantigens, but not the frequency per nonsynonymous mutation, correlated with response (fig. S9).

We next sought to assess whether anti-PD-1 therapy can alter neoantigen-specific T cell reactivity. To directly test this, identified candidate neoantigens were examined in a patient (Study ID no. 9 in Fig. 3 and table S3) with exceptional response to pembrolizumab and available peripheral blood lymphocytes (PBLs). Predicted HLA-A-restricted peptides were synthesized to screen for ex vivo autologous T cell reactivity in serially collected PBLs (days 0, 21, 44, 63, 256, and 297, where day 0 is the first date of treatment) using a validated high-throughput major histocompatibility complex (MHC) multimer screening strategy (*29*, *30*). This analysis revealed a CD8+ T cell response against a neoantigen resulting from a *HERC1* P3278S mutation (ASNA**S**SAAK) (Fig. 4C). Notably, this T cell response could only be detected upon the start of therapy (level of detection 0.005%). Three weeks after therapy initiation, the magnitude of response was 0.040%

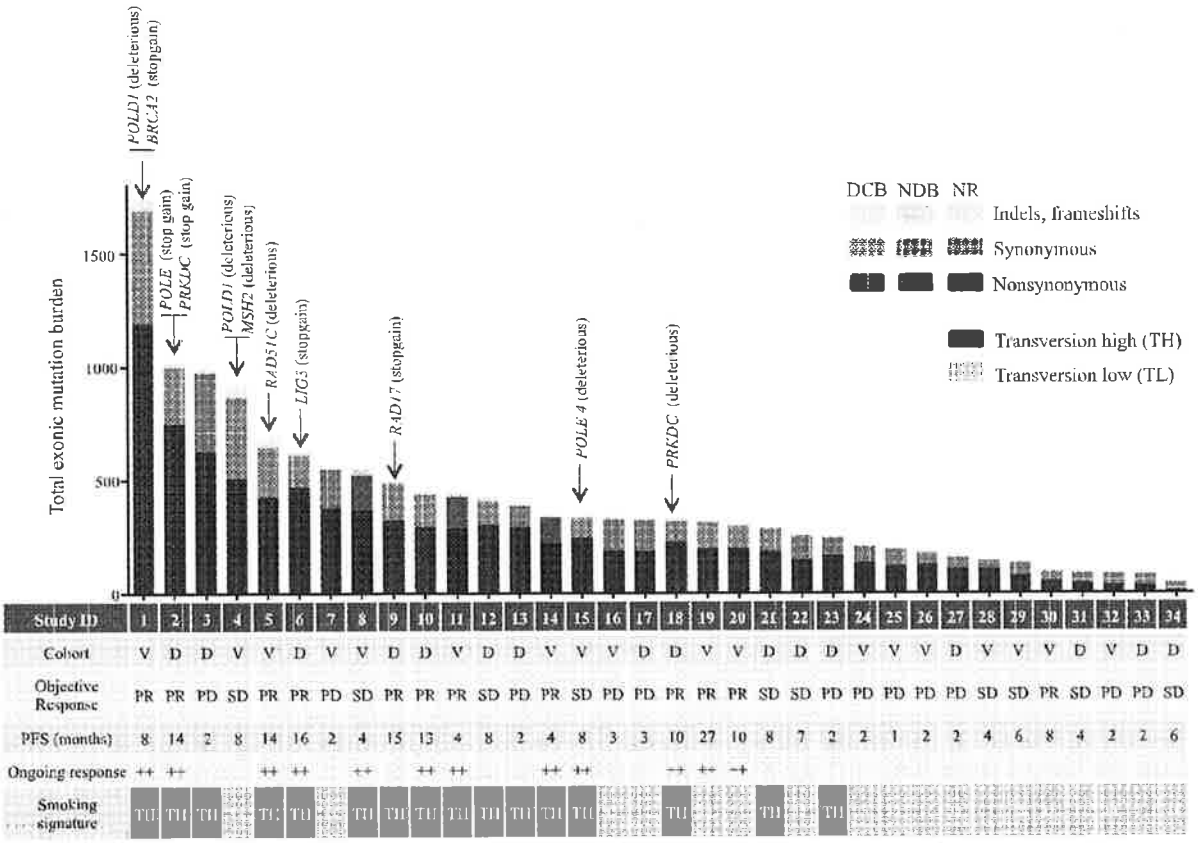

Fig. 3. Mutation burden, clinical response, and factors contributing to mutation burden. Total exonic mutation burden for each sequenced tumor with nonsynonymous (dark shading), synonymous (medium shading), and indels/frameshift mutations (light shading) displayed in the histogram. Columns are shaded to indicate clinical benefit status: DCB, green; NDB, red; not reached 6 months follow-up (NR), blue. The cohort identification (D, discovery; V, validation), best objective response (PR, partial response; SD, stable disease; PD, progression of disease), and PFS (censored at the time of data lock) are reported in the table. Those with ongoing progression-free survival are labeled with ++. The presence of the molecular smoking signature is displayed in the table with TH cases (purple) and TL cases (orange). The presence of deleterious mutations in specific DNA repair/replication genes is indicated by the arrows.

of CD8+ T cells, and this response was maintained at Day 44. This rapid induction of T cell reactivity correlated with tumor regression, and this T cell response returned to levels just above background in the subsequent months as tumor regression plateaued (Fig. 4D). HERC1 P3278S-multimer-reactive T cells from PBLs collected on day 44 were characterized by a CD45RA-CCR7-HLA-DR+LAG-3 phenotype, consistent with an activated effector population (fig. S10). These data reveal autologous T cell responses against cancer neoantigens in the context of a clinical response to anti-PD-1 therapy.

To validate the specificity of the neoantigen-reactive T cells, PBLs from days 63 and 297 were expanded in vitro in the presence of mutant peptide and subsequently restimulated with either mutant or wild-type peptide (ASNA**S**SAAK versus ASNA**P**SAAK), and intracellular cytokines were analyzed. At both time points, a substantial population of polyfunctional CD8+ T cells [characterized by production of the cytokines interferon (IFN) γ and tumor necrosis factor (TNF) α, the marker of cytotoxic activity CD107a, and the chemokine CCL4] was detected in response to mutant but not wild-type peptide (Fig. 4E and fig. S11).

In the current study, we show that in NSCLCs treated with pembrolizumab, elevated nonsynonymous mutation burden strongly associates with clinical efficacy. Additionally, clinical efficacy correlates with a molecular signature characteristic of tobacco carcinogen-related mutagenesis, certain DNA repair mutations, and the burden of neoantigens. The molecular smoking signature correlated with efficacy, whereas self-reported smoking status did not, highlighting the power of this classifier to identify molecularly related tumors within a heterogeneous group.

Previous studies have reported that pretreatment PD-L1 expression enriches for response to anti–PD-1 therapies (*3*, *8*, *31*), but many tumors deemed PD-L1 positive do not respond, and some responses occur in PD-L1–negative tumors (*8*, *31*). Semiquantitative PD-L1 staining results were available for 30 of 34 patients, where strong staining represented ≥50% PD-L1 expression, weak represented 1 to 49%, and negative represented <1% [clone 22C3, Merck (*8*)]. As this trial largely enrolled patients with PD-L1 tumor expression, most samples had some degree of PD-L1 expression (24 of 30, 80%) (table S3), limiting the capacity to determine relationships between mutation burden and PD-L1 expression. Among those with high nonsynonymous mutation burden

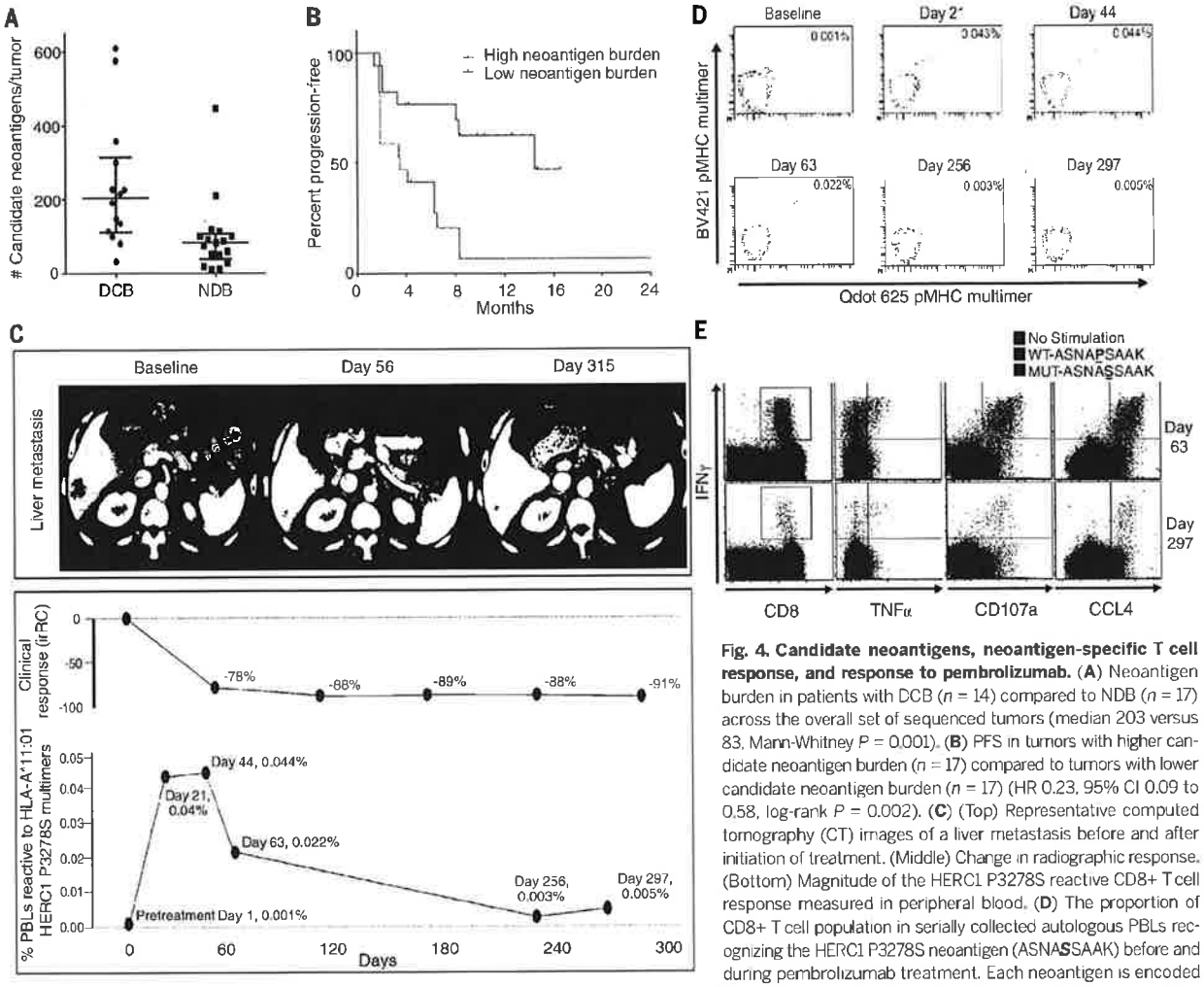

Fig. 4. Candidate neoantigens, neoantigen-specific T cell response, and response to pembrolizumab. (**A**) Neoantigen burden in patients with DCB (n = 14) compared to NDB (n = 17) across the overall set of sequenced tumors (median 203 versus 83, Mann-Whitney P = 0.001). (**B**) PFS in tumors with higher candidate neoantigen burden (n = 17) compared to tumors with lower candidate neoantigen burden (n = 17) (HR 0.23, 95% CI 0.09 to 0.58, log-rank P = 0.002). (**C**) (Top) Representative computed tomography (CT) images of a liver metastasis before and after initiation of treatment. (Middle) Change in radiographic response. (Bottom) Magnitude of the HERC1 P3278S reactive CD8+ T cell response measured in peripheral blood. (**D**) The proportion of CD8+ T cell population in serially collected autologous PBLs recognizing the HERC1 P3278S neoantigen (ASNA**S**SAAK) before and during pembrolizumab treatment. Each neoantigen is encoded by a unique combination of two fluorescently labeled peptide-MHC complexes (represented individually on each axis); neoantigen-specific T cells are represented by the events in the double positive position indicated with black dots. Percentages indicate the number of CD8+ MHC multimer+ cells out of total CD8 cells. (**E**) Autologous T cell response to wild-type HERC1 peptide (black), mutant HERC1 P3278S neoantigen (red), or no stimulation (blue), as detected by intracellular cytokine staining. T cell costains for IFNγ and CD8, TNFα, CD107a, and CCL4, respectively, are displayed for the Day 63 and Day 297 time points.

(>200, above median of overall cohort) and some degree of PD-L1 expression (weak/strong), the rate of DCB was 91% (10 of 11, 95% CI 59 to 99%). In contrast, in those with low mutation burden and some degree of PD-L1 expression, the rate of DCB was only 10% (1 of 10, 95% CI 0 to 44%). When exclusively examining patients with weak PD-L1 expression, high nonsynonymous mutation burden was associated with DCB in 75% (3 of 4, 95% CI 19 to 99%), and low mutation burden was associated with DCB in 11% (1 of 9, 0 to 48%). Large-scale studies are needed to determine the relationship between PD-L1 intensity and mutation burden. Additionally, recent data have demonstrated that the localization of PD-L1 expression within the tumor microenvironment [on infiltrating immune cells (*32*), at the invasive margin, tumor core, and so forth (*33*)] may affect the use of PD-L1 as a biomarker.

T cell recognition of cancers relies upon presentation of tumor-specific antigens on MHC molecules (*34*). A few preclinical (*35*–*41*) and clinical reports have demonstrated that neoantigen-specific effector T cell response can recognize (*25*, *42*–*45*) and shrink established tumors (*46*). Our finding that nonsynonymous mutation burden more closely associates with pembrolizumab clinical benefit than total exonic mutation burden suggests the importance of neoantigens in dictating response.

The observation that anti–PD-1–induced neoantigen-specific T cell reactivity can be observed within the peripheral blood compartment may open the door to development of blood-based assays to monitor response during anti–PD-1 therapy. We believe that our findings have an important impact on our understanding of response to anti–PD-1 therapy and on the application of these agents in the clinic.

REFERENCES AND NOTES

1. W. B. Coley, *Clin. Orthop. Relat. Res.* **1991**(262), 3–11 (1991).
2. F. S. Hodi *et al.*, *N. Engl. J. Med.* **363**, 711–723 (2010).
3. S. L. Topalian *et al.*, *N. Engl. J. Med.* **366**, 2443–2454 (2012).
4. J. D. Wolchok *et al.*, *N. Engl. J. Med.* **369**, 122–133 (2013).
5. C. Robert *et al.*, *Lancet* **384**, 1109–1117 (2014).
6. T. Powles *et al.*, *Nature* **515**, 558–562 (2014).
7. S. M. Ansell *et al.*, *N. Engl. J. Med.* **372**, 311–319 (2015).
8. E. B. Garon *et al.*, *Ann. Oncol.* **25**, LBA43 (2014).
9. G. P. Pfeifer, Y. H. You, A. Besaratinia, *Mutat. Res.* **571**, 19–31 (2005).
10. G. P. Pfeifer *et al.*, *Oncogene* **21**, 7435–7451 (2002).
11. M. S. Lawrence *et al.*, *Nature* **499**, 214–218 (2013).
12. L. B. Alexandrov *et al.*, *Nature* **500**, 415–421 (2013).
13. B. Vogelstein *et al.*, *Science* **339**, 1546–1558 (2013).
14. R. Govindan *et al.*, *Cell* **150**, 1121–1134 (2012).
15. See supplementary text available on *Science* Online.
16. P. S. Hammerman *et al.*, *Nature* **489**, 519–525 (2012).
17. Cancer Genome Atlas Research Network, *Nature* **511**, 543–550 (2014).
18. O. D. Abaan *et al.*, *Cancer Res.* **73**, 4372–4382 (2013).
19. D. Hoffmann, I. Hoffmann, K. El-Bayoumy, *Chem. Res. Toxicol.* **14**, 767–790 (2001).
20. R. Hirdes, U. Hübscher, *Biol. Chem.* **378**, 345–362 (1997).
21. C. Palles *et al.*, *Nat. Genet.* **45**, 136–144 (2013).
22. J. F. Goodwin, K. E. Knudsen, *Cancer Discov.* **4**, 1126–1139 (2014).
23. X. Wang *et al.*, *Genes Dev.* **17**, 965–970 (2003).
24. S. Dogan *et al.*, *Clin. Cancer Res.* **18**, 6169–6177 (2012).
25. A. Snyder *et al.*, *N. Engl. J. Med.* **371**, 2189–2199 (2014).
26. M. Nielsen *et al.*, *Protein Sci.* **12**, 1007–1017 (2003).
27. C. Lundegaard *et al.*, *Nucleic Acids Res.* **36** (Web Server), W509–W512 (2008).
28. M. S. Roorey, S. A. Shukla, C. J. Wu, G. Getz, N. Hacohen, *Cell* **160**, 48–61 (2015).
29. B. Rodenko *et al.*, *Nat. Protoc.* **1**, 1120–1132 (2006).
30. R. S. Andersen *et al.*, *Nat. Protoc.* **7**, 891–902 (2012).
31. J. M. Taube *et al.*, *Clin. Cancer Res.* **20**, 5064–5074 (2014).
32. R. S. Herbst *et al.*, *Nature* **515**, 563–567 (2014).
33. P. C. Tumeh *et al.*, *Nature* **515**, 568–571 (2014).
34. R. D. Schreiber, L. J. Old, M. J. Smyth, *Science* **331**, 1565–1570 (2011).
35. T. Matsutake, P. K. Srivastava, *Proc. Natl. Acad. Sci. U.S.A.* **98**, 3992–3997 (2001).
36. H. Matsushita *et al.*, *Nature* **482**, 400–404 (2012).
37. J. C. Castle *et al.*, *Cancer Res.* **72**, 1081–1091 (2012).
38. T. Schumacher *et al.*, *Nature* **512**, 324–327 (2014).
39. M. M. Gubin *et al.*, *Nature* **515**, 577–581 (2014).
40. M. Yadav *et al.*, *Nature* **515**, 572–576 (2014).
41. F. Duan *et al.*, *J. Exp. Med.* **211**, 2231–2248 (2014).
42. N. van Rooij *et al.*, *J. Clin. Oncol.* **31**, e439–e442 (2013).
43. P. F. Robbins *et al.*, *Nat. Med.* **19**, 747–752 (2013).
44. M. Rajasagi *et al.*, *Blood* **124**, 453–462 (2014).
45. C. Linnemann *et al.*, *Nat. Med.* **21**, 81–85 (2015).
46. E. Tran *et al.*, *Science* **344**, 641–645 (2014).

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SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/348/6230/124/suppl/DC1
Materials and Methods
Figs. S1 to S12
Tables S1 to S6
References (*47*–*68*)

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GENE EXPRESSION

MicroRNA control of protein expression noise

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MicroRNAs (miRNAs) repress the expression of many genes in metazoans by accelerating messenger RNA degradation and inhibiting translation, thereby reducing the level of protein. However, miRNAs only slightly reduce the mean expression of most targeted proteins, leading to speculation about their role in the variability, or noise, of protein expression. We used mathematical modeling and single-cell reporter assays to show that miRNAs, in conjunction with increased transcription, decrease protein expression noise for lowly expressed genes but increase noise for highly expressed genes. Genes that are regulated by multiple miRNAs show more-pronounced noise reduction. We estimate that hundreds of (lowly expressed) genes in mouse embryonic stem cells have reduced noise due to substantial miRNA regulation. Our findings suggest that miRNAs confer precision to protein expression and thus offer plausible explanations for the commonly observed combinatorial targeting of endogenous genes by multiple miRNAs, as well as the preferential targeting of lowly expressed genes.

MicroRNAs (miRNAs) regulate numerous genes in metazoan organisms (*1*–*5*) by accelerating mRNA degradation and inhibiting translation (*6*, *7*). Although the physiological function of some miRNAs is known in detail (*1*, *2*, *8*, *9*), it is unclear why miRNA regulation is so ubiquitous and conserved, because individual miRNAs only weakly repress the vast majority of their target genes (*10*, *11*), and knockouts rarely show phenotypes (*12*). One proposed reason for this widespread regulation is the ability of miRNAs to provide precision to gene expression (*13*). Previous work has hypothesized that miRNAs could reduce protein expression variability (noise) when their repressive posttranscriptional effects are antagonized by accelerated transcriptional dynamics (*14*, *15*). However, because miRNA levels are themselves variable, one should expect the propagation of their fluctuations to introduce additional noise (Fig. 1A).

To test the effects of endogenous miRNAs, we quantified protein levels and fluctuations in mouse embryonic stem cells (mESCs) using a dual fluorescent reporter system (*16*), in which two different reporters (ZsGreen and mCherry) are transcribed from a common bidirectional promoter (Fig. 1B). One of the reporters (mCherry) contained several variants and numbers of miRNA binding sites in its 3′ untranslated region (3′UTR),

Science
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Mutational landscape determines sensitivity to PD-1 blockade in non–small cell lung cancer

Naiyer A. Rizvi *et al.*

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REVIEWS

Adoptive cell transfer as personalized immunotherapy for human cancer

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Adoptive cell therapy (ACT) is a highly personalized cancer therapy that involves administration to the cancer-bearing host of immune cells with direct anticancer activity. ACT using naturally occurring tumor-reactive lymphocytes has mediated durable, complete regressions in patients with melanoma, probably by targeting somatic mutations exclusive to each cancer. These results have expanded the reach of ACT to the treatment of common epithelial cancers. In addition, the ability to genetically engineer lymphocytes to express conventional T cell receptors or chimeric antigen receptors has further extended the successful application of ACT for cancer treatment.

Adoptive cell therapy (ACT) has multiple advantages compared with other forms of cancer immunotherapy that rely on the active in vivo development of sufficient numbers of antitumor T cells with the functions necessary to mediate cancer regression. For use in ACT, large numbers of antitumor lymphocytes (up to 10^{11}) can be readily grown in vitro and selected for high-avidity recognition of the tumor, as well as for the effector functions required to mediate cancer regression. In vitro activation allows such cells to be released from the inhibitory factors that exist in vivo. Perhaps most importantly, ACT enables the manipulation of the host before cell transfer to provide a favorable microenvironment that better supports antitumor immunity. ACT is a "living" treatment because the administered cells can proliferate in vivo and maintain their antitumor effector functions.

A major factor limiting the successful use of ACT in humans is the identification of cells that can target antigens selectively expressed on the cancer and not on essential normal tissues. ACT has used either natural host cells that exhibit antitumor reactivity or host cells that have been genetically engineered with antitumor T cell receptors (TCRs) or chimeric antigen receptors (CARs). With the use of these approaches, ACT has mediated dramatic regressions in a variety of cancer histologies, including melanoma, cervical cancer, lymphoma, leukemia, bile duct cancer, and neuroblastoma. This Review will discuss the current state of ACT for the treatment of human cancer, as well as the principles of effective treatment that point toward improvements in this approach.

A brief history of ACT

Very little was known about the function of T lymphocytes until the 1960s, when it was shown that lymphocytes were the mediators of allograft rejection in experimental animals. Attempts to use T cells to treat transplanted murine tumors were limited by the inability to expand and manipulate T cells in culture. Thus, ACT used transfer of syngeneic lymphocytes from rodents heavily immunized against the tumor, and modest growth inhibition of small established tumors was observed (*1*, *2*). In early preclinical studies, the importance of host inhibitory factors was suggested by findings that lymphodepletion using either chemotherapy or radiation before cell transfer enhanced the ability of transferred lymphocytes to treat established tumors (*3*, *4*).

The ability to use ACT was facilitated by the description of T cell growth factor [interleukin-2 (IL-2)] in 1976, which provided a means to grow T lymphocytes ex vivo, often without loss of effector functions (*5*). The direct administration of high doses of IL-2 could inhibit tumor growth in mice (*6*), and studies in 1982 demonstrated that the intravenous injection of immune lymphocytes expanded in IL-2 could effectively treat bulky subcutaneous FBL3 lymphomas (*7*). In addition, administration of IL-2 after cell transfer could enhance the therapeutic potential of these adoptively transferred lymphocytes (*8*). The demonstration in 1985 that IL-2 administration could result in complete durable tumor regressions in some patients with metastatic melanoma (*9*) provided a stimulus to identify the specific T cells and their cognate antigens involved in this cancer immunotherapy. Lymphocytes infiltrating into the stroma of growing, transplantable tumors were shown to represent a concentrated source of lymphocytes capable of recognizing tumor in vitro, and studies in murine tumor models demonstrated that the adoptive transfer of these syngeneic tumor-infiltrating lymphocytes (TILs) expanded in IL-2 could mediate regression of established lung and liver tumors (*10*). In vitro studies in 1986 showed that human TILs obtained from resected melanomas contained cells capable of specific recognition of autologous tumors (*11*), and these studies led in 1988 to the first demonstration that ACT using autologous TILs could mediate objective regression of cancer in patients with metastatic melanoma (*12*).

Populations of TILs that grow from tumors are generally mixtures of $CD8^-$ and $CD4^-$ T cells with few if any major contaminating cells in mature cultures. The ability of pure populations of T lymphocytes to mediate cancer regression in patients provided the first direct evidence that T cells played a vital role in human cancer immunotherapy. However, responses were often of short

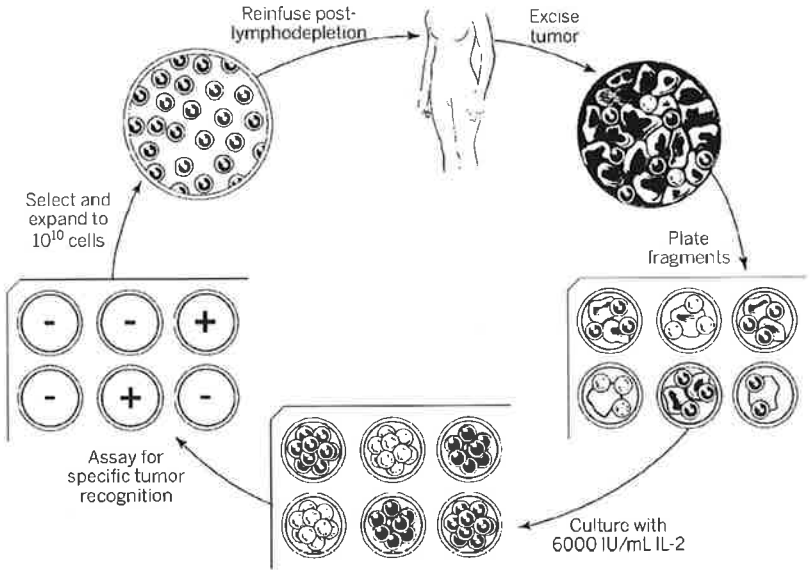

Fig. 1. General schema for using the adoptive cell transfer of naturally occurring autologous TILs. The resected melanoma specimen is digested into a single-cell suspension or divided into multiple tumor fragments that are individually grown in IL-2. Lymphocytes overgrow, destroy tumors within 2 to 3 weeks, and generate pure cultures of lymphocytes that can be tested for reactivity in coculture assays. Individual cultures are then rapidly expanded in the presence of excess irradiated feeder lymphocytes, OKT3, and IL-2. By approximately 5 to 6 weeks after resecting the tumor, up to 10^{11} lymphocytes can be obtained for infusion into patients.

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duration, and the transferred cells could rarely be found in the circulation just days after administration. A critical improvement in the application of ACT to the treatment of human cancer was reported in 2002, when it was shown that lymphodepletion using a nonmyeloablative chemotherapy regimen administered immediately before TIL transfer could lead to increased cancer regression, as well as the persistent oligoclonal repopulation of the host with the transferred antitumor lymphocytes (*13*). In some patients, the administered antitumor cells represented up to 80% of the $CD8^+$ T cells in the circulation months after the infusion.

Lymphocyte cultures can be grown from many tumor histologies; however, melanoma appeared to be the only cancer that reproducibly gave rise to TIL cultures capable of specific antitumor recognition. The stimulus to more widely apply ACT to treat multiple human cancers led to studies of the genetic engineering of lymphocytes to express antitumor receptors. Following mouse models (*14*), it was shown for the first time in humans in 2006 that administration of normal circulating lymphocytes transduced with a retrovirus encoding a TCR that recognized the MART-1 melanoma-melanocyte antigen could mediate tumor regression (*15*). Administration of lymphocytes genetically engineered to express a chimeric antigen receptor (CAR) against the B cell antigen CD19 was shown in 2010 to mediate regression of an advanced B cell lymphoma (*16*). These findings of the use of either naturally occurring or genetically engineered antitumor T cells set the stage for the extended development of ACT for the treatment of human cancer.

ACT using TILs is an effective immunotherapy for patients with metastatic melanoma

Adoptive cell therapy using autologous TILs is the most effective approach to induce complete durable regressions in patients with metastatic melanoma (Table 1). The general approach for growing and administering human TILs is shown in Fig. 1. The resected melanoma specimen is digested into a single-cell suspension or divided into multiple tumor fragments that are individually grown in IL-2. Lymphocytes overgrow, destroy tumors within 2 to 3 weeks, and give rise to pure cultures of lymphocytes that can be tested for reactivity against tumors, if available, in coculture assays. Individual cultures are then rapidly expanded in the presence of excess irradiated feeder lymphocytes, an antibody targeting the epsilon subunit within the human CD3 complex of the TCR, and IL-2. By ~5 to 6 weeks after resecting the tumor, up to 10^{11} lymphocytes can be obtained for infusion into patients. A substantial increase in cell persistence and the incidence and duration of clinical responses was seen when patients received a lymphodepleting preparative regimen before the cell infusion (*13*). It might be possible to optimize the intensity or duration of the lymphodepletion that is employed, but the most frequently used lymphodepleting preparative regimen consists of 60 mg/kg cyclophosphamide for 2 days and 25 mg/m^2 fludarabine administered for 5 days followed by cells and IL-2 given at 720,000 IU/kg to tolerance (Fig. 2). In a pilot study in the Surgery Branch, National Cancer Institute (NCI), objective cancer regressions by RECIST criteria (Response Evaluation Criteria in Solid Tumors) were seen in 21 of 43 patients (49%), including 5 patients (12%) who underwent complete cancer regression (*13*). When 200 or 1200 centigray (cGy; 1 Gy = 100 rads) total-body irradiation (TBI) was added to the preparative regimen in pilot trials of 25 patients each, objective response (OR) rates of 52 and 72% were seen, including 20 and 40% complete regressions. However, there were no statistically significant differences in the OR rates between preparative regimens (*13*, *17*). Twenty of the 93 patients (22%) in these trials had complete regressions, and 19 (20%) have not experienced recurrences at follow-up times of 5 to 10 years and are probably cured. A prospective randomized study comparing the chemotherapy preparative regimen alone versus chemotherapy plus the addition of 1200 cGy TBI in 101 patients was recently concluded at the NCI, National Institutes of Health (NIH), and results are pending.

In the combined experience of the treatment of 194 patients using TILs grown from individual melanoma fragments at the NCI (Bethesda, Maryland), 107 patients (55%) have shown ORs. Similar OR rates to TIL therapy have been reported by multiple groups, including those from the Moffitt Cancer Center (Tampa, Florida) (38% OR rate) (*18*), the MD Anderson Cancer Center (Houston, Texas) (48% OR rate) (*19*), and the Ella Cancer Institute (Ramat Gan, Israel) (40% OR rate) (*20*) (Table 1).

There is no relation between the bulk of disease or the site of metastases and the likelihood of achieving a complete cancer regression (*17*). Of the 34 complete responders thus far seen in the two trials at the NCI, only one has recurred, and only one patient with complete regression received more than one treatment. The brain is not a sanctuary site, and regression of brain metastases has been observed (*21*). Prior treatment with targeted therapy using the Braf inhibitor vemurafenib (Zelboraf) does not appear to affect the likelihood of having an OR to ACT treatment in patients with melanoma. ACT can also be effective after other immunotherapies have failed. Of the 194 patients treated in the NCI trials, OR rates in patients who had no prior therapy or who progressed through IL-2, antibody to cytotoxic T lymphocyte–associated protein 4 (anti-CTLA-4), anti-PD1, or Braf inhibitors were 48, 63, 42, 50, and 43%, respectively.

Lymphodepletion appears to be an important component of ACT, and mouse models have shown that lymphodepletion given before cell transfer can increase the effectiveness of treatment more than 10-fold. In the clinic, the persistence of T cells was once a rarity (*22*), but in trials conducted after the initiation of lymphodepleting therapy, adoptively transferred T cells could comprise the majority of the peripheral blood $CD8^+$ cells 1 month after transfer (*13*). The cellular basis of the effect of lymphodepletion is complex and still not completely understood. In mouse models, myeloid-derived suppressor cells and $CD4^+$ FoxP3 regulatory T cells can be found at high levels in tumors in vivo and can depress immune responses in the mouse tumor microenvironment (*23*). In accord with these preclinical findings, preparative chemotherapy in humans severely depletes lymphocytes and myeloid cells from the circulation at the time of cell infusion, although the rate of reappearance of FoxP3 inhibitory T cells after lymphodepletion was inversely correlated with clinical response (*24*).

Lymphodepletion prior to T cell transfer is followed by immune reconstitution

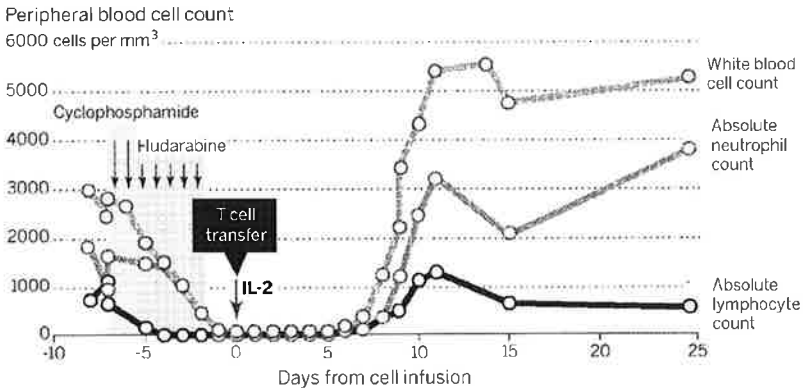

Fig. 2. A substantial increase in cell persistence and the incidence and duration of clinical responses is observed when patients received a lymphodepleting preparative regimen before the cell infusion. The most frequently used lymphodepletirg preparative regimen consists of 60 mg/kg cyclophosphamide given for 2 days and 25 mg/m^2 fludarabine administered over 5 days, followed by T cells and IL-2 administration.

Table 1. Selected clinical trials of ACT for the treatment of human cancer. CLL, chronic lymphocytic leukemia; ALL, acute lymphocytic leukemia; CR, complete response; HPC, human papillomavirus; allo-HSCT, allogeneic hematopoietic stem cell transplantation; DLBCL, diffuse large B cell lymphoma; EBV, Epstein-Barr virus. Dashes indicate not applicable.

CELLS USED FOR ACT	YEAR	CANCER HISTOLOGY	MOLECULAR TARGET	PATIENTS	NUMBER OF ORS	COMMENTS
Tumor-infiltrating lymphocytes*	1998	Melanoma (*12*)		20	55%	Original use TIL ACT
	1994	Melanoma (*88*)		86	34%	
	2002	Melanoma (*13*)		13	46%	Lymphodepletion before cell transfer
	2011	Melanoma (*17*)		93	56%	20% CR beyond 5 years
	2012	Melanoma (*19*)		31	48%	
	2012	Melanoma (*18*)		13	38%	Intention to treat: 26% OR rate
	2013	Melanoma (*20*)		57	40%	Intention to treat: 29% OR rate
	2014	Cervical cancer (*89*)		9	33%	Probably targeting HPV antigens
	2014	Bile duct (*44*)	Mutated ERB2	1	–	Selected to target a somatic mutation
In vitro sensitization	2008	Melanoma (*90*)	NY-ESO-1	9	33%	Clones reactive against cancer-testes antigens
	2014	Leukemia (*91*)	WT-1	11	–	Many treated at high risk for relapse
Genetically engineered with CARs	2010	Lymphoma (*16*)	CD19	1	100%	First use of anti-CD19 CAR
	2011	CLL (*68*)	CD19	3	100%	Lentivirus used for transduction
	2013	ALL (*70*)	CD19	5	100%	Four of five then underwent allo-HSCT
	2014	ALL (*92*)	CD19	30	90%	CR in 90%
	2014	Lymphoma (*71*)	CD19	15	80%	Four of seven CR in DLBCL
	2014	ALL (*93*)	CD19	16	88%	Many moved to allo-HSCT
	2014	ALL (*94*)	CD19	21	67%	Dose-escalation study
	2011	Neuroblastoma (*78*)	GD2	11	27%	CR2 CARs into EBV-reactive cells
Genetically engineered with TCRs	2011	Synovial sarcoma (*81*)	NY-ESO-1	6	67%	First report targeting nonmelanoma solid tumor
	2006	Melanoma (*15, 32*)	MART-1	11	45%	

*Molecular targets of TIL in melanoma appear to be exomic mutations expressed by the cancer (*39, 40, 44*)

Levels of homeostatic cytokines, which promote T cell proliferation and survival, are dramatically induced upon lymphodepletion (*25*) in mouse models. In humans, lymphodepletion leads to the appearance in the circulation of the T cell growth factor IL-15, which serves to promote the expansion of the transferred cells in the absence of competing endogenous lymphocytes (*26*). Further, lymphodepletion can enhance the translocation of commensal microflora across mucosal barriers in the mouse, and this can enhance the effect of ACT by stimulating Toll-like receptors (*27*) to activate antigen-presenting cells (APCs). These preclinical results have highly affected clinical translation, and it seems likely that immune ablation will be a part of future cell-based treatments in patients with cancer.

Adoptive cell therapy is a "living" treatment, and administered lymphocytes can expand more than 1000-fold after administration. Studies in mouse models, including those involving the injection of human cells into immunodeficient animals, have emphasized the importance of the differentiation state of the infused cells (*28, 29*). The phenotypic and functional status of less differentiated murine cells is highly positively correlated with their ability to eliminate vascularized tumor in vivo. These findings are in accordance with the high positive correlation between the persistence of the transferred TILs in the circulation of patients at 1 month and with the induction of partial and complete clinical responses (*17*). Further, one clinical study showed a strong correlation between expression of the phenotypic marker CD27, which is associated with cells early in their differentiation pathway, and clinical response (*17*). The presence of longer telomeres as a correlate of clinical response was seen in one study (*17*) but not in another (*18*).

The observation that melanoma TILs can mediate durable, complete, and probably curative cancer regression in patients with metastatic melanoma has raised considerable interest in the possible use of TILs for the treatment of multiple cancer types. Although TILs can be grown in vitro from virtually all tumors, only melanomas consistently give rise to TILs with antitumor reactivity. In an attempt to gain insight into the possible extension of ACT to the treatment of other common cancers, extensive studies of the antigens recognized by TILs have been pursued.

Melanoma TILs recognize the products of cancer mutations

Early studies identified two nonmutated melanoma-melanocyte differentiation proteins, MART-1 and gp100, that were often recognized by melanoma TILs (*30, 31*). Melanocytes in the skin, eye, and ear express the MART-1 and gp100 proteins, and yet toxicity targeting these proteins was not seen in the majority of patients treated with TILs who underwent complete cancer regression. In contrast, when a high-affinity TCR against MART-1 or gp100 was inserted into lymphocytes used for ACT, profound eye and ear toxicity was often seen in the absence of antitumor activity, which suggests that the reactivity against melanoma-melanocyte antigens was not the decisive target resulting in the in vivo antitumor activity of melanoma TILs (*32*).

A study of exomic mutation rates in more than 3000 tumor-normal pairs revealed that the frequency of nonsynonymous mutations varied more than 1000-fold across different cancer types (*33*). Pediatric cancers exhibited mutation frequencies as low as 0.1/Mb, whereas melanomas and lung cancers often exceeded 100 mutations/Mb.

The suggestion that mutations might be targets of immune recognition of tumor cells has been around for some time (*34*). The responsiveness of melanoma to a variety of immunotherapy approaches such as ACT, IL-2, anti-CTLA-4, and anti-PD-1 suggested that peptide epitopes encoded by the large number of mutations in melanoma might be the targets of TIL therapy (*35*). Support for this hypothesis comes from recent observations that anti-PD-1 can mediate ORs not only in patients with melanoma but also in patients with lung and bladder cancer, the two tumor types closest to melanoma with a high frequency of mutations (*36*). A patient successfully treated with anti-CTLA-4 generated circulating T cells that recognized a distinct mutation in the melanoma (*37*). Another study suggested that increased numbers of exomic mutations in a cancer correlated with better outcomes (*38*).

New approaches using whole-exomic sequencing of tumor-normal pairs in patients with melanoma have consistently identified nonsynonymous cancer mutations recognized by autologous TILs that mediated complete cancer regressions (*39*, *40*). However, not all expressed mutations can be recognized by T cells. Proteins incorporating the mutations must be processed to short peptides of ~9 amino acids for major histocompatibility complex (MHC) class 1 and a bit longer for MHC class 2; these peptides are then presented on the cell surface. One approach to identify the immunogenic mutations that we have taken is to identify 21- to 25-amino acid polypeptides, each one containing a mutated amino acid flanked by 10 to 12 normal residues. Using peptide-MHC binding algorithms, these polypeptides can then be scanned to identify peptides with high binding to individual MHC molecules of the patient. The top-predicted binding peptides are then synthesized and tested for recognition by coculture with TILs that mediated cancer regression. This method depends on the accuracy of peptide-MHC binding algorithms, which are often inadequate for many of the less frequent MHC molecules (*39*).

An alternate method eliminates the need for predicted peptide binding to MHC and enables the screening of all candidate peptides on all MHC loci in a single test (*40*) (Fig. 3). As above, minigenes, rather than polypeptides, are constructed that encode each mutated amino acid flanked by 10 to 12 amino acids. Strings of 6 to 20 minigenes are then linked into tandem minigenes, and these DNA constructs are subsequently cloned into an expression plasmid and in vitro transcribed to RNA, which is electroporated into the patient's autologous APCs. These APCs present all mutated peptides capable of being processed and binding to any of the patient's class 1 or class 2 MHC molecules. Culture of the patient's TILs with these APCs can identify the tandem minigene as well as the individual minigene responsible for tumor recognition. Using these approaches, TILs from 21 patients with melanoma that responded to ACT identified 45 mutations presented on a variety of class 1 and class 2 MHC molecules. Thus far, every mutation recognized by TILs was distinct (i.e., each from a different expressed protein), with none shared by another melanoma in the set studied. These findings provide suggestive evidence that melanoma TILs capable of mediating antitumor responses were recognizing random somatic mutations in the cancer. In many cases, multiple mutations were recognized by an individual TIL population. The concept that cancer regressions after immunotherapy are the result of targeting mutations explains why patients can experience tumor regression without autoimmune sequelae. Conversely, the ineffectiveness of the vast number of therapeutic cancer vaccines that targeted nonmutated self-proteins can also be explained (*41*, *42*). Whereas strong reactivity to self-antigens causes autoimmune toxicity, vaccines against self-antigens trigger the expansion of low-affinity TCRs against self-proteins that escaped negative selection in the thymus. This raises the possibility that vaccines targeting mutated immunogenic epitopes may be much more effective. The specific targeting of individual mutated antigens in a patient's cancer presents a daunting problem for widespread therapeutic application of ACT but also presents an opportunity to develop treatments for multiple cancer types. Schumacher and Schreiber discuss additional aspects for targeting mutated antigens in this issue (*43*).

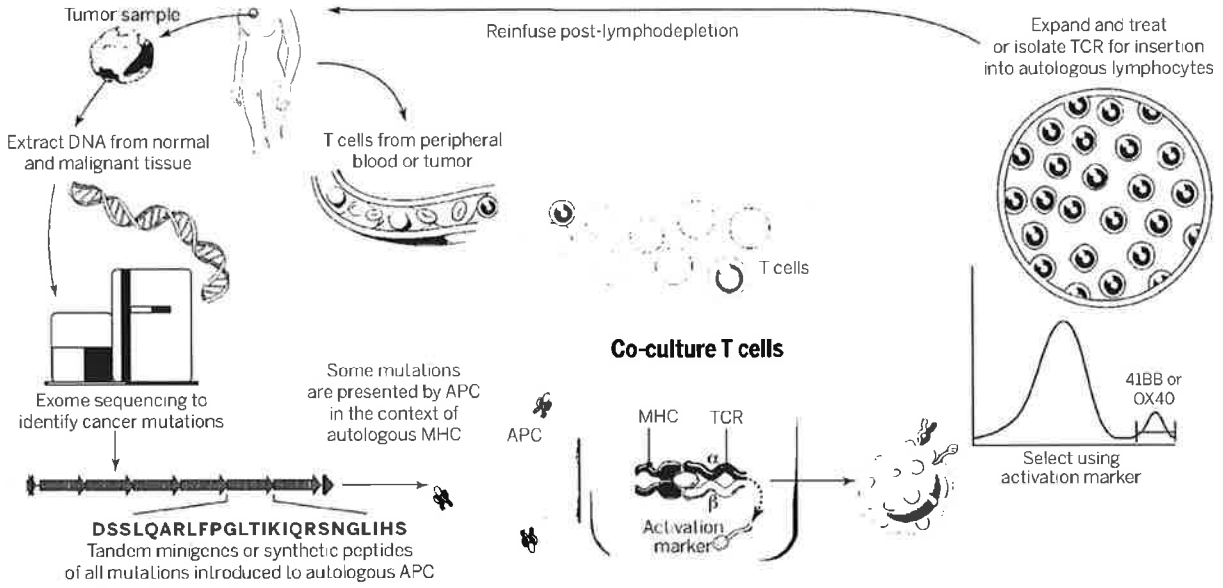

Fig. 3. A "blueprint" for the treatment of patients with T cells recognizing tumor-specific mutations. The sequences of exomic DNA from tumor cells and normal cells from the same patient are compared to identify tumor-specific mutations. Knowledge of these mutations can then be used to synthesize either minigenes or polypeptides encoding each mutated amino acid flanked by 10 to 12 amino acids. These peptides or minigenes can be expressed by a patient's autologous APCs, where they are processed and presented in the context of a patient's MHC. Coculture of the patient's T cells with these APCs can be used to identify all mutations processed and presented in the context of all of a patient's MHC class I and class II molecules. The identification of individual mutations responsible for tumor recognition is possible because T cells express activation markers, such as 41BB ($CD8^+$ T cells) and OX40 ($CD4^+$ T cells), when they recognize their cognate target antigen. T cells expressing the activation marker can then by purified using flow cytometry before their expansion and reinfusion into the tumor-bearing patient.

TILs from common epithelial cancers can also recognize cancer mutations

A recent report has shown that the mutated antigens in a nonmelanoma epithelial cancer can give rise to immune responses, despite the low number of mutations in these cancers (*44*). Exomic sequencing of a metastatic cholangiocarcinoma in a patient who had progressed through multiple chemotherapies revealed 26 nonsynonymous mutations. Tandem minigenes that encoded each mutated amino acid and its flanking sequences were constructed and electroporated into the patient's APCs. CD4 cells from TIL cultures from this patient's tumor recognized the ERBB2IP mutation restricted by the MHC class 2 antigen HLA-DQ 06. ERBB2IP is a tumor suppressor that binds to ERBB2 and attenuates downstream RAS/ERK signaling. Despite the lack of an objective clinical response to the administration of bulk autologous TILs in this patient, administration of TILs that were selected to contain more than 95% ERBB2IP mutation-reactive TILs mediated a dramatic regression of liver and lung metastases ongoing beyond 1 year. This result provides compelling evidence that mutation-reactive T cells are capable of mediating in vivo tumor regression in patients with this epithelial cancer. Further, the findings suggest that this treatment approach may be suitable for patients with other common epithelial cancers that are not normally considered to be immunogenic.

Mutations that are targeted may be driver mutations essential for the malignant phenotype of the cell, or alternatively, the TILs may contain reactivity against multiple immunogenic passenger mutations, which would decrease the likelihood that the loss of any individual antigen would subvert the clinical antitumor response. TIL populations can be highly polyclonal and thus are likely to be capable of potentially recognizing multiple antigens simultaneously. Given their curative potential, it seems likely that TILs are able to recognize antigens expressed by cancer stem cells. Although some of the mutations are probably driver mutations because they are found in expressed genes associated with known oncogenic pathways (e.g., mutated β-catenin), many of the targets of TILs may well be passenger mutations.

Genetic engineering of lymphocytes for use in ACT

In an attempt to broaden the reach of ACT to other cancers, techniques were developed to introduce antitumor receptors into normal T cells that could be used for therapy (Fig. 4). The specificity of T cells can be redirected by the integration of genes encoding either conventional alpha-beta TCRs or CARs. CARs were pioneered by Gross and colleagues in the late 1980s (*45*) and can be constructed by linking the variable regions of the antibody heavy and light chains to intracellular signaling chains such as CD3-zeta, often including costimulatory domains encoding CD28 (*46*) or CD137 to fully activate T cells (*47*, *48*). CARs can provide non-MHC-restricted recognition of cell surface components and can be introduced into T cells with high efficiency using viral vectors.

An important question confronting the use of genetically engineered cells in the ACT of cancer involves selection of the ideal human T cell subpopulation into which the gene should be introduced, as well as the selection of appropriate antigenic targets of the introduced TCRs or CARs. Preclinical studies in mouse models strongly suggest that improved antitumor responses are seen when T cells in early stages of differentiation (such as naïve or central memory cells) are transduced (*49*), a result supported by studies in monkeys showing improved in vivo persistence of infused central memory compared with effector memory cells (*50*). $CD8^+$ T cells can be categorized into distinct memory subsets based on their differentiation states. We and others have found that $CD8^+$ T cells follow a progressive pathway of differentiation from naïve T cells into central memory and effector memory T cell populations [summarized in (*51*)]. $CD8^+$ T cells paradoxically lose antitumor T cell functionality as they acquire the ability to lyse target cells and to produce the cytokine interferon-γ, qualities thought to be important in their antitumor efficacy (*52*). The differentiation state of $CD8^+$ T cells is inversely related to their capacity to proliferate and persist (*52*–*54*). These

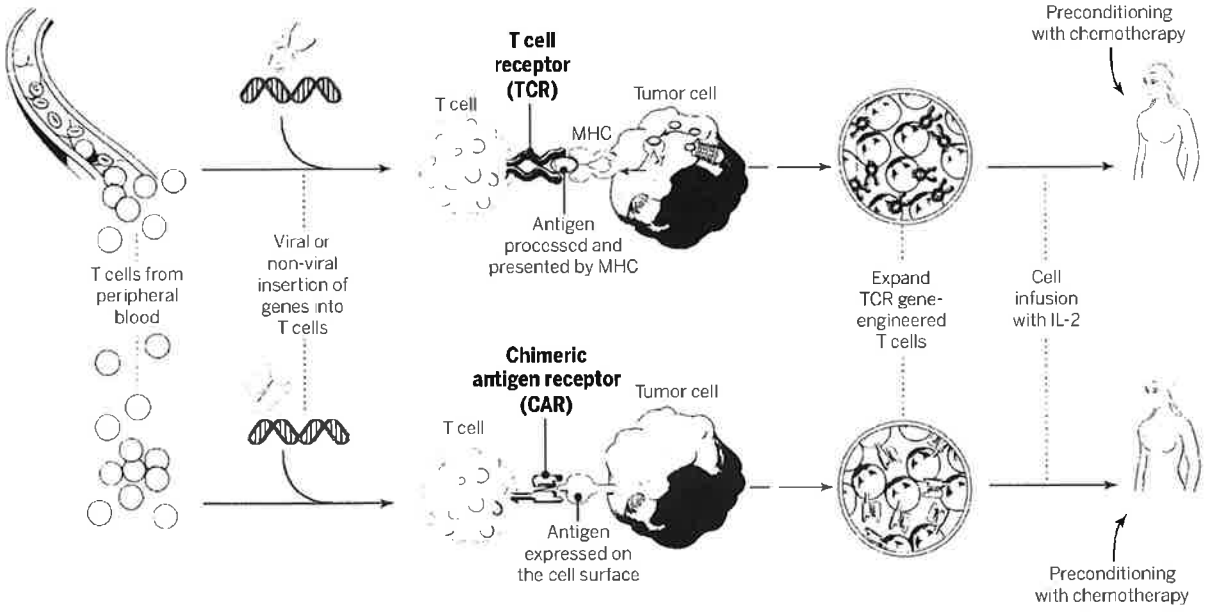

Fig. 4. Gene-modification of peripheral blood lymphocytes. In an attempt to broaden the reach of ACT to other cancers, techniques are being developed to introduce antitumor receptors into normal T cells that could be used for therapy. The top panel shows the insertion of a conventional TCR into a patient's T lymphocytes, followed by the expansion and infusion back into the patient. The bottom panel shows the insertion of a CAR into a patient's T cell, followed by the expansion of these cells and their re-infusion. TCRs and CARs are fundamentally different in their structures and in the structures that they recognize. TCRs are composed of one α chain and one β chain, and they recognize antigens that have been processed and presented by one of the patient's own MHC molecules. CARs are artificial receptors that can be constructed by linking the variable regions of the antibody heavy and light chains to intracellular signaling chains (such as CD3-zeta, CD28, 41BB) alone or in combination with other signaling moieties. CARs recognize antigens that do not need to be MHC-restricted, but they must be presented on the tumor cell surface.

findings may be clinically relevant, and younger T cells are statistically positively correlated with clinical effectiveness in ACT trials (*17*). It seems clear that, like many organ systems in the body, $CD8^+$ T cells can exist in a stem cell–like state, capable of clonal repopulation. Human T memory stem cells express a gene program that enables them to proliferate extensively and can further differentiate into other T cell populations (*29*).

Much of the existing work in cancer immunotherapy has focused on $CD8^+$ T cells. However, $CD4^+$ T cells can also efficiently promote tumor rejection. $CD4^+$ T cells do not merely enhance $CD8^+$ T cell function, but they also play a more direct role in tumor elimination. This notion has been validated recently in humans (*44*). The roles that $CD4^+$ T cells play in the antitumor immune response crucially depend on their polarization, which is determined by their expression of key transcription factors. $CD4^+$ cells can destroy tumor cells, and recent evidence suggests that adoptively transferred T helper 17 cells can promote long-lived antitumor immunity (*55*).

Toxicity of ACT when targeting antigens shared by tumors and normal tissue

The marked potency of T cells enables the recognition of minute levels of antigen expressed on normal cells. Thus, targeting normal, nonmutated antigenic targets that are expressed on normal tissues but overexpressed on tumors has led to severe on-target, off-tumor toxicity in patients. Suitable antigens to target are those presented exclusively on the cancer or, alternatively, on normal cells that are not essential for survival.

The first successful application of ACT using genetically engineered lymphocytes treated 17 patients with metastatic melanoma using autologous T cells transduced with a weakly avid human TCR recognizing the MART-1 melanoma-melanocyte differentiation antigen (*15*). Two patients experienced objective partial regressions of metastatic melanoma, and in both patients the transferred cells could be found in the peripheral blood 1 year after cell infusion. This approach was expanded to 36 patients with metastatic melanoma who received high-avidity TCRs that recognized either the MART-1 or gp100 melanoma-melanocyte antigens (*32*). Although objective cancer regressions were observed in 30 and 19% of patients who received the MART-1 or gp100 TCR, respectively, severe off-tumor, on-target toxicity was seen in the skin, eyes, and ears of patients due to the expression of melanocytes in these organs. These findings coincided with severe eye toxicity seen in mice when targeting melanocyte antigens and provided an early demonstration of the power of T cell therapy (*56*). The treatment of patients with renal cancer using T cells encoding a CAR against carbonic anhydrase 9, which is overexpressed in renal cancer, led to severe liver toxicity due to expression of this antigen in biliary duct epithelium (*57*). A high-affinity TCR against the carcinoembryonic antigen was used to treat patients with metastatic colorectal cancer that expressed high levels of this antigen (*58*). All three patients experienced life-threatening colitis and colonic hemorrhage that precluded further use of this TCR, even though one patient exhibited a partial response of liver metastases. Unexpected toxicities can also result when previously unknown cross-reactivities are seen that target normal self-proteins expressed in vital organs. MAGE-A3, a cancer-testes antigen to be discussed in more detail below, is not known to be expressed in any normal tissues. However, targeting an HLA-A*0201–restricted peptide in MAGE-A3 caused severe damage to gray matter in the brain, resulting in two deaths because this TCR recognized a different but related epitope expressed by MAGE-A12, expressed at very low levels in the brain (*59*). It should also be noted that CARs are capable of toxicity against self-antigens as well. Acute pulmonary toxicity resulting in death was observed after infusion of CAR T cells specific for ERBB2, which seemed likely due to the recognition of low levels of this antigen on pulmonary epithelium (*60*).

Several groups have attempted to affinity-enhance TCRs by altering amino acids in the antigen-combining sites of the TCR (*61*, *62*). By removing the protective effects of negative thymic selection that eliminate high-affinity TCRs against normal proteins, these modified TCRs could potentially recognize new and unrelated determinants. Two patients (one with multiple myeloma and one with melanoma) were treated with an HLA-A1–restricted MAGE-A3–specific TCR whose affinity was enhanced by this site-specific mutagenesis, and both experienced fatal cardiogenic shock due to the recognition of an HLA-A1–restricted peptide derived from an unrelated protein, titin, present in cardiac muscle (*63*). Thus, methods aimed at enhancing the affinities of TCRs can be fraught with problems of unexpected toxicities, which remain difficult to predict. Of course, the same pitfalls of unexpected toxicities may apply to the use of novel CARs.

Targeting antigens expressed on cancers and nonessential human tissues

Cancers that express target molecules shared with nonessential normal organs represent potential targets for human cancer immunotherapy using ACT. A prominent example of such an antigen is the CD19 molecule expressed on more than 90% of B cell malignancies and on B cells at all stages of differentiation, excluding plasma cells. Following preclinical work by many groups [summarized in (*64*–*67*)], the first successful clinical application of anti-CD19 CAR gene therapy in humans was reported in 2010 (*16*). Administration of autologous cells expressing the anti-CD19 CAR to a patient with refractory lymphoma resulted in cancer regression in a patient who remains progression-free after two cycles of treatment ongoing 4 years after treatment. Multiple groups have now shown the effectiveness of ACT targeting CD19 in patients with follicular lymphoma, large-cell lymphomas, chronic lymphocytic leukemia, and acute lymphocytic leukemia (*68*–*72*). On-target toxicity against CD19 results in B cell loss in the circulation and in the bone marrow and can be overcome by the periodic administration of immunoglobulin infusions. Substantial toxicity can be seen by the excessive release of cytokines by CAR-expressing cells, and thus, careful selection of the lymphodepleting preparative regimen and the cell dose is required to safely apply ACT targeting CD19, as well as many other antigens now under experimental study (*72*).

Dramatic regressions of lymphomas and leukemias with ACT have elicited considerable enthusiasm, although most reports contain fewer than 20 patients, and fewer than 200 patients have been treated worldwide. The introduction of CARs into lymphocytes has mainly used gammaretroviruses and lentiviruses, although nonviral approaches such as transposon-transposase systems (*73*) and CRISPR-cas (CRISPR, clustered regularly interspaced palindromic repeat) technology to introduce genes are also being explored (*74*). The single-chain antibody governs recognition of the antigen to be targeted, although the T cell is activated via the CD3-zeta chain signaling domain. In addition to the zeta chain, a variety of costimulatory molecules have been employed in retroviral constructs such as CD27, CD28, CD134, CD137, or ICOS that can profoundly influence the function of the CAR [reviewed in (*64*–*66*)]. Optimization of these costimulatory domains is a subject of active study. The results of CAR therapy for B cell malignancies might be confounded by the sensitivity of lymphomas and leukemias to the preparative chemotherapy regimen. Thus, delineation between the effects of the preparative therapy and those of the CAR T cells needs to be considered.

Multiple other B cell antigens are being studied as targets, including CD22, CD23, ROR-1, and the immunoglobulin light-chain idiotype expressed by the individual cancer (*65*). CARs targeting either CD33 or CD123 have been studied as a therapy for patients with acute myeloid leukemia, though the expression of these molecules on normal precursors can lead to prolonged myeloablation (*75*). BCMA is a tumor necrosis factor receptor family protein expressed on mature B cells and plasma cells and can be targeted on multiple myeloma (*65*). The Reed-Sternberg cell expresses CD30, and this target is being explored as a treatment for patients with refractory Hodgkin lymphoma (*75*–*77*).

Although CARs are being successfully applied to the treatment of hematologic malignancies, the lack of shared antigens on the surface of solid tumors that are not also expressed on essential normal tissues has severely limited the application of CARs to the treatment of solid tumors. Thyroglobulin is a potential target for some patients with thyroid cancers because thyroglobulin is present only in the thyroid gland and not on solid tissues. Neuroblastomas express GD2, which has been targeted by CARs (*78*). Mesothelin has also been forwarded as a potential target, although it is also expressed on normal tissues, including cells in the pericardium and pleural and peritoneal linings (*79*). A search is ongoing for other tissue-specific surface antigens expressed on tissues that are not essential for survival.

Cancer-testis antigens are a family of intracellular proteins that are expressed during fetal development but have highly restricted expression in adult normal tissues (*80*). There are more than

100 different members of this family of molecules whose expression is epigenetically up-regulated from 10 to 80% of cancer types using highly sensitive techniques. However, initial enthusiasm for targeting cancer-testes antigens has been tempered by the lack of high levels of protein expression of these antigens. Approximately 10% of common cancers appear to express enough protein to be suitable targets for antitumor T cells. There are low levels of some cancer-testes antigens expressed on normal tissues, and this can lead to untoward toxicities. The NYESO-1 cancer-testes antigen has been targeted via a human TCR transduced into autologous cells (*81*). ORs were seen in 5 of 11 patients with metastatic melanoma and 4 of 6 patients with highly refractory synovial cell sarcoma.

Looking to the future of ACT for the treatment of cancer

The continued development of ACT, as well as other immunologic approaches to the treatment of cancer, depends on the identification of suitable targets for immunologic attack. Although CARs have been successful in the treatment of hematologic malignancies and are likely to soon join the mainstream of oncologic treatment, the ability to treat common epithelial solid cancers, which account for ~90% of all cancer fatalities, is severely limited by the lack of suitable targets exclusive to cancer. Extensive searches for monoclonal antibodies that can recognize distinct determinants on the surface of solid cancers but not normal tissues have been in progress for more than 30 years, but few suitable determinants have been found. The EGFRvIII mutation on ~40% of high-grade glioblastomas is a rare example of a shared-surface mutation, and attempts to target this molecule using CARs are in progress (*82*). Shared mutations in intracellular proteins involved in oncogenesis—such as Braf in melanomas and Kras in pancreatic and other solid cancers—would be ideal ACT targets using conventional alpha-beta TCRs, though immunogenic epitopes have not yet been identified in these molecules. Driver and random somatic mutations occurring in many solid cancers may represent excellent targets for the treatment of solid tumors.

Opportunities to improve ACT involve the identification and development of specific antitumor T cells with the functional properties optimal for tumor destruction (*83*). One approach under active evaluation is the growth of cells under conditions that enable in vitro proliferation while limiting differentiation, such as the use of IL-21 or inhibitors that target the kinase AKT (*84*, *85*). Improved specific lymphodepleting preparative regimens and better design of the transducing vectors, including the incorporation of optimal costimulatory molecules, are likely to improve clinical results. Introduction of genes encoding other molecules such as the cytokine IL-12, which can profoundly alter the tumor microenvironment to favor antitumor immunity, has shown substantial promise in animal models (*86*). Enhanced methods for regulating the expression of these highly potent cytokine genes would be an important part of incorporating them into clinical treatment. The incorporation of "suicide" genes that can enable destruction of the transferred cells could add an extra level of safety when exploring genetic changes in lymphocytes (*87*).

Adoptive cell therapy is a more complex approach to the delivery of cancer treatment than many other types of immunotherapy and has often been criticized as impractical and too costly for widespread application. The need to develop highly personalized treatments for each patient does not fit into the paradigm of major pharmaceutical companies that depend on "off-the-shelf" reagents that can be widely distributed. However, curative immunotherapies for patients with common epithelial cancers will probably dictate the need for more personalized approaches. Several new biotechnology companies have arisen to meet the need to expand a patient's lymphocytes, and detailed genetic analysis of individual tumors is already commonplace at large academically affiliated medical centers. Although multiple commercial models have been proposed, widespread application of ACT will probably depend on the development of centralized facilities for producing tumor-reactive TILs or genetically modified lymphocytes that can then be delivered to the treating institution. The effectiveness of treatment will need to trump convenience of administration in the application of new effective approaches to cancer immunotherapy.

REFERENCES AND NOTES

1. E. J. Deforme, P. Alexander, *Lancet* **284**, 117–120 (1964).
2. A. Fefer, *Cancer Res.* **29**, 2177–2183 (1969).
3. E. Fernandez-Cruz, B. A. Woda, J. D. Feldman, *J. Exp. Med.* **152**, 823–841 (1980).
4. M. J. Berendt, R. J. North, *J. Exp. Med.* **151**, 69–80 (1980).
5. D. A. Morgan, F. W. Ruscetti, R. Gallo, *Science* **193**, 1007–1008 (1976).
6. S. A. Rosenberg, J. J. Mulé, P. J. Spiess, C. M. Reichert, S. L. Schwarz, *J. Exp. Med.* **161**, 1169–1188 (1985).
7. T. J. Eberlein, M. Rosenstein, S. A. Rosenberg, *J. Exp. Med.* **156**, 385–397 (1982).
8. J. H. Donohue *et al.*, *J. Immunol.* **132**, 2123–2128 (1984).
9. S. A. Rosenberg *et al.*, *N. Engl. J. Med.* **313**, 1485–1492 (1985).
10. S. A. Rosenberg, P. Spiess, R. Lafreniere, *Science* **233**, 1318–1321 (1986).
11. L. M. Muul, P. J. Spiess, E. P. Director, S. A. Rosenberg, *J. Immunol.* **138**, 989–995 (1987).
12. S. A. Rosenberg *et al.*, *N. Engl. J. Med.* **319**, 1676–1680 (1988).
13. M. E. Dudley *et al.*, *Science* **298**, 850–854 (2002).
14. H. W. H. G. Kessels, M. C. Wolkers, M. D. van den Boom, M. A. van den Valk, T. N. M. Schumacher, *Nat. Immunol.* **2**, 957–961 (2001).
15. R. A. Morgan *et al.*, *Science* **314**, 126–129 (2006).
16. J. N. Kochenderfer *et al.*, *Blood* **116**, 4099–4102 (2010).
17. S. A. Rosenberg *et al.*, *Clin. Cancer Res.* **17**, 4550–4557 (2011).
18. S. Pilon-Thomas *et al.*, *J. Immunother.* **35**, 615–620 (2012).
19. L. G. Radvanyi *et al.*, *Clin. Cancer Res.* **18**, 6758–6770 (2012).
20. M. J. Besser *et al.*, *Clin. Cancer Res.* **19**, 4792–4800 (2013).
21. J. J. Hong *et al.*, *Clin. Cancer Res.* **16**, 4892–4898 (2010).
22. S. A. Rosenberg *et al.*, *N. Engl. J. Med.* **323**, 570–578 (1990).
23. V. Bronte *et al.*, *J. Immunol.* **161**, 5313–5320 (1998).
24. X. Yao *et al.*, *Blood* **119**, 5688–5696 (2012).
25. L. Gattinoni *et al.*, *J. Exp. Med.* **202**, 907–912 (2005).
26. M. E. Dudley *et al.*, *J. Clin. Oncol.* **26**, 5233–5239 (2008).
27. C. M. Paulos *et al.*, *J. Clin. Invest.* **117**, 2197–2204 (2007).
28. N. P. Restifo, M. E. Dudley, S. A. Rosenberg, *Nat. Rev. Immunol.* **12**, 269–281 (2012).
29. L. Gattinoni *et al.*, *Nat. Med.* **17**, 1290–1297 (2011).
30. Y. Kawakami *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **91**, 6458–6462 (1994).
31. Y. Kawakami *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **91**, 3515–3519 (1994).
32. L. A. Johnson *et al.*, *Blood* **114**, 535–546 (2009).
33. M. S. Lawrence *et al.*, *Nature* **499**, 214–218 (2013).
34. T. Wölfel *et al.*, *Science* **269**, 1281–1284 (1995).
35. M. M. Gubin *et al.*, *Nature* **515**, 577–581 (2014).
36. S. L. Topalian *et al.*, *N. Engl. J. Med.* **366**, 2443–2454 (2012).
37. R. N. van Rooij *et al.*, *J. Clin. Oncol.* **31**, e439–e442 (2013).
38. S. D. Brown *et al.*, *Genome Res.* **24**, 743–750 (2014).
39. P. F. Robbins *et al.*, *Nat. Med.* **19**, 747–752 (2013).
40. Y. C. Lu *et al.*, *Clin. Cancer Res.* **20**, 3401–3410 (2014).
41. S. A. Rosenberg, J. C. Yang, N. P. Restifo, *Nat. Med.* **10**, 909–915 (2004).
42. C. A. Klebanoff, N. Acquavella, Z. Yu, N. P. Restifo, *Immunol. Rev.* **239**, 27–44 (2011).
43. T. N. Schumacher, R. D. Schreiber, *Science* **348**, 69–74 (2015).
44. E. Tran *et al.*, *Science* **344**, 641–645 (2014).
45. G. Gross, T. Waks, Z. Eshhar, *Proc. Natl. Acad. Sci. U.S.A.* **86**, 10024–10028 (1989).
46. J. Maher, R. J. Brentjens, G. Gunset, I. Rivière, M. Sadelain, *Nat. Biotechnol.* **20**, 70–75 (2002).
47. C. Imai *et al.*, *Leukemia* **18**, 676–684 (2004).
48. D. G. Song *et al.*, *Cancer Res.* **71**, 4617–4627 (2011).
49. C. A. Klebanoff *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **102**, 9571–9576 (2005).
50. C. Berger *et al.*, *J. Clin. Invest.* **118**, 294–305 (2008).
51. L. Gattinoni, D. J. Powell Jr., S. A. Rosenberg, N. P. Restifo, *Nat. Rev. Immunol.* **6**, 383–393 (2006).
52. L. Gattinoni *et al.*, *J. Clin. Invest.* **115**, 1616–1626 (2005).
53. V. R. Buchholz *et al.*, *Science* **340**, 630–635 (2013).
54. C. Gerlach *et al.*, *Science* **340**, 635–639 (2013).
55. P. Muranski *et al.*, *Immunity* **35**, 972–985 (2011).
56. D. C. Palmer *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **105**, 8061–8066 (2008).
57. C. H. Lamers *et al.*, *Mol. Ther.* **21**, 904–912 (2013).
58. M. R. Parkhurst *et al.*, *Mol. Ther.* **19**, 620–626 (2011).
59. R. A. Morgan *et al.*, *J. Immunother.* **36**, 133–151 (2013).
60. R. A. Morgan *et al.*, *Mol. Ther.* **18**, 843–851 (2010).
61. Y. Li *et al.*, *Nat. Biotechnol.* **23**, 349–354 (2005).
62. P. F. Robbins *et al.*, *J. Immunol.* **180**, 6116–6131 (2008).
63. G. P. Linette *et al.*, *Blood* **122**, 863–871 (2013).
64. R. A. Gardner, M. C. Jensen, *Cancer J.* **20**, 107–111 (2014).
65. S. Gill, C. H. June, *Immunol. Rev.* **263**, 68–89 (2015).
66. M. Sadelain, R. Brentjens, I. Rivière, *Cancer Discov.* **3**, 388–398 (2013).
67. J. N. Kochenderfer, S. A. Rosenberg, *Nat. Rev. Clin. Oncol.* **10**, 267–276 (2013).
68. M. Kalos *et al.*, *Sci. Transl. Med.* **3**, 95ra73 (2011).
69. S. A. Grupp *et al.*, *N. Engl. J. Med.* **368**, 1509–1518 (2013).
70. R. J. Brentjens *et al.*, *Sci. Transl. Med.* **5**, 177ra38 (2013).
71. J. N. Kochenderfer *et al.*, *J. Clin. Oncol.* **33**, 540–549 (2015).
72. D. W. Lee *et al.*, *Blood* **124**, 188–195 (2014).
73. H. Singh, H. Huls, P. Kebriaei, L. J. Cooper, *Immunol. Rev.* **257**, 181–190 (2014).
74. J. A. Doudna, E. Charpentier, *Science* **346**, 1258096 (2014).
75. I. Pizzitola *et al.*, *Leukemia* **28**, 1596–1605 (2014).
76. B. Savoldo *et al.*, *Blood* **110**, 2620–2630 (2007).
77. A. K. Gopal *et al.*, *Blood* **125**, 1236–1243 (2015).
78. C. U. Louis *et al.*, *Blood* **118**, 6050–6056 (2011).
79. Y. Zhao *et al.*, *Cancer Res.* **70**, 9053–9061 (2010).
80. M. J. Scanlan, A. O. Gure, A. A. Jungbluth, L. J. Old, Y. T. Chen, *Immunol. Rev.* **188**, 22–32 (2002).
81. P. F. Robbins *et al.*, *J. Clin. Oncol.* **29**, 917–924 (2011).
82. R. A. Morgan *et al.*, *Hum. Gene Ther.* **23**, 1043–1053 (2012).
83. A. Gros *et al.*, *J. Clin. Invest.* **124**, 2246–2259 (2014).
84. Y. Li, M. Bleakley, C. Yee, *J. Immunol.* **175**, 2261–2269 (2005).
85. J. G. Crompton *et al.*, *Cancer Res.* **75**, 296–305 (2015).
86. S. P. Kerkar *et al.*, *J. Clin. Invest.* **121**, 4746–4757 (2011).
87. A. Di Stasi *et al.*, *N. Engl. J. Med.* **365**, 1673–1683 (2011).
88. S. A. Rosenberg *et al.*, *J. Natl. Cancer Inst.* **86**, 1159–1166 (1994).
89. C. S. Hinrichs *et al.*, 2014 American Society of Clinical Oncology (ASCO) Annual Meeting, Chicago, IL, 30 May to 3 June 1014 (ASCO, Alexandria, VA, 2014). abstract LBA3008; http://meetinglibrary.asco.org/content/129263-144.
90. N. N. Huntcer *et al.*, *N. Engl. J. Med.* **358**, 2698–2703 (2008).
91. A. G. Chapuis *et al.*, *Sci. Transl. Med.* **5**, 174ra27 (2013).
92. S. L. Maude *et al.*, *N. Engl. J. Med.* **371**, 1507–1517 (2014).
93. M. L. Davila *et al.*, *Sci. Transl. Med.* **6**, 224ra25 (2014).
94. D. W. Lee *et al.*, *Lancet* **385**, 517–528 (2015).

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Neoantigens in cancer immunotherapy

Ton N. Schumacher[1]* and Robert D. Schreiber[2]*

The clinical relevance of T cells in the control of a diverse set of human cancers is now beyond doubt. However, the nature of the antigens that allow the immune system to distinguish cancer cells from noncancer cells has long remained obscure. Recent technological innovations have made it possible to dissect the immune response to patient-specific neoantigens that arise as a consequence of tumor-specific mutations, and emerging data suggest that recognition of such neoantigens is a major factor in the activity of clinical immunotherapies. These observations indicate that neoantigen load may form a biomarker in cancer immunotherapy and provide an incentive for the development of novel therapeutic approaches that selectively enhance T cell reactivity against this class of antigens.

Immunotherapies that boost the ability of endogenous T cells to destroy cancer cells have demonstrated therapeutic efficacy in a variety of human malignancies. Until recently, evidence that the endogenous T cell compartment could help control tumor growth was in large part restricted to preclinical mouse tumor models and to human melanoma. Specifically, mice lacking an intact immune system were shown to be more susceptible to carcinogen-induced and spontaneous cancers compared with their immunocompetent counterparts (*1*). With respect to human studies, the effects of the T cell cytokine interleukin-2 in a small subset of melanoma patients provided early clinical evidence of the potential of immunotherapy in this disease. In 2010, the field was revitalized by a landmark randomized clinical trial that demonstrated that treatment with ipilimumab, an antibody that targets the T cell checkpoint protein CTLA-4, improved overall survival of patients with metastatic melanoma (*2*). As a direct test of the tumoricidal potential of the endogenous T cell compartment, work by Rosenberg and colleagues demonstrated that infusion of autologous ex vivo expanded tumor-infiltrating lymphocytes can induce objective clinical responses in metastatic melanoma (*3*), and at least part of this clinical activity is due to cytotoxic T cells (*4*). Importantly, recent studies demonstrate that T cell–based immunotherapies are also effective in a range of other human malignancies. In particular, early-phase trials of antibodies that interfere with the T cell checkpoint molecule PD-1 have shown clinical activity in tumor types as diverse as melanoma, lung cancer, bladder cancer, stomach cancer, renal cell cancer, head and neck cancer, and Hodgkin's lymphoma (*5*). Based on the relationship between pretherapy CD8+ T cell infiltrates and response to PD-1 blockade in melanoma, cytotoxic T cell activity also appears to play a central role in this form of cancer immunotherapy (*6*).

An implicit conclusion from these clinical data is that in a substantial fraction of patients, the endogenous T cell compartment is able to recognize peptide epitopes that are displayed on major histocompatibility complexes (MHCs) on the surface of the malignant cells. On theoretical grounds, such cancer rejection epitopes may be derived from two classes of antigens. A first class of potential cancer rejection antigens is formed by nonmutated proteins to which T cell tolerance is incomplete—for instance, because of their restricted tissue expression pattern. A second class of potential cancer rejection antigens is formed by peptides that are entirely absent from the normal human genome, so-called neoantigens. For the large group of human tumors without a viral etiology, such neo-epitopes are solely created by tumor-specific DNA alterations that result in the formation of novel protein sequences. For virus-associated tumors, such as cervical cancer and a subset of head and neck cancers, epitopes derived from viral open reading frames also contribute to the pool of neoantigens.

As compared with nonmutated self-antigens, neoantigens have been postulated to be of particular relevance to tumor control, as the quality of the T cell pool that is available for these antigens is not affected by central T cell tolerance (*7*). Although a number of heroic studies provided early evidence for the immunogenicity of mutation-derived neoantigens [reviewed in (*8*)], technology to systemically analyze T cell reactivity against these antigens only became available recently. Here, we review our emerging understanding of the role of patient-specific neoantigens in current cancer immunotherapies and the implications of these data for the development of next-generation immunotherapies.

Exome-guided neoantigen identification: Process considerations

A large fraction of the mutations in human tumors is not shared between patients at

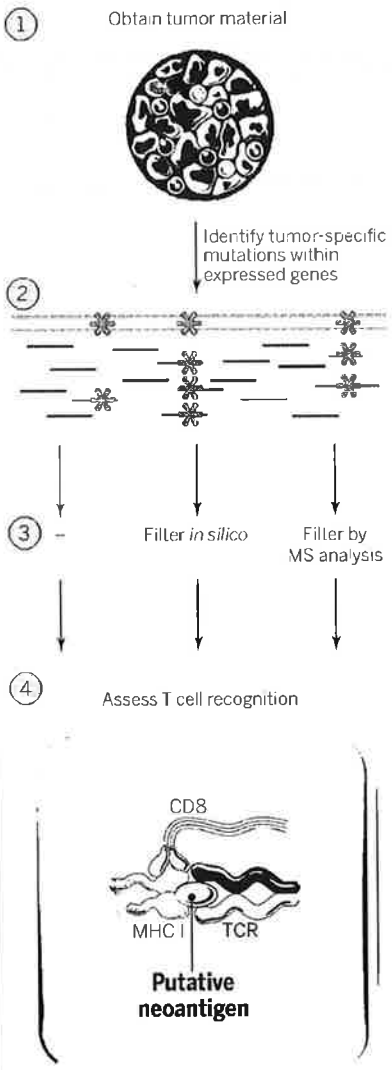

Fig. 1. Cancer exome–based identification of neoantigens. Tumor material is analyzed for nonsynonymous somatic mutations. When available, RNA sequencing data are used to focus on mutations in expressed genes. Peptide stretches containing any of the identified nonsynonymous mutations are generated in silico and are either left unfiltered (*16, 17*), filtered through the use of prediction algorithms [e.g., (*10–13*)], or used to identify MHC-associated neoantigens in mass spectrometry data (*15, 20*). Modeling of the effect of mutations on the resulting peptide-MHC complex may be used as an additional filter (*20*). Resulting epitope sets are used to identify physiologically occurring neoantigen-specific T cell responses by MHC multimer–based screens (*13, 22*) or functional assays [e.g., (*11, 12*)], within both CD8+ [e.g., (*11–13, 19, 39*)] and CD4+ (*16, 18*) T cell populations. Alternatively, T cell induction strategies are used to validate predicted neoantigens [e.g., (*10, 20*)].

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meaningful frequencies and may therefore be considered patient-specific. Because of this, technologies to interrogate T cell reactivity against putative mutation-derived neoantigens need to be based on the genome of an individual tumor. With the development of deep-sequencing technologies, it has become feasible to identify the mutations present within the protein-encoding part of the genome (the exome) of an individual tumor with relative ease and thereby predict potential neoantigens (*9*). Two studies in mouse models provided the first direct evidence that such a cancer exome–based approach can be used to identify neoantigens that can be recognized by T cells (*10*, *11*). In brief, for all mutations that resulted in the formation of novel protein sequence, potential MHC binding peptides were predicted, and the resulting set of potential neoantigens was used to query T cell reactivity. Subsequent studies have demonstrated that cancer exome–based analyses can also be exploited in a clinical setting, to dissect T cell reactivity in patients who are treated by either tumor-infiltrating lymphocyte (TIL) cell therapy or checkpoint blockade (*12*, *13*). Furthermore, following this early work, the identification of neoantigens on the basis of cancer exome data has been documented in a variety of experimental model systems and human malignancies (*10*–*22*).

The technological pipeline used to identify neoantigens in these different studies has varied substantially, and further optimization is likely possible (Fig. 1). Accepting the limitations of probing the mutational profile of a tumor in a single biopsy (*23*), the genetic analysis of the tumor itself can be considered a robust process. Specifically, based on the analysis of neoantigens previously identified by other means, the false-negative rate of cancer exome sequencing is low—i.e., the vast majority of neoantigens occur within exonic sequence for which coverage is sufficient (*24*). At the same time, it is apparent from unbiased screening efforts—in which the entire collection of identified mutations was used to query T cell reactivity—that the vast majority of mutations within expressed genes do not lead to the formation of neoantigens that are recognized by autologous T cells (*16*, *17*). Because of this, a robust pipeline that can be used for the filtering of cancer exome data is essential, in particular for tumors with high mutational loads.

How can such filtering be performed? With the set of mutations within expressed genes as a starting point, two additional requirements can be formulated. First, a mutated protein needs to be processed and then presented as a mutant peptide by MHC molecules. Second, T cells need to be present that can recognize this peptide-MHC complex. In two recent preclinical studies, presentation of a handful of predicted neoantigens by MHC molecules was experimentally demonstrated by mass spectrometry (*15*, *20*), and this approach may form a valuable strategy to further optimize MHC presentation algorithms. At the same time, the sensitivity of mass spectrometry is presently still limited, thereby likely resulting in a substantial fraction of false negatives. For this reason, but also because of logistical issues, implementation of this approach in a clinical setting is unlikely to happen soon. Lacking direct evidence for MHC presentation, as can be provided by mass spectrometry, presentation of neoantigens by MHC class I molecules may be predicted using previously established algorithms that analyze aspects such as the likelihood of proteasomal processing, transport into the endoplasmic reticulum, and affinity for the relevant MHC class I alleles. In addition, gene expression levels (or perhaps preferably protein translation levels) may potentially also be used to help predict epitope abundance (*25*).

Although most neoantigen identification studies have successfully used criteria for epitope prediction that are similar to those previously established for the identification of pathogen-derived epitopes [e.g., (*12*, *13*)], Srivastava and colleagues have argued that neoantigens in a transplantable mouse tumor model display very different properties from viral antigens and generally have a very low affinity for MHC class I (*14*). Although lacking a satisfactory explanation to reconcile these findings, we do note that the vast majority of human neoantigens that have been identified in unbiased screens do display a high predicted MHC binding affinity (*24*, *26*). Likewise, minor histocompatibility antigens, an antigen class that is conceptually similar to neoantigens, are correctly identified by classical MHC binding algorithms (*27*). Moreover, the mutations that were identified in a recent preclinical study as forming tumor-specific mutant antigens that could induce therapeutic tumor rejection when used in tumor vaccines (*15*) were not predicted to be significant using the Srivastava approach. Another potential filter step that has been suggested examines whether the mutation is expected to improve MHC binding, rather than solely alter the T cell receptor (TCR)–exposed surface of the mutant peptide. However, with examples of both categories in both mouse models and human data, the added value of such a filter may be relatively modest (*11*, *15*, *20*, *26*). For MHC class I restricted neoantigens, conceivably the biggest gain in prediction algorithms can be made with respect to identification of the subset of MHC binding peptides that can successfully be recognized

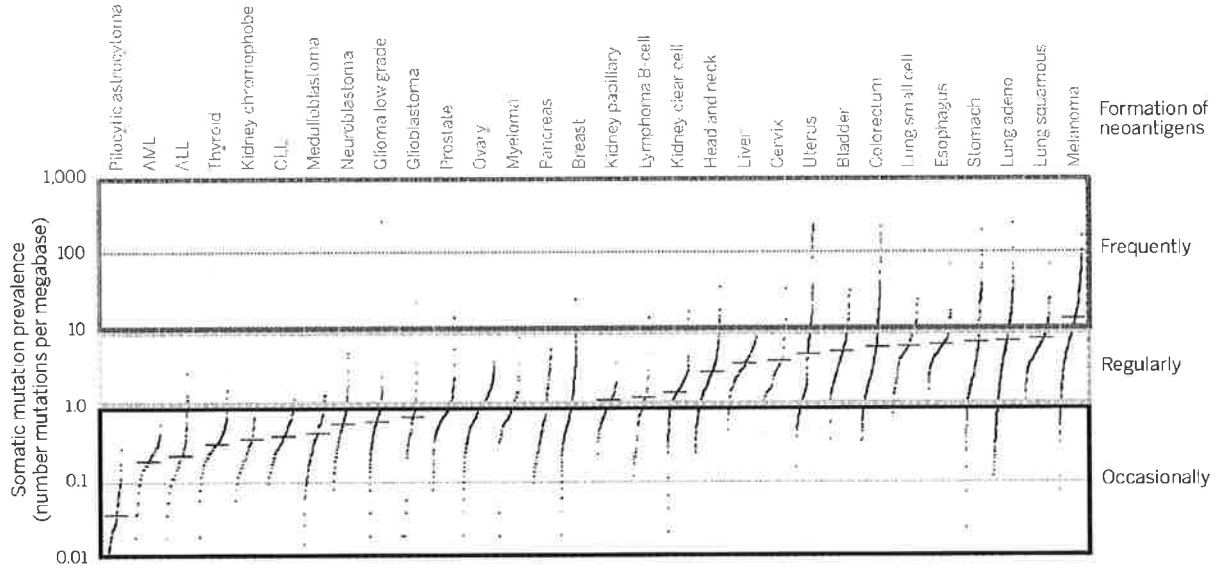

Fig. 2. Estimate of the neoantigen repertoire in human cancer. Data depict the number of somatic mutations in individual tumors. Categories on the right indicate current estimates of the likelihood of neoantigen formation in different tumor types. Adapted from (*50*). It is possible that the immune system in melanoma patients picks up on only a fraction of the available neoantigen repertoire, in which case the current analysis will be an underestimate. A value of 10 somatic mutations per Mb of coding DNA corresponds to ~150 nonsynonymous mutations within expressed genes.

by the TCR repertoire. With respect to this, the nature of the central TCR-exposed residues of MHC-bound peptides has been shown to be associated with peptide immunogenicity (*28*). By the same token, alterations at these sites may potentially be picked up by the immune system more readily (*20*). However, a substantial further experimental effort is required to evaluate to what extent algorithms that predict immunogenicity can facilitate the identification of MHC class I–restricted neoantigens. For MHC class II–restricted neoantigens, it will be important to obtain a better understanding not only of peptide immunogenicity but also of the basic factors that determine the efficiency of epitope presentation.

Size and nature of the neoantigen repertoire

Large-scale analyses of neoantigen-specific T cell reactivity have now been carried out for a substantial number of patients, mostly in melanoma (*12*, *13*, *16*, *17*). With the caveat of a potential selection bias toward patients with a clinical benefit upon immunotherapeutic intervention, these analyses provide a first estimate of the frequency with which the immune system recognizes the neoantigens that are formed as a consequence of mutations. The first and arguably most important conclusion that can be drawn from these analyses is that the T cell–based immune system reacts to both MHC class I–restricted (*12*, *13*, *17*) and MHC class II–restricted neoantigens (*16*) in a large fraction of melanoma patients. The second conclusion that can be drawn from these analyses is that only a very small fraction of the nonsynonymous mutations in expressed genes in these tumors leads to the formation of a neoantigen for which CD4+ or CD8+ T cell reactivity can be detected within tumor-infiltrating lymphocytes.

What do these observations mean for the potential formation of neoantigen repertoires in other human malignancies? Most human melanomas have a mutational load above 10 somatic mutations per megabase (Mb) of coding DNA, and this is apparently sufficient to lead to the frequent formation of neoantigens that can be seen by T cells. Based on these data, formation of neoantigens that can potentially be recognized by autologous T cells is expected to also be common for other tumors with a mutational load above 10 somatic mutations per Mb (corresponding to approximately 150 nonsynonymous mutations within expressed genes) (Fig. 2). This group contains a sizable fraction of high-prevalence tumor types such as lung cancer and colorectal cancer. If formation of neoantigens is a frequent event in tumors with mutational loads above 10 somatic mutations per Mb, many tumors with a mutational load of 1 to 10 per Mb may still be expected to carry neoantigens that can be recognized by T cells. However, as based on the fact that even for melanomas with a mutational load around 10 mutations per Mb, T cell reactivity is not always observed (*16*), tumor types with a mutational load below 1 mutation per Mb appear less likely to commonly express neoantigens that can be recognized by autologous T cells.

Although this analysis provides a useful first sketch of the expected relevance of neoantigens in different tumor types, three important factors should be taken into account. First, by relying on the presence of preexisting T cell reactivity as a readout, the human studies carried out to date will only detect neoantigens that were immunogenic during in vivo tumor outgrowth (either spontaneously or boosted by therapy). It is conceivable that not all tumor-expressed neoantigens induce an autologous T cell response—for instance, because they are not efficiently cross presented. In addition, at least in preclinical models, there is evidence for immunodominance of tumor antigens, where the immune system becomes so fixated on particular antigens that it ignores other antigens that are both present and detectable in the tumor (*29*). If only a fraction of the available neoantigens would normally elicit T cell reactivity, the analyses carried out to date may underestimate the actual neoantigen repertoire. As a second consideration, it is important to realize that the formation of neoantigens is a probabilistic process in which each additional mutation increases the odds that a relevant neoantigen is created. Thus, in this "neoantigen lottery," there will be cases in which despite a high mutational load, neoantigen-specific T cell reactivity is lacking or, vice versa, in which a tumor with only a handful of mutations will express an MHC class I– or class II–restricted neoantigen. Third, although we here make a prediction with regard to the frequency with which neoantigens that can potentially be recognized by the TCR repertoire are formed, it should be kept in mind that the presence of a neoantigen does not equal the induction of T cell reactivity. Human tumors vary substantially in the composition of their microenvironment, and this is likely to influence the ability of the T cell pool to respond to mutated antigens. Related to this, from a conceptual point of view, therapeutic manipulation of T cell reactivity would seem particularly attractive for tumor types that do express large numbers of antigens but in which the tumor microenvironment hinders the activation of the T cells that recognize them.

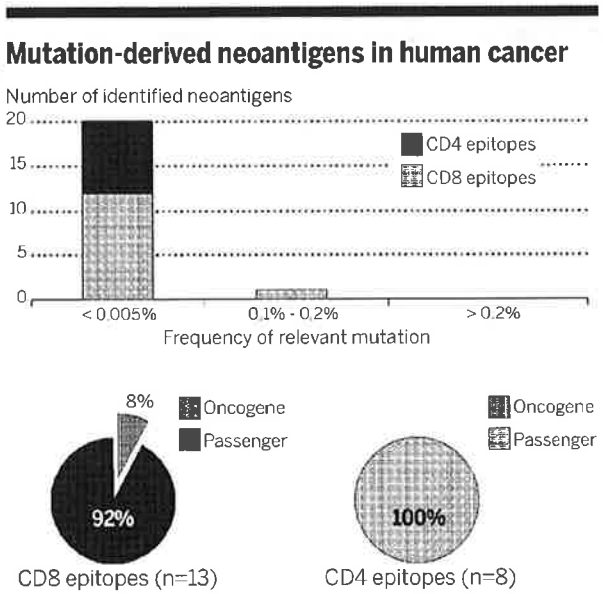

Fig. 3. Characteristics of melanoma neoantigens. (**Top**) For a group of CD4+ T cell neoantigens (8 epitopes) and CD8+ T cell neoantigens (13 epitopes) identified by cancer exome–based screens, the frequency of mutation of that residue in a cohort of ~20,000 human tumor samples (*51*) is depicted. (**Bottom**) For the same group of CD4+ T cell and CD8+ T cell neoantigens, the fraction of encoding mutations that occurs within known oncogenes (*52*) is depicted.

What are the characteristics of mutation-derived neoantigens in human cancer, both with respect to the genes from which they are derived and the frequency with which they occur within the patient population? In an ideal world, neoantigens would be derived from essential oncogenes and occur in large patient groups, to both reduce the likelihood of escape and facilitate clinical interventions that enhance T cell reactivity against them. Clearly, T cell responses do sometimes occur against MHC class I–restricted (*30*) and MHC class II–restricted neoantigens in validated oncogenes that are shared between subgroups of patients (*31*). At the same time, it is apparent that, at least in melanoma, the bulk of the neoantigen-specific T cell response is directed toward mutated proteins that are essentially unique to that tumor and that are unlikely to play a key role in cellular transformation (Fig. 3, top and bottom) (*16*). A direct implication of this bias in neoantigen-specific T cell reactivity toward patient-specific passenger mutations is that the targeting of defined neoantigens will likely require the development of personalized immunotherapies.

Extrinsic influences on the tumor antigenic landscape

The neoantigen repertoire expressed in a clinically apparent cancer may have been substantially influenced by the developing tumor's interaction with the immune system that occurs even before it becomes clinically apparent. This is the process of "cancer immunoediting" that has been well documented in preclinical cancer models (*1*, *32*, *33*). In its most complex form, cancer immunoediting may occur in three phases: elimination, in which the innate and adaptive immune systems work

together to recognize a developing tumor and destroy it before it becomes clinically apparent; equilibrium, in which residual occult tumor cells not destroyed in the elimination phase are held in a state of tumor dormancy as a consequence of adaptive immune system activity and undergo "editing"; and escape, in which edited tumor cells are no longer recognized or controlled by immune processes, begin to grow progressively, induce an immunosuppressive tumor microenvironment, and then emerge as clinically apparent cancers. Recent work has demonstrated that T cells play a major role in shaping the immunogenicity of developing cancers—i.e., "edit" tumor immunogenicity—and exert this effect by at least two mechanisms. First, T cells can shape tumor antigenicity/immunogenicity through an immunoselection process by destroying tumor cells that express strong tumor-specific mutant antigens, leaving behind tumor cells that either express weaker antigens (some of which may still be mutant tumor antigens) or are incapable of expressing antigens (e.g., those that have developed mutations in antigen processing or presentation) (*11*). Second, chronic T cell attack on a tumor has been shown to silence expression of certain tumor-specific antigens through epigenetic mechanisms in a preclinical model (*34*). Strikingly, a recent study, based on analysis of thousands of the Cancer Genome Atlas solid tumor samples, showed that, in particular in colorectal cancer, mutated peptides predicted to bind to autologous MHC class I molecules are less frequent than expected by chance, an observation that is consistent with immune-based selection (*35*). By extension, the combination of cell-extrinsic forces such as cancer immunoediting and the stochastic nature of epitopes arising from tumor-specific mutations may help drive the heterogeneous mutational—and by inference, antigenic—landscapes that have been noted in certain tumors (*23*). As such, the antigenic heterogeneity of tumors might explain some of the differences in response that individual patients display to checkpoint blockade therapy. Individuals who develop durable responses to checkpoint blockade may be those whose tumors retain sufficient antigenicity to render them sensitive to the heightened immune function that accompanies cancer immunotherapy, despite not being controlled by naturally occurring antitumor immune responses.

Role of neoantigens in cancer immunotherapy

On theoretical grounds, two factors should determine the relative importance of neoantigens and nonmutated self-antigens in the effects of cancer immunotherapies such as checkpoint blockade and TIL therapy: first, the frequency with which T cell responses against the two antigen classes occur; second, the relative potency of T cell responses specific for the two antigen classes. Recent work in mouse models using transplantable carcinogen-induced cancers has demonstrated that checkpoint blockade alters both the quality of the neoantigen-specific intratumoral T cell response (as reflected by common- and treatment-specific changes in gene expression in CD8+ TILs isolated from tumor-bearing mice treated with antibodies to CTLA-4 and/or PD-1) and the magnitude of this T cell response (seen with CTLA-4 or combined CTLA-4/PD-1 blockade but not with PD-1 blockade only) (*15*). Because the neoantigens identified in this model serve as cancer rejection antigens, these data provide compelling evidence that checkpoint blockade acts at least in part through neoantigen-specific T cell reactivity in this setting. However, in the case of human melanoma, where autochthonous tumors may be in contact with the immune system for years, the situation is more complicated. As discussed above, T cell reactivity against neoantigens is common in melanoma. Furthermore, a case report has shown that such reactivity can be enhanced by anti–CTLA-4 treatment (*13*). However, T cell reactivity against nonmutated shared antigens is also observed in the majority of melanoma patients, and broadening of this T cell response has been documented following both TIL therapy and anti–CTLA-4 treatment (*36*, *37*). Thus, although the murine data show that neoantigen-specific T cell reactivity can be critical to the effects of checkpoint blockade, the human data are presently only consistent with this possibility.

What other data are available with respect to this issue? If recognition of neoantigens is an important component of cancer immunotherapy, one would expect tumor types with high numbers of mutations to be characterized by strong T cell responses and to be particularly sensitive to immunotherapy. Furthermore, also within a given tumor type, response rate should correlate with mutational load. Evidence for a role of neoantigens in driving the strength of the intratumoral T cell response is provided by the observation that the presence of CD8+ T cells in cancer lesions, as read out using RNA sequencing data, is higher in tumors with a high mutational burden (*38*). Furthermore, an extensive analysis by Hacohen and colleagues has demonstrated that the level of transcripts associated with cytolytic activity of natural killer cells and T cells correlates with mutational load in a large series of human tumors (*35*). With respect to the effects of immunotherapy in tumors with different mutational loads, in non–small cell lung cancer patients treated with anti–PD-1, mutational load shows a strong correlation with clinical response (*22*). Likewise, in melanoma patients treated with ipilimumab, an antibody to CTLA-4, long-term benefit is also associated with a higher mutational load, although the effect appears less profound in this setting (*39*). A striking observation in the latter study has been that the predicted MHC binding neoantigens in patients with a long-term clinical benefit were enriched for a large series of tetrapeptide motifs that were not found in tumors of patients with no or minimal clinical benefit. An appealing interpretation of these data is that the neoantigen-specific T cell response is preferentially directed toward a subset of mutant sequences, something that could facilitate bioinformatic identification of neoantigens for therapeutic targeting. However, analysis of the sequence properties of human neoantigens identified in other studies does not show the profound bias toward these tetrapeptide signatures that would be predicted if their role were central in the tumor-specific T cell response (*40*), and conceivably the identified tetrapeptide motifs play a different role.

"The genetic damage that on the one hand leads to oncogenic outgrowth can also be targeted by the immune system to control malignancies."

It will be valuable to extend the analysis of genomic determinants of tumor cell sensitivity to cancer immunotherapeutics to other malignancies. However, because of the probabilistic nature of neoantigen generation, mutational load will by itself always remain an imperfect biomarker, even in a situation in which neoantigen reactivity is the sole tumor-specific T cell reactivity that is relevant to tumor control. Furthermore, the formation of tumor-specific antigens is only one of a number of essential conditions for a successful immune attack on cancer cells, a concept that is well described by the cancer-immunity cycle introduced by Chen and Mellman (*41*). As an example, genetic inactivation of the β_2-microglobulin subunit of MHC class I molecules is a relatively frequent event in some tumor types (*42*). In addition, a recent analysis of genetic alterations that are present in tumors with high immune activity provides evidence for a series of other escape mechanisms (*35*). In such cases, in which the cancer-immunity cycle is disrupted at another site, the number of neoantigens produced is unlikely to still be of much relevance. Because of this interdependence of different phases of the cancer-immunity cycle, the combined use of assay systems that report on these different phases appears warranted.

Arguably the most direct data on the relevance of neoantigen-specific T cells in human tumor control comes from a small number of clinical studies that involve infusion of defined T cell populations or infusion of TCR-transduced T cells. Encouragingly, a recent case report demonstrated regression of a metastatic cholangiocarcinoma by infusion of a CD4+ T cell product that was highly enriched for reactivity against an MHC class II–restricted neoantigen (*18*). Combined with the observation that, at least in melanoma, CD4+ T cell recognition of neoantigens is a frequent event (*16*), these data underscore the potential clinical relevance of MHC class II–restricted neoantigens. Comparison of the clinical effects of TIL therapy with that of T cells modified with TCRs recognizing different shared antigens can also be considered informative. Infusion of T cells modified with TCRs directed against the gp100 and MART-1

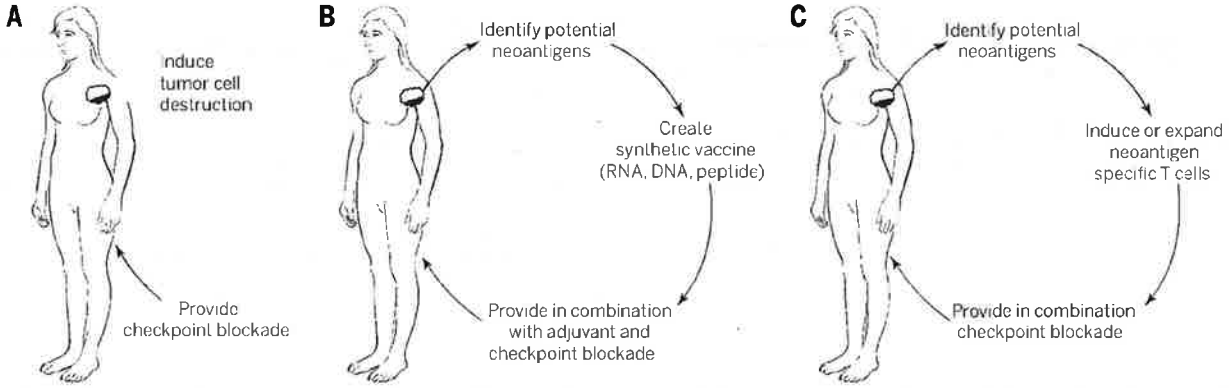

Fig. 4. Strategies to target the patient-specific neoantigen repertoire. (**A**) Immunotherapy is given in combination with interventions such as radiotherapy that enhance exposure to autologous neoantigens. (**B**) Potential neoantigens are identified as in Fig. 1 steps 1 to 3, a patient-specific vaccine is produced, and this vaccine is given together with adjuvant and T cell checkpoint-blocking antibodies. (**C**) Potential neoantigens are identified as in Fig. 1 steps 1 to 3, T cells that are specific for these neoantigens are induced or expanded in vitro, and the resulting T cell product is given together with T cell checkpoint-blocking antibodies.

melanocyte differentiation antigens, a prominent class of self-antigens in melanoma, shows a relatively modest clinical effect that is accompanied by substantial on-target toxicity against healthy melanocytes (*43*). Because this toxicity is relatively infrequent in TIL therapy, these data strongly suggest that T cell reactivity against the melanocyte differentiation antigens is not a major driver of the antitumor activity of this therapy. At the same time, there is data showing that T cell products directed against NY-eso-1, one of the nonmutant self-antigens from the family of cancer/germline antigens that show very limited expression in healthy tissue, can display substantial antitumor activity (*44*, *45*). Thus, although the available data support the notion that T cell recognition of neoantigens contributes substantially to the effects of the currently used immunotherapies, it would not be justified to dismiss a potential contribution of T cell responses against a subset of nonmutant antigens. A direct comparison of the antitumor activity of neoantigen-specific and self-antigen–specific T cells obtained from individual patients would be useful to further address this issue.

Therapeutic use of the patient-specific neoantigen repertoire

Based on the fact that, at least in tumors with high mutational loads, the amount of DNA damage is sufficient for the immune system to see one or multiple epitopes as foreign, it becomes of interest to stimulate neoantigen-specific T cell responses in cancer patients. Such stimulation can obviously only be of value if the strength of the neoantigen-specific T cell response is otherwise a limiting factor in tumor control. Human data on this important issue are lacking. However, in mouse models, vaccination with defined neoantigens has been shown to result in increased tumor control (*10*, *14*, *15*, *20*), providing sufficient rationale for the clinical development of neoantigen-directed therapeutics. Because the majority of possible neoantigens are specific to the individual being treated (Fig. 3), such therapeutic approaches will in most cases entail personalized immunotherapies that exploit either the antigen repertoire in the tumor cells themselves or information on that repertoire, as obtained by tumor sequencing (Fig. 4). As a first approach, a combination of checkpoint-blocking antibodies with therapeutic interventions—such as tumor radiotherapy, oncolytic viruses, or autologous tumor cell vaccines—that can increase neoantigen exposure to the T cell–based immune system may be synergistic (Fig. 4A). As a downside, as compared to molecularly defined vaccines, the neoantigens released by such strategies will be diluted by the large amount of nonmutant peptides that are also present. In addition, control over the maturation signals received by antigen-presenting cells is relatively limited. Nevertheless, because of the relative ease of clinical development of some of these combination therapies, extensive testing of such therapies is warranted.

To allow a more defined targeting of the neoantigen repertoire in human tumors, two alternative approaches should be considered, in both cases relying on sets of potential neoantigens as identified by sequencing of tumor material (Fig. 4, B and C). First, synthetic vaccines may be produced that contain or encode a set of predicted neoantigens. Although still a substantial departure from the classical pharmaceutical model, clinical development of such personalized vaccines is within reach (*46*–*48*). Mouse model data support the clinical translation of this approach, and the two most pressing questions appear to be (i) whether our ability to predict the most relevant neoantigens is already sufficiently advanced and (ii) how such vaccines may best be administered. Second, the information obtained from tumor sequencing may be used to create neoantigen-specific T cell products in vitro. This may involve either the expansion of neoantigen-specific T cell populations that can already be detected within tumor tissue or in blood or the de novo induction of such cells.

Regardless of the strategy used to enhance neoantigen-specific T cell reactivity, it will likely prove important to target multiple neoantigens simultaneously in order to prevent tumor escape by editing of the mutated epitope concerned (*1*). In addition, it may be prudent to avoid the targeting of mutations in gene products that are seen by the immune system in autoimmune disease to avoid induction of or exacerbation of cancer-associated autoimmune disease (*49*).

Concluding remarks

Based on data obtained over the past few years, it is plausible that neoantigen-specific T cell reactivity forms a major "active ingredient" of successful cancer immunotherapies. In other words, the genetic damage that on the one hand leads to oncogenic outgrowth can also be targeted by the immune system to control malignancies. Based on this finding, it will be important to engineer therapeutic interventions by which neoantigen-specific T cell reactivity is selectively enhanced. Because of the tumor-restricted expression of the antigens that are being targeted, these personalized cancer immunotherapies offer the promise of high specificity and safety. Conceivably, the boosting of neoantigen-specific T cell reactivity that can be achieved with such personalized immunotherapies will further increase the spectrum of human malignancies that respond to cancer immunotherapy.

REFERENCES AND NOTES

1. R. D. Schreiber, L. J. Old, M. J. Smyth, *Science* **331**, 1565–1570 (2011).
2. F. S. Hodi *et al.*, *N. Engl. J. Med.* **363**, 711–723 (2010).
3. C. S. Hinrichs, S. A. Rosenberg, *Immunol. Rev.* **257**, 56–71 (2014).
4. M. E. Dudley *et al.*, *J. Clin. Oncol.* **31**, 2152–2159 (2013).
5. P. Sharma, J. P. Allison, *Science* **348**, 56–61 (2015).
6. P. C. Tumeh *et al.*, *Nature* **515**, 568–571 (2014).
7. E. Gilboa, *Immunity* **11**, 263–270 (1999).
8. B. Heemskerk, P. Kvistborg, T. N. Schumacher, *EMBO J.* **32**, 194–203 (2013).

9. N. H. Segal *et al.*, *Cancer Res.* **68**, 889–892 (2008).
10. J. C. Castle *et al.*, *Cancer Res.* **72**, 1081–1091 (2012).
11. H. Matsushita *et al.*, *Nature* **482**, 400–404 (2012).
12. P. F. Robbins *et al.*, *Nat. Med.* **19**, 747–752 (2013).
13. N. van Rooij *et al.*, *J. Clin. Oncol.* **31**, e439–e442 (2013).
14. F. Duan *et al.*, *J. Exp. Med.* **211**, 2231–2248 (2014).
15. M. M. Gubin *et al.*, *Nature* **515**, 577–581 (2014).
16. C. Linnemann *et al.*, *Nat. Med.* **21**, 81–85 (2015).
17. Y. C. Lu *et al.*, *Clin. Cancer Res.* **20**, 3401–3410 (2014).
18. E. Tran *et al.*, *Science* **344**, 641–645 (2014).
19. D. A. Wick *et al.*, *Clin. Cancer Res.* **20**, 1125–1134 (2014).
20. M. Yadav *et al.*, *Nature* **515**, 572–576 (2014).
21. M. Rajasagi *et al.*, *Blood* **124**, 453–462 (2014).
22. N. A. Rizvi *et al.*, *Science* **348**, 124–128 (2015).
23. M. Gerlinger *et al.*, *N. Engl. J. Med.* **366**, 883–892 (2012).
24. M. M. van Buuren, J. J. Calis, T. N. Schumacher, *Oncoimmunology* **3**, e28836 (2014).
25. M. H. Fortier *et al.*, *J. Exp. Med.* **205**, 595–610 (2008).
26. E. F. Fritsch *et al.*, *Cancer Immunol. Res.* **2**, 522–529 (2014).
27. C. A. Van Bergen *et al.*, *Cancer Res.* **70**, 9073–9083 (2010).
28. J. J. A. Calis *et al.*, *PLOS Comput. Biol.* **9**, e1003266 (2013).
29. M. E. Dudley, D. C. Roopenian, *J. Exp. Med.* **184**, 441–447 (1996).
30. I. Wölfel *et al.*, *Science* **269**, 1281–1284 (1995).
31. T. Schumacher *et al.*, *Nature* **512**, 324–327 (2014).
32. C. M. Koebel *et al.*, *Nature* **450**, 903–907 (2007).
33. V. Shankaran *et al.*, *Nature* **410**, 1107–1111 (2001).
34. M. DuPage, C. Mazumdar, L. M. Schmidt, A. F. Cheung, T. Jacks, *Nature* **482**, 405–409 (2012).
35. M. S. Rooney, S. A. Shukla, C. J. Wu, G. Getz, N. Hacohen, *Cell* **160**, 48–61 (2015).
36. P. Kvistborg *et al.*, *Sci. Transl. Med.* **6**, 254ra128 (2014).
37. P. Kvistborg *et al.*, *Oncoimmunology* **1**, 409–418 (2012).
38. S. D. Brown *et al.*, *Genome Res.* **24**, 743–750 (2014).
39. A. Snyder *et al.*, *N. Engl. J. Med.* **371**, 2189–2199 (2014).
40. T. N. Schumacher, C. Kesmir, M. M. van Buuren, *Cancer Cell* **27**, 12–14 (2015).
41. D. S. Chen, I. Mellman, *Immunity* **39**, 1–10 (2013).
42. C. M. Cabrera *et al.*, *Tissue Antigens* **61**, 211–219 (2003).
43. L. A. Johnson *et al.*, *Blood* **114**, 535–546 (2009).
44. N. N. Hunder *et al.*, *N. Engl. J. Med.* **358**, 2698–2703 (2008).
45. P. F. Robbins *et al.*, *Clin. Cancer Res.* **21**, 1019–1027 (2015).
46. V. Boisgérin *et al.*, *Br. J. Cancer* **111**, 1469–1475 (2014).
47. E. F. Fritsch, N. Hacohen, C. J. Wu, *Oncoimmunology* **3**, e29311 (2014).
48. R. H. Vonderheide, K. L. Nathanson, *Nat. Med.* **19**, 1098–1100 (2013).
49. C. G. Joseph *et al.*, *Science* **343**, 152–157 (2014).
50. L. B. Alexandrov *et al.*, *Nature* **500**, 415–421 (2013).
51. S. A. Forbes *et al.*, *Nucleic Acids Res.* **43**, D805–D811 (2015).
52. P. A. Futreal *et al.*, *Nature Rev. Cancer* **4**, 177 (2004).

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REVIEWS

T cell exclusion, immune privilege, and the tumor microenvironment

Johanna A. Joyce[1]* and Douglas T. Fearon[2,3]*

Effective immunotherapy promotes the killing of cancer cells by cytotoxic T cells. This requires not only that cancer-specific T cells be generated, but also that these T cells physically contact cancer cells. The coexistence in some patients of cancer cells and T cells that recognize them indicates that tumors may exhibit the phenomenon of immune privilege, in which immunogenic tissue is protected from immune attack. Here, we review the evidence that stromal cells of the tumor microenvironment mediate this restriction by excluding T cells from the vicinity of cancer cells. Overcoming this T cell checkpoint may thus enable optimal immunotherapy.

The microenvironment of tumors contains numerous cell types in addition to cancer cells, which include bone marrow–derived inflammatory cells, lymphocytes, blood vessels, fibroblastic cells, and the extracellular matrix composed of collagen and proteoglycans (*1*, *2*). The importance of a stromal microenvironment, especially one that has characteristics of a "wound" or regenerating tissue, has been recognized for at least a century (*3*), but its possible role in blunting an immune attack of cancer cells awaited the discovery of adaptive cellular immunity. In 1960, Klein and colleagues found that when mice developed primary methylcholanthrene-induced sarcomas, they also developed an antitumor immune response mediated by lymph node cells to a secondary challenge comprising cancer cells derived from the primary tumor (*4*). The paradoxical and critical finding of the study was that this anticancer immune response did not control the growth of the primary tumor, despite its ability to prevent the establishment of a secondary tumor comprising cancer cells derived from the primary tumor. In traditional immunological terminology, the primary tumor evaded immune control by establishing an immune-privileged microenvironment that is functionally analogous to that of certain normal tissues, such as the eye (*5*).

Unambiguous evidence for the inability in humans of a systemic immune response to eliminate immunogenic cancer cells was provided by Boon's studies 30 years later of the antigens that elicit specific $CD8^+$ T cell responses in melanoma patients (*6*). Cloned $CD8^+$ T cells from a melanoma patient were used to identify the antigen expressed by that patient's cancer: MAGE-A1. The explicit demonstration of the coexistence of a progressing melanoma with melanoma-specific T cells in this patient implicitly raised the question of why the T cells did not control the growth of the cancer. Immunoediting, or the elimination of immunogenic cancer cells (*7*), could be excluded, which left the possibility of immune suppression by the tumor microenvironment (TME). Despite this evidence that the presence of antigen-specific $CD8^+$ T cells alone may not be sufficient for the control of cancer, a major pharmaceutical company recently conducted phase III trials in patients with non–small cell lung cancer (NSCLC) of the clinical efficacy of vaccination with the MAGE-A3 antigen (MAGRIT, NCT00480025). The study did not meet its primary end point of extending disease-free survival and was discontinued in 2014. Moreover, Rosenberg and colleagues reported evidence of disease recurrence in melanoma patients despite very high levels of vaccine-induced circulating T cells and no evidence of antigen loss by the cancer cells (*8*).

The discovery of melanoma-specific T cells in patients led to another strategy to increase the frequency of cancer-specific T cells in patients, that of adoptively transferring large numbers of in vitro expanded tumor-infiltrating lymphocytes (TILs). As discussed elsewhere in this issue of *Science* (*9*), this approach has shown some efficacy, which has been of major importance to the field by serving as proof that the immune system has the potential to control cancer (*10*). However, adoptive T cell therapy (ACT) with TILs has not had the dramatic success of ACT with virus-specific $CD8^+$ T cells to immunodeficient bone marrow transplant recipients with cytomegalovirus infection (*11*) or Epstein-Barr virus–associated lymphoproliferative disorders (*12*). Differences in the microenvironments of virally infected tissues and cancers may account for these distinct outcomes, with the latter being immune-suppressive. Another important point of comparison is that the TME of solid cancers is likely to be fundamentally different to that of the leukemias, in which clinical trials of ACT with T cells expressing chimeric antigen receptors, so-called CAR T cells, have demonstrable efficacy (*9*). These findings raise the possibility that increasing the frequency of cancer-specific T cells, by whatever means, may be more effective if combined with an approach that alters the immune-suppressive TME.

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Neoantigens in cancer immunotherapy

Ton N. Schumacher and Robert D. Schreiber

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From: David Chang [DChang@KitePharma.com]
Sent: Tuesday, April 14, 2015 12:08 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
CC: Arie Belldegrun
Subject: Kite: NCI visit on April 23

Hi Steve,

The attendees from Kite will be :

- Adrian Bot
- Jeff Wiezorek
- Tony Polverino (VP, Research)
- Margo Roberts
- Myself
- There are two additional people I forgot to mention:
  - Rajul Jain, MD, PhD, senior director of clinical development under Jeff W
  - Stephanie Astrow (senior director of translational research under Adrian Bot)

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Look forward to seeing you next Thursday.

David

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From: David Chang [DChang@KitePharma.com]
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To: Rosenberg, Steven A. (NIH/NCI) [E]
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Subject: RE: Kite: NCI visit on April 23

Dear Steve,

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Thanks

David

From: David Chang
Sent: Tuesday, April 14, 2015 9:08 AM
To: Steve Rosenberg (SAR@nih.gov)
Cc: Arie Belldegrun
Subject: Kite: NCI visit on April 23

Hi Steve,

The attendees from Kite will be :

- Adrian Bot
- Jeff Wiezorek
- Tony Polverino (VP, Research)
- Margo Roberts
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From: Rosenberg, Steven A. (NIH/NCI) [E]
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To: David Chang MD PhD (dchang@kitepharma.com)
Subject: FW: SOP

FYI

Steven A. Rosenberg M.D., Ph.D.
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301-496-4164
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-----Original Message-----
From: Miettinen, Markku (NIH/NCI) [E]
Sent: Friday, April 10, 2015 3:10 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: RE: SOP

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From: Rosenberg, Steven A. (NIH/NCI) [E]
Sent: Thursday, April 09, 2015 9:26 AM
To: Miettinen, Markku (NIH/NCI) [E]
Subject: FW: SOP

Markku

Could you please call me about this?

Steve

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-----Original Message-----
From: Raffeld, Mark (NIH/NCI) [E]
Sent: Sunday, February 15, 2015 6:31 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Re: SOP

Hi Steve,

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Mark

On 2/15/15 11:36 AM, "Rosenberg, Steven A. (NIH/NCI) [E]"
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>Mark
>

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>Steve
>
>Steven A. Rosenberg M.D., Ph.D.
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>-----Original Message-----
>From: Toomey, Mary Ann (NIH/NCI) [E]
>Sent: Thursday, February 12, 2015 5:13 PM
>To: Rosenberg, Steven A. (NIH/NCI) [E]
>Subject: FW: SOP
>

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>-----Original Message-----
>From: Raffeld, Mark (NIH/NCI) [E]
>Sent: Friday, October 03, 2014 1:31 PM
>To: Rosenberg, Steven A. (NIH/NCI) [E]
>Cc: Toomey, Mary Ann (NIH/NCI) [E]
>Subject: Re: SOP
>

>Hi Steve, Mary,
>Here are the conditions for the PROPRIETARY INFORMATION,REDACTED PER AGREEMENT
>Mark

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>
>
>On 10/3/14 11:57 AM, "Rosenberg, Steven A. (NIH/NCI) [E]"
><sar@mail.nih.gov> wrote:
>
>>Mark
>>

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>>Steve
>>
>>
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From: David Chang [DChang@KitePharma.com]
Sent: Thursday, April 16, 2015 8:28 PM
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Steve,

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Thanks you.

David

-----Original Message-----
From: Rosenberg, Steven A. (NIH/NCI) [E] [mailto:sar@mail.nih.gov]
Sent: Thursday, April 16, 2015 8:54 AM
To: David Chang
Subject: FW: SOP

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Sent: Friday, April 10, 2015 3:10 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: RE: SOP

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

From: Rosenberg, Steven A. (NIH/NCI) [E]
Sent: Thursday, April 09, 2015 9:26 AM
To: Miettinen, Markku (NIH/NCI) [E]
Subject: FW: SOP

Markku

Could you please call me about this?

Steve

Steven A. Rosenberg M.D., Ph.D.

Chief, Surgery Branch
National Cancer Institute
10 Center Drive MSC 1201
CRC Room 3-3940
Bethesda, MD 20892
301-496-4164
sar@nih.gov

-----Original Message-----
From: Raffeld, Mark (NIH/NCI) [E]
Sent: Sunday, February 15, 2015 6:31 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Re: SOP

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

On 2/15/15 11:36 AM, "Rosenberg, Steven A. (NIH/NCI) [E]"
<sar@mail.nih.gov> wrote:

>
PROPRIETARY INFORMATION,REDACTED PER AGREEMENT
>
>Steve
>
>Steven A. Rosenberg M.D., Ph.D.
>Chief, Surgery Branch
>National Cancer Institute
>10 Center Drive MSC 1201
>CRC Room 3-3940
>Bethesda, MD 20892
>301-496-4164
>sar@nih.gov
>
>
>
>-----Original Message-----

>From: Toomey, Mary Ann (NIH/NCI) [E]
>Sent: Thursday, February 12, 2015 5:13 PM
>To: Rosenberg, Steven A. (NIH/NCI) [E]
>Subject: FW: SOP
>

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

>

>-----Original Message-----
>From: Raffeld, Mark (NIH/NCI) [E]
>Sent: Friday, October 03, 2014 1:31 PM
>To: Rosenberg, Steven A. (NIH/NCI) [E]
>Cc: Toomey, Mary Ann (NIH/NCI) [E]
>Subject: Re: SOP
>

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

>
>On 10/3/14 11:57 AM, "Rosenberg, Steven A. (NIH/NCI) [E]"
><sar@mail.nih.gov> wrote:
>
>>Mark
>>

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

>>
>>Steve
>>
>>
>>Steven A. Rosenberg M.D., Ph.D.
>>Chief, Surgery Branch
>>National Cancer Institute
>>10 Center Drive MSC 1201
>>CRC Room 3-3940
>>Bethesda, MD 20892
>>301-496-4164
>>sar@nih.gov
>>
>

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Sunday, April 19, 2015 8:06 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Fwd: Juno Therapeutics Inc: UPenn Mesothelin CAR-T Data Suggest More Work Ahead in Solid Tumors

Hi Steve,

FYI. A Morgan Stanley report, PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Arie

Sent from my iPad

From: Matthew Harrison [mailto:Matthew.Harrison@morganstanley.com]
Sent: Sunday, April 19, 2015 4:53 PM
To: Craig Gordon (CRDG)
Subject: Juno Therapeutics Inc: UPenn Mesothelin CAR-T Data Suggest More Work Ahead in Solid Tumors

Morgan Stanley

APRIL 19, 2015 GMT

Juno Therapeutics Inc (JUNO.O)

UPenn Mesothelin CAR-T Data Suggest More Work Ahead in Solid Tumors

Morgan Stanley Research
North America

Matthew Harrison
+1 212 761-8055
Matthew S Pommer
+1 212 761-3335
Amy Le
+1 212 761-0840

Juno Therapeutics Inc
Stock Rating : Equal-weight

Biotechnology
Industry View : In-Line

Download the complete report (5 pgs)

Initial data from 6 subjects treated with UPenn's CART-meso construct achieved limited cell expansion (2x below CD19), persistence (~28 days) and efficacy (4/6 stable disease). While safety was encouraging, the limited cell persistence and expansion may have been the key factor in limiting AEs.

UPenn data on mesothelin directed CAR-T presented at AACR on 4/19: Six subjects were given a mesothelin directed CAR-T construct using an anti-mesothelin murine derived single-chain variable fragment (SS1) and 4-1BB as the costimulatory domain. The cells were transduced with a lentiviral vector as opposed to the prior mRNA vector. Doses ranged from 1-3x10^7 to 1-3x10^8 cells/m^2 and there was no pre-treatment ablative chemotherapy. 2 pts had mesothelioma, 2 pancreatic cancer and 2 ovarian cancer. Prior chemotherapies ranges from 4-12 with 1-3 prior surgeries in addition.

Key efficacy conclusions: 4/6 patients achieved stable disease at 28 days, suggesting limited efficacy. Peak cell expansion occurred around day 7-21, with cell persistence no longer than 28 days. The limited cell persistence and expansion were likely related to the murine scFv as well as the lack of pre-treatment chemo and the presence of B-cells (unlike those with hematological malignancies). Importantly, T-cells did reach the correct target sites, incl. the peritoneum, mesenterium and liver.

Key safety conclusions: Gr3/4 AEs included sepsis, anemia, pleural effusions, tachypnea and dyspnea. Investigators pointed to no cytokine release or macrophage activation syndrome. However, given the low achieved cell doses and lack of efficacy, we can't be sure if the better than expected tolerability for the target (given that it is widely express on the lungs and cardiac tissue) is due to the low dose and limited persistence of the cells or actual safety of the construct.

While CAR-T stocks ran on the abstract title, data suggests still a lot more work in solid tumors: Given the lack of efficacy and its subsequent impact on establishing the safety profile of the CART-meso construct, we continue to believe solid tumors represent a sig. opportunity for CAR-T, but much more work remains before we can have confidence that CAR-T therapy will be able to access the solid tumor market. While Juno has interesting solid tumor constructs (armored CARs, bi-specific CARSs) which could modulate the tumor microenvironment, we await initial data before forming any conclusions.

Download the complete report (5 pgs)

iPad, iPhone, and Android: visit the Apple App Store or Android Market and download the Morgan Stanley Research app

---

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Monday, April 20, 2015 2:15 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: FW: Pressure on CAR-T Stocks Overdone; More to Come on CAR-T Cell Therapies Tomorrow at AACR - Guggenheim Securities, LLC

FYI

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Arie Belldegrun, M.D.,FACS
President and CEO
Chairman, Board of Directors; Founder
Kite Pharma Inc.

2225 Colorado Avenue
Santa Monica, CA 90404
Tel: 310-622-9093
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arie@kitepharma.com

www.kitepharma.com

From: Lisa Burns [mailto:LBurns@burnsmc.com]
Sent: Monday, April 20, 2015 10:56 AM
To: Arie Belldegrun; Cynthia Butitta
Cc: Kate Bechtold; Linda Barnes; Carol Werther; Justin Jackson; Ilana Portner; Rebecca Cohen
Subject: Pressure on CAR-T Stocks Overdone; More to Come on CAR-T Cell Therapies Tomorrow at AACR - Guggenheim Securities, LLC

From: Butler, Tony [mailto:tony.butler@guggenheimpartners.com]
Sent: Monday, April 20, 2015 1:32 PM
To: Lisa Burns
Subject: Pressure on CAR-T Stocks Overdone; More to Come on CAR-T Cell Therapies Tomorrow at AACR - Guggenheim Securities, LLC

GUGGENHEIM

People. Ideas. Success.

Pressure on CAR-T Stocks Overdone; More to Come on CAR-T Cell Therapies Tomorrow at AACR

SECTOR: Biopharmaceuticals

April 20, 2015

Tony Butler, PhD, Analyst | 212 823 6540 | tony.butler@guggenheimpartners.com

CLICK HERE TO ACCESS THIS REPORT

CAR-T stocks down on solid tumor data at AACR: KITE (BUY, intraday $59.43) and JUNO (NEUTRAL, intraday $58.69) are down 8.84% and 9.70% percent, respectively, versus the S&P, which is up 0.96% since the prior trading session. This may be due to lack of responses in a CAR-T cell response directed at a solid tumor. These data were presented yesterday at AACR in Philadelphia. In our view, pressure on the CAR-T stocks may be somewhat overdone.

Yesterday, Dr. Janos Tanyi, MD, PhD, from the University of Pennsylvania reported new data on CAR-T cells targeting mesothelin on solid tumors (2 ovarian, 2 epithelial mesothelioma, and 1 pancreatic). The presentation was titled: Safety and feasibility of chimeric antigen receptor modified T cells directed against mesothelin (CART-meso) in patients with mesothelin expressing cancers. The data demonstrated no responses in this solid tumor. KITE, JUNO, and Novartis (NVS, NC, intraday $102.64) to date, have been doing studies in blood tumors, and strong efficacy data was presented at ASH'14. The lack of responses could be due to many factors, but in our view, it was due to a lack of "persistence" of the CAR-T cells in the body.

Data demonstrated no responses in solid tumor: UPenn presented updates on their CAR-T meso program (n=6) in mesothelioma (n=2), pancreatic (n=2) and ovarian carcinoma (n=2) that did not show any responses. Six subjects treated with UPenn's CART-meso construct achieved limited cell expansion at 2x below CD19 (peak cell expansion occurred around day 7-21, with cell persistence maxing out at 28 days). 4/6 patients achieved stable disease at 28 days, which leads us to believe additional data on efficacy will be needed to achieve successful valuation in solid tumors.

Safety positive, but could be correlated with low efficacy: Key Grade 3 and 4 AE's included anemia, sepsis, pleural effusions and tachypnea/dyspnea. No cytokine release (CR) was cited. However, the low dose and viral persistence of the cells could be affecting tolerability, so we await further readouts to make conclusions on true safety of the construct.

Lack of responses due to persistence of the CAR in the body: Looking at the data, the limited cell persistence and expansion could likely be related to two main points: 1) the murine scFv, 2) the lack of chemotherapy "pre-conditioning" as noted in previous CAR-T infusion processes. This is an advantage in chemo pre-conditioning inclusive processes as lymphodepletion kills off current immune cells that allow new ones to form, which may be more active in mounting an immune response.

CAR-T stocks ran ahead of conference based on abstract, but data suggests still more work on solid tumors below: JUNO has interesting solid tumor constructs (armored CARs and bi-specific CARs as described in our initiation here), which can modulate the tumor micro-evironment, but we await further data before considering this in our valuation. Competitors Ziopharm Oncology (ZIOP, NC, intraday $10.87)/Intrexon (XON, NC, intraday $41.90) offer inducible CAR-T's using their RheoSwitch technology (currently being tested in breast and melanoma), which allows access to the cells after they have been infused to modulate their activity. As we have mentioned in previous notes, we believe data in solid tumors could provide significant potential upside and would be a primary driver of sustainable earnings power and differentiated for the CAR-T companies beyond competition in liquid tumors.

Still positive on CAR-T, upcoming AACR presentations: Data to date has been in blood tumors and has had excellent results. Much research is going on into understanding how to increase persistence of CAR-T cells in the body, understanding the tumor microenvironment, and appropriately preparing the patient to maximize a response. It has, and continues to be our view, that future therapy in oncology will include CAR-T cell and TCR modalities. Tomorrow at AACR presentations by Carl June, Michel Sedelain Philip Greenberg and Malcolm Brenner will discuss adoptive T-Cell therapy and the utility of CARs/TCRs in greater depth.

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Monday, April 20, 2015 8:08 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: RE: Pressure on CAR-T Stocks Overdone; More to Come on CAR-T Cell Therapies Tomorrow at AACR - Guggenheim Securities, LLC

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Thank you for all your help.

Arie Belldegrun, M.D., FACS
President and CEO
Chairman of the Board; Founder
Kite Pharma Inc.

2225 Colorado Ave
Santa Monica, CA 90404

310 824-9999 x102
arie@kitepharma.com

www.kitepharma.com

From: Rosenberg, Steven A. (NIH/NCI) [E] [mailto:sar@mail.nih.gov]
Sent: Monday, April 20, 2015 1:55 PM
To: Arie Belldegrun
Subject: RE: Pressure on CAR-T Stocks Overdone; More to Come on CAR-T Cell Therapies Tomorrow at AACR - Guggenheim Securities, LLC

Arie

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Attached is the 1 hour talk I gave at AACR on Saturday. Many of the Kite people were at the talk.

Steve

Steven A. Rosenberg M.D., Ph.D.
Chief, Surgery Branch
National Cancer Institute
10 Center Drive MSC 1201
CRC Room 3-3940
Bethesda, MD 20892
301-496-4164
sar@nih.gov

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Arie Belldegrun, M.D.,FACS
President and CEO
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Tel: 310-622-9093
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arie@kitepharma.com

www.kitepharma.com

From: Lisa Burns [mailto:LBurns@burnsmc.com]

Sent: Monday, April 20, 2015 10:56 AM
To: Arie Belldegrun; Cynthia Butitta
Cc: Kate Bechtold; Linda Barnes; Carol Werther; Justin Jackson; Ilana Portner; Rebecca Cohen
Subject: Pressure on CAR-T Stocks Overdone; More to Come on CAR-T Cell Therapies Tomorrow at AACR - Guggenheim Securities, LLC

From: Butler, Tony [mailto:tony.butler@guggenheimpartners.com]
Sent: Monday, April 20, 2015 1:32 PM
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GUGGENHEIM People. Ideas. Success.

Pressure on CAR-T Stocks Overdone; More to Come on CAR-T Cell Therapies Tomorrow at AACR

SECTOR: Biopharmaceuticals April 20, 2015

Tony Butler, PhD, Analyst | 212 823 6540 | tony.butler@guggenheimpartners.com

CLICK HERE TO ACCESS THIS REPORT

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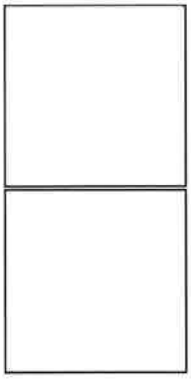

From: David Chang [DChang@KitePharma.com]
Sent: Tuesday, April 21, 2015 2:50 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]; Antoni Ribas - Med-Hemat & Onc (aribas@mednet.ucla.edu); Arie Belldegrun; Cynthia Butitta; Ton Schumacher; Helen Kim
Subject: Kite TCR
Attachments: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

All the best,
David

David D. Chang, MD, PhD
Executive Vice President of R&D
and Chief Medical Officer
Kite Pharma, Inc
office: 310-622-9094
PERSONAL INFORMATION,REDACTED PER AGREEMENT

www.kitepharma.com

Email Attachment

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT,WITHHELD THROUGH THE NEXT 6 pages

From: David Chang [DChang@KitePharma.com]
Sent: Tuesday, April 21, 2015 2:50 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]; Antoni Ribas - Med-Hemat & Onc (aribas@mednet.ucla.edu); Arie Belldegrun; Cynthia Butitta; Ton Schumacher; Helen Kim
Subject: Kite TCR
Attachments: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

All the best,
David

David D. Chang, MD, PhD
Executive Vice President of R&D
and Chief Medical Officer
Kite Pharma, Inc
office: 310-622-9094
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www.kitepharma.com

Email Attachment

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT,WITHHELD THROUGH THE NEXT 6 Pages

From: David Chang [DChang@KitePharma.com]
Sent: Tuesday, April 21, 2015 5:47 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Kite- NCI visit this Thursday

Hi Steve,

Is there a schedule for Kite team's visit this Thursday? Some folks are traveling from the AACR and would like to know when to show up to NCI.

Thanks,

David

David D. Chang, M.D., Ph.D.
office: (310) 622-9094
PERSONAL INFORMATION,REDACTED PER AGREEMENT

www.kitepharma.com

Sent from my iPhone

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Tuesday, April 21, 2015 6:17 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: FW: Thank you

Thank you so much for your time and participation.
See below,

Arie Belldegrun, M.D.,FACS
President and CEO
Chairman, Board of Directors; Founder
Kite Pharma Inc.

2225 Colorado Avenue
Santa Monica, CA 90404
Tel: 310-622-9093
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arie@kitepharma.com

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-----Original Message-----
From: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT
Sent: Tuesday, April 21, 2015 2:44 PM
To: Arie Belldegrun; David Chang; Cynthia Butitta; Helen Kim; Margo Roberts; Ton Schumacher
Cc: Rubino, Stephen
Subject: Thank you

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

From: David Chang [DChang@KitePharma.com]
Sent: Wednesday, April 22, 2015 1:07 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
CC: Cofield, Laila (NIH/NCI) [E]
Subject: FW: Kite: NCI visit on April 23

Hi Steve,

I am will be boarding on a plane to Dulles in about 2 hours. Just in case, the email below outlines our visit team and the meetings we would like to have.

Thanks,
David

From: David Chang
Sent: Tuesday, April 14, 2015 4:17 PM
To: Steve Rosenberg (SAR@nih.gov)
Cc: Arie Belldegrun
Subject: RE: Kite: NCI visit on April 23

Dear Steve,

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Thanks

David

From: David Chang
Sent: Tuesday, April 14, 2015 9:08 AM
To: Steve Rosenberg (SAR@nih.gov)
Cc: Arie Belldegrun
Subject: Kite: NCI visit on April 23

Hi Steve,

The attendees from Kite will be :

- Adrian Bot
- Jeff Wiezorek
- Tony Polverino (VP, Research)
- Margo Roberts
- Myself
- There are two additional people I forgot to mention:
  - Rajul Jain, MD, PhD, senior director of clinical development under Jeff W
  - Stephanie Astrow (senior director of translational research under Adrian Bot)

Meetings we would like to have:

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Look forward to seeing you next Thursday.

David

David D. Chang, MD, PhD
Executive Vice President of R&D
and Chief Medical Officer
Kite Pharma, Inc
office: 310-622-9094
PERSONAL INFORMATION,REDACTED PER AGREEMENT

www.kitepharma.com

From: David Chang [DChang@KitePharma.com]
Sent: Thursday, April 23, 2015 4:20 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Kite

Steve,

Thank you for arranging a very productive schedule for Kite team.

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

David

David D. Chang, M.D., Ph.D.
office: (310) 622-9094
PERSONAL INFORMATION,REDACTED PER AGREEMENT

www.kitepharma.com

Sent from my iPad

From: David Chang [DChang@KitePharma.com]
Sent: Thursday, April 23, 2015 4:25 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Fwd: Kite Pharma (KITE, BUY): Competitor CAR-T to EGFRviii to Show Preliminary Data at ASGCT Meeting
Attachments: ATT00001.png

FYI.

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Thanks,

David

David D. Chang, M.D., Ph.D.
office: (310) 622-9094
PERSONAL INFORMATION,REDACTED PER AGREEMENT

www.kitepharma.com

Sent from my iPad

Begin forwarded message:

From: Cynthia Butitta <CButitta@KitePharma.com>
Date: April 23, 2015 at 10:56:21 AM PDT
To: Aric Belldegrun <Aric@kitepharma.com>, David Chang <DChang@KitePharma.com>, Helen Kim <HKim@KitePharma.com>
Subject: FW: Kite Pharma (KITE, BUY): Competitor CAR-T to EGFRviii to Show Preliminary Data at ASGCT Meeting

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

From: Biren Amin [mailto:bamin@jefferies.com]
Sent: Thursday, April 23, 2015 6:56 AM
To: Cynthia Butitta
Subject: Kite Pharma (KITE, BUY): Competitor CAR-T to EGFRviii to Show Preliminary Data at ASGCT Meeting

Thank you for considering Biren Amin (Biotechnology) in the 2015 Institutional Investor All-America Research Poll.
Click here to request a ballot.

Kite Pharma (KITE): Competitor CAR-T to EGFRviii to Show Preliminary Data at ASGCT Meeting

Rating BUY
Price Target $84.00
Price $57.56

Key Takeaway
Novartis/UPenn will be presenting preliminary data from its pilot study on the first 3 patients that have been treated v autologous CAR-T towards the EGFRviii mutation at the ASGCT Meeting on Thurs, May 14. Given Novartis appears comn to moving the CART-EGFRviii program forward, we believe early data from this pilot trial may be informative on the outlo KITE/NCI's EGFRviii CAR-T program.

Novartis to Present Preliminary Data for EGFRviii CAR-T in First-In-Human Pilot Study at ASGCT Meeting in May: No

(NOVN VX, CHF100.20, Buy) will be presenting preliminary data from its first-in-human pilot study on the first three patients that been treated w/ its autologous CAR-T directed towards the EGFRviii mutation at the American Society of Gene & Cell Therapy (AS Meeting on Thurs morning, May 14 '15. To date, Novartis/UPenn have found that the infusion of the CART-EGFRviii cells to be sa no evidence of off-target toxicity, including cross-reactivity to WT-EGFR. There were no clinical or laboratory signs of systemic cyt release syndrome (CRS), and all three patients showed significant expansion of CART-EGFRviii cells despite the use of steroids pts. At this meeting, the investigators will present preliminary response data as measured by MRI. The pilot trial is expected to enr pts w/ recurrent GBM or residual GBM after resection in pts that are positive for EGFRviii.

Data May Provide Glimpse into Outlook of KITE's CART-EGFRviii in GBM: We note that the data may provide a glimpse int outlook of the PI/II trial of CART-EGFRviii in GBM being run by the NCI and which may be one of the next IND candidates for KITE NCI study is an open-label, single arm PI/II study of 160 pts ages 18-66 w/ malignant gliomas expressing EGFRviii. Pts will rece non-myeloablative but lymphocyte depleting preparative regimen (cyclophosphamide and fludarabine) followed by intravenous infus CART-EGFRviii and aldesleukin, and pts in the NCI trial will remain in the hospital for ~4 wks for tx and will return on a monthly bas follow-up. The 1 EP will be to evaluate the safety of administration of CART-EGFRviii and determine the safe number cells that c infused, and to determine the 6-mo PFS. Once an MTD has been established patients will be enrolled in one of two recurrent groups - those receiving steroids at outset of treatment vs those not treated w/ steroids at initiation of cell therapy treatment. We would like to highlight that the EGFRviii CAR-T program is currently not in our estimates for KITE and therefore could offer add'l ups

Biren Amin *, Equity Analyst
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Hugo Ong, Ph.D. *, Equity Associate
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Shaunak Deepak *, Equity Analyst
(212) 284-2020 sdeepak@jefferies.com
Sridhar Vempati, PhD *, Equity Associate
(212) 284-2535 svempati@jefferies.com
Timothy Chou *, Equity Associate
(212) 284-2571 tchou@jefferies.com

*** Jefferies LLC**

Jefferies

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Thursday, April 23, 2015 8:40 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: RE: Kite Pharma (KITE, BUY): Competitor CAR-T to EGFRviii to Show Preliminary Data at ASGCT Meeting

Steve,

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Thanks,

Arie Belldegrun, M.D.,FACS
President and CEO
Chairman, Board of Directors; Founder
Kite Pharma Inc.

2225 Colorado Avenue
Santa Monica, CA 90404
Tel: 310-622-9093
PERSONAL INFORMATION,REDACTED PER AGREEMENT
arie@kitepharma.com

www.kitepharma.com

From: Rosenberg, Steven A. (NIH/NCI) [E] [mailto:sar@mail.nih.gov]
Sent: Thursday, April 23, 2015 8:33 AM
To: Arie Belldegrun
Subject: RE: Kite Pharma (KITE, BUY): Competitor CAR-T to EGFRviii to Show Preliminary Data at ASGCT Meeting

Arie

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Steven A. Rosenberg M.D., Ph.D.
Chief, Surgery Branch
National Cancer Institute
10 Center Drive MSC 1201
CRC Room 3-3940
Bethesda, MD 20892
301-496-4164
sar@nih.gov

From: Arie Belldegrun [mailto:Arie@kitepharma.com]
Sent: Thursday, April 23, 2015 10:07 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Fwd: Kite Pharma (KITE, BUY): Competitor CAR-T to EGFRviii to Show Preliminary Data at ASGCT Meeting

Another UPENN venture of early data release....

Arie Belldegrun, MD FACS
President and CEO, Chairman
Kite Pharma

www.kitepharma.com

Begin forwarded message:

> **From:** Ran Nussbaum <ran@pontifax.com>
> **Date:** April 23, 2015 at 06:57:51 PDT
> **To:** Ohad Hammer <ohad@pontifax.com>, William Go <wgo@kitepharma.com>, "Margo Roberts" <MRoberts@kitepharma.com>, Jeff Wiczorek <JWiezorek@kitepharma.com>, Helen Kim <HKim@kitepharma.com>, David Chang <DChang@kitepharma.com>, "Cynthia Butitta" <CButitta@kitepharma.com>, Arie Belldegrun <arie@kitepharma.com>, Antoni Ribas <ARibas@mednet.ucla.edu>, Adrian Bot <ABot@kitepharma.com>
> **Subject: Fwd: Kite Pharma (KITE, BUY): Competitor CAR-T to EGFRviii to Show Preliminary Data at ASGCT Meeting**

Best Regards,
Ran Nussbaum
(Sent from my iPhone)

Begin forwarded message:

> **From:** Biren Amin <bamin@jefferies.com>
> **Date:** 23 באפריל 2015 בשעה 16:56:50 GMT+3
> **To:** <ran@pontifax.com>
> **Subject: Kite Pharma (KITE, BUY): Competitor CAR-T to EGFRviii to Show Preliminary Data at ASGCT Meeting**
> **Reply-To:** "Biren Amin" <bamin@jefferies.com>

Kite Pharma (KITE): Competitor CAR-T to EGFRviii to Show Preliminary Data at ASGCT Meeting

Rating BUY
Price Target $84.00
Price $57.56

Key Takeaway

Novartis/UPenn will be presenting preliminary data from its pilot study on the first 3 patients that have been treated w/ its autologous CAR-T towards the EGFRvii mutation at the ASGCT Meeting on Thurs, May 14. Given Novartis appears committed to moving the CART-EGFRviii program forward, we believe early data fro pilot trial may be informative on the outlook of KITE/NCI's EGFRviii CAR-T program.

Novartis to Present Preliminary Data for EGFRviii CAR-T in First-In-Human Pilot Study at ASGCT Meeting in May: Novartis (NOVN VX, CHF100.20, Buy) will b presenting preliminary data from its first-in-human pilot study on the first three patients that have been treated w/ its autologous CAR-T directed towards the EGFRviii mutati American Society of Gene & Cell Therapy (ASGCT) Meeting on Thurs morning, May 14 '15. To date, Novartis/UPenn have found that the infusion of the CART-EGFRviii safe w/ no evidence of off-target toxicity, including cross-reactivity to WT-EGFR. There were no clinical or laboratory signs of systemic cytokine release syndrome (CRS), a patients showed significant expansion of CART-EGFRviii cells despite the use of steroids in 2/3 pts. At this meeting, the investigators will present preliminary response data measured by MRI. The pilot trial is expected to enroll 12 pts w/ recurrent GBM or residual GBM after resection in pts that are positive for EGFRviii.

Data May Provide Glimpse into Outlook of KITE's CART-EGFRviii in GBM: We note that the data may provide a glimpse into the outlook of the PI/II trial of CART-E GBM being run by the NCI and which may be one of the next IND candidates for KITE. The NCI study is an open-label, single arm PI/II study of 160 pts ages 18-66 w/ mali gliomas expressing EGFRviii. Pts will receive a non-myeloablative but lymphocyte depleting preparative regimen (cyclophosphamide and fludarabine) followed by intraveno infusion of CART-EGFRviii and aldesleukin, and pts in the NCI trial will remain in the hospital for ~4 wks for tx and will return on a monthly basis for follow-up. The 1 EP evaluate the safety of administration of CART-EGFRviii and determine the safe number cells that can be infused, and to determine the 6-mo PFS. Once an MTD has been est patients will be enrolled in one of two recurrent GBM groups - those receiving steroids at outset of treatment vs those not treated w/ steroids at initiation of cell therapy treatm also would like to highlight that the EGFRviii CAR-T program is currently not in our estimates for KITE and therefore could offer add'l upside.

Biren Amin *, Equity Analyst
(212) 284-8162 bamin@jefferies.com
Hugo Ong, Ph.D. *, Equity Associate
(212) 323-3364 hong@jefferies.com
Shaunak Deepak *, Equity Analyst
(212) 284-2020 sdeepak@jefferies.com
Sridhar Vempati, PhD *, Equity Associate
(212) 284-2535 svempati@jefferies.com
Timothy Chou *, Equity Associate
(212) 284-2571 tchou@jefferies.com

*** Jefferies LLC**

From: David Chang [DChang@KitePharma.com]
Sent: Thursday, April 30, 2015 9:21 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Kite - Topics for May-01-15

Dear Steve,

Below are the topics that I would like to cover tomorrow:

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

All the best,
David

David D. Chang, MD, PhD
Executive Vice President of R&D
and Chief Medical Officer
Kite Pharma, Inc
office: 310-622-9094
PERSONAL INFORMATION,REDACTED PER AGREEMENT

www.kitepharma.com

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Wednesday, May 06, 2015 11:23 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Fwd: QUICK TAKE - KITE - Leading The Way In DLBCL And So Much More - Cowen and Company
Attachments: ATT00001.png; ATT00002.gif

Hi Steve,

David and I just finished an analyst/VC tour in NY and Boston , the summary of which is enclosed .

Thanks for everything!

Arie

Arie Belldegrun, MD FACS
President and CEO, Chairman
Kite Pharma

www.kitepharma.com

Begin forwarded message:

> **From:** Lisa Burns <LBurns@burnsmc.com>
> **Date:** May 6, 2015 at 04:30:22 PDT
> **To:** Arie <arie@kitepharma.com>, C Butitta <cbutitta@kitepharma.com>
> **Cc:** Kate Bechtold <kbechtold@kitepharma.com>, Linda Barnes <lbarnes@kitepharma.com>, Justin Jackson <JJackson@burnsmc.com>, "Carol Werther" <cwerther@burnsmc.com>, Rebecca Cohen <rcohen@burnsmc.com>, "Ilana Portner" <iportner@burnsmc.com>
> **Subject: Fwd: QUICK TAKE - KITE - Leading The Way In DLBCL And So Much More - Cowen and Company**
>
> Good Morning !
>
> Sent from my iPhone
>
> Begin forwarded message:
>
> > **From:** Eric Schmidt <eric.schmidt@cowen.com>
> > **Date:** 6 May 2015 6:03:22 am GMT-4
> > **To:** Lisa Burns <LBurns@burnsmc.com>
> > **Subject: QUICK TAKE - KITE - Leading The Way In DLBCL And So Much More - Cowen and Company**
> > **Reply-To:** Eric Schmidt <eric.schmidt@cowen.com>

LINK TO FULL REPORT & DISCLOSURES

Biotechnology

Kite Pharma

Equity Research

May 6, 2015

Price: $54.28 (05/4/2015)
Price Target: NA

OUTPERFORM (1)

Eric Schmidt, Ph.D.
646.562.1345
eric.schmidt@cowen.com

Marc Frahm, Ph.D.
646.562.1394
marc.frahm@cowen.com

Key Data

Symbol	NASDAQ: KITE

Quick Take: Company Update

Leading The Way In DLBCL And So Much More

The Cowen Insight

We hosted investor meetings with Dr. Arie Belldegrun (Chairman and CEO) and Dr. David Chang (CMO). Kite remains on-track to generate potentially pivotal data for KTE-C19 in DLBCL during 2016. Through its multiple BD transactions Kite has also significantly broadened its platform and pipeline to become the leader in engineered T cells. We remain at Outperform.

Corporate Mission Is To Become The Leading Producer Of T Cell Therapies...

While much investor attention has been focused on Kite and its competitors' CD19 directed CAR therapies, Kite has quietly assembled what it believes is (1) the best platform from which new

Market Cap (MM)	$2,430.3

CAR/TCR based therapies can be developed and (2) the broadest pipeline of engineered T cell therapies. Kite has worked with the NCI to optimize T cell production methods, completed tech transfer to an external CMO, and is now the only company with an FDA cleared, corporately held CAR T cell IND (KTE-C19). Kite is also in the process of building commercial scale (5000 patients/yr capacity) and clinical scale (300 patients/yr capacity) manufacturing facilities in Los Angeles from which to rapidly move promising preclinical product candidates into the clinic and ultimately market without the need for external tech transfer. This will also form a platform to quickly test emerging engineered T cell technologies (e.g. gene editing, switches, etc.) as needed. Through its CRADA with the National Cancer Institute (NCI), Kite has active clinical programs utilizing two CAR constructs (CD19 and EGFRvIII) and four TCR constructs (NY-ESO-1, MAGE A3, MAGE A6, and HPV-16 E6). NCI is also working on additional clinical and preclinical constructs to which Kite has development rights including a mesothelin CAR and HPV-16 E7, SSX2, and personalized neo-antigen TCRs. In addition, Kite has gained access to multiple oncology targets through a 50:50 partnership with Amgen. Finally, the recent acquisition of T Cell Factory (TCF) has given Kite a proprietary high-throughput method for identifying and cloning rare TCR sequences from patient samples. Following this acquisition, Kite possesses many of the leading minds in engineered T cells and immune-therapy as internal employees (Drs. Margo Roberts and Ton Schumacher), collaborators (Dr. Steven Rosenberg), or scientific advisors (Drs. Ron Levy, Toni Ribas, and Owen Witte). Presentations from many of these people will be featured when Kite reviews its platform, pipeline, and future directions at an R&D day in NYC on June 23, 2015.

...And Leverage This To Become The Partner Of Choice

Kite intends to leverage its leading platform (and IP) to become the partner of choice as new T cell modifications prove themselves necessary in the clinic. In January, Amgen partnered with Kite. In return for access to Kite's expertise, Amgen provided Kite with multiple oncology targets and 50% economics on the proposed products. We believe the Amgen partnership in January provides the first validation of this approach. Management described currently proposed T cell modifications such as combination therapies, cytokine secretion, gene editing, suicide genes, and switches as nice theories deserving of study but possessing no clinical data. Due to the often poor translatability of preclinical models to human immune-therapy, Kite plans to generally wait on clinical data before partnering its platform with outside technologies. However, its seminal IP in the CAR space could become important sooner as competitors move towards planned 2016 BLA filings in ALL.

2014 Was And 2015 Is All About Execution

At the time of its 2014 IPO, Kite management outlined a plan to (1) work with NCI to identify an ideal conditioning regimen and cell dose for KTE-C19 in DLBCL, (2) transfer manufacturing outside of NCI to enable multicenter trials and (3) file a corporate IND for KTE-C19 in order to support (4) initiating a potentially pivotal DLBCL trial in H1:15, (5) generating pivotal data in 2016, and (6) potentially gaining FDA approval in 2017. While simultaneously expanding Kite's breadth, management has successfully executed on the first three tasks. Kite's management reports that its tech transfer process has been completed, the FDA has granted an IND, a conditioning regimen and cell dose has been settled, and a potentially pivotal Phase I/II trial protocol is "fully active". Management has completed IRB approval and contract negotiations with at least three clinical trial sites (City of Hope, Moffitt, and Washington University). Kite has also conducted multiple "dummy runs" with these clinical sites and its contract manufacturer (PCT). With these three sites now activated

(and MD Anderson to join soon), management expects to dose the first patient in the 6 patient Phase I portion of the trial during Q2:15. This landmark event is expected to be press released. For competitive reasons management does not plan to disclose the conditioning regimen or cell dose until it presents the full Phase I dataset (anticipated for ASH 2015). The Phase I portion is designed to ensure that T cell production outside of NCI is not generating vastly different results. Management intends to progress to the pivotal Phase II portion if grade 3 or greater AEs (primarily CRS) are seen in no more than two of the six Phase I patients. Kite also expects to begin pivotal trials of KTE-C19 in MCL, ALL, and CLL during 2015. Finally, Kite plans to file its first corporate IND for a TCR therapy (likely HPV-16 E6) by YE:15.

2016 Will Be A Year Of Data In Liquid And Solid Tumors

The Phase II portion of the initial pivotal KTE-C19 trial will utilize ~25 sites to enroll a 72 patient DLBCL cohort (cohort 1) and a 40 patient PMBCL and TFL cohort (cohort 2). The primary endpoint of the trial is ORR and a potentially pivotal efficacy analysis will be conducted on the first 50 DLBCL patients (H2:16). Kite believes historical data indicates a <20% ORR and 4-5month mOS would be expected. Therefore, an ORR of at least 40% with a mOS of at least 6 months is expected to be approvable. If the interim analysis is successful, Kite expects to file for a BLA by YE:16. As a result, approval for KTE-C19 in DLBCL could come in 2017. Kite's partner NCI has also dosed patients in clinical trials for multiple Kite owned engineered T cell constructs in solid tumors. These include an (1) EGFRvIII specific CAR for glioblastoma and head and neck cancers (2) NY-ESO-1 TCR for urothelial carcinoma, sarcoma, and NSCLC, (3) HPV-16 E6 TCR in anal, cervical, and head and neck cancers (4) MAGE A3/A6 TCR and (5) MAGE A3 TCR both for NSCLC, breast, gastric, ovarian, pancreatic, and prostate cancers. Data from all five solid tumor programs is expected to be presented in 2016. Kite appeared particularly excited by the HPV-16 E6 program. This excitement stems from HPV's central role in ~5% of all cancers and HPV antigen expression being restricted to tumor cells. Importantly, management cautions that Penn/NVS's recent mesothelin CAR T cell presentation is far from definitive for the solid tumor opportunity. First, Kite believes the patient cohort is too small to draw significant conclusions from. Second and likely far more important, the researchers did not utilize a conditioning regimen. Kite/NCI's extensive work on conditioning regimens with the CD19 product have demonstrated that conditioning intensity can impact efficacy. In addition, the only publicly disclosed responses from engineered T cell therapy in solid tumors (NY-ESO-1 TCR) utilized a preconditioning regimen.

Building For The Future With T Cell Factory And Neo-Antigens

Emerging clinical data from TIL and checkpoint therapies indicates that a major correlate of efficacy in immune-therapy is the presence of T cells that recognize tumor neo-antigens. As a result, Dr. Steven Rosenberg used his plenary presentation at ASH 2014 to present an initial proof of concept and set the goal of commercializing engineered TCR therapies for a patient's specific neo-antigens. We initially thought this goal was admirable but a long way from becoming practical. Dr. Chang admits that his initial reaction over a year ago was much the same. However, Kite revealed that Dr. Rosenberg is currently able to conduct the neo-antigen sequencing, TCR isolation, and T cell production processes within 10 weeks. Through the recent acquisition of T cell Factory (TCF) and its high throughput TCR screening technology, as well as other streamlining efforts, Dr. Chang believes Kite and NCI can shorten the process to 6 weeks in the near future. He believes this timeframe is commercially viable. TCF will be leveraged to fill out Kite's TCR

pipeline with neo-antigen (including KRAS) products as well as TCRs specific for cancer testis antigen and viral antigens from oncogenic viruses.

COWEN

From: David Chang [DChang@KitePharma.com]
Sent: Wednesday, May 06, 2015 5:54 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]; Restifo, Nicholas P. (NIH/NCI) [E]
Subject: Fwd: FATE - CAR-T Partnership and Positive PUMA Data Update - Cowen and Company
Attachments: ATT00002.gif

FYI. PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

David

David D. Chang, M.D., Ph.D.
office: (310) 622-9094
mobile: PERSONAL INFORMATION,REDACTED PER AGREEMENT

www.kitepharma.com

Sent from my iPad

Begin forwarded message:

From: Lisa Burns <LBurns@burnsmc.com>
Date: May 6, 2015 at 2:25:32 PM PDT
To: Arie <arie@kitepharma.com>, C Butitta <cbutitta@kitepharma.com>, "David Chang M.D. D. Ph. D (dchang@kitepharma.com)" <dchang@kitepharma.com>
Cc: "Catherine Bechtold (kbechtold@kitepharma.com)" <kbechtold@kitepharma.com>, "Linda Barnes (lbarnes@kitepharma.com)" <lbarnes@kitepharma.com>
Subject: FW: FATE - CAR-T Partnership and Positive PUMA Data Update - Cowen and Company

From: Boris Peaker, Ph.D., CFA [mailto:boris.peaker@cowen.com]
Sent: Wednesday, May 06, 2015 4:46 PM
To: Lisa Burns
Subject: FATE - CAR-T Partnership and Positive PUMA Data Update - Cowen and Company

LINK TO FULL REPORT & DISCLOSURES

Biotechnology

Fate Therapeutics

Equity Research

May 6, 2015

Price: $7.24 (05/6/2015)
Price Target: NA
OUTPERFORM (1)

Company Update

CAR-T Partnership and Positive PUMA Data Update

Boris Peaker, Ph.D., CFA
646.562.1377
boris.peaker@cowen.com
Joseph Catanzaro, Ph.D.
646.562.1387
joseph.catanzaro@cowen.com
George Chen
646.562.1306
george.chen@cowen.com

Key Data

Symbol	NASDAQ: FATE
52-Week Range	$8.78 - 3.50
Market Cap (MM)	$149.4
Net Debt (MM)	$(29.5)
Cash/Share	$2.39
Dil. Shares Out (MM)	20.6

The Cowen Insight
Today FATE announced a research collaboration with Juno Therapeutics to develop small molecule modulators for Juno's CAR-T therapies. As part of the agreement Juno will buy 1 million shares of FATE at $8/share, a 61% premium on last night's closing price of $4.96/share. Additionally, Fate reported positive update from the PUMA study, reaffirming PROHEMA's activity in bone marrow transplant.

Deal Terms Highly Favorable For Fate and Juno
Juno agreed to pay Fate $5MM to develop a cocktail of small molecules to enhance the therapeutic profile of CAR-T cells. Fate will receive $50MM in milestones and a low single digit royalty on each product developed under the agreement. Juno also agreed to fund all mutual collaboration activities for an exclusive four year period and will purchase 1MM shares of Fate at $8/share (61% premium). The terms of the deal are highly favorable for Fate but also for Juno as the agreement will give Juno an edge in the highly competitive CAR-T space. We believe the deal underscores both the discount in the shares and potential of Fate's ex-vivo hematopoietic cell modulation platform to enhance other immuno-oncology cell therapies.

Ex Vivo Modulation May Enhance CAR-T Therapies

Enterprise Value (MM)	$119.9
ROIC	NA
ROE (LTM)	NA
BV/Share	$1.38
Dividend	NA

FY (Dec)	2014A	2015E	2016E
Earnings Per Share			
Q1	$(0.34)	$(0.39)	-
Q2	$(0.30)	$(0.32)	-
Q3	$(0.30)	$1.15	-
Q4	$(0.30)	$(0.31)	-
Year	$(1.27)	$0.45	$(1.32)
P/E	NM	16.1x	NM
Consensus EPS	$(1.27)	$(1.29)	$(1.26)
Consensus source: Thomson Reuters			
Revenue (MM)			
Year	$0.0	$50.0	$0.0
EV/S	-	2.4x	-

CAR-T cells are T cells which have been modified ex vivo via viral infection to express a mutated T-Cell receptor (TCR). CAR-T cells showed impressive results in targeting CD19 in ALL, and are being investigated in other indications, including solid tumors. Fate's ex vivo HSC modulation platform has demonstrated the ability to upregulate the expression of key homing proteins which allow stem cells to find targets outside the blood stream. Ex vivo modulation via small molecule may also have to potential to suppress cell surface expression of CTLA-4, PD-1, ICOS, or other checkpoint inhibitors which tumors use to evade native T Cells. These effects may enhance the activity of many different types of T-cell therapies, like CAR-T and TILs (tumor infiltrating lymphocytes).

PROHEMA Continues To Perform In PUMA Study

Update on Phase II PUMA study in adult hematopoietic malignancies included data on 8 additional patients on ProHema and 12 control patients. Of the 18 patients ProHema patients, 14 achieved engraftment 14/16 or 88% (recall 2 patients died due to MAB conditioning prior to engraftment) with a 6 days reduction in engraftment. The control arm achieved similar engraftment rate (11 of 12, or 92%), with a median engraftment of one day less than historical controls. As we have discussed in our previous note, in our view the reduction in engraftment times is clinically meaningful. Additionally, CMV reactivation was reduced by 36% and infection-related AEs were reduced by 11% in ProHema vs. control patients. Full data, including overall survival and GvHD incidence on the Phase II study is expected in Q3.

From: David Chang [DChang@KitePharma.com]
Sent: Thursday, May 07, 2015 9:54 AM
To: Restifo, Nicholas P. (NIH/NCI) [E]
CC: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Re: FATE - CAR-T Partnership and Positive PUMA Data Update - Cowen and Company

Nick - PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

David D. Chang, M.D., Ph.D.
office: (310) 622-9094
mobile: PERSONAL INFORMATION,REDACTED PER AGREEMENT

www.kitepharma.com

Sent from my iPad

On May 6, 2015, at 9:07 PM, Restifo, Nicholas P. (NIH/NCI) [E] <restifon@mail.nih.gov> wrote:

Hi David,

Thank you for sending this interesting analysis from the Cowen Group. PROPRIETARY INFORMATION,REDACTED PER AGREEMENT PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Nick

From: David Chang [mailto:DChang@KitePharma.com]
Sent: Wednesday, May 06, 2015 5:54 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]; Restifo, Nicholas P. (NIH/NCI) [E]
Subject: Fwd: FATE - CAR-T Partnership and Positive PUMA Data Update - Cowen and Company

FYI. PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

David

David D. Chang, M.D., Ph.D.
office: (310) 622-9094
PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

www.kitepharma.com

Sent from my iPad

Begin forwarded message:

From: Lisa Burns <LBurns@burnsmc.com>
Date: May 6, 2015 at 2:25:32 PM PDT
To: Arie <arie@kitepharma.com>, C Butitta <cbutitta@kitepharma.com>, "David Chang M.D. D. Ph. D. (dchang@kitepharma.com)" <dchang@kitepharma.com>
Cc: "Catherine Bechtold (kbechtold@kitepharma.com)" <kbechtold@kitepharma.com>, "Linda Barnes (lbarnes@kitepharma.com)" <lbarnes@kitepharma.com>
Subject: FW: FATE - CAR-T Partnership and Positive PUMA Data Update - Cowen and Company

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Price Target: NA
OUTPERFORM (1)

CAR-T Partnership and Positive PUMA Data Update

Boris Peaker, Ph.D., CFA
646.562.1377
boris.peaker@cowen.com
Joseph Catanzaro, Ph.D.
646.562.1387
joseph.catanzaro@cowen.com
George Chen
646.562.1306
george.chen@cowen.com

Key Data

Symbol	NASDAQ: FATE
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Market Cap (MM)	$149.4
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Consensus source: Thomson Reuters			
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From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Thursday, May 21, 2015 10:58 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Fwd:

HinSteve,

Please see below from Ton, PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Arie Belldegrun, MD FACS
President and CEO, Chairman
Kite Pharma

www.kitepharma.com

Begin forwarded message:

From: Ton Schumacher <tschumacher@kitepharma.com>
Date: May 21, 2015 at 17:51:05 GMT+3
To: Arie Belldegrun <Arie@kitepharma.com>

Dear Arie,

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Sent from mobile

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Monday, June 01, 2015 10:14 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Fwd: SA Alert

FYI

Arie Belldegrun, MD FACS
President and CEO, Chairman
Kite Pharma

www.kitepharma.com

Begin forwarded message:

> **From:** StreetAccount <service@streetaccount.com>
> **Date:** June 1, 2015 at 07:04:21 CDT
> **To:** <arie@kitepharma.com>
> **Subject: SA Alert**
> **Reply-To:** <feedback@streetaccount.com>
>
> 08:04 ET 6/01/15 [StreetAccount] JUNO **Juno Therapeutics presents Phase 1 clinical data from JCAR014 in B-cell cancers at ASCO** ($52.64)
>
> - In an oral presentation on Monday, 1-Jun-15 entitled, "Immunotherapy with CD19-specific chimeric antigen receptor (CAR)-modified T cells of defined subset composition" updated Phase I results in a total of 52 patients treated with JCAR014 against B-cell malignancies will be reported from this ongoing trial:
>   - Twenty-four patients with acute lymphoblastic leukemia (ALL), 23 patients with non-Hodgkin lymphoma (NHL), and 5 patients with chronic lymphocytic leukemia (CLL) were treated with JCAR014.
>   - CD19 CAR T cells of defined subset composition demonstrated potent anti-tumor activity: CR as documented by flow cytometry was observed in 21/23 (91%) of evaluable patients with relapsed or refractory (r/r) B-cell ALL; complete or partial responses were observed in 12/19 (63%) of patients with r/r NHL; and complete responses were obtained in 2/5 patients with r/r chronic lymphocytic leukemia.
>   - Translational insights included:
>   - Dramatically improved CAR T cell peak and persistence following optimization of the lymphodepletion conditioning regimen.
>   - Early indications that these improved kinetic properties are translating to improved clinical activity with complete or partial responses in 6/7 (86%) of evaluable NHL patients.
>   - The CAR T in vivo expansion in NHL with this optimization of the lymphodepletion regimen is similar to what was previously observed in the ALL portion of this trial. Correspondingly, and similar to previously reported ALL data, the highest dose of 2X107 cells/kg exceeds the maximally tolerated dose, as two treatment-related deaths were observed in NHL with this cell dose. There have been no treatment-related deaths to date at 2x106 cells/kg or lower, and the side effect profile has been consistent with what has been previously reported.
>   - CAR T cell persistence may be limited by transgene immunogenicity directed against the murine scFv in a subset of patients.
>   - Increased CAR T cell expansion and persistence in ALL patients with higher bone marrow disease burden. Severe CRS was reported in 7/24 (29%) of ALL patients and 4/28 (14%) of CLL/NHL patients.

- Juno currently does not plan to advance JCAR014 into registration trials

  Reference Link: Company press release

StreetAccount alert for portfolio(s):
- IMMUNO-ONCOLOGY (JUNO)
- BioPharma (JUNO)

Tickers mentioned in/related to this story; follow link for 30-day news history: JUNO

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Monday, June 01, 2015 10:16 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Fwd: KITE - BUY - KITE at ASCO 2015; If You Only Read One Note Read This THREE - Guggenheim Securities, LLC

Review of our joint abstract! Hundreds of visitors lined up to watch it.....

Arie Belldegrun, MD FACS
President and CEO, Chairman
Kite Pharma

www.kitepharma.com

Begin forwarded message:

> **From:** Lisa Burns <LBurns@burnsmc.com>
> **Date:** June 1, 2015 at 07:04:56 CDT
> **To:** Arie <arie@kitepharma.com>, C Butitta <cbutitta@kitepharma.com>, "David Chang M.D. D. Ph. D. (dchang@kitepharma.com)" <dchang@kitepharma.com>
> **Cc:** "Linda Barnes (lbarnes@kitepharma.com)" <lbarnes@kitepharma.com>, "Catherine Bechtold (kbechtold@kitepharma.com)" <kbechtold@kitepharma.com>, Kite Team <Kite_Team@burnsmc.com>
> **Subject: FW: KITE - BUY - KITE at ASCO 2015; If You Only Read One Note Read This THREE - Guggenheim Securities, LLC**

From: Butler, Tony [mailto:tony.butler@guggenheimpartners.com]
Sent: Monday, June 01, 2015 6:12 AM
To: Lisa Burns
Subject: KITE - BUY - KITE at ASCO 2015; If You Only Read One Note Read This THREE - Guggenheim Securities, LLC

People. Ideas. Su

KITE PHARMA, INC.
KITE - BUY - KITE at ASCO 2015; If You Only Read One Note Read This THREE

SECTOR: Biopharmaceuticals

June 1

Tony Butler, PhD, Analyst | 212 823 6540 | tony.butler@guggenheimpartners.com

☐CLICK HERE TO ACCESS THIS REPORT

Guggenheim Securities, LLC thanks you for consideration of our equity research analysts in the Institutional Investor 2015 All-America Research Poll. Click here to request a ballot.

At ASCO 2015, Kite Pharma (KITE, BUY, $55.15) presented data from a small cohort of patients illustrating that it may be able to discern functional biomarkers that could be predictive of patient res to CARs. Autologous CAR-engineered T cell therapy has been shown promising in relapsed/refractory B cell tumors. Kite has evaluated T cell product characteristics and a number of biomarkers in patients trea anti-CD19 CAR T cells.

In 29 evaluable patients with non-Hodgkin's lymphoma (NHL) or chronic lymphocytic leukemia (CLL), anti-CD19 CAR T cells induced objective responses. The complete response rate was 38% (76% overall r rate). Clearing of CAR-T cells in blood and recovery of normal B cells was frequent in patients with durable clinical responses. This was an outcome we did not expect. Pre-conditioning with cyclophospham fludarabine induced immune homeostatic cytokines (IL-15, IL-7), chemokines (MCP-1), and pro-inflammatory markers including CRP and PLGF. Clinical responders showed *in vivo* expansion of CAR+ T c considerable range of 15-300 CAR+ PBMC/µL within 14 days post-treatment.

Finally, Kite looked at the composition of T cells but not of CAR-T cells post-treatment to determine if manufacturing time in culture of engineered CAR-T cells influenced outcomes.

Conclusion:

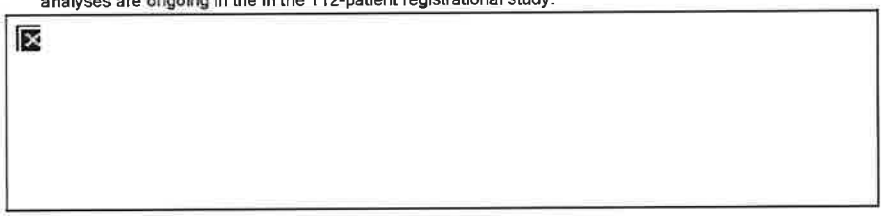
<!--[if !supportLists]-->• <!--[endif]-->Kite was able to conclude that durable clinical responses could occur without long-lasting CAR-T cells in circulation. This allows for normal B cell recovery.

<!--[if !supportLists]-->• <!--[endif]-->The method used for pre-conditioning the patient does affect activation and trafficking of T cells. This can be key in clinical trials.

<!--[if !supportLists]-->• <!--[endif]-->A shorter manufacturing process produces CAR T cells with higher CD4+ naïve and central memory T cells. Post infusion CAR-T cells showed a di population of differentiating T cell as well as naïve T cells.

<!--[if !supportLists]-->• <!--[endif]-->CAR-T cell treatment results in elevation and resolution of circulating cytokines within three weeks after treatment.

<!--[if !supportLists]-->• <!--[endif]-->The merit of this functional analysis generates the hypothesis that Kite may be able to prognosticate patients that respond better or best with CAR therapy analyses are ongoing in the in the 112-patient registrational study.



From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Monday, June 01, 2015 10:17 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Fwd: QUICK TAKE - KITE - KTE-C19 Heading Into Open Waters, Much More Below The Surface - Cowen and Company
Attachments: ATT00001.png; ATT00002.gif

Fresh from ASCO...

Arie Belldegrun, MD FACS
President and CEO, Chairman
Kite Pharma

www.kitepharma.com

Begin forwarded message:

From: Lisa Burns <LBurns@burnsmc.com>
Date: June 1, 2015 at 01:57:07 CDT
To: Arie <arie@kitepharma.com>, C Butitta <cbutitta@kitepharma.com>, "David Chang M.D. D. Ph. D. (dchang@kitepharma.com)" <dchang@kitepharma.com>
Cc: "Linda Barnes " <lbarnes@kitepharma.com>, "Catherine Bechtold (kbechtold@kitepharma.com)" <kbechtold@kitepharma.com>, Kite Team <Kite_Team@burnsmc.com>
Subject: FW: QUICK TAKE - KITE - KTE-C19 Heading Into Open Waters, Much More Below The Surface - Cowen and Company

From: Eric Schmidt, Ph.D. [mailto:eric.schmidt@cowen.com]
Sent: Monday, June 01, 2015 2:35 AM
To: Lisa Burns
Subject: QUICK TAKE - KITE - KTE-C19 Heading Into Open Waters, Much More Below The Surface - Cowen and Company

LINK TO FULL REPORT & DISCLOSURES

Biotechnology
Kite Pharma

Equity Research

June 1, 2015

Price: $55.15 (05/29/2015)
Price Target: NA
OUTPERFORM (1)

Eric Schmidt, Ph.D.
646.562.1345
eric.schmidt@cowen.com
Marc Frahm, Ph.D.
646.562.1394
marc.frahm@cowen.com

Key Data

Symbol	NASDAQ: KITE
Market Cap (MM)	$2,374.7

Quick Take: Company Update

KTE-C19 Heading Into Open Waters, Much More Below The Surface

The Cowen Insight
In conjunction with ASCO we hosted a dinner with senior Kite management. KTE-C19 is enrolling patients into a potentially pivotal Phase I/II trial. Management indicates its solid tumor pipeline has generated responses and is set for further expansion. We continue to view Kite as a leader in immune oncology and remain at Outperform.

Laying The Foundation To Be A Major Player In IO
Last night we hosted an investor dinner with Kite's CEO Arie Belldegrun, CMO David Chang, and other senior members of the clinical development team. In the past 18 months Kite has raised ~$500MM, expanded from 6 employees to 100+, signed a collaboration with Amgen, and now begun a potentially pivotal trial on KTE-C19. Management reviewed what it has learned about engineered T cells and where it sees the field heading as it approaches commercialization in 2017. Our discussions included data on the persistence of CARs, KTE-C19's pivotal trial, Kite's engineered T cell programs in solid tumors, and the future direction of Kite's NCI and Amgen collaborations.

Long-Term Persistence Not Required For Durable DLBCL Responses

Management reviewed the results of a correlative analysis that was presented in a poster session at ASCO. Kite conducted an in-depth analysis of samples from 29 DLBCL patients treated with CD19-CAR T cells at the NCI. Among these patients, 22 responses (11 CRs and 11 PRs) were observed. Responders were divided into two groups. The first representing those with responses lasting <1yr (n=10) and

the second representing ongoing responses of at least 1yr (n=11). Both patient groups had median peripheral CD19 CAR T cell persistence of 29 days. In fact, the responder with the longest T cell persistence (184 days) experienced a response lasting <1yr. Conversely the responder with the least persistency (11 days) has an ongoing response of >1yr. In addition, 7/11 long-term responders have experienced B cell recovery and are no longer using prophylactic immunoglobulin therapy. This further indicates that long-term maintenance of a peripheral CD19 CAR population is not necessary for a durable response in DLBCL. Kite's data in DLBCL stands in contrast to statements from Juno and Novartis' collaborators at Penn regarding their datasets in ALL. It is not clear if the disparate conclusions regarding persistency is due to (1) differences in cellular therapies, (2) differences in the indications studied, or (3) the limited size of the datasets.

Kite's presentation also examined serum cytokine levels prior to preconditioning, following preconditioning, and following the infusion of CD19-CAR T cells. This analysis revealed that preconditioning causes the body to produce a number of homeostatic cytokines including IL-7 and IL-15. These cytokines are important regulators of T cell expansion. Importantly, data across all CD19 programs indicates that T cell expansion following infusion is highly correlated with the generation of a clinical response. Furthermore, management reports that its extensive work on perfecting the preconditioning regimen has taught Kite how to generate these homeostatic cytokines. Competitor solid tumor programs have generally struggled to generate T cell expansion following the infusion of T cells. We believe this proprietary dataset could be a key enabler for generating solid tumor efficacy.

First Corporate CAR T Cell Trial Now Enrolling.

In May, Kite announced that the Phase I portion of its Phase I/II trial on KTE-C19 for refractory diffuse large B cell lymphoma (DLBCL) had enrolled its first patient. The Phase I lead-in is designed to ensure that T cell production outside of NCI is generating similar efficacy and safety data as that previously reported from the NCI. Management intends to present data from this n=6 patient cohort at ASH 2015. The company will also press release the start of the Phase II portion of the trial. In the meantime, no news from the study is good news as any major safety or efficacy challenges that might merit a change in strategy would need to be disclosed. For competitive reasons, management is not disclosing the chemotherapy conditioning regimen or cell dose, but Kite did say that T cells expanded for six days appear to have optimal properties for transplantation, so where possible (assuming enough T cells can be collected) we assume Kite is employing a six day T cell expansion process. Management noted that enrollment does not appear to be an issue as centers are highly interested in participating. Nonetheless the company will limit the pace of the study to ensure logistics are smooth and protocols are followed closely.

Kite remains on track to start Phase II trials of KTE-C19 in MCL, ALL, and CLL in 2015 using the optimized Phase I protocol from DLBCL. As with DLBCL, these studies could potentially support registration. In Europe, the acquisition of T Cell Factory has given Kite the necessary resources to develop KTE-C19 on its own. Discussions with the EMA over regulatory strategy are proceeding and clinical development might begin in H1:16.

Kite is also in the process of building commercial scale (5000 patients/yr capacity) and clinical scale (300 patients/yr capacity) manufacturing facilities in Los Angeles from which to rapidly move promising preclinical product candidates into the clinic and ultimately market without the need for external tech transfer. This will also form a platform to quickly test emerging engineered T cell technologies (e.g. gene editing, switches, etc.) as needed. Last night Kite reported that the 300 patient clinical scale facility will be online within the next month. The commercial scale facility remains on-track for completion in Q1:16. This will allow for its FDA approval in advance of or simultaneous to KTE-C19's BLA approval.

Multiple Constructs Have Now Shown Activity In Solid Tumors; Pipeline Getting Bigger

Under its CRADA with the NCI, Kite is conducting a wide-ranging development program. With five CAR/TCR (EGFRvIII, NY-ESO-1, MAGE A3/A6, MAGE A3, and HPV-16 E6) constructs currently enrolling patients and two additional constructs (HPV-16 E7 and SSX2) set to enter the clinic soon, we believe Kite has the broadest clinical pipeline in the engineered T cell space. Importantly, all of these programs are directed at antigens found on solid tumors. We believe it is simply a matter of time before at least one of Kite's programs bears fruit. Last night, Kite indicated that it has observed responses in at least three solid tumor indications. Kite expects NCI will present data from these programs in 2016 once robust datasets have been accrued. Meanwhile the company continues to guide toward disclosing its first solid tumor-directed corporate IND by year end.

Beyond its CRADA with the NCI, management indicates that its Amgen collaboration is also progressing according to plan. Under this collaboration Kite and Amgen will work together on CAR constructs in pairs. Each CAR pair will consist of one Kite-owned program (with a single-digit Amgen royalty) and one

Amgen-owned candidate (with a high single to double-digit royalty to Kite). The collaboration is expected to result in its first IND filing within 18 months of it being signed. Therefore, the first Kite:Amgen IND should occur around mid-2016. A steady stream of INDs is expected to follow with programs alternating between the Kite and Amgen pipelines.

KITE Also Holds A Leadership Position In Neo-antigens.

Termed the "ultimate personalized therapy" neo-antigen T cell therapy refers to autologous T cells that have been engineered to recognize neo-antigens within a specific patient's tumor cells. At ASH 2014, Dr. Rosenberg presented an initial proof-of-concept for how the NCI can conduct the neo-antigen sequencing, TCR isolation, and T cell production required to deliver such a therapy within 10 weeks, Kite believes that in order for this approach to be commercially viable, turn around times will need to be shortened to 4-6 weeks, The company believes the scientific progress in this field is rapid, and it is now just a matter of time before neo-antigen based TCR therapy becomes a reality. It believes clinical trials might be possible within 3-5 years. By virtue of its association with Dr. Rosenberg and Ton Schumacher (Kite Europe), we believe Kite is far and away the leader in this cutting edge area of immune oncology,

COWEN

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Monday, June 01, 2015 11:03 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
CC: Justin Jackson
Subject: Fwd: Current Status of ASCO data release review at NCI

Hi steve,

Can you approve please the press release. We need it out today, if possible.

Thanks,

Arie Belldegrun, MD FACS
President and CEO, Chairman
Kite Pharma

www.kitepharma.com

Begin forwarded message:

> **From:** Cynthia Butitta <CButitta@KitePharma.com>
> **Date:** June 1, 2015 at 09:59:29 CDT
> **To:** Arie Belldegrun <Arie@kitepharma.com>, David Chang <DChang@KitePharma.com>
> **Cc:** Justin Jackson <JJackson@burnsmc.com>
> **Subject: Fwd: Current Status of ASCO data release review at NCI**
>
> Our PR is waiting for Rosenberg's approval. If this doesn't get out today, it will be stale news.
>
> Cindy
>
> Sent from my iPhone
>
> Begin forwarded message:
>
> > **From:** Justin Jackson <JJackson@burnsmc.com>
> > **Date:** June 1, 2015 at 7:56:21 AM PDT
> > **To:** C Butitta <cbutitta@kitepharma.com>
> > **Cc:** David Chang <DChang@KitePharma.com>, Kate Bechtold <kbechtold@kitepharma.com>, Veer Bhavnagri <veer@kitepharma.com>, Lisa Burns <LBurns@burnsmc.com>, Carol Werther <cwerther@burnsmc.com>, Rebecca Cohen <rcohen@burnsmc.com>, Ilana Portner <iportner@burnsmc.com>
> > **Subject: RE: Current Status of ASCO data release review at NCI**
> >
> > Thanks, Cindy.
> >
> > I believe the remaining critical step is to achieve Steve Rosenberg's sign-off. Once Steve can approve the release, I can move it quickly through the communications office.
> >
> > I've been working with Liz Lovoy and her group since last week and am in close touch with them throughout the morning.

Our goal is to set up the release for distribution as soon as Steve can consent, but we don't have timing yet on his expected turnaround.

Thx!

Justin W. Jackson
Executive Vice President
Burns McClellan, Inc.
257 Park Avenue South
15th Floor
New York, NY 10010
212-213-0006, ext. 327

From: Cynthia Butitta [mailto:CButitta@KitePharma.com]
Sent: Monday, June 01, 2015 10:40 AM
To: Justin Jackson
Cc: David Chang; Kate Bechtold; Veer Bhavnagri; Lisa Burns; Carol Werther; Rebecca Cohen; Ilana Portner
Subject: Re: Current Status of ASCO data release review at NCI

Justin,

We need to get this out.

Cindy

Sent from my iPhone

On Jun 1, 2015, at 2:56 AM, Justin Jackson <JJackson@burnsmc.com> wrote:

> Good morning, all.
>
> We haven't received final input on the ASCO data release yet.
>
> We will contact Liz Lovoy this morning when she is in the office to gain her feedback and then will come back to you with the information.
>
> Thank you!

From: Justin Jackson
Sent: Saturday, May 30, 2015 1:33 PM
To: C Butitta; David D. Chang, MD PhD; Kate Bechtold (kbechtold@kitepharma.com)
Cc: Veer Bhavnagri (veer@kitepharma.com); Lisa Burns; Carol Werther; Rebecca Cohen; Ilana Portner
Subject: Current Status of ASCO data release review at NCI

Hello, I hope the conference is going very well!

Attached and below please find the ASCO data release draft provided to the NCI on Thursday.

Liz Lovoy in the Technology Transfer Center at NCI reviewed the release and provided it to Steve Rosenberg for review. I don't think that Steve has had a chance to provide his comments yet since he's been at the conference.

We will continue to monitor throughout the weekend for progress. The NCI is aware the Company would plan to release the news as soon as feedback has been provided.

Thank you!

Kite Pharma Presents Clinical Biomarker Results in Patients Treated with Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy at the 2015 ASCO Annual Meeting

- ASCO Presentation Highlights Durable Responses, T-Cell Activity and Composition -

SANTA MONICA, Calif., June 1, 2015 -- Kite Pharma, Inc., (Nasdaq:KITE), today announced clinical biomarker data from patients with relapsed/refractory B cell malignancies treated with anti-CD19 chimeric antigen receptor (CAR) T-cell therapy in a poster presentation during the 51st Annual Meeting of the American Society of Clinical Oncology (ASCO), which is taking place in Chicago. In an ongoing Phase 1 clinical trial at the National Cancer Institute (NCI), patients with diverse B cell tumors are conditioned with cyclophosphamide and fludarabine, then dosed with their own T cells genetically modified to express a CAR designed to target the antigen CD19, a protein expressed on the cell surface of B-cell lymphomas and leukemias. As reported at last year's ASCO meeting, 76% of evaluable patients (N=29) achieved an overall response rate in this study. In this updated biomarker analysis, conducted under a Cooperative Research and Development Agreement (CRADA) between Kite Pharma and the NCI, conditioning chemotherapy was associated with a significant rise in homeostatic cytokines and chemokines, which could favor expansion, activation, and trafficking of CAR T cells. In addition, the recovery of B cells was seen in 7 of 12 patients with ongoing response duration greater than 12 months.

David Chang, M.D., Ph.D., Kite Pharma's Executive Vice President, Research and Development, and Chief Medical Officer, and an author on the poster, commented, "The results being reported at ASCO provide additional key insights and further deepen our understanding of CAR T-cell therapy. We will continue to investigate biomarkers that may predict the clinical outcome in our ongoing KTE-C19 (anti-CD19 CAR T) clinical program which initiated patient dosing last month."

The ASCO meeting poster, titled "Biomarker Analysis of Patients Treated with Anti-CD19 Chimeric Antigen Receptor (CAR) T Cells" (Abstract # 3028), is available on the Kite Pharma website at http://www.kitepharma.com/c/news/publications.php. Further information on the NCI clinical trial protocols can be found at ClinicalTrials.gov, using Identifier NCT: 00924326.

About Kite Pharma

Kite Pharma, Inc., is a clinical-stage biopharmaceutical company engaged

in the development of novel cancer immunotherapy products, with a primary focus on engineered autologous T-cell therapy (eACT™) designed to restore the immune system's ability to recognize and eradicate tumors. Kite is based in Santa Monica, CA.

Cautionary Note on Forward-Looking Statements

This press release contains forward-looking statements for purposes of the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. Kite may, in some cases, use terms such as "predicts," "believes," "potential," "proposed," "continue," "estimates," "anticipates," "expects," "plans," "intends," "may," "could," "might," "will," "should" or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. Forward-looking statements include statements regarding Kite's intentions, beliefs, projections, outlook, analyses or current expectations concerning, among other things: the success and timing of the Phase 1/2 KTE-C19 clinical trial for the treatment of DLBCL, PMBCL and TFL, obtaining results from the trial, commercially launching KTE-C19, and conducting additional clinical trials of KTE-C19. Various factors may cause differences between Kite's expectations and actual results as discussed in greater detail under the heading "Risk Factors" in the Form 10-Q for the quarter ended March 31, 2015. Any forward-looking statements that Kite makes in this press release speak only as of the date of this press release. Kite assumes no obligation to update its forward-looking statements whether as a result of new information, future events or otherwise, after the date of this press release.

CONTACT: Kite Pharma
Cynthia M. Butitta
Chief Financial Officer and Chief Operating Officer
310-824-9999

For Media: Justin Jackson
For Investor Inquiries: Lisa Burns and Carol Werther
Burns McClellan
212-213-0006
jjackson@burnsmc.com
lburns@burnsmc.com
cwerther@burnsmc.com

From: Justin Jackson
Sent: Friday, May 29, 2015 3:27 PM
To: Cynthia M. Butitta; Kate Bechtold (kbechtold@kitepharma.com)
Cc: Veer Bhavnagri (veer@kitepharma.com); Ilana Portner
Subject: Status of ASCO data release review

Cindy and Kate,

Liz Lovoy at NCI forwarded the ASCO data release internally yesterday, but she has not yet received feedback on the release text.

We'll continue to monitor for comments, in case they are able to reply later today or this weekend and come back to you as there is more info on the status.

Thanks!

Justin W. Jackson
Executive Vice President
Burns McClellan, Inc.
257 Park Avenue South
15th Floor
New York, NY 10010
212-213-0006, ext. 327

From: Rosenberg, Steven A. (NIH/NCI) [E]
Sent: Monday, June 01, 2015 12:50 PM
To: 'Arie Belldegrun'
CC: Justin Jackson
Subject: RE: Current Status of ASCO data release review at NCI

Send me the release and I will look at it immediately. I was away the weekend.

Steven A. Rosenberg M.D., Ph.D.
Chief, Surgery Branch
National Cancer Institute
10 Center Drive MSC 1201
CRC Room 3-3940
Bethesda, MD 20892
301-496-4164
sar@nih.gov

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Sent: Saturday, May 30, 2015 1:33 PM
To: C Butitta; David D. Chang, MD PhD; Kate Bechtold (kbechtold@kitepharma.com)
Cc: Veer Bhavnagri (veer@kitepharma.com); Lisa Burns; Carol Werther; Rebecca Cohen; Ilana Portner
Subject: Current Status of ASCO data release review at NCI

Hello, I hope the conference is going very well!

Attached and below please find the ASCO data release draft provided to the NCI on Thursday.

Liz Lovoy in the Technology Transfer Center at NCI reviewed the release and provided it to Steve Rosenberg for review. I don't think that Steve has had a chance to provide his comments yet since he's been at the conference.

We will continue to monitor throughout the weekend for progress. The NCI is aware the Company would plan to release the news as soon as feedback has been provided.

Thank you!

Kite Pharma Presents Clinical Biomarker Results in Patients Treated with Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy at the 2015 ASCO Annual Meeting

- ASCO Presentation Highlights Durable Responses, T-Cell Activity and Composition -

SANTA MONICA, Calif., June 1, 2015 -- Kite Pharma, Inc., (Nasdaq:KITE), today announced clinical biomarker data from patients with relapsed/refractory B cell malignancies treated with anti-CD19 chimeric antigen receptor (CAR) T-cell therapy in a poster presentation during the 51st Annual Meeting of the American Society of Clinical Oncology (ASCO), which is taking place in Chicago. In an ongoing Phase 1 clinical trial at the National Cancer Institute (NCI), patients with diverse B cell tumors are conditioned with cyclophosphamide and fludarabine, then dosed with their own T cells genetically modified to express a CAR designed to target the antigen CD19, a protein expressed on the cell surface of B-cell lymphomas and leukemias. As reported at last year's ASCO meeting, 76% of evaluable patients (N=29) achieved an overall response rate in this study. In this updated biomarker analysis, conducted under a Cooperative Research and Development Agreement (CRADA) between Kite Pharma and the NCI, conditioning chemotherapy was associated with a significant rise in homeostatic cytokines and chemokines, which could favor expansion, activation, and trafficking of CAR T cells. In addition, the recovery of B cells was seen in 7 of 12 patients with ongoing response duration greater than 12 months.

David Chang, M.D., Ph.D., Kite Pharma's Executive Vice President, Research and Development, and Chief Medical Officer, and an author on the poster, commented, "The results being reported at ASCO provide additional key insights and further deepen our understanding of CAR T-cell therapy. We will continue to investigate biomarkers that may predict the clinical outcome in our ongoing KTE-C19 (anti-CD19 CAR T) clinical program which initiated patient dosing last month."

The ASCO meeting poster, titled "Biomarker Analysis of Patients Treated with Anti-CD19 Chimeric Antigen Receptor (CAR) T Cells" (Abstract # 3028), is available on the Kite Pharma website at http://www.kitepharma.com/c/news/publications.php. Further information on the NCI clinical trial protocols can be found at ClinicalTrials.gov, using Identifier NCT: 00924326.

About Kite Pharma

Kite Pharma, Inc., is a clinical-stage biopharmaceutical company engaged in the development of novel cancer immunotherapy products, with a primary focus on engineered autologous T-cell therapy (eACT™) designed to restore the immune system's ability to recognize and eradicate tumors. Kite is based in Santa Monica, CA.

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CONTACT: Kite Pharma
Cynthia M. Butitta

Chief Financial Officer and Chief Operating Officer
310-824-9999

For Media: Justin Jackson
For Investor Inquiries: Lisa Burns and Carol Werther
Burns McClellan
212-213-0006
jjackson@burnsmc.com
lburns@burnsmc.com
cwerther@burnsmc.com

From: Justin Jackson
Sent: Friday, May 29, 2015 3:27 PM
To: Cynthia M. Butitta; Kate Bechtold (kbechtold@kitepharma.com)
Cc: Veer Bhavnagri (veer@kitepharma.com); Ilana Portner
Subject: Status of ASCO data release review

Cindy and Kate,

Liz Lovoy at NCI forwarded the ASCO data release internally yesterday, but she has not yet received feedback on the release text.

We'll continue to monitor for comments, in case they are able to reply later today or this weekend and come back to you as there is more info on the status.

Thanks!

Justin W. Jackson
Executive Vice President
Burns McClellan, Inc.
257 Park Avenue South
15th Floor
New York, NY 10010
212-213-0006, ext. 327

From: Rosenberg, Steven A. (NIH/NCI) [E]
Sent: Monday, June 01, 2015 2:44 PM
To: 'Arie Belldegrun'
CC: Justin Jackson; Lovoy, Liz (NIH/NCI) [E]
Subject: RE: Current Status of ASCO data release review at NCI

Press release is ok with me.

Steven A. Rosenberg M.D., Ph.D.
Chief, Surgery Branch
National Cancer Institute
10 Center Drive MSC 1201
CRC Room 3-3940
Bethesda, MD 20892
301-496-4164
sar@nih.gov

From: Arie Belldegrun [mailto:Arie@kitepharma.com]
Sent: Monday, June 01, 2015 11:03 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Cc: Justin Jackson
Subject: Fwd: Current Status of ASCO data release review at NCI

Hi steve,

Can you approve please the press release. We need it out today, if possible.

Thanks,

Arie Belldegrun, MD FACS
President and CEO, Chairman
Kite Pharma

www.kitepharma.com

Begin forwarded message:

> **From:** Cynthia Butitta <CButitta@KitePharma.com>
> **Date:** June 1, 2015 at 09:59:29 CDT
> **To:** Arie Belldegrun <Arie@kitepharma.com>, David Chang <DChang@KitePharma.com>
> **Cc:** Justin Jackson <JJackson@burnsmc.com>
> **Subject: Fwd: Current Status of ASCO data release review at NCI**
>
> Our PR is waiting for Rosenberg's approval. If this doesn't get out today, it will be stale news.
>
> Cindy
>
> Sent from my iPhone
>
> Begin forwarded message:
>
> > **From:** Justin Jackson <JJackson@burnsmc.com>
> > **Date:** June 1, 2015 at 7:56:21 AM PDT

To: C Butitta <cbutitta@kitepharma.com>
Cc: David Chang <DChang@KitePharma.com>, Kate Bechtold <kbechtold@kitepharma.com>, Veer Bhavnagri <veer@kitepharma.com>, Lisa Burns <LBurns@burnsmc.com>, Carol Werther <cwerther@burnsmc.com>, Rebecca Cohen <rcohen@burnsmc.com>, Ilana Portner <iportner@burnsmc.com>
Subject: RE: Current Status of ASCO data release review at NCI

Thanks, Cindy.

I believe the remaining critical step is to achieve Steve Rosenberg's sign-off. Once Steve can approve the release, I can move it quickly through the communications office.

I've been working with Liz Lovoy and her group since last week and am in close touch with them throughout the morning.

Our goal is to set up the release for distribution as soon as Steve can consent, but we don't have timing yet on his expected turnaround.

Thx!

Justin W. Jackson
Executive Vice President
Burns McClellan, Inc.
257 Park Avenue South
15th Floor
New York, NY 10010
212-213-0006, ext. 327

From: Cynthia Butitta [mailto:CButitta@KitePharma.com]
Sent: Monday, June 01, 2015 10:40 AM
To: Justin Jackson
Cc: David Chang; Kate Bechtold; Veer Bhavnagri; Lisa Burns; Carol Werther; Rebecca Cohen; Ilana Portner
Subject: Re: Current Status of ASCO data release review at NCI

Justin,

We need to get this out.

Cindy

Sent from my iPhone

On Jun 1, 2015, at 2:56 AM, Justin Jackson <JJackson@burnsmc.com> wrote:

Good morning, all.

We haven't received final input on the ASCO data release yet.

We will contact Liz Lovoy this morning when she is in the office to gain her feedback and then will come back to you with the information.

Thank you!

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Sent: Saturday, May 30, 2015 1:33 PM
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257 Park Avenue South
15th Floor
New York, NY 10010
212-213-0006, ext. 327

From: David Chang [DChang@KitePharma.com]
Sent: Thursday, June 04, 2015 4:26 PM
To: Kochenderfer, James (NIH/NCI) [E]; Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Fwd: CTL019 and JCAR presentations at ASCO
Attachments: 111707_slide_ppt.pptx; ATT00001.htm; 103954_slide_ppt.pptx; ATT00002.htm; 110503_slide_ppt.pptx; ATT00003.htm; 111706_slide_ppt.pptx; ATT00004.htm

A few of the CAR T presentations at ASCO.

David D. Chang, M.D., Ph.D.
office: (310) 622-9094
PERSONAL INFORMATION,REDACTED PER AGREEMENT

www.kitepharma.com

Sent from my iPhone

Begin forwarded message:

From: "David Chang" <DChang@KitePharma.com>
To: "Jeff Wiezorek" <JWiezorek@kitepharma.com>, "Margo Roberts" <mroberts@kitepharma.com>, "Tony Polverino" <TPolverino@kitepharma.com>, "Rajul Jain" <RJain@kitepharma.com>, "William Go" <wgo@kitepharma.com>, "Adrian Bot" <abot@kitepharma.com>
Cc: "Arie Belldegrun" <Arie@kitepharma.com>, "Helen Kim" <HKim@kitepharma.com>, "Cynthia Butitta" <cbutitta@kitepharma.com>
Subject: CTL019 and JCAR presentations at ASCO

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

All the best,
David

David D. Chang, MD, PhD
Executive Vice President of R&D
and Chief Medical Officer
Kite Pharma, Inc
office: 310-622-9094
PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

www.kitepharma.com<http://www.kitepharma.com>

Phase IIa Trial of Chimeric Antigen Receptor Modified T Cells Directed Against CD19 (CTL019) in Patients with Relapsed or Refractory CD19+ Lymphomas

Stephen J. Schuster[1], Jakub Svoboda[1], Sunita Nasta[1], David L. Porter[1], Anthony Mato[1], Gaurav D. Shah[2], Daniel J. Landsburg[1], Elise A. Chong[1], Simon F. Lacey[1], Jan J. Melenhorst[1], Anne Chew[1], Jens Hasskarl[2], Nirav N. Shah[1], Mariusz A. Wasik[1], Katherine Marcucci[1], Zhaohui Zheng[1], Bruce Levine[1], Carl H. June[1]

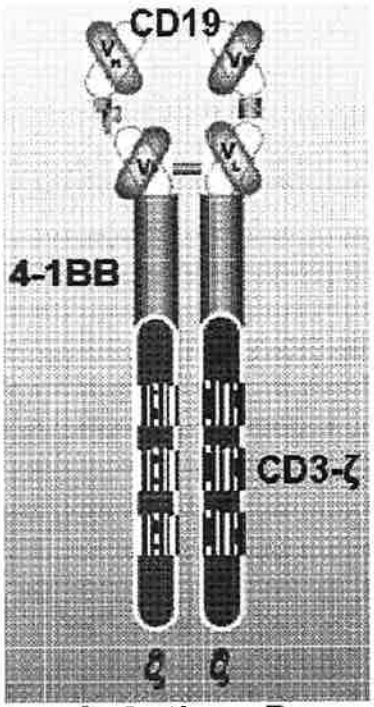
[1]Abramson Cancer Center, University of Pennsylvania
[2]Novartis, New Jersey and Basel

PRESENTED AT: ASCO Annual '15 Meeting

Presented By Stephen Schuster at 2015 ASCO Annual Meeting

Background

- CTL019 engineered T cells express a chimeric antigen receptor (CAR) with specificity for CD19 and activation and costimulatory signaling via CD3-zeta and CD137 (4-1BB) domains, respectively
- Chimeric antigen receptor-modified T cell therapy against CD19 is effective in treating relapsed and refractory ALL[1, 2] and CLL[3]



Chimeric Antigen Receptor (CAR)

1. Maude *et al.* N Engl J Med 2014; 371:1507-17.
2. Grupp *et al.* N Engl J Med 2013; 368:1509-18.
3. Porter *et al.* N Engl J Med 2011; 365:725-33.

PRESENTED AT: ASCO Annual '15 Meeting

Study Design: Hypothesis and Objective

Hypothesis:

- Chimeric antigen receptor modified T cells directed against CD19 (CTL019) will result in antitumor responses in patients with advanced CD19+ B-cell non-Hodgkin lymphomas (NHL)

Primary Objectives:

- Determine the overall response rate (ORR) at 3 months
- Determine response rate by lymphoma histology

Secondary Objectives:

- Determine CTL019 cell manufacturing feasibility
- Determine the safety and tolerability of CTL019 cells in NHL subjects
- Evaluate progression-free and overall survival rates
- Determine the characteristics of CTL019 *in vivo* (persistence, trafficking, and function)
- Determine effects on B cells and CD19 expression *in vivo*

Study Design: Inclusion and Exclusion

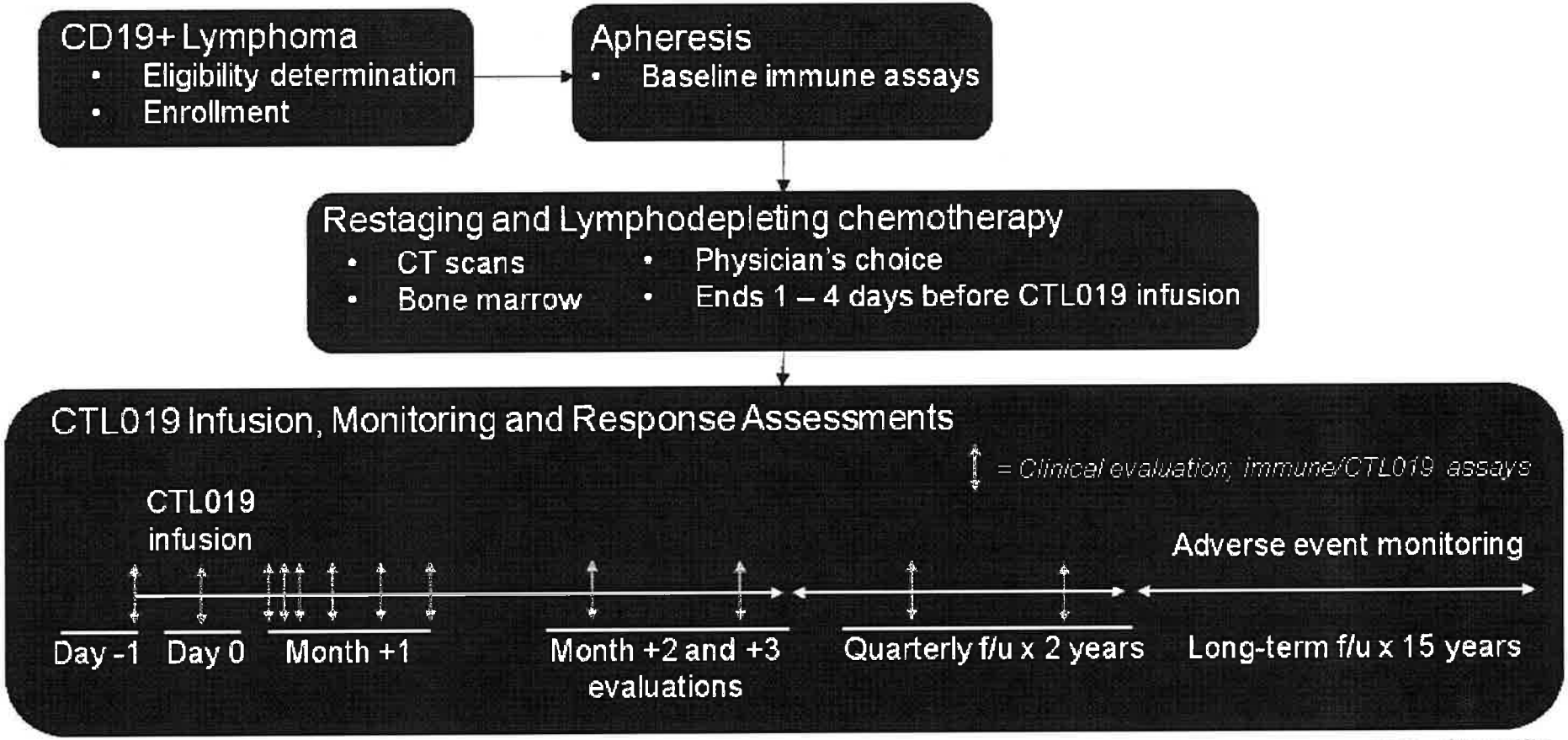
Inclusion Criteria:

- CD19+ B cell lymphoma patients with no available curative treatment options
- Age ≥18, expected survival ≥12 weeks, measurable disease, ECOG PS 0 or 1
- Diffuse large B cell lymphoma: relapsed/refractory disease after ASCT or ineligible for ASCT; transformation from CLL/SLL or FL allowed
- Follicular lymphoma: at least 2 prior immunochemotherapy regimens and progression <2 years after most recent line of therapy
- Mantle cell lymphoma: beyond 1st CR with relapsed disease, progressive disease during first line rituximab-chemotherapy, or persistent disease after first line rituximab-chemotherapy and not eligible or appropriate for conventional allogeneic or autologous SCT; Relapsed after prior autologous SCT

Exclusion Criteria:

- Pregnancy, uncontrolled active infection, HIV, active hepatitis B/C, concurrent use of steroids, active CNS involvement, patients in complete remission

Protocol Schema



PRESENTED AT: ASCO Annual '15 Meeting

Patient allocation

Patients enrolled (n = 30)
- DLBCL (n = 19)
- FL (n = 8)
- MCL (n = 3)

Received protocol-specified cell dose (n = 22)
- DLBCL (n = 13)
- FL (n = 7)
- MCL (n = 2)

Results: Diffuse Large B Cell Lymphoma

DLBCL: Patient Characteristics (n = 19 enrolled)

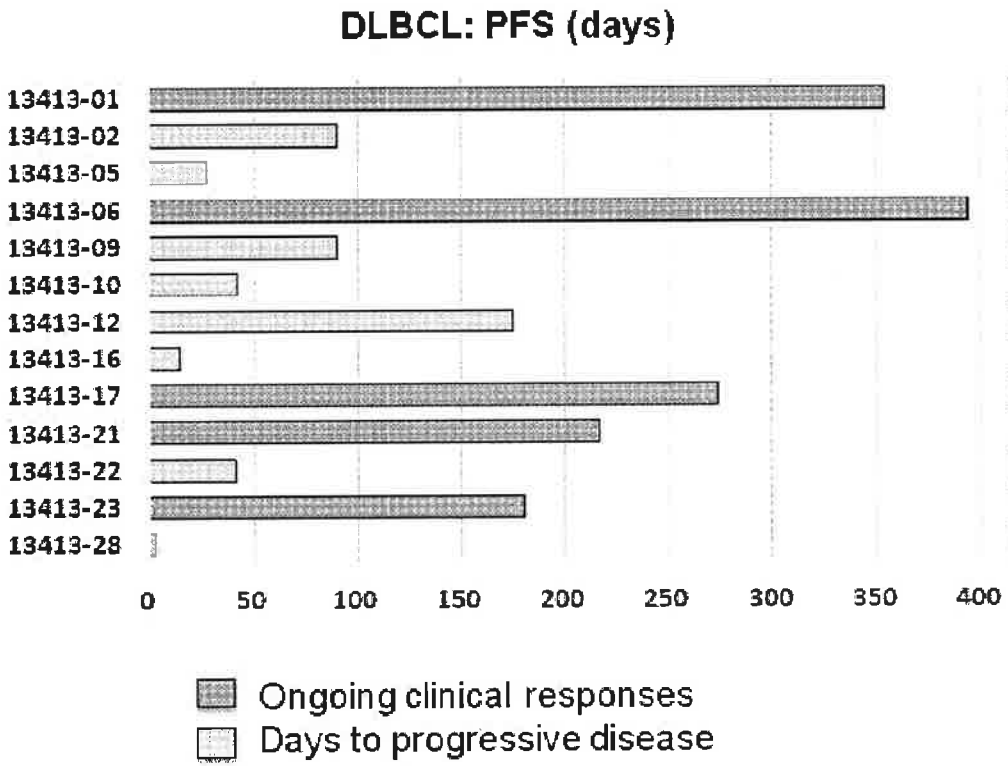
Median age	56 years (range 25 - 77)
Sex	13 (68%) men
Median prior therapies	4 (range 1 - 8)
Prior stem cell transplant	7 (37%)
Stage III – IV (enrollment)	12 (63%)
Increased LDH (enrollment)	14 (74%)
> 1 extranodal site (enrollment)	6 (32%)
Median ECOG PS (enrollment)	1 (range 0 - 1)
Lymphodepleting therapy (n = 13)	2 EPOCH (w/o vincristine); 6 hyperfractionated cyclophosphamide (1.8 gm/M2); 1 bendamustine (180 mg/M2); 2 cyclophosphamide (1 gm/M2); 1 XRT (4000 cGy) + cyclophosphamide (750 mg/M2); 1 infusional etoposide + bolus cyclophosphamide ("EPOCH" dosing)

Response Rates: Diffuse Large B Cell Lymphoma

DLBCL: ORR at 3 months 50% (N = 13)	DLBCL: Best Response Rate 50% (N = 13)
- CR: 2 - PR: 4 - PD: 6 - Response not yet assessed: 1	- CR: 5 - PR: 1 - PD: 6 - Response not yet assessed: 1

- 3 patients with PRs by CT criteria at 3 months converted to CRs by 6 months
- 1 patient with PR at 3 months had PD at 6 months

Results: Diffuse Large B Cell Lymphoma

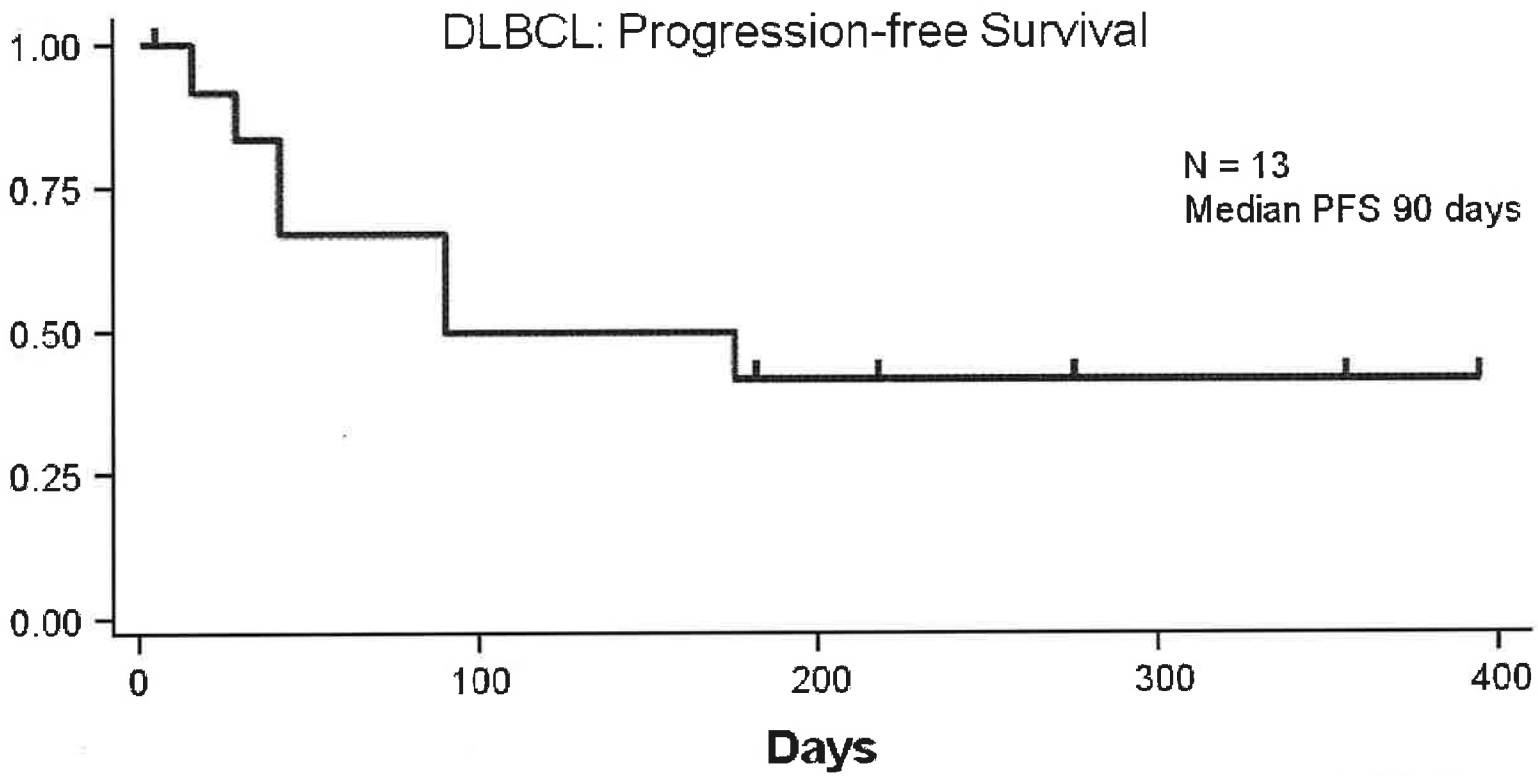


ID	Total CTL019 Dose	Peak %CD3+CAR19+	Peak Day
13413-01	5.00E+08	28.30%	D+10
13413-02	5.00E+08	29.30%	D+7
13413-05	5.00E+08	5.30%	D+7
13413-06	5.00E+08	6.90%	D+7
13413-09	5.00E+08	3.90%	D+7
13413-10	5.00E+08	43.10%	D+14
13413-12	5.00E+08	4.10%	D+2
13413-16	5.00E+08	2.50%	D+7
13413-17	5.00E+08	12.20%	D+7
13413-21	5.00E+08	5.70%	D+7
13413-22	5.00E+08	16.50%	D+10
13413-23	5.00E+08	17.80%	D+10
13413-28	1.93E+08	4.10%	D+10

01 May 2015
PRESENTED AT: ASCO Annual '15 Meeting

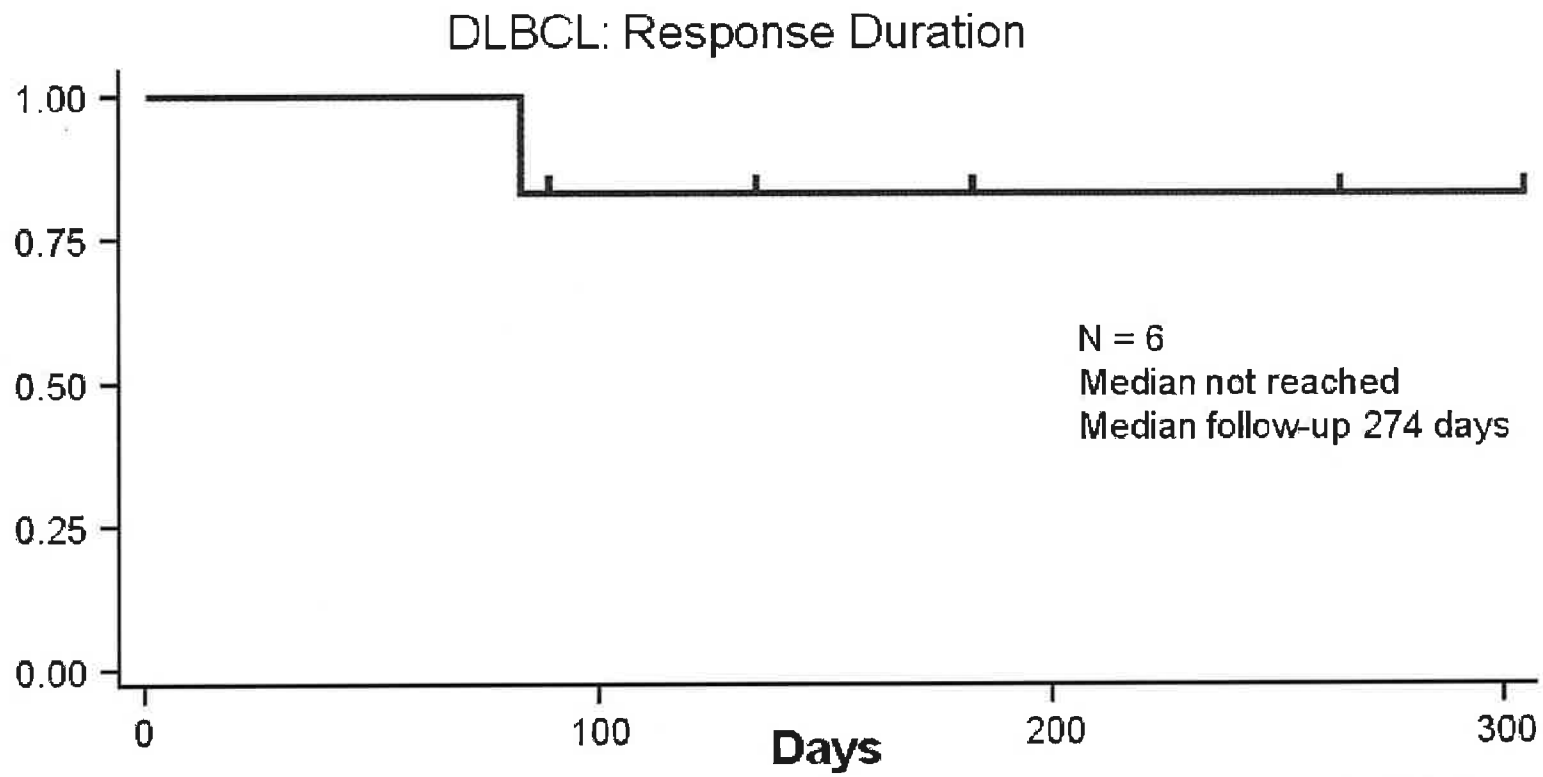
Presented By Stephen Schuster at 2015 ASCO Annual Meeting

Results: Diffuse Large B Cell Lymphoma



Presented By Stephen Schuster at 2015 ASCO Annual Meeting

Results: Diffuse Large B Cell Lymphoma



01 May 2015

PRESENTED AT: ASCO Annual '15 Meeting

Presented By Stephen Schuster at 2015 ASCO Annual Meeting

Results: Follicular Lymphoma

FL: Patient Characteristics (n = 8 enrolled)

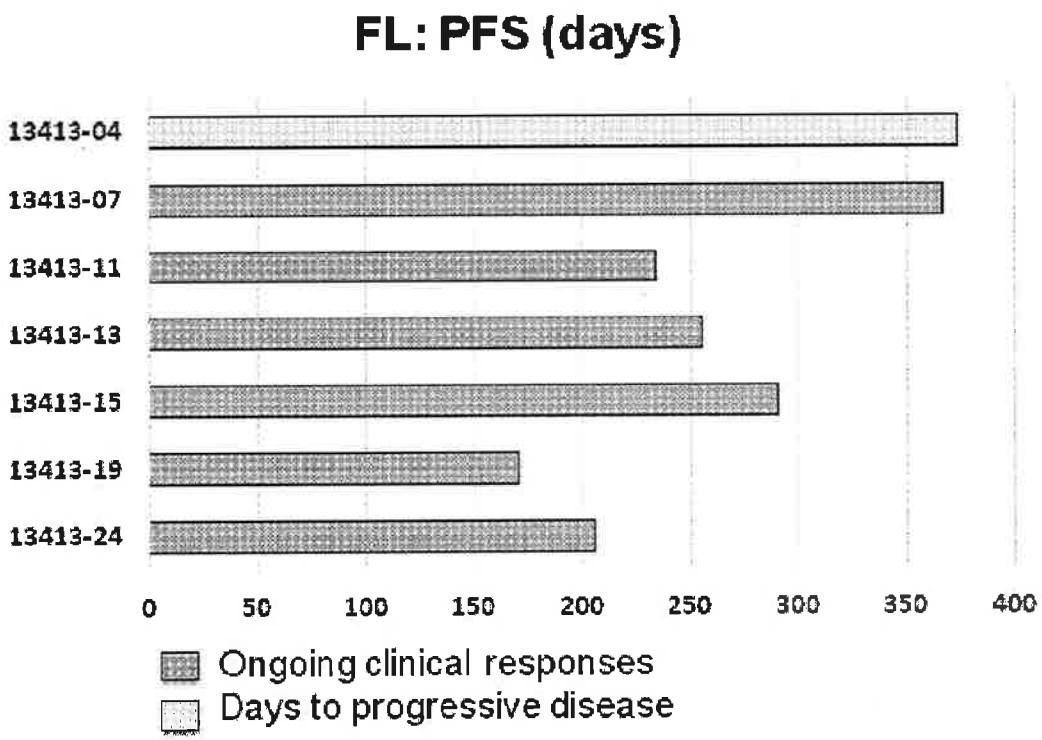
Median age	60.5 years (range 43 - 71)
Sex	3 (38%) men
Median prior therapies	5.5 (range 4 - 8)
Prior transplant %	2 (25%)
Stage III – IV (enrollment)	7 (88%)
Increased LDH (enrollment)	5 (63%)
> 1 extranodal site (enrollment)	1 (13%)
Median ECOG PS (enrollment)	0 (range 0 – 1)
Lymphodepleting therapy (n = 7)	4 bendamustine (90 mg/M2) daily x 2; 1 cyclophosphamide (200 mg/M2) + fludarabine (20 mg/M2) daily x 3; 1 XRT (400 cGy) + cyclophosphamide (1 gm/M2); 1 cyclophosphamide (1 gm/M2)

Response Rates: Follicular Lymphoma

FL: ORR at 3 Months 100% (N = 7)	FL: Best Response Rate 100% (N = 7)
- CR: 3 - PR: 4	- CR: 6 - PR: 1

- 3 patients with PRs by CT/MR criteria at 3 months converted to CRs by 6 months
- 1 patient with PR at 3 months who remained in PR at 6 and 9 months had PD at approximately 12 months

Results: Follicular Lymphoma



ID	Total CTL019 Dose	%CD3+CAR19+ Peak	Peak Day
13413-04	3.76E+08	0.70%	D+7
13413-07	5.00E+08	3.00%	D+10
13413-11	5.00E+08	38.20%	D+7
13413-13	5.00E+08	3.20%	D+7
13413-15	5.00E+08	40.50%	D+7
13413-19	1.79E+08	1.00%	D+7
13413-24	5.00E+08	8.40%	D+10

01 May 2015
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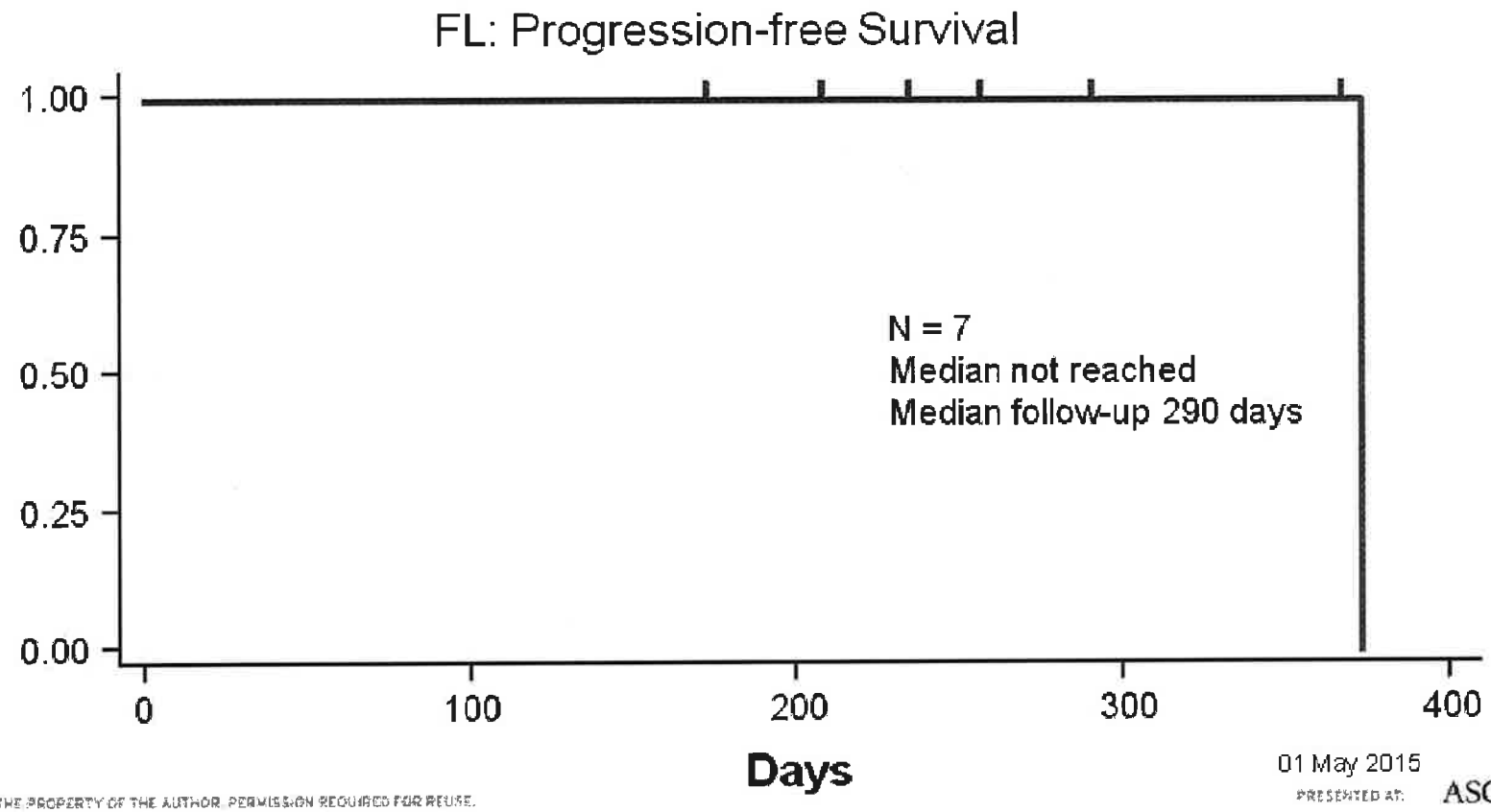
Results: Follicular Lymphoma



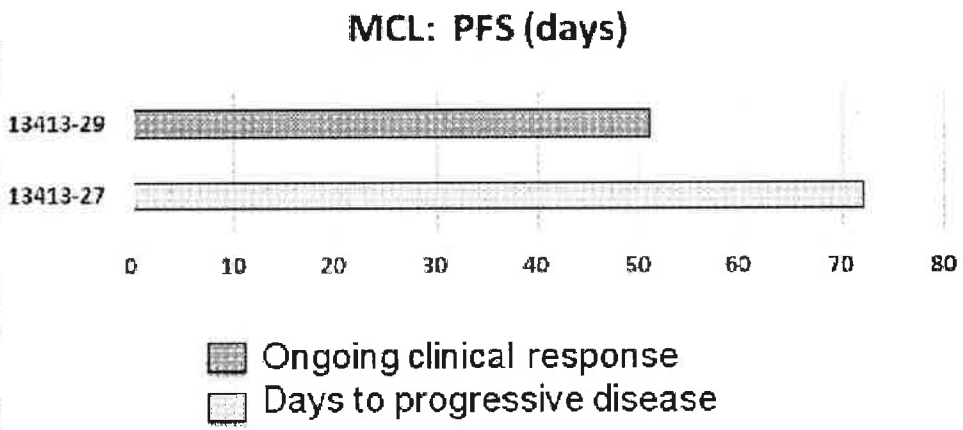
01 May 2015

PRESENTED AT: ASCO Annual '15 Meeting

Presented By Stephen Schuster at 2015 ASCO Annual Meeting

Results: Mantle Cell Lymphoma

MCL: Patient Characteristics (n = 3 enrolled)	
Median age	55 (range 55–61)
Sex	66% male
Median prior therapies	4 (range 3-6)
Prior transplant	30%
Stage III – IV (enrollment)	100%
Increased LDH (enrollment)	66%
>1 extranodal site (enrollment)	100%
Median ECOG PS (enrollment)	1 (range 0-1)
Received protocol-specified cell dose	2
Evaluable for response at ≥ 3 mos.	0
Lymphodepleting therapy (n = 2)	1 hyperfractionated cyclophosphamide (1.8 gm/M²), 1 bendamustine (90 mg/M²) daily x 2



ID	Total CTL019 Dose	Peak %CD3+CAR19+	Peak Day
13413-29	5.00E+08	42.60%	D+7
13413-27	5.00E+08	0.00%	NA

01 May 2015
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All Adverse Events in >2 Patients Regardless of Attribution: Only ≥ Grade 3 Shown

AE	G3	G4	G5	Total ≥ G3
Acute kidney injury	2			2
Anemia	1			1
CRS	1	1		2
Delirium	1			1
Fever	1			1
Hypertension	2			2
Hypocalcemia	1			1
Hypokalemia	1			1
Hyponatremia	1			1

AE	G3	G4	G5	Total ≥ G3
Infections	2			2
Hypophosphatemia	3	1		4
Hypotension	1	1		2
Leukopenia	3	2		5
Lymphopenia	10	8		18
Neutropenia	3	6		9
Thrombocytopenia	1			1
Transaminitis	1			1

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01 May 2015

Adverse Events at Least Possibly Related: ≥ Grade 3

AE	G3	G4	G5	Total ≥ G3
Acute kidney injury	2			2
Acidosis	1			1
Cytokine release syndrome	1	1		2
Encephalopathy			1	1
Delirium	1			1
Fever	1			1
Hypertension	1			1
Hypotension	1	1		2
Infection	1			1

01 May 2015
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Conclusions

- Chimeric antigen receptor modified T cells directed against CD19 (CTL019) can achieve durable responses in patients with relapsed or refractory CD19+ diffuse large B cell and follicular lymphomas.
  - All patients who achieved CR remain in CR.

- The toxicity of this therapeutic approach appears acceptable.
  - Cytokine release syndrome was generally grade 2.
  - There were no deaths from cytokine release syndrome.

Thanks to:

- Our patients and their families
- My collaborators at UPenn and Novartis

PLACER SHEET

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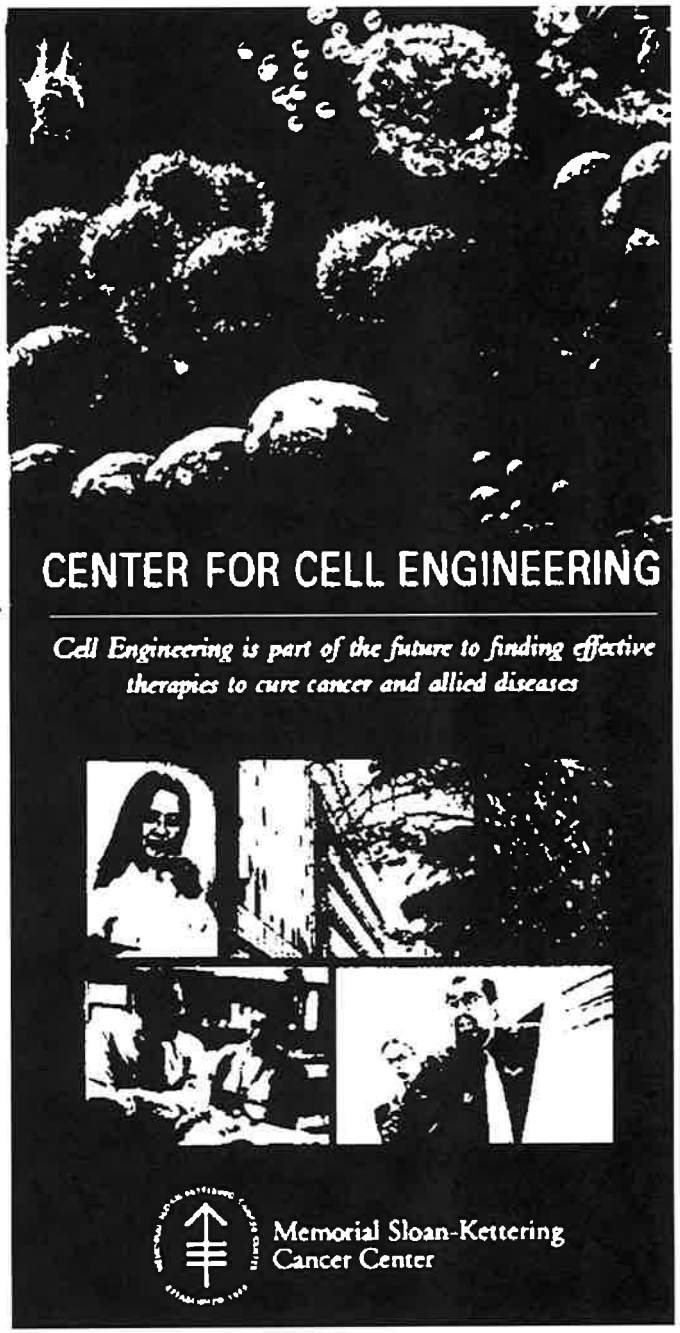
CD19 CAR Therapy for ALL

ASCO, May 29, 2015

Michel Sadelain, MD, PhD
Director, Center for Cell Engineering
Immunology Program, Sloan-Kettering Institute
Departments of Medicine and Pediatrics
Memorial Sloan Kettering Cancer Center
New York, NY



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Disclosure

Presented By Michel Sadelain at 2015 ASCO Annual Meeting

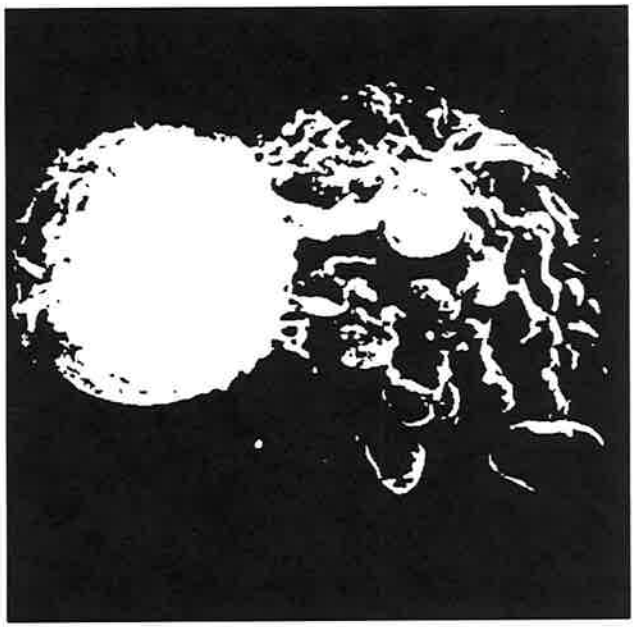
The rise of engineered T cells as cancer drugs

- A major limitation of most existing cancer therapeutics is the lack of of specificity or curative potential.
- The goal of T cell immunotherapy is to achieve curative potential combining potency, specificity and persistence.

- Safety
- Efficacy

↕

- Potency
- Specificity
- Long-acting



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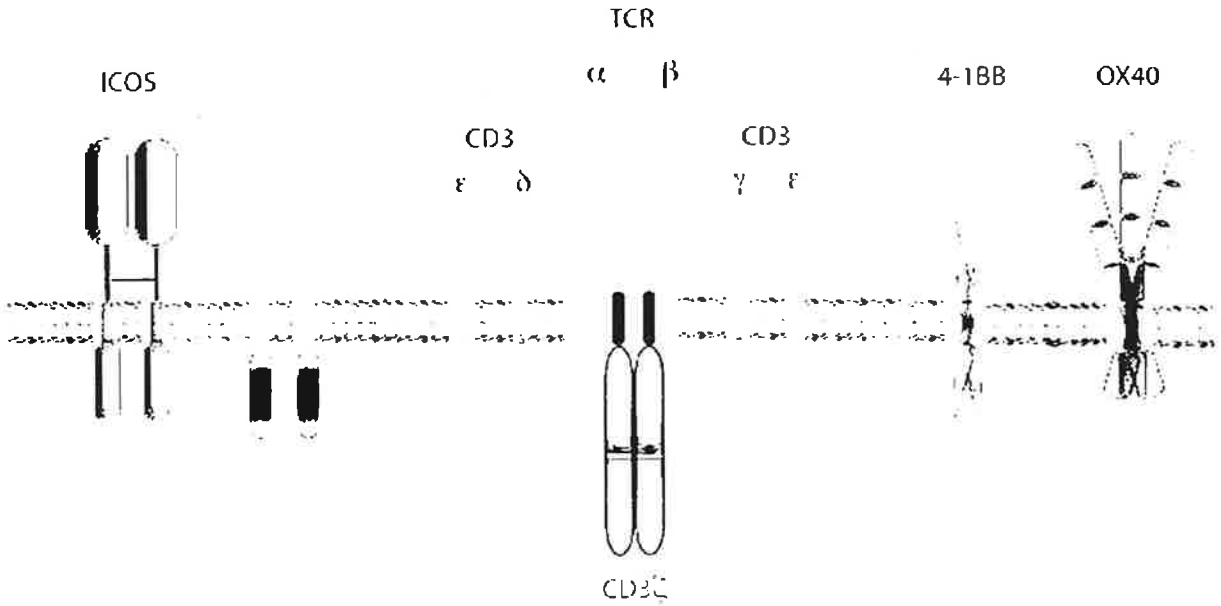
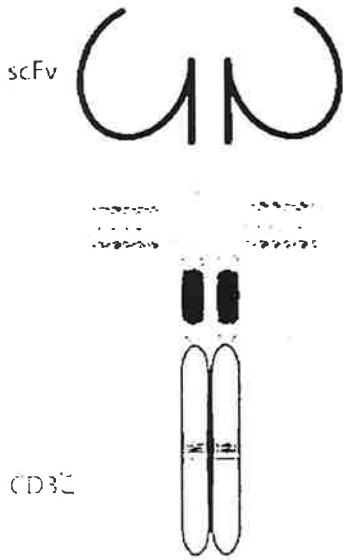
Physiological and synthetic receptors for T cell engineering

The TCR/CD3 complex and costimulatory constellation



CARs



Sadelain, Riviere & Brentjens, *Nat Rev Cancer*, 2003
Sadelain, *AACR Education Program*, 2014

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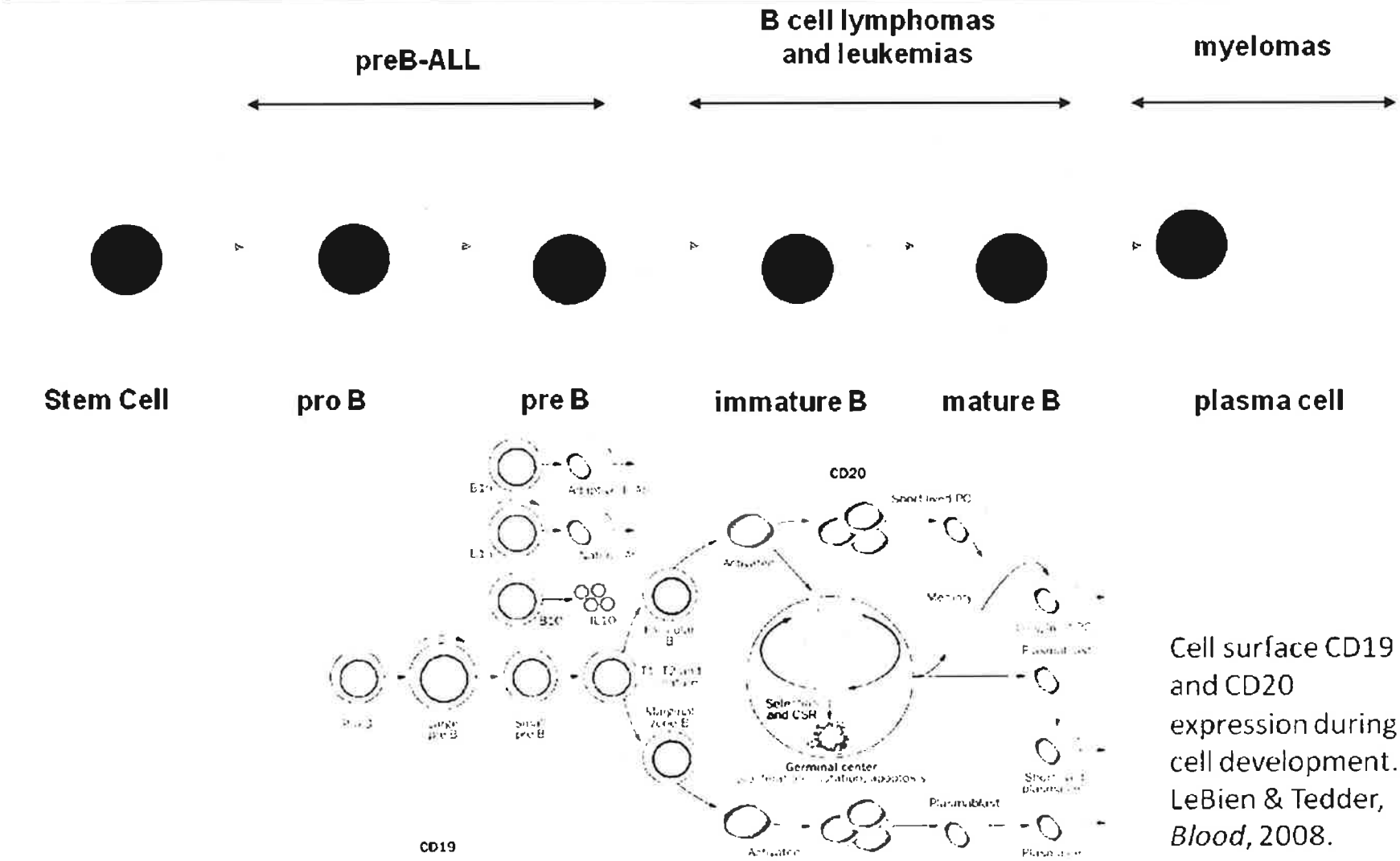
Selecting CD19 as a target for CAR therapy



Cell surface CD19 and CD20 expression during B-cell development. LeBien & Tedder, *Blood*, 2008.

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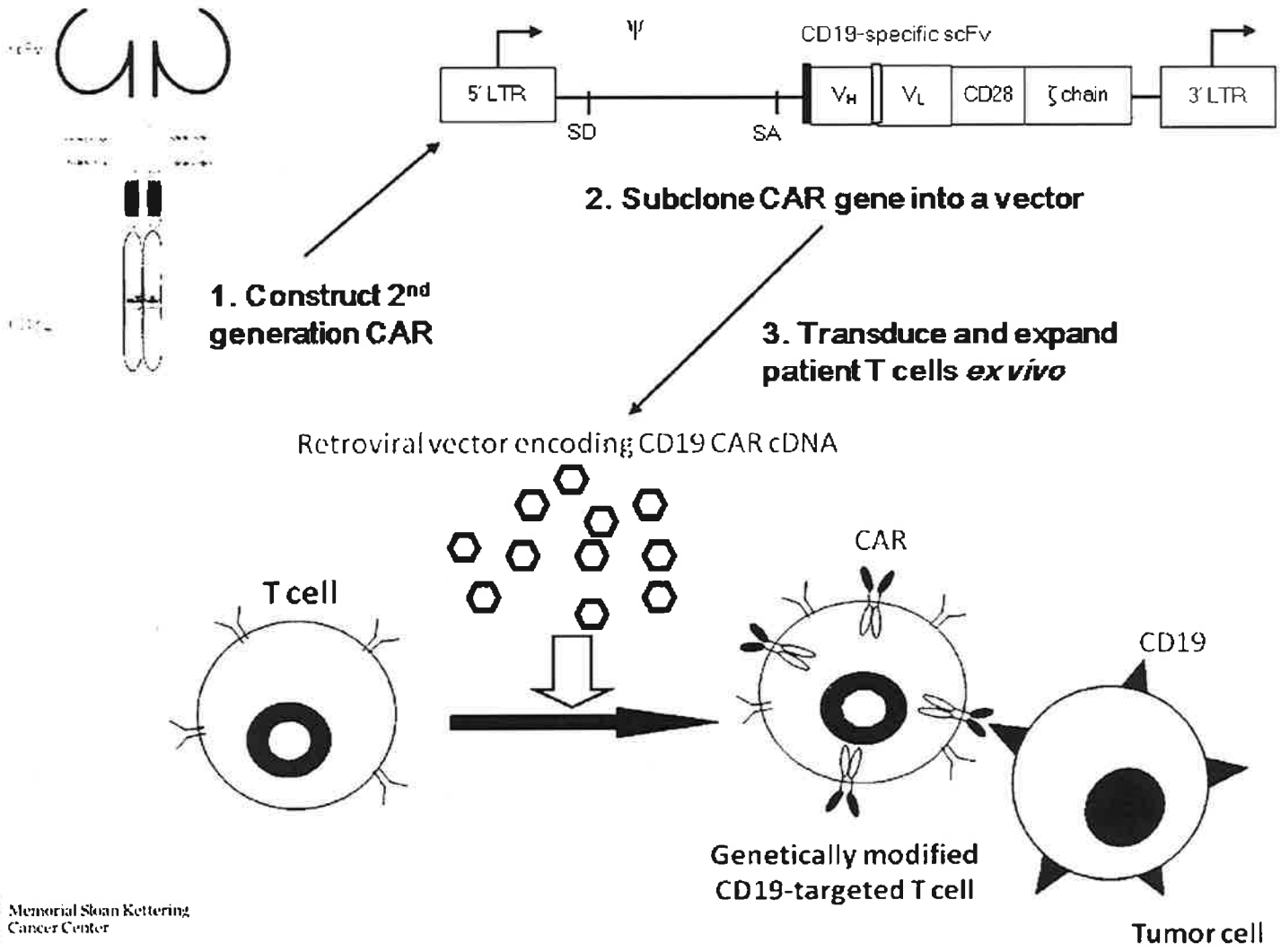
Generation of 19-28z CAR T Cells



Memorial Sloan Kettering Cancer Center

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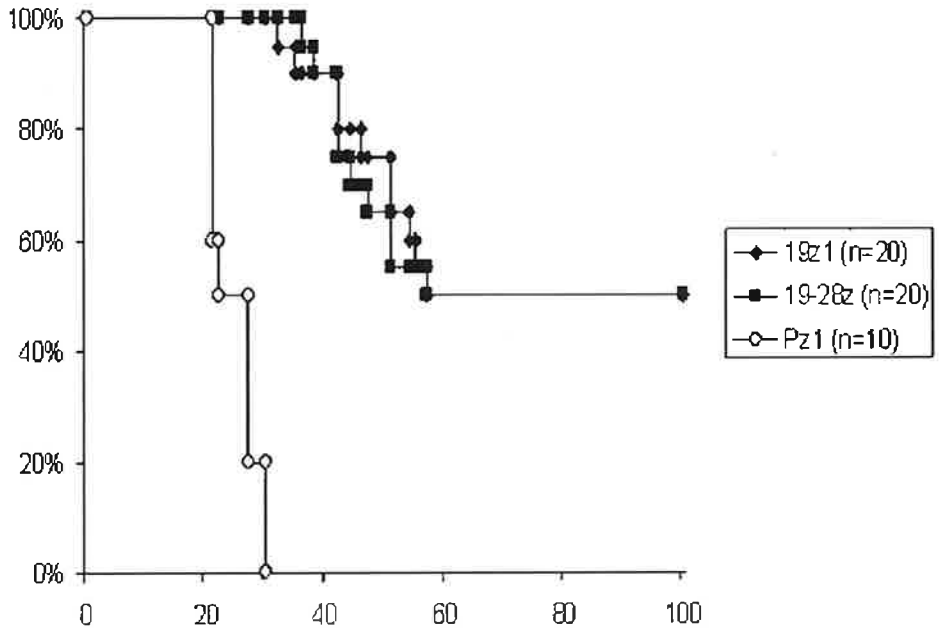
19z1 CART cells expanded on CD19+CD80+IL15+ AAPCs eradicate established systemic Raji in SCID-beige mice

Tumor Free

Untreated
4 weeks



Brentjens et al, *Nat Med*, 2003

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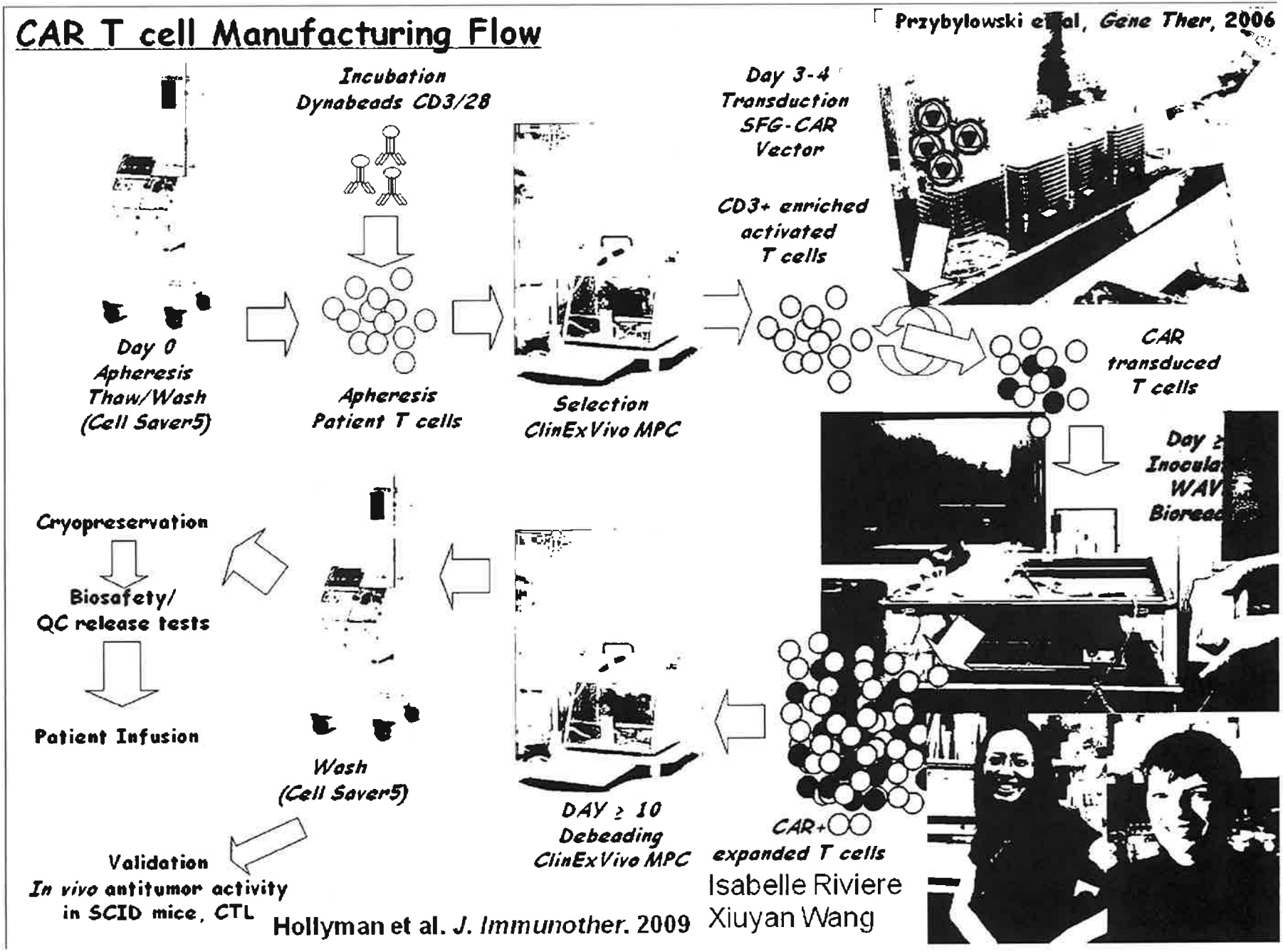
CAR T cell Manufacturing Flow



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A Phase I trial of precursor B cell Acute Lymphoblastic Leukemia (B-ALL) treated with autologous T cells genetically targeted to the B cell specific antigen CD19
(PI: J. Park; Past PI : M. Davila; co-PIs: R. Brentjens, M. Sadelain, I. Rivière)

- **Enrollment Criteria:**
  Patients with relapsed B-ALL initially treated with re-induction chemotherapy followed by consolidation with cyclophosphamide and 1928z+ T cells

- **Protocol Design:**
  Escalating T cell dose (3×10^6 19-28z+T cells/kg, 10^7 19-28z+T cells/kg, 3×10^7 19-28z+ T cells/kg) in combination with cyclophosphamide ($3.0 g/m^2$)

- **Primary Endpoint:**
  To assess the toxicity of adoptively transferred 1928z+ T cells

- **Secondary Endpoints:**
  1928z+ T cell survival
  Role of CY T cell survival
  1928z+ T cell homing
  B cell aplasias

Jae Park Marco Davila Renier Brentjens

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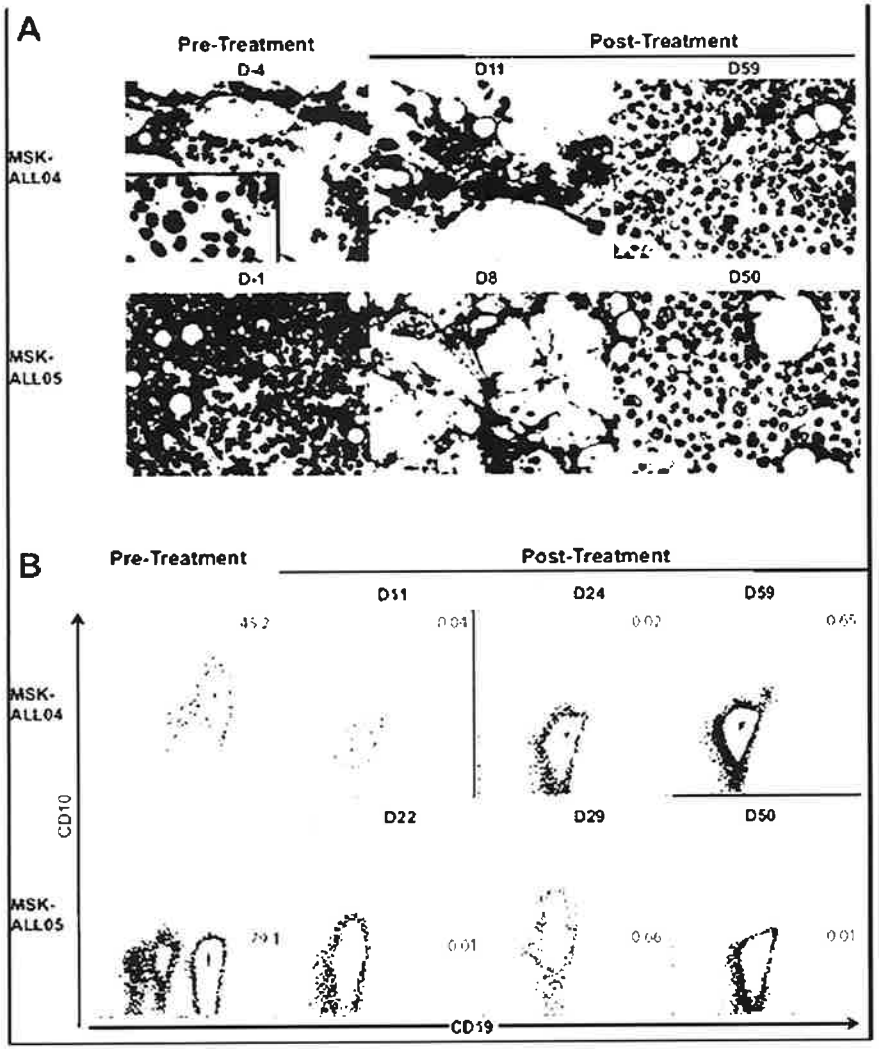
Rapid tumor elimination mediated by 19-28z T cells



A. BM aspirates pre and post treatment with 19 28z T cells in 2 patients with morphologic chemotherapy refractory B ALL. Cyclophosphamide was given at Day 1 and CD19 CAR targeted T cells were infused on Days 1 and 2. Left panels. BM prior to CAR modified T cell therapy demonstrated predominant blast cells with an absence of normal BM precursors. For MSK ALL04 the left panel includes an inset with 100x magnification. Middle panels are BM aspirates done shortly after 19 28z T cell infusion and is hypocellular with normal stromal elements, histiocytes, and no evidence of blasts. Right panels. By 1 to 2 months after CAR modified T cell therapy there is BM recovery with normal hematopoiesis and no evidence of abnormal blasts.

B. B. Flow cytometry for CD19 and CD10 expression in BM pre and post treatment. Cells were gated on CD45+7AAD cells.

Brentjens, Davila, Riviere et al, *Science Transl Med*, 2013

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Deep Sequencing for IgH rearrangements before and after CD19 CAR-targeted T cell therapy

Patient ID	Day of Treatment	Total # IgH rearrangements	Total # malignant IgH rearrangements
MSK-ALL01*	-1: 55:	57,480 15,925	58 0
MSK-ALL03*	-5: 30:	1,084 0	0 0
MSK-ALL04	-4: 11: 24: 59:	2,430,058 2,407 1,144 995,563	2,426,898 1,316 637 0
MSK-ALL05*	-1: 8: 29:	3,307,494 1,880 8,270	3,300,732 0 0
MSK-ALL06	-34: 18: 39:	255,301 5,429 1,866,851	174,698 4 0

Adaptive Biotechnologies performed multiplex PCR and Deep Sequencing on genomic DNA prepared from BM aspirated on the noted day. Malignant IgH rearrangement refers to IgH rearrangements associated with the B ALL tumor cells. Total # of IgH rearrangements are derived from both malignant and non malignant B cells. * Patient has gone to allo SCT and is off study.

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Baseline Patient Characteristics

Characteristic	Number of Patients N=28 (%)
Sex	
Male	21 (75)
Female	7 (25)
Age at infusion (years)	
18-29	7 (2)
30-59	12 (43)
≥60	9 (32)
Median (range)	55 (23-74)
Disease burden immediately prior to T cells	
Morphologic disease (5-100%, median 63%)	16 (57)
Minimal disease (<5%)	12 (43)

Baseline Disease Characteristics

Characteristic	Number of Patients, N=28 (%)
Prior Lines of Therapy	
2	18 (64)
3	5 (18)
≥4	5 (18)
Prior Remission Duration	
Primary refractory	2 (7)
<12 months	20 (71)
12-24 months	0 (0)
>24 months	6 (22)
Prior allogeneic HSCT	
Yes	8 (29)
No	20 (71)
Philadelphia chromosome (Ph)+	9 (32)
T315I mutation	3 (11)

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Summary of Clinical Outcome

	Number of Patients, N=27
Overall CR Rate MRD Negative CR Rate	24/27 (89%) 21/24 (88%)
Median Time to CR	22.5 days

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CR Rates by Subgroups

Subgroups	Number of Patients, N=27 (%)
Pre-T cell Disease Burden	
Morphologic disease	12/15 (80)
Minimal disease	12/12 (100)
Prior Allogeneic HSCT	
Yes	6/7 (86)
No	18/20 (90)
Ph+ Status	
Yes	8/9 (89)
No	16/18 (89)
Prior Remission Duration	
Primary refractory	2/2 (100)
<12 months	16/19 (84)
>24 months	6/6 (100)

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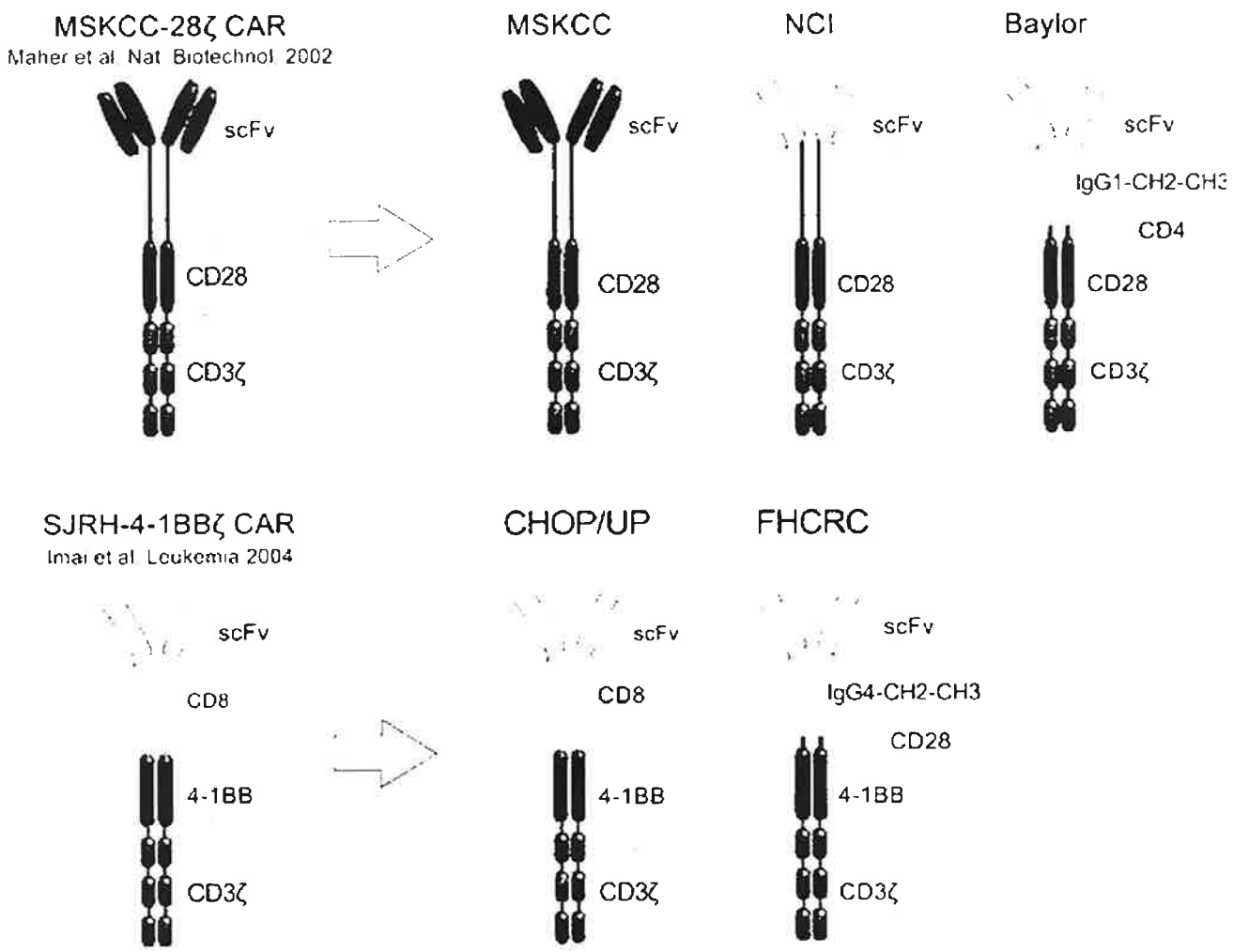
CD19 CARs: original CARs and variants in clinical trials



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Patient numbers/outcomes with CD19 CAR therapy for ALL

Publication/meeting date	Number/age of subjects	Complete remission rate
Brentjens, *Sci Transl Med*, March 21, 2013	5 adults	100%
Grupp, *New Engl J Med*, April 18, 2013	2 children	100 %
Davila, *Sci Transl Med*, February 19, 2014	16 adults	88%
Lee, *Lancet*, AOL, October 13, 2014	20 children	70%
Maude, *N Engl J Med*, October 16, 2014	25 children, 5 adults	90% 100%
Park, *ASH 2014*, December 6, 2014	27 adults	89%
Frey, *ASH 2014*, December 6, 2014	12 adults	89%

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Cancer **Immunotherapy**

Memorial Sloan-Kettering Cancer Center in New York reported that the T cell therapy in their studies put 45 of 75 adults and children with leukemia into complete remission, although some later relapsed. CAR therapy is now the focus of numerous clinical trials. Researchers hope that it, like the antibodies, can target an assortment of cancers. Engineered T cells are still experimental.

Online
sciencemag.org

Seek and destroy

cancer cells

Pharmaceutical companies cried foul. Bristol-Myers Squibb's anti-CTLA-4 treatment, called ipilimumab for metastatic melanoma. The cost is high. The company charges $120,000 for a course of therapy. In 2012, Suzanne Topalian of Hopkins, Mario Sznol of Yale University and their colleagues reported results for anti-PD-1 therapy in nearly 300 people and they provided an update earlier this year. Tumors shrank by about half or more in 31% of those with melanoma, 29% with kidney cancer and 17% with lung cancer.

This year brought even more encouragement. Bristol-Myers Squibb reported that half of 1,800 melanoma patients treated with ipilimumab 3 years later. In June, researchers reported that combining ipilimumab and anti-PD-1 led to "deep and rapid tumor regression" in almost a third of melanoma patients. Drugs blocking the PD-1 pathway have not yet been proven to extend life, although survival rates so far have doctors optimistic that they do.

For physicians accustomed to losing every patient with advanced disease, the numbers bring a hope they couldn't have fathomed a few years ago. For those with metastatic cancer, the odds remain long. Today's immunotherapies don't help everyone, and researchers are largely clueless as to why some don't benefit. They are racing to identify biomarkers that might offer answers and experimenting with ways to make therapies more potent. It's likely that some cancers will not yield to immunotherapy for many years, if ever.

Even in the third wave of cancer oncology now truly is self, this much is certain. One book has closed, and a new one has opened. How it will end is anyone's guess.

–JENNIFER COUZIN-FRANKEL

Future directions in CAR therapy

- Curbing the severe cytokine response syndrome
  - From identification to treatment to prevention
- Target cell identification
  - Combinatorial antigen recognition
  - iCARs (CTLA-4mut, PD1)
  - Target discovery
  - Overcoming antigen escape
- Increasing T cell potency (solid tumors)
  - Combination therapy (checkpoint blockade, small molecules)
  - Cytokine co-expression (e.g., IL12)
  - Graded costimulatory support
  - Trans-costimulation
  - Optimizing delivery (regional, e.g. pleural)
- Autologous T cells and alternative T cell sources

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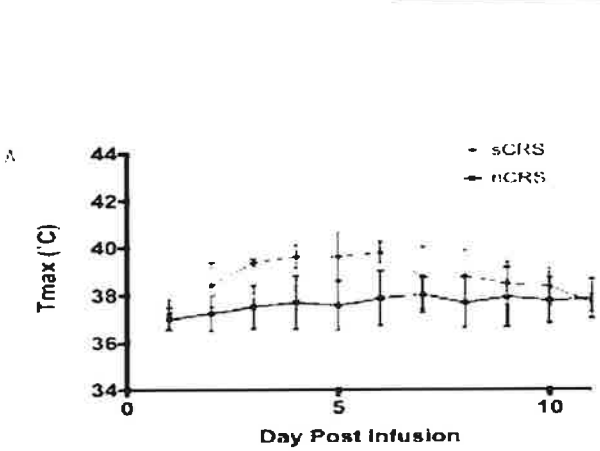
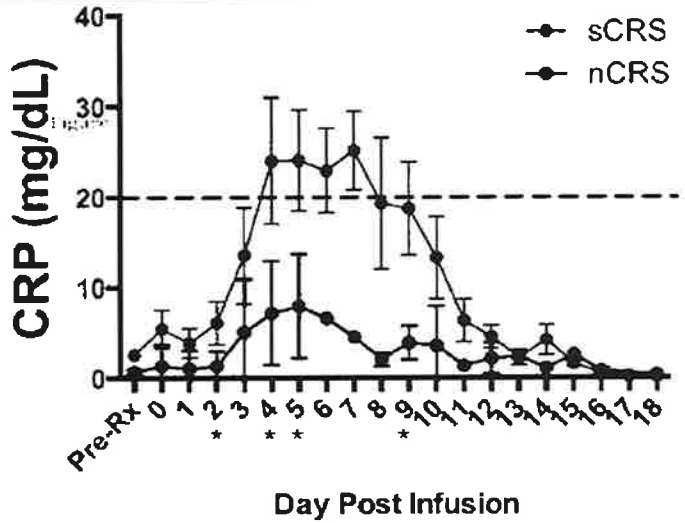
Toxicity definition and biomarkers

Criteria for sCRS

- Fevers for at least 3 consecutive days
- 2 cytokine max fold changes of at least 75
  OR
  1 cytokine max fold change of at least 250
- At least one clinical sign of toxicity such as
  hypotension (requiring at least one intravenous vasoactive pressor)
  hypoxia (PO_2 < 90%)
  neurologic disorders (including mental status changes, obtundation, and seizures)

Davila, *Science TM*, 2014





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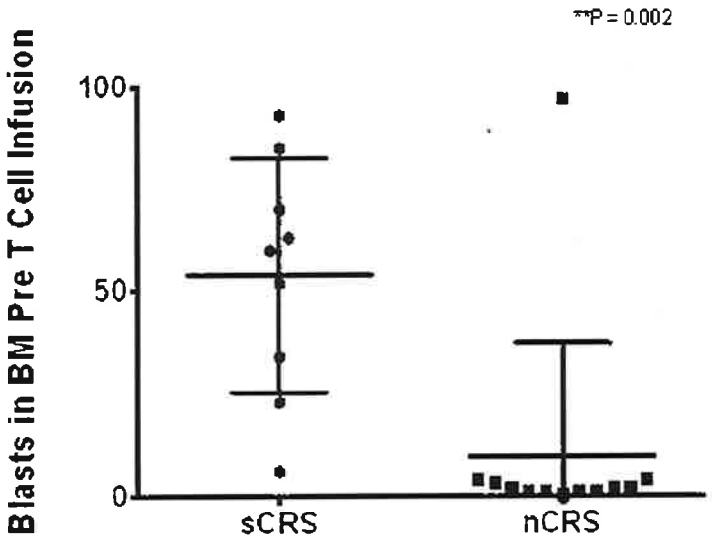
Pre-Infusion Disease Burden and CRS



Patients with Gross Residual Disease at Infusion*			Patients with Minimal Residual Disease at Infusion*		
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	Y*	[illegible]	[illegible]	N*
[illegible]	[illegible]	Y*	[illegible]	[illegible]	N*
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[illegible]	[illegible]	Y*	[illegible]	[illegible]	N*
[illegible]	[illegible]		[illegible]	[illegible]	N*

- 0/10 sCRS in MRD patients
- 8/11 sCRS in morphologic pts

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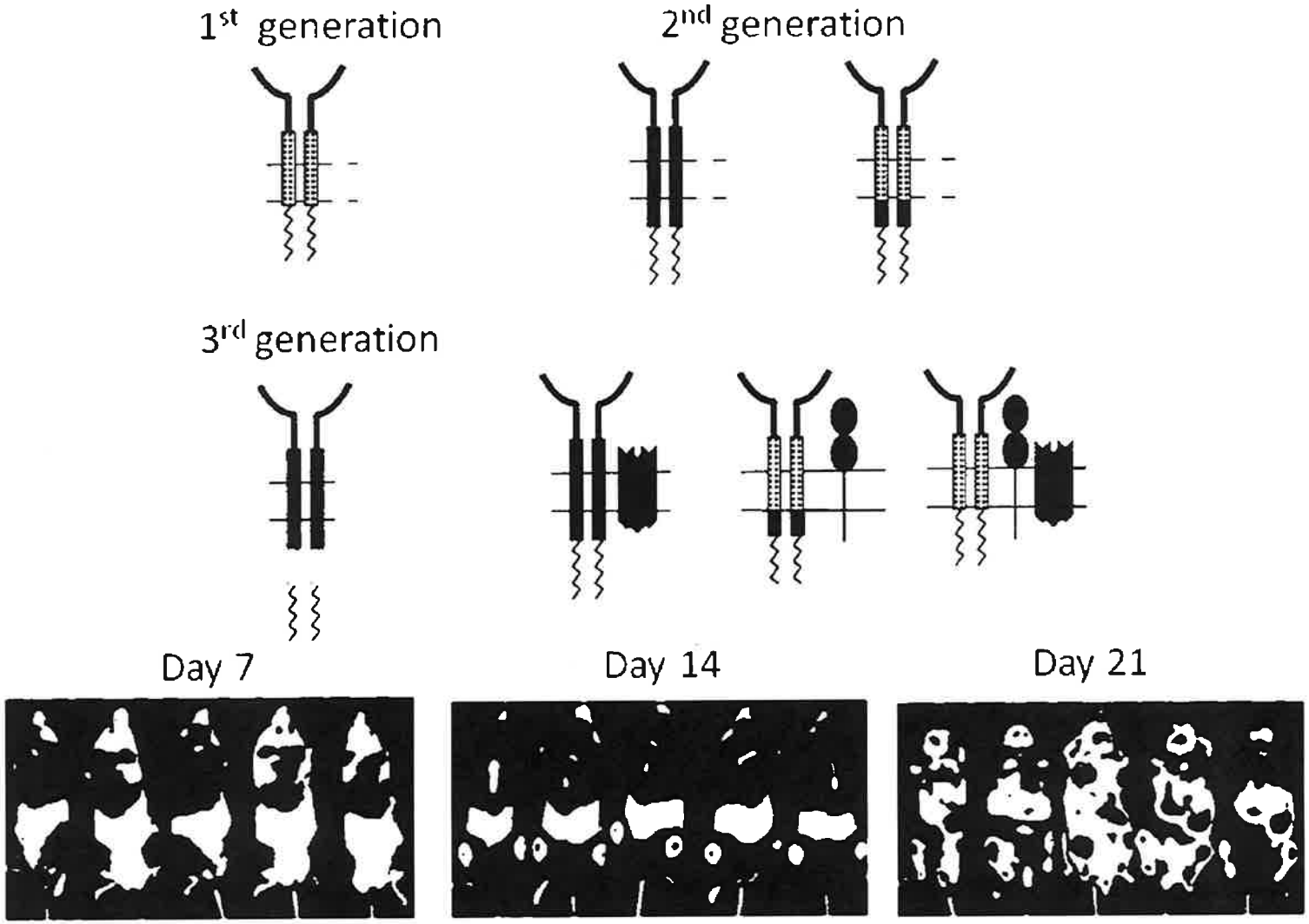
Assays for T cell potency: the ***CAR stress test***



The NALM/6 B-ALL NSG model

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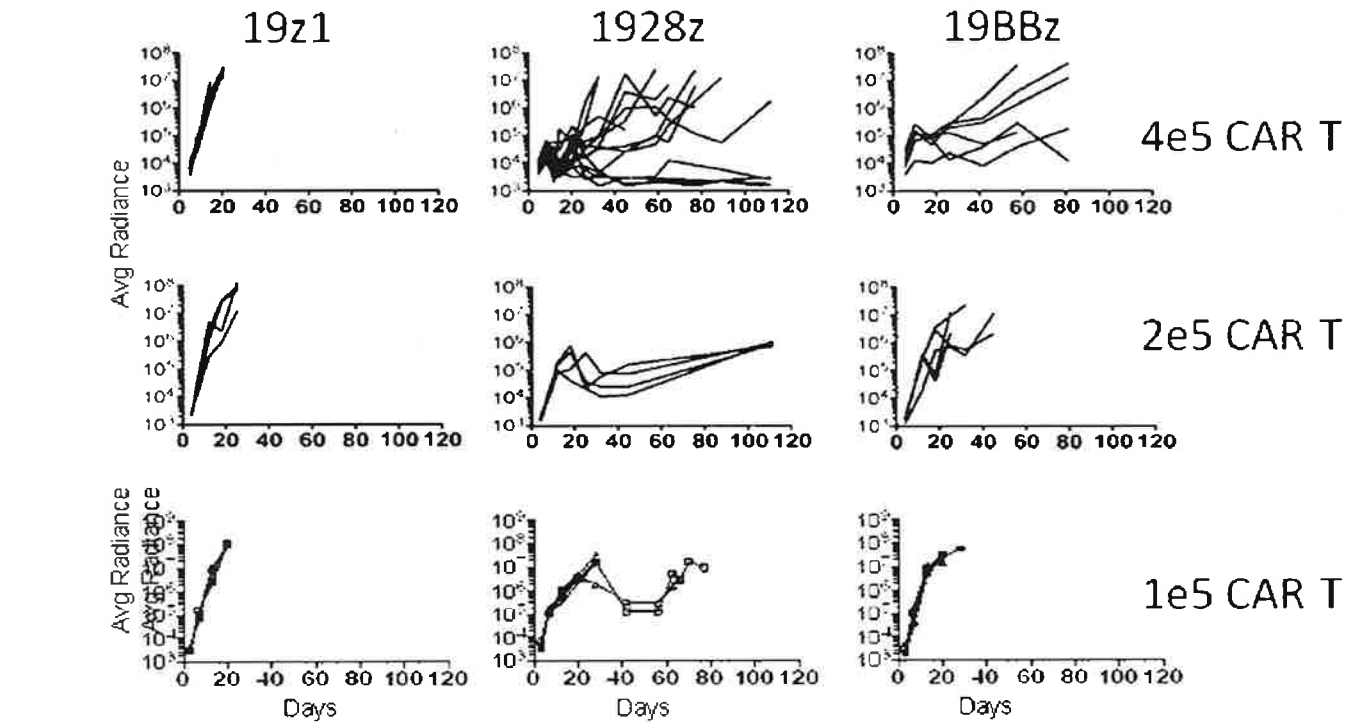

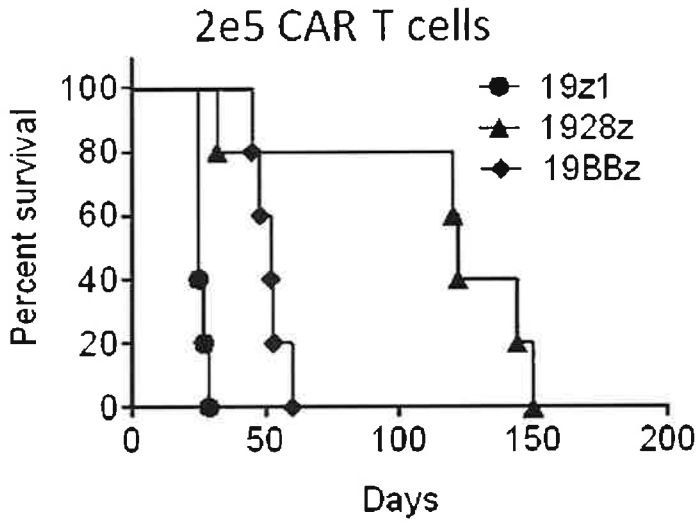

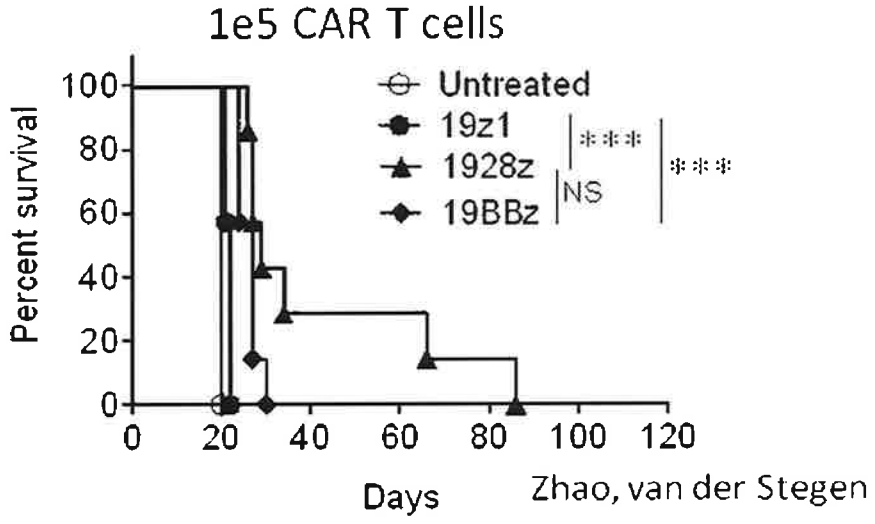

Zhao, van der Stegen

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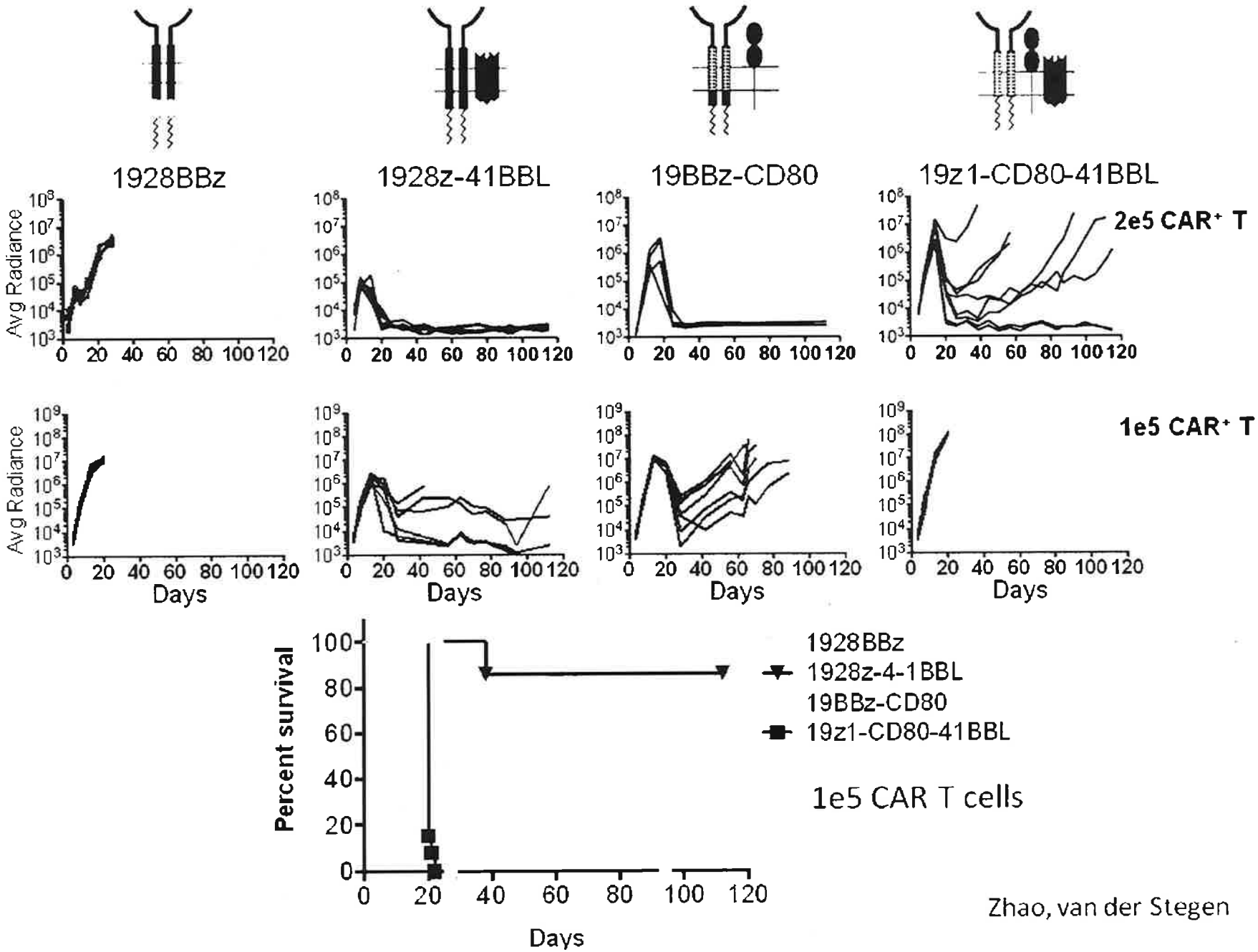

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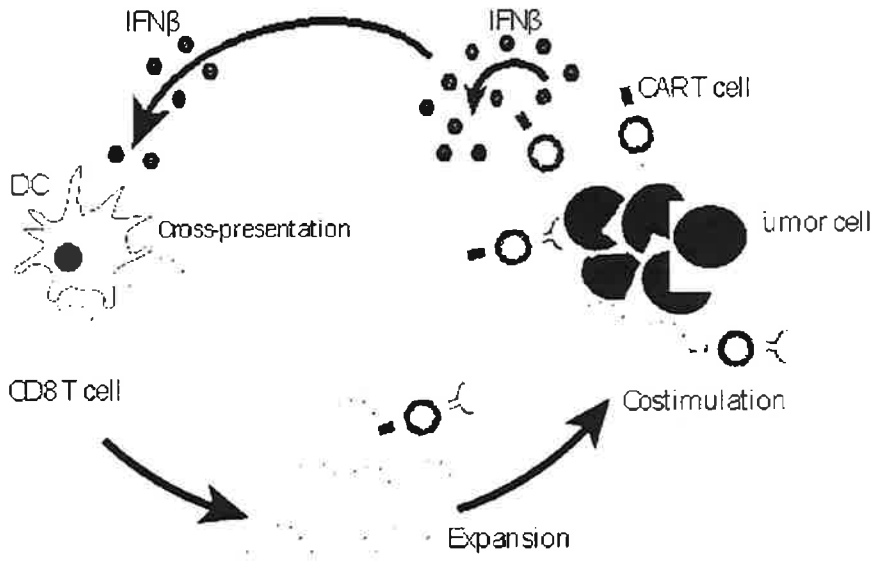
Summary

- 2nd-gen CARs retarget and functionally enhance T cells
- CAR T cells induce CRs where chemotherapy drugs have failed ("the CD19 paradigm")
- CAR T cells can be engineered to graded potency levels
- CAR T cells are not just "tumor killers" and can be harnessed to reprogram the TME (trans-costimulation, IFN-ß)



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Memorial Sloan Kettering Cancer Center

STAND UP TO

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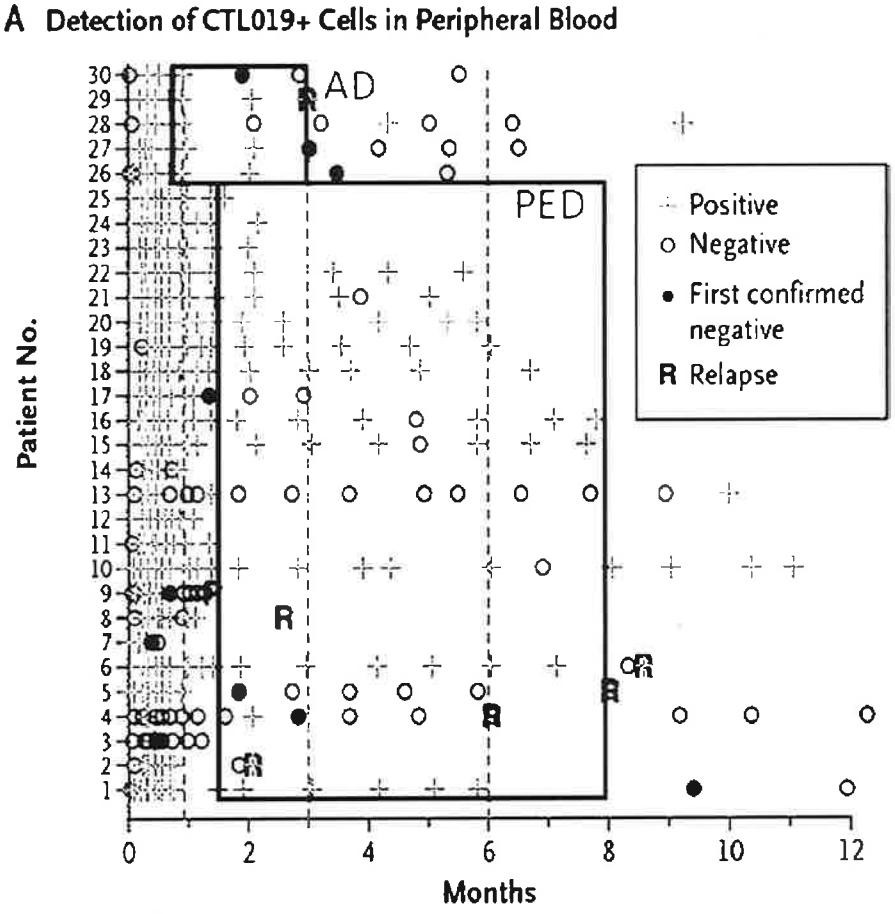
CD19 CAR T cell persistence in adult ALL

Patient ID	CAR T cells	Patient ID	CAR T cells
MSK-ALL01	D[illegible] 2,628 D23: 1,307 D99: 0	MSK-ALL09	D-2: D18: 377 D35: 732 D130: 0
MSK-ALL03	D16: 1,642 D23: 3,098 D30: 3,012 D419: 0	MSK-ALL10	D2[illegible] 23 D125: 0
MSK-ALL04 (received steroids)	D-4: D11: 425 D24: 0 D59: 0 D100: 0	MSK-ALL11	D23: 91
MSK-ALL05 (received steroids)	D-1: D8: 282 D22: 57 D50: 0 D253: 0	MSK-ALL12	D-3 D5[illegible] 61
MSK-ALL06	D-34 D18: 0 D39: 0 D281: 0	MSK-ALL13 (received tocilizumab)	D-29 D27: 6654 D57: 26 D120:54
MSK-ALL07 (received steroids and tocilizumab)	D-4: D16: 2715 D45: 628 D77: 253 D146: 0	MSK-ALL14 (received tocilizumab)	D20: 8084 D4[illegible] 44
		MSK-ALL15	D-7 D9: 1880 D34: 48
		MSK-ALL16	D29: 0
		MSK-ALL17 (received tocilizumab)	D41: 922

From Table S2, Davila et al., *Science Transl Med*, 2014



From Fig 2, Maude et al, *New Engl J Med*, 2014

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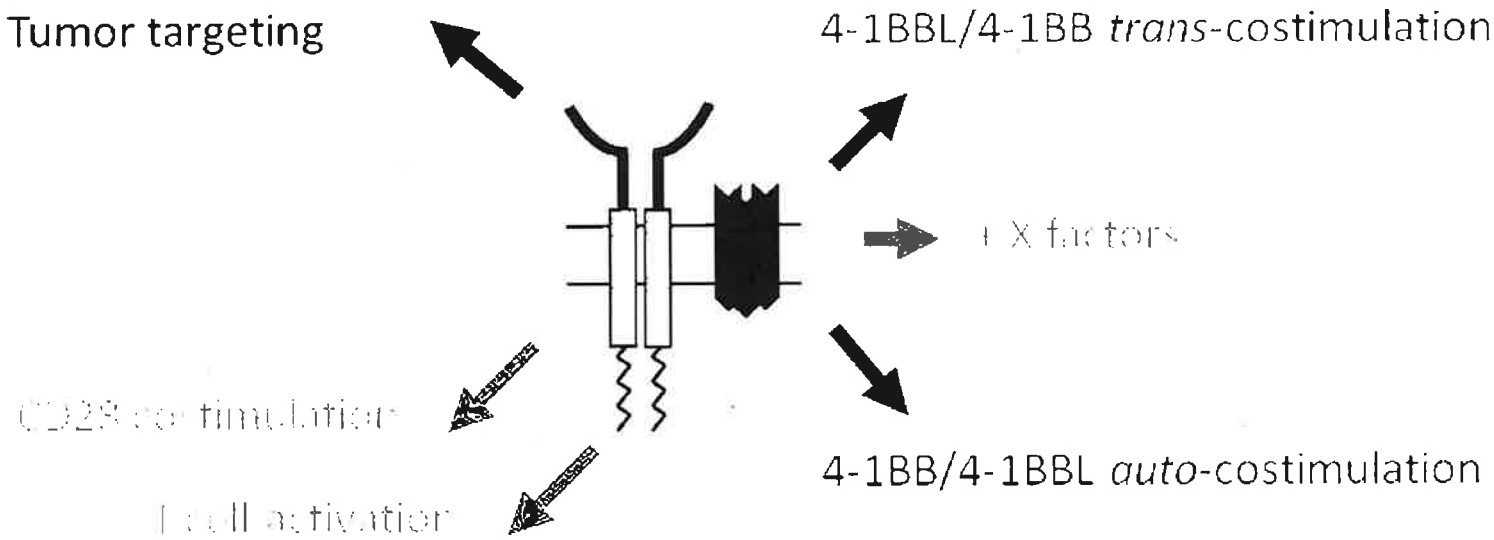
Altering the tumor microenvironment by *trans*-costimulation… and more

The "28z + 4-1BBL" CAR model



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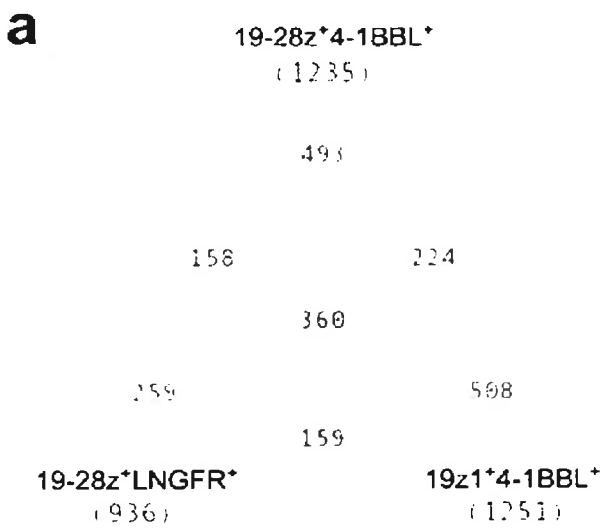
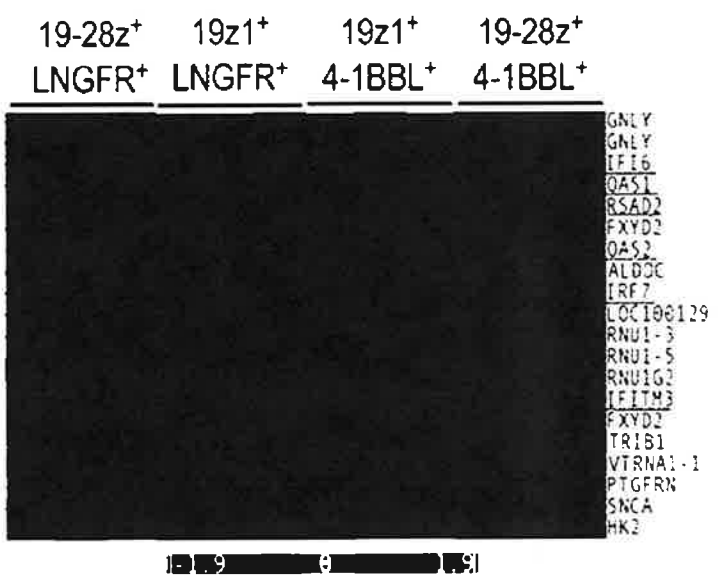
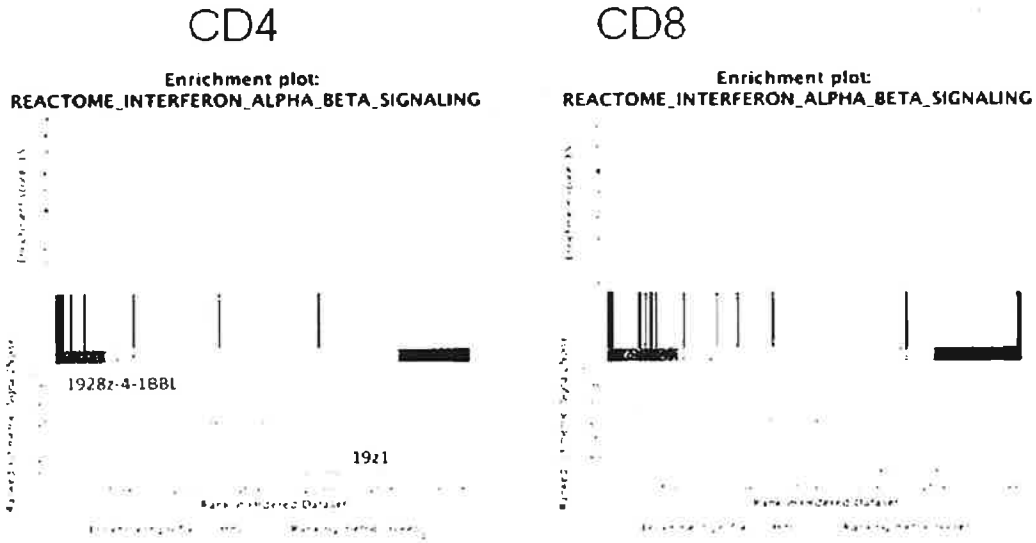
Microarray studies reveal strong induction of IRF7/IFNß in 19-28z/4-1BBL T cells







Maud Condomines,
Fabiana Perna

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Phase I Clinical Trial of CD19-Targeted 19-28z CAR Modified T Cells in Adult Patients with Relapsed or Refractory B-ALL

(Abstract #7010)

Jae H. Park, Isabelle Riviere, Xiuyan Wang, Yvette Bernal, Elizabeth Halton, Hilda Quintanilla, Kevin Curran, Craig Sauter, Michel Sadelain, and Renier J. Brentjens

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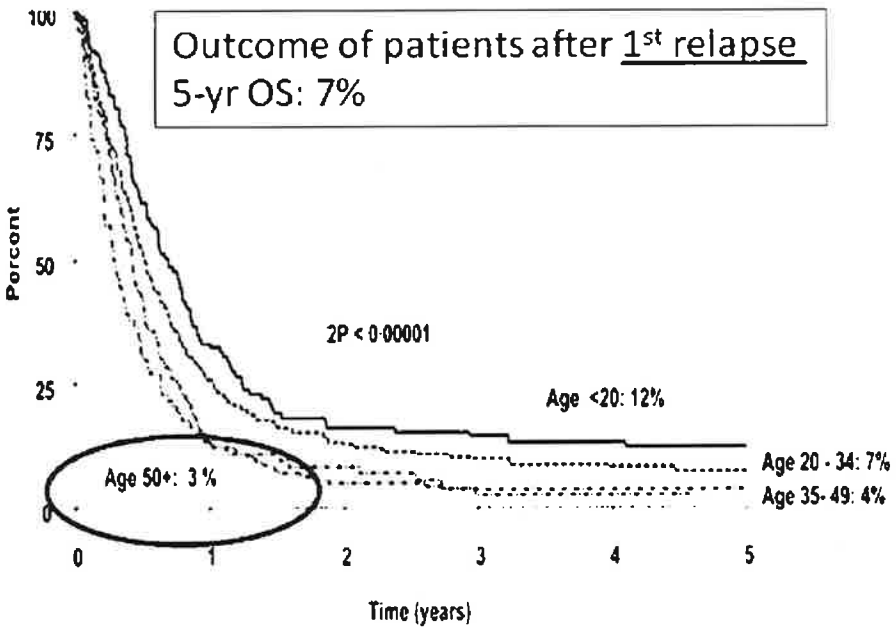
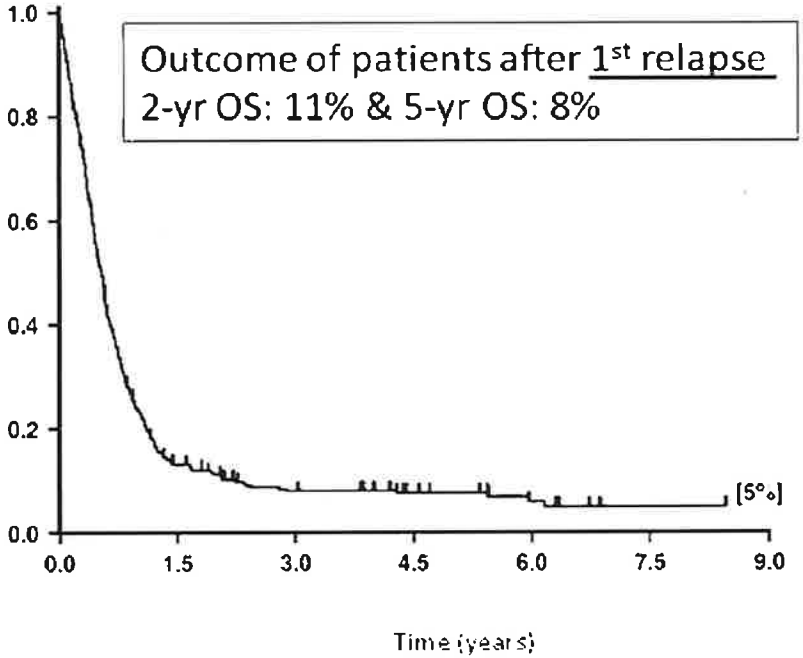
Poor Prognosis of Relapsed ALL in Adults

MRC UKALL2/ ECOG2993 Study (n=609)



Fielding A, et al. *Blood* 2007;109(3):944 950.

LALA-94 Study (n=421)



Tavernier E, et al. *Leukemia* 2007;21:1907 1914.

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Common conventional treatment regimens may yield varying responses (CR 18-45%) in R/R ALL

	Study Author	Relapsed Patient Population	Median Age (range)	No. of Pts	Study Endpoints	
1st Relapse	Tavernier et al, 2007	LALA Trial – France, Switzerland, Australia	34 (15-62)	421	CR-Overall CR-High Risk CR-Standard Risk	44% 37% 52%
1st Relapse	Oriol et al, 2010	Spain PETHEMA Study Group Data from 4 trials	33 (15-69)	263	CR-15-30 yr olds CR-30-55 yr olds CR-55-70 yr olds	47% 48% 20%
1st Relapse	Gökbuget, 2012	German pts GMALL (2 clinical trials)	33 (15-55)	588	CR Overall Early Relapse Late Relapse	42% 36% 58%
2nd Relapse	O'Brien et al, 2008	US, MD Anderson	33 (14-76)	288	CR Overall	18%
2nd Relapse	O'Brien et al, 2012	US, Multicenter (Liposomal Vincristine)	31 (19-83)	65	CR/CRi Overall	20%

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Tavernier at al. *Leukemia* 2007: Oriol et al. *Haematologica* 2010: Gol buget et al. *Blood* 2012: O'Brien et al. *Cancer* 2008: O'Brien et al. *JCO* 2012.

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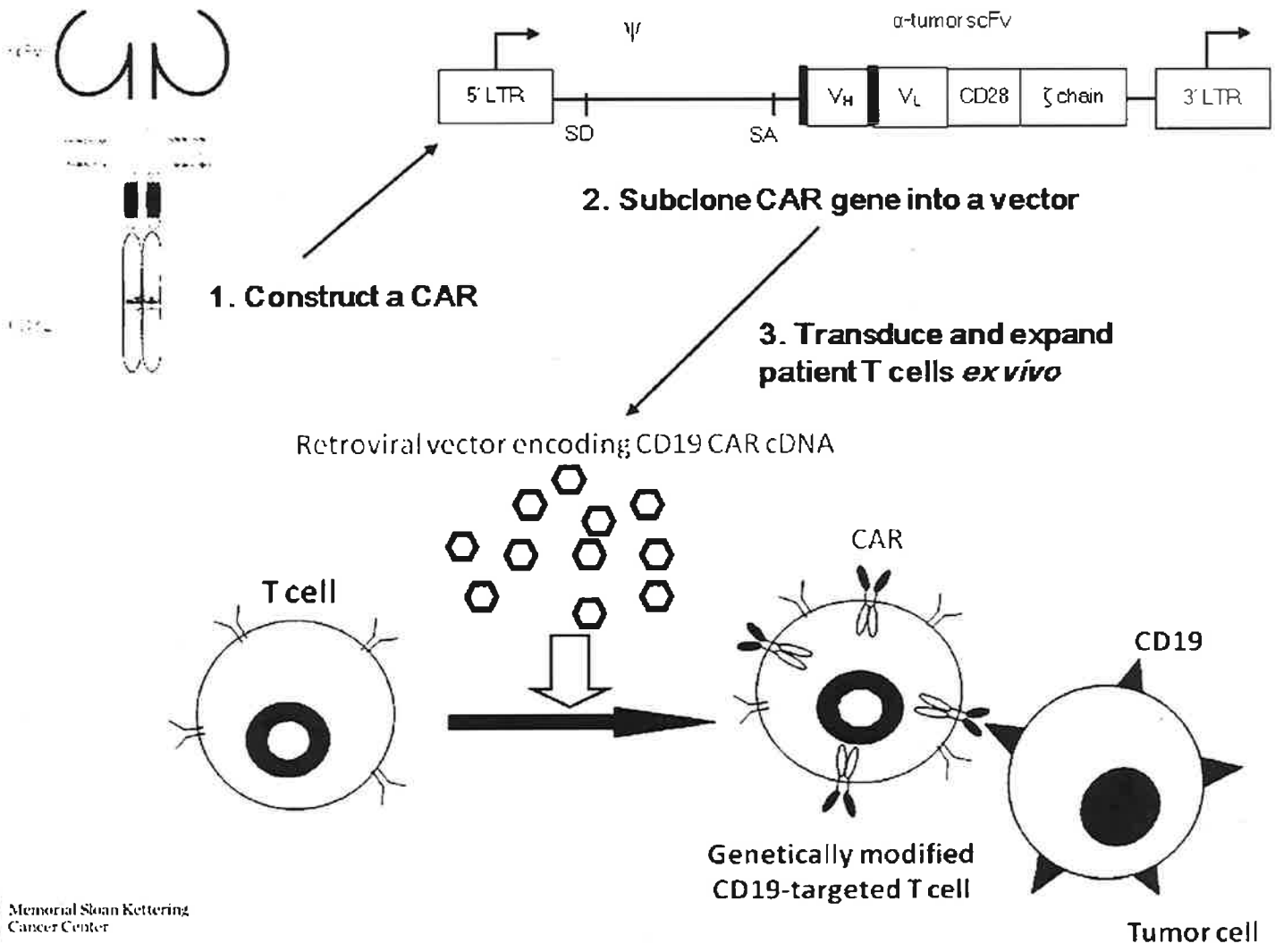
Generation of 19-28z CAR T Cells



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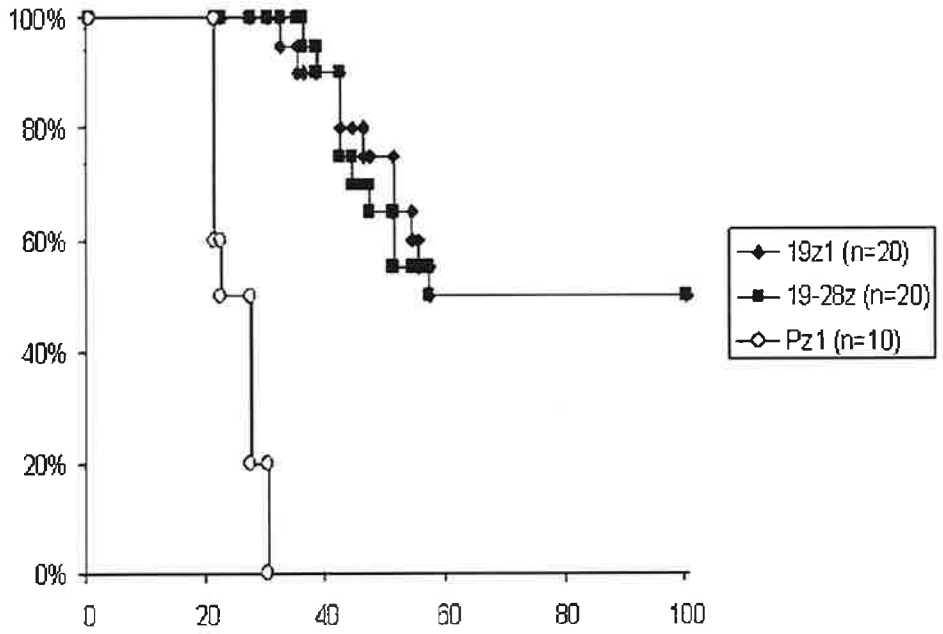
19z1 CAR T cells can eradicate systemic ALL in SCID-beige mice



Brentjens et al, *Nat Med*, 2003

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A Phase I trial of precursor B cell Acute Lymphoblastic Leukemia (B-ALL) treated with autologous T cells genetically targeted to the B cell specific antigen CD19

- **Inclusion Criteria:**
  - Adult patients, age ≥18
  - Relapsed or refractory CD19+ B-ALL
  - Relapsed after allogeneic HSCT allowed
- **Exclusion Criteria:**
  - Active CNS disease
  - Active GvHD requiring immunosuppressants
  - Significant heart disease (MI ≤ 6 months or NYHA III/IV CHF or EF <40%)

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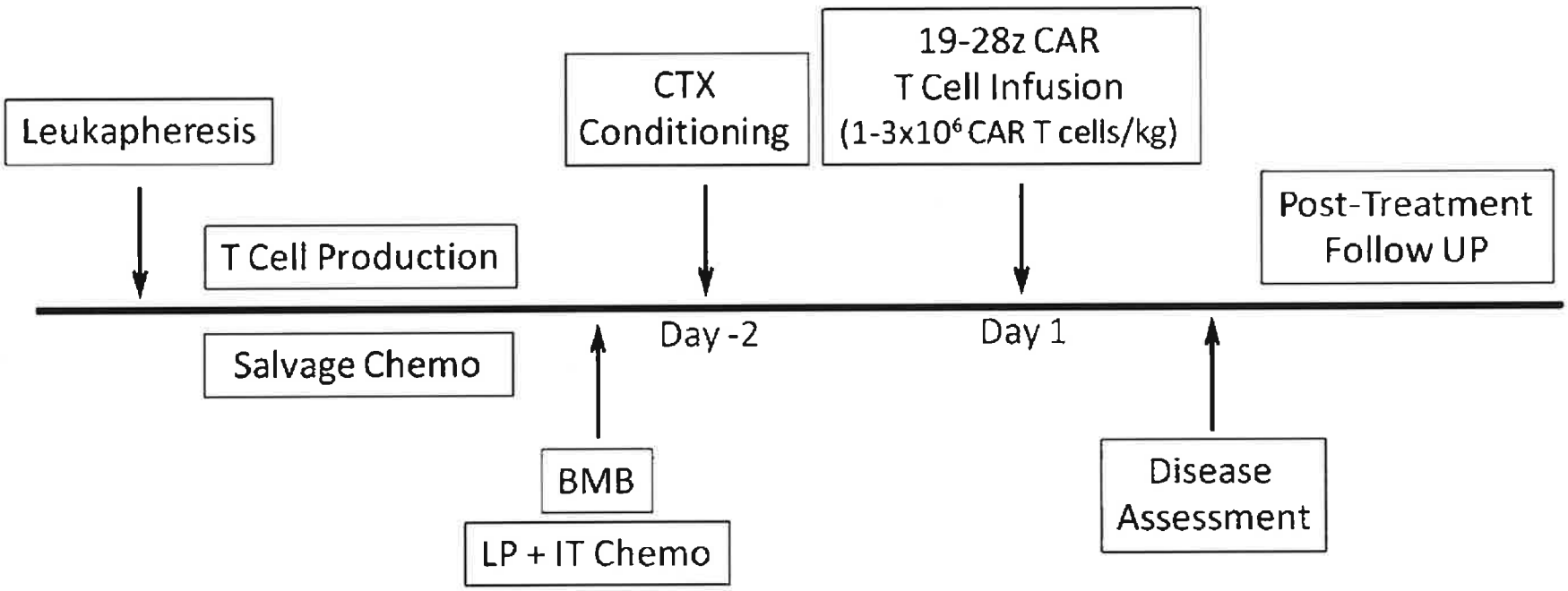
Study Design



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Study Progress

- As of 30 March 2015, 39 adult patients with relapsed/refractory ALL treated with 19-28z CAR T cells at MSKCC
  - 39 patients evaluable for toxicity assessment
  - 38 patients evaluable for response assessment with ≥1 month follow up

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Baseline Patient Characteristics

Characteristic	Number of Patients N=39 (%)
Sex	
Male	29 (76)
Female	10 (24)
Age at infusion (years)	
18-29	10 (26)
30-59	19 (49)
≥60	10 (26)
Median (range)	45 (22-74)
Disease burden immediately prior to T cells	
Morphologic disease (5-100%, median 52%)	21 (54)
Minimal residual disease (<5%)	18 (46)

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Baseline Disease Characteristics

Characteristic	Number of Patients, N=39 (%)
Prior Lines of Therapy	
2	19 (49)
3	9 (23)
≥4	11 (28)
Prior allogeneic HSCT	
Yes	14 (36)
No	25 (64)
Philadelphia chromosome (Ph)+	13 (33)
T315I mutation	4 (11)

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Summary of Clinical Outcomes

	Number of Patients, N=38
Overall CR Rate, n (%) [95% CI]	33/38 (87%) [72, 96]
MRD Negative CR Rate, n (%) [95% CI]	26/32 (81%) [64, 93]
Median Time to CR (Range)	23.0 days (8 – 46)

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CR Rates by Subgroups

Subgroups	CR Rate (%)	MRD Negative CR Rate (%)
Pre-T cell Disease Burden		
Morphologic disease	16/20 (80)	13/15 (87)
Minimal residual disease	17/18 (94)	13/17 (76)
Prior Allogeneic HSCT		
Yes	11/13 (85)	9/10 (90)
No	22/25 (88)	17/22 (77)
Ph+ Status		
Yes	12/13 (92)	8/12 (67)
No	21/25 (84)	18/20 (90)
Age at infusion (years)		
18-29	9/10 (90)	7/9 (78)
30-59	16/18(89)	11/15 (73)
≥60	8/10 (80)	8/8 (100)
Prior Lines of Therapy		
2	16/18 (89)	13/16 (81)
3	7/9 (78)	5/7 (71)
≥4	10/11 (91)	8/9 (89)

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Post-CAR T Cell Follow Up

- Median follow-up: 5.6 months (1-38+ months)
- Median duration of response or relapse free-survival: 5.3 months (95% CI: 3-9)
- 14 patients remain disease-free: 10 patients w/o HSCT
  - 6 patients with > 1 year follow up
- 11 patients proceeded to allogeneic HSCT
- 14 patients relapsed during follow-up
  - 3 relapses post-HSCT (2 patient with CD19 negative blasts)
  - 10 relapses without HSCT

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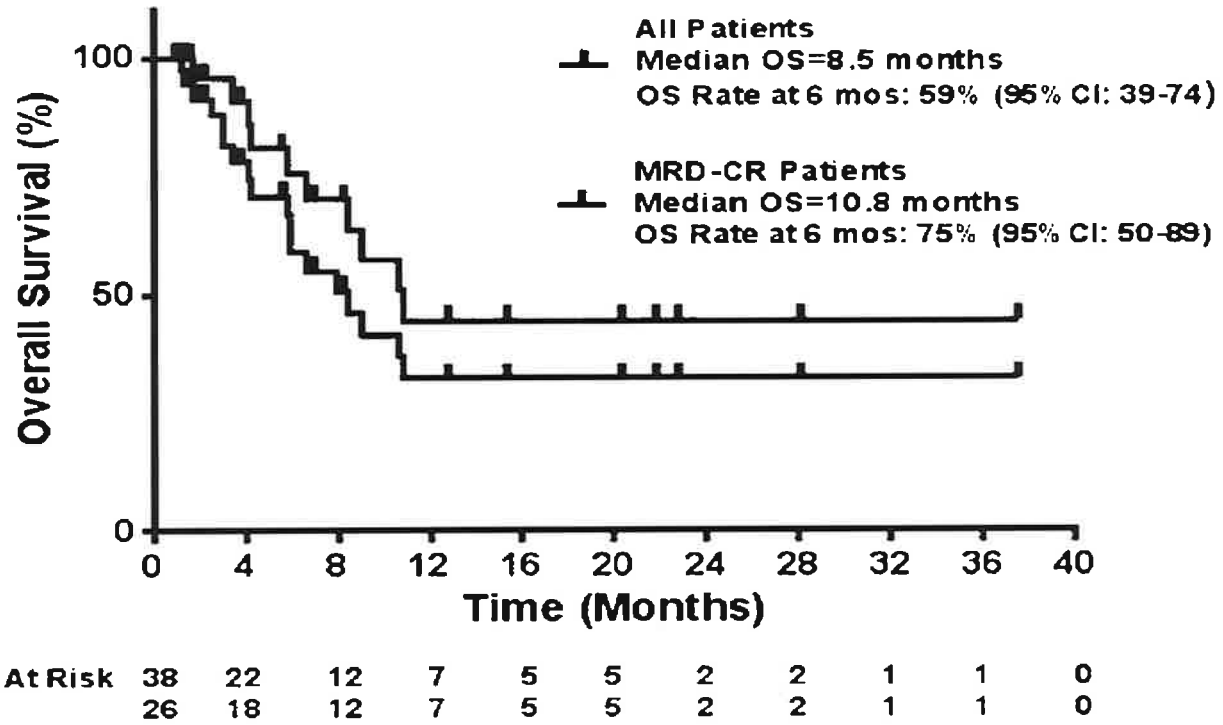
Overall Survival: All Patients



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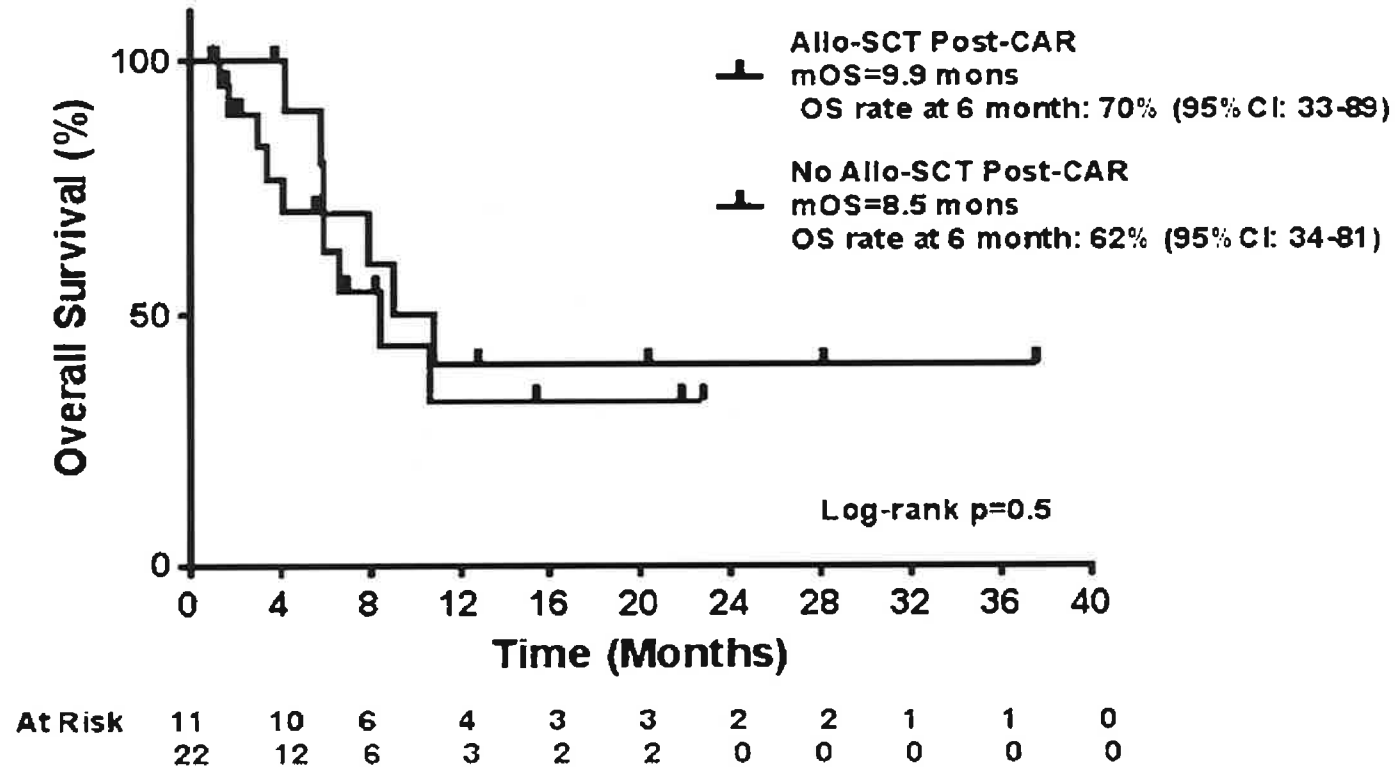
Overall Survival:
By Allo-SCT Status Among CR Subjects



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19-28z CAR T Cell Expansion & Persistence

- 19-28z CAR T cells were measured in PB and BM by qPCR and flow cytometry
- Maximum T cell expansion occurred between days 7 – 14, and correlated with occurrence of CRS
- T cells persisted 1 – 3 months following T cell infusion

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Adverse Events

- Cytokine release syndrome (CRS)
  - Fever
  - Hypotension
  - Respiratory insufficiency
- Neurological changes
  - Delirium
  - Global encephalopathy
  - Aphasia
  - Seizure-like activities/seizure

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CRS & Neurological Toxicities

Subgroups	Severe CRS*	Grade 3/4 Neurotoxicity	Grade 5 Toxicity
Overall (n=39)	9 (23)	11 (28)	3 (8)¶
Pre-T cell Disease Burden			
Morphologic disease (n=21)	9 (43)	8 (38)	2 (10)
MRD (n=18)	0 (0)	3 (17)	1 (6)

*Requiring vasopressors and/or mechanical ventilation for hypoxia

¶1 pt with ventricular arrhythmia (DNR); 1 pt had seizure, but unknown cause of death; and 1pt died of sepsis.

- Severity of CRS correlated with disease burden.
- CRS managed with IL-6R inhibitor (4 pts), steroid (2 pts), IL-6R inhibitor+steroid (9 pts)
- Neurological symptoms are reversible, and can occur independent of CRS

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Conclusions

- 39 adult patients with relapsed or refractory B-ALL have been treated with 19-28z CAR T cells, and 38 patients are evaluable for response
- High CR rate (87%) can be achieved in adults with R/R B-ALL
  - Majority of CR is MRD negative (81%)
  - Similar CR rates regardless of disease status, Ph+, age or prior alloHSCT
- Median time to CR is 23 days
- 33% of patients proceeded to alloHSCT after achieving CR with CAR T cells
- Durable responses have been observed in a subset of patients with no subsequent alloHSCT
  - Depth of response (*i.e.* MRD negativity) is correlated with overall survival
- Severe CRS (23%) and neurological toxicities (28%) have been observed and correlate with disease burden and response

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Omar Abdel-Wahab
M12 NP
Nursing Staff

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ASCO CDA

Our Patients!!!

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Phase I Trial of 19-28z Chimeric Antigen Receptor Modified T cells (19-28z CAR-T) Post-High Dose Therapy and Autologous Stem Cell Transplant (HDT-ASCT) for Relapsed and Refractory (rel/ref) Aggressive B Cell Non-Hodgkin Lymphoma (B-NHL)

Craig S. Sauter[1], Isabelle Rivière[1,3], Yvette Bernal[1], Xiuyan Wang[3], Terence J. Purdon[1], Sarah Yoo[1], Craig H. Moskowitz[1], Sergio Giralt[1], Matthew J. Matasar[1], Kevin J. Curran[2], Jae Park[1], Michel Sadelain[1,3], Renier J. Brentjens[1,3].

[1]Department of Medicine, [2]Department of Pediatrics, [3]Center for Cell Engineering, Memorial Sloan Kettering Cancer Center, New York, N.Y.

PRESENTED AT: ASCO Annual '15 Meeting

HDT-ASCT for Chemosensitive rel/ref DLBCL: Standard of Care

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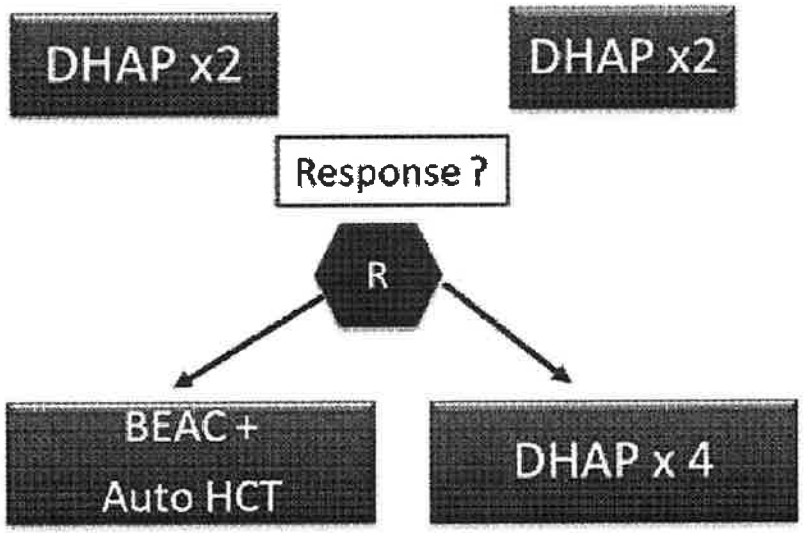
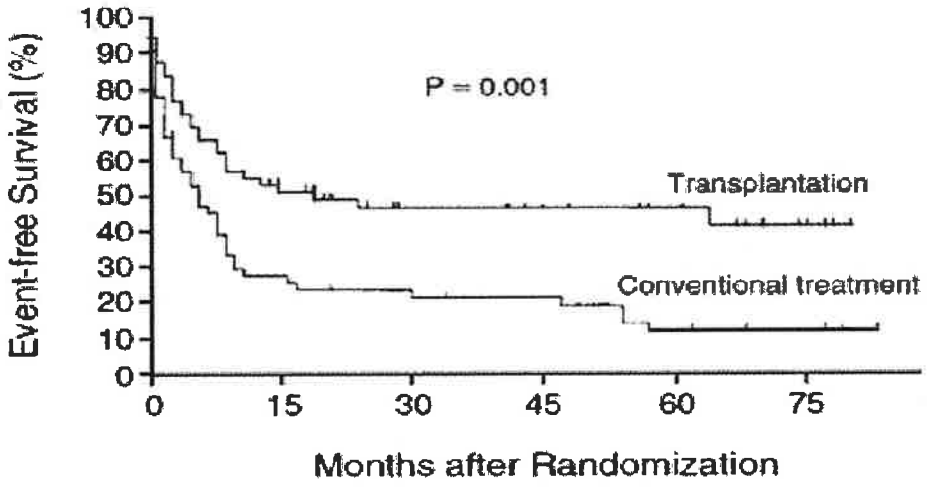
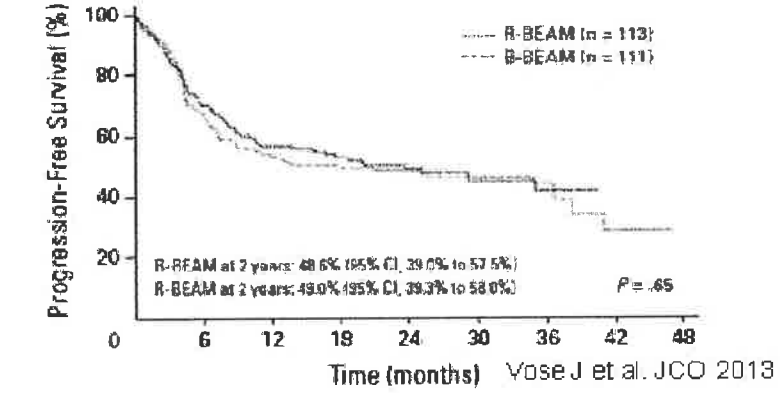




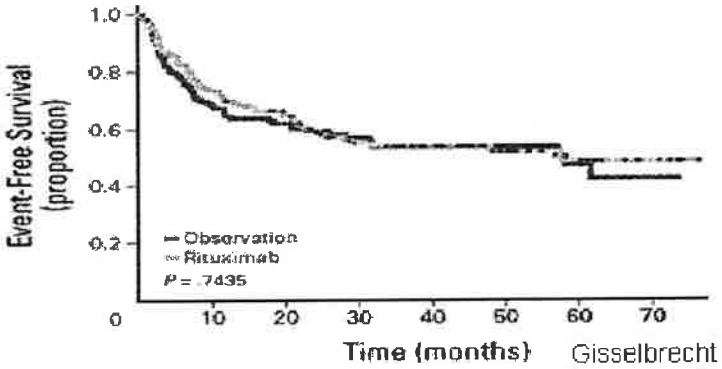
Philip et al. *N Engl J Med. 1995;333:1540-1545.*

PRESENTED AT: ASCO Annual '15 Meeting

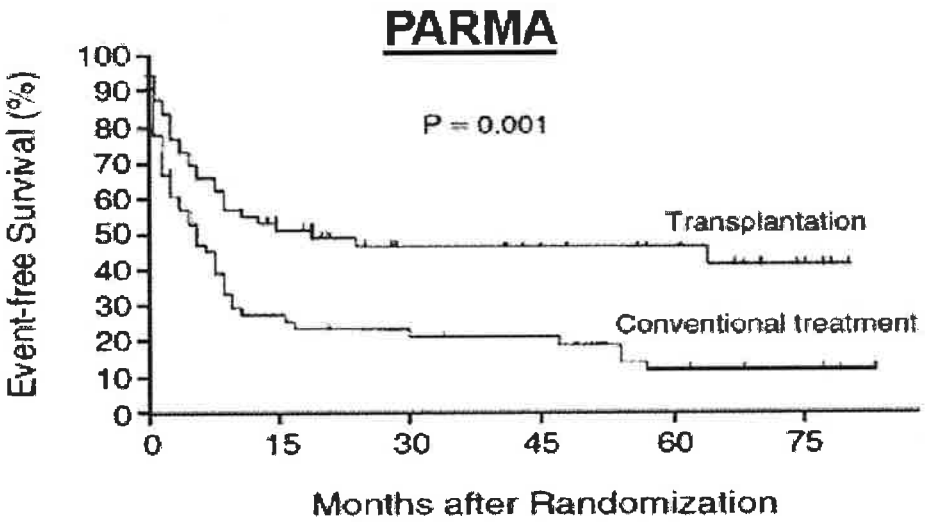
PFS/EFS in Chemosensitive rel/ref DLBCL Proceeding to ASCT: Little Progress in ~20 years



Vose J et al. JCO 2013



Gisselbrecht et al. JCO 2012



Philip et al. *N Engl J Med. 1995;333:1540-1545.*

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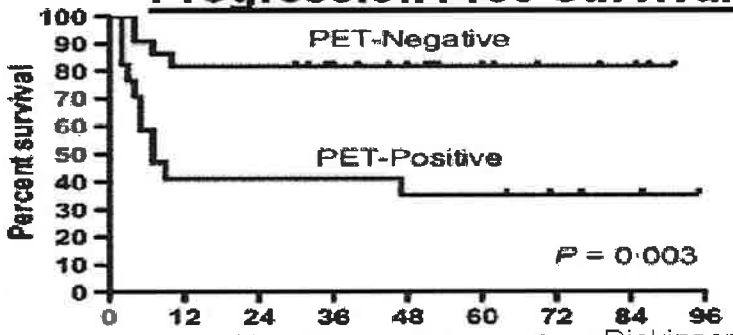
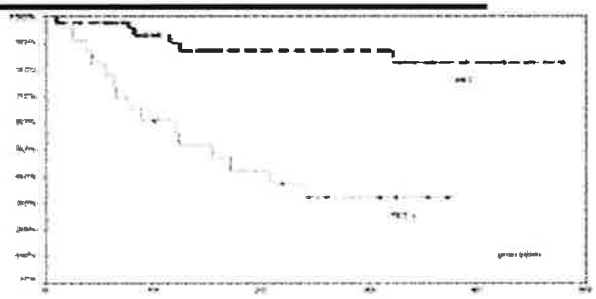
Functional Imaging (PET) Response to Salvage Therapy prior to HDT-ASCT

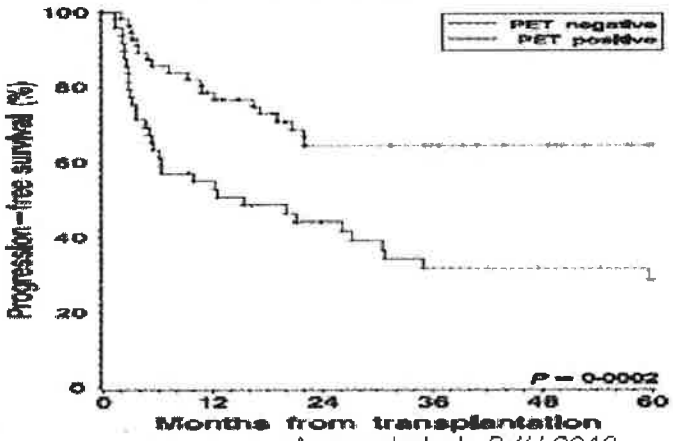
Progression Free Survival Post ASCT Chemosensitive Patients



Dickinson et al, *BJH* 2010

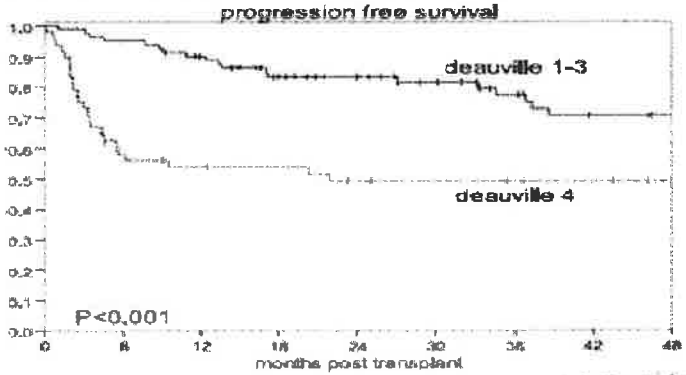


Derenzini et al, *Cancer* 2008



Armand et al, *BJH* 2013

MSKCC: 2002-2012 rel/ref DLBCL

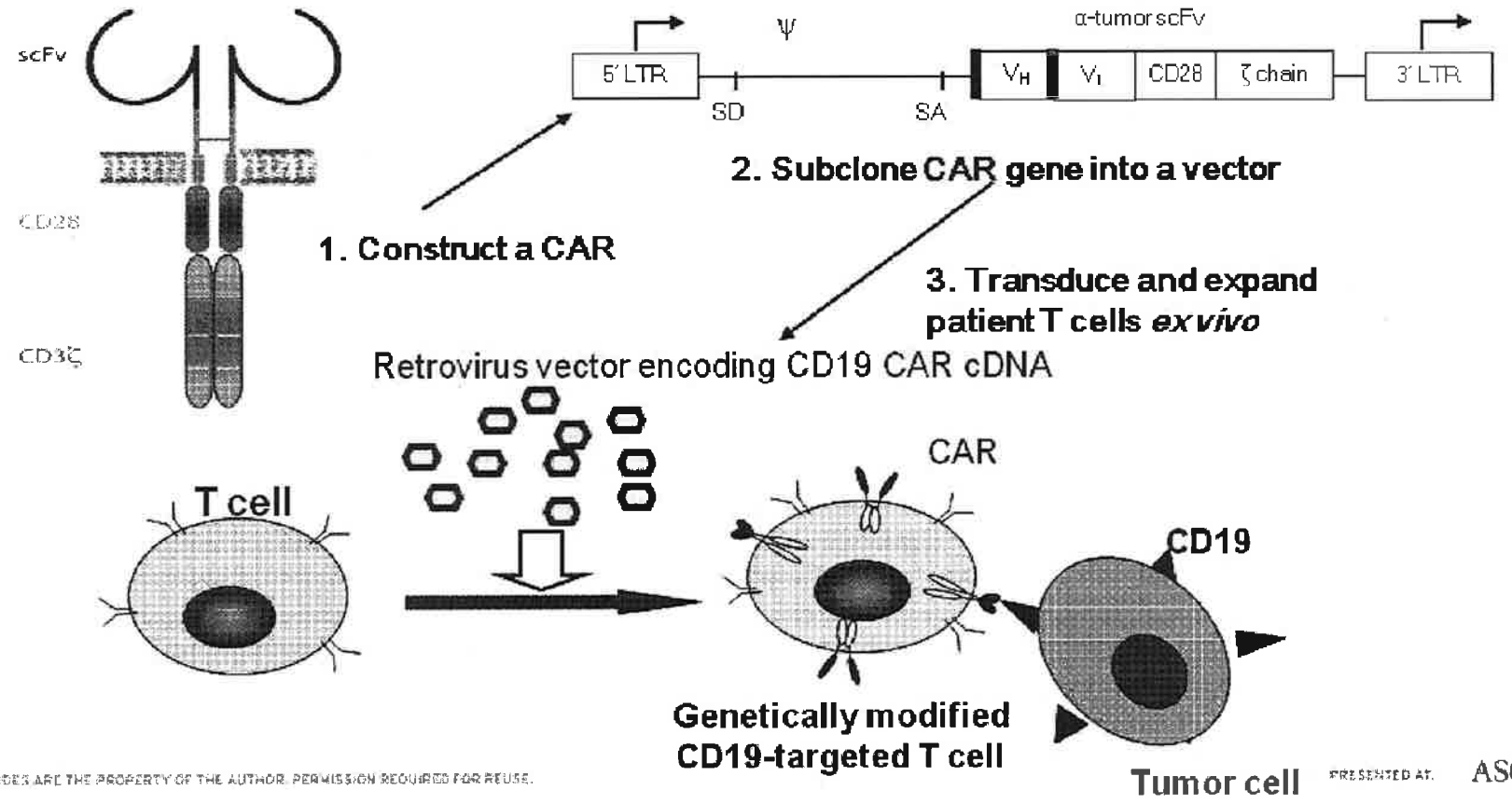


Sauter et al, *Blood* 2015

PRESENTED AT: ASCO Annual '15 Meeting

Presented By Craig Sauter at 2015 ASCO Annual Meeting

Generation of 19-28z CAR T Cells



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Advantages of 19-28z CAR T cells Post-Ablative Chemotherapy and ASCT

- Modulation of a hostile immune suppressive tumor microenvironment
  - elimination of regulatory T cells, myeloid derived suppressor cells
- Elimination of cytokine "sinks" for optimized proliferative expansion of 19-28z CAR T cells

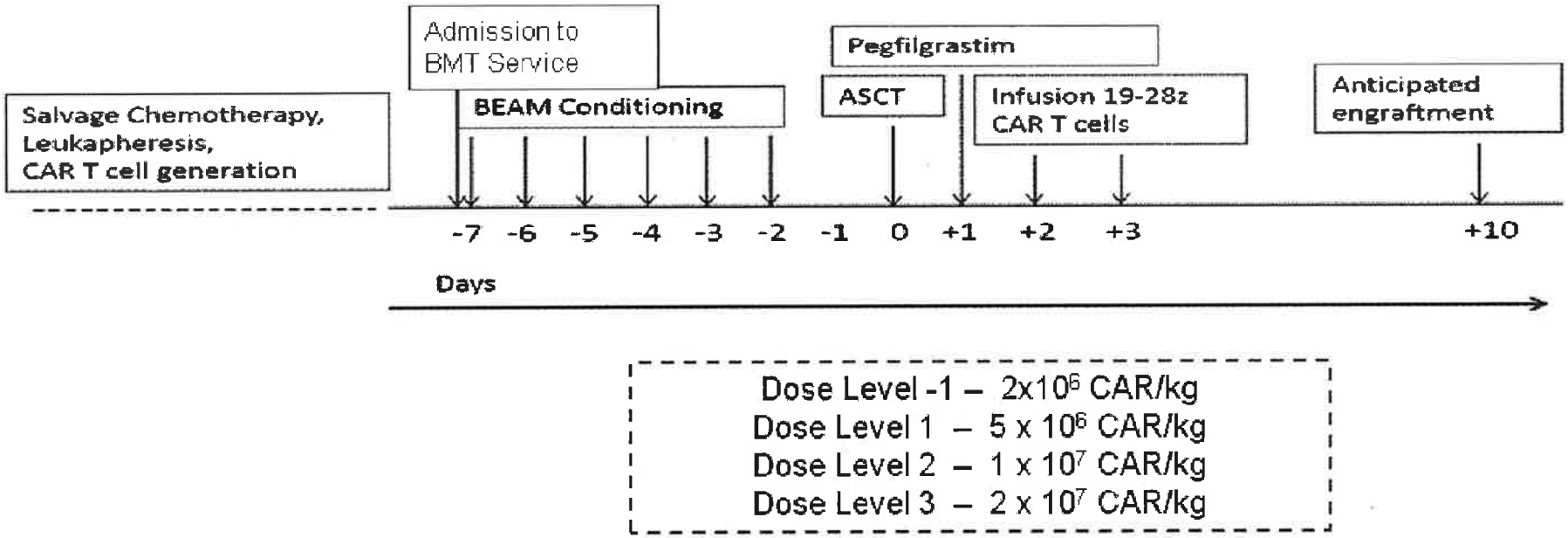
Eligibility Criteria

- Patients ≥ 18 years old with relapsed or refractory aggressive histology B-NHL meeting at least one of the following criteria:
  - PET positive disease following ≥2 cycles of salvage chemotherapy, though still achieving chemosensitive status per 1999 IWG CT criteria.
  - Bone marrow involvement at the time of relapse or refractory disease and not appropriate for allogeneic transplantation.

Adequate organ function:

- cardiac function (LVEF>40%)
- pulmonary function as assessed by DLCO of ≥ 45%
- renal function GFR ≥ 50 cc/min or serum creatinine ≤ 1.5 mg/dL
- liver function AST/ALT < 3x upper limit of normal bilirubin < 2 mg/dL

Schema



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Objectives

Primary Objective:

- To assess the safety and maximum tolerated dose (MTD) of 19-28z CAR T cell infusion following high dose therapy and CD34+ autologous stem transplantation for CD 19+ relapsed and refractory aggressive histology B-NHL.

Secondary Objectives:

- 1 and 2 year PFS.
- Assess for modified T cell persistence.

Patient #	Age	histology/ #lines of therapy	Status at HDT-ASCT	Dose CAR-T ($x10^6$/kg)	Clinically Relevant ≥ grade 3 non-heme AE	Cytokine release syndrome[1] (CRS)/Rx	Peak CRP (mg/dL)	Best Response/ PFS (months)	Current Status
1	34	tFL/3	PET(+) PR	5	Gr3 CRS (mental status (MS) changes)	Yes/Toc* x1	27.3 (D4)	CR/20+	CR
2	68	DLBCL/4	PET(+) PR	5	Gr3 febrile neutropenia, Gr3 MS changes	Yes/None	16.5 (D4)	CR/21+	CR
3	55	tMZL/2	PET(+) PR BM involved	5	Gr3 hypophosphatemia	No	17.6 (D3)	CR/12	Alive, POD
4	59	tFL/DHL/2	PET(+) PR	10	Gr3 hypocalcemia, Gr3 AST/ALT, Gr4 CRS (hypotension, AM, MS changes)	Yes/Toc* x1+dex	43.1 (D3)	CR/15+	CR
5	66	DLBCL/3	PET(+) PR	5	Gr3 hyperglycemia	No	5 (D3)	CR/13+	CR
6	64	CD5+ DLBCL/2	PET(+) PR	5	none	No	7.9 (D4)	SD/6	Alive, POD
7	85	BL/2	PET(+) PR BM involved	5	Gr3 CRS (MS changes) Gr3 febrile neutropenia, Gr3 hyperglycemia	Yes/Toc*x1	11.8 (D7)	CR/2	POD/ DOD
8	56	DLBCL/ DHL/2	PET (+) PR	5	Gr3 electrolytes, Gr3 CRS (seizure) Gr3 respiratory failure, Gr3 febrile neutropenia, Gr4 cytopenias, Gr5 infection (mucormycosis)	Yes/Toc* x1	18.1 (D4)	Not-evaluated (NE)	NRM /1 month
9	51	DLBCL/2	PET (+) PR	5	Gr3 febrile neutropenia	No	31.8 (D3)	POD/2	DOD
10	61	blastoid MCL/4	PET CR, leukemic phase	5	Gr3 CRS (MS changes)	Yes/Toc* x 1+dex	16.5 (D5)	POD/2	Alive
11	75	Richter's/2	PET (+) PR	5	Gr 3 febrile neutropenia, Gr 4 CRS (encephalopathy)	Yes/Toc* x 1+dex	22.8 (D5)	NE current d30	NE

[1] Lee et al Blood 124(2): 2014

■ Dose-limiting toxicity, *tocilizumab, +continuous response
NRM: non-relapse mortality, POD: progression of disease, DOD: dead of disease

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Age	histology/ #lines of therapy	Status at HDT-ASCT
34	tFL/3	PET(+) PR
68	DLBCL/4	PET(+) PR
56	tMZL/2	PET(+) PR BM involved
59	tFL/DHL/2	PET(+) PR
66	DLBCL/3	PET(+) PR
64	CD5+ DLBCL/2	PET(+) PR
65	BL/2	PET(+) PR BM involved
56	DLBCL/ DHL/2	PET (+) PR
51	DLBCL/2	PET (+) PR
61	blastoid MCL/4	PET CR, leukemic phase
75	Richter's/2	PET (+) PR

Median age 61 years
(range: 34-75 years)

Median no. lines therapy: 2
(range: 2-4)

7/11 patients CRS

Clinically Relevant ≥ grade 3 non-heme AE	Cytokine release syndrome[1] (CRS)/Rx	Peak CRP (mg/dL)
Gr3 CRS (mental status (MS) changes)	Yes/Toc* x1	27.3 (D4)
Gr3 febrile neutropenia, Gr3 MS changes	Yes/None	16.5 (D4)
Gr3 hypophosphatemia	No	17.6 (D3)
Gr3 hypocalcemia, Gr3 AST/ALT, Gr4 CRS (hypotension, AKI, MS changes)	Yes/Toc* x1+dex	43.1 (D3)
Gr3 hyperglycemia	No	5 (D3)
none	No	7.9 (D4)
Gr3 CRS (MS changes,) Gr3 febrile neutropenia, Gr3 hyperglycemia	Yes/Toc*x1	11.8 (D7)
Gr3 electrolytes, Gr3 CRS (seizure) Gr3 respiratory failure, Gr3 febrile neutropenia, Gr4 cytopenias, Gr5 infection (mucormycosis)	Yes/Toc* x1	18.1 (D4)
Gr3 febrile neutropenia	No	31.8 (D3)
Gr3 CRS (MS changes)	Yes/Toc* x 1+dex	16.5 (D5)
Gr 3 febrile neutropenia, Gr 4 CRS (encephalopathy)	Yes/Toc* x 1+dex	22.8 (D5)

[1] Lee et al Blood 124(2): 2014

*tocilizumab

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histology/ #lines of therapy	Status at HDT-ASCT	Best Response/ PFS (months)	Current Status
tFL/3	PET(+) PR	CR/20+	CR
DLBCL/4	PET(+) PR	CR/21+	CR
tMZL/2	PET(+) PR BM involved	CR/12	Alive, POD
tFL/DHL/2	PET(+) PR	CR/15+	CR
DLBCL/3	PET(+) PR	CR/13+	CR
CD5+ DLBCL/2	PET(+) PR	SD/6	Alive, POD
BL/2	PET(+) PR BM involved	CR/2	POD/ DOD
DLBCL/ DHL/2	PET (+) PR	Not-evaluated (NE)	NRM /1 month
DLBCL/2	PET (+) PR	POD/2	DOD
blastoid MCL/4	PET CR, leukemic phase	POD/2	Alive
Richter's/2	PET (+) PR	NE current d30	NE

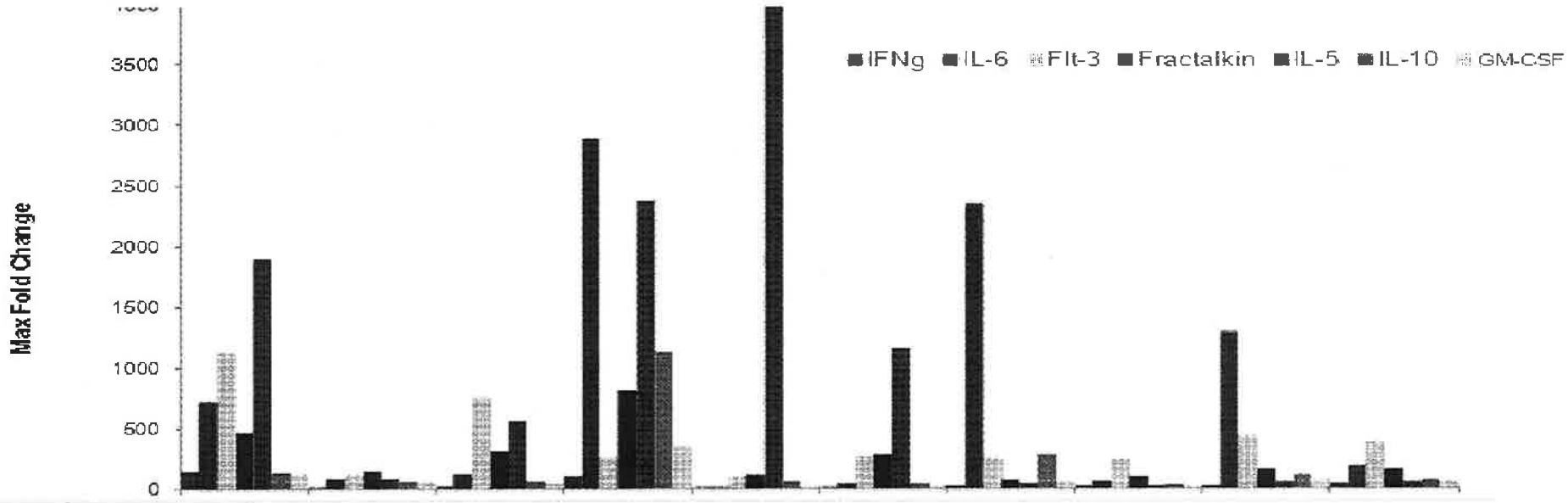
Median follow-up survivors: 14 months
4/10 evaluable progression-free

*tocilizumab, +continuous response

NRM: non-relapse mortality, POD: progression of disease, DOD: dead of disease

ASCO Annual '15 Meeting

△ Cytokines, CRS, CAR T cell expansion

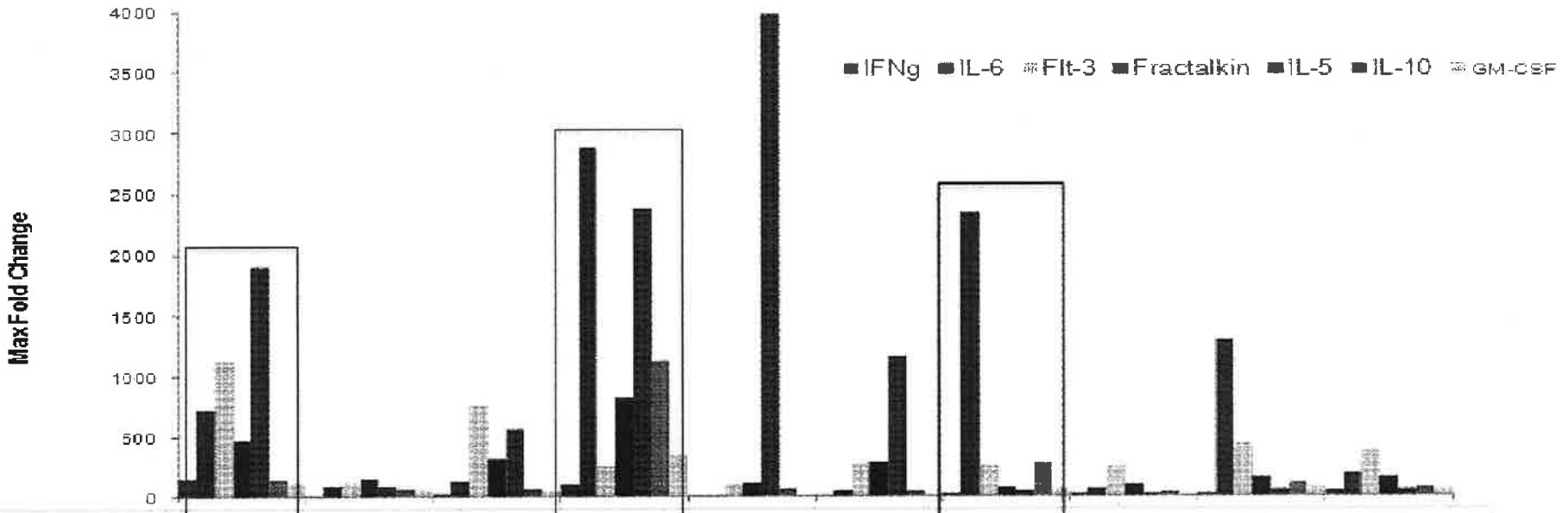


Patient #	1	2	3	4	5	6	7	8	9	10
CRS	+	+	-	+	-	-	+	+	-	+
Peak CAR-T/µL	8	9	77	32	42	3	54	1	252	2
			POD			POD	POD	NRM	POD	POD

NRM: non-relapse mortality, POD: progression of disease

Presented By Craig Sauter at 2015 ASCO Annual Meeting

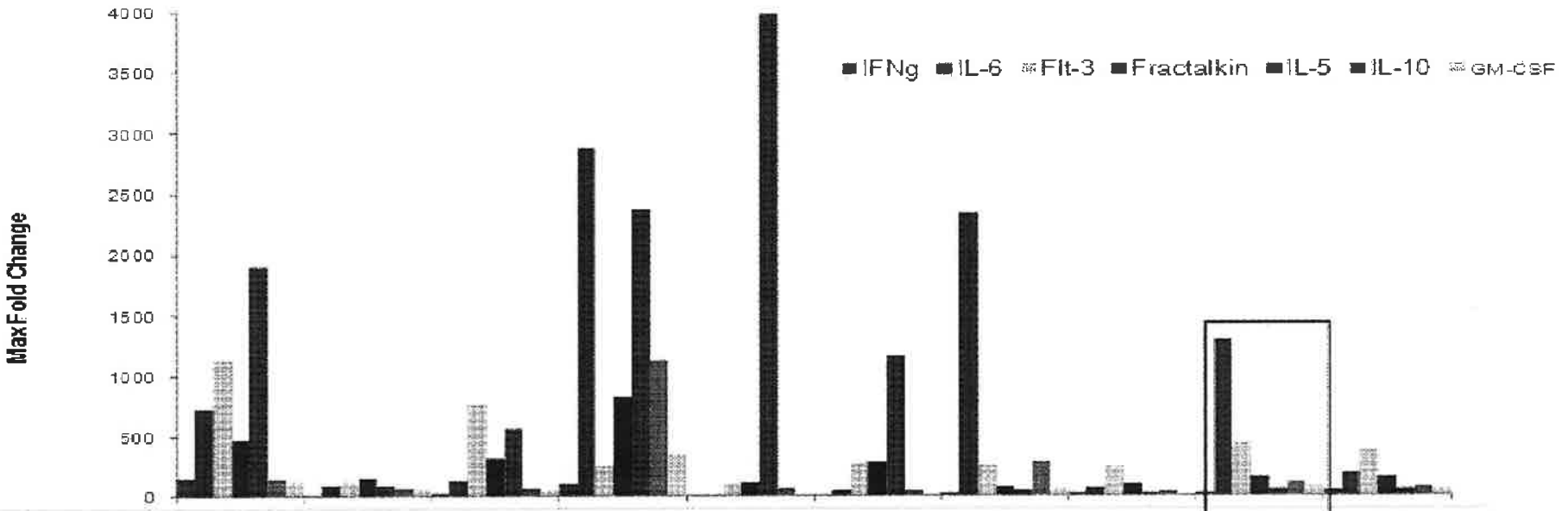
△ Cytokines, CRS, CAR T cell expansion



NRM: non-relapse mortality, POD: progression of disease

Presented By Craig Sauter at 2015 ASCO Annual Meeting

△ Cytokines, CRS, CAR T cell expansion

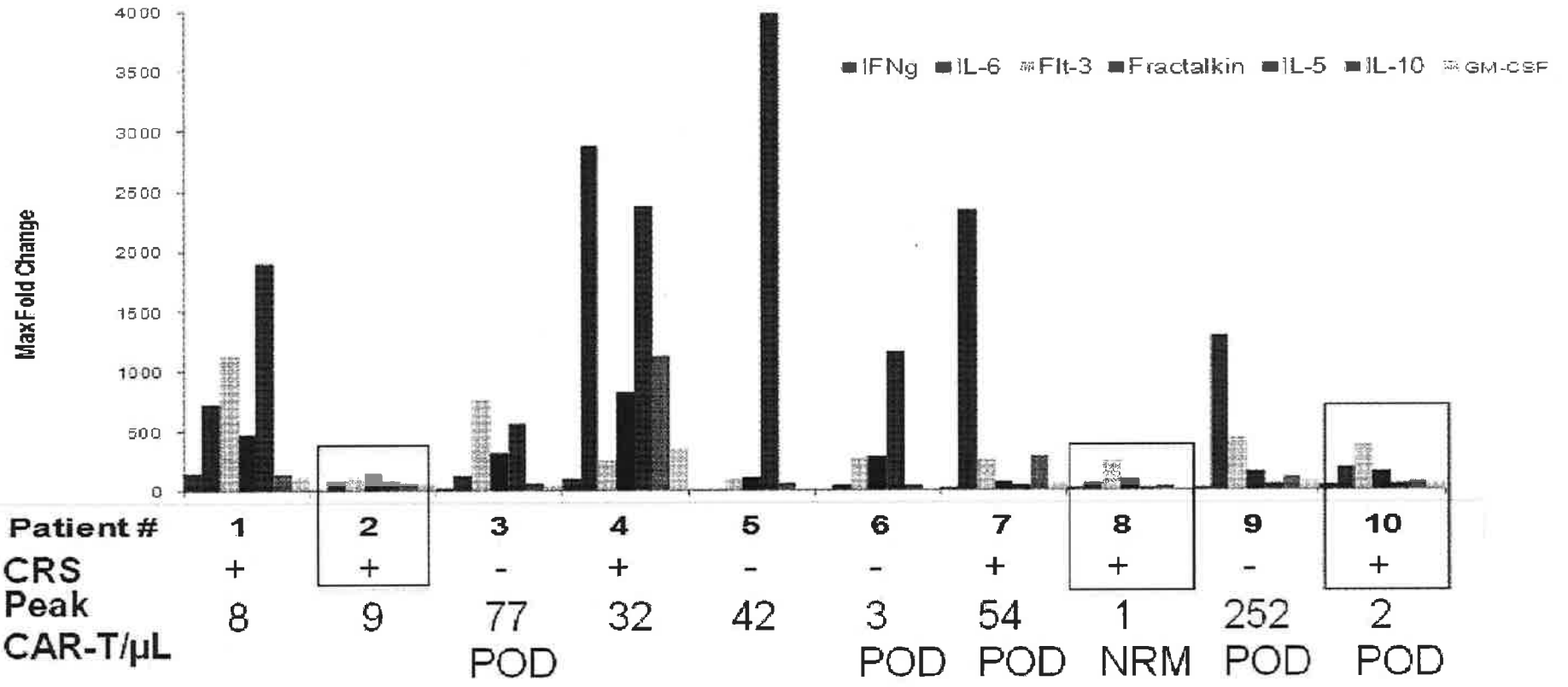


Patient #	1	2	3	4	5	6	7	8	9	10
CRS	+	+	-	+	-	-	+	+	-	+
Peak CAR-T/µL	8	9	77	32	42	3	54	1	252	2
			POD			POD	POD	NRM	POD	POD

NRM: non-relapse mortality, POD: progression of disease

Presented By Craig Sauter at 2015 ASCO Annual Meeting

△ Cytokines, CRS, CAR T cell expansion



NRM: non-relapse mortality, POD: progression of disease

Presented By Craig Sauter at 2015 ASCO Annual Meeting

Conclusions

- 19-28z CAR T cells are safe post HDT-ASCT at $5x10^6$/kg (DLT 1/10 patients)
- 7 of 11 patients experienced $\geq$ grade 3 CRS, predominately CNS toxicity, with full reversibility
- variable IL-6 and CRP with or without CRS
- 4 of 10 evaluable patients remain progression-free at 13-21 months post HDT-ASCT
- Currently expanding dose level #1 (5 x 10^6/kg 19-28z CAR T cells) to further establish safety

Acknowledgments

Cellular Therapeutics Center:
Renier Brentjens, MD PhD
Michel Sadelain, MD PhD
Isabelle Riviere, PhD
Kevin Curran, MD
Jae Park, MD

Mentor:
Craig Moskowitz, M.D.

Data Management:
Yvette Bernal, B.A.
Christina Macaulay, B.A.

Funding:
•ASBMT Young Investigator Award
•Cycle for Survival
•MSKCC Society

****Patients and Families**

Adult BMT Service:
Sergio Giralt, M.D. (Chief)
Juliet Barker, M.B.B.S
Hugo Castro-Malaspina, M.D.
David Chung, M.D. PhD
Boglarka Gyurkocza, M.D.
Alan Hanash, M.D. PhD
Katherine Hsu, M.D., Ph.D
Ann A. Jakubowski, MD, PhD
Robert Jenq, M.D.
Guenther Koehne, MD, PhD
Heather Landau, M.D.
Matthew Matasar, M.D.
Esperanza Papadopoulos, M.D
Miguel-Angel Perales, M.D.
Doris Ponce, M.D.
Brian Shaffer, MD
Marcel van den Brink, M.D., Ph.D (Division Head)
James Young, M.D.

Lymphoma Service:
Anas Younes, M.D. (Chief)
John Gerecitano, M.D, PhD
Paul Hamlin, M.D.
Alison Moskowitz, M.D
Craig Moskowitz, M.D.
Ariela Noy, M.D.
Lia Palomba M.D.
Steven Horwitz, M.D
Matthew Matasar, M.D.
Carol Portlock M.D.
David Straus, M.D.
Achy Yahalom, M.D.
Andrew Zelenetz, M.D., PhD

PRESENTED AT: ASCO Annual '15 Meeting

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Wednesday, June 10, 2015 7:51 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Fwd: BBB news

Steve,

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Begin forwarded message:

From: Helen Kim <HKim@KitePharma.com>
Date: June 10, 2015 at 12:08:28 PM EDT
To: Arie Belldegrun <Arie@kitepharma.com>, Cynthia Butitta <CButitta@KitePharma.com>, David Chang <DChang@KitePharma.com>
Cc: Veer Bhavnagri <veer@kitepharma.com>, Edmund Kim <EKim@kitepharma.com>
Subject: BBB news

June 10, 2015
By Riley McDermid, BioSpace.com Breaking News Sr. Editor

A panel of scientists convened by the National Institutes of Health (NIH) Recombinant DNA Advisory Committee has recommended that freshly IPO'd biotech darling Bluebird Bio delay its two upcoming trials of beta thalassemia for one to two years in order to gather more safety information—and Bluebird has decided to ignore that advice. The RAC committee was most concerned that Bluebird halt testing its LentiGlobin BB305 gene therapy on children until more adults have been studied for side effects and safety concerns. Nonetheless, Bluebird said late Tuesday it would continue laying the groundwork for its planned clinical trials HGB-207 and HGB-208, both of which will test LentiGlobin BB305 further, in attempt to have enough trial data to receive regulatory approval for the therapy from the U.S and European regulators. Because the RAC's recommendation is nonbinding, Bluebird has chosen to steer its own course, said execs. "We appreciate the recommendations from the RAC members regarding the HGB-208 pediatric study protocol," said David Davidson, chief medical officer in Bluebird. "We will take the RAC feedback on the timing of initiating HGB-208 under advisement as we advance the clinical development of our LentiGlobin BB305 product candidate for patients with beta-thalassemia major," he said. "The HGB-207 trial protocol did not require further review by the RAC, and we will continue to work closely with the regulatory authorities and our clinical study sites to pursue appropriate accelerated regulatory approval pathways in the U.S. and the EU." Bluebird CEO Nick Leschly went one step further, telling closely watched biotech columnist Adam Feuerstein at The Street that the company disagrees with the RAC's conclusion.. "We respect RAC and the process. RAC took a reasonable position when it comes to dealing with kids," said Leschly. "We disagree and believe the decision [to proceed with a gene therapy pediatric study] should be placed in the hands of the institutional review boards, the physicians of patients and their families," said Leschly. On Feb. 2, 2015, Bluebird announced that the U.S. Food and Drug Administration (FDA) had granted LentiGlobin BB305 Breakthrough Therapy designation, which is used to expedite the development and review of a potential drug candidate that is expected to be used to treat a serious or life-threatening diseases. In the case of LentiGlobin BB305, initial data last fall from an ongoing Phase I/II Northstar (HGB-204) and HGB-205 studies looked at eight patients with beta-thalassemia that were treated with LentiGlobin. In the first four patients, treatment resulted in sufficient hemoglobin production to decrease the need for transfusion support among the patients.

That news sent shares of the company up 70 percent the day it was announced, as the market looked eagerly for signs that Bluebird's LentiGlobin BB305 could be a panacea for blood diseases. In mid-May, Bluebird announced one of the patients treated in the earlier study has not had to seek hospitalization for his sickle cell since and has even started producing anti-sickling properties.

"The early data included in our abstract provide further validation for our approach and important insights into the safety and mechanism of action of LentiGlobin in both beta-thalassemia and sickle cell disease," said Davidson, chief medical officer for Bluebird. "As noted in the abstract, we are pleased to report that the two patients with beta-thalassemia major, on whom we first reported last year at EHA, remained transfusion independent at 14 and 11 months post-transplant," he said. "In addition, it is very encouraging that the patient with sickle cell disease is increasing production of HbAT87Q, which has anti-sickling properties, and has not had a post-treatment hospitalization for a sickle cell disease-related event. At EHA we will present further follow up data on all three subjects." That news had both analysts and Wall Street investors cheering, because it shows LentiGlobin is on track. "Our recent deep dive on LentiGlobin combined with this update keep us confident that BLUE is on the cusp of a dramatic breakthrough for many sickle cell disease patients and we await further updates," wrote Joshua Schimmer, a biotech analyst for Piper Jaffray, in a note to investors. Bluebird's LentiGlobin BB305 extracts blood stem cells and then infuses them with a working version of the malfunctioning gene that had caused the disease. People with the disease must undergo monthly blood transfusions in order to survive—but if Bluebird's therapy continues to be successful, they may now be freed from that burden. The number of people affected is not huge, but is certainly significant: Around 40,000 babies world-wide and between 1,000 and 3,000 in the U.S. are born with the condition each year. The new therapy is so effective, Wall Street is champing at the bit to see it be rushed into later-stage trials to bring it to market more quickly. Some analysts have long said Bluebird has a "robust" proof of concept for the therapy so far, said Schimmer. "The abstract notes the peripheral blood T87Q vector copy number is an impressive 2.4. This should be a good marker for what's happening in the bone marrow, meaning that a majority of cells have a copy of the corrected gene," he wrote in his note. "This also means that BLUE's busulfan myeloablation regimen was effective in establishing chimerism with the LentiGlobin cells. And this also means that as the patient continues to be weaned from transfusions, the corrected cells should be easily able to ramp up production and eliminate sickling and its consequences." The results of this data, though hardly extensive, are apparently promising enough for the FDA and the EMA to consider conditional approval for use of the drug.

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Wednesday, June 17, 2015 10:48 PM
To: Jeff Wiezorek; David Chang; Adrian Bot; William Go; Rajul Jain; Jim Economou; Allan Pantuck; Owen Witte; Antoni Ribas MD PhD; Margo Roberts; Tony Polverino; Marc Better; Rizwana Sproule; Kerr Clark; Kochenderfer, James (NIH/NCI) [E]; Somerville, Robert (NIH/NCI) [E]; Robbins, Paul (NIH/NCI) [E]; Rosenberg, Steven A. (NIH/NCI) [E]; Toomey, Mary Ann (NIH/NCI) [E]; Feldman, Steven (NIH/NCI) [E]; Shell, Linda (NIH/NCI) [E]
CC: Linda Barnes; Chantel Cox; Katae Long-Phelps; Shell, Linda (NIH/NCI) [E]
Subject: RE: NCI-Kite Monthly Team Meeting [large group]

Unfortunately I will be on a flight to the east Coast. Sorry to miss it.

Arie Belldegrun, M.D., FACS
President and CEO
Chairman of the Board; Founder
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310 824-9999 x102
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From: Jeff Wiezorek
Sent: Wednesday, June 17, 2015 10:46 AM
To: David Chang; Adrian Bot; William Go; Rajul Jain; Arie Belldegrun; Jim Economou; Allan Pantuck; Owen Witte; Antoni Ribas MD PhD; Margo Roberts; Tony Polverino; Marc Better; Rizwana Sproule; Kerr Clark; James Kochenderfer (kochendj@mail.nih.gov); Robert Somerville (robert.somerville@nih.gov); Paul Robbins; Steven A. Rosenberg M.D., Ph.D. (sar@mail.nih.gov); Mary Ann Toomey (toomeym@mail.nih.gov); Steven Feldman (Feldmanst@mail.nih.gov); Linda Shell (shelll@mail.nih.gov)
Cc: Linda Barnes; Chantel Cox; Katae Long-Phelps; Shell, Linda (NIH/NCI) [E]
Subject: RE: NCI-Kite Monthly Team Meeting [large group]

The agenda for tomorrow's meeting is attached. Please let me know if there are additional items for discussion.

Jeff

<< File: NCI-KITE Team Agenda 6-18-15.docx >>

-----Original Appointment-----
From: Patricia Lettner **On Behalf Of** Jeff Wiezorek
Sent: Monday, June 15, 2015 3:56 PM
To: Jeff Wiezorek; David D. Chang, M.D., Ph. D. (dchang@kitepharma.com); Adrian Bot; William "Will" Go MD PhD (wgo@kitepharma.com); Rajul Jain; Arie Belldegrun; Jim Economou; Allan Pantuck; Owen Witte; Antoni Ribas MD PhD; Margo Roberts; Tony Polverino; Marc Better; Rizwana Sproule (rsproule@kitepharma.com); Kerr Clark; James Kochenderfer (kochendj@mail.nih.gov); Robert Somerville (robert.somerville@nih.gov); Paul Robbins; Steven A. Rosenberg M.D., Ph.D. (sar@mail.nih.gov); Mary Ann Toomey (toomeym@mail.nih.gov); Steven Feldman (Feldmanst@mail.nih.gov); Linda Shell (shelll@mail.nih.gov)

Cc: Linda Barnes; Chantel Cox (CCox@kitepharma.com); Katae Long-Phelps; Shell, Linda (NIH/NCI) [E]
Subject: NCI-Kite Monthly Team Meeting [large group]
When: Thursday, June 18, 2015 12:30 PM-2:00 PM (UTC-08:00) Pacific Time (US & Canada).

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Wednesday, June 17, 2015 10:48 PM
To: Jeff Wiezorek; David Chang; Adrian Bot; William Go; Rajul Jain; Jim Economou; Allan Pantuck; Owen Witte; Antoni Ribas MD PhD; Margo Roberts; Tony Polverino; Marc Better; Rizwana Sproule; Kerr Clark; Kochenderfer, James (NIH/NCI) [E]; Somerville, Robert (NIH/NCI) [E]; Robbins, Paul (NIH/NCI) [E]; Rosenberg, Steven A. (NIH/NCI) [E]; Toomey, Mary Ann (NIH/NCI) [E]; Feldman, Steven (NIH/NCI) [E]; Shell, Linda (NIH/NCI) [E]
CC: Linda Barnes; Chantel Cox; Katae Long-Phelps; Shell, Linda (NIH/NCI) [E]
Subject: RE: NCI-Kite Monthly Team Meeting [large group]

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Chairman of the Board; Founder
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Sent: Wednesday, June 17, 2015 10:46 AM
To: David Chang; Adrian Bot; William Go; Rajul Jain; Arie Belldegrun; Jim Economou; Allan Pantuck; Owen Witte; Antoni Ribas MD PhD; Margo Roberts; Tony Polverino; Marc Better; Rizwana Sproule; Kerr Clark; James Kochenderfer (kochendj@mail.nih.gov); Robert Somerville (robert.somerville@nih.gov); Paul Robbins; Steven A. Rosenberg M.D., Ph.D. (sar@mail.nih.gov); Mary Ann Toomey (toomeym@mail.nih.gov); Steven Feldman (Feldmanst@mail.nih.gov); Linda Shell (shelll@mail.nih.gov)
Cc: Linda Barnes; Chantel Cox; Katae Long-Phelps; Shell, Linda (NIH/NCI) [E]
Subject: RE: NCI-Kite Monthly Team Meeting [large group]

The agenda for tomorrow's meeting is attached. Please let me know if there are additional items for discussion.

Jeff

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-----Original Appointment-----
From: Patricia Lettner **On Behalf Of** Jeff Wiezorek
Sent: Monday, June 15, 2015 3:56 PM
To: Jeff Wiezorek; David D. Chang, M.D., Ph. D. (dchang@kitepharma.com); Adrian Bot; William "Will" Go MD PhD (wgo@kitepharma.com); Rajul Jain; Arie Belldegrun; Jim Economou; Allan Pantuck; Owen Witte; Antoni Ribas MD PhD; Margo Roberts; Tony Polverino; Marc Better; Rizwana Sproule (rsproule@kitepharma.com); Kerr Clark; James Kochenderfer (kochendj@mail.nih.gov); Robert Somerville (robert.somerville@nih.gov); Paul Robbins; Steven A. Rosenberg M.D., Ph.D. (sar@mail.nih.gov); Mary Ann Toomey (toomeym@mail.nih.gov); Steven Feldman (Feldmanst@mail.nih.gov); Linda Shell (shelll@mail.nih.gov)

Cc: Linda Barnes; Chantel Cox (CCox@kitepharma.com); Katae Long-Phelps; Shell, Linda (NIH/NCI) [E]
Subject: NCI-Kite Monthly Team Meeting [large group]
When: Thursday, June 18, 2015 12:30 PM-2:00 PM (UTC-08:00) Pacific Time (US & Canada).

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

From: David Chang [DChang@KitePharma.com]
Sent: Thursday, June 18, 2015 10:10 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Dear Steve,

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

I will speak with you in persone when we are in NYC next week, but I wanted to give you a heads up.

Thanks, David

David D. Chang, MD, PhD
Executive Vice President of R&D
and Chief Medical Officer
Kite Pharma, Inc
office: 310-622-9094
PERSONAL INFORMATION,REDACTED PER AGREEMENT

www.kitepharma.com

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Thursday, June 18, 2015 4:26 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: FW:

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

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From: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT
Sent: Thursday, June 18, 2015 1:37 PM
To: Arie Belldegrun ; Cynthia Butitta ; Helen Kim (HKim@kitepharma.com); Skye Drynan
Subject:

Home

June 18, 2015; Blood: 125 (25)

Tumor indoleamine 2,3-dioxygenase (IDO) inhibits CD19-CAR T cells and is downregulated by lymphodepleting drugs

Soranobu Ninomiya[1],
Neeharika Narala[1],
Leslie Huye[1],
Shigeki Yagyu[1],
Barbara Savoldo[1,2],
Gianpietro Dotti[1,3],
Helen E. Heslop[1,2,3],
Malcolm K. Brenner[1,2,3],
Cliona M. Rooney[1,2,4], **and**
Carlos A. Ramos[1,3]
Author Affiliations

Article

Figures & Data

Info & Metrics

E-Letters

PDF

Key Points

Tumor IDO inhibits CD19-CART activity, likely via induction of the kynurenine pathway, whose metabolites directly inhibit T cells.

Fludarabine and cyclophosphamide, frequently used before CART administration, downregulate IDO expression in lymphoma cells.

Abstract

Although T cells expressing CD19-specific chimeric antigen receptors (CARs) are a promising new therapy for B-cell malignancies, objective responses are observed at lower frequencies in patients with lymphoma than in those with acute B-cell leukemia. We postulated that the tumor microenvironment suppresses CAR-expressing T cells (CARTs) through the activity of indoleamine 2,3-dioxygenase (IDO), an intracellular enzyme that converts tryptophan into metabolites that inhibit T-cell activity. To investigate the effects of tumor IDO on CD19-CART therapy, we used a xenograft lymphoma model expressing IDO as a transgene. CD19-CARTs inhibited IDO-negative tumor growth but had no effect on IDO-positive tumors. An IDO inhibitor (1-methyl-tryptophan) restored IDO-positive tumor control. Moreover, tryptophan metabolites inhibited interleukin (IL)-2–, IL-7–, and IL-15–dependent expansion of CARTs; diminished their proliferation, cytotoxicity, and cytokine secretion in vitro in response to CD19 recognition; and increased their apoptosis. Inhibition of CD19-CARTs was not mitigated by the incorporation of costimulatory domains, such as 4-1BB, into the CD19-CAR. Finally, we found that fludarabine and cyclophosphamide, frequently used before CART administration, downregulated IDO expression in lymphoma cells and improved the antitumor activity of CD19-CART in vivo. Because tumor IDO inhibits CD19-CARTs, antagonizing this enzyme may benefit CD19-CART therapy.

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Monday, June 22, 2015 8:56 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Fwd: Kite Pharma and bluebird bio Announce Strategic Collaboration to Advance Second Generation TCR Cell Therapy Products to Treat HPV-Associated Cancers

FYI from this morning. PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

See you tomorrow.

Arie

Sent from my iPad

Begin forwarded message:

From: "Kite Pharma, Inc." <jjackson@burnsmc.com>
Date: June 22, 2015 at 8:04:22 AM EDT
To: <Arie@kitepharma.com>
Subject: Kite Pharma and bluebird bio Announce Strategic Collaboration to Advance Second Generation TCR Cell Therapy Products to Treat HPV-Associated Cancers

Kite Pharma bluebirdbio

Kite Pharma and bluebird bio Announce Strategic Collaboration to Advance Second Generation TCR Cell Therapy Products to Treat HPV-Associated Cancers

Collaboration Combines bluebird bio's Gene Editing and Lentiviral Gene Delivery Technologies and Kite's TCR Capabilities and Exclusive Rights to a TCR Directed Against the HPV-16 E6 Oncoprotein

Exclusive Worldwide Co-Development and Co-Commercialization Collaboration

SANTA MONICA, Calif. and CAMBRIDGE, Mass., June 22, 2015 (GLOBE NEWSWIRE) -- Kite Pharma, Inc. (Nasdaq:KITE) and bluebird bio, Inc. (Nasdaq:BLUE) today announced that they have entered into a collaboration agreement to co-develop and co-commercialize second generation T cell receptor (TCR) product candidates directed against the human papillomavirus type 16 E6 (HPV-16 E6) oncoprotein incorporating gene editing and lentiviral technologies. bluebird bio has a platform comprised of lentiviral gene delivery and gene editing capabilities, with a focus on rare diseases and cancer immunotherapies. Kite has a broad existing pipeline of TCR product candidates and will continue to develop its existing and wholly-owned TCR programs directed against high-risk HPV, which are unaffected by this collaboration, including HPV-16 E6 TCR, currently in a Phase I study, and HPV-16 E7 TCR. The collaboration brings together the powerful technologies and capabilities of these two leading immunotherapy companies.

Under the terms of the agreement, both companies will jointly develop and commercialize second generation TCR product candidates directed against the HPV-16 E6 oncoprotein, incorporating gene editing to efficiently modify certain genes to enhance T cell function. In addition, the companies will explore using lentiviral vectors to optimize delivery of HPV-16 E6 TCRs into patient T cells.

Kite will lead the program in the U.S., and bluebird bio will have the option to lead the program in the European Union. Both companies will share overall costs, including research and development and sales and marketing expenses, and profits will be equally split between the companies. Additionally, Kite will have a co-promotion option in the European Union, and bluebird will have a co-promotion option in the U.S.

"As we continue to build a differentiated immuno-oncology portfolio, we are delighted to partner with Kite in a collaboration that combines their leadership in T cell-based immunotherapies with our expertise in gene editing and industry-leading lentiviral vector platform," said Nick Leschly, chief bluebird. "We believe partnering with Kite will allow us to deliver game-changing T cell therapies to patients through great science and great capabilities."

"This partnership is a natural fit with our mission to develop and deliver novel immunotherapies for cancer patients, and collaborating globally with bluebird bio will allow us to benefit from the strengths and capabilities of both companies in immuno-oncology. Through this collaboration, we will have access to our partner's strong science expertise and enabling technologies to further enhance one of our key TCR programs and to evaluate gene editing technology in the context of T cell therapy," said Arie Belldegrun, M.D., FACS, Kite's Chairman, President and Chief Executive Officer.

Kite will discuss further details of this collaboration at its upcoming Investor Day event on June 23rd that will be webcast at www.kitepharma.com.

About HPV-Associated Cancers

Human papillomavirus (HPV) is the most common viral infection of the reproductive tract, with two viral strains, HPV type 16 and type 18, believed to cause 70% of cervical cancers and precancerous cervical lesions, as well as other urogenital cancers.[1] There were over 500,000 new cases and about 270,000 deaths attributable to cervical cancer worldwide in 2012.[2]

Additionally, HPV infection has become established as an etiologic risk factor for oropharyngeal head and neck cancers. The incidence of HPV-associated oropharyngeal cancers has been increasing for at least the past decade, and recent studies show that about 70 percent of oropharyngeal cancers may be linked to HPV[3,4]. According to the CDC, there are over 12,000 new cases of oropharyngeal cancers in the U.S., of which an estimated 7,500 new cases are attributable to HPV-16.[4]

About Kite Pharma, Inc.

Kite Pharma, Inc., is a clinical-stage biopharmaceutical company engaged in the development of novel cancer immunotherapy products, with a primary focus on eACT™ designed to restore the immune system's ability to recognize and eradicate tumors. Kite is based in Santa Monica, CA. For more information on Kite Pharma, please visit www.kitepharma.com.

About bluebird bio, Inc.

With its lentiviral-based gene therapy and gene editing capabilities, bluebird bio has built an integrated product platform with broad potential application to severe genetic diseases and T cell-based immunotherapy. bluebird bio's clinical programs include Lenti-D™, currently in a Phase 2/3 study, called the Starbeam Study, for the treatment of childhood cerebral adrenoleukodystrophy, and LentiGlobin®, currently in three clinical studies: a global Phase 1/2 study, called the Northstar Study,

for the treatment of beta-thalassemia major; a single-center Phase 1/2 study in France (HGB-205) for the treatment of beta-thalassemia major or severe sickle cell disease; and a separate U.S. Phase 1 study for the treatment of sickle cell disease (HGB-206). bluebird bio also has ongoing preclinical CAR T immuno-oncology programs, as well as discovery research programs utilizing megaTALs/homing endonuclease gene editing technologies.

bluebird bio has operations in Cambridge, Massachusetts, Seattle, Washington, and Paris, France. For more information, please visit www.bluebirdbio.com.

Kite Pharma, Inc. Forward-Looking Statements

This press release contains forward-looking statements for purposes of the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. The press release may, in some cases, use terms such as "predicts," "believes," "potential," "proposed," "continue," "estimates," "anticipates," "expects," "plans," "intends," "may," "could," "might," "will," "should" or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. Forward-looking statements include statements regarding intentions, beliefs, projections, outlook, analyses or current expectations concerning, among other things: the success of the collaboration between Kite and bluebird; the ability to research and develop existing and new therapeutic candidates, including TCR products directed against HPV antigens; and the expectations regarding the clinical effectiveness and safety of T cell therapies. Various factors may cause differences between Kite's expectations and actual results as discussed in greater detail in Kite's filings with the Securities and Exchange Commission, including without limitation in its Form 10-Q for the quarter ended March 31, 2015. Any forward-looking statements that is made in this press release speak only as of the date of this press release. Kite assumes no obligation to update the forward-looking statements whether as a result of new information, future events or otherwise, after the date of this press release.

bluebird bio, Inc. Forward-Looking Statements

This release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, including statements regarding the research, development and advancement of bluebird bio's immuno-oncology product candidates and research programs. Any forward-looking statements are based on management's current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to, the risk that bluebird bio's immuno-oncology research programs, including those shared with Kite will be unsuccessful and not identify any viable product candidates or will not be safe or effective in clinical trials, the risk of cessation or delay of any of the planned clinical studies and/or our development of our immuno-oncology product candidates, the risk of a delay in the enrollment of patients in bluebird's clinical studies, the risk that our collaboration with Kite around HPV-16 E6 product candidates will not continue or will not be successful, and the risk that any one or more of our product candidates will not be successfully developed and commercialized. For a discussion of other risks and uncertainties, and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, see the section entitled "Risk Factors" in our most recent quarterly report on Form 10-Q, as well as discussions of potential risks, uncertainties, and other important factors in our subsequent filings with the Securities and Exchange Commission. All information in this press release is as of the date of the release, and bluebird bio undertakes no duty to update this information unless required by law.

[1] World Health Organization, Human papillomavirus (HPV) and cervical cancer, Fact sheet N°380, accessed 6/10/15.

[2] GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012 (http://globocan.iarc.fr/Default.aspx), accessed 6/10/15.

[3] Human papillomavirus and rising oropharyngeal cancer incidence in the United States, Journal of Clinical Oncology, 2011: 29(32):4294-4301.

[4] CDC: How Many Cancers Are Linked with HPV Each Year? (http://www.cdc.gov/cancer/hpv/statistics/cases.htm), accessed 6/10/15.

CONTACT: Kite Pharma, Inc.
Investor Relations:
Cynthia M. Butitta
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bluebird bio, Inc.
Investor Relations:
Manisha Pai, 617-245-2107
mpai@bluebirdbio.com
or
Media:
Pure Communications
Dan Budwick, 973-271-6085

Source: Kite Pharma, Inc.

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Tuesday, June 23, 2015 10:05 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Fwd: NVS
Attachments: image001.jpg

Please see from today. That have timed it around your talk today!! Questions will follow from analysts!

Arie

Begin forwarded message:

> **From:** Ran Nussbaum <ran@pontifax.com>
> **Date:** June 23, 2015 at 08:49:24 EDT
> **To:** David Chang <DChang@KitePharma.com>, Arie Belldegrun <Arie@kitepharma.com>, Helen Kim <HKim@KitePharma.com>, Margo Roberts <mroberts@kitepharma.com>
> **Cc:** Jeff Rowbottom <jeff@pontifax.com>, Cynthia Butitta <CButitta@KitePharma.com>
> **Subject: NVS**
>
> **Novartis Institute For Biomedical Research (NIBR)**
> **CART**
> NVS's pivotal Phase III trial in pediatric r/r ALL started in March and initiation of the pivotal DLBCL trial is expected to start in H2:15. Filing in these indications is expected for late 2016 (ALL) and 2017 (DLBCL). CART targeting EGFRvIII to treat glioma has entered the clinic with early data presented at ASCGT. Additional CARTs targeting MM and AML are expected to enter the clinic in H2:15. Despite the enthusiasm around CART in hematological malignancies, Novartis cautioned that finding a safe target in solid tumors is challenging. Most targets overexpressed in solid tumors have some levels of expression in normal tissue and their targeting can lead to severe side effects. For example, HER2 is expressed at low levels in the lining of the lungs and a CART approach against HER2 in breast cancer led to severe respiratory toxicity. CTL019 sales are forecast at $500MM in 2020.
>
> Best Regards,
> Ran Nussbaum
> Managing partner
>
> Tel +97299725617
> Fax +97299725618
> Ran@pontifax.com
> 2.png

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Tuesday, June 23, 2015 10:04 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: FW: STIFEL: KITE ($62.72, Buy) - Kite Investor Day Update and Bluebird Bio Collaboration
Attachments: ATT00002.png; ATT00003.gif; ATT00001

Hi Steve,

Thank you so much for making the efforts to come to NY. I heard only raving reviews about your presence and presentation.

Here is the first report. The next ones will be sent to you separately.

Thanks,

Arie

Arie Belldegrun, MD FACS
President and CEO, Founder
Chairman, Board of Directors
Kite Pharma

2225 Colorado Ave
Santa Monica, CA 90404
Tel:310-622-9093
www.kitepharma.com

From: Lisa Burns [mailto:LBurns@burnsmc.com]
Sent: Tuesday, June 23, 2015 6:33 PM
To: Arie Belldegrun; Cynthia Butitta; David Chang
Cc: Linda Barnes; Kate Bechtold; Kite Team
Subject: Fwd: STIFEL: KITE ($62.72, Buy) - Kite Investor Day Update and Bluebird Bio Collaboration

Sent from my iPhone

Begin forwarded message:

From: Thomas Shrader <shradert@stifel.com>
Date: 23 Jun 2015 9:30:08 pm GMT-4
To: Lisa Burns <LBurns@burnsmc.com>

Subject: STIFEL: KITE ($62.72, Buy) - Kite Investor Day Update and Bluebird Bio Collaboration
Reply-To: "Thomas Shrader" <shradert@stifel.com>

June 23, 2015

Kite Pharma,
KITE – NASD

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Kite Investor Day Update and Bluebird Bio Collaboration

This afternoon we attended Kite Pharma's Investor Day where management provided a corporate overview and the company's key collaborator at the NCI (Steven Rosenberg) ga overview of the field that hinted at some potentially earthshaking data to come (see below). Kite's recent collaboration with Bluebird was reviewed and looks like a high-level holding exercise as both companies look to enter new areas without wasting time. As expected, the next IND will involve TCRs targeting HPV proteins which are increasingly viewed as the best TCR target outside of neoantigens.

Rosenberg's Next Miracle? Steven Rosenberg delivered principally an overview of the field but also showed a slide of some patients where **his group at the N isolated both neoantigens and their recognizing TCRs** from tumors other than melanoma – specifically gastrointestinal cancers. As a result, we expect he has treatec patients with TCR therapeutics and early data can't be far away (SR has been mentioning this program since ASH). We believe if these data are compelling and CRs ar for neoantigen-based TCR therapeutics it will be viewed as a major proof-of-concept for Kite's focus on the neoantigen approach in solid tumors. As we have said in pr notes – the operational hurdles for this approach to treating solid tumors are non-trivial – but the approach puts cure on the table for as many as 50% of patients wit tumors.

The Bluebird Collaboration. The two companies yesterday announced a collaboration agreement to co-develop second generation TCR proc specifically product candidates directed against the HPV-16 E6 oncoprotein. With Bluebird being a gene-editing focused company anc specializing in T-Cell therapeutics, the two will leverage each other's strengths to design next-generation T-Cell therapeutics. Kite is a certainly looking to modify TCR therapeutics to combat the immunosuppressive tumor environment. As a result, we expect they are knockir some of the receptors found on T-Cells that tumors use to put tumor-hunting TCRs to sleep. As reported at ASCO 2015, KTE019 T-Cells be express PD-1 after introduction into patients and tumor cells are expected to express PD-L1 and the resultant interaction potentially rec efficacy. As a result, knocking out PD-1 in TCR (and CAR-T) therapeutics seems like an obvious things to try. The subsequent list of canc genes to delete to stimulate TCR therapeutics is very long – probably spurring Kite's urge to find an expert partner.

Next IND – HPV. As was probably expected, Kite's second IND submission will be a TCR therapeutic targeting Human papillomavirus (HPV,

generation

Target Price Methodology/Risks

We use a multiple of future earnings to derive our $83 target price for KITE. Specifically, to generate our valuation for development-stage biotech companies, we use a 30x mul future earnings, which represents a discount to the 20-year average earnings multiple for profitable biotech companies of 37x. Kite's valuation is driven primarily by KTE-C19, curr Phase I/IIa testing. We apply a 25% discount rate, which we feel reflects the degree of uncertainty surrounding KTE-C19. With a multiple of 30x, we calculate a $83 target price ba our 2022 diluted EPS estimate of $15.92, discounted back 7.5 years.

Development risk for KTE-C19 - If Kite is not able to successfully develop the experimental CAR-T technology, we would have to lower our revenue estimates.

Competitive risk for KTE-C19 - If a competitor proves more effective or tolerable in the treatment of DLBCL, or their drugs are easier to produce, our estimates could prove optimisti

Regulatory risk for KTE-C19 - The FDA has never approved a CAR-T-based therapy before and there exists no precedent for the approval of a genetica ly engineered autologc product. If KTE-C19 is not approved on the timeline that we envision, we would have to reduce our estimates.

Changes	Previous	Current
Rating	—	Buy
Target Price	—	$83.00
FY15E EPS	—	$(1.49)
FY16E EPS	—	$0.02

Price (06/23/15)	$62.72
52-Week Range:	$89 – $21
Market Cap (mm):	2,665.6
Dividend($ / %)	$0.00 / 0.0%

Thomas Shrader, PhD, CFA
shradert@stifel.com
(212) 271-3577

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Tuesday, June 23, 2015 10:07 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: FW: QUICK TAKE - KITE - Depth Of Scientific Expertise Highlighted At Investor Day - Cowen and Company
Attachments: ATT00001.png; ATT00002.gif

One more- from top analyst and most respected- Eric Schmidt from Cowen.

Arie Belldegrun, MD FACS
President and CEO, Founder
Chairman, Board of Directors
Kite Pharma

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Santa Monica, CA 90404
Tel:310-622-9093
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From: Lisa Burns [mailto:LBurns@burnsmc.com]
Sent: Tuesday, June 23, 2015 4:32 PM
To: Arie Belldegrun; Cynthia Butitta; David Chang
Cc: Linda Barnes; Kate Bechtold; Kite Team
Subject: Fwd: QUICK TAKE - KITE - Depth Of Scientific Expertise Highlighted At Investor Day - Cowen and Company

Sent from my iPhone

Begin forwarded message:

> **From:** Eric Schmidt <eric.schmidt@cowen.com>
> **Date:** 23 Jun 2015 7:21:14 pm GMT-4
> **To:** Lisa Burns <LBurns@burnsmc.com>
> **Subject: QUICK TAKE - KITE - Depth Of Scientific Expertise Highlighted At Investor Day - Cowen and Company**
> **Reply-To:** Eric Schmidt <eric.schmidt@cowen.com>

LINK TO FULL REPORT & DISCLOSURES

Biotechnology

Kite Pharma

Equity Research
June 23, 2015

Quick Take: Company Update

Price: $62.72
(06/23/2015)
Price Target: NA

Depth Of

OUTPERFORM (1)

Scientific Expertise Highlighted At Investor Day

Eric Schmidt, Ph.D.
646.562.1345
eric.schmidt@cowen.com
Marc Frahm, Ph.D.
646.562.1394
marc.frahm@cowen.com

Key Data

Symbol	NASDAQ: KITE
Market Cap (MM)	$2,700.7

The Cowen Insight

At yesterday's analyst day in NYC, Kite unveiled new technologies, reviewed its scientific foundation and aspirations, and provided a pipeline update. Kite's Phase I/II DLBCL trial continues to enroll patients and an ongoing HPV E6 TCR trial has generated responses in solid tumors. We continue to view Kite as the leader in engineered T cells and remain at Outperform.

Much Progress Has Been Made, But Kite Isn't Resting

Yesterday, Kite hosted an analyst event in New York. Management reviewed the significant progress it has made over the past year since its IPO. Kite has transitioned chimeric antigen receptor (CAR) T cell manufacturing outside of NCI, initiated a potentially pivotal program in DLBCL, begun construction of commercial manufacturing facilities, and significantly expanded its scientific expertise via the acquisition of T Cell Factory, a broadened CRADA with NCI, and collaborations with Amgen and bluebird bio. In addition, Kite set out its vision for the future of engineered T cell therapy. This vision includes new methods for manipulating the activation/inhibition of T cells, a significant focus on T cell receptor (TCR) -based therapies for shared antigens, and ultimately TCRs specific for an individual patient's neo-antigens.

Kite Is Leading On The Science

There are three major approaches to cancer immunotherapy, (1) nonspecific activation of immune cells via stimulation (e.g. IL-2) or blocking inhibitory signals (e.g. PD-1), (2) immunization (e.g. Provenge, T-Vec), or (3) the transfer of *ex vivo* activated immune cells (eg. TILs, CAR T cells). Kite is focused on developing therapies belonging to the last category of immunotherapies. Specifically, Kite is developing engineered T cells that express CARs or TCRs specific for cancer antigens. Kite highlighted the immense depth of scientific experience in engineered T cells, immunology, oncology, and product development represented across the organization both through internal employees (Drs. Chang, Roberts, and Schumacher) and key external advisors/collaborators (Drs. Levy, Rosenberg, and Witte). Together these individuals were instrumental in the creation of the first CAR administered to humans (Dr. Roberts), the first successful cancer immunotherapy (Dr. Rosenberg), and multiple revolutionary cancer drugs including Rituxan (Dr. Levy) and Gleevec (Dr. Witte). Kite and others have presented data indicating significant efficacy with CD19 CARs and NY-ESO-1 TCRs. We believe Kite has assembled the team required to make engineered T cells applicable to a broad portion of oncology. To accomplish this goal, Kite's efforts are focused on two primary methods to

increase the breadth of tumors addressable by engineered T cells. First is identifying the appropriate cancer specific antigens to attack and second is developing secondary technologies to improve the activity of engineered T cells.

First Generation CARs Are Great But More Is Needed

Kite's collaborators discussed that CD19 is a nearly perfect antigen given its uniform expression across multiple tumor types and restriction to a healthy cell type (B cells) that can live without. Kite and its collaborators believe additional attractive antigens exist. One such antigen is EGFRvIII. Working with NCI, Kite has treated ~15 patients (GBM and head and neck cancers) at NCI using an EGFRvIII CAR construct. Dr. Rosenberg reported that dose escalation has just now reached the level where one could imagine seeing efficacy but that as of now no responses have been observed. Kite's collaboration with Amgen should provide additional attractive CAR candidates. This collaboration is directed at converting Amgen's library of antigen targets and antibody sequences into CAR constructs for the treatment of AML, multiple myeloma, kidney, and lung cancers. The first IND from this collaboration is expected in H2:16. While hopeful for these efforts, Kite and its collaborators noted that 20+ years of antibody development had likely identified the few targets that fit the CD19-like expression

criteria. Therefore, Kite is pursuing two mechanisms to broaden the list of potential tumor targets.

Second Generation CAR Therapies Bring Intelligence To The T Cell

First, Kite is working preclinically to develop second generation "logic gated" CAR therapies that require a targeted cell to either simultaneously express two antigens or perhaps more significantly express one antigen but not a second. These engineered T cells will simultaneously express two CAR constructs. In order to introduce an "and" operator the constructs will separately contain the primary stimulation (e.g. CD3) and secondary stimulation (e.g. CD28) signaling domains. Conversely, an "and not" operator can be introduced by using a traditional CAR construct containing both the primary and secondary stimulation domains in combination with a second CAR construct that contains an inhibitory domain. Consequently, if an off-target cell expresses the target antigen but also the inhibitory antigen it will be spared whereas a tumor cell that only expresses the target antigen will be killed. Kite believes second generation CAR therapies are 2-3 years away from the clinic.

TCRs Triple The Potentially Addressable Antigens

Second, Kite is using T cell receptors to pursue the ~75% of proteins that are expressed intracellularly and are

therefore inaccessible to antibody recognition. Kite currently has four TCR constructs (NY-ESO-1, MAGE A3/A6, MAGE A3, and HPV-16 E6) in the clinic and plans to initiate clinical trials on at least three additional constructs (HPV-16 E7, SSX2, and KRAS) within the next 18 months.
Kite acquired Dr. Ton Schumacher's T Cell Factory (TCF) to further expand the TCR pipeline. TCF's core TCR GENErator technology allows for the rapid isolation of high-affinity TCR sequences. Since TCR based therapies' target populations are restricted by MHC expression (ex. HLA-A2 is only expressed by ~50% of Caucasians) the TCF technology will be deployed to identify TCR sequences that utilize alternative MHC sequences to target the same antigen. Kite believes three TCR sequences per antigen are sufficient to cover >80% of the global population and approximately five sequences can cover >90% of the global population. In addition, the TCR GENErator will be deployed to identify TCRs specific for neo-antigens being identified under the NCI CRADA. Dr. Rosenberg reports that his lab is able to complete exome sequencing of tumor samples within 48 hours of receiving the sample. Within an additional 48 hours Dr. Rosenberg's group is able to identify the subset of peptides that are actually presented on MHC molecules within the tumor. Dr. Rosenberg has now performed this protocol using samples

from >25 melanoma and 16 GI cancer patients. Published data on the melanoma patients indicates that neo-antigens were presented universally, but each patient contained unique neo-antigens. Dr. Rosenberg disclosed that he has since found at least one melanoma patient with shared neo-antigens. Among the GI cancer patients, 15 were found to present neo-antigens. These neo-antigen profiles have not been published yet. With the TCR GENErator, Kite now possesses a high-throughput manner by which high-affinity TCRs specific to neo-antigen peptides can be isolated. Drs. Rosenberg and Schumacher believe that experience with TIL therapy indicates the simultaneous use of two to three neo-antigen TCR specificities should be sufficient to control many tumors. Kite has previously indicated that this ultimate in personalized medicine could be ready for clinical trials in 3-5 years.

HPV E6 TCR Shows Efficacy In Solid Tumors

Human papilloma virus (HPV) is associated with numerous cancers including anal, head and neck, and the majority of cervical cancers. These cancers lead to ~15,000 deaths/yr in the U.S. Dr. Rosenberg recently published proof of concept data showing durable responses in two out of nine patients treated with HPV specific tumor infiltrating lymphocytes (TILs). Kite and Dr. Rosenberg have followed up these findings with an HPV E6 specific TCR product. Dr.

Rosenberg disclosed for the first time that using this construct he has observed "multiple responses". As a result, Kite plans to transition the HPV-16 E6 program from an NCI held IND to a Kite held IND in early 2016.

Kite Is Also Working To Increase T Cell Activity

Beyond expanding the list of antigen targets, Kite is also developing methods by which it can make its T cells more potent. Preclinical studies have shown that IL-7 and IL-15 expression is vital for the engraftment and efficacy of CAR T cells. Working with NCI, Kite has conducted work to optimize the preconditioning regimen for among other parameters the generation of IL-7 and IL-15 expression. Preclinical work has also demonstrated that engineered T cells that have undergone less *ex vivo* differentiation generate superior efficacy. Kite and NCI have developed a small molecule (KTE-SM01) that is capable of decoupling T cell proliferation and differentiation. The identity of KTE-SM01's target was not disclosed, but based upon a literature review we believe it to be an AKT kinase inhibitor. Using KTE-SM01, Kite hopes to generate T cell products that are skewed towards a stem cell memory phenotype. Kite is now working to include KTE-SM01 in its next generation T cell manufacturing protocol. Kite is also pursuing strategies to combine engineered T cells with additional therapeutic

manipulations including checkpoint inhibition and/or coexpression of cytokines. Kite intends to develop a second generation HPV E6 TCR therapy that contains an additional modification(s). Earlier this week, Kite signed a collaboration with bluebird bio for this project. Under the collaboration Kite and bluebird bio will develop an engineered T cell product using (1) Kite's HPV E6 TCR sequence, (2) bluebird's lentiviral delivery system and (3) bluebird's gene editing platform to modify activating/inhibitory pathways. Kite indicated that this project could result in clinical trials in 2-3 years.

KTE-C19's Pivotal DLBCL Trial Progressing Well; More Trials Starting In H2:15

Kite has successfully transitioned production of KTE-C19 from NCI to its contract manufacturer (PTC). Last month, PTC produced cells were used to dose the first patient in Kite's potentially pivotal Phase I/II trial of KTE-C19 in DLBCL. For the Phase I portion, Kite is currently enrolling patients at four clinical sites. If no more than two dose limiting toxicities are observed among the first six patients, Kite will progress to the Phase II portion and enroll 50 patients from 20-25 clinical sites. This is expected to occur in H2:15. Data from the Phase I portion, including the trial's cell dose and preconditioning regimen will be presented at ASH 2015. Phase II data is expected to be released in 2016. Kite believes historical data indicates a <20% ORR

and 4-5 month mOS would be expected. Therefore, an ORR of at least 40% with a mOS of at least 6 months is expected to be approvable. Simultaneous to beginning the Phase II portion of the DLBCL trial, Kite intends to initiate a Phase II trial of KTE-C19 in MCL. Also in H2:15, Kite plans to initiate a Phase I/II ALL trial and a Phase II CLL trial.

From: David Chang [DChang@KitePharma.com]
Sent: Tuesday, June 23, 2015 11:25 PM
To: Owen N. Witte; Ron Levy; Rosenberg, Steven A. (NIH/NCI) [E]; Ton Schumacher
CC: Margo Roberts; Marc Better; Jeff Wiezorek
Subject: Fwd: STIFEL: KITE ($62.72, Buy) - Kite Investor Day Update and Bluebird Bio Collaboration
Attachments: ATT00002.png; ATT00003.gif; ATT00001

FYI.

David Chang, MD, PhD
office: (310) 622-9094
PERSONAL INFORMATION,REDACTED PER AGREEMENT
www.kitepharma.com

Sent from my iPad

Begin forwarded message:

> **From:** Lisa Burns <LBurns@burnsmc.com>
> **Date:** June 23, 2015 at 9:32:59 PM EDT
> **To:** Arie <arie@kitepharma.com>, C Butitta <cbutitta@kitepharma.com>, "David Chang" <dchang@kitepharma.com>
> **Cc:** Linda Barnes <lbarnes@kitepharma.com>, Kate Bechtold <kbechtold@kitepharma.com>, Kite Team <Kite_Team@burnsmc.com>
> **Subject: Fwd: STIFEL: KITE ($62.72, Buy) - Kite Investor Day Update and Bluebird Bio Collaboration**
>
> Sent from my iPhone
>
> Begin forwarded message:
>
> > **From:** Thomas Shrader <shradert@stifel.com>
> > **Date:** 23 Jun 2015 9:30:08 pm GMT-4
> > **To:** Lisa Burns <LBurns@burnsmc.com>
> > **Subject: STIFEL: KITE ($62.72, Buy) - Kite Investor Day Update and Bluebird Bio Collaboration**
> > **Reply-To:** "Thomas Shrader" <shradert@stifel.com>

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Target Price Methodology/Risks

We use a multiple of future earnings to derive our $83 target price for KITE. Specifically, to generate our valuation for development-stage biotech companies, we use a 30x multiple of fu which represents a discount to the 20-year average earnings multiple for profitable biotech companies of 37x. Kite's valuation is driven primarily by KTE-C19, currently in Phase I/IIa testin 25% discount rate, which we feel reflects the degree of uncertainty surrounding KTE-C19. With a multiple of 30x, we calculate a $83 target price based on our 2022 diluted EPS estim discounted back 7.5 years.

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Changes	Previous	Current
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Target Price	—	$83.00
FY15E EPS	—	$(1.49)
FY16E EPS	—	$0.02

Price (06/23/15):	$62.72
52-Week Range:	$89 – $21
Market Cap (mm):	2,665.6
Dividend($ / %)	$0.00 / 0.0%

Thomas Shrader, PhD, CFA
shradert@stifel.com
(212) 271-3577

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Access to the App is restricted to Stifel clients.

From: David Chang |DChang@KitePharma.com|
Sent: Tuesday, June 23, 2015 11:25 PM
To: Owen N. Witte; Ron Levy; Rosenberg, Steven A. (NIH/NCI) [E]; Ton Schumacher
CC: Margo Roberts; Marc Better; Jeff Wiezorek
Subject: Fwd: STIFEL: KITE ($62.72, Buy) - Kite Investor Day Update and Bluebird Bio Collaboration
Attachments: ATT00002.png; ATT00003.gif; ATT00001

FYI.

David Chang, MD, PhD
office: (310) 622-9094
PROPRIETARY INFORMATION,REDACTED PER AGREEMENT
www.kitepharma.com

Sent from my iPad

Begin forwarded message:

> **From:** Lisa Burns <LBurns@burnsmc.com>
> **Date:** June 23, 2015 at 9:32:59 PM EDT
> **To:** Arie <arie@kitepharma.com>, C Butitta <cbutitta@kitepharma.com>, "David Chang" <dchang@kitepharma.com>
> **Cc:** Linda Barnes <lbarnes@kitepharma.com>, Kate Bechtold <kbechtold@kitepharma.com>, Kite Team <Kite_Team@burnsmc.com>
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>
> Sent from my iPhone
>
> Begin forwarded message:
>
> > **From:** Thomas Shrader <shradert@stifel.com>
> > **Date:** 23 Jun 2015 9:30:08 pm GMT-4
> > **To:** Lisa Burns <LBurns@burnsmc.com>
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LINK TO FULL REPORT & DISCLOSURES

Biotechnology

Kite Pharma

Equity Research

June 23, 2015

Price: $62.72 (06/23/2015)
Price Target: NA

OUTPERFORM (1)

Eric Schmidt, Ph.D.
646.562.1345
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Marc Frahm, Ph.D.
646.562.1394
marc.frahm@cowen.com

Key Data

Symbol	NASDAQ: KITE
Market Cap (MM)	$2,700.7

Quick Take: Company Update

Depth Of Scientific Expertise Highlighted At Investor Day

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Much Progress Has Been Made, But Kite Isn't Resting

Yesterday, Kite hosted an analyst event in New York. Management reviewed the significant progress it has made over the past year since its IPO. Kite has transitioned chimeric antigen receptor (CAR) T cell manufacturing outside of NCI, initiated a potentially pivotal program in DLBCL, begun construction of commercial manufacturing

facilities, and significantly expanded its scientific expertise via the acquisition of T Cell Factory, a broadened CRADA with NCI, and collaborations with Amgen and bluebird bio. In addition, Kite set out its vision for the future of engineered T cell therapy. This vision includes new methods for manipulating the activation/inhibition of T cells, a significant focus on T cell receptor (TCR) -based therapies for shared antigens, and ultimately TCRs specific for an individual patient's neo-antigens.

Kite Is Leading On The Science

There are three major approaches to cancer immunotherapy, (1) nonspecific activation of immune cells via stimulation (e.g. IL-2) or blocking inhibitory signals (e.g. PD-1), (2) immunization (e.g. Provenge, T-Vec), or (3) the transfer of *ex vivo* activated immune cells (eg. TILs, CAR T cells). Kite is focused on developing therapies belonging to the last category of immunotherapies. Specifically, Kite is developing engineered T cells that express CARs or TCRs specific for cancer antigens. Kite highlighted the immense depth of scientific experience in engineered T cells, immunology, oncology, and product development represented across the organization both through internal employees (Drs. Chang, Roberts, and Schumacher) and key external advisors/collaborators (Drs. Levy, Rosenberg, and Witte). Together these individuals were instrumental in the creation of the first CAR administered to humans (Dr. Roberts), the first successful cancer immunotherapy (Dr. Rosenberg), and multiple revolutionary cancer drugs including Rituxan (Dr. Levy) and Gleevec (Dr. Witte). Kite and others have presented data indicating significant efficacy with CD19 CARs and NY-ESO-1 TCRs. We believe Kite has assembled the team required to make engineered T cells applicable to a broad portion of oncology. To accomplish this goal, Kite's efforts are focused on two primary methods to increase the breadth of tumors addressable by engineered T cells. First is identifying the appropriate cancer specific antigens to attack and second is developing secondary technologies to improve the activity of engineered T cells.

First Generation CARs Are Great But More Is Needed

Kite's collaborators discussed that CD19 is a nearly perfect antigen given its uniform expression across multiple tumor types and restriction to a healthy cell type (B cells) that can live without. Kite and its collaborators believe additional attractive antigens exist. One such antigen is EGFRvIII. Working with NCI, Kite has treated ~15 patients (GBM and head and neck cancers) at NCI using an EGFRvIII CAR construct. Dr. Rosenberg reported that dose escalation has just now reached the level where one could imagine seeing efficacy but that as of now no responses have been observed. Kite's collaboration with Amgen should provide additional attractive CAR candidates. This collaboration is directed at converting Amgen's library of antigen targets and antibody sequences into CAR constructs for the treatment of AML, multiple myeloma, kidney, and lung cancers. The first IND from this collaboration is expected in H2:16. While hopeful for these efforts, Kite and its collaborators noted that 20+ years of antibody development had likely identified the few targets that fit the CD19-like expression criteria. Therefore, Kite is pursuing two mechanisms to broaden the list of potential tumor targets.

Second Generation CAR Therapies Bring Intelligence To The T Cell

First, Kite is working preclinically to develop second generation "logic gated" CAR therapies that require a targeted cell to either simultaneously express two antigens or perhaps more significantly express one antigen but not a second. These engineered T cells will simultaneously express two CAR constructs. In order to introduce an

"and" operator the constructs will separately contain the primary stimulation (e.g. CD3) and secondary stimulation (e.g. CD28) signaling domains. Conversely, an "and not" operator can be introduced by using a traditional CAR construct containing both the primary and secondary stimulation domains in combination with a second CAR construct that contains an inhibitory domain. Consequently, if an off-target cell expresses the target antigen but also the inhibitory antigen it will be spared whereas a tumor cell that only expresses the target antigen will be killed. Kite believes second generation CAR therapies are 2-3 years away from the clinic.

TCRs Triple The Potentially Addressable Antigens

Second, Kite is using T cell receptors to pursue the ~75% of proteins that are expressed intracellularly and are therefore inaccessible to antibody recognition. Kite currently has four TCR constructs (NY-ESO-1, MAGE A3/A6, MAGE A3, and HPV-16 E6) in the clinic and plans to initiate clinical trials on at least three additional constructs (HPV-16 E7, SSX2, and KRAS) within the next 18 months.
Kite acquired Dr. Ton Schumacher's T Cell Factory (TCF) to further expand the TCR pipeline. TCF's core TCR GENErator technology allows for the rapid isolation of high-affinity TCR sequences. Since TCR based therapies' target populations are restricted by MHC expression (ex. HLA-A2 is only expressed by ~50% of Caucasians) the TCF technology will be deployed to identify TCR sequences that utilize alternative MHC sequences to target the same antigen. Kite believes three TCR sequences per antigen are sufficient to cover >80% of the global population and approximately five sequences can cover >90% of the global population. In addition, the TCR GENErator will be deployed to identify TCRs specific for neo-antigens being identified under the NCI CRADA. Dr. Rosenberg reports that his lab is able to complete exome sequencing of tumor samples within 48 hours of receiving the sample. Within an additional 48 hours Dr. Rosenberg's group is able to identify the subset of peptides that are actually presented on MHC molecules within the tumor. Dr. Rosenberg has now performed this protocol using samples from >25 melanoma and 16 GI cancer patients. Published data on the melanoma patients indicates that neo-antigens were presented universally, but each patient contained unique neo-antigens. Dr. Rosenberg disclosed that he has since found at least one melanoma patient with shared neo-antigens. Among the GI cancer patients, 15 were found to present neo-antigens. These neo-antigen profiles have not been published yet. With the TCR GENErator, Kite now possesses a high-throughput manner by which high-affinity TCRs specific to neo-antigen peptides can be isolated. Drs. Rosenberg and Schumacher believe that experience with TIL therapy indicates the simultaneous use of two to three neo-antigen TCR specificities should be sufficient to control many tumors. Kite has previously indicated that this ultimate in personalized medicine could be ready for clinical trials in 3-5 years.

HPV E6 TCR Shows Efficacy In Solid Tumors

Human papilloma virus (HPV) is associated with numerous cancers including anal, head and neck, and the majority of cervical cancers. These cancers lead to ~15,000 deaths/yr in the U.S. Dr. Rosenberg recently published proof of concept data showing durable responses in two out of nine patients treated with HPV specific tumor infiltrating lymphocytes (TILs). Kite and Dr. Rosenberg have followed up these findings with an HPV E6 specific TCR product. Dr. Rosenberg disclosed for the first time that using this construct he has observed "multiple responses". As a result, Kite plans to transition the HPV-16 E6 program from an NCI held IND to a Kite held IND in early 2016.

Kite Is Also Working To Increase T Cell Activity

Beyond expanding the list of antigen targets, Kite is also developing methods by which it can make its T cells more potent. Preclinical studies have shown that IL-7 and IL-15 expression is vital for the engraftment and efficacy of CAR T cells. Working with NCI, Kite has conducted work to optimize the preconditioning regimen for among other parameters the generation of IL-7 and IL-15 expression. Preclinical work has also demonstrated that engineered T cells that have undergone less *ex vivo* differentiation generate superior efficacy. Kite and NCI have developed a small molecule (KTE-SM01) that is capable of decoupling T cell proliferation and differentiation. The identity of KTE-SM01's target was not disclosed, but based upon a literature review we believe it to be an AKT kinase inhibitor. Using KTE-SM01, Kite hopes to generate T cell products that are skewed towards a stem cell memory phenotype. Kite is now working to include KTE-SM01 in its next generation T cell manufacturing protocol.

Kite is also pursuing strategies to combine engineered T cells with additional therapeutic manipulations including checkpoint inhibition and/or coexpression of cytokines. Kite intends to develop a second generation HPV E6 TCR therapy that contains an additional modification(s). Earlier this week, Kite signed a collaboration with bluebird bio for this project. Under the collaboration Kite and bluebird bio will develop an engineered T cell product using (1) Kite's HPV E6 TCR sequence, (2) bluebird's lentiviral delivery system and (3) bluebird's gene editing platform to modify activating/inhibitory pathways. Kite indicated that this project could result in clinical trials in 2-3 years.

KTE-C19's Pivotal DLBCL Trial Progressing Well; More Trials Starting In H2:15

Kite has successfully transitioned production of KTE-C19 from NCI to its contract manufacturer (PTC). Last month, PTC produced cells were used to dose the first patient in Kite's potentially pivotal Phase I/II trial of KTE-C19 in DLBCL. For the Phase I portion, Kite is currently enrolling patients at four clinical sites. If no more than two dose limiting toxicities are observed among the first six patients, Kite will progress to the Phase II portion and enroll 50 patients from 20-25 clinical sites. This is expected to occur in H2:15. Data from the Phase I portion, including the trial's cell dose and preconditioning regimen will be presented at ASH 2015. Phase II data is expected to be released in 2016. Kite believes historical data indicates a <20% ORR and 4-5 month mOS would be expected. Therefore, an ORR of at least 40% with a mOS of at least 6 months is expected to be approvable. Simultaneous to beginning the Phase II portion of the DLBCL trial, Kite intends to initiate a Phase II trial of KTE-C19 in MCL. Also in H2:15, Kite plans to initiate a Phase I/II ALL trial and a Phase II CLL trial.

From: David Chang [DChang@KitePharma.com]
Sent: Tuesday, June 23, 2015 11:25 PM
To: Owen N. Witte; Ron Levy; Rosenberg, Steven A. (NIH/NCI) [E]; Ton Schumacher
CC: Margo Roberts; Marc Better; Jeff Wiezorek; Rajul Jain
Subject: Fwd: QUICK TAKE - KITE - Depth Of Scientific Expertise Highlighted At Investor Day - Cowen and Company
Attachments: ATT00001.png; ATT00002.gif

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Biotechnology
Kite Pharma

Equity Research

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Price: $62.72 (06/23/2015)
Price Target: NA

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From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Wednesday, June 24, 2015 6:26 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]; Ron Levy; Owen N. Witte MD; Ton Schumacher
Subject: Fwd: Investor Day Analyst Reports
Attachments: Kite June 23-24 analyst reports.docx; ATT00001.htm; CanaccordJune242015.pdf; ATT00002.htm; CowenJune232015.pdf; ATT00003.htm; GuggenheimJune242015.pdf; ATT00004.htm; JefferiesJune242015.pdf; ATT00005.htm; MizuhoJune242015.pdf; ATT00006.htm; StifelJune232015.pdf; ATT00007.htm

Steve, Ron, Owen, and Ton,

Thank you all for yesterday's stellar performance. You were truly a dream team!

I am sending you an unbiased report on the event yesterday, as perceived by the analysts who covered it, and the originals from the write ups so far.

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

I started today at 6.30 AM at CNBC for a morning show and interview, and spent the rest of the day at the offices of WSJ (steve, Ron Winslow will call you for further interview), Bloomberg , and Forbes for additional interviews.
I am happy to be now on my way to LA!

Thanks again.

Arie

Begin forwarded message:

From: "Carol Werther" <cwerther@burnsmc.com>
To: "Arie Belldegrun" <Arie@kitepharma.com>, "David Chang" <DChang@KitePharma.com>, "Cynthia Butitta" <CButitta@KitePharma.com>, "Helen Kim" <HKim@KitePharma.com>, "Margo Roberts" <MRoberts@KitePharma.com>, "Marc Better" <MBetter@KitePharma.com>, "Jeff Wiezorek" <JWiezorek@KitePharma.com>, "Ton Schumacher" <tschumacher@kitepharma.com>, "Rajul Jain" <RJain@KitePharma.com>, "Kate Bechtold" <kbechtold@kitepharma.com>, "Linda Barnes" <LBarnes@KitePharma.com>
Cc: "Kite Team" <Kite_Team@burnsmc.com>
Subject: Investor Day Analyst Reports

Dear Arie, Cindy, David, Jeff, Marc, Margo, Ton, Helen, Rajul, Kate and Linda,

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Sincerely,

BMC KITE team

Summary of Analyst Kite Comments:

Jefferies, Biren Amin: BUY, PT $83.00
Title: Kite Shares Its Vision at Analyst Day
Key Takeaways: KITE hosted an analyst day where it reiterated its clinical development plan for KTE-C19, plans to move add'l CAR/TCR targets to clinical trials, and pot'l new strategies to improve T-cell expansion and the introduction of a pot'l CAR to prevent off-target effects on healthy cells. The company is on track to disclosing topline data from the pilot trial enrolling patients with diffuse large B-cell lymphoma (DLBCL) at ASH '15.

Notes on Biren's Take:

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Title: KITE Investor Day Update and Bluebird Bio Collaboration
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Notes on Tom's Take:

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Guggenheim, Tony Butler: BUY, PT $73.00
Title: KITE – BUY – Investor day 2015; Kite and Bluebird Soar Together into TCR's
Notes on Tony's Take:

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

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Cowen, Eric Schmidt, No PT
Title: Depth of Scientific Expertise Highlighted At Investor Day
Summary: The Cowen Insight: At yesterday's analyst day in NYC, Kite unveiled new technologies, reviewed its scientific foundation and aspirations, and provided a pipeline update. Kite's Phase I/II DLBCL trial continues to enroll patients and an ongoing HPV E6 TCR trial has generated responses in solid tumors. We continue to view Kite as the leader in engineered T cells and remain at Outperform.

Notes on Eric's Take:

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Canaccord, John Newman: BUY, PT $90.00

Title: TCRs center stage at R&D day, KRAS , HPV - 16 E7 enter clinic in 2015
Notes on John's Take:

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Mizuho, Peter Lawson; PT $90
Title: Investor Day – Under the Hood; No Near-Term Changes.
Notes on Peter's Take:

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

carol**werther** | Vice President, Investor Relations
Burns McClellan | 257 Park Ave South, 15 | New York, NY 10010 | T: 212.213.0006
cwerther@burnsmc.com | www.burnsmc.com

June 24, 2015

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Stifel, Tom Shrader: BUY, PT $83.00

Title: KITE Investor Day Update and Bluebird Bio Collaboration

Summary: This afternoon we attended Kite Pharma's Investor Day where management provided a corporate overview and the company's key collaborator at the NCI (Steven Rosenberg) gave an overview of the field that hinted at some potentially earthshaking data to come (see below). Kite's recent collaboration with Bluebird was reviewed and looks like a high-level hand-holding exercise as both companies look to enter new areas without wasting time. As expected, the next IND will involve TCRs targeting HPV proteins which are increasingly being viewed as the best TCR target outside of neoantigens.

Notes on Tom's Take:

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Guggenheim, Tony Butler: BUY, PT $73.00

Title: KITE – BUY – Investor day 2015; Kite and Bluebird Soar Together into TCR's

Notes on Tony's Take:

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Cowen, Eric Schmidt, No PT

Title: Depth of Scientific Expertise Highlighted At Investor Day

Summary: The Cowen Insight: At yesterday's analyst day in NYC, Kite unveiled new technologies, reviewed its scientific foundation and aspirations, and provided a pipeline update. Kite's Phase I/II DLBCL trial continues to enroll patients and an ongoing HPV E6 TCR trial has generated responses in solid tumors. We continue to view Kite as the leader in engineered T cells and remain at Outperform.

Notes on Eric's Take:

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Canaccord, John Newman: BUY, PT $90.00

Title: TCRs center stage at R&D day, KRAS , HPV-16 E7 enter clinic in 2015

Notes on John's Take:

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Mizuho, Peter Lawson; PT $90

Title: Investor Day – Under the Hood; No Near-Term Changes.

Notes on Peter's Take:

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

CANACCORD Genuity

To us there are no foreign markets.

Kite Pha[illegible]

Biotechnology

US Equity Research
24 June 2015

John Newman, PhD | Canaccord Genuity Inc. (US) | JNewman@canaccordgenuity.com | 212.389.8042

BUY
unchanged

PRICE TARGET	US$90.00
unchanged	
Price (23-Jun)	US$62.72
Ticker	KITE-NASDAQ

52-Week Range (US$):	21.00 - 89.21
Avg Daily Vol (M)	895.3
Shares Out. (M)	38.3
Market Cap (US$M):	2,404

FYE Dec	2014A	2015E	2016E
Revenue (US$M)	0.0	2,881.0	0.0
EPS Adj&Dil (US$)	(1.91)	(0.95)	(1.02)

Quarterly Revenue	Q1	Q2	Q3	Q4
2014A	0.0	0.0	0.0	0.0
2015E	2,881.0	0.0	0.0	0.0
2016E	-	-	-	-

Quarterly EPS Adj&Dil	Q1	Q2	Q3	Q4
2014A	(0.66)	(2.27)	(0.24)	(0.33)
2015E	(0.20)	(0.25)	(0.25)	(0.25)
2016E	-	-	-	-

Kite Pharma is focused on development of novel cancer immunotherapy using engineered autologous cell therapy (eACT).

Company Update

TCRs center stage at R&D day, KRAS, HPV-16 E7 enter clinic in 2015

KRAS and HPV-16 E7 TCRs to enter clinic in 2015

TCR constructs targeting HPV-16 E7 and KRAs will enter human testing during 2015, broadening KITE's push into solid tumors. Mutated KRAS is present in colorectal, lung, and pancreatic cancer, three very large commercial markets. We note that prior investor disappointment with mesothelin studies is not necessarily indicative of other antigens. In addition, dose escalation for TCR constructs usually proceeds slowly, with early data not necessarily indicative of the final result at higher doses.

Phase 1 pivotal DLBCL data expected at ASH, Dec 2015

Kite gave details on its pivotal Phase 1/2 DLBCL program, with pivotal Phase 1 data expected at ASH in December 2015. Importantly, patients will be treated in the hospital setting during Phase 1 and observed for toxicity. Assuming the rate of severe toxicity is acceptable, the trial will proceed to Phase 2. Interestingly, the conditioning regimen intensity has been established as a range of "low" to "high." We look to understand additional detail regarding any potential differences in conditioning intensity versus the NCI Phase 1 pilot study going forward.

Next-generation manufacturing and CAR fidelity interesting

We suspect Kite will utilize akt inhibitors in next-gen manufacturing of Chimeric Antigen Receptor constructs, which may mitigate terminal differentiation and preserve central memory phenotype, and result in enhanced T-cell persistence. Dr. Steven Rosenberg mentioned the akt inhibition technique and has previously published on this topic, and the idea was mentioned at the R&D day. We also believe that Kite's "CAR fidelity" approach may mitigate off-target toxicity by adding a second inhibitory receptor towards targets on healthy cells but not tumor cells.

TCR melanoma data previously established solid tumor viability

As previously discussed, we firmly believe that TCR efficacy has been demonstrated in solid tumors based on previously published melanoma data. NCI data in melanoma targeting NY-ESO-1 (n=19) have previously shown a 53% ORR (32% PR, 21% CR). We believe that both the existing NCI study in melanoma and the upcoming TCR studies against KRAS and HPV will provide additional proof-of-concept data in solid tumors, holding meaningful upside.

Appendix: Important Disclosures

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Target Price / Valuation Methodology:

Kite Pharma - KITE

Our target price is $90, based on a probability adjusted NPV valuation.

Risks to achieving Target Price / Valuation:

Kite Pharma - KITE

Although NCI is conducting a phase 1-2a trial of anti-CD19 CAR T-cell therapy, KITE's KTE-C19 trial has not begun. Any delays or significant negative results from NCI's clinical trials could negatively affect Kite's IND application and delay the timing to start their own phase 1-2 clinical trial. KITE is highly dependent on the third parties for R&D and early clinical testing of CAR and TCR product candidates. These collaborations related to the intellectual property licensed from the NIH relating to product candidates targeting the EGFRvIII antigen, the SSX2 antigen and the NY-ESO-1 antigen and from Cabaret for intellectual property relating to KTE-C19. The differences in manufacturing compared to NCI may render the product incomparable, particularly with respect to clinical trials, which could negatively affect our valuation. Although plans for manufacturing and processing is based on current approach undertaken by the NCI, the company cannot ensure that even minor changes in the product process will not result in significantly different T-cells that may not have similar efficacy or toxicity. KTE-C19 could fail in clinical studies, resulting in significant downside to our price target and shares of the stock. Kite faces significant competition from other biotechnology and pharmaceutical companies in the space of immunotherapy, including Novartis, Juno, Bluebird, Cellectis and Adaptimmune, as well as companies developing novel targeted therapies for cancer.

Distribution of Ratings:

Global Stock Ratings (as of 06/24/15)

Rating	Coverage Universe		IB Clients
	#	%	%
Buy	590	59.24%	33.05%
Hold	320	32.13%	15.62%
Sell	38	3.82%	2.63%
Speculative Buy	48	4.82%	54.17%
	996*	100.0%	

*Total includes stocks that are Under Review

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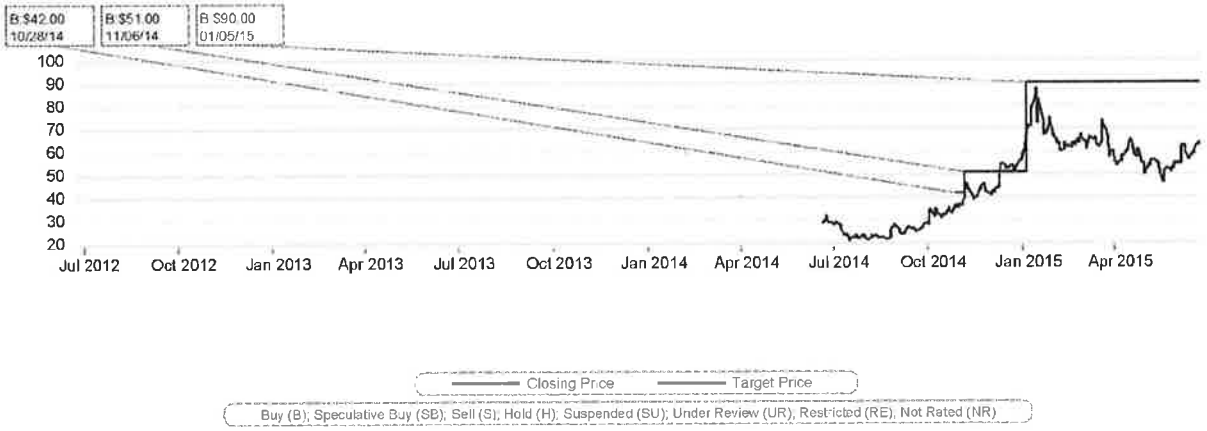

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COWEN
AND COMPANY

Biotechnology

Kite Pharma

Equity Research

Quick Take: Company Update

June 23, 2015

Price: $62.72 (06/23/2015)
Price Target: NA

OUTPERFORM (1)

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Key Data

Symbol	NASDAQ: KITE
Market Cap (MM)	$2,700.7

Depth Of Scientific Expertise Highlighted At Investor Day

The Cowen Insight

At yesterday's analyst day in NYC, Kite unveiled new technologies, reviewed its scientific foundation and aspirations, and provided a pipeline update. Kite's Phase I/II DLBCL trial continues to enroll patients and an ongoing HPV E6 TCR trial has generated responses in solid tumors. We continue to view Kite as the leader in engineered T cells and remain at Outperform.

Much Progress Has Been Made, But Kite Isn't Resting

Yesterday, Kite hosted an analyst event in New York. Management reviewed the significant progress it has made over the past year since its IPO. Kite has transitioned chimeric antigen receptor (CAR) T cell manufacturing outside of NCI, initiated a potentially pivotal program in DLBCL, begun construction of commercial manufacturing facilities, and significantly expanded its scientific expertise via the acquisition of T Cell Factory, a broadened CRADA with NCI, and collaborations with Amgen and bluebird bio. In addition, Kite set out its vision for the future of engineered T cell therapy. This vision includes new methods for manipulating the activation/ inhibition of T cells, a significant focus on T cell receptor (TCR) -based therapies for shared antigens, and ultimately TCRs specific for an individual patient's neo-antigens.

Kite Is Leading On The Science

There are three major approaches to cancer immunotherapy, (1) nonspecific activation of immune cells via stimulation (e.g. IL-2) or blocking inhibitory signals (e.g. PD-1), (2) immunization (e.g. Provenge, T-Vec), or (3) the transfer of *ex vivo* activated immune cells (eg. TILs, CAR T cells). Kite is focused on developing therapies belonging to the last category of immunotherapies. Specifically, Kite is developing engineered T cells that express CARs or TCRs specific for cancer antigens. Kite highlighted the immense depth of scientific experience in engineered T cells, immunology, oncology, and product development represented across the organization both through internal employees (Drs. Chang, Roberts, and Schumacher) and key external advisors/ collaborators (Drs. Levy, Rosenberg, and Witte). Together these individuals were instrumental in the creation of the first CAR administered to humans (Dr. Roberts), the first successful cancer immunotherapy (Dr. Rosenberg), and multiple revolutionary cancer drugs including Rituxan (Dr. Levy) and Gleevec (Dr. Witte). Kite and others have presented data indicating significant efficacy with CD19 CARs and NY-ESO-1 TCRs. We believe Kite has assembled the team required to make engineered T cells applicable to a broad portion of oncology. To accomplish this goal, Kite's efforts are focused on two primary methods to increase the breadth of tumors addressable by engineered T cells. First is identifying the appropriate cancer specific antigens to attack and second is developing secondary technologies to improve the activity of engineered T cells.

First Generation CARs Are Great But More Is Needed

Kite's collaborators discussed that CD19 is a nearly perfect antigen given its uniform expression across multiple tumor types and restriction to a healthy cell type (B cells) that can live without. Kite and its collaborators believe additional attractive antigens exist. One such antigen is EGFRvIII. Working with NCI, Kite has treated ~15 patients (GBM and head and neck cancers) at NCI using an EGFRvIII CAR construct. Dr. Rosenberg reported that dose escalation has just now reached the level where one could imagine seeing efficacy but that as of now no responses have been observed. Kite's collaboration with Amgen should provide additional attractive CAR candidates. This collaboration is directed at converting Amgen's library of antigen targets and antibody sequences into CAR constructs for the treatment of AML, multiple myeloma, kidney, and lung cancers. The first IND from this collaboration is expected in H2:16. While hopeful for these efforts, Kite and its collaborators noted that 20+ years of antibody development had likely identified the few targets that fit the CD19-like expression criteria. Therefore, Kite is pursuing two mechanisms to broaden the list of potential tumor targets.

Second Generation CAR Therapies Bring Intelligence To The T Cell

First, Kite is working preclinically to develop second generation "logic gated" CAR therapies that require a targeted cell to either simultaneously express two antigens or perhaps more significantly express one antigen but not a second. These engineered T cells will simultaneously express two CAR constructs. In order to introduce an "and" operator the constructs will separately contain the primary stimulation (e.g. CD3) and secondary stimulation (e.g. CD28) signaling domains. Conversely, an "and not" operator can be introduced by using a traditional CAR construct containing both the primary and secondary stimulation domains in combination with a second CAR construct that contains an inhibitory domain. Consequently, if an off-target cell expresses the target antigen but also the inhibitory antigen it will be spared whereas a tumor cell that only expresses the target antigen will be killed. Kite believes second generation CAR therapies are 2-3 years away from the clinic.

TCRs Triple The Potentially Addressable Antigens

Second, Kite is using T cell receptors to pursue the ~75% of proteins that are expressed intracellularly and are therefore inaccessible to antibody recognition. Kite currently has four TCR constructs (NY-ESO-1, MAGE A3/A6, MAGE A3, and HPV-16 E6) in the clinic and plans to initiate clinical trials on at least three additional constructs (HPV-16 E7, SSX2, and KRAS) within the next 18 months.

Kite acquired Dr. Ton Schumacher's T Cell Factory (TCF) to further expand the TCR pipeline. TCF's core TCR GENErator technology allows for the rapid isolation of high-affinity TCR sequences. Since TCR based therapies' target populations are restricted by MHC expression (ex. HLA-A2 is only expressed by ~50% of Caucasians) the TCF technology will be deployed to identify TCR sequences that utilize alternative MHC sequences to target the same antigen. Kite believes three TCR sequences per antigen are sufficient to cover >80% of the global population and approximately five sequences can cover >90% of the global population. In addition, the TCR GENErator will be deployed to identify TCRs specific for neo-antigens being identified under the NCI CRADA. Dr. Rosenberg reports that his lab is able to complete exome sequencing of tumor samples within 48 hours of receiving the sample. Within an additional 48 hours Dr. Rosenberg's group is able to identify the subset of peptides that are actually presented on MHC molecules within the tumor. Dr. Rosenberg has now performed this protocol using samples from >25 melanoma and 16 GI cancer patients. Published data on the melanoma patients indicates that neo-antigens were presented universally, but each patient contained unique neo-antigens. Dr. Rosenberg disclosed that he has since found at least one melanoma patient with shared neo-antigens. Among the GI cancer patients, 15 were found to present neo-antigens.

These neo-antigen profiles have not been published yet. With the TCR GENErator, Kite now possesses a high-throughput manner by which high-affinity TCRs specific to neo-antigen peptides can be isolated. Drs. Rosenberg and Schumacher believe that experience with TIL therapy indicates the simultaneous use of two to three neo-antigen TCR specificities should be sufficient to control many tumors. Kite has previously indicated that this ultimate in personalized medicine could be ready for clinical trials in 3-5 years.

HPV E6 TCR Shows Efficacy In Solid Tumors

Human papilloma virus (HPV) is associated with numerous cancers including anal, head and neck, and the majority of cervical cancers. These cancers lead to ~15,000 deaths/yr in the U.S. Dr. Rosenberg recently published proof of concept data showing durable responses in two out of nine patients treated with HPV specific tumor infiltrating lymphocytes (TILs). Kite and Dr. Rosenberg have followed up these findings with an HPV E6 specific TCR product. Dr. Rosenberg disclosed for the first time that using this construct he has observed "multiple responses". As a result, Kite plans to transition the HPV-16 E6 program from an NCI held IND to a Kite held IND in early 2016.

Kite Is Also Working To Increase T Cell Activity

Beyond expanding the list of antigen targets, Kite is also developing methods by which it can make its T cells more potent. Preclinical studies have shown that IL-7 and IL-15 expression is vital for the engraftment and efficacy of CAR T cells. Working with NCI, Kite has conducted work to optimize the preconditioning regimen for among other parameters the generation of IL-7 and IL-15 expression. Preclinical work has also demonstrated that engineered T cells that have undergone less *ex vivo* differentiation generate superior efficacy. Kite and NCI have developed a small molecule (KTE-SM01) that is capable of decoupling T cell proliferation and differentiation. The identity of KTE-SM01's target was not disclosed, but based upon a literature review we believe it to be an AKT kinase inhibitor. Using KTE-SM01, Kite hopes to generate T cell products that are skewed towards a stem cell memory phenotype. Kite is now working to include KTE-SM01 in its next generation T cell manufacturing protocol.

Kite is also pursuing strategies to combine engineered T cells with additional therapeutic manipulations including checkpoint inhibition and/or coexpression of cytokines. Kite intends to develop a second generation HPV E6 TCR therapy that contains an additional modification(s). Earlier this week, Kite signed a collaboration with bluebird bio for this project. Under the collaboration Kite and bluebird bio will develop an engineered T cell product using (1) Kite's HPV E6 TCR sequence, (2) bluebird's lentiviral delivery system and (3) bluebird's gene editing platform to modify activating/inhibitory pathways. Kite indicated that this project could result in clinical trials in 2-3 years.

KTE-C19's Pivotal DLBCL Trial Progressing Well; More Trials Starting In H2:15

Kite has successfully transitioned production of KTE-C19 from NCI to its contract manufacturer (PTC). Last month, PTC produced cells were used to dose the first patient in Kite's potentially pivotal Phase I/II trial of KTE-C19 in DLBCL. For the Phase I portion, Kite is currently enrolling patients at four clinical sites. If no more than two dose limiting toxicities are observed among the first six patients, Kite will progress to the Phase II portion and enroll 50 patients from 20-25 clinical sites. This is expected to occur in H2:15. Data from the Phase I portion, including the trial's cell dose and preconditioning regimen will be presented at ASH 2015. Phase II data is expected to be released in 2016. Kite believes historical data indicates a <20% ORR and 4-5 month mOS would be expected. Therefore, an ORR of at least 40% with a mOS of at least 6 months is expected to be approvable. Simultaneous to beginning the Phase II

[redacted]

portion of the DLBCL trial, Kite intends to initiate a Phase II trial of KTE-C19 in MCL. Also in H2:15, Kite plans to initiate a Phase I/II ALL trial and a Phase II CLL trial.

Valuation Methodology And Risks

Valuation Methodology

Biotechnology:

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Investment Risks

Biotechnology:

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Risks To The Price Target

Kite Pharma is unprofitable, has no approved products, and will likely need to raise additional capital from the public markets prior to turning profitable. There is limited clinical trial experience on lead candidate KTE-C19, and eACTs more broadly. Moreover, KTE-C19 faces a number of clinical, regulatory, and commercial hurdles prior to becoming successful, and projecting any future sales for KTE-C19 is inherently difficult.

We make investment recommendations on early stage (pre-commercial) biotechnology companies based upon a an assessment of their technology, the probability of pipeline success, and the potential market opportunity in the event of success. However, because these companies lack traditional financial metrics, we do not believe it there are any good methodologies for assigning a specific target price to such stocks.

Addendum

Stocks Mentioned In Important Disclosures

Ticker	Company Name
KITE	Kite Pharma

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Outperform (1): The stock is expected to achieve a total positive return of at least 15% over the next 12 months

Market Perform (2): The stock is expected to have a total return that falls between the parameters of an Outperform and Underperform over the next 12 months

Underperform (3): Stock is expected to achieve a total negative return of at least 10% over the next 12 months

Assumption: The expected total return calculation includes anticipated dividend yield

Cowen and Company Rating System until May 25, 2013

Outperform (1): Stock expected to outperform the S&P 500

Neutral (2): Stock expected to perform in line with the S&P 500

Underperform (3): Stock expected to underperform the S&P 500

Assumptions: Time horizon is 12 months; S&P 500 is flat over forecast period

Cowen Securities, formerly known as Dahlman Rose & Company, Rating System until May 25, 2013

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Rating	Count	Ratings Distribution	Count	IB Services/Past 12 Months
Buy (a)	450	58.67%	103	22.89%
Hold (b)	302	39.37%	8	2.65%
Sell (c)	15	1.96%	0	0.00%

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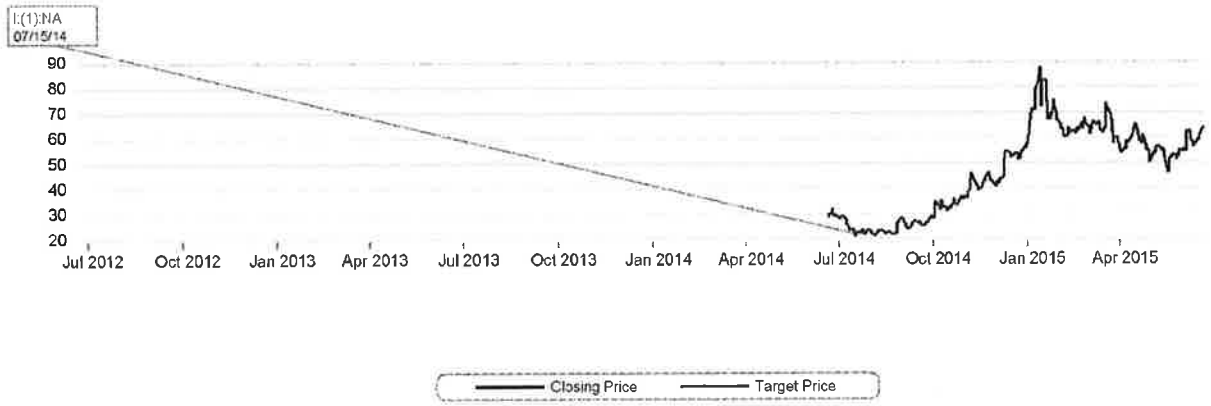

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Kite Pharma, Inc.

KITE – BUY – Investor Day 2015; Kite and Bluebird Soar Together into TCR's

June 24, 2015

- We attended the Kite Investor Day yesterday, June 23, 2015. KITE has grown significantly over the past year and a half since its IPO, growing from 8 employees at launch to over 100 employees today and raising over $400M to date to develop their programs, including 6 products in clinical development.
- KITE develops engineered T cells that redirect the patient's immune system to kill cancer cells. Such engineered T cells can eradicate cancer without harming normal tissue.
- KITE focused on several topics, including their collaborations (NCI, AMGN, NKI, UCLA, Tel Aviv, and now bluebird bio), product development (KTE-C19 being advanced to pivotal trials later this year), and building out the TCR franchise (recent agreement with bluebird on HPV-16 TCRs, AMGN collab, and other TCRs including NY-ESO and MAGE TCRs).
- KITE is also expanding manufacturing (Santa Monica facility opening in October, El Segundo facility in 2017, with existing PCT site in Mountain View and a CMO in EU) to support the over 300 patients who will be treated in KTE-C19 trials as well as further development of other candidates in the future.
- We await pivotal Ph. 1 data on KTE-C19 in aggressive NHL/DLBCL at ASH in December, while the remaining CAR and TCR pipeline is advancing rapidly with 3 additional pivotal studies in KTE-C19 (IND submission planned 2H16) as well as KRAS and HPV16 E7 TCRs initiating clinical trials in 2H15.

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KITE BUY

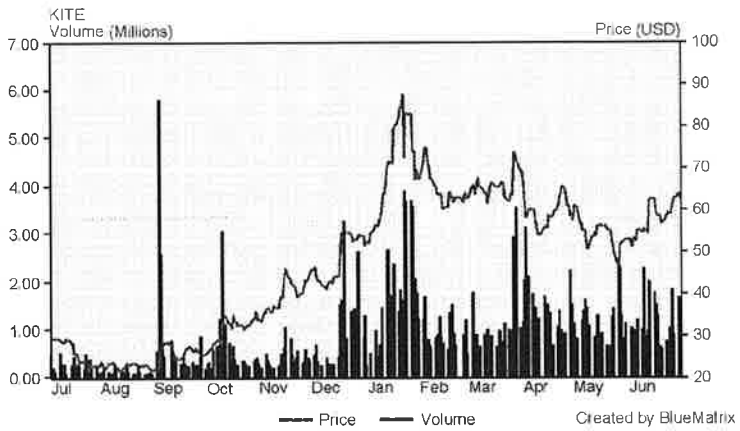
COMPANY UPDATE

Investment Thesis: Growth

SHARE PRICE	$62.72
PRICE TARGET	$73.00

EPS ($) (FY Dec)	1Q	2Q	3Q	4Q	FY
2014	—	—	—	(0.19)	(0.94)
P/E					NM
2015	(0.20)	(0.23)E	(0.24)E	(0.29)E	(0.87)E
P/E					NM
2016	—	—	—	—	(1.34)E
P/E					NM

Market Data	
52-Week Range	$21.00 - $89.21
Shares Out (M)	43.1
Market Cap (M)	$2,701
ADV (3 mo, 000)	1,268



Birds of a feather fly together: KITE and bluebird bio collaborate on TCRs: KITE and bluebird bio (BLUE, NC, $174.31) announced a new collaboration to develop second generation TCR product candidates directed against human papillomavirus type 16 E6 (HPV-16 E6) oncoprotein. Bluebird bio has demonstrated expertise and substantial promise using their lentivirus/gene therapy technologies to treat Beta-thalassemia and sickle cell disease. The collaboration will likely primarily allow for both companies to share intellectual property and methodologies to develop the second generation TCR therapies to target HPV-16 E6. Expenses for development and profits will be split equally between the companies, and none of the existing KITE HPV programs will be affected by this standalone agreement.

The HPV-16 E6 oncoprotein is constitutively expressed on HPV-16+ cancer cells and is absent from healthy tissues, allowing HPV-16-directed T cells to target and kill only cancer cells. Primary HPV-associated cancers include cervical and oropharyngeal head and neck cancers, which combined can constitute up to a yearly incidence of 42,500 eligible patients. KITE is currently evaluating a first generation HPV-16 E6 TCR for diverse HPV-16+ cancers in a Phase 1/2 study with an estimated enrollment of up to 61 patients and expected completion in May 2019.

Getting KTE-C19 to market in DLBCL: One of the key focuses of the Investor Day was what steps are necessary to begin the KTE-C19 program and what trial designs will be used. KITE has already started the pivotal study in DLBCL, and they indicated they will begin the pivotal studies in MCL, ALL, and aggressive NHL later this year (table below provides an overview of pivotal trial design). Dr. Jeff Wiezorek, VP of Clinical Development detailed an overview of the trial designs, mentioning that many of the same sites will be performing both Ph. 1 and 2 studies. Chemo-conditioned patients will be hospitalized around the infusion, which follows a 6-8 day manufacturing period (which KITE is still optimizing with automation steps and other measures) post-leukapheresis. Following the hospitalization, the follow up period begins with first tumor assessment on day 30. In aggressive NHL, KITE is targeting a BLA filing for KTE-C19 by YE 2016, with Ph. 1 data presented this December at ASH and Ph. 2 data to follow sometime next year. Over the life span of all KTE-C19 pivotal trials, over 300 patients will be treated.

KITE KTE-C19 Pivotal Trial Designs 101-103 in NHL, MCL, and ALL

Trial	Indication	Size of Ph. 2 (n)	Key eligibility criteria	Endpoints
KTE-C19 101	Aggressive NHL	· Cohort 1 in DLBCL: n=72 · Cohort 2 in PMBCL/TFL (n=40)	· DLBCL, PMBCL or TFL · Chemotherapy refractory disease - SD or PD to last therapy or - Relapsed post transplant within 1 year · Adequate prior therapy - At minimum, anthracycline-containing regimen and anti-CD20 mAb · ECOG 0 or 1	· Incidence of DLT (primary phase 1) · Objective response rate (primary phase 2) · Duration of response, PFS, OS and safety
KTE-C19 102	MCL	· n=70	· Pathologically confirmed MCL · Relapsed or refractory disease · Adequate prior therapy - Anthracycline or bendamustine-chemo and - Anti-CD20 monoclonal antibody therapy and - Ibrutinib · ECOG 0 or 1 · Age >18 · Adequate hepatic, renal, cardiac function	· Objective response rate (primary) · Duration of response, PFS, OS and safety
KTE-C19 103	ALL	· n=50	· Relapsed or refractory B-precursor ALL - Primary refractory disease - Untreated first relapse with first remission ≤ 12 months – Relapsed or refractory disease after first or later salvage therapy - Relapsed or refractory disease after allogeneic transplant · M1 or greater bone marrow · ECOG 0 or 1 · Age >18 · Adequate hepatic, renal, cardiac function	· Complete response rate (primary) · Duration of response, MRD-CR rate, allogeneic SCT rate and safety

**Source: KITE presentations*

Improving DLBCL/NHL therapy: KITE reiterated the emphasis of lymphodepletion and chemotherapy preconditioning as necessary for the CAR-T therapy process. At ASCO, KITE presented data demonstrating that chemo-conditioning with cyclophosphamide and fludarabine induced immune homeostatic cytokines (IL-15, IL-7), chemokines (MCP-1), and pro-inflammatory markers including CRP and PLGF. The method used for pre-conditioning the patient does therefore affect activation and trafficking of T cells. This will be key in clinical trials, and KITE intends to optimize this factor in CAR therapy. As presented at ASCO, KITE and Rosenberg mentioned that durable responses can occur without long lasting CAR-T cells in circulation, allowing for normal B cell recovery. Rosenberg commented that many robust responses have been achieved in several weeks post T-cell administration. KITE also emphasized CAR kinetics, in that the rapidity of achieving a CR as well as the ability to then sterilize the body of tumor cells is important. We note that this message differs slightly from JUNO's, who highlighted at ASCO that it seeks to improve the LT plateau of the KM curve in DLBCL patients by first improving cell persistence. Initial JCAR017 data in DLBCL reads out sometime next year, and JUNO's goal is to achieve a high CR rate as well as a durable tail.

DLBCL is KITE's lead indication, with a market size of ~22,000 patients in the U.S. Wiezorek emphasized that DLBCL in particular poses a large unmet need (table below outlining non-CD19 CAR responses), while CD-19 directed CARs have demonstrated response rates north of 60%, with many durable responses as well.

KITE Anti-CD19 CAR T induced objective responses in pts with r/r NHL and CLL		
Tumor type	**ORR**	**CRR**
Any (n=29)	76%	38%
DLBCL/PMBCL (n=17)	65%	35%
CLL (n=7)	86%	57%
Indolent NHL (n=5)	100%	20%

Source: ASCO 2015 data, Kochenderfer et al, Blood 2012 and JCO 2015 data

Responses in DLBCL by Line of Therapy (outside of KTE C19)		
Line of therapy	**Overall outcomes**	**Refractory outcomes**
1L	CR 76%' 10-yr OS ~44%	N/A
2L	ORR 11-97%	ORR <26%
3L+	ORR 0-40%	ORR<20%
Relapse post-ASCT	>1 yr: median OS 27 mos.	<1 yr: median OS 8 mos.

**Source: KITE presentations*

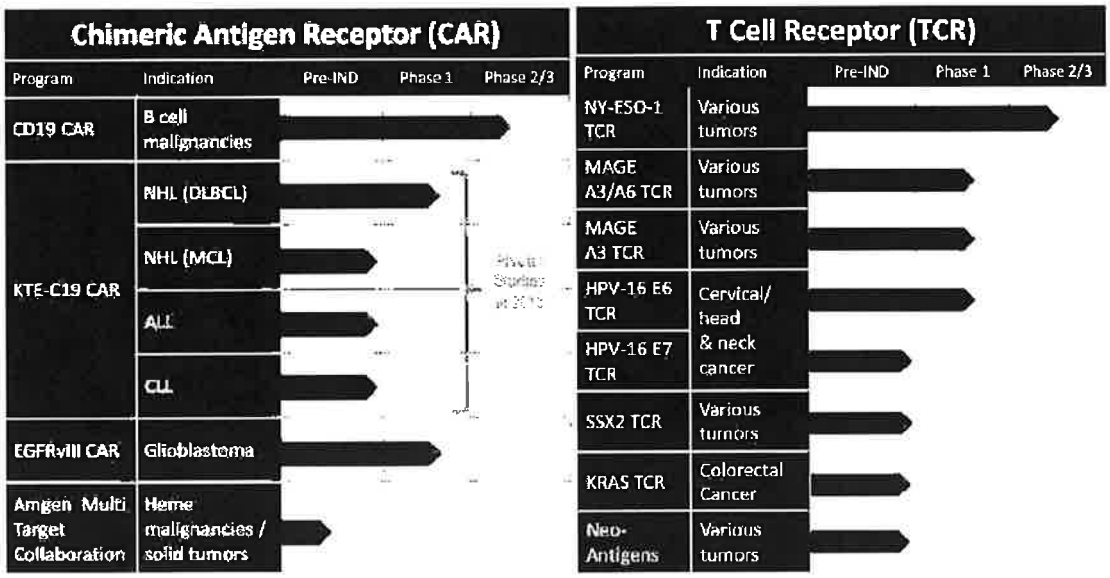
Ramping up manufacturing; commercial manufacturing ready for KTE-C19 launch in 2017: KITE will treat approximately 300 patients over the next year and a half, requiring a fairly extensive manufacturing build-out to support this development. In addition to relying on PCT in Mountain View, CA (used primarily for the DLBCL program) KITE has also built out a facility in Santa Monica that is anticipated to open in October. Along with KITE's EU program, led by Dr. Ton N. M. Schumacher, KITE is also engaging facilities for CMO production in Europe. The company is also building a facility in El Segundo, CA near the LA airport with an expected launch in 2017. Dr. Marc Better, VP of Product Sciences, commented that they fully expect the Santa Monica facility to be able to support manufacturing for the KTE-C19 program by YE. KITE believes its engineering process, which is relatively shorter compared to competitors at 6-8 days, offers superiority in the young phenotype of the product (not too many rounds of expansion) as well as no bead selection.

Where KTE-C19 fits into the treatment paradigm of new immunotherapies: Dr. Ron Levy from Stanford School of Medicine said that KTE-C19 fills a unique niche in the emerging landscape of new immunotherapies. While Rituximab raised the cure rate for DLBCL from 30% to 50%, CD-19 CARs are achieving RR's north of 60% that are durable, and Levy believes that CAR-T therapies such as KTE-C19 can eventually replace bone marrow transplants. In terms of comparing to other new immunotherapies such as ADC's, BTK inhibitors, and PI3K-delta inhibitors, Levy mentioned that they do not work especially well with DLBCL, achieving short-duration RR's of ~20-30%, as such therapies tend to work better in slower growing, low grade lymphomas such as follicular lymphoma. CAR-T therapies, in comparison, induce responses that are complete, durable and long lasting.

TCR franchise buildout: Dr. Ton Schumacher, CSO of KITE Europe and head of the KITE's collaboration with the Netherlands Cancer Institute, presented an overview of KITE's next-gen TCR programs. While CAR targets represent ~27% of the human proteome, TCR targets are more numerous due to TCR's ability to access intracellular targets, representing ~73% of the human proteome. KITE EU's proprietary TCR GENErator technology allows high-affinity of TCRs, though he emphasized the importance of an optimal affinity that is still within the natural range and binds tightly to the peptide MHC complex. KITE has active protocols at the NCI surgery branch, including HPV-16 E6 and HPV-18 E6 and E7 in cervical, head and neck cancers, mNY-ESO1 in pancreas and other cancers, Kras (G12D and G12V) in colorectal, and MAGE A3in various tumors. The collaboration with bluebird expands this portfolio, and KITE commented that filing is 2-3 years out for 2nd gen TCRs, while it files in 1H16 in the first-generation HPV-16 E6 program.

Future combos with checkpoint inhibitors: During the later Q&A panel, Dr.Levy commented that he believes combining checkpoint blockade with CAR-T's is the most exciting potential development in cancer immunotherapy. While checkpoint blocking antibodies have demonstrated tremendous efficacy, they only work on a certain subset of patients, so the question remains how to expand to a broader population. Some CAR-T players have already partnered on checkpoint inhibitors and CAR-T therapies: Juno (JUNO, NEUTRAL, $51.40) and AstraZeneca (AZN, NC, $67.59) announced their partnership on a PD-L1/CD19-CAR in NHL April 23. The study, which initiates later this year, assesses the impact that inhibiting PD-L1 with AZN's MEDI4736 has on the safety and efficacy of Juno's CAR-T construct. Inhibiting PD-1/PD-L1 would essentially prevent cancer cells from avoiding the host immune system, directly allowing increased exposure and efficacy of CAR-T engineered T cells. In addition, epitope spreading could be enhanced due to the immune response bolstered by the combo therapy further triggering an autoimmune response against proteins found on the surface of tumor cells.

Upcoming catalysts: 1) Pivotal Ph. 1 data at ASH in Dec. 2015 in aggressive NHL, 2) 3 additional pivotal trials in KTE-C19 initiating 2H15, 3) HPV-16 E6 TCR submitting IND in 1H16, 4) KRAS and HPV16 E7 TCRs initiating clinical trials under KITE-NCI CRADA in 2015, 5) KITE-AMGN CAR programs submitting IND's in 2H16, and 6) Ph. 2 pivotal data in KTE-C19 aggressive NHL in 1H16 and BLA filing for KTE-C19 by YE 2016.



Source: KITE presentations

KITE Valuation: As data continue to emerge supporting the viability of KITE's program/platform, we believe the risk could reduce and value could increase. Value should increase because the net present value of commercialization rises. We believe KITE may generate revenue by 2018. We estimate peak sales in second and third line NHL, assuming $200-250k per treatment, approach $1.5B by 2021. Medivation (MDVN, NC, $116.06) and Pharmacyclics (PCYC, NC, $261.25) are similar companies with early-stage product launches by partner companies and have market valuations approaching $9.7 billion and $19.7 billion, respectively. We estimate, at a current market cap of ~$2.2 billion, it is possible KITE could grow to 7-9 times its current size by 2022. We discount that valuation to today by 15% annually, which yields our price target of $73 (unchanged).

Key KITE Risks: KITE is an experimental stage company very early in development. Poor clinical readouts or inability to successfully commercialize its products is a risk. Risk of side effects of CAR-T therapies is also high, notably with cytokine release syndrome with even death in some patients, potentially limiting its use in earlier lines of therapy. There is also limited data outside of ALL, and establishing a durable response is critical to commercial success. Moreover, manufacturing and process development is not at commercial scale yet, and we note being able to deliver CAR-T to patients with affordable COGS is imperative. Further, given the number of companies currently in the CAR-T space, KITE's lead and platform could be commoditized. We believe profitability is several years away. Therefore, the stock can and may be highly volatile.

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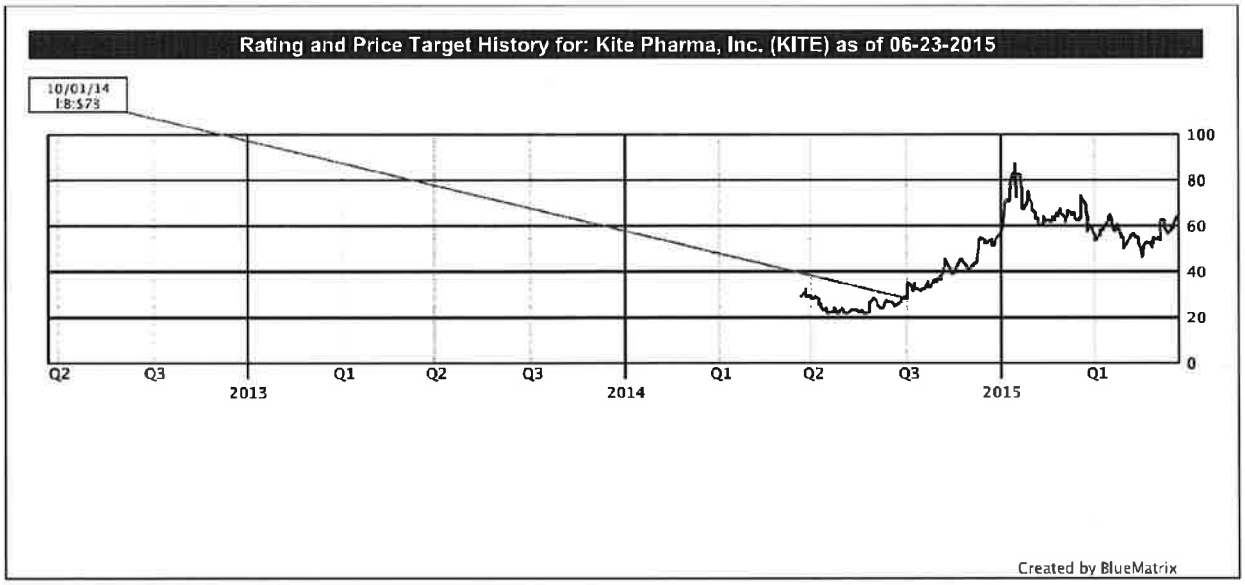

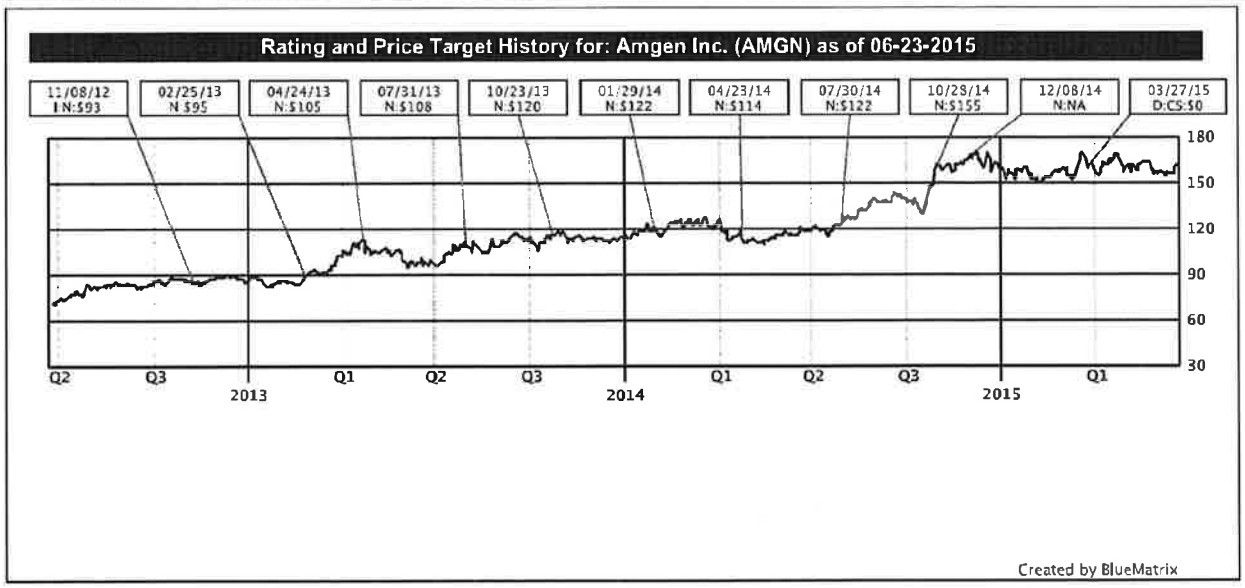

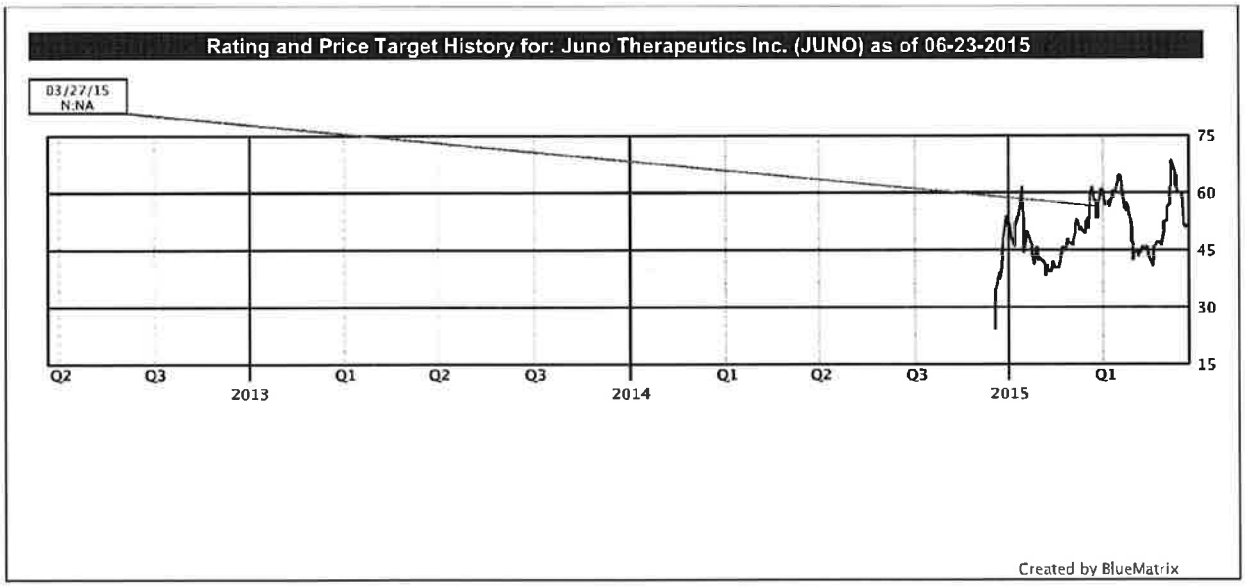

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GUGGENHEIM SECURITIES, LLC

Company Update

USA | Healthcare | Biotechnology

June 24, 2015

Jefferies

Kite Pharma (KITE)

Kite Shares Its Vision At Analyst Day

BUY
Price target $83.00
Price $62.72

EQUITY RESEARCH AMERICAS

Key Takeaway

KITE hosted an analyst day where it reiterated its clinical development plan for KTE-C19, plans to move add'l CAR/TCR targets to clinical trials, and pot'l new strategies to improve T-cell expansion and the introduction of a pot'l CAR to prevent off-target effects on healthy cells. The company is on track to disclosing topline data from the pilot trial enrolling patients with diffuse large B-cell lymphoma (DLBCL) at ASH '15.

KTE-C19 Data At ASH '15: KITE has started enrolling pts in its pilot study with KTE-C19, a CD19 CAR-T in DLBCL this quarter with pivotal trial initiating in Q4. The company acknowledged that it is testing a new lymphodepletion regimen which falls btwn the NCI regimen and the "low" dose regimen presented at ASH '14. Based on data from the pilot study, KITE could modify the lymphodepletion regimen for the pivotal studies and the add'l PII studies evaluating KTE-C19. The company will be requiring all patients in the PII trial to enroll in the hospital for the 1st 7 days after infusion as a pre-cautionary measure and a req't similar to the NCI PI/II study. We think this is a prudent measure which may help address any pot'l toxicity issue(s) that may arise in the DLBCL trial. Based on learnings from this trial, the company may reduce/eliminate this req't longer-term. Interim data from the 1st 50 patients in the pivotal trial would drive a BLA filing by YE '16. KITE expects to complete patient enrollment by YE '16. The 1 EP is ORR with data expected in 2016. KITE also plans to initiate trials in acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL) which would initiate by YE '15.

Pipeline Programs Advance: The National Cancer Institute (NCI) has currently five ongoing trials with various targets with KITE having rights to the following cancer antigen targets - NY-ESO1 and HPV-16 E6 w/ KITE anticipating on filing an IND in 1H '16. The company announced NCI plans to initiate clinical testing w/ a KRAS TCR in pancreatic/ colorectal cancer and HPV-16 E7 TCR in cervical cancer in '15. We gained further insights into these programs from NCI's Chief of Surgery Branch, Dr. Steven Rosenberg, who provided his opinions into pot'l optimal targets for solid tumors. Rosenberg believes HPV-16 E6 is de-risked given data in 9 refractory cervical cancer patients treated with TIL therapy and observing 2 CRs and 1 PR with duration of response lasting 22, 15, and 3 mos, respectively (at end of April). Dr. Rosenberg believes EGFRviii could observe activity given the target resides on the tumor cell surface and could be targeted by CAR technology. A trial is currently ongoing evaluating EGFRviii in glioblastoma and have treated 15 patients to date in a slow dose escalation. NCI has not observed any clinical responses however the trial may be somewhat premature given patients have not been treated w/ therapeutic doses. The NCI is also evaluating NY-ESO1 TCR in various tumors and 4 patients have been treated, however, Dr. Rosenberg is less sanguine about the prospects of NY-ESO1 given less than 2% of all patients express the target at less than 50%. In comparison, MAGE A3 could be a better target given it is more commonly expressed. Lastly, Dr. Rosenberg also commented on the UPenn study at AACR evaluating 6 patients w/ mesothelin CAR-T and believes mesothelin may not be an appropriate target given it also is expressed in healthy tissues.

Next Gen Technologies Focused On Improving T Cell Expansion and Preventing Off-Target Effects: KITE introduced two concepts - one focused on generating T cells utilizing pharmacological molecules which may yield younger T cells w/ greater persistence. We think this technology is based on NCI research which focused on Akt inhibition (Crompton et al, Cancer Research 2015) leading to enhanced cell persistence of memory T cells. KITE is also developing a control CAR which at the presence of a healthy cell could signal the self-destruction of the CAR-T cell.

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Company Description

Kite Pharma, Inc. operates as a clinical stage biotechnology company which engages in the development of novel cancer immunotherapeutic products with focus on engineered autologous T cell therapeutics targeted to different tumor types. In addition, the company is advancing a novel therapeutic cancer vaccine aimed to trigger potent and specific immunity against multiple epithelial cancers, which has the potential to complement its eACT programs.

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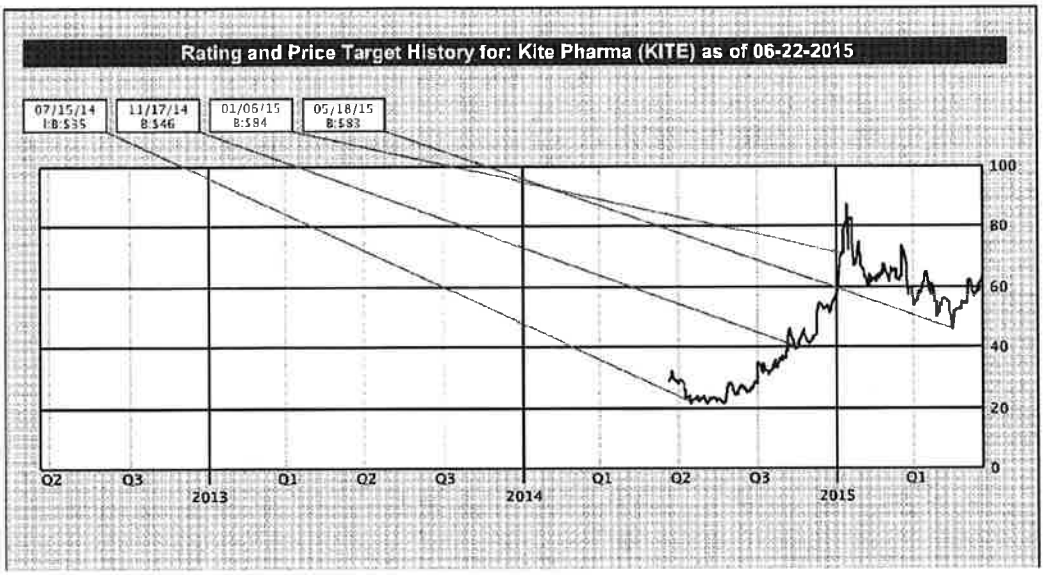

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Rating	Count	Percent	IB Serv./Past 12 Mos. Count	Percent
BUY	1087	52.16%	299	27.51%
HOLD	832	39.92%	161	19.35%
UNDERPERFORM	165	7.92%	13	7.88%

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Jefferies

Kite Pharma, Inc.

Investor Day— Under the Hood; No Near-Term Changes

Summary

We are reiterating our Buy rating and $90 PT following KITE's first Investor Day. While there were no clinical data updates or significant announcements, we gained 1) a deeper understanding of the platform and 2) a frank KOL discussion into the future of cancer immunotherapy. Industry collaborations and close academic ties put KITE in a strong position as therapy moves out of lymphoma. "Off-the-shelf" approaches were downplayed, as was the importance of defined-cell populations and long-term persistence, contrasting with some competitors. Catalysts remain 4Q data (ASH) and 2016 readouts.

Key Points

- **Manufacturing techniques to keep cells less differentiated.** KITE is focusing development on new processes and pharmacologic agents that block differentiation and keep a more youthful cell phenotype, which appears to be needed for efficacy. An overview of KITE's TCR GENErator platform technology was provided, which could give KITE a competitive advantage in TCR development. A new commercial manufacturing facility under construction will be ready for a commercial launch of KTE-C19 by 2017, and support 4,000-5,000 doses per year.

- **Catalysts were broadly reiterated.** Key upcoming catalysts are 1) KTE-C19 Phase I NHL data at ASH year-end, and Phase II pivotal data in 2016, 2) initiation of MCL, ALL and CLL pivotal trials in 2H15, and 3) HPV-16 E6 TCR IND submission in 1H16, followed by KTE-C19 BLA filing by YE 2016.

- **Defined-cell populations and long-term persistence were downplayed.** In contrast to competitors that have focused on defined-cell populations as an important aspect of manufacturing, KITE appears to be playing down the importance at this stage. Regarding persistence of CAR T-cells, panelists at the meeting thought that the current evidence points to needing the CAR to persist for only a couple of weeks to a month in order to produce effective treatment, which downplays the need to substantially improve persistence.

- **Panel members see combo therapy as an eventuality.** The panel expects that CAR and TCR will evolve into an integral part of combination therapy. Dr. Steven Rosenberg, Chief of Surgery at NCI and a key collaborator, had a substantial part of his talk and comments focused on increasing the personalization of CARs. The panel was negative on off-the-shelf approaches to CAR therapy, which would be a negative for companies like CLLS (Not Rated, $36.54) and ZIOP (Neutral-rated).

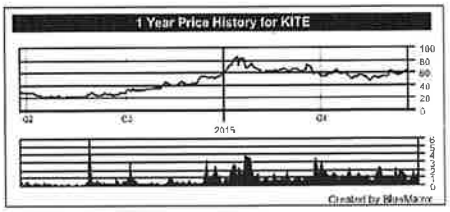
Rating	**Buy**
Previous Rating	No Change
Price (6/23)	**$62.72**
Price Target	**$90.00**
Previous Price Target	No Change

Key Data

Symbol	KITE (NASDAQ)
52-Week Range	$89.21 - $21.00
Market Cap ($mm)	$2,701
Shares Outstanding (mm)	43.1
Float	27.7
Average Daily Volume	1,268,003
Dividend per Share ($)	NA

Fiscal Year-End: Dec 31

	2014A	2015E Prior	2015E Curr	2016E Prior	2016E Curr
Revenue ($mm)					
1Q	0.0A	–	2.9A	–	–
2Q	0.0A	–	2.9E	–	–
3Q	0.0A	–	2.9E	–	–
4Q	0.0A	–	2.9E	–	–
Yr	**0.0A**	–	**11.5E**	–	**34.9E**
P/ Revenue	NM	–	NM	–	77.4x
Earnings per Share ($) Non-GAAP					
1Q	(0.60)A	–	(0.36)A	–	–
2Q	(1.41)A	–	(0.50)E	–	–
3Q	(0.24)A	–	(0.60)E	–	–
4Q	(0.33)A	–	(0.70)E	–	–
Yr	**(1.60)A**	–	**(2.16)E**	–	**(2.52)E**
P/E	NM	–	NM	–	NM



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Manufacturing Techniques to Keep Cell Products Less Differentiated, and TCR Development

CSO Margo Roberts, who received a patent on a second generation CAR in 1995, presented a look at KITE's design approach for CAR's, which can be as quick as 18 months from the initial design of the single chain variable fragment (scFv) that targets the CAR to the tumor, to IND filing. While using precisely defined cell populations were less of a concern for KITE, having a T cell population that was in general composed of less differentiated, more "youthful" T cells that drive proliferation (more stem cell memory and central memory cells) was important. KITE is focusing development on new processes and pharmacologic agents that block differentiation and keep a more youthful cell phenotype.

KITE's European CSO, Ton Schumacher, presented an overview of TCR development, which has been overshadowed by CAR development but could target 2x-3x more antigens. In particular was an overview of the TCR GENErator platform technology acquired with KITE's acquisition of T-Cell Factory B.V. in March. The platform, which could provide KITE with an advantage in TCR development, enables high-throughput generation of peptide-MHC (pMHC) complexes that are used to select the most promising TCRs for development.

Manufacturing and Scale Always a Concern

KITE is actively investing in developing both capacity and manufacturing protocols. KITE's new commercial manufacturing facility, under construction now, will be ready for a commercial launch of KTE-C19 in 2017, and support 4,000-5,000 doses per year.

Catalysts Broadly Reiterated

HPV-16 E6 TCR will be next product for IND submission, in 1H16, and the expanded NCI CRADA announced in March will include KRAS, a colorectal cancer target (93,000 new cases per year in the U.S.). Key upcoming catalysts are 1) lead program KTE-C19 Phase I NHL data at ASH year-end, and Phase II pivotal data in 2016, 2) initiation of MCL, ALL and CLL pivotal trials in 2H15, and 3) HPV-16 E6 TCR IND submission in 1H16, followed by KTE-C19 BLA filing and IND filings from the AMGN (Not Rated, $161.69) collaboration by YE 2016.

Importance of Defined-cell Populations and Long-term Persistence Downplayed

In contrast to competitors like JUNO (Not Rated, $51.40) that have focused on defined-cell populations as an important aspect of CAR and TCR manufacturing, KITE appears to be playing down its importance at this stage from both a clinical efficacy and manufacturing perspective (as was shown in ASCO data), though has not ruled it out entirely as a factor.

Regarding persistence of CAR T-cells, panelists at the meeting thought that the current evidence points to needing the CAR to persist for only a couple of weeks to a month in order to produce effective treatment, which downplays the need to substantially improve persistence. As far as CAR design, substantial, basic work still needs to be done across the industry- for instance, there has not been a robust study yet on the best co-stimulatory domain to use.

Limited Insight into New bluebird bio Collaboration

We know the BLUE (Not Rated, $174.31) collaboration will focus on a next-gen HPV-16 E6 TCR, which is likely 2-3 years away. The collaboration could also enable editing of T-cells to be more resilient in the tumor micro-environment, a key obstacle to overcome to improve solid tumor efficacy. The negative reaction to mesothelin solid-tumor data from UPenn appeared to be largely anticipated by the experts, who had a history of working with the target and didn't believe it would be among the promising targets.

Panel Members See Combo therapy as an Eventuality

The panel expects that CAR and TCR will evolve into an integral part of combination therapy, such as combining with checkpoint inhibitors, or developing effective sequencing of different therapies which will include CARs. Dr. Steven Rosenberg, Chief of Surgery at NCI and a key collaborator, had a substantial part of his talk and comments focused on increasing the personalization of treatment, with the use of tumor neoantigens especially prominent- for instance, exomic sequencing of the tumor and identification of integral antigens, followed by development of a personalized CAR, all within the span of a couple of weeks. The panel was negative on off-the-shelf approaches to CAR therapy, which would be a negative for companies like CLLS (Not Rated, $36.54) and ZIOP (Neutral-rated) that are making allogenic, off-the-shelf development more of a focus.

KITE Catalysts and Milestones

Candidate	Setting	Trial / Milestone	Time
KTE-C19	DLBCL, PMBCL, TFL	KITE-sponsored P1 data	ASH 2015
KTE-C19	DLBCL, PMBCL, TFL	KTE-C19-101 study P1 safety analysis- After 50 patients; Study details: n=72 DLBCL, n=40 PBMCL, FL; refractory disease, ORR primary endpoint, 25 centers; Conditioning therapy (fludarabine and cyclophosphamide) followed by single CAR transfusion @ 2x10^6 cells/kg)	Early 2016
KTE-C19	DLBCL, PMBCL, TFL	Complete P1/2 enrollment	1H 2016
KTE-C19	DLBCL, PMBCL, TFL	Initial P2 data	2016
KTE-C19	DLBCL, PMBCL, TFL	BLA filing	YE 2016
KTE-C19	DLBCL, PMBCL, TFL	Initiate P3- Confirmatory trial for accelerated approval	2016
KTE-C19	R/R/ MCL	Initiate P2 KTE-C19-102, n=70, ORR primary endpoint	2H 2015
KTE-C19	R/R CLL	Initiate P2 trial	2H 2015
KTE-C19	R/R ALL	Initiate P2 KTE-C19-103 trial, n=50, CR primary endpoint	2H 2015
anti-CD19 (NCI)	R/R B cell lymphomas and leukemias	NCI update	2015
EGFRvIII CAR	Glioblastoma	P1 data	2H 2015
NY-ESO-1 TCR	Solid tumors	Phase II data - NCI-sponsored- murine TCR	2015
NY-ESO-1 TCR	Solid tumors	Submit IND	Late 2015
EGFRvIII CAR	Glioblastoma	Submit IND	2016
MAGE A3	MAGE-A3 expressing tumors	P1/2 data - NCI trial	2015
SSX2 TCR	SSX2-expressing tumors	Initiate P1/2 NCI trial	2015
HPV-16 E6 TCR	Cervical, head & neck	IND sumbission	1H 2016
HPV-16 E6 TCR	Cervical, head & neck	P1/2 data - NCI trial	2015
KRAS TCR	Colorectal	Submit IND	2016
NA	NA	KITE/AMGN CAR IND submissions	2H 2016

Source: Company reports and Mizuho Securities USA, Inc.

Kite Pharma
Annual Income Statement

($ in millions, except per share data)

FY-ending Dec 31,	2012	2013	2014	2015E	2016E	2017E	2018E
Revenue							
KTE-C19 Product revenue	$ -	$ -	$ -	$ -	$ 23.3	$ 202.9	$ 482.3
KTE-C19 Royalty revenue	$ -	$ -	$ -	$ -	$ -	$ -	$ 3.7
Collaboration revenue	$ -	$ -	$ -	$ 11.5	$ 11.5	$ 11.5	$ 11.5
Total Revenue	$ 0.0	$ 0.0	$ 0.0	$ 11.5	$ 34.9	$ 214.5	$ 497.5
Cost of Sales	$ -	$ -	$ -	$ -	$ 15.2	$ 101.5	$ 192.9
Gross Profit	$ 0.0	$ 0.0	$ 0.0	$ 11.5	$ 19.7	$ 113.0	$ 304.6
Gross Margin	—	—	—	*100.0%*	*56.5%*	*52.7%*	*61.2%*
Operating Expenses							
Research and Development	$ 1.8	$ 5.1	$ 23.1	$ 59.8	$ 77.8	$ 85.6	$ 89.8
SG&A	0.8	1.3	$ 13.6	48.7	58.7	78.7	88.7
Total Operating Expenses	**2.6**	**6.4**	**36.7**	**108.5**	**136.5**	**164.3**	**178.5**
Operating Income	$ (2.6)	$ (6.4)	$ (36.7)	$ (97.0)	$ (116.8)	$ (51.3)	$ 126.1
Net Interest & Other	0.0	0.1	0.2	1.9	1.0	1.0	1.0
Pretax Income	$ (2.6)	$ (6.4)	$ (36.5)	$ (95.1)	$ (115.8)	$ (50.3)	$ 127.1
Income Tax Expense	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 44.5
Tax Rate	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*35.0%*
Net Income (Operating)	$ (2.6)	$ (6.4)	$ (36.5)	$ (95.1)	$ (115.8)	$ (50.3)	$ 82.6
Extra. & Amortization	0.0	(1.4)	(7.2)	0.0	0.0	0.0	0.0
Net Income (GAAP)	$ (2.6)	$ (7.8)	$ (43.7)	$ (95.1)	$ (115.8)	$ (50.3)	$ 82.6
Adjusted EPS	**($0.07)**	**($1.16)**	**($1.60)**	**($2.16)**	**($2.52)**	**($1.04)**	**$1.64**
Diluted GAAP EPS	($0.07)	($1.43)	($1.91)	($2.16)	($2.52)	($1.04)	$1.64
Diluted Shares Outstanding	38.4	5.5	22.8	44.0	46.0	48.1	50.3

Source: Company Reports and Mizuho Securities USA Inc. estimates

($ in millions, except per share data)

FY-ending Dec 31,	2013				2014				2015E			
	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2QE	3QE	4QE
Revenue												
KTE-C19 Product revenue												
KTE-C19 Royalty revenue												
Collaboration revenue									$ 2.9	$ 2.9	$ 2.9	$ 2.9
Total Revenue	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 2.9	$ 2.9	$ 2.9	$ 2.9
Cost of Sales	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0
Gross Profit	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 2.9	$ 2.9	$ 2.9	$ 2.9
Gross Margin	—	—	—	—	—	—	—	—	*100.0%*	*100.0%*	*100.0%*	*100.0%*
Operating Expenses												
Research and Development	$ 0.9	$ 1.1	$ 1.2	$ 1.9	$ 2.1	$ 7.4	$ 5.7	$ 7.9	$ 9.3	$ 13.9	$ 16.9	$ 19.9
SG&A	0.2	0.3	0.3	0.5	1.1	3.7	3.4	5.4	9.2	11.2	13.2	15.2
Total Operating Expenses	$ 1.1	$ 1.4	$ 1.5	$ 2.4	$ 3.2	$ 11.1	$ 9.1	$ 13.3	$ 18.4	$ 25.0	$ 30.0	$ 35.0
Operating Income	$ (1.1)	$ (1.4)	$ (1.5)	$ (2.4)	$ (3.2)	$ (11.1)	$ (9.1)	$ (13.3)	$ (15.6)	$ (22.2)	$ (27.2)	$ (32.2)
Net Interest & Other	0.0	(0.0)	0.0	0.0	(0.1)	0.0	0.1	0.2	0.5	0.5	0.5	0.5
Pretax Income	(1.1)	(1.4)	(1.5)	(2.4)	(3.3)	(11.1)	(9.1)	(13.0)	(15.1)	(21.7)	(26.7)	$ (31.7)
Income Tax Expense	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0
Tax Rate	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
Net Income (Operating)	$ (1.1)	$ (1.4)	$ (1.5)	$ (2.4)	$ (3.3)	$ (11.1)	$ (9.1)	$ (13.0)	$ (15.1)	$ (21.7)	$ (26.7)	$ (31.7)
Extra. & Amortization	(0.0)	(0.3)	(0.6)	(0.6)	(6.6)	(0.5)	(0.1)	0.0	0.0	0.0	0.0	0.0
Net Income (GAAP)	(1.1)	(1.7)	(2.1)	$ (2.9)	$ (9.9)	$ (11.6)	$ (9.2)	$ (13.0)	$ (15.1)	$ (21.7)	$ (26.7)	$ (31.7)
Adjusted EPS	($0.19)	($0.26)	($0.27)	($0.43)	($0.60)	($1.41)	($0.24)	($0.33)	($0.36)	($0.50)	($0.60)	($0.70)
Diluted GAAP EPS	($0.20)	($0.32)	($0.37)	($0.54)	($1.79)	($1.47)	($0.24)	($0.33)	($0.36)	($0.50)	($0.60)	($0.70)
Diluted Shares Outstanding	5.5	5.5	5.5	5.5	5.5	7.9	38.3	39.0	42.5	43.5	44.5	45.5

Source: Company Reports and Mizuho Securities USA Inc. estimates

Kite Pharma
Annual Cash Flow Statement

($ in millions, except per share data)

FY-ending Dec 31,	2012	2013	2014	2015E	2016E	2017E	2018E
Operating Activities							
Net Income	$ (2.6)	$ (7.8)	$ (36.5)	$ (95.1)	$ (115.8)	$ (50.3)	$ 82.6
Depreciation & Amortization	0.0	0.0	0.2	2.0	4.0	6.0	8.0
Working Capital	(0.3)	0.6	3.4	(0.4)	(10.1)	(12.0)	(14.2)
Other	0.1	1.5	(8.5)	60.0	0.0	0.0	0.0
Net Cash from Operations	**$ (2.8)**	**$ (5.6)**	**$ (41.3)**	**$ (33.5)**	**$ (121.9)**	**$ (56.3)**	**$ 76.4**
Investing Activities							
Acquisitions, net	$ 0.0	$ 0.0	$ 0.0	$ (20.0)	$ 0.0	$ 0.0	$ 0.0
Capital Expenditures	(0.0)	(0.3)	(2.0)	(20.0)	(20.0)	(10.0)	(10.0)
Other	0.0	0.0	(116.5)	0.0	0.0	150.0	0.0
Net Cash from Investing	**$ (0.0)**	**$ (0.3)**	**$ (118.5)**	**$ (40.0)**	**$ (20.0)**	**$ 140.0**	**$ (10.0)**
Financing Activities							
Issuance / Reduction of Debt	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0
Issuance of Common Stock	0.0	19.6	379.6	16.0	0.0	10.0	10.0
Dividends	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Other	0.3	0.0	(32.8)	0.0	0.0	0.0	0.0
Net Cash from Financing	**$ 0.3**	**$ 19.6**	**$ 346.8**	**$ 16.0**	**$ -**	**$ 10.0**	**$ 10.0**
Net Exchange rate effect	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Net Change in Cash	**$ (2.5)**	**$ 13.7**	**$ 187.0**	**$ (57.5)**	**$ (141.9)**	**$ 93.7**	**$ 76.4**
Cash from Prior Period	11.2	8.7	22.3	209.3	151.8	9.8	103.6
Net Cash	**$ 8.7**	**$ 22.3**	**$ 209.3**	**$ 151.8**	**$ 9.8**	**$ 103.6**	**$ 180.0**
Cash Flow	**$ (2.6)**	**$ (6.3)**	**$ (36.2)**	**$ (93.1)**	**$ (111.8)**	**$ (44.3)**	**$ 90.6**
Cash Flow Per Share	($0.07)	($1.16)	($1.59)	($2.12)	($2.43)	($0.92)	$1.80
EBITDA	**$ (2.6)**	**$ (6.4)**	**$ (36.4)**	**$ (95.0)**	**$ (112.8)**	**$ (45.3)**	**$ 134.1**
EBITDA per Share	($0.07)	($1.17)	($1.60)	($2.16)	($2.45)	($0.94)	$2.67
Free Cash Flow	**$ (2.8)**	**$ (6.0)**	**$ (34.8)**	**$ (113.5)**	**$ (141.9)**	**$ (66.3)**	**$ 66.4**
Free Cash Per Share	($0.07)	($1.10)	($1.53)	($2.58)	($3.09)	($1.38)	$1.32

Source: Company Reports and Mizuho Securities USA Inc. estimates

Kite Pharma
Annual Balance Sheet

($ in millions, except per share data)

FY-ending Dec 31,	2012	2013	2014	2015E	2016E	2017E	2018E
Assets							
Current Assets:							
Cash + Equivalents + ST inv	$ 160.0	$ 22.4	$ 367.1	$ 347.0	$ 205.0	$ 148.7	$ 225.2
Receivables - net	1.8	0.0	0.0	0.0	1.7	10.7	24.9
Inventories	0.0	0.0	0.0	0.0	1.5	10.1	19.3
Other	0.8	0.2	1.3	6.4	6.4	6.4	6.4
Total Current Assets	**$ 162.7**	**$ 22.6**	**$ 368.4**	**$ 353.4**	**$ 214.7**	**$ 176.0**	**$ 275.8**
PP & E, net	$ 2.1	$ 0.3	$ 2.3	$ 17.8	$ 33.8	$ 37.8	$ 39.8
Goodwill	0.0	0.0	0.0	39.9	39.9	39.9	39.9
Other Assets	0.8	0.1	0.1	11.5	11.5	11.5	11.5
Total Assets	**$ 165.5**	**$ 23.0**	**$ 370.8**	**$ 422.6**	**$ 299.9**	**$ 265.3**	**$ 367.0**
Liabilities and Shareholders' Equity							
Current Liabilities:							
Current Debt	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0
Accounts Payable	3.0	0.4	6.7	11.4	4.6	10.1	19.3
Accruals & Other	32.5	1.0	0.0	45.4	45.4	45.4	45.4
Total Current Liabs.	**$ 35.5**	**$ 1.4**	**$ 6.7**	**$ 56.9**	**$ 50.0**	**$ 55.6**	**$ 64.7**
Long-Term Debt	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0
Other Liabilities	43.0	0.0	1.4	39.0	27.4	15.8	4.2
Stockholders Equity	17.9	21.6	362.6	326.8	222.6	193.9	298.1
Total Liabs. & Equity	**$ 96.4**	**$ 23.0**	**$ 370.8**	**$ 422.6**	**$ 299.9**	**$ 265.3**	**$ 367.0**

Kite Pharma
Ratio Analysis

FY-ending Dec 31,	2012	2013	2014	2015E	2016E	2017E	2018E
Book Value per share	$0.47	$3.94	$15.89	$7.43	$4.84	$4.03	$5.93
Cash per share	$4.17	$4.08	$16.08	$7.89	$4.46	$3.09	$4.48
Net Cash per share	$4.17	$4.08	$16.08	$7.89	$4.46	$3.09	$4.48
Current Ratio	4.6	16.6	54.8	6.2	4.3	3.2	4.3
Total Debt / Equity	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Total Debt / Total Capital	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Source: Company Reports and Mizuho Securities USA Inc. estimates

Price Target Calculation and Key Risks

We derive our price target by applying both a discounted cash flow analysis and discounted P/E analysis to yield a price target of $90. Risks to our price target outside of clinical failure relate to 1) platform risk, 2) competitive risk and 3) commercialization risk.

Companies Mentioned (prices as of 6/23)
Amgen Inc (AMGN- Not Rated)
ZIOPHARM Oncology, Inc. (ZIOP- Neutral $11.79)

IMPORTANT DISCLOSURES

The disclosures for the subject companies of this report as well as the disclosures for Mizuho Securities USA Inc. entire coverage universe can be found at https://msusa.bluematrix.com/sellside/Disclosures.action or obtained by contacting EQSupervisoryAnalystUS@us.mizuho-sc.com or via postal mail at Equity Research Editorial Department, Mizuho Securities USA Inc., 320 Park Avenue, 12th Floor, New York NY, 10022.

Ownership Disclosures and Material Conflicts of Interest or Position as Officer or Director

None

Receipt of Compensation

Mizuho Securities USA Inc. and or its affiliates makes a market in the following securities: Kite Pharma, Inc., Amgen Inc and ZIOPHARM Oncology, Inc.

Mizuho Securities USA Inc. and or its affiliates has received compensation for investment banking services for Amgen Inc and ZIOPHARM Oncology, Inc. in the past 12 months.

Mizuho Securities USA Inc. and or its affiliates expects to receive or intends to seek compensation for investment banking services for Amgen Inc in the next 3 months.

Mizuho Securities USA Inc. and or its affiliates has managed or co-managed a public offering of securities for Amgen Inc and ZIOPHARM Oncology, Inc. in the past 12 months.
The compensation of the research analyst writing this report, in whole or part, is based on MSUSA's annual revenue and earnings and is not directly related to any specific investment banking compensation. MSUSA's internal policies and procedures prohibit research analysts from receiving compensation from companies covered in the research reports.

Regulation Analyst Certification (AC)

I, Peter Lawson, hereby certify that the views expressed in this research report accurately reflect my personal views about any and all the subject companies. No part of my compensation was, is or will be, directly or indirectly, related to the specific recommendations or views expressed in this research report.

Rating Definitions

As of October 3, 2011

Mizuho Securities USA investment ratings are based on the following definitions. Anticipated share price change is based on a 6- to 12-month time frame. Return expectation excludes dividends.

Buy:	Stocks for which the anticipated share price appreciation exceeds 10%.
Neutral:	Stocks for which the anticipated share price appreciation is within 10% of the share price.
Underperform:	Stocks for which the anticipated share price falls by 10% or more.
RS:	Rating Suspended - rating and price objective temporarily suspended.
NR:	No Rating - not covered, and therefore not assigned a rating.

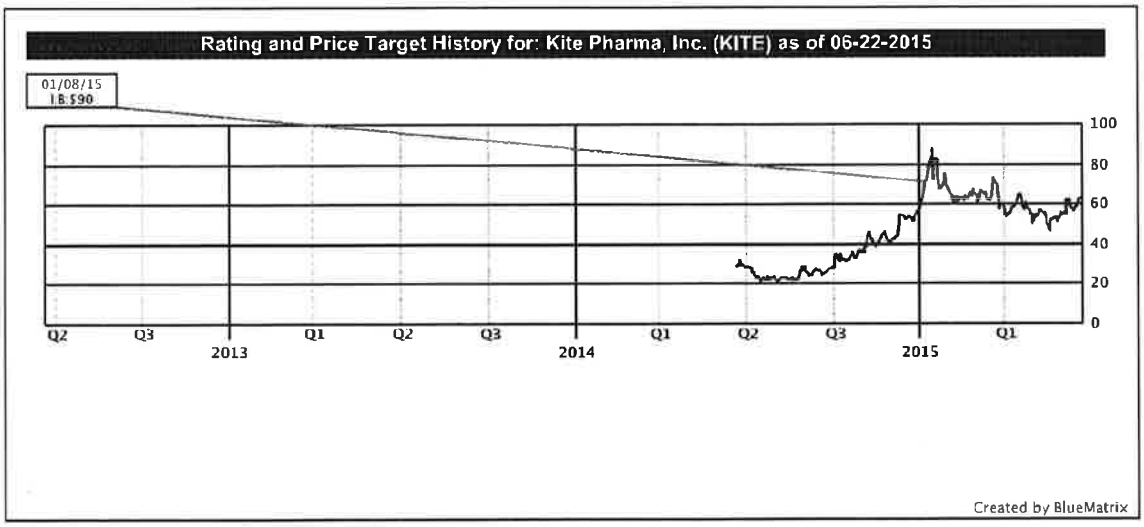
Prior to October 3, 2011

Buy:	Estimated stock price appreciation of 20% or more.
Outperform:	Outperform the stock market averages by 12% or more.
Neutral:	Perform in line with the stock market averages (Hold).
Underperform:	Underperform the stock market averages by 12% or more.
Sell:	Estimated stock price decline of 20% or more.

Rating Distribution

(As of 6/23)	% of coverage	IB service past 12 mo
Buy (Buy)	53.70%	35.63%
Hold (Neutral)	45.06%	19.18%
Sell (Underperform)	1.23%	0.00%

For disclosure purposes only (NYSE and FINRA ratings distribution requirements), our Buy, Neutral and Underperform ratings are displayed as Buy, Hold and Sell, respectively. However, our Buy, Neutral and Underperform ratings are determined on a relative basis (please refer to definitions above).


Rating and Price Target History for: Kite Pharma, Inc. (KITE) as of 06-22-2015
01/08/15
I:B:$90
100
80
60
40
20
0
Q2
Q3
2013
Q1
Q2
Q3
2014
Q1
Q2
Q3
2015
Q1
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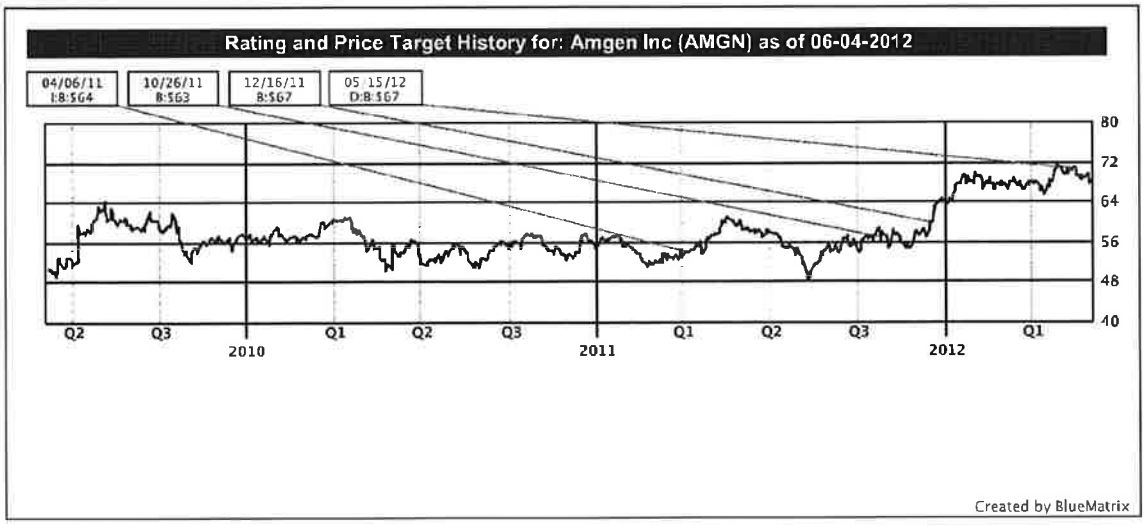
Rating and Price Target History for: Amgen Inc (AMGN) as of 06-04-2012
04/06/11
I:B:$64
10/26/11
B:$63
12/16/11
B:$67
05/15/12
D:B:$67
80
72
64
56
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Q3
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Q2
Q3
2011
Q1
Q2
Q3
2012
Q1
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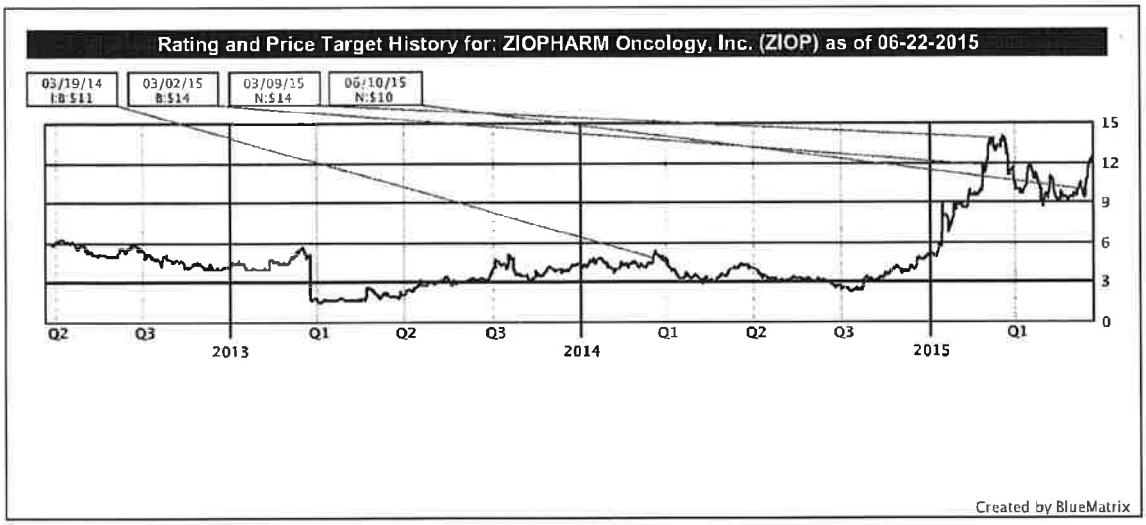
Rating and Price Target History for: ZIOPHARM Oncology, Inc. (ZIOP) as of 06-22-2015
03/19/14
I:B:$11
03/02/15
B:$14
03/09/15
N:$14
06/10/15
N:$10
15
12
9
6
3
0
Q2
Q3
2013
Q1
Q2
Q3
2014
Q1
Q2
Q3
2015
Q1
Created by BlueMatrix

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One Year Price Chart

June 23, 2015

Kite Pharma, Inc.
KITE – NASDAQ
Buy
Biotechnology

Company Update

Kite Investor Day Update and Bluebird Bio Collaboration

This afternoon we attended Kite Pharma's Investor Day where management provided a corporate overview and the company's key collaborator at the NCI (Steven Rosenberg) gave an overview of the field that hinted at some potentially earthshaking data to come (see below). Kite's recent collaboration with Bluebird was reviewed and looks like a high-level hand-holding exercise as both companies look to enter new areas without wasting time. As expected, the next IND will involve TCRs targeting HPV proteins which are increasingly being viewed as the best TCR target outside of neoantigens.

Changes	Previous	Current
Rating	—	Buy
Target Price	—	$83.00
FY15E EPS	—	$(1.49)
FY16E EPS	—	$0.02

Price (06/23/15):	$62.72
52-Week Range:	$89 – $21
Market Cap.(mm):	2,665.6
Shr O/S-Diluted (mm):	42.5
Avg Daily Vol (3 Mo):	1,268,003
Net Cash/Share:	$5.31
Cash (mm):	$203
Debt (mm):	$0.0
Dividend($ / %)	$0.00 / 0.0%
S&P Index	2,124.20

EPS	2014A	2015E	2016E
Q1	$(0.56)	$(0.36)A	$NE
Q2	(2.27)	(0.35)	NE
Q3	(0.24)	(0.38)	NE
Q4	(0.33)	(0.40)	NE
FY Dec	$(1.91)A	$(1.49)	$0.02

Quarterly EPS do not sum to annual due to the issuance of shares.

Rosenberg's Next Miracle? Steven Rosenberg delivered principally an overview of the field but also showed a slide of some patients where **his group at the NCI has isolated both neoantigens and their recognizing TCRs** from tumors other than melanoma – specifically gastrointestinal cancers. As a result, we expect he has treated these patients with TCR therapeutics and early data can't be far away (SR has been mentioning this program since ASH). We believe if these data are compelling and CRs are seen for neoantigen-based TCR therapeutics it will be viewed as a major proof-of-concept for Kite's focus on the neoantigen approach in solid tumors. As we have said in previous notes – the operational hurdles for this approach to treating solid tumors are non-trivial – but the approach puts cure on the table for as many as 50% of patients with solid tumors.

The Bluebird Collaboration. The two companies yesterday announced a collaboration agreement to co-develop second generation TCR products, specifically product candidates directed against the HPV-16 E6 oncoprotein. With Bluebird being a gene-editing focused company and Kite specializing in T-Cell therapeutics, the two will leverage each other's strengths to design next-generation T-Cell therapeutics. Kite is almost certainly looking to modify TCR therapeutics to combat the immunosuppressive tumor environment. As a result, we expect they are knocking out some of the receptors found on T-Cells that tumors use to put tumor-hunting TCRs to sleep. As reported at ASCO 2015, KTE019 T-Cells begin to express PD-1 after introduction into patients and tumor cells are expected to express PD-L1 and the resultant interaction potentially reduces efficacy. As a result, knocking out PD-1 in TCR (and CAR-T) therapeutics seems like an obvious things to try. The subsequent list of candidate genes to delete to stimulate TCR therapeutics is very long – probably spurring Kite's urge to find an expert partner.

Next IND – HPV. As was probably expected, Kite's second IND submission will be a TCR therapeutic targeting Human papillomavirus (HPV, a first generation

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Stifel Equity Trading Desk (800) 424-8870

approach outside the Bluebird deal). This is a large market opportunity as HPV is the most common viral infection of the reproduction tract, with two viral strains, type 16 & type 18, believed to cause 70% of cervical cancers and a significant percentage of head and neck cancers. In addition, HPV antigens are expected to be very clan as normal cells are not expected to express this target – by definition. Furthermore, HPV antigens are considered excellent targets due to their expression on "essentially every cell" of a tumor. All in all – we view this program very favorably and view it as a second example of our theme that Kite is very close to showing the world definitively that T-Cell therapeutics will treat a lot more than pediatric leukemias.

Target Price Methodology/Risks

We use a multiple of future earnings to derive our $83 target price for KITE. Specifically, to generate our valuation for development-stage biotech companies, we use a 30x multiple of future earnings, which represents a discount to the 20-year average earnings multiple for profitable biotech companies of 37x. Kite's valuation is driven primarily by KTE-C19, currently in Phase I/IIa testing. We apply a 25% discount rate, which we feel reflects the degree of uncertainty surrounding KTE-C19. With a multiple of 30x, we calculate a $83 target price based on our 2022 diluted EPS estimate of $15.92, discounted back 7.5 years.

Development risk for KTE-C19 - If Kite is not able to successfully develop the experimental CAR-T technology, we would have to lower our revenue estimates.

Competitive risk for KTE-C19 - If a competitor proves more effective or tolerable in the treatment of DLBCL, or their drugs are easier to produce, our estimates could prove optimistic.

Regulatory risk for KTE-C19 - The FDA has never approved a CAR-T-based therapy before and there exists no precedent for the approval of a genetically engineered autologous cell product. If KTE-C19 is not approved on the timeline that we envision, we would have to reduce our estimates.

Company Description

Kite Pharma, Inc. is a clinical-stage biopharmaceutical company focused on the development and commercialization of novel cancer immunotherapy products designed to harness the power of a patient's own immune system to eradicate cancer cells. To achieve this, Kite is developing a pipeline of product candidates for the treatment of advanced solid and hematological malignancies using the engineered autologous cell therapy system, in which a patient's own immune system is engineered to recognize and destroy their cancer. Kite's products use engineered chimeric antigen receptor T-cells (CAR-T) or T-cell receptors (TCRs). Kite's technology has been developed through a collaboration agreement with the NCI-Surgery Branch. Kite's most advanced product is KTE-C19, a CAR-T therapy that recognized CD19 and will be developed for diffuse large B-cell lymphoma.

Stifel

Tom Shrader 212.271.3577

Kite Pharma (KITE)

Income Statement

(In $Millions, except for per share data)

	2012	2013	2014A	1QA	2QE	3QE	4QE	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E
KTE-C19 U.S. end user sales (a)											$ 34.0	$ 489.3	$ 1,470.8	$ 2,209.9	$ 2,832.5
KTE-C19 Ex-U.S. end user sales (a)											$ -	$ 77.2	$ 691.0	$ 1,661.2	$ 2,245.2
WW KTE-C19 End-user sales											**$ 34.0**	**$ 566.5**	**$ 2,161.9**	**$ 3,871.1**	**$ 5,077.8**
KTE-C19 Ex-U.S. royalty to Kite (b)											$ -	$ 8.8	$ 84.6	$ 214.6	$ 325.3
Milestones and licensing revenue			$ -	2.8	4.0	4.0	4.0	$ 14.8	$ 120.0	$ 26.2	$ 5.2	$ 5.3	$ 5.5	$ 5.6	$ 5.8
Total revenue	-	-	-	2.8	4.0	4.0	4.0	**14.8**	**120.0**	**26.2**	**39.1**	**503.4**	**1,560.9**	**2,430.1**	**3,163.7**
Research & development	1.8	5.1	23.1	9.3	9.8	10.3	10.8	40.1	76.2	114.2	171.4	201.3	312.2	401.6	506.2
SG&A	0.8	1.3	13.6	9.1	9.6	10.0	10.5	39.2	43.1	107.9	334.4	176.2	312.2	413.1	537.8
Total operating expenses	2.6	6.4	36.7	18.4	19.3	20.3	21.3	79.3	119.3	222.1	517.3	539.0	1,095.0	1,521.9	1,922.1
Income (loss) from operations	(2.6)	(6.4)	(36.7)	(15.6)	(15.3)	(16.3)	(17.3)	(64.5)	0.7	(195.9)	(478.1)	(35.6)	465.9	908.3	1,241.6
Total other income (expense)	0.0	0.1	(5.9)	0.2	0.2	0.2	0.2	1.0	0.2	0.2	0.2	0.3	0.7	1.3	2.2
Income (loss) before income taxes	(2.6)	(6.4)	(42.6)	(15.4)	(15.1)	(16.0)	(17.3)	(63.8)	0.9	(195.7)	(478.0)	(35.3)	466.5	909.6	1,243.8
Provision for income taxes	-	-	-	-	-	-	-	-	-	-	-	-	(70.0)	(227.4)	(373.1)
Net income (loss)	(2.6)	(6.4)	(43.7)	(15.4)	(15.1)	(16.0)	(17.3)	(63.8)	0.9	(195.7)	(478.0)	(35.3)	396.5	682.2	870.6
Stick Dividend (Series A)			(0.5)					-							
EPS (basic)	**(0.48)**	**(1.16)**	**$ (1.91)**	**(0.36)**	**(0.35)**	**(0.38)**	**(0.40)**	**$ (1.49)**	**$ 0.02**	**$ (3.94)**	**$ (9.55)**	**$ (0.70)**	**$ 7.81**	**$ 13.35**	**$ 16.93**
EPS (diluted)	**(0.48)**	**$ (1.16)**	**$ (1.91)**	**(0.36)**	**(0.35)**	**(0.38)**	**(0.40)**	**$ (1.49)**	**$ 0.02**	**$ (3.80)**	**$ (9.17)**	**$ (0.67)**	**$ 7.43**	**$ 12.62**	**$ 15.92**
Basic shares	5.3	5.5	22.8	42.5	42.6	42.8	42.9	42.7	49.4	49.7	50.1	50.4	50.8	51.1	51.4
Diluted shares	5.3	5.5	22.8	42.5	42.6	42.8	42.9	42.7	50.8	51.5	52.1	52.8	53.4	54.0	54.7
Cash															
Long-term debt															
Margin Analysis															
COGS (% of sales)		NM	NM	NM	NM	NM	NM	NM	NM	NM	34%	33%	32%	32%	31%
R&D (% of total revenue)		NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	40%	20%	17%	16%
SG&A (% of total revenue)		NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	35%	20%	17%	17%
Effective Tax Rate		NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	15%	25%	30%
Gross Margin		NM	NM	NM	NM	NM	NM	100%	NM	NM	66%	71%	78%	82%	83%
Operating Margin		NM	NM	NM	NM	NM	NM	NM	1%	NM	NM	NM	30%	37%	38%
Pretax Margin		NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	(7%)	30%	37%	39%
Net Margin		NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	(7%)	25%	26%	28%
Annual Percentage Change															
KTE-C19 WW Sales		NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	1567%	282%	79%	31%
KTE-C19 US Sales		NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	1340%	201%	50%	28%
KTE-C19 ex-US sales		NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	795%	140%	35%
Total revenue		NM	NM	NM	NM	NM	NM	NM	NM	(75%)	49%	1186%	210%	56%	30%
COGS		NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	192%	50%	24%
R&D		181%	354%	NM	NM	NM	NM	74%	#REF!	50%	50%	17%	55%	29%	26%
SG&A		74%	913%	NM	NM	NM	NM	189%	#REF!	150%	210%	(47%)	77%	32%	30%
Operating income		(149%)	(470%)	NM	NM	NM	NM	(76%)	#REF!	(28257%)	(144%)	93%	1408%	95%	37%
Net income		(148%)	(586%)	NM	NM	NM	NM	(46%)	#REF!	(21637%)	(144%)	93%	1224%	72%	28%
EPS		(140%)	(64%)	NM	NM	NM	NM	22%	#REF!	(21688%)	(143%)	93%	1217%	71%	27%

(a) Assumes full revenues from US sales; no revenues from ex-US, instead recieving partnership royalites

(b) Assumes 17-21% ex-US royalty

(c) As of March 31st, 2014, Kite had 5,588,632 options outstanding at an average excise price of $1.00

Source: Company reports and Stifel estimates

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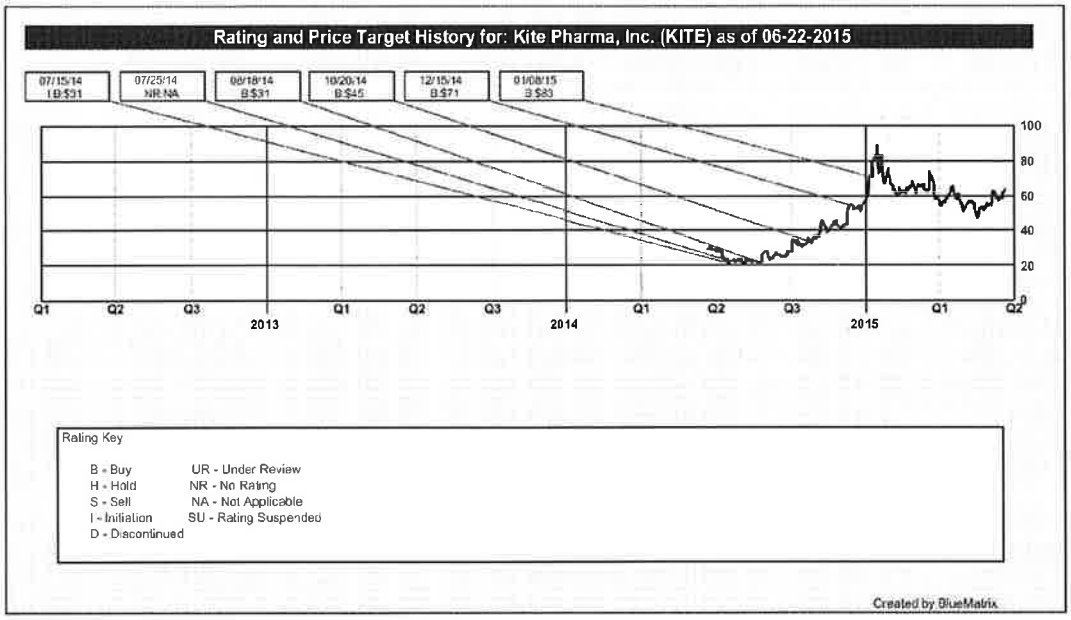

For a price chart with our ratings and any applicable target price changes for KITE go to http://sf.bluematrix.com/bluematrix/Disclosure?ticker=KITE

The rating and target price history for Kite Pharma, Inc. and its securities prior to February 25, 2015, on the above price chart reflects the research analyst's views under a different rating system than currently utilized at Stifel. For a description of the investment rating system previously utilized go to.www.stifel.com.

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From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Wednesday, June 24, 2015 6:26 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]; Ron Levy; Owen N. Witte MD; Ton Schumacher
Subject: Fwd: Investor Day Analyst Reports
Attachments: Kite June 23-24 analyst reports.docx; ATT00001.htm; CanaccordJune242015.pdf; ATT00002.htm; CowenJune232015.pdf; ATT00003.htm; GuggenheimJune242015.pdf; ATT00004.htm; JefferiesJune242015.pdf; ATT00005.htm; MizuhoJune242015.pdf; ATT00006.htm; StifelJune232015.pdf; ATT00007.htm

Steve, Ron, Owen, and Ton,

Thank you all for yesterday's stellar performance. You were truly a dream team!

I am sending you an unbiased report on the event yesterday, as perceived by the analysts who covered it, and the originals from the write ups so far.

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

I started today at 6.30 AM at CNBC for a morning show and interview, and spent the rest of the day at the offices of WSJ (steve, Ron Winslow will call you for further interview), Bloomberg , and Forbes for additional interviews.
I am happy to be now on my way to LA!

Thanks again.

Arie

Begin forwarded message:

From: "Carol Werther" <cwerther@burnsmc.com>
To: "Arie Belldegrun" <Arie@kitepharma.com>, "David Chang" <DChang@KitePharma.com>, "Cynthia Butitta" <CButitta@KitePharma.com>, "Helen Kim" <HKim@KitePharma.com>, "Margo Roberts" <MRoberts@KitePharma.com>, "Marc Better" <MBetter@KitePharma.com>, "Jeff Wiezorek" <JWiezorek@KitePharma.com>, "Ton Schumacher" <tschumacher@kitepharma.com>, "Rajul Jain" <RJain@KitePharma.com>, "Kate Bechtold" <kbechtold@kitepharma.com>, "Linda Barnes" <LBarnes@KitePharma.com>
Cc: "Kite Team" <Kite_Team@burnsmc.com>
Subject: Investor Day Analyst Reports

Dear Arie, Cindy, David, Jeff, Marc, Margo, Ton, Helen, Rajul, Kate and Linda,

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PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Sincerely,

BMC KITE team

Summary of Analyst Kite Comments:

Jefferies, Biren Amin: BUY, PT $83.00
Title: Kite Shares Its Vision at Analyst Day
Key Takeaways: KITE hosted an analyst day where it reiterated its clinical development plan for KTE-C19, plans to move add'l CAR/TCR targets to clinical trials, and pot'l new strategies to improve T-cell expansion and the introduction of a pot'l CAR to prevent off-target effects on healthy cells. The company is on track to disclosing topline data from the pilot trial enrolling patients with diffuse large B-cell lymphoma (DLBCL) at ASH '15.

Notes on Biren's Take:

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Stifel, Tom Shrader: BUY, PT $83.00
Title: KITE Investor Day Update and Bluebird Bio Collaboration
Summary: This afternoon we attended Kite Pharma's Investor Day where management provided a corporate overview and the company's key collaborator at the NCI (Steven Rosenberg) gave an overview of the field that hinted at some potentially earthshaking data to come (see below). Kite's recent collaboration with Bluebird was reviewed and looks like a high-level hand-holding exercise as both companies look to enter new areas without wasting time. As expected, the next IND will involve TCRs targeting HPV proteins which are increasingly being viewed as the best TCR target outside of neoantigens.

Notes on Tom's Take:

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Guggenheim, Tony Butler: BUY, PT $73.00
Title: KITE – BUY – Investor day 2015; Kite and Bluebird Soar Together into TCR's

Notes on Tony's Take:

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Cowen, Eric Schmidt, No PT
Title: Depth of Scientific Expertise Highlighted At Investor Day
Summary: The Cowen Insight: At yesterday's analyst day in NYC, Kite unveiled new technologies, reviewed its scientific foundation and aspirations, and provided a pipeline update. Kite's Phase I/II DLBCL trial continues to enroll patients and an ongoing HPV E6 TCR trial has generated responses in solid tumors. We continue to view Kite as the leader in engineered T cells and remain at Outperform.

Notes on Eric's Take:

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Canaccord, John Newman: BUY, PT $90.00

Title: TCRs center stage at R&D day, KRAS , HPV - 16 E7 enter clinic in 2015
Notes on John's Take:

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Mizuho, Peter Lawson; PT $90
Title: Investor Day – Under the Hood; No Near-Term Changes.
Notes on Peter's Take:

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

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Burns McClellan | 257 Park Ave South, 15 | New York, NY 10010 | T: 212.213.0006
cwerther@burnsmc.com | www.burnsmc.com

June 24, 2015

Dear Arie, Cindy, David, Jeff, Marc, Margo, Ton, Kate and Linda,

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Sincerely,

BMC KITE Team

Summary of Analyst Kite Comments:

Jefferies, Biren Amin: BUY, PT $83.00

Title: Kite Shares Its Vision at Analyst Day

Key Takeaways: KITE hosted an analyst day where it reiterated its clinical development plan for KTE-C19, plans to move add'l CAR/TCR targets to clinical trials, and pot'l new strategies to improve T-cell expansion and the introduction of a pot'l CAR to prevent off-target effects on healthy cells. The company is on track to disclosing topline data from the pilot trial enrolling patients with diffuse large B-cell lymphoma (DLBCL) at ASH '15.

Notes on Biren's Take:

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Stifel, Tom Shrader: BUY, PT $83.00

Title: KITE Investor Day Update and Bluebird Bio Collaboration

Summary: This afternoon we attended Kite Pharma's Investor Day where management provided a corporate overview and the company's key collaborator at the NCI (Steven Rosenberg) gave an overview of the field that hinted at some potentially earthshaking data to come (see below). Kite's recent collaboration with Bluebird was reviewed and looks like a high-level hand-holding exercise as both companies look to enter new areas without wasting time. As expected, the next IND will involve TCRs targeting HPV proteins which are increasingly being viewed as the best TCR target outside of neoantigens.

Notes on Tom's Take:

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Guggenheim, Tony Butler: BUY, PT $73.00

Title: KITE – BUY – Investor day 2015; Kite and Bluebird Soar Together into TCR's

Notes on Tony's Take:

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Cowen, Eric Schmidt, No PT

Title: Depth of Scientific Expertise Highlighted At Investor Day

Summary: The Cowen Insight: At yesterday's analyst day in NYC, Kite unveiled new technologies, reviewed its scientific foundation and aspirations, and provided a pipeline update. Kite's Phase I/II DLBCL trial continues to enroll patients and an ongoing HPV E6 TCR trial has generated responses in solid tumors. We continue to view Kite as the leader in engineered T cells and remain at Outperform.

Notes on Eric's Take:

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Canaccord, John Newman: BUY, PT $90.00

Title: TCRs center stage at R&D day, KRAS , HPV-16 E7 enter clinic in 2015

Notes on John's Take:

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Mizuho, Peter Lawson; PT $90

Title: Investor Day – Under the Hood; No Near-Term Changes.

Notes on Peter's Take:

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US Equity Research
24 June 2015

BUY
unchanged
PRICE TARGET US$90.00
unchanged
Price (23-Jun) US$62.72
Ticker KITE-NASDAQ

52-Week Range (US$)	21.00 - 89.21
Avg Daily Vol (M)	895.3
Shares Out. (M)	38.3
Market Cap. (US$M)	2,404

FYE Dec	2014A	2015E	2016E
Revenue (US$M)	0.0	2,881.0	0.0
EPS Adj&Dil (US$)	(1.91)	(0.95)	(1.02)

Quarterly Revenue	Q1	Q2	Q3	Q4
2014A	0.0	0.0	0.0	0.0
2015E	2,881.0	0.0	0.0	0.0
2016E	-	-	-	-

Quarterly EPS Adj&Dil	Q1	Q2	Q3	Q4
2014A	(0.66)	(2.27)	(0.24)	(0.33)
2015E	(0.20)	(0.25)	(0.25)	(0.25)
2016E	-	-	-	-

Kite Pharma is focused on development of novel cancer immunotherapy using engineered autologous cell therapy (eACT).

John Newman, PhD | Canaccord Genuity Inc. (US) | JNewman@canaccordgenuity.com | 212.389.8042

Company Update

TCRs center stage at R&D day, KRAS, HPV-16 E7 enter clinic in 2015

KRAS and HPV-16 E7 TCRs to enter clinic in 2015

TCR constructs targeting HPV-16 E7 and KRAs will enter human testing during 2015, broadening KITE's push into solid tumors. Mutated KRAS is present in colorectal, lung, and pancreatic cancer, three very large commercial markets. We note that prior investor disappointment with mesothelin studies is not necessarily indicative of other antigens. In addition, dose escalation for TCR constructs usually proceeds slowly, with early data not necessarily indicative of the final result at higher doses.

Phase 1 pivotal DLBCL data expected at ASH, Dec 2015

Kite gave details on its pivotal Phase 1/2 DLBCL program, with pivotal Phase 1 data expected at ASH in December 2015. Importantly, patients will be treated in the hospital setting during Phase 1 and observed for toxicity. Assuming the rate of severe toxicity is acceptable, the trial will proceed to Phase 2. Interestingly, the conditioning regimen intensity has been established as a range of "low" to "high." We look to understand additional detail regarding any potential differences in conditioning intensity versus the NCI Phase 1 pilot study going forward.

Next-generation manufacturing and CAR fidelity interesting

We suspect Kite will utilize akt inhibitors in next-gen manufacturing of Chimeric Antigen Receptor constructs, which may mitigate terminal differentiation and preserve central memory phenotype, and result in enhanced T-cell persistence. Dr. Steven Rosenberg mentioned the akt inhibition technique and has previously published on this topic, and the idea was mentioned at the R&D day. We also believe that Kite's "CAR fidelity" approach may mitigate off-target toxicity by adding a second inhibitory receptor towards targets on healthy cells but not tumor cells.

TCR melanoma data previously established solid tumor viability

As previously discussed, we firmly believe that TCR efficacy has been demonstrated in solid tumors based on previously published melanoma data. NCI data in melanoma targeting NY-ESO-1 (n=19) have previously shown a 53% ORR (32% PR, 21% CR). We believe that both the existing NCI study in melanoma and the upcoming TCR studies against KRAS and HPV will provide additional proof-of-concept data in solid tumors, holding meaningful upside.

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Target Price / Valuation Methodology:

Kite Pharma - KITE

Our target price is $90, based on a probability adjusted NPV valuation.

Risks to achieving Target Price / Valuation:

Kite Pharma - KITE

Although NCI is conducting a phase 1-2a trial of anti-CD19 CAR T-cell therapy, KITE's KTE-C19 trial has not begun. Any delays or significant negative results from NCI's clinical trials could negatively affect Kite's IND application and delay the timing to start their own phase 1-2 clinical trial. KITE is highly dependent on the third parties for R&D and early clinical testing of CAR and TCR product candidates. These collaborations related to the intellectual property licensed from the NIH relating to product candidates targeting the EGFRvIII antigen, the SSX2 antigen and the NY-ESO-1 antigen and from Cabaret for intellectual property relating to KTE-C19. The differences in manufacturing compared to NCI may render the product incomparable, particularly with respect to clinical trials, which could negatively affect our valuation. Although plans for manufacturing and processing is based on current approach undertaken by the NCI, the company cannot ensure that even minor changes in the product process will not result in significantly different T-cells that may not have similar efficacy or toxicity. KTE-C19 could fail in clinical studies, resulting in significant downside to our price target and shares of the stock. Kite faces significant competition from other biotechnology and pharmaceutical companies in the space of immunotherapy, including Novartis, Juno, Bluebird, Cellectis and Adaptimmune, as well as companies developing novel targeted therapies for cancer.

Distribution of Ratings:

Global Stock Ratings (as of 06/24/15)

Rating	Coverage Universe		IB Clients
	#	%	%
Buy	590	59.24%	33.05%
Hold	320	32.13%	15.62%
Sell	38	3.82%	2.63%
Speculative Buy	48	4.82%	54.17%
	996*	100.0%	

*Total includes stocks that are Under Review

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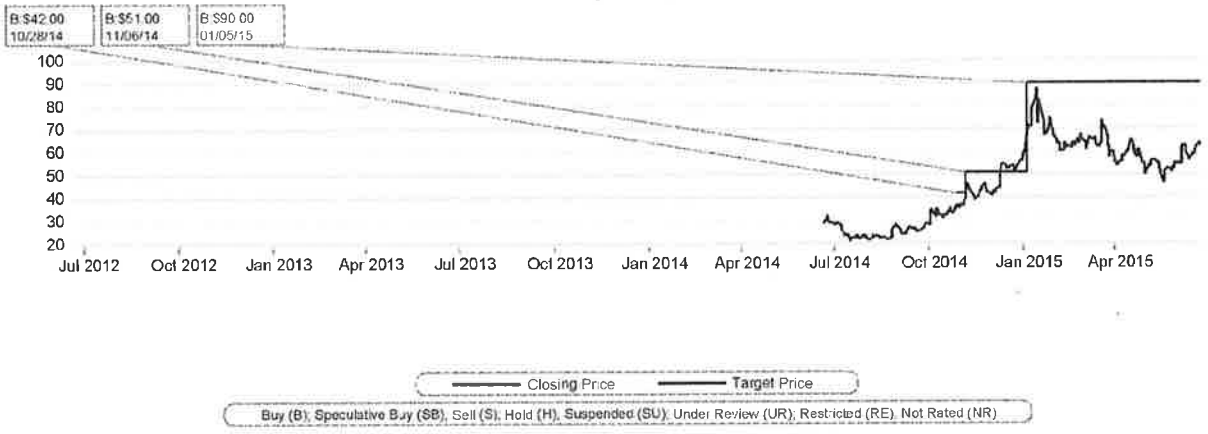

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Additional information is available on request.

COWEN
AND COMPANY

Biotechnology

Kite Pharma

Equity Research

Quick Take: Company Update

June 23, 2015

Price: $62.72 (06/23/2015)
Price Target: NA

OUTPERFORM (1)

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Key Data

Symbol	NASDAQ: KITE
Market Cap (MM)	$2,700.7

Depth Of Scientific Expertise Highlighted At Investor Day

The Cowen Insight

At yesterday's analyst day in NYC, Kite unveiled new technologies, reviewed its scientific foundation and aspirations, and provided a pipeline update. Kite's Phase I/II DLBCL trial continues to enroll patients and an ongoing HPV E6 TCR trial has generated responses in solid tumors. We continue to view Kite as the leader in engineered T cells and remain at Outperform.

Much Progress Has Been Made, But Kite Isn't Resting

Yesterday, Kite hosted an analyst event in New York. Management reviewed the significant progress it has made over the past year since its IPO. Kite has transitioned chimeric antigen receptor (CAR) T cell manufacturing outside of NCI, initiated a potentially pivotal program in DLBCL, begun construction of commercial manufacturing facilities, and significantly expanded its scientific expertise via the acquisition of T Cell Factory, a broadened CRADA with NCI, and collaborations with Amgen and bluebird bio. In addition, Kite set out its vision for the future of engineered T cell therapy. This vision includes new methods for manipulating the activation/ inhibition of T cells, a significant focus on T cell receptor (TCR) -based therapies for shared antigens, and ultimately TCRs specific for an individual patient's neo-antigens.

Kite Is Leading On The Science

There are three major approaches to cancer immunotherapy, (1) nonspecific activation of immune cells via stimulation (e.g. IL-2) or blocking inhibitory signals (e.g. PD-1), (2) immunization (e.g. Provenge, T-Vec), or (3) the transfer of *ex vivo* activated immune cells (eg. TILs, CAR T cells). Kite is focused on developing therapies belonging to the last category of immunotherapies. Specifically, Kite is developing engineered T cells that express CARs or TCRs specific for cancer antigens. Kite highlighted the immense depth of scientific experience in engineered T cells, immunology, oncology, and product development represented across the organization both through internal employees (Drs. Chang, Roberts, and Schumacher) and key external advisors/ collaborators (Drs. Levy, Rosenberg, and Witte). Together these individuals were instrumental in the creation of the first CAR administered to humans (Dr. Roberts), the first successful cancer immunotherapy (Dr. Rosenberg), and multiple revolutionary cancer drugs including Rituxan (Dr. Levy) and Gleevec (Dr. Witte). Kite and others have presented data indicating significant efficacy with CD19 CARs and NY-ESO-1 TCRs. We believe Kite has assembled the team required to make engineered T cells applicable to a broad portion of oncology. To accomplish this goal, Kite's efforts are focused on two primary methods to increase the breadth of tumors addressable by engineered T cells. First is identifying the appropriate cancer specific antigens to attack and second is developing secondary technologies to improve the activity of engineered T cells.

First Generation CARs Are Great But More Is Needed

Kite's collaborators discussed that CD19 is a nearly perfect antigen given its uniform expression across multiple tumor types and restriction to a healthy cell type (B cells) that can live without. Kite and its collaborators believe additional attractive antigens exist. One such antigen is EGFRvIII. Working with NCI, Kite has treated ~15 patients (GBM and head and neck cancers) at NCI using an EGFRvIII CAR construct. Dr. Rosenberg reported that dose escalation has just now reached the level where one could imagine seeing efficacy but that as of now no responses have been observed. Kite's collaboration with Amgen should provide additional attractive CAR candidates. This collaboration is directed at converting Amgen's library of antigen targets and antibody sequences into CAR constructs for the treatment of AML, multiple myeloma, kidney, and lung cancers. The first IND from this collaboration is expected in H2:16. While hopeful for these efforts, Kite and its collaborators noted that 20+ years of antibody development had likely identified the few targets that fit the CD19-like expression criteria. Therefore, Kite is pursuing two mechanisms to broaden the list of potential tumor targets.

Second Generation CAR Therapies Bring Intelligence To The T Cell

First, Kite is working preclinically to develop second generation "logic gated" CAR therapies that require a targeted cell to either simultaneously express two antigens or perhaps more significantly express one antigen but not a second. These engineered T cells will simultaneously express two CAR constructs. In order to introduce an "and" operator the constructs will separately contain the primary stimulation (e.g. CD3) and secondary stimulation (e.g. CD28) signaling domains. Conversely, an "and not" operator can be introduced by using a traditional CAR construct containing both the primary and secondary stimulation domains in combination with a second CAR construct that contains an inhibitory domain. Consequently, if an off-target cell expresses the target antigen but also the inhibitory antigen it will be spared whereas a tumor cell that only expresses the target antigen will be killed. Kite believes second generation CAR therapies are 2-3 years away from the clinic.

TCRs Triple The Potentially Addressable Antigens

Second, Kite is using T cell receptors to pursue the ~75% of proteins that are expressed intracellularly and are therefore inaccessible to antibody recognition. Kite currently has four TCR constructs (NY-ESO-1, MAGE A3/A6, MAGE A3, and HPV-16 E6) in the clinic and plans to initiate clinical trials on at least three additional constructs (HPV-16 E7, SSX2, and KRAS) within the next 18 months.

Kite acquired Dr. Ton Schumacher's T Cell Factory (TCF) to further expand the TCR pipeline. TCF's core TCR GENErator technology allows for the rapid isolation of high-affinity TCR sequences. Since TCR based therapies' target populations are restricted by MHC expression (ex. HLA-A2 is only expressed by ~50% of Caucasians) the TCF technology will be deployed to identify TCR sequences that utilize alternative MHC sequences to target the same antigen. Kite believes three TCR sequences per antigen are sufficient to cover >80% of the global population and approximately five sequences can cover >90% of the global population. In addition, the TCR GENErator will be deployed to identify TCRs specific for neo-antigens being identified under the NCI CRADA. Dr. Rosenberg reports that his lab is able to complete exome sequencing of tumor samples within 48 hours of receiving the sample. Within an additional 48 hours Dr. Rosenberg's group is able to identify the subset of peptides that are actually presented on MHC molecules within the tumor. Dr. Rosenberg has now performed this protocol using samples from >25 melanoma and 16 GI cancer patients. Published data on the melanoma patients indicates that neo-antigens were presented universally, but each patient contained unique neo-antigens. Dr. Rosenberg disclosed that he has since found at least one melanoma patient with shared neo-antigens. Among the GI cancer patients, 15 were found to present neo-antigens.

These neo-antigen profiles have not been published yet. With the TCR GENErator, Kite now possesses a high-throughput manner by which high-affinity TCRs specific to neo-antigen peptides can be isolated. Drs. Rosenberg and Schumacher believe that experience with TIL therapy indicates the simultaneous use of two to three neo-antigen TCR specificities should be sufficient to control many tumors. Kite has previously indicated that this ultimate in personalized medicine could be ready for clinical trials in 3-5 years.

HPV E6 TCR Shows Efficacy In Solid Tumors

Human papilloma virus (HPV) is associated with numerous cancers including anal, head and neck, and the majority of cervical cancers. These cancers lead to ~15,000 deaths/yr in the U.S. Dr. Rosenberg recently published proof of concept data showing durable responses in two out of nine patients treated with HPV specific tumor infiltrating lymphocytes (TILs). Kite and Dr. Rosenberg have followed up these findings with an HPV E6 specific TCR product. Dr. Rosenberg disclosed for the first time that using this construct he has observed "multiple responses". As a result, Kite plans to transition the HPV-16 E6 program from an NCI held IND to a Kite held IND in early 2016.

Kite Is Also Working To Increase T Cell Activity

Beyond expanding the list of antigen targets, Kite is also developing methods by which it can make its T cells more potent. Preclinical studies have shown that IL-7 and IL-15 expression is vital for the engraftment and efficacy of CAR T cells. Working with NCI, Kite has conducted work to optimize the preconditioning regimen for among other parameters the generation of IL-7 and IL-15 expression. Preclinical work has also demonstrated that engineered T cells that have undergone less *ex vivo* differentiation generate superior efficacy. Kite and NCI have developed a small molecule (KTE-SM01) that is capable of decoupling T cell proliferation and differentiation. The identity of KTE-SM01's target was not disclosed, but based upon a literature review we believe it to be an AKT kinase inhibitor. Using KTE-SM01, Kite hopes to generate T cell products that are skewed towards a stem cell memory phenotype. Kite is now working to include KTE-SM01 in its next generation T cell manufacturing protocol.

Kite is also pursuing strategies to combine engineered T cells with additional therapeutic manipulations including checkpoint inhibition and/or coexpression of cytokines. Kite intends to develop a second generation HPV E6 TCR therapy that contains an additional modification(s). Earlier this week, Kite signed a collaboration with bluebird bio for this project. Under the collaboration Kite and bluebird bio will develop an engineered T cell product using (1) Kite's HPV E6 TCR sequence, (2) bluebird's lentiviral delivery system and (3) bluebird's gene editing platform to modify activating/inhibitory pathways. Kite indicated that this project could result in clinical trials in 2-3 years.

KTE-C19's Pivotal DLBCL Trial Progressing Well; More Trials Starting In H2:15

Kite has successfully transitioned production of KTE-C19 from NCI to its contract manufacturer (PTC). Last month, PTC produced cells were used to dose the first patient in Kite's potentially pivotal Phase I/II trial of KTE-C19 in DLBCL. For the Phase I portion, Kite is currently enrolling patients at four clinical sites. If no more than two dose limiting toxicities are observed among the first six patients, Kite will progress to the Phase II portion and enroll 50 patients from 20-25 clinical sites. This is expected to occur in H2:15. Data from the Phase I portion, including the trial's cell dose and preconditioning regimen will be presented at ASH 2015. Phase II data is expected to be released in 2016. Kite believes historical data indicates a <20% ORR and 4-5 month mOS would be expected. Therefore, an ORR of at least 40% with a mOS of at least 6 months is expected to be approvable. Simultaneous to beginning the Phase II

portion of the DLBCL trial, Kite intends to initiate a Phase II trial of KTE-C19 in MCL. Also in H2:15, Kite plans to initiate a Phase I/II ALL trial and a Phase II CLL trial.

Valuation Methodology And Risks

Valuation Methodology

Biotechnology:

In calculating our 12-month target price, we employ one or more valuation methodologies, which include a discounted earnings analysis, discounted cash flow analysis, net present value analysis and/or a comparable company analysis. These analyses may or may not require the use of objective measures such as price-to-earnings or price-to-sales multiples as well as subjective measures such as discount rates.

We make investment recommendations on early stage (pre-commercial) biotechnology companies based upon an assessment of their technology, the probability of pipeline success, and the potential market opportunity in the event of success. However, because these companies lack traditional financial metrics, we do not believe there are any good methodologies for assigning a specific target price to such stocks.

Investment Risks

Biotechnology:

There are multiple risks that are inherent with an investment in the biotechnology sector. Beyond systemic risk, there is also clinical, regulatory, and commercial risk. Additionally, biotechnology companies require significant amounts of capital in order to develop their clinical programs. The capital-raising environment is always changing and there is risk that necessary capital to complete development may not be readily available.

Risks To The Price Target

Kite Pharma is unprofitable, has no approved products, and will likely need to raise additional capital from the public markets prior to turning profitable. There is limited clinical trial experience on lead candidate KTE-C19, and eACT's more broadly. Moreover, KTE-C19 faces a number of clinical, regulatory, and commercial hurdles prior to becoming successful, and projecting any future sales for KTE-C19 is inherently difficult.

We make investment recommendations on early stage (pre-commercial) biotechnology companies based upon a an assessment of their technology, the probability of pipeline success, and the potential market opportunity in the event of success. However, because these companies lack traditional financial metrics, we do not believe it there are any good methodologies for assigning a specific target price to such stocks.

Addendum

Stocks Mentioned In Important Disclosures

Ticker	Company Name
KITE	Kite Pharma

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Outperform (1): The stock is expected to achieve a total positive return of at least 15% over the next 12 months

Market Perform (2): The stock is expected to have a total return that falls between the parameters of an Outperform and Underperform over the next 12 months

Underperform (3): Stock is expected to achieve a total negative return of at least 10% over the next 12 months

Assumption: The expected total return calculation includes anticipated dividend yield

Cowen and Company Rating System until May 25, 2013

Outperform (1): Stock expected to outperform the S&P 500

Neutral (2): Stock expected to perform in line with the S&P 500

Underperform (3): Stock expected to underperform the S&P 500

Assumptions: Time horizon is 12 months; S&P 500 is flat over forecast period

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Hold – The fundamentals/valuations of the subject company are neither improving nor deteriorating and the investment return is expected to be in line with the general market return

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Buy (a)	450	58.67%	103	22.89%
Hold (b)	302	39.37%	8	2.65%
Sell (c)	15	1.96%	0	0.00%

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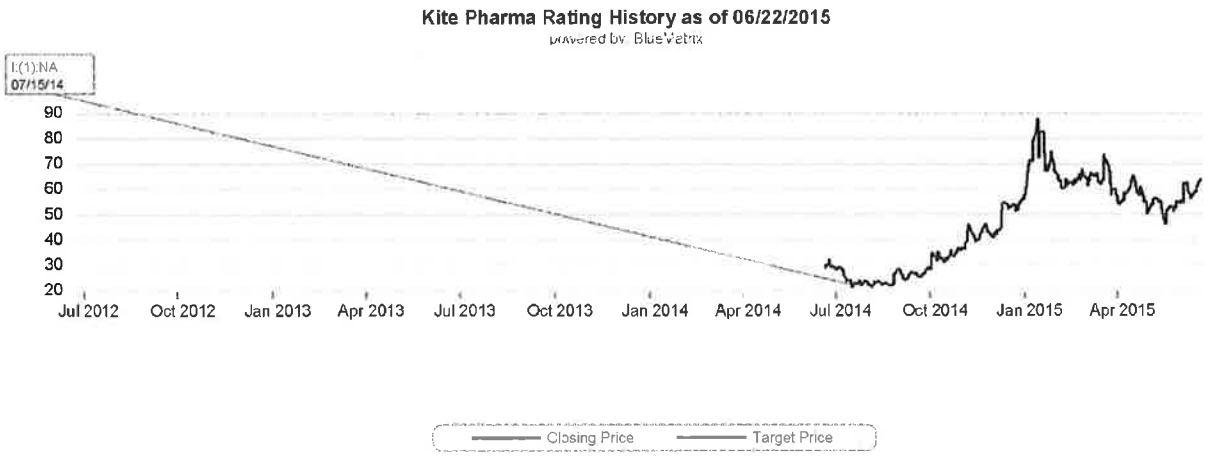

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Kite Pharma, Inc.

KITE – BUY – Investor Day 2015; Kite and Bluebird Soar Together into TCR's June 24, 2015

- We attended the Kite Investor Day yesterday, June 23, 2015. KITE has grown significantly over the past year and a half since its IPO, growing from 8 employees at launch to over 100 employees today and raising over $400M to date to develop their programs, including 6 products in clinical development.
- KITE develops engineered T cells that redirect the patient's immune system to kill cancer cells. Such engineered T cells can eradicate cancer without harming normal tissue.
- KITE focused on several topics, including their collaborations (NCI, AMGN, NKI, UCLA, Tel Aviv, and now bluebird bio), product development (KTE-C19 being advanced to pivotal trials later this year), and building out the TCR franchise (recent agreement with bluebird on HPV-16 TCRs, AMGN collab, and other TCRs including NY-ESO and MAGE TCRs).
- KITE is also expanding manufacturing (Santa Monica facility opening in October, El Segundo facility in 2017, with existing PCT site in Mountain View and a CMO in EU) to support the over 300 patients who will be treated in KTE-C19 trials as well as further development of other candidates in the future.
- We await pivotal Ph. 1 data on KTE-C19 in aggressive NHL/DLBCL at ASH in December, while the remaining CAR and TCR pipeline is advancing rapidly with 3 additional pivotal studies in KTE-C19 (IND submission planned 2H16) as well as KRAS and HPV16 E7 TCRs initiating clinical trials in 2H15.

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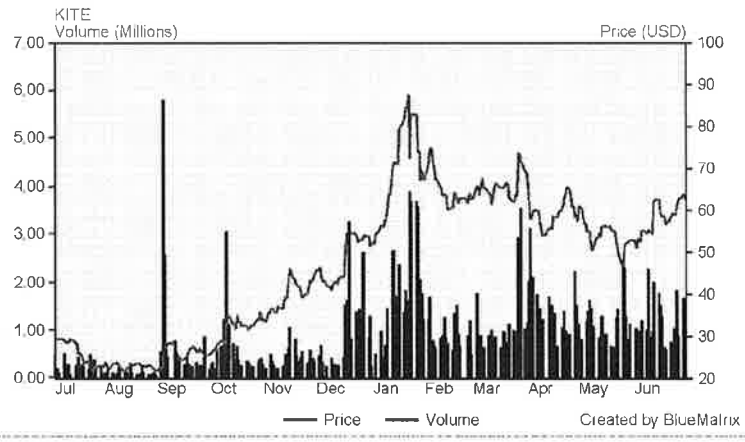
KITE BUY
COMPANY UPDATE

Investment Thesis: Growth

SHARE PRICE	$62.72
PRICE TARGET	$73.00

EPS ($) (FY Dec)	1Q	2Q	3Q	4Q	FY
2014	—	—	—	(0.19)	(0.94)
P/E					NM
2015	(0.20)	(0.23)E	(0.24)E	(0.29)E	(0.87)E
P/E					NM
2016	—	—	—	—	(1.34)E
P/E					NM

Market Data	
52-Week Range	$21.00 - $89.21
Shares Out (M)	43.1
Market Cap (M)	$2,701
ADV (3 mo. 000)	1,268



Birds of a feather fly together: KITE and bluebird bio collaborate on TCRs: KITE and bluebird bio (BLUE, NC, $174.31) announced a new collaboration to develop second generation TCR product candidates directed against human papillomavirus type 16 E6 (HPV-16 E6) oncoprotein. Bluebird bio has demonstrated expertise and substantial promise using their lentivirus/gene therapy technologies to treat Beta-thalassemia and sickle cell disease. The collaboration will likely primarily allow for both companies to share intellectual property and methodologies to develop the second generation TCR therapies to target HPV-16 E6. Expenses for development and profits will be split equally between the companies, and none of the existing KITE HPV programs will be affected by this standalone agreement.

The HPV-16 E6 oncoprotein is constitutively expressed on HPV-16+ cancer cells and is absent from healthy tissues, allowing HPV-16-directed T cells to target and kill only cancer cells. Primary HPV-associated cancers include cervical and oropharyngeal head and neck cancers, which combined can constitute up to a yearly incidence of 42,500 eligible patients. KITE is currently evaluating a first generation HPV-16 E6 TCR for diverse HPV-16+ cancers in a Phase 1/2 study with an estimated enrollment of up to 61 patients and expected completion in May 2019.

Getting KTE-C19 to market in DLBCL: One of the key focuses of the Investor Day was what steps are necessary to begin the KTE-C19 program and what trial designs will be used. KITE has already started the pivotal study in DLBCL, and they indicated they will begin the pivotal studies in MCL, ALL, and aggressive NHL later this year (table below provides an overview of pivotal trial design). Dr. Jeff Wiezorek, VP of Clinical Development detailed an overview of the trial designs, mentioning that many of the same sites will be performing both Ph. 1 and 2 studies. Chemo-conditioned patients will be hospitalized around the infusion, which follows a 6-8 day manufacturing period (which KITE is still optimizing with automation steps and other measures) post-leukapheresis. Following the hospitalization, the follow up period begins with first tumor assessment on day 30. In aggressive NHL, KITE is targeting a BLA filing for KTE-C19 by YE 2016, with Ph. 1 data presented this December at ASH and Ph. 2 data to follow sometime next year. Over the life span of all KTE-C19 pivotal trials, over 300 patients will be treated.

KITE KTE-C19 Pivotal Trial Designs 101-103 in NHL, MCL, and ALL

Trial	Indication	Size of Ph. 2 (n)	Key eligibility criteria	Endpoints
KTE-C19 101	Aggressive NHL	· Cohort 1 in DLBCL: n=72 · Cohort 2 in PMBCL/TFL (n=40)	· DLBCL, PMBCL or TFL · Chemotherapy refractory disease - SD or PD to last therapy or - Relapsed post transplant within 1 year · Adequate prior therapy - At minimum, anthracycline-containing regimen and anti-CD20 mAb · ECOG 0 or 1	· Incidence of DLT (primary phase 1) · Objective response rate (primary phase 2) · Duration of response, PFS, OS and safety
KTE-C19 102	MCL	· n=70	· Pathologically confirmed MCL · Relapsed or refractory disease · Adequate prior therapy - Anthracycline or bendamustine-chemo and - Anti-CD20 monoclonal antibody therapy and - Ibrutinib · ECOG 0 or 1 · Age >18 · Adequate hepatic, renal, cardiac function	· Objective response rate (primary) · Duration of response, PFS, OS and safety
KTE-C19 103	ALL	· n=50	· Relapsed or refractory B-precursor ALL - Primary refractory disease - Untreated first relapse with first remission ≤ 12 months – Relapsed or refractory disease after first or later salvage therapy - Relapsed or refractory disease after allogeneic transplant · M1 or greater bone marrow · ECOG 0 or 1 · Age >18 · Adequate hepatic, renal, cardiac function	· Complete response rate (primary) · Duration of response, MRD-CR rate, allogeneic SCT rate and safety

**Source: KITE presentations*

Improving DLBCL/NHL therapy: KITE reiterated the emphasis of lymphodepletion and chemotherapy preconditioning as necessary for the CAR-T therapy process. At ASCO, KITE presented data demonstrating that chemo-conditioning with cyclophosphamide and fludarabine induced immune homeostatic cytokines (IL-15, IL-7), chemokines (MCP-1), and pro-inflammatory markers including CRP and PLGF. The method used for pre-conditioning the patient does therefore affect activation and trafficking of T cells. This will be key in clinical trials, and KITE intends to optimize this factor in CAR therapy. As presented at ASCO, KITE and Rosenberg mentioned that durable responses can occur without long lasting CAR-T cells in circulation, allowing for normal B cell recovery. Rosenberg commented that many robust responses have been achieved in several weeks post T-cell administration. KITE also emphasized CAR kinetics, in that the rapidity of achieving a CR as well as the ability to then sterilize the body of tumor cells is important. We note that this message differs slightly from JUNO's, who highlighted at ASCO that it seeks to improve the LT plateau of the KM curve in DLBCL patients by first improving cell persistence. Initial JCAR017 data in DLBCL reads out sometime next year, and JUNO's goal is to achieve a high CR rate as well as a durable tail.

DLBCL is KITE's lead indication, with a market size of ~22,000 patients in the U.S. Wiezorek emphasized that DLBCL in particular poses a large unmet need (table below outlining non-CD19 CAR responses), while CD-19 directed CARs have demonstrated response rates north of 60%, with many durable responses as well.

KITE Anti-CD19 CAR T induced objective responses in pts with r/r NHL and CLL		
Tumor type	ORR	CRR
Any (n=29)	76%	38%
DLBCL/PMBCL (n=17)	65%	35%
CLL (n=7)	86%	57%
Indolent NHL (n=5)	100%	20%

Source: ASCO 2015 data, Kochenderfer et al, Blood 2012 and JCO 2015 data

Responses in DLBCL by Line of Therapy (outside of KTE C19)		
Line of therapy	Overall outcomes	Refractory outcomes
1L	CR 76%' 10-yr OS ~44%	N/A
2L	ORR 11-97%	ORR <26%
3L+	ORR 0-40%	ORR<20%
Relapse post-ASCT	>1 yr: median OS 27 mos.	<1 yr: median OS 8 mos.

**Source: KITE presentations*

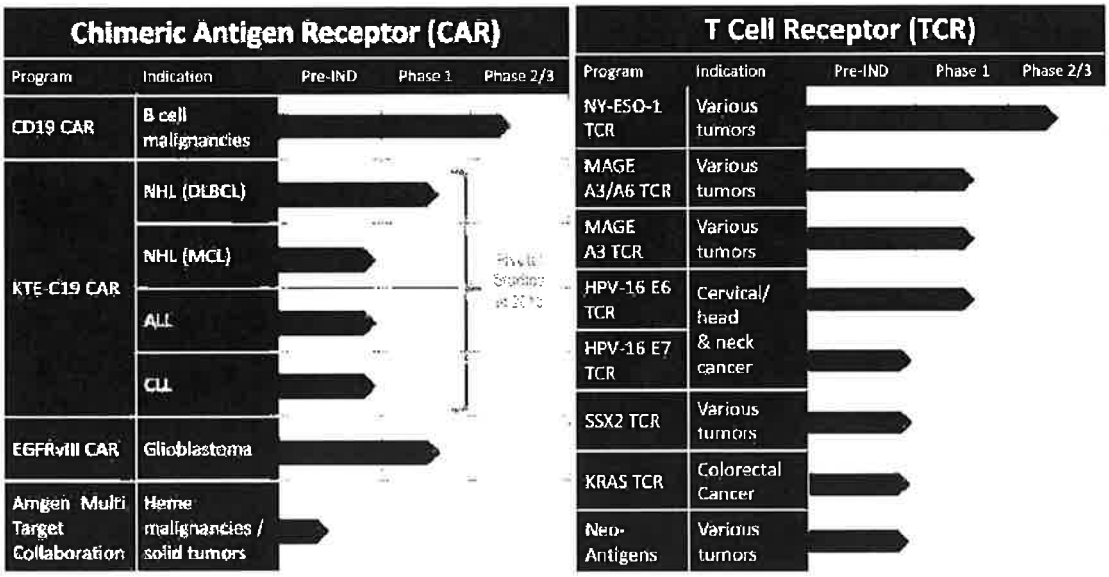
Ramping up manufacturing; commercial manufacturing ready for KTE-C19 launch in 2017: KITE will treat approximately 300 patients over the next year and a half, requiring a fairly extensive manufacturing build-out to support this development. In addition to relying on PCT in Mountain View, CA (used primarily for the DLBCL program) KITE has also built out a facility in Santa Monica that is anticipated to open in October. Along with KITE's EU program, led by Dr. Ton N. M. Schumacher, KITE is also engaging facilities for CMO production in Europe. The company is also building a facility in El Segundo, CA near the LA airport with an expected launch in 2017. Dr. Marc Better, VP of Product Sciences, commented that they fully expect the Santa Monica facility to be able to support manufacturing for the KTE-C19 program by YE. KITE believes its engineering process, which is relatively shorter compared to competitors at 6-8 days, offers superiority in the young phenotype of the product (not too many rounds of expansion) as well as no bead selection.

Where KTE-C19 fits into the treatment paradigm of new immunotherapies: Dr. Ron Levy from Stanford School of Medicine said that KTE-C19 fills a unique niche in the emerging landscape of new immunotherapies. While Rituximab raised the cure rate for DLBCL from 30% to 50%, CD-19 CARs are achieving RR's north of 60% that are durable, and Levy believes that CAR-T therapies such as KTE-C19 can eventually replace bone marrow transplants. In terms of comparing to other new immunotherapies such as ADC's, BTK inhibitors, and PI3K-delta inhibitors, Levy mentioned that they do not work especially well with DLBCL, achieving short-duration RR's of ~20-30%, as such therapies tend to work better in slower growing, low grade lymphomas such as follicular lymphoma. CAR-T therapies, in comparison, induce responses that are complete, durable and long lasting.

TCR franchise buildout: Dr. Ton Schumacher, CSO of KITE Europe and head of the KITE's collaboration with the Netherlands Cancer Institute, presented an overview of KITE's next-gen TCR programs. While CAR targets represent ~27% of the human proteome, TCR targets are more numerous due to TCR's ability to access intracellular targets, representing ~73% of the human proteome. KITE EU's proprietary TCR GENErator technology allows high-affinity of TCRs, though he emphasized the importance of an optimal affinity that is still within the natural range and binds tightly to the peptide MHC complex. KITE has active protocols at the NCI surgery branch, including HPV-16 E6 and HPV-18 E6 and E7 in cervical, head and neck cancers, mNY-ESO1 in pancreas and other cancers, Kras (G12D and G12V) in colorectal, and MAGE A3in various tumors. The collaboration with bluebird expands this portfolio, and KITE commented that filing is 2-3 years out for 2nd gen TCRs, while it files in 1H16 in the first-generation HPV-16 E6 program.

Future combos with checkpoint inhibitors: During the later Q&A panel, Dr.Levy commented that he believes combining checkpoint blockade with CAR-T's is the most exciting potential development in cancer immunotherapy. While checkpoint blocking antibodies have demonstrated tremendous efficacy, they only work on a certain subset of patients, so the question remains how to expand to a broader population. Some CAR-T players have already partnered on checkpoint inhibitors and CAR-T therapies: Juno (JUNO, NEUTRAL, $51.40) and AstraZeneca (AZN, NC, $67.59) announced their partnership on a PD-L1/CD19-CAR in NHL April 23. The study, which initiates later this year, assesses the impact that inhibiting PD-L1 with AZN's MEDI4736 has on the safety and efficacy of Juno's CAR-T construct. Inhibiting PD-1/PD-L1 would essentially prevent cancer cells from avoiding the host immune system, directly allowing increased exposure and efficacy of CAR-T engineered T cells. In addition, epitope spreading could be enhanced due to the immune response bolstered by the combo therapy further triggering an autoimmune response against proteins found on the surface of tumor cells.

Upcoming catalysts: 1) Pivotal Ph. 1 data at ASH in Dec. 2015 in aggressive NHL, 2) 3 additional pivotal trials in KTE-C19 initiating 2H15, 3) HPV-16 E6 TCR submitting IND in 1H16, 4) KRAS and HPV16 E7 TCRs initiating clinical trials under KITE-NCI CRADA in 2015, 5) KITE-AMGN CAR programs submitting IND's in 2H16, and 6) Ph. 2 pivotal data in KTE-C19 aggressive NHL in 1H16 and BLA filing for KTE-C19 by YE 2016.



Source: KITE presentations

KITE Valuation: As data continue to emerge supporting the viability of KITE's program/platform, we believe the risk could reduce and value could increase. Value should increase because the net present value of commercialization rises. We believe KITE may generate revenue by 2018. We estimate peak sales in second and third line NHL, assuming $200-250k per treatment, approach $1.5B by 2021. Medivation (MDVN, NC, $116.06) and Pharmacyclics (PCYC, NC, $261.25) are similar companies with early-stage product launches by partner companies and have market valuations approaching $9.7 billion and $19.7 billion, respectively. We estimate, at a current market cap of ~$2.2 billion, it is possible KITE could grow to 7-9 times its current size by 2022. We discount that valuation to today by 15% annually, which yields our price target of $73 (unchanged).

Key KITE Risks: KITE is an experimental stage company very early in development. Poor clinical readouts or inability to successfully commercialize its products is a risk. Risk of side effects of CAR-T therapies is also high, notably with cytokine release syndrome with even death in some patients, potentially limiting its use in earlier lines of therapy. There is also limited data outside of ALL, and establishing a durable response is critical to commercial success. Moreover, manufacturing and process development is not at commercial scale yet, and we note being able to deliver CAR-T to patients with affordable COGS is imperative. Further, given the number of companies currently in the CAR-T space, KITE's lead and platform could be commoditized. We believe profitability is several years away. Therefore, the stock can and may be highly volatile.

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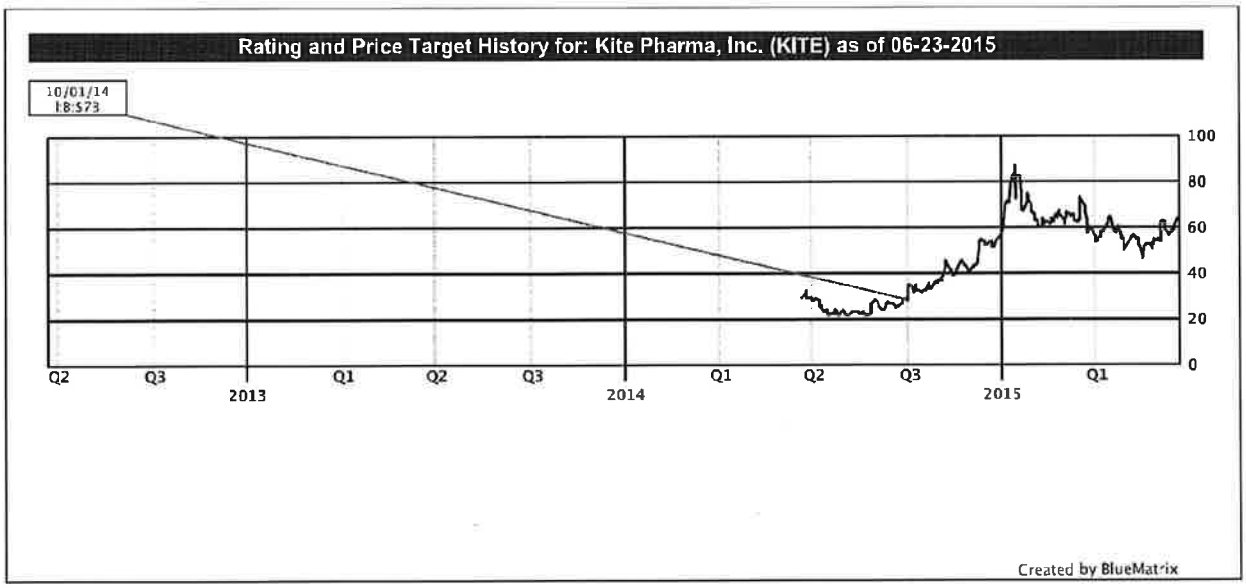

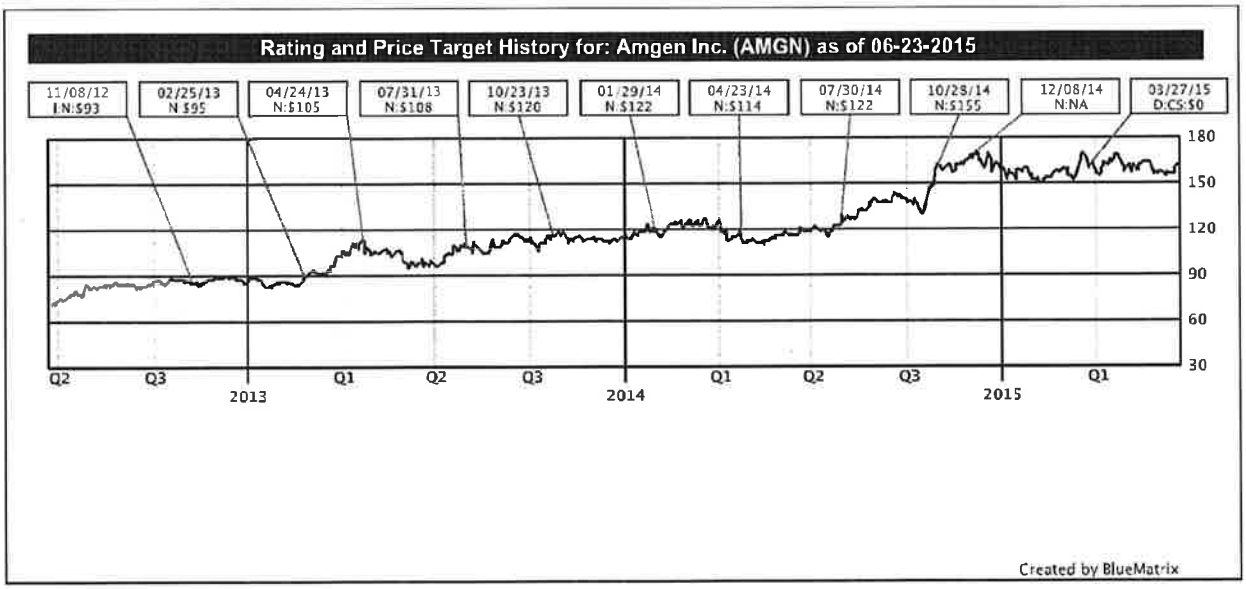

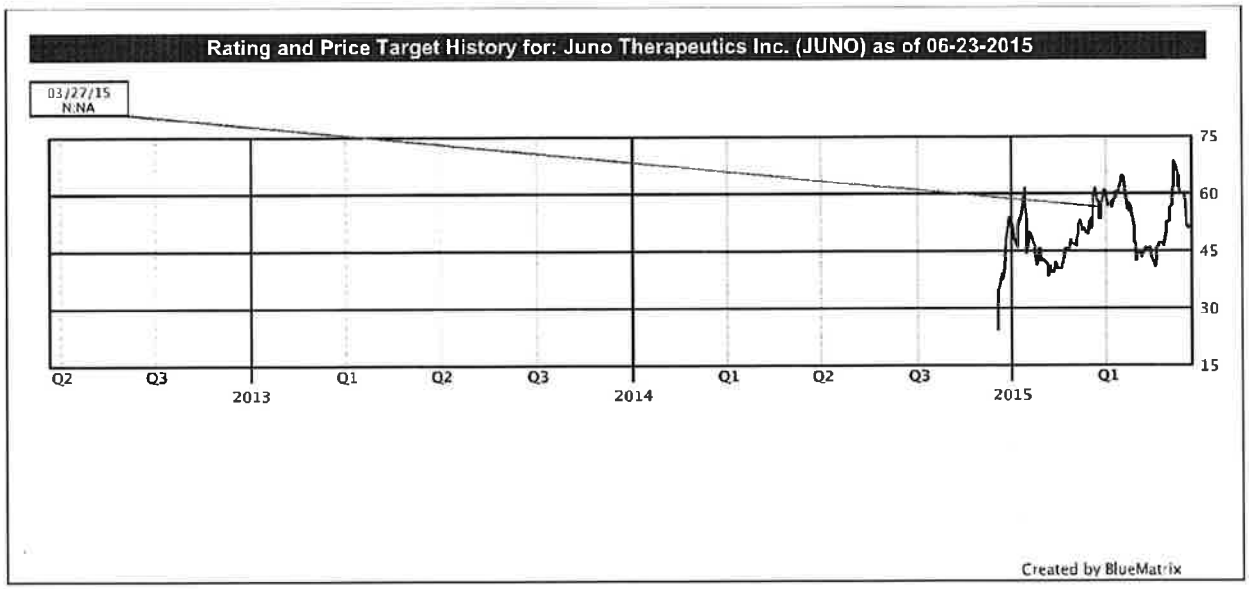

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			IB Serv./ Past 12Mos.	
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Sell	0	0.00%	0	0.00%

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GUGGENHEIM SECURITIES, LLC

Company Update

USA | Healthcare | Biotechnology

June 24, 2015

Jefferies

Kite Pharma (KITE)

Kite Shares Its Vision At Analyst Day

BUY
Price target $83.00
Price $62.72

EQUITY RESEARCH AMERICAS

Key Takeaway

KITE hosted an analyst day where it reiterated its clinical development plan for KTE-C19, plans to move add'l CAR/TCR targets to clinical trials, and pot'l new strategies to improve T-cell expansion and the introduction of a pot'l CAR to prevent off-target effects on healthy cells. The company is on track to disclosing topline data from the pilot trial enrolling patients with diffuse large B-cell lymphoma (DLBCL) at ASH '15.

KTE-C19 Data At ASH '15: KITE has started enrolling pts in its pilot study with KTE-C19, a CD19 CAR-T in DLBCL this quarter with pivotal trial initiating in Q4. The company acknowledged that it is testing a new lymphodepletion regimen which falls btwn the NCI regimen and the "low" dose regimen presented at ASH '14. Based on data from the pilot study, KITE could modify the lymphodepletion regimen for the pivotal studies and the add'l PII studies evaluating KTE-C19. The company will be requiring all patients in the PII trial to enroll in the hospital for the 1st 7 days after infusion as a pre-cautionary measure and a req't similar to the NCI PI/II study. We think this is a prudent measure which may help address any pot'l toxicity issue(s) that may arise in the DLBCL trial. Based on learnings from this trial, the company may reduce/eliminate this req't longer-term. Interim data from the 1st 50 patients in the pivotal trial would drive a BLA filing by YE '16. KITE expects to complete patient enrollment by YE '16. The 1 EP is ORR with data expected in 2016. KITE also plans to initiate trials in acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL) which would initiate by YE '15.

Pipeline Programs Advance: The National Cancer Institute (NCI) has currently five ongoing trials with various targets with KITE having rights to the following cancer antigen targets - NY-ESO1 and HPV-16 E6 w/ KITE anticipating on filing an IND in 1H '16. The company announced NCI plans to initiate clinical testing w/ a KRAS TCR in pancreatic/ colorectal cancer and HPV-16 E7 TCR in cervical cancer in '15. We gained further insights into these programs from NCI's Chief of Surgery Branch, Dr. Steven Rosenberg, who provided his opinions into pot'l optimal targets for solid tumors. Rosenberg believes HPV-16 E6 is de-risked given data in 9 refractory cervical cancer patients treated with TIL therapy and observing 2 CRs and 1 PR with duration of response lasting 22, 15, and 3 mos, respectively (at end of April). Dr. Rosenberg believes EGFRviii could observe activity given the target resides on the tumor cell surface and could be targeted by CAR technology. A trial is currently ongoing evaluating EGFRviii in glioblastoma and have treated 15 patients to date in a slow dose escalation. NCI has not observed any clinical responses however the trial may be somewhat premature given patients have not been treated w/ therapeutic doses. The NCI is also evaluating NY-ESO1 TCR in various tumors and 4 patients have been treated, however, Dr. Rosenberg is less sanguine about the prospects of NY-ESO1 given less than 2% of all patients express the target at less than 50%. In comparison, MAGE A3 could be a better target given it is more commonly expressed. Lastly, Dr. Rosenberg also commented on the UPenn study at AACR evaluating 6 patients w/ mesothelin CAR-T and believes mesothelin may not be an appropriate target given it also is expressed in healthy tissues.

Next Gen Technologies Focused On Improving T Cell Expansion and Preventing Off-Target Effects: KITE introduced two concepts - one focused on generating T cells utilizing pharmacological molecules which may yield younger T cells w/ greater persistence. We think this technology is based on NCI research which focused on Akt inhibition (Crompton et al, Cancer Research 2015) leading to enhanced cell persistence of memory T cells. KITE is also developing a control CAR which at the presence of a healthy cell could signal the self-destruction of the CAR-T cell.

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Company Description

Kite Pharma, Inc. operates as a clinical stage biotechnology company which engages in the development of novel cancer immunotherapeutic products with focus on engineered autologous T cell therapeutics targeted to different tumor types. In addition, the company is advancing a novel therapeutic cancer vaccine aimed to trigger potent and specific immunity against multiple epithelial cancers, which has the potential to complement its eACT programs.

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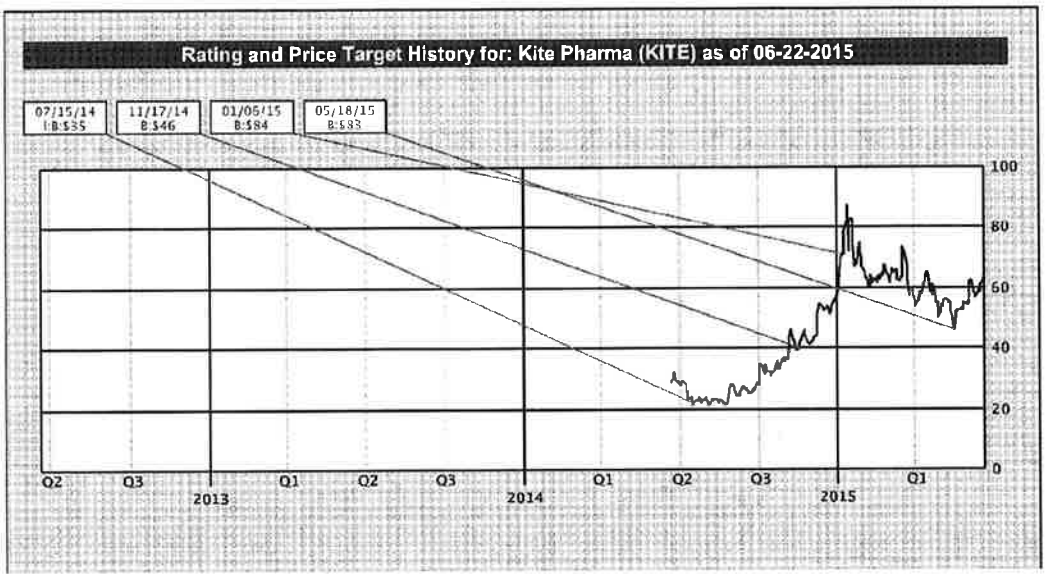

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HOLD	832	39.92%	161	19.35%
UNDERPERFORM	165	7.92%	13	7.88%

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Kite Pharma, Inc.

Investor Day— Under the Hood; No Near-Term Changes

Summary

We are reiterating our Buy rating and $90 PT following KITE's first Investor Day. While there were no clinical data updates or significant announcements, we gained 1) a deeper understanding of the platform and 2) a frank KOL discussion into the future of cancer immunotherapy. Industry collaborations and close academic ties put KITE in a strong position as therapy moves out of lymphoma. "Off-the-shelf" approaches were downplayed, as was the importance of defined-cell populations and long-term persistence, contrasting with some competitors. Catalysts remain 4Q data (ASH) and 2016 readouts.

Key Points

- **Manufacturing techniques to keep cells less differentiated.** KITE is focusing development on new processes and pharmacologic agents that block differentiation and keep a more youthful cell phenotype, which appears to be needed for efficacy. An overview of KITE's TCR GENErator platform technology was provided, which could give KITE a competitive advantage in TCR development. A new commercial manufacturing facility under construction will be ready for a commercial launch of KTE-C19 by 2017, and support 4,000-5,000 doses per year.

- **Catalysts were broadly reiterated.** Key upcoming catalysts are 1) KTE-C19 Phase I NHL data at ASH year-end, and Phase II pivotal data in 2016, 2) initiation of MCL, ALL and CLL pivotal trials in 2H15, and 3) HPV-16 E6 TCR IND submission in 1H16, followed by KTE-C19 BLA filing by YE 2016.

- **Defined-cell populations and long-term persistence were downplayed.** In contrast to competitors that have focused on defined-cell populations as an important aspect of manufacturing, KITE appears to be playing down the importance at this stage. Regarding persistence of CAR T-cells, panelists at the meeting thought that the current evidence points to needing the CAR to persist for only a couple of weeks to a month in order to produce effective treatment, which downplays the need to substantially improve persistence.

- **Panel members see combo therapy as an eventuality.** The panel expects that CAR and TCR will evolve into an integral part of combination therapy. Dr. Steven Rosenberg, Chief of Surgery at NCI and a key collaborator, had a substantial part of his talk and comments focused on increasing the personalization of CARs. The panel was negative on off-the-shelf approaches to CAR therapy, which would be a negative for companies like CLLS (Not Rated, $36.54) and ZIOP (Neutral-rated).

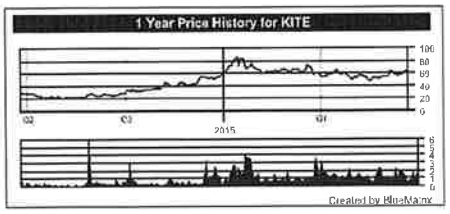
Rating	**Buy**
Previous Rating	No Change
Price (6/23)	**$62.72**
Price Target	**$90.00**
Previous Price Target	No Change

Key Data

Symbol	KITE (NASDAQ)
52-Week Range	$89.21 - $21.00
Market Cap ($mm)	$2,701
Shares Outstanding (mm)	43.1
Float	27.7
Average Daily Volume	1,268,003
Dividend per Share ($)	NA

Fiscal Year-End: Dec 31

	2014A	2015E Prior	2015E Curr	2016E Prior	2016E Curr
Revenue ($mm)					
1Q	0.0A	–	2.9A	–	–
2Q	0.0A	–	2.9E	–	–
3Q	0.0A	–	2.9E	–	–
4Q	0.0A	–	2.9E	–	–
Yr	**0.0A**	–	**11.5E**	–	**34.9E**
P/ Revenue	NM	–	NM	–	77.4x
Earnings per Share ($) Non-GAAP					
1Q	(0.60)A	–	(0.36)A	–	–
2Q	(1.41)A	–	(0.50)E	–	–
3Q	(0.24)A	–	(0.60)E	–	–
4Q	(0.33)A	–	(0.70)E	–	–
Yr	**(1.60)A**	–	**(2.16)E**	–	**(2.52)E**
P/E	NM	–	NM	–	NM



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Manufacturing Techniques to Keep Cell Products Less Differentiated, and TCR Development

CSO Margo Roberts, who received a patent on a second generation CAR in 1995, presented a look at KITE's design approach for CAR's, which can be as quick as 18 months from the initial design of the single chain variable fragment (scFv) that targets the CAR to the tumor, to IND filing. While using precisely defined cell populations were less of a concern for KITE, having a T cell population that was in general composed of less differentiated, more "youthful" T cells that drive proliferation (more stem cell memory and central memory cells) was important. KITE is focusing development on new processes and pharmacologic agents that block differentiation and keep a more youthful cell phenotype.

KITE's European CSO, Ton Schumacher, presented an overview of TCR development, which has been overshadowed by CAR development but could target 2x-3x more antigens. In particular was an overview of the TCR GENErator platform technology acquired with KITE's acquisition of T-Cell Factory B.V. in March. The platform, which could provide KITE with an advantage in TCR development, enables high-throughput generation of peptide-MHC (pMHC) complexes that are used to select the most promising TCRs for development.

Manufacturing and Scale Always a Concern

KITE is actively investing in developing both capacity and manufacturing protocols. KITE's new commercial manufacturing facility, under construction now, will be ready for a commercial launch of KTE-C19 in 2017, and support 4,000-5,000 doses per year.

Catalysts Broadly Reiterated

HPV-16 E6 TCR will be next product for IND submission, in 1H16, and the expanded NCI CRADA announced in March will include KRAS, a colorectal cancer target (93,000 new cases per year in the U.S.). Key upcoming catalysts are 1) lead program KTE-C19 Phase I NHL data at ASH year-end, and Phase II pivotal data in 2016, 2) initiation of MCL, ALL and CLL pivotal trials in 2H15, and 3) HPV-16 E6 TCR IND submission in 1H16, followed by KTE-C19 BLA filing and IND filings from the AMGN (Not Rated, $161.69) collaboration by YE 2016.

Importance of Defined-cell Populations and Long-term Persistence Downplayed

In contrast to competitors like JUNO (Not Rated, $51.40) that have focused on defined-cell populations as an important aspect of CAR and TCR manufacturing, KITE appears to be playing down its importance at this stage from both a clinical efficacy and manufacturing perspective (as was shown in ASCO data), though has not ruled it out entirely as a factor.

Regarding persistence of CAR T-cells, panelists at the meeting thought that the current evidence points to needing the CAR to persist for only a couple of weeks to a month in order to produce effective treatment, which downplays the need to substantially improve persistence. As far as CAR design, substantial, basic work still needs to be done across the industry- for instance, there has not been a robust study yet on the best co-stimulatory domain to use.

Limited Insight into New bluebird bio Collaboration

We know the BLUE (Not Rated, $174.31) collaboration will focus on a next-gen HPV-16 E6 TCR, which is likely 2-3 years away. The collaboration could also enable editing of T-cells to be more resilient in the tumor micro-environment, a key obstacle to overcome to improve solid tumor efficacy. The negative reaction to mesothelin solid-tumor data from UPenn appeared to be largely anticipated by the experts, who had a history of working with the target and didn't believe it would be among the promising targets.

Panel Members See Combo therapy as an Eventuality

The panel expects that CAR and TCR will evolve into an integral part of combination therapy, such as combining with checkpoint inhibitors, or developing effective sequencing of different therapies which will include CARs. Dr. Steven Rosenberg, Chief of Surgery at NCI and a key collaborator, had a substantial part of his talk and comments focused on increasing the personalization of treatment, with the use of tumor neoantigens especially prominent- for instance, exomic sequencing of the tumor and identification of integral antigens, followed by development of a personalized CAR, all within the span of a couple of weeks. The panel was negative on off-the-shelf approaches to CAR therapy, which would be a negative for companies like CLLS (Not Rated, $36.54) and ZIOP (Neutral-rated) that are making allogenic, off-the-shelf development more of a focus.

KITE Catalysts and Milestones

Candidate	Setting	Trial / Milestone	Time
KTE-C19	DLBCL, PMBCL, TFL	KITE-sponsored P1 data	ASH 2015
KTE-C19	DLBCL, PMBCL, TFL	KTE-C19-101 study P1 safety analysis- After 50 patients; Study details: n=72 DLBCL, n=40 PBMCL, FL; refractory disease, ORR primary endpoint, 25 centers; Conditioning therapy (fludarabine and cyclophosphamide) followed by single CAR transfusion @ 2x10^6 cells/kg)	Early 2016
KTE-C19	DLBCL, PMBCL, TFL	Complete P1/2 enrollment	1H 2016
KTE-C19	DLBCL, PMBCL, TFL	Initial P2 data	2016
KTE-C19	DLBCL, PMBCL, TFL	BLA filing	YE 2016
KTE-C19	DLBCL, PMBCL, TFL	Initiate P3- Confirmatory trial for accelerated approval	2016
KTE-C19	R/R/ MCL	Initiate P2 KTE-C19-102, n=70, ORR primary endpoint	2H 2015
KTE-C19	R/R CLL	Initiate P2 trial	2H 2015
KTE-C19	R/R ALL	Initiate P2 KTE-C19-103 trial, n=50, CR primary endpoint	2H 2015
anti-CD19 (NCI)	R/R B cell lymphomas and leukemias	NCI update	2015
EGFRvIII CAR	Glioblastoma	P1 data	2H 2015
NY-ESO-1 TCR	Solid tumors	Phase II data - NCI-sponsored- murine TCR	2015
NY-ESO-1 TCR	Solid tumors	Submit IND	Late 2015
EGFRvIII CAR	Glioblastoma	Submit IND	2016
MAGE A3	MAGE-A3 expressing tumors	P1/2 data - NCI trial	2015
SSX2 TCR	SSX2-expressing tumors	Initiate P1/2 NCI trial	2015
HPV-16 E6 TCR	Cervical, head & neck	IND sumbission	1H 2016
HPV-16 E6 TCR	Cervical, head & neck	P1/2 data - NCI trial	2015
KRAS TCR	Colorectal	Submit IND	2016
NA	NA	KITE/AMGN CAR IND submissions	2H 2016

Source: Company reports and Mizuho Securities USA, Inc.

Kite Pharma
Annual Income Statement

($ in millions, except per share data)

FY-ending Dec 31,	2012	2013	2014	2015E	2016E	2017E	2018E
Revenue							
KTE-C19 Product revenue	$ -	$ -	$ -	$ -	$ 23.3	$ 202.9	$ 482.3
KTE-C19 Royalty revenue	$ -	$ -	$ -	$ -	$ -	$ -	$ 3.7
Collaboration revenue	$ -	$ -	$ -	$ 11.5	$ 11.5	$ 11.5	$ 11.5
Total Revenue	$ 0.0	$ 0.0	$ 0.0	$ 11.5	$ 34.9	$ 214.5	$ 497.5
Cost of Sales	$ -	$ -	$ -	$ -	$ 15.2	$ 101.5	$ 192.9
Gross Profit	$ 0.0	$ 0.0	$ 0.0	$ 11.5	$ 19.7	$ 113.0	$ 304.6
Gross Margin	—	—	—	*100.0%*	*56.5%*	*52.7%*	*61.2%*
Operating Expenses							
Research and Development	$ 1.8	$ 5.1	$ 23.1	$ 59.8	$ 77.8	$ 85.6	$ 89.8
SG&A	0.8	1.3	$ 13.6	48.7	58.7	78.7	88.7
Total Operating Expenses	2.6	6.4	36.7	108.5	136.5	164.3	178.5
Operating Income	$ (2.6)	$ (6.4)	$ (36.7)	$ (97.0)	$ (116.8)	$ (51.3)	$ 126.1
Net Interest & Other	0.0	0.1	0.2	1.9	1.0	1.0	1.0
Pretax Income	$ (2.6)	$ (6.4)	$ (36.5)	$ (95.1)	$ (115.8)	$ (50.3)	$ 127.1
Income Tax Expense	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 44.5
Tax Rate	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*35.0%*
Net Income (Operating)	$ (2.6)	$ (6.4)	$ (36.5)	$ (95.1)	$ (115.8)	$ (50.3)	$ 82.6
Extra. & Amortization	0.0	(1.4)	(7.2)	0.0	0.0	0.0	0.0
Net Income (GAAP)	$ (2.6)	$ (7.8)	$ (43.7)	$ (95.1)	$ (115.8)	$ (50.3)	$ 82.6
Adjusted EPS	($0.07)	($1.16)	($1.60)	($2.16)	($2.52)	($1.04)	$1.64
Diluted GAAP EPS	($0.07)	($1.43)	($1.91)	($2.16)	($2.52)	($1.04)	$1.64
Diluted Shares Outstanding	38.4	5.5	22.8	44.0	46.0	48.1	50.3

Source: Company Reports and Mizuho Securities USA Inc. estimates

($ in millions, except per share data)												
FY ending Dec 31,	2013				2014				2015E			
	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2QE	3QE	4QE
Revenue												
KTE-C19 Product revenue												
KTE-C19 Royalty revenue												
Collaboration revenue									$ 2.9	$ 2.9	$ 2.9	$ 2.9
Total Revenue	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 2.9	$ 2.9	$ 2.9	$ 2.9
Cost of Sales	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0
Gross Profit	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 2.9	$ 2.9	$ 2.9	$ 2.9
Gross Margin	—	—	—	—	—	—	—	—	*100.0%*	*100.0%*	*100.0%*	*100.0%*
Operating Expenses												
Research and Development	$ 0.9	$ 1.1	$ 1.2	$ 1.9	$ 2.1	$ 7.4	$ 5.7	$ 7.9	$ 9.3	$ 13.9	$ 16.9	$ 19.9
SG&A	0.2	0.3	0.3	0.5	1.1	3.7	3.4	5.4	9.2	11.2	13.2	15.2
Total Operating Expenses	$ 1.1	$ 1.4	$ 1.5	$ 2.4	$ 3.2	$ 11.1	$ 9.1	$ 13.3	$ 18.4	$ 25.0	$ 30.0	$ 35.0
Operating Income	$ (1.1)	$ (1.4)	$ (1.5)	$ (2.4)	$ (3.2)	$ (11.1)	$ (9.1)	$ (13.3)	$ (15.6)	$ (22.2)	$ (27.2)	$ (32.2)
Net Interest & Other	0.0	(0.0)	0.0	0.0	(0.1)	0.0	0.1	0.2	0.5	0.5	0.5	0.5
Pretax Income	(1.1)	(1.4)	(1.5)	(2.4)	(3.3)	(11.1)	(9.1)	(13.0)	(15.1)	(21.7)	(26.7)	$ (31.7)
Income Tax Expense	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0
Tax Rate	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
Net Income (Operating)	$ (1.1)	$ (1.4)	$ (1.5)	$ (2.4)	$ (3.3)	$ (11.1)	$ (9.1)	$ (13.0)	$ (15.1)	$ (21.7)	$ (26.7)	$ (31.7)
Extra. & Amortization	(0.0)	(0.3)	(0.6)	(0.6)	(6.6)	(0.5)	(0.1)	0.0	0.0	0.0	0.0	0.0
Net Income (GAAP)	(1.1)	(1.7)	(2.1)	$ (2.9)	$ (9.9)	$ (11.6)	$ (9.2)	$ (13.0)	$ (15.1)	$ (21.7)	$ (26.7)	$ (31.7)
Adjusted EPS	($0.19)	($0.26)	($0.27)	($0.43)	($0.60)	($1.41)	($0.24)	($0.33)	($0.36)	($0.50)	($0.60)	($0.70)
Diluted GAAP EPS	($0.20)	($0.32)	($0.37)	($0.54)	($1.79)	($1.47)	($0.24)	($0.33)	($0.36)	($0.50)	($0.60)	($0.70)
Diluted Shares Outstanding	5.5	5.5	5.5	5.5	5.5	7.9	38.3	39.0	42.5	43.5	44.5	45.5

Source: Company Reports and Mizuho Securities USA Inc. estimates

Kite Pharma
Annual Cash Flow Statement

($ in millions, except per share data)

FY-ending Dec 31,	2012	2013	2014	2015E	2016E	2017E	2018E
Operating Activities							
Net Income	$ (2.6)	$ (7.8)	$ (36.5)	$ (95.1)	$ (115.8)	$ (50.3)	$ 82.6
Depreciation & Amortization	0.0	0.0	0.2	2.0	4.0	6.0	8.0
Working Capital	(0.3)	0.6	3.4	(0.4)	(10.1)	(12.0)	(14.2)
Other	0.1	1.5	(8.5)	60.0	0.0	0.0	0.0
Net Cash from Operations	**$ (2.8)**	**$ (5.6)**	**$ (41.3)**	**$ (33.5)**	**$ (121.9)**	**$ (56.3)**	**$ 76.4**
Investing Activities							
Acquisitions, net	$ 0.0	$ 0.0	$ 0.0	$ (20.0)	$ 0.0	$ 0.0	$ 0.0
Capital Expenditures	(0.0)	(0.3)	(2.0)	(20.0)	(20.0)	(10.0)	(10.0)
Other	0.0	0.0	(116.5)	0.0	0.0	150.0	0.0
Net Cash from Investing	**$ (0.0)**	**$ (0.3)**	**$ (118.5)**	**$ (40.0)**	**$ (20.0)**	**$ 140.0**	**$ (10.0)**
Financing Activities							
Issuance / Reduction of Debt	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0
Issuance of Common Stock	0.0	19.6	379.6	16.0	0.0	10.0	10.0
Dividends	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Other	0.3	0.0	(32.8)	0.0	0.0	0.0	0.0
Net Cash from Financing	**$ 0.3**	**$ 19.6**	**$ 346.8**	**$ 16.0**	**$ -**	**$ 10.0**	**$ 10.0**
Net Exchange rate effect	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Net Change in Cash	**$ (2.5)**	**$ 13.7**	**$ 187.0**	**$ (57.5)**	**$ (141.9)**	**$ 93.7**	**$ 76.4**
Cash from Prior Period	11.2	8.7	22.3	209.3	151.8	9.8	103.6
Net Cash	**$ 8.7**	**$ 22.3**	**$ 209.3**	**$ 151.8**	**$ 9.8**	**$ 103.6**	**$ 180.0**
Cash Flow	**$ (2.6)**	**$ (6.3)**	**$ (36.2)**	**$ (93.1)**	**$ (111.8)**	**$ (44.3)**	**$ 90.6**
Cash Flow Per Share	($0.07)	($1.16)	($1.59)	($2.12)	($2.43)	($0.92)	$1.80
EBITDA	**$ (2.6)**	**$ (6.4)**	**$ (36.4)**	**$ (95.0)**	**$ (112.8)**	**$ (45.3)**	**$ 134.1**
EBITDA per Share	($0.07)	($1.17)	($1.60)	($2.16)	($2.45)	($0.94)	$2.67
Free Cash Flow	**$ (2.8)**	**$ (6.0)**	**$ (34.8)**	**$ (113.5)**	**$ (141.9)**	**$ (66.3)**	**$ 66.4**
Free Cash Per Share	($0.07)	($1.10)	($1.53)	($2.58)	($3.09)	($1.38)	$1.32

Source: Company Reports and Mizuho Securities USA Inc. estimates

Kite Pharma
Annual Balance Sheet

($ in millions, except per share data)

FY-ending Dec 31,	2012	2013	2014	2015E	2016E	2017E	2018E
Assets							
Current Assets:							
Cash + Equivalents + ST inv	$ 160.0	$ 22.4	$ 367.1	$ 347.0	$ 205.0	$ 148.7	$ 225.2
Receivables - net	1.8	0.0	0.0	0.0	1.7	10.7	24.9
Inventories	0.0	0.0	0.0	0.0	1.5	10.1	19.3
Other	0.8	0.2	1.3	6.4	6.4	6.4	6.4
Total Current Assets	**$ 162.7**	**$ 22.6**	**$ 368.4**	**$ 353.4**	**$ 214.7**	**$ 176.0**	**$ 275.8**
PP & E, net	$ 2.1	$ 0.3	$ 2.3	$ 17.8	$ 33.8	$ 37.8	$ 39.8
Goodwill	0.0	0.0	0.0	39.9	39.9	39.9	39.9
Other Assets	0.8	0.1	0.1	11.5	11.5	11.5	11.5
Total Assets	**$ 165.5**	**$ 23.0**	**$ 370.8**	**$ 422.6**	**$ 299.9**	**$ 265.3**	**$ 367.0**
Liabilities and Shareholders' Equity							
Current Liabilities:							
Current Debt	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0
Accounts Payable	3.0	0.4	6.7	11.4	4.6	10.1	19.3
Accruals & Other	32.5	1.0	0.0	45.4	45.4	45.4	45.4
Total Current Liabs.	**$ 35.5**	**$ 1.4**	**$ 6.7**	**$ 56.9**	**$ 50.0**	**$ 55.6**	**$ 64.7**
Long-Term Debt	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0	$ 0.0
Other Liabilities	43.0	0.0	1.4	39.0	27.4	15.8	4.2
Stockholders Equity	17.9	21.6	362.6	326.8	222.6	193.9	298.1
Total Liabs. & Equity	**$ 96.4**	**$ 23.0**	**$ 370.8**	**$ 422.6**	**$ 299.9**	**$ 265.3**	**$ 367.0**

Kite Pharma
Ratio Analysis

FY-ending Dec 31,	2012	2013	2014	2015E	2016E	2017E	2018E
Book Value per share	$0.47	$3.94	$15.89	$7.43	$4.84	$4.03	$5.93
Cash per share	$4.17	$4.08	$16.08	$7.89	$4.46	$3.09	$4.48
Net Cash per share	$4.17	$4.08	$16.08	$7.89	$4.46	$3.09	$4.48
Current Ratio	4.6	16.6	54.8	6.2	4.3	3.2	4.3
Total Debt / Equity	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Total Debt / Total Capital	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Source: Company Reports and Mizuho Securities USA Inc. estimates

Price Target Calculation and Key Risks

We derive our price target by applying both a discounted cash flow analysis and discounted P/E analysis to yield a price target of $90. Risks to our price target outside of clinical failure relate to 1) platform risk, 2) competitive risk and 3) commercialization risk.

Companies Mentioned (prices as of 6/23)
Amgen Inc (AMGN- Not Rated)

ZIOPHARM Oncology, Inc. (ZIOP- Neutral $11.79)

IMPORTANT DISCLOSURES

The disclosures for the subject companies of this report as well as the disclosures for Mizuho Securities USA Inc. entire coverage universe can be found at https://msusa.bluematrix.com/sellside/Disclosures.action or obtained by contacting EQSupervisoryAnalystUS@us.mizuho-sc.com or via postal mail at Equity Research Editorial Department, Mizuho Securities USA Inc., 320 Park Avenue, 12th Floor, New York NY, 10022.

Ownership Disclosures and Material Conflicts of Interest or Position as Officer or Director

None

Receipt of Compensation

Mizuho Securities USA Inc. and or its affiliates makes a market in the following securities: Kite Pharma, Inc., Amgen Inc and ZIOPHARM Oncology, Inc.

Mizuho Securities USA Inc. and or its affiliates has received compensation for investment banking services for Amgen Inc and ZIOPHARM Oncology, Inc. in the past 12 months.

Mizuho Securities USA Inc. and or its affiliates expects to receive or intends to seek compensation for investment banking services for Amgen Inc in the next 3 months.

Mizuho Securities USA Inc. and or its affiliates has managed or co-managed a public offering of securities for Amgen Inc and ZIOPHARM Oncology, Inc. in the past 12 months.

The compensation of the research analyst writing this report, in whole or part, is based on MSUSA's annual revenue and earnings and is not directly related to any specific investment banking compensation. MSUSA's internal policies and procedures prohibit research analysts from receiving compensation from companies covered in the research reports.

Regulation Analyst Certification (AC)

I, Peter Lawson, hereby certify that the views expressed in this research report accurately reflect my personal views about any and all the subject companies. No part of my compensation was, is or will be, directly or indirectly, related to the specific recommendations or views expressed in this research report.

Rating Definitions

As of October 3, 2011

Mizuho Securities USA investment ratings are based on the following definitions. Anticipated share price change is based on a 6- to 12-month time frame. Return expectation excludes dividends.

Buy:	Stocks for which the anticipated share price appreciation exceeds 10%.
Neutral:	Stocks for which the anticipated share price appreciation is within 10% of the share price.
Underperform:	Stocks for which the anticipated share price falls by 10% or more.
RS:	Rating Suspended - rating and price objective temporarily suspended.
NR:	No Rating - not covered, and therefore not assigned a rating.

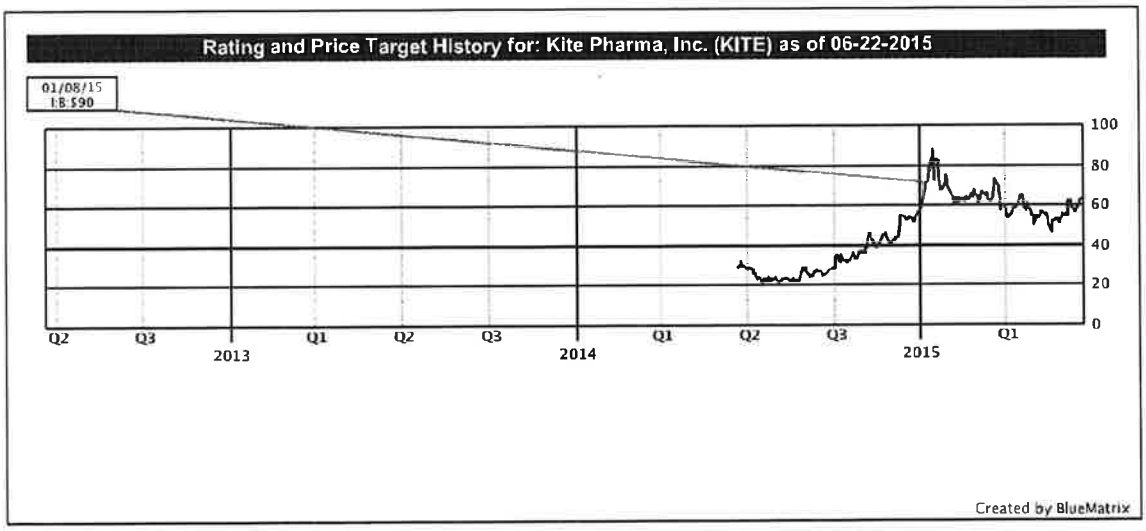
Prior to October 3, 2011

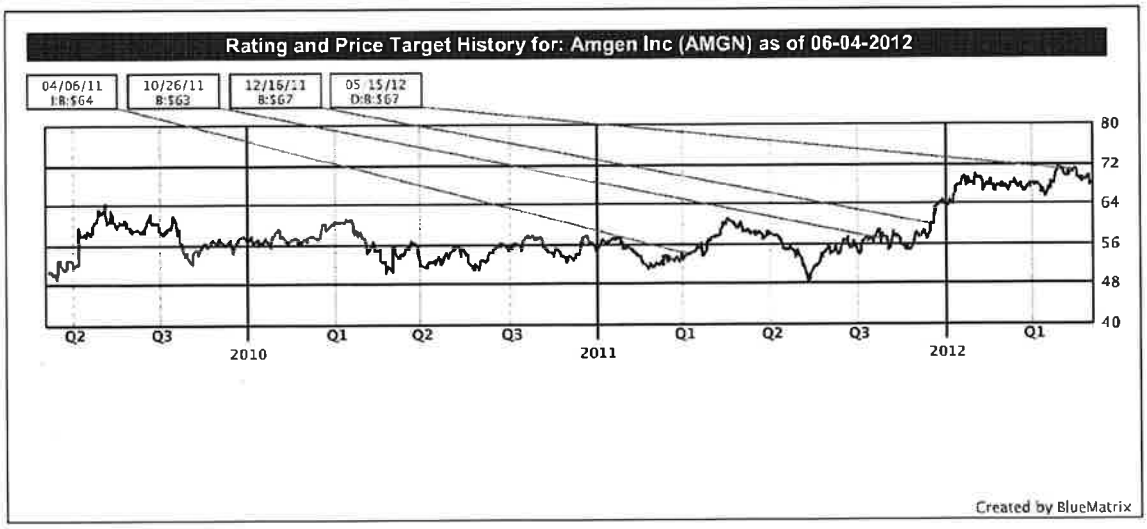
Buy:	Estimated stock price appreciation of 20% or more.
Outperform:	Outperform the stock market averages by 12% or more.
Neutral:	Perform in line with the stock market averages (Hold).
Underperform:	Underperform the stock market averages by 12% or more.
Sell:	Estimated stock price decline of 20% or more.

Rating Distribution

(As of 6/23)	% of coverage	IB service past 12 mo
Buy (Buy)	53.70%	35.63%
Hold (Neutral)	45.06%	19.18%
Sell (Underperform)	1.23%	0.00%

For disclosure purposes only (NYSE and FINRA ratings distribution requirements), our Buy, Neutral and Underperform ratings are displayed as Buy, Hold and Sell, respectively. However, our Buy, Neutral and Underperform ratings are determined on a relative basis (please refer to definitions above).


Rating and Price Target History for: Kite Pharma, Inc. (KITE) as of 06-22-2015
01/08/15
I:B:$90
100
80
60
40
20
0
Q2
Q3
Q1
Q2
Q3
Q1
Q2
Q3
Q1
2013
2014
2015
Created by BlueMatrix


Rating and Price Target History for: Amgen Inc (AMGN) as of 06-04-2012
04/06/11
I:B:$64
10/26/11
B:$63
12/16/11
B:$67
05/15/12
O:B:$67
80
72
64
56
48
40
Q2
Q3
Q1
Q2
Q3
Q1
Q2
Q3
Q1
2010
2011
2012
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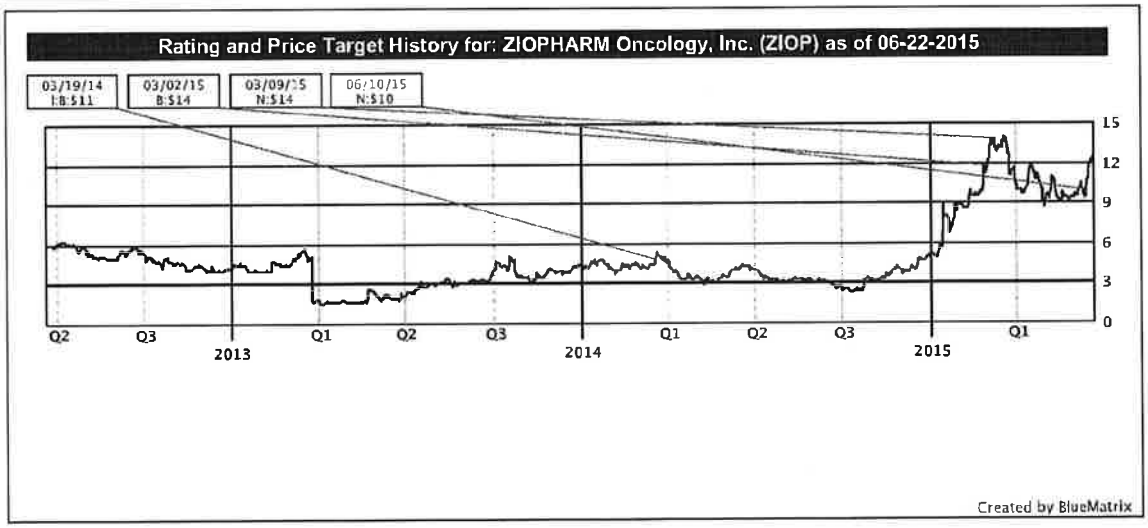
Rating and Price Target History for: ZIOPHARM Oncology, Inc. (ZIOP) as of 06-22-2015
03/19/14
I:B:$11
03/02/15
B:$14
03/09/15
N:$14
06/10/15
N:$10
15
12
9
6
3
0
Q2
Q3
Q1
Q2
Q3
Q1
Q2
Q3
Q1
2013
2014
2015
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One Year Price Chart

June 23, 2015

Kite Pharma, Inc.
KITE – NASDAQ
Buy
Biotechnology

Company Update

Kite Investor Day Update and Bluebird Bio Collaboration

This afternoon we attended Kite Pharma's Investor Day where management provided a corporate overview and the company's key collaborator at the NCI (Steven Rosenberg) gave an overview of the field that hinted at some potentially earthshaking data to come (see below). Kite's recent collaboration with Bluebird was reviewed and looks like a high-level hand-holding exercise as both companies look to enter new areas without wasting time. As expected, the next IND will involve TCRs targeting HPV proteins which are increasingly being viewed as the best TCR target outside of neoantigens.

Changes	Previous	Current
Rating	—	Buy
Target Price	—	$83.00
FY15E EPS	—	$(1.49)
FY16E EPS	—	$0.02

Price (06/23/15):	$62.72
52-Week Range:	$89 – $21
Market Cap.(mm):	2,665.6
Shr.O/S-Diluted (mm):	42.5
Avg Daily Vol (3 Mo):	1,268,003
Net Cash/Share:	$5.31
Cash (mm):	$203
Debt (mm):	$0.0
Dividend($ / %)	$0.00 / 0.0%
S&P Index	2,124.20

EPS	2014A	2015E	2016E
Q1	$(0.56)	$(0.36)A	$NE
Q2	(2.27)	(0.35)	NE
Q3	(0.24)	(0.38)	NE
Q4	(0.33)	(0.40)	NE
FY Dec	$(1.91)A	$(1.49)	$0.02

Quarterly EPS do not sum to annual due to the issuance of shares.

Rosenberg's Next Miracle? Steven Rosenberg delivered principally an overview of the field but also showed a slide of some patients where **his group at the NCI has isolated both neoantigens and their recognizing TCRs** from tumors other than melanoma – specifically gastrointestinal cancers. As a result, we expect he has treated these patients with TCR therapeutics and early data can't be far away (SR has been mentioning this program since ASH). We believe if these data are compelling and CRs are seen for neoantigen-based TCR therapeutics it will be viewed as a major proof-of-concept for Kite's focus on the neoantigen approach in solid tumors. As we have said in previous notes – the operational hurdles for this approach to treating solid tumors are non-trivial – but the approach puts cure on the table for as many as 50% of patients with solid tumors.

The Bluebird Collaboration. The two companies yesterday announced a collaboration agreement to co-develop second generation TCR products, specifically product candidates directed against the HPV-16 E6 oncoprotein. With Bluebird being a gene-editing focused company and Kite specializing in T-Cell therapeutics, the two will leverage each other's strengths to design next-generation T-Cell therapeutics. Kite is almost certainly looking to modify TCR therapeutics to combat the immunosuppressive tumor environment. As a result, we expect they are knocking out some of the receptors found on T-Cells that tumors use to put tumor-hunting TCRs to sleep. As reported at ASCO 2015, KTE019 T-Cells begin to express PD-1 after introduction into patients and tumor cells are expected to express PD-L1 and the resultant interaction potentially reduces efficacy. As a result, knocking out PD-1 in TCR (and CAR-T) therapeutics seems like an obvious things to try. The subsequent list of candidate genes to delete to stimulate TCR therapeutics is very long – probably spurring Kite's urge to find an expert partner.

Next IND – HPV. As was probably expected, Kite's second IND submission will be a TCR therapeutic targeting Human papillomavirus (HPV, a first generation

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approach outside the Bluebird deal). This is a large market opportunity as HPV is the most common viral infection of the reproduction tract, with two viral strains, type 16 & type 18, believed to cause 70% of cervical cancers and a significant percentage of head and neck cancers. In addition, HPV antigens are expected to be very clan as normal cells are not expected to express this target – by definition. Furthermore, HPV antigens are considered excellent targets due to their expression on "essentially every cell" of a tumor. All in all – we view this program very favorably and view it as a second example of our theme that Kite is very close to showing the world definitively that T-Cell therapeutics will treat a lot more than pediatric leukemias.

Target Price Methodology/Risks

We use a multiple of future earnings to derive our $83 target price for KITE. Specifically, to generate our valuation for development-stage biotech companies, we use a 30x multiple of future earnings, which represents a discount to the 20-year average earnings multiple for profitable biotech companies of 37x. Kite's valuation is driven primarily by KTE-C19, currently in Phase I/IIa testing. We apply a 25% discount rate, which we feel reflects the degree of uncertainty surrounding KTE-C19. With a multiple of 30x, we calculate a $83 target price based on our 2022 diluted EPS estimate of $15.92, discounted back 7.5 years.

Development risk for KTE-C19 - If Kite is not able to successfully develop the experimental CAR-T technology, we would have to lower our revenue estimates.

Competitive risk for KTE-C19 - If a competitor proves more effective or tolerable in the treatment of DLBCL, or their drugs are easier to produce, our estimates could prove optimistic.

Regulatory risk for KTE-C19 - The FDA has never approved a CAR-T-based therapy before and there exists no precedent for the approval of a genetically engineered autologous cell product. If KTE-C19 is not approved on the timeline that we envision, we would have to reduce our estimates.

Company Description

Kite Pharma, Inc. is a clinical-stage biopharmaceutical company focused on the development and commercialization of novel cancer immunotherapy products designed to harness the power of a patient's own immune system to eradicate cancer cells. To achieve this, Kite is developing a pipeline of product candidates for the treatment of advanced solid and hematological malignancies using the engineered autologous cell therapy system, in which a patient's own immune system is engineered to recognize and destroy their cancer. Kite's products use engineered chimeric antigen receptor T-cells (CAR-T) or T-cell receptors (TCRs). Kite's technology has been developed through a collaboration agreement with the NCI-Surgery Branch. Kite's most advanced product is KTE-C19, a CAR-T therapy that recognized CD19 and will be developed for diffuse large B-cell lymphoma.

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Tom Shrader 212.271.3577

Kite Pharma (KITE)

Income Statement

(In $Millions, except for per share data)

	2012	2013	2014A	1QA	2QE	3QE	4QE	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E
KTE-C19 U.S. end user sales (a)											$ 34.0	$ 489.3	$ 1,470.8	$ 2,209.9	$ 2,832.5
KTE-C19 Ex-U.S. end user sales (a)											$ -	$ 77.2	$ 691.0	$ 1,661.2	$ 2,245.2
WW KTE-C19 End-user sales											**$ 34.0**	**$ 566.5**	**$ 2,161.9**	**$ 3,871.1**	**$ 5,077.8**
KTE-C19 Ex-U.S. royalty to Kite (b)											$ -	$ 8.8	$ 84.6	$ 214.6	$ 325.3
Milestones and licensing revenue			$ -	2.8	4.0	4.0	4.0	$ 14.8	$ 120.0	$ 26.2	$ 5.2	$ 5.3	$ 5.5	$ 5.6	$ 5.8
Total revenue	-	-	-	2.8	4.0	4.0	4.0	**14.8**	**120.0**	**26.2**	**39.1**	**503.4**	**1,560.9**	**2,430.1**	**3,163.7**
Research & development	1.8	5.1	23.1	9.3	9.8	10.3	10.8	40.1	76.2	114.2	171.4	201.3	312.2	401.6	506.2
SG&A	0.8	1.3	13.6	9.1	9.6	10.0	10.5	39.2	43.1	107.9	334.4	176.2	312.2	413.1	537.8
Total operating expenses	2.6	6.4	36.7	18.4	19.3	20.3	21.3	79.3	119.3	222.1	517.3	539.0	1,095.0	1,521.9	1,922.1
Income (loss) from operations	(2.6)	(6.4)	(36.7)	(15.6)	(15.3)	(16.3)	(17.3)	(64.5)	0.7	(195.9)	(478.1)	(35.6)	465.9	908.3	1,241.6
Total other income (expense)	0.0	0.1	(5.9)	0.2	0.2	0.2	0.2	1.0	0.2	0.2	0.2	0.3	0.7	1.3	2.2
Income (loss) before income taxes	(2.6)	(6.4)	(42.6)	(15.4)	(15.1)	(16.0)	(17.3)	(63.8)	0.9	(195.7)	(478.0)	(35.3)	466.5	909.6	1,243.8
Provision for income taxes	-	-	-	-	-	-	-	-	-	-	-	-	(70.0)	(227.4)	(373.1)
Net income (loss)	(2.6)	(6.4)	(43.7)	(15.4)	(15.1)	(16.0)	(17.3)	(63.8)	0.9	(195.7)	(478.0)	(35.3)	396.5	682.2	870.6
Stick Dividend (Series A)			(0.5)					-							
EPS (basic)	(0.48)	(1.16)	$ (1.91)	(0.36)	(0.35)	(0.38)	(0.40)	$ (1.49)	$ 0.02	$ (3.94)	$ (9.55)	$ (0.70)	$ 7.81	$ 13.35	$ 16.93
EPS (diluted)	(0.48)	$ (1.16)	$ (1.91)	(0.36)	(0.35)	(0.38)	(0.40)	$ (1.49)	$ 0.02	$ (3.80)	$ (9.17)	$ (0.67)	$ 7.43	$ 12.62	$ 15.92
Basic shares	5.3	5.5	22.8	42.5	42.6	42.8	42.9	42.7	49.4	49.7	50.1	50.4	50.8	51.1	51.4
Diluted shares	5.3	5.5	22.8	42.5	42.6	42.8	42.9	42.7	50.8	51.5	52.1	52.8	53.4	54.0	54.7
Cash															
Long-term debt															
Margin Analysis															
COGS (% of sales)		NM	NM	NM	NM	NM	NM	NM	NM	NM	34%	33%	32%	32%	31%
R&D (% of total revenue)		NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	40%	20%	17%	16%
SG&A (% of total revenue)		NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	35%	20%	17%	17%
Effective Tax Rate		NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	15%	25%	30%
Gross Margin		NM	NM	NM	NM	NM	NM	100%	NM	NM	66%	71%	78%	82%	83%
Operating Margin		NM	NM	NM	NM	NM	NM	NM	1%	NM	NM	NM	30%	37%	39%
Pretax Margin		NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	(7%)	30%	37%	39%
Net Margin		NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	(7%)	25%	28%	28%
Annual Percentage Change															
KTE-C19 WW Sales		NM	NV	NM	NM	NM	NM	NM	NM	NM	NM	1567%	282%	79%	31%
KTE-C19 US Sales		NM	NV	NM	NM	NM	NM	NM	NM	NM	NM	1340%	201%	50%	28%
KTE-C19 ex-US sales		NM	NV	NM	NM	NM	NM	NM	NM	NM	NM	NM	795%	140%	35%
Total revenue		NM	NV	NM	NM	NM	NM	NM	NM	(78%)	49%	1186%	210%	56%	30%
COGS		NM	NV	NM	NM	NM	NM	NM	NM	NM	NM	NM	192%	50%	24%
R&D		181%	354%	NM	NM	NM	NM	74%	#REF!	50%	50%	17%	55%	29%	26%
SG&A		74%	913%	NM	NM	NM	NM	189%	#REF!	150%	210%	(47%)	77%	32%	30%
Operating income		(149%)	(470%)	NM	NM	NM	NM	(76%)	#REF!	(28257%)	(144%)	93%	1408%	95%	37%
Net income		(148%)	(586%)	NM	NM	NM	NM	(46%)	#REF!	(21837%)	(144%)	93%	1224%	72%	28%
EPS		(140%)	(64%)	NM	NM	NM	NM	22%	#REF!	(21688%)	(143%)	93%	1217%	71%	27%

(a) Assumes full revenues from US sales; no revenues from ex-US, instead recieving partnership royalites

(b) Assumes 17-21% ex-US royalty

(c) As of March 31st, 2014, Kite had 5,588,632 options outstanding at an average excise price of $1.00

Source: Company reports and Stifel estimates

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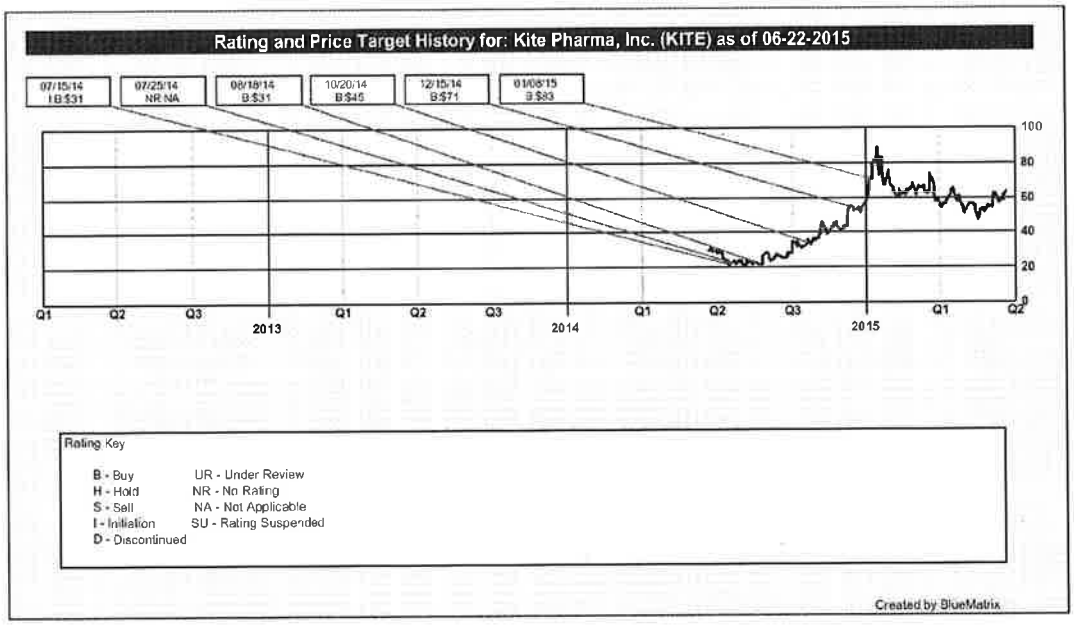

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Sent: Wednesday, July 01, 2015 7:22 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Fwd: Juno Therapeutics : Takeaways from Lunch with Management

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Arie Belldegrun, MD FACS
President and CEO, Chairman
Kite Pharma

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Begin forwarded message:

From: Ran Nussbaum <ran@pontifax.com>
Date: July 1, 2015 at 05:40:22 GMT+3
To: Ohad Hammer <ohad@pontifax.com>, William Go <wgo@kitepharma.com>, "Margo Roberts" <MRoberts@kitepharma.com>, Jeff Wiezorek <JWiezorek@kitepharma.com>, Helen Kim <HKim@kitepharma.com>, David Chang <DChang@kitepharma.com>, Cynthia Butitta <CButitta@kitepharma.com>, Arie Belldegrun <arie@kitepharma.com>, Antoni Ribas <ARibas@mednet.ucla.edu>, Adrian Bot <ABot@kitepharma.com>, Farah Champsi <fchampsi@altapartners.com>, Jon Peacock <jon.peacock@bellerophon.com>, Joshua Kazam <jak@tworiver.com>, "David Bonderman" <dbonderman@tpg.com>
Subject: Fwd: Juno Therapeutics : Takeaways from Lunch with Management

Abstract: Earlier today we hosted a lunch with JUNO's CEO Hans Bishop and CFO Steve Harr in Boston on the back of last night's announcement of a collaboration with CELG (see our note here). Overall not much meaningfully new came out of the discussion, which focused largely on the potential of JUNO's platform and future directions as the company works to improve cell persistence and enter the solid tumor space. On the CELG deal, JUNO largely reiterated comments from last night's conference call, underscoring that this amount of capital (recall CELG will pay JUNO $1B) can really be transformative. Management also highlighted the "importance of being broad" to remain competitive, pointing to the focus on continued BD and the access to some of CELG's pipeline as important for future success. A few additional takeaways from the meeting are provided below. Maintain OW.

Persistence of cells remains a key focus for JUNO to improve upon efficacy. While some others in the field aren't as focused on T cell persistence, JUNO continues to think it is one of the major hurdles to overcome for long term durability of response… otherwise, management noted, why are we seeing patients relapsing from CRs with CD19+ disease? Management reviewed JCAR014 data presented at ASCO that included fludarabine in the preconditioning regimen, noting this data is the first validation that cell persistence correlates with improved clinical benefits. Additionally, JUNO talked about the importance of fully human CARs (given the immune response to the murine based receptors); its first CD19 fully human CAR will enter the clinic later this year and a trial with its fully human CD22 CAR is already underway.

With the CELG collaboration, JUNO gains access to a global clinical network that will accelerate the pace of studies as products move into multi center trials. In addition to the clinical trial infrastructure, JUNO also noted that the expanded operational capabilities that come with the deal shouldn't be minimized. JUNO can focus on what it does best (cell therapies), but as they learn more about T cell biology, the collaborators can make use of those learnings not only with JUNO's cell therapies but also proteins and small molecules (CELG's area of expertise). Additionally, on the BD front management reiterated the CELG/JUNO team is more attractive given the potential for multi-modality combinations. A company could now look to partner its small molecule/other therapy with CELG's small molecule/protein pipeline, in addition to JUNO's cell therapies (plus JUNO can benefit from the reputation of a great partner).

For solid tumors, JUNO reiterated it believes it has 4 promising targets in its current pipeline.... and mesothelin isn't one of them. Recall Penn/NVS presented initial data with a mesothelin CAR at AACR that left investors disappointed. Interestingly, JUNO noted that one of its founding institutions has a fully human mesothelin CAR-T ready to go into the clinic, but that JUNO isn't investing in that as it doesn't believe it is a viable target with current technologies (given its expression on healthy tissue in addition to tumor). JUNO did indicate that a "logic gated" CAR-T cell could make a target like mesothelin more attractive, wherein, for example, one CAR on the T-cell recognizes mesothelin and activates the cell, while another CAR could recognize an antigen expressed only on healthy tissue to "turn off" the CAR-T activity against healthy tissue. Animal data coming out of the Sadelain lab (MSKCC) is very promising here, though the company noted that the biology is complicated (and it has yet to be tested in humans).

Link: https://jpmm.com/research/content/GPS-1749240-0

Date: Tue Jun 30 22:22:19 EDT 2015

From: David Chang [DChang@KitePharma.com]
Sent: Thursday, July 09, 2015 7:14 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]; Jae Park
Subject: CD19 CAR experience

Hi Steve,

I am copying Jae Park as a way of e-introduction. As we discussed last week, Jae is leading the CD19 CAR ALL program at MSKCC.

Best, David

David Chang, MD, PhD
office: (310) 622-9094
PERSONAL INFORMATION,REDACTED PER AGREEMENT

www.kitepharma.com

Sent from my iPad

From: Dr Arie Belldegrun [arie@belldegrun.com]
Sent: Saturday, July 11, 2015 7:17 PM
To: PROPRIETARY INFORMATI Kochenderfer, James (NIH/NCI) [E]; Rosenberg, Steven A. (NIH/NCI) [E]; 'Nimer, Stephen D'; William Go
Subject: RE: patient from PERSONAL INFORMATION

Hi Joe and Steve,

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

I know that Dr. Rosenberg will be in touch with you all soon.

All the best,

Arie

-----Original Message-----
From: PERSONAL INFORMATION,REDACTED PER AGREEMENT
Sent: Friday, July 10, 2015 2:58 PM
To: kochendj@mail.nih.gov; sar@mail.nih.gov
Cc: Nimer, Stephen D
Subject: FW: patient from PERSONAL INFORMATION

Dear Steve and James:

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Monday, July 20, 2015 11:44 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Adaptimmune's NY-ESO-1 TCR-engineered T-Cells Demonstrate Durable Persistence, Clinical Activity and Tolerability in Clinical Study in Multiple Myeloma Patients

Hi Steve,

Please take a look at the NY ESO 1 Nature Med paper,

Arie

http://finance.yahoo.com/news/adaptimmunes-ny-eso-1-tcr-150100385.html

Via Yahoo Finance.

Arie Belldegrun, MD FACS
President and CEO, Chairman
Kite Pharma

www.kitepharma.com

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Friday, July 24, 2015 11:22 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Fwd: ADAP - Executing Toward Major Milestones - Cowen and Company

See below

Arie Belldegrun, MD FACS
President and CEO, Chairman
Kite Pharma

www.kitepharma.com

Begin forwarded message:

From: Lisa Burns <LBurns@burnsmc.com>
Date: July 24, 2015 at 12:21:08 GMT+2
To: Arie <arie@kitepharma.com>, C Butitta <cbutitta@kitepharma.com>, "David Chang M.D. D. Ph. D. (dchang@kitepharma.com)" <dchang@kitepharma.com>, "Helen Kim (Kite Pharma)" <hkim@kitepharma.com>
Cc: "Catherine Bechtold (kbechtold@kitepharma.com)" <kbechtold@kitepharma.com>, "Linda Barnes (lbarnes@kitepharma.com)" <lbarnes@kitepharma.com>, Kite Team <Kite_Team@burnsmc.com>
Subject: ADAP - Executing Toward Major Milestones - Cowen and Company

From: Eric Schmidt, Ph.D. [mailto:eric.schmidt@cowen.com]
Sent: Friday, July 24, 2015 4:01 AM
To: Lisa Burns
Subject: QUICK TAKE - ADAP - Executing Toward Major Milestones - Cowen and Company

LINK TO FULL REPORT & DISCLOSURES

COWEN
AND COMPANY

Biotechnology
Adaptimmune

Equity Research

July 24, 2015

Price: $16.59 (07/23/2015)
Price Target: NA
OUTPERFORM (1)

Eric Schmidt, Ph.D.
646.562.1345
eric.schmidt@cowen.com
Marc Frahm, Ph.D.
646.562.1394
marc.frahm@cowen.com

Key Data

Symbol	NASDAQ: ADAP
Market Cap (MM)	$1,174.3

Quick Take: Company Update

Executing Toward Major Milestones

The Cowen Insight
We hosted meetings with Adaptimmune's CEO James Noble, COO Helen Tayton-Martin, CFO Adrian Rawcliffe, VP of IR Will Roberts. Adaptimmune is focused on leveraging its antigen/peptide identification and TCR engineering platforms to develop engineered T cell therapies for multiple tumor types. H2:15 will see the initiation of multiple new cohorts/trials, and lay the groundwork for a data-rich 2016.

Remind Me What Adaptimmune Does Again?
Adaptimmune is developing engineered T cell therapies for oncology. Adaptimmune has a fully integrated R&D platform that (1) identifies novel antigen targets expressed within tumors, (2) engineers high affinity T cell receptors (TCRs) specific to these targets, and (3) deploys these TCR constructs in engineered T cell therapies. Adaptimmune's most advanced product, NY-ESO-1, is partnered with GSK and has generated positive early data in synovial sarcoma and multiple myeloma. Adaptimmune's lead wholly-owned candidate, MAGE A10, is set to enter the clinic this year. With a preclinical pipeline of at least 30 targets, we expect multiple additional candidates to begin clinical development in the coming years and Adaptimmune to emerge as a leader in TCR-based cell therapies for cancer.

NY-ESO-1 Generates Durable Responses In Sarcoma; Much Data In 2016

NY-ESO-1 is a cancer testes antigen that is expressed during embryonic development, but is generally not expressed in healthy adult tissues. Its expression is reactivated in many cancer cells including those found in esophageal, melanoma, NSCLC, ovarian, multiple myeloma, and synovial sarcoma tumors. Adaptimmune has previously presented multicenter Phase I/II data indicating an ORR of 60% (including 1 CR) in synovial sarcoma and a nCR/CR rate of 59% in post-transplant multiple myeloma. While early, these datasets compare favorably

to existing standards of care. In terms of durability of effect, management reports that long-term persistence of NY-ESO TCR cells along with responses continue beyond two years in the multiple myeloma study and one year in the synovial study (with the aid of surgical resection). The primary reason for increased durability in myeloma is that this study predates the synovial study by >1 year. During 2016, management intends to release updated data from these trials as well as begin trials in esophageal, lung, ovarian, melanoma, and salvage setting multiple myeloma.

MAGE-A10 IND Active, Dose Escalation To Begin In H2

MAGE A10 is another cancer testes antigen. Data from Adaptimmune and others indicates that MAGE A10's expression is turned on in many bladder, breast, GI, head and neck, lung, melanoma, and ovarian cancers. Adaptimmune has identified an HLA-A2 presented peptide specific to MAGE A10 and engineered a high affinity TCR specific for this MHC:peptide complex. At the time of its IPO, Adaptimmune's MAGE A10 TCR construct had completed its NIH RAC review. Last week, Adaptimmune announced that its IND had been cleared by the FDA. In meetings with investors, Adaptimmune outlined the initial steps in MAGE A10's clinical development. During H2:15 (likely Q4), Adaptimmune will initiate a Phase I dose escalation trial for MAGE A10 in NSCLC. This trial will treat patients with 100K, 1B, or 5B transduced T cells. Management believes at least 1B cells are required to see any signs of efficacy. Data from this trial is expected to be presented in H2:16. If management observes T cell expansion without any major toxicity signals (e.g., significant off-tumor responses) it will expand the MAGE A10 program beyond NSCLC to bladder, breast, head and neck, and GI cancers. Management has not decided if it will begin this expansion as a "basket trial" enrolling any HLA-A2$^+$, MAGE A10$^+$ cancer patient or with separate tumor specific trials. This trial(s) is expected to begin in 2016.

AFP To Enter The Clinic In 2016

Alpha fetoprotein (AFP) is primarily expressed within hepatocellular carcinoma cells. Adaptimmune has nominated AFP as the next target to enter the clinic. Management highlighted preclinical data from this program demonstrating the power of its TCR engineering platform. This data demonstrates that a wild-type AFP specific TCR had a K_D of 754uM and showed minimal ability to generate a T cell response to AFP$^+$ cell lines. After engineering the TCR to possess a K_D of 20uM (38X increase in affinity) the TCR was able to efficiently generate T cell responses against some AFP$^+$ cell lines but not others. TCRs with a K_D of ~10uM (1X further increase in affinity) were able to recognize additional AFP$^+$ cell lines. However, TCRs with a K_D of <5uM demonstrated significant cross-reactivity with AFP$^-$ cell lines. This demonstrates the high level of sensitivity TCRs have for changes in affinity and reaffirms our belief that Adaptimmune's TCR engineering platform could be critical for the successful development of cell therapies against many cancer antigens.

Two INDs Per Year Beginning In 2017

Management reports that its antigen discovery platform has identified cancer specific MHC presented peptides from 30+ antigens (including NY-ESO-1, MAGE A10 and AFP). Adaptimmune reports that of these 30 antigens only 9 are the previously described cancer testes antigens. In addition, 12 of the 30+ targets are under active development. Within these 12 active R&D programs, GSK only has rights to NY-ESO and one additional unnamed target. Therefore, Adaptimmune has retained the vast majority of the economics on its lead programs. Management believes its pipeline of cancer specific targets can supply an average of two INDs per year from 2017 onwards. In order to provide manufacturing capacity for this level of clinical activity, Adaptimmune plans to build a pilot cell production facility. This facility will be located in Philadelphia and be capable of supplying cells for "several hundred" patients per year. Management hopes to sign a property lease soon and have the plant active in 2017.

From: David Chang [DChang@KitePharma.com]
Sent: Friday, August 14, 2015 6:47 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
CC: Justin Jackson; Helen Kim; Jeff Wiezorek; Arie Belldegrun
Subject: FW: LLS PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Dear Steve,

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Thanks,
David

From: Chu, Keting (National Office) [mailto:Keting.Chu@lls.org]
Sent: Thursday, August 13, 2015 1:31 PM
To: David Chang <DChang@KitePharma.com>
Subject: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Hi David,

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

:: keting Chu, MD. PhD | VP, Research Therapy Acceleration Program
:: The Leukemia & Lymphoma Society | 1311 Mamaroneck Ave., Suite 310, White Plains, NY 10605
:: Tel: 914-821-8843 | VOIP 8843 | Fax: 914-821-3343| www.lls.org | keting.chu@lls.org

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Monday, August 17, 2015 1:01 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: tomorrow morning at 9AM
Attachments: PRESS RELEASE 8-17-15 - FINAL.DOCX; SCRIPT 8-17-15 - FINAL.DOCX

Hi Steve,

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

I am enclosing the Press release and the script of my speech for tomorrow morning to Wall Street FYI.

All the best,

Arie Belldegrun, M.D., FACS
President and CEO
Chairman of the Board; Founder
Kite Pharma Inc.

2225 Colorado Ave
Santa Monica, CA 90404

310 824-9999 x102
arie@kitepharma.com

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Kite Pharma Provides Update on KTE-C19 Clinical Trial

Kite KTE-C19 Trial on Track to Advance to Pivotal Phase 2

Kite to Host Conference Call and Webcast on August 17, 2015 at 9:00am Eastern Time

SANTA MONICA, Calif., August 17, 2015 (GLOBE NEWSWIRE) -- Kite Pharma, Inc. (Kite) (Nasdaq:KITE) today provided an update from the Company's ongoing Phase 1/2 clinical trial of KTE-C19 in patients with refractory aggressive non-Hodgkin's lymphoma (NHL) who have failed prior chemotherapy treatments and have a poor prognosis. KTE-C19 is an investigational therapy in which a patient's T cells are genetically modified to express a Chimeric Antigen Receptor (CAR) designed to target the antigen CD19, a protein expressed on the cell surface of B-cell lymphomas and leukemias.

In May, Kite announced that the first patient was treated with KTE-C19 in the Phase 1 portion of the trial and we have since treated multiple patients. Complete responses have been observed by investigators. The responses happened shortly after treatment was administered and Kite is monitoring these patients to determine durability of treatment. To date, toxicities associated with treatment have been similar to those observed in the National Cancer Institute's study of anti-CD19 CAR T cell therapy. There was one patient death early in the study, which was determined to be unrelated to KTE-C19 by the study investigator. After appropriate discussions with the U.S. Food and Drug Administration (FDA), Kite continued to enroll and treat patients in its study and the study was never placed on clinical hold. Kite has submitted an abstract and plans to present top-line data from the Phase 1 portion of the trial at the upcoming 2015 American Society of Hematology (ASH) Annual Meeting, to take place in Orlando, FL, December 5-8, 2015.

"We are encouraged by the progress of the KTE-C19 clinical trial and excited by the responses we have seen so far. We believe the KTE-C19 clinical findings are in line with previous results demonstrating the potential of this promising therapeutic approach," said Arie Belldegrun, M.D., FACS, Chairman, President and Chief Executive Officer of Kite. "In agreement with ASH, we have taken this exceptional step of providing an update on the trial in order to address recent misinformation in the market related to our clinical program. We are on track to transition to the Phase 2 portion of the trial and plan to present Phase 1 data at ASH later this year."

Kite's Phase 1/2 clinical trial of KTE-C19 is a single arm, open-label, multi-center study, designed to determine the safety and efficacy of KTE-C19 in patients with refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), or transformed follicular lymphoma (TFL). Upon completion of the Phase 1 portion of the study, Kite expects to proceed with the Phase 2 portion that will include a total of approximately 112 patients. Additional information about Kite's Phase 1/2 study may be found at ClinicalTrials.gov, using Identifier NCT: 02348216.

Conference Call and Webcast Details

Kite will host a live conference call and webcast on Monday, August 17, 2015, at 9:00am Eastern Time to provide a corporate update. The live webcast and subsequent replay may be accessed by visiting the Company's website at ir.kitepharma.com. Please connect to the Company's website at least 5-10 minutes prior to the live webcast to ensure adequate time for any necessary software download. Alternatively, please call (844) 856-8656 (U.S.) or (443) 877-4062 (international) to listen to the live conference call. The conference ID number for the live call is 15633524. Please dial

in approximately 10 minutes prior to the call. The webcast will be available on the Company's website for two weeks following the call.

About Kite Pharma, Inc.

Kite Pharma, Inc., is a clinical-stage biopharmaceutical company engaged in the development of novel cancer immunotherapy products, with a primary focus on engineered autologous T-cell (eACT™) designed to restore the immune system's ability to recognize and eradicate tumors. Kite is based in Santa Monica, CA.

Kite Pharma, Inc. Forward-Looking Statements

This press release contains forward-looking statements for purposes of the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. The press release may, in some cases, use terms such as "predicts," "believes," "potential," "proposed," "continue," "estimates," "anticipates," "expects," "plans," "intends," "may," "could," "might," "will," "should" or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. Forward-looking statements include statements regarding intentions, beliefs, projections, outlook, analyses or current expectations concerning, among other things: the success and timing of the Phase 1/2 KTE-C19 clinical trial and the ability of Kite to present at ASH. Various factors may cause differences between Kite's expectations and actual results as discussed in greater detail in Kite's filings with the Securities and Exchange Commission, including without limitation in its Form 10-Q for the quarter ended June 30, 2015. Any forward-looking statements that are made in this press release speak only as of the date of this press release. Kite assumes no obligation to update the forward-looking statements whether as a result of new information, future events or otherwise, after the date of this press release.

# # #

CONTACT: Kite Pharma
Cynthia M. Butitta
Chief Financial Officer and Chief Operating Officer
310-824-9999

For Media: Justin Jackson
For Investor Inquiries: Lisa Burns and Carol Werther
Burns McClellan
212-213-0006
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lburns@burnsmc.com
cwerther@burnsmc.com

Kite Pharma
Focused on the Cure
Draft as of 8/16/15

Kite Pharma Conference Call Script For August 17, 2015

Kite Pharma Participants:

Arie Belldegrun, MD, FACS, Chairman, President, and Chief Executive Officer

David D. Chang, MD, PhD, Executive Vice President, Research & Development, and Chief Medical Officer

Kate Bechtold, Investor Relations

Operator

Good morning, ladies and gentlemen. Thank you for standing by, and welcome to Kite Pharma's Conference Call. At this time, all participants are in listen-only mode. Later, we will conduct a question-and-answer session, and instructions will follow at that time. Please be aware that today's conference call is being recorded. I would now like to turn the conference over to your host Kate Bechtold of Kite's Investor Relations. Please go ahead.

Kate Bechtold: Welcome & Forward-looking Statement

Thank you, Operator. Good morning and thank you for joining us for today's conference call. In addition, today's call is being webcast live on our website and will be available for replay.

Joining me on the call today are Dr. Arie Belldegrun, our Chairman, President, and Chief Executive Officer, and Dr. David Chang, Kite's Executive Vice President of Research & Development, and Chief Medical Officer.

As a reminder, during today's call, we will be making certain forward-looking statements. These statements may include statements regarding the success, results, and timing of our ongoing and planned clinical trials, among other things. These forward-looking statements are based on current information, assumptions, and expectations that are subject to change and involve a

number of risks and uncertainties that may cause actual results to differ materially from those contained in the forward-looking statements. These and other risks are described in our periodic filings made with the Securities and Exchange Commission, including our form 10Q for the quarter ending June 30th, 2015, as filed with the SEC. You are cautioned not to place undue reliance on these forward-looking statements, and the Company disclaims any obligation to update such statements.

I will now turn the call over to Dr. Arie Belldegrun.

Dr. Arie Belldegrun

Thank you, Kate. Good morning, everyone. As some of you are aware, we believe there has been a high level of noise and misinformation recently in the market concerning Kite's ongoing Phase 1/2 clinical trial of KTE-C19 in patients with refractory aggressive Non-Hodgkin Lymphoma (NHL). While it is not our desire or practice to disclose information regarding on-going clinical studies, and we are under no obligation to do so, we have decided to take the exceptional step of holding this call to address the misinformation relating to our clinical trial.

Let me start off this morning by addressing misinformation that has been brought to our attention and make something perfectly clear – Kite's groundbreaking Phase 1/2 clinical trial of KTE-C19 in patients with refractory aggressive NHL has treated multiple patients, continues to advance and it is not now, nor has it ever been on any type of clinical hold by the FDA or any other regulatory body. As we said on our quarterly report call last week, we believe that we will move into the Phase II portion of this trial as well as commencing additional Phase II trials in other indications later this year. We not only remain on track, but are excited about the impressive clinical responses we have seen to date. More on that a bit later.

Please keep in mind that there is a very important reason for not publicizing clinical information in an ongoing trial. It is not about stock price or competitive advantages. It is about the health,

safety and welfare of subjects in the study, our patients and their families, and their treating physicians who are considering potentially life-altering treatment options offered by our clinical trial. Also it is important not to introduce any bias based on partial information that may compromise the scientific integrity of study. Decisions should not be made based upon anecdotes or selective information leaked into the market. I have dedicated my entire professional life to the care and treatment of patients and have personally conducted countless clinical trials in an academic setting. At Kite, I am far from the exception. We have assembled a stunning array of talented men and women similarly dedicating their lives to others. Collectively, the clinical development team at Kite and the amazing investigators assembled for this groundbreaking study, have decades of experience of treating very sick and dying patients. We know that information about our ongoing trial would never be disclosed by any of the professionals at Kite, and we remain committed to protecting patient information, complying with our regulatory obligations, and preserving scientific integrity.

For those following Kite, you know that 2015 has been an amazing year of "firsts" for the company, which I hope have not gotten lost in the market noise of the last few days. Perhaps most importantly, in May, we announced that we treated our first patient with KTE-C19. We are very pleased to report that we have successfully treated a small but growing number of patients in a multi-center setting using a centralized and proprietary cell manufacturing process. Toxicities associated with the treatment were similar to those observed in the NCI study and complete responses have been observed by investigators.

Our clinical trial was designed to treat patients with aggressive refractory NHL. For many listening to this call, you immediately understand what this means. To others, let me explain: Patients who enroll in this study MUST have disease that has progressed through or early after the use of known and accepted treatments. We expect that patients in our trial will have failed on average between 4 to 5 prior rounds of often debilitating chemo -and immune- therapy and, despite this treatment, the prognosis for all of the patients in our study by definition and design is very poor. We took on the risk of moving forward with KTE-C19 in this extremely challenging

patient population with our eyes open — Why? Because we are committed to helping patients who have no other alternatives.

Months ago and very early in our study, a patient with advanced disease died. This was a sad and unfortunate situation for all those involved. A clinical investigator of the study conducted an in-depth review of the death and concluded that this death was unrelated to our product candidate, KTE-C19. This conclusion was not made or influenced in any way by anyone at Kite As the sponsor, even before the death, we notified the FDA that the patient's health had worsened, and following the patient's death, we submitted all required and necessary information to the FDA as well as to the institutional IRBs that oversee the well-being and interest of clinical trial participants.

With all of the relevant information before us and after proper consultation and discourse with the FDA, we continued enrolling and treating patients. While I will not be reporting detailed data here today, we are extremely pleased and excited about the results we have seen in the ongoing KTE-C19 clinical trial from both before and after the one patient's death. We have seen tumors melting away in weeks and complete responses in a very sick and desperate group of patients with one of the worst types of aggressive cancers. Obviously, longer follow-up is necessary to determine how long these impressive responses last and the durability of this treatment. Nonetheless, these early clinical responses are extremely gratifying and we continue to believe that engineered CD-19 T cell therapy offers the best possible hope for patients with no other viable alternatives.

In addition to the exciting initial results, we have been able to demonstrate that KTE-C19 can be successfully manufactured and delivered to patients across multiple centers throughout the United States, which is a strong validation of the potential for immuno-oncology to be a viable treatment option for patients. Kite is fully committed to bring KTE-C19 and other future engineered T cell products to patients across the country and beyond, so that patients can receive CAR therapy at a treatment facility near their home or convenient to their family.

While we are encouraged by what we have seen in the elimination of tumors, it is still too early in the study to provide additional details, including with respect to durability. Accordingly, we are enthusiastic to discuss the detailed clinical results, including the most updated follow up, from the first portion of our historic trial at a scientific meeting, and we have submitted an abstract detailing the study results to the upcoming 57th American Society of Hematology (or ASH) Annual Meeting, which will take place in Orlando, Florida, in early December.

In addition, we are affirming our current intention to transition to the Phase II portion of our trial and begin additional studies of KTE-C19 in other indications this year. We expect that this will be a registration trial leading to the filing of our BLA by the end of 2016.

I would also like to take this opportunity to quickly refer to our recent filing of a petition with the US Patent Office for an Inter Partes Review (or IPR) of a patent issued to Memorial Sloan Kettering Cancer Center, subsequently licensed to Juno Therapeutics. I want to reiterate that based upon the conclusions of the top intellectual property attorneys in this country, we at Kite believe that with our ownership of the seminal and broad patent portfolio from Professor Zelig Eshhar we have freedom to operate in our space. We look forward to the resolution of our petition by the Patent Office. Again, we do not believe there are any valid, issued patents that would impact our freedom to operate on KTE-C19.

In closing, I want to once again underscore that we are proud to have initiated the first company-sponsored multi-center clinical trial in patients with aggressive refractory NHL and to have observed KTE-C19 delivering initial complete responses, very much in line with what has been reported from the NCI trial. This therapy is active and, in my professional opinion as a cancer doctor, the early results are impressive. Despite challenges, we believe that, based on the information we have today, we are advancing the most effective therapy for patients with aggressive refractory NHL, allowing us to give hope to terminally ill patients who have no other options. And, we remain on track to potentially commercialize KTE-C19 in 2017.

With that, Operator, could you please open the line for questions?

Q&A Portion

Closing Statement from Dr. Arie Belldegrun

Thank you, all, for your time today. We are excited by the progress we have made and look forward to reporting additional data from our KTE-C19 study later this year. As always, we want to thank all the patients, their caregivers, the members of the medical community who have participated in our clinical trials, and, of course, all our employees and shareholders for their continued support. We believe we are closer than ever to delivering potentially curative therapies to patients.

Thank you for your participation on our call, and, Operator, you may now disconnect.

# # #

From: David Chang [DChang@KitePharma.com]
Sent: Monday, August 17, 2015 10:11 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
CC: Arie Belldegrun; Jeff Wiezorek
Subject: FW: kite call.

Steve,

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Thanks,
David

From: Shrader, Thomas [mailto:shradert@stifel.com]
Sent: Monday, August 17, 2015 6:32 AM
To: Arie Belldegrun <Arie@kitepharma.com>; David Chang <DChang@KitePharma.com>
Subject: FW: kite call.

Link to my question. I was asked to ask – but thank you for the answer and the call.

https://clinicaltrials.gov/ct2/show/NCT01795976?recr=Suspended&lup_s=07%2F30%2F2015&lup_d=14&show_rss=Y&sel_rss=mod14

Suspected Unexpected Serious Adverse Reaction: serious adverse reactions in subjects given a drug, that may or may not be dose related, but are unexpected, as they are not consistent with current information. A SUSAR may occur during clinical trials or clinical care. Reporting is mandatory for clinical investigators in the EU. In the USA, reporting of adverse events during clinical trials is mandatory, but during clinical care, it is voluntary

From: David Chang [DChang@KitePharma.com]
Sent: Tuesday, August 18, 2015 9:20 PM
To: Owen N. Witte - HHMI/Microbio, Immunology & Mol Genet/BSCRC (owenwitte@mednet.ucla.edu); James S. Economou - V Chancellor for Research/Surg-Onc (jeconomou@mednet.ucla.edu); Zelig Eshhar (zelig.eshhar@weizmann.ac.il); Donald B. Kohn - MIMG (dkohn@mednet.ucla.edu); Antoni Ribas - Med-Hemat & Onc (aribas@mednet.ucla.edu); Pantuck, Allan; Rosenberg, Steven A. (NIH/NCI) [E]; Inder Verma (verma@salk.edu)
CC: Margo Roberts; Ton Schumacher; Arie Belldegrun
Subject: Kite SAB 17Aug2015

Dear SAB members,

I am very grateful for your participation in today's Kite SAB meeting. Your advice and guidance on both technical and strategic issues will continue to shape Kite's R&D as they have done over the years – they are becoming more impactful as we expand our research activities.

It is rare for any company to receive scientific inputs at the level that we have benefited at Kite, and I am very grateful. If you have any follow up comments or suggestions, please direct them to me, Margo, or Ton.

All the best,
David

David D. Chang, MD, PhD
Executive Vice President of R&D
and Chief Medical Officer
Kite Pharma, Inc
office: 310-622-9094
PERSONAL INFORMATION,REDACTED PER AGREEMENT

www.kitepharma.com

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Thursday, September 03, 2015 1:18 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
CC: David Chang; Jeff Wiezorek
Subject: Fwd: Industry News - September 3, 2015

Hi Steve,

Please take a look at the last article below, describing long-term U-PENN survivors after CAR- T cell therapy.

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Thanks,

Arie

Arie Belldegrun, MD FACS
President and CEO, Chairman
Kite Pharma

www.kitepharma.com

Begin forwarded message:

> **From:** Alex Gray <agray@burnsmc.com>
> **Date:** September 3, 2015 at 06:48:31 PDT
> **To:** BMC All <BMC.ALL@burnsmc.com>
> **Cc:** The Lisa Burns Friends and Family <LisaBurnsFriendsandFamily@burnsmc.com>
> **Subject: Industry News - September 3, 2015**
>
> **INDUSTRY NEWS – September 3, 2015**
>
> GENERAL HEALTH
>
> WSJ – September 2, 2015, "Seven VA Home Residents in Illinois Die of Legionnaires'."
>
> NYTimes – September 2, 2015, "Polio Paralyzes 2 Children in West Ukraine Outbreak."
>
> Forbes – September 2, 2015, "Hospitals Say Aetna-Humana Deal Endangers Medicare Advantage."
>
> INDUSTRY NEWS
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> WSJ – September 2, 2015, "Court Decision Could Allow Novartis to Sell Copy of Amgen's Neupogen."
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> WSJ – September 2, 2015, "Lannett to Acquire UCB's Kremers Urban Pharmaceuticals Unit for $1.23 Billion."
>
> WSJ – September 2, 2015. "Medtronic Results to Provide Checkup on Covidien Deal."
>
> PHARMA/BIOTECH NEWS
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> NYTimes – September 2, 2015, "Insurer Says Clients on Daily Pill Have Stayed H.I.V.-Free."

Forbes – September 2, 2015, "UK Study Indicates that the Cardiovascular Risk of Celebrex No Different from Other Pain Drugs."

Fierce Biotech – September 3, 2015, "Novartis Team Tracks Remissions of 4-Plus Years in a Pioneering CAR-T study."

GENERAL HEALTH

Wall Street Journal

Seven VA Home Residents in Illinois Die of Legionnaires'

By Ben Kesling

September 2, 2015

Seven elderly veterans have died from Legionnaires' disease, and dozens more have contracted the ailment at a group home in Illinois, according to state Veterans' Affairs officials, who have yet to determine the cause of the outbreak.

By Wednesday, 45 veterans had tested positive for the disease, which can cause pneumonia, according to a spokesman for the state's Department of Veterans Affairs. The veterans all live at the Illinois Veterans' Home in Quincy. No further veterans have been admitted to local hospitals with symptoms in the past 48 hours, the spokesman said Wednesday afternoon.

Those who have died all had underlying health problems and an average age of 88, according to the state VA spokesman, Ryan Yantis.

Legionella bacteria, which cause Legionnaires', often thrive in lukewarm water, according to Justin DeWitt, chief engineer with the state's Department of Public Health. The disease spreads through inhaling bacteria-laden misted water, like from a shower or hot tub, or when misted water blows onto people in public places like near fountains or commercial cooling towers. It is not transmitted person-to-person.

Late summer can be the perfect growing season for bacteria, said Mr. DeWitt, because temperature shifts can make cold water just warm enough to harbor them and slight temperature changes can upset commercial water systems and cause a spike in bacterial growth. Legionella is always present in water systems, he said, and engineers can never really purge it from systems. "Trying to eliminate it, it's a false hope," he said.

The Quincy home is in compliance with state and federal health codes, according to the state VA spokesman. The facility houses about 400 residents on a 200-acre campus with 40 buildings, some of which date back to the 19th century, though Mr. DeWitt said the age and configuration of pipes doesn't affect water safety as much as proper maintenance.

The facility is run by the Illinois Department of Veterans' Affairs, not by the federal VA, which

declined to comment on the Illinois outbreak.

In 2011-12, the federal VA saw a high-profile outbreak of Legionnaires' at its Pittsburgh health-care facility; nearly two dozen people were infected and five died. The outbreak prompted congressional hearings, internal investigations and policy re-evaluations at the VA. That hospital now has a more robust water-treatment system.

Illinois first confirmed the most recent outbreak last week and requested aid from the U.S. Centers for Disease Control and Prevention in determining the cause. Facilities test results take up to two weeks, according to state health officials.

The Illinois outbreak comes as state officials in California work to determine the cause of a Legionnaires' outbreak at the San Quentin State Prison, which has six confirmed cases of the disease and more than 80 possible cases, according to prison officials.

Earlier this summer, New York City was hit by dozens of cases of the disease traced to mist produced by a hotel cooling tower.

Between 8,000 and 18,000 people are infected with Legionnaires' each year, according to the CDC, though only about 3,000 report the illness. The bacteria are common and people often come into contact with them, according to the CDC, though it typically only infects the very young, very old or others with compromised immune systems.

New York Times

Polio Paralyzes 2 Children in West Ukraine Outbreak

By Donald McNeil Jr.

September 2, 2015

Two children in western Ukraine have been paralyzed by polio, in the first cases of the disease seen in Europe in five years, the World Health Organization announced Wednesday.

Although the infections are a setback in the global drive against polio, the W.H.O.'s director of polio eradication, Dr. Hamid Jafari, said that the outbreak appeared to be small and that similar ones had been quickly snuffed out.

The two children, an infant and a 4-year-old, were not paralyzed by the "wild-type virus" that is now known to be circulating only in Pakistan and Afghanistan, but by a strain derived from the oral polio vaccine itself.

The oral vaccine contains three strains of weakened live virus, and very occasionally — the W.H.O. estimates it as once in a million vaccinations — one mutates to become more virulent. Then, like wild virus, it can be shed in feces and spread to others in sewage.

Outbreaks of vaccine-derived virus are usually limited and can be stopped by immunizing children in areas around all known cases. Ukraine has a large supply of polio vaccine on hand and is

preparing a vaccination drive, Dr. Jafari said.

The two new cases occurred in villages only about 30 miles apart, and sewage sampling suggests the outbreak is not widespread. Polio thrives in hot weather, and Ukraine's cold winter should slow any spread.

The challenge, Dr. Jafari said, is that half of Ukraine's children are not fully immunized against polio and many other diseases.

That shortfall is not related to the struggles with Russia in the eastern part of the country, he said. The outbreak is in the west, near the borders with Romania, Slovakia, Hungary and Poland.

Rather, many Ukrainian parents resist vaccines because of a 2008 case in which a high school student died, apparently of sepsis, shortly after getting a shot for measles, mumps and rubella.

The Health Ministry and the United Nations Children's Fund, which supplied the vaccine, insisted then that the death was a coincidence and that the vaccine was safe. But panic spread, and nearly 100 students went to hospitals complaining of headaches, fevers and sore throats.

The president at the time, Viktor A. Yushchenko, ordered all measles immunizations halted while officials investigated. Since then, about a third of Ukrainian parents have told pollsters that they fear vaccines, and vaccination rates have plummeted.

The incidence of measles rose from 100 cases in 2010 to 12,700 two years later. In 2013, Unicef warned that Ukraine was at risk of a polio outbreak.

"How Ukraine's officials handle communications strategy will be important," Dr. Jafari said.

Forbes

Hospitals Say Aetna-Humana Deal Endangers Medicare Advantage

By Bruce Japsen

September 2, 2015

The nation's powerful hospital lobby, the American Hospital Association, urged the U.S. Justice Department to closely scrutinize the proposed $37 billion acquisition by Aetna (AET) of Humana (HUM), saying it threatens competition in the business of providing health benefits to seniors in the growing privately run portion of the Medicare program.

Specifically, the AHA, which represents some 5,000 U.S. hospitals, says the combination of the two health insurance giants would give a larger Aetna too much power to potentially raise prices and end choices for seniors who buy Medicare Advantage plans, which contract with the

government to provide traditional Medicare coverage plus extras that include wellness care, preventive screenings and prescription drugs.

Enrollment in Medicare Advantage plans has soared in recent years and hospitals fear insurers with too much control in this growing market.

"The deal will not just eliminate current competition between Humana and Aetna, it will eliminate future competition between them," Melinda Hatton, senior vice president and general counsel at the AHA said in her letter this week to Assistant U.S. Attorney General William Baer in the Justice Department's antitrust division and U.S. Secretary of Health and Human Services Sylvia Burwell. "Humana is the second largest insurer of Medicare Advantage lives in the country. Aetna is the fourth largest."

The hospital industry appears to be the first among health care providers to aggressively challenge health plan mergers. Providers are also expected to launch a legal and political assault on the proposed merger between Anthem (ANTM) and Cigna (CI).

Hospitals say almost one in three Medicare beneficiaries, or nearly 17 million Americans, obtain coverage through an Advantage plan and the combined Humana and Aetna would lead to market dominance in more than 1,000 markets that would "become highly concentrated."

Aetna and Humana and supporters of the deal say the larger insurer would allow the plans to extract price cuts from doctors and hospitals, which would be a good thing. Health plans also say they need to consolidate to reduce overhead and comply with rules under the Affordable Care Act that demand more dollars be spent on medical care rather than administrative costs.

But while the hospitals admit that the larger insurer could reduce prices but overall it would "materially may harm competition in multiple ways" in large part because there would be an enormous barrier of entry for any new health plans to enter Medicare Advantage.

"It may create monopsony power and enable the merged firm to exploit small, relatively powerless providers," AHA's Hatton said in her letter to the justice department. "Second, the merger may create downstream market power, which could offset the desirable effects of countervailing power and raise premiums to consumers. Finally, the merger might create countervailing power but the merged firm might exercise it in anticompetitive ways, harming consumers or small providers."

For their part, Aetna and Humana say a larger entity would invest more in benefits and health programs that benefit seniors saying they already score well on Medicare's five-star quality ratings system. They also say there have been more than 30 new parent companies that have entered the Medicare Advantage market in the last four years including providers of medical care.

"Aetna and Humana have the greatest number of plans rated four stars and higher in this highly competitive environment," Aetna said in a statement. "Because of this, Medicare beneficiaries will experience strong quality and value with our plans."

INDUSTRY NEWS

Wall Street Journal

Court Decision Could Allow Novartis to Sell Copy of Amgen's Neupogen

By Peter Loftus

September 2, 2015

A federal appeals court in Washington denied Amgen Inc.'s request for a temporary injunction to block Novartis AG from selling a copycat version of the blockbuster drug Neupogen in the U.S.

The decision by the U.S. Court of Appeals for the Federal Circuit could clear the way for Novartis to begin selling Zarxio, a knockoff version of Neupogen that was approved by the U.S. Food and Drug Administration in March. The U.S. market accounted for more than 70% of Amgen's $1.16 billion in global sales last year of Neupogen, a drug prescribed to chemotherapy patients.

Zarxio was the first biosimilar—a copy of a biotechnology drug—approved by the FDA under abbreviated criteria enabled by a provision of the 2010 Affordable Care Act. But the product's introduction has been held up by a legal dispute between Amgen and Novartis.

The drug industry and its lawyers are closely watching the Neupogen biosimilar case because the outcome could shape the path to market for a coming wave of biosimilar drugs that are expected to cost less than the original brands.

A Novartis spokesman said the company welcomed Wednesday's decision, but didn't provide plans for selling Zarxio. An Amgen spokeswoman said the company will "compete effectively" but declined to comment directly on the court decision.

The same appeals court issued a ruling in July that largely sided with Novartis, but ordered an injunction on Zarxio's sale until Wednesday. Amgen subsequently asked for a temporary injunction that would bar the sale of Zarxio beyond Wednesday, while Amgen pursues further legal options. The court denied Amgen's request without explanation in an order issued Wednesday.

Novartis hasn't announced a price for Zarxio. In Europe, where biosimilars have been available for several years, they typically cost 15% to 30% less than the original brands.

The dispute began when Amgen filed a lawsuit in federal court in San Francisco last year, accusing Novartis of failing to disclose certain information about its copycat product to Amgen, which Amgen said was required under the new criteria for FDA approval of biosimilars. Amgen also

alleged Zarxio would infringe upon a patent for Neupogen. Novartis denies the allegations.

Wall Street Journal

Lannett to Acquire UCB's Kremers Urban Pharmaceuticals Unit for $1.23 Billion

By Maria Armental

September 2, 2015

Lannett Company Inc. has agreed to buy UCB SA's Kremers Urban Pharmaceuticals Inc. for $1.23 billion.

The deal, with tax benefits expected to top $100 million, also calls for potential contingency payments under sales and timing thresholds. Lannett said it expects the deal to close in the fourth quarter.

Lannett's shares, up 15% this year, rose nearly 18% to $58.25 in late trading.

Philadelphia-based Lannett, which is borrowing up to $1.29 billion, in part to fund the transaction, estimated a mid- to high-single-digit increase in adjusted profit in fiscal 2016 and 20% to 25% increase in fiscal 2017.

On a pro forma basis, Lannett said the deal will leave it with about $225 million left in its credit line.

"KU brings considerable manufacturing capacity, a first class research and development team and the potential for advancing our active pharmaceutical ingredients business," Lannett Chief Executive Arthur Bedrosian said.

Kremers Urban, based in Princeton, N.J., is a specialty generic-drug maker. Its main drug is a generic form of Johnson & Johnson's Concerta, used to treat attention deficit hyperactivity disorder.

Belgian pharmaceutical company UCB, which acquired Kremers Urban when it bought Schwarz Pharma in 2006, tried to sell it last year to private-equity firms Advent International and Avista Capital Partners for $1.53 billion. The deal was called off when the Food and Drug Administration changed the ratings for two Concerta generics and requested additional information showing bioequivalency to Concerta.

The contingency payments in the Lannett deal are tied to the FDA's restoring the rating. Kremers Urban submitted the final results of new bioequivalence studies in June. Under the current rating,

its methylphenidate hydrochloride extended-release tablets can be prescribed but may not be automatically substituted for Concerta at pharmacy counters.

Wall Street Journal

Medtronic Results to Provide Checkup on Covidien Deal

By Charley Grant

September 2, 2015

Multibillion-dollar acquisitions can be thrilling for investors. What happens next, though less exciting, can be just as important.

Medtronic PLC on Thursday reports first-quarter results for its fiscal 2016 year ending in April. This will mark the second round of results since the device manufacturer's $50 billion acquisition of Covidien PLC closed in January.

Analysts see Medtronic posting $7.1 billion in sales and $1.01 in adjusted earnings per share. The legacy Covidien business, now known as the minimally invasive therapies group, is expected to contribute about a third of total revenue.

The Covidien purchase allowed Medtronic to complement its existing cardiac, spinal and diabetes products with surgical offerings. Plus, Medtronic expects to achieve $850 million in annual cost savings through the first three years of the deal, including $300 million to $350 million in fiscal 2016. Importantly, the deal allowed Medtronic to relocate its headquarters to Ireland and reduce its tax rate to about 16% to 18%.

And the story could get more attractive. For instance, cost synergies could be realized sooner than expected, and revenue gains within Medtronic's product line that weren't forecast could yet be achieved.

Meanwhile, the negative effects of the strong dollar are baked into the full-year guidance for adjusted earnings. Medtronic said in June that it expects to earn $4.30 to $4.40 a share this year, which reflects a negative currency impact of 40 to 50 cents. That could prove conservative if the dollar's recent fall against the euro were to pick up steam.

All this made the purchase a hit with investors. The stock rose by 25% between the deal's announcement in June 2014 and its completion.

Still, the transaction came at a cost to Medtronic's balance sheet, adding $16 billion in new debt. And the early glow has worn off: The stock is down 6% since the deal closed.

The problem is that Medtronic needs to deliver on the deal's promise and exceed expectations. Its market value adjusted for net debt now exceeds 11 times forward earnings before interest, taxes, depreciation and amortization. That is well above the pre-acquisition valuation of about nine times.

With the stock market starting to wobble, Medtronic has to show that there is proof in this deal pudding.

PHARMA/BIOTECH NEWS

New York Times

Insurer Says Clients on Daily Pill Have Stayed H.I.V.-Free

By Donald McNeil Jr.

September 2, 2015

Demonstrating that taking a daily pill to prevent H.I.V. infection can work in the real world, San Francisco's largest private health insurer announced Wednesday that not one of its 657 clients receiving the drug had become infected over a period of more than two years.

That outcome contradicted some critics' predictions that so-called pre-exposure prophylaxis, or PrEP, would lead to less condom use and more H.I.V. infections.

A study published in Clinical Infectious Diseases found that the San Franciscans on PrEP, almost all of whom were gay men, did use fewer condoms — and contracted several other venereal diseases as a result. But none got H.I.V.

Most other sexual infections, while potentially dangerous, can be cured with antibiotics. H.I.V. cannot, though it can be controlled with antiretroviral drugs taken for life.

"This is very reassuring data," said Dr. Jonathan E. Volk, an epidemiologist for the insurer, Kaiser Permanente of San Francisco, and the study's lead author. "It tells us that PrEP works even in a high-risk population."

Observational studies like this one are not considered as scientifically rigorous as randomized

clinical trials in which some participants receive a placebo.

But Dr. Volk and his colleagues followed a large number of men engaged in very risky behavior from mid-2012, when the Food and Drug Administration approved the use of a two-drug combination called Truvada for prevention of H.I.V. infection, through February of this year.

That amounts to 388 "person years" of observation.

By contrast, in a 2014 clinical trial among gay men in England, participants who received a placebo instead of Truvada had nine infections for every 100 person years of observation, said Dr. Anthony S. Fauci, the director of the National Institute for Allergy and Infectious Diseases.

That trial, nicknamed the Proud study, was one of several that were stopped early because researchers decided it was unethical to keep some participants on a placebo once it had become abundantly clear that PrEP worked.

"This shows that the effectiveness of PrEP is really strikingly high," Dr. Fauci said. "And this study takes it out of the realm of clinical trials and into the real world."

The newest study "fills in a critical gap by showing that PrEP can prevent infections in a real-world public health program," said Mitchell J. Warren, the executive director of AVAC, an organization lobbying for AIDS prevention.

About a third of all San Franciscans with private health insurance use Kaiser Permanente, which has its own hospitals, doctors and pharmacies and tracks all of its patients in one electronic records system.

About a third of all San Franciscans on PrEP receive the drug through Kaiser, and its doctors urge all their clients who are at risk to ask if PrEP is right for them, Dr. Volk said.

All but four of the 657 participants in the Kaiser study were gay men, and 84 percent of them reported multiple sexual partners.

After starting PrEP, half of them became infected with syphilis, gonorrhea or chlamydia within a year.

After the participants had six months of PrEP use, Dr. Volk's team surveyed 143 about their sexual behavior.

More than 40 percent said that their use of condoms had decreased.

The vast majority, 74 percent, said that their number of sexual partners had remained the same.

Previous studies have shown that PrEP is highly effective at preventing infection when participants take all or most of their daily pills.

The Kaiser study did not take blood samples to see whether its clients were taking the Truvada regularly, but all the men were on PrEP specifically because they had asked their primary care doctors for it and so presumably intended to take it, Dr. Volk said.

Although it is possible that PrEP contributed to higher rates of syphilis, gonorrhea and chlamydia, rates of those infections had begun climbing among gay men even before PrEP became available, Dr. Volk said.

The authors of the English study noted the same phenomenon.

The infections may have begun rising, Dr. Volk said, as some gay men began "sero-sorting" — choosing to have condomless sex only with men of the same H.I.V. status as themselves — or because H.I.V.-negative men agreed to have condomless sex with infected men who were taking their antiretroviral drugs so regularly that their blood levels of H.I.V. were undetectable, meaning they almost certainly could not pass that infection on.

"PrEP is another line of defense," Dr. Volk said. "This is exciting news."

Forbes

UK Study Indicates that the Cardiovascular Risk of Celebrex No Different from Other Pain Drugs

By John LaMattina

September 2, 2015

An important, yet underpublicized, study among the hundreds presented at this week's European Society of Cardiology conference held in London was "The Standard Care versus Celecoxib Outcome Trial" (SCOT). As you may recall, Merck took Vioxx, its COX-2 inhibiting pain reliever, off the market in 2004 for concerns over increased cardiovascular events such as heart attacks and strokes. Shortly thereafter, the FDA held a three day Advisory Committee meeting in Washington, DC, to assess the potential that this was a class effect of COX-2 inhibitors and not just specific to Vioxx. A major revelation at this meeting was that ALL non-steroidal anti-inflammatory drugs (NSAIDs) – including popular drugs such as ibuprofen and diclofenac, not just COX-2 inhibitors — have the potential of increasing cardiovascular events. As a result of these deliberations, Celebrex remained on the market, but the labels of these drugs were changed to reflect this risk.

Physicians, however, were left in a bit of a quandary. After all, most arthritic patients tend to have characteristics that make them prone to cardiovascular events: >65 years old, overweight, high blood pressure, high cholesterol, etc. Should they avoid using COX-2 inhibitors in these types of patients, even if the patients appear free of cardiovascular disease?

To answer this question, "The Standard Care versus Celecoxib Outcome Trial" (SCOT) was undertaken. This was a pragmatic trial designed to mimic the real world setting of the situations that doctors face daily in treating their patients with pain. The study was sponsored by the University of Dundee and funded via an investigator initiated research grant from Pfizer , the manufacturer of celecoxib (generic name for Celebrex). This study was required by the European Medicines Agency (EMA) as a post-approval commitment for Celebrex. Using primary care practices across the UK, Denmark, and the Netherlands, 7,297 patients were recruited for the study. They were all over 60 years old, were free of cardiovascular disease, and were already chronically taking NSAIDs (predominantly diclofenac and ibuprofen). In SCOT, half of these patients were switched to Celebrex while the other half stayed on the NSAID that they had already been taking.

These patients were then followed on average for 3.2 years (the study itself took almost 10 years to run). The patients were monitored during this period with the primary endpoints being hospitalization for non-fatal MI, non-fatal stroke, or cardiovascular death. Cardiovascular events were adjudicated by an independent monitoring committee.

The first surprise was that, on treatment, there was on average about 1 primary event per 100 patient years. One might have expected more than that given the characteristics of this patient population. Furthermore, the event rate was no different between the two groups. The study also monitored adverse GI events as COX-2 inhibitors were designed to minimize this adverse effect. Here a statistically significant benefit was indeed observed as there were 38 serious adverse gastrointestinal reactions with Celebrex versus 66 with the traditional NSAIDs although here, too, there were fewer GI events than expected.

The authors of the SCOT study concluded that:

"In patients with arthritis, without known cardiovascular disease, CV event rates were low and serious ulcer-related complication rates very low, and neither outcome differed significantly between NSAIDs and celecoxib. In the study population, NSAIDs and celecoxib both appeared acceptably safe. In patients who get significant symptomatic relief from these medicines, the benefit/risk balance appears positive."

Of course, SCOT was conducted in patients without cardiovascular disease. But what about those with heart disease who also suffer from arthritis or other chronic pain conditions? To answer that question, the "Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen and Naproxen" (PRECISION) trial was initiated in 2006 by the Cleveland Clinic. Funded by Pfizer, and likely costing upwards of $300 million, this study has been fully recruited and, according to Clinicaltrials.com (NCT00346216), should be completed next March. The results of this trial, in combination with the SCOT results, will be invaluable to physicians and patients as they seek optimal ways of controlling their pain. But for those free of cardiovascular disease, Celebrex appears to offer no increased cardiovascular risk compared to traditional NSAIDs like ibuprofen and diclofenac. Many would have bet against such an outcome 10 years ago.

Fierce Biotech

Novartis Team Tracks Remissions of 4-Plus Years in a Pioneering CAR-T study

By John Carroll

September 3, 2015

Five years after the University of Pennsylvania began recruiting a small group of 14 patients with hard-to-treat chronic lymphocytic leukemia, researchers are still tracking three of them who are still alive with no signs of their cancer returning after being treated with a first-generation CAR-T therapy.

The study offers a glimpse into the promise of a durable response for reengineered T cells--in this case taking the T cells out of patients and then adding a chimeric antigen receptor for a treatment called CTL019, which is owned by Novartis-while outlining the challenges involved in keeping patients safe from a severe and common reaction and devising new approaches to overcome some of the personalized treatment's limitations as the first of these drugs move closer to a possible marketing approval.

Out of the 14, four experienced complete remissions, meaning their cancer was no longer detectable. One of those four later died of other causes. Four patients had partial responses, with two of them dying after 10 months and 27 months of therapy. One of the partial-response patients died from a pulmonary embolism, and the other was switched to a different therapy after 13 months and died after three years.

Six of the patients did not respond to the therapy. And of the three patients still alive, two were treated more than four years ago, making them the longest running remissions in the CAR-T field.

The key takeaway:

"Importantly, our tests of patients who experienced complete remissions showed that the modified cells remain in patients' bodies for years after their infusions, with no sign of cancerous or normal B cells," said the study's senior author, Dr. Carl June, one of the pioneers in immunotherapy, which is emerging as a multibillion-dollar market. "This suggests that at least some of the CTL019 cells retain their ability to hunt for cancerous cells for long periods of time."

All of the patients who responded to the therapy experienced a potentially life-threatening case of cytokine release syndrome, sometimes called a cytokine storm, with the drug triggering high fevers and in several cases difficulty with breathing and low blood pressure. Doctors responded with the antibody drug tocilizumab and steroids, and all of the patients survived.

In a small study like this, investigators can learn as much from failure as they can from success. Testing the 6 patients who did not respond, the scientists said that their customized T cell populations did not expand as aggressively as in the patients who were first flattened by a cytokine storm in their first response to the solo treatment.

The Novartis/Penn team as well as rivals Juno and Kite and a whole pack of companies jumping into the game have been studying new technology that can be used to amp up the T-cell attack on cancer cells. A whole host are also tackling the challenge of moving past B cells to solid tumors and off-the-shelf therapies, which represent a big challenge--and a much bigger market.

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Thursday, September 03, 2015 1:19 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Fwd: | 09.03.15 | Novartis tracks 4-year remissions in landmark CAR-T study; Regeneron targets rare bone disease

Here is the original article I mentioned in the previous mail.

Arie Belldegrun, MD FACS
President and CEO, Chairman
Kite Pharma

www.kitepharma.com

Begin forwarded message:

From: FierceBiotech <editors@fiercebiotech.com>
Date: September 3, 2015 at 10:10:41 PDT
To: arie@kitepharma.com
Subject: | 09.03.15 | Novartis tracks 4-year remissions in landmark CAR-T study; Regeneron targets rare bone disease
Reply-To: <editors@fiercebiotech.com>

FierceBiotech
THE BIOTECH INDUSTRY'S DAILY MONITOR

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3. Regeneron team IDs a candidate for ultra-rare bone disease
4. Booming Gilead gets a blueprint for a big new HQ addition
5. Acadia finally delivers long-delayed application for 'breakthrough' Parkinson's drug

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Pfizer bristles at calls for trial transparency; Targacept vet takes the helm at Faraday; and **much more...**

Novartis finally gets to roll out inaugural biosim Zarxio. What will payers and docs do?

The age of biosimilars in the U.S. has finally dawned with the launch of Novartis' Zarxio, a copy of Amgen's Neupogen

(filgrastim). And it's arriving with a 15% discount to win scripts over from the brand. Thursday, the Swiss pharma giant announced its Sandoz generics unit had begun rolling out the med in the U.S., which the FDA green-lighted back in March after years of drawing up a biosimilars regulatory approval pathway. **Read more from *FiercePharma* >> | Subscribe**

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Today's Top News

1. Novartis team tracks remissions of 4-plus years in a pioneering CAR-T study

By John Carroll Comment | Forward | Twitter | Facebook | LinkedIn

Dr. Carl June

Five years after the University of Pennsylvania began recruiting a small group of 14 patients with hard-to-treat chronic lymphocytic leukemia, researchers are still tracking three of them who are still alive with no signs of their cancer returning after being treated with a first-generation CAR-T therapy.

The study offers a glimpse into the promise of a durable response for reengineered T cells--in this case taking the T cells out of patients and then adding a chimeric antigen receptor for a treatment called CTL019, which is owned by Novartis ($NVS)--while outlining the challenges involved in keeping patients safe from a severe and common reaction and devising new approaches to overcome some of the personalized treatment's limitations as the first of these drugs move closer to a possible marketing approval. The results were published in *Science Translational Medicine*.

Out of the 14, four experienced complete remissions, meaning their cancer was no longer detectable. One of those four later died of other causes. Four patients had partial responses, with two of them dying after 10 months and 27 months of therapy.

One of the partial-response patients died from a pulmonary embolism, and the other was switched to a different therapy after 13 months and died after three years.

Six of the patients did not respond to the therapy. And of the three patients still alive, two were treated more than four years ago, making them the longest running remissions in the CAR-T field.

The key takeaway:

"Importantly, our tests of patients who experienced complete remissions showed that the modified cells remain in patients' bodies for years after their infusions, with no sign of cancerous or normal B cells," said the study's senior author, Dr. Carl June, one of the pioneers in immunotherapy, which is emerging as a multibillion-dollar market. "This suggests that at least some of the CTL019 cells retain their ability to hunt for cancerous cells for long periods of time."

All of the patients who responded to the therapy experienced a potentially life-threatening case of cytokine release syndrome, sometimes called a cytokine storm, with the drug triggering high fevers and in several cases difficulty with breathing and low blood pressure. Doctors responded with the antibody drug tocilizumab and steroids, and all of the patients survived.

In a small study like this, investigators can learn as much from failure as they can from success. Testing the 6 patients who did not respond, the scientists said that their customized T cell populations did not expand as aggressively as in the patients who were first flattened by a cytokine storm in their first response to the solo treatment.

The Novartis/Penn team as well as rivals Juno ($JUNO) and Kite ($KITE) and a whole pack of companies jumping into the game have been studying new technology that can be used to amp up the T-cell attack on cancer cells. A whole host are also tackling the challenge of moving past B cells to solid tumors and off-the-shelf therapies, which represent a big challenge--and a much bigger market.

- here's the release
- get the research abstract

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Novartis adds to CAR-T's luster with more excellent cancer data
Penn-Novartis team 'amazed' at remissions, responses in leukemia CAR-T study
Novartis commits $20M to build a new CAR-T development center at Penn

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2. Sage sees a future in tremor treatment after a 'probe' study

By Damian Garde Comment | Forward | Twitter | Facebook | LinkedIn

Sage CEO Jeff Jonas

Sage Therapeutics ($SAGE) is pressing forward in the field of tremor treatment after its lead drug notched a positive--though not statistically significant--effect on the debilitating condition in Phase II, results the company believes will help light the way for a bigger trial.

In a 25-patient study, the intravenous SAGE-547 improved the severity of shaking compared with placebo for sufferers of essential tremor, the company said. Sage is saving full results for a later medical meeting but noted that patients taking SAGE-547 charted clinically relevant results, with one-third achieving at least a 30% improvement in tremor amplitude, while only 16% on placebo reached the same threshold.

The drug didn't reach statistical significance on its secondary efficacy goals, but Sage says that was never the point: The trial, which the company calls a "signal-finding study," was designed to determine whether SAGE-547's mechanism--modulating the brain's $GABA_A$ receptors--could move the needle in essential tremor. The drug, which must be pumped into patients, could never serve as a treatment for a chronic disease like essential tremor, CEO Jeff Jonas said. Instead, the idea behind the study was to determine whether one of Sage's oral $GABA_A$ modulators had a future in the disease, he said.

"What we're doing in this study--which is really a probe study--is asking one question: Would you continue to develop a more active drug with this mechanism for this disease?" Jonas said.

And the answer, for Sage, is yes. The company points to post-hoc analysis in which the 17 patients who stayed on for an open-label extension study experienced a dose-dependent effect on tremor amplitude. That, combined with the placebo-controlled results, is enough of a signal to establish a relationship between $GABA_A$ modulation and a beneficial effect on essential tremor, the company believes, and the plan now is to take a next-generation molecule into a Phase II study on its own.

And Sage has a candidate in mind: SAGE-217, an oral $GABA_A$ treatment, is slated to enter Phase I this year, and if it proves itself safe and tolerable, the company plans to push it into a Phase II essential tremor study in 2016.

The overarching strategy, Jonas said, is to use SAGE-547, already in Phase III for a rare seizure disorder, as a sort of battering ram for $GABA_A$ modulators further down the pipeline. By testing SAGE-547 in broader indications, the company can get an idea of whether its mechanism can make a difference in a given disease, using the results to determine which of--or whether--its other candidates can pick up the baton.

"If there were no signal," Jonas said, "we would just abandon the indication altogether."

Sage employed the same principle in a small, open-label study disclosed earlier this summer, in which SAGE-547 demonstrated a marked effect on four women with postpartum depression. Satisfied with the signal, the company is now plotting a larger, placebo-controlled trial in that condition.

Meanwhile, SAGE-547 is in the midst of a Phase III trial in super-refractory status epilepticus (SRSE), a severe seizure disorder that can be fatal. The FDA awarded Sage its fast-track designation in SRSE, promising a speedy review if the drug can achieve its goals in late-stage development.

Essential tremor affects about 10 million people in the U.S., according to Sage, causing involuntary shaking that often forces patients to abandon their careers. Existing treatments are only moderately effective, the company said, and roughly one-third of patients quit taking them due to either unpleasant side effects or middling efficacy.

- read the statement

Related Articles:
Sage gets a peek at success treating postpartum depression, and its shares soar
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Biotech upstart Sage sees early efficacy for rare brain seizure drug

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3. Regeneron team IDs a candidate for ultra-rare bone disease

By John Carroll


Aris Economides

A fast-growing Regeneron ($REGN) says a team of top researchers has identified a clear target for a rare genetic bone disease. And they have an antibody in preclinical testing that could correct the disorder.

Fibrodysplasia ossificans progressiva, or FOP, is a genetic disease that triggers the conversion of muscle and other tissue into bone. The way Regeneron explains it, the disease is triggered by mutations in ACVR1, a gene that encodes for the ACVR1 receptor protein. The ligand Activin-A typically interacts with the ACVR1 gene to regulate bone growth, turning off signaling of bone morphogenetic proteins. But the process--confirmed in a mouse model the investigators created--is skewed by the genetic mutation, causing the bone morphogenetic proteins to switch on rather than switch off, turning soft tissue into bone.

There are some 800 known cases in the world, with 200 of those cases in the U.S.

To counter the cascade of events, the Regeneron team used the company's antibody development platform, VelocImmune, to come up with a way to block Activin-A, shutting down the process.

"Gaining insight into the Activin A-related mechanism is a tremendous step forward for researchers, and the knowledge gained about receptor-ligand interactions and signaling in this system may prove relevant in other diseases, as well," says Aris Economides,

who co-founded the genetics center in Tarrytown, NY.

Regeneron has benefited from the rapid growth of Eylea sales and recently earned a blockbuster approval for a new PCSK9 cholesterol drug, which is partnered with Sanofi ($SNY).

Back at the beginning of 2014 the biotech revealed that it had been developing a new genetics research center. While this study was not connected to the new center, it does reflect the keen interest the company has in the field. Regeneron seems determined to have a full pipeline that extends from preclinical research all the way through new studies on approved treatments. And it's been investing a significant part of its revenue to accomplish that goal.

- here's the release (PDF)

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Booming Regeneron snaps up more office/lab space in fast-growing campus
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How Regeneron's Yancopoulos became the top-paid executive in biotech

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4. Booming Gilead gets a blueprint for a big new HQ addition

By John Carroll

Gilead ($GILD) isn't finished booming. The big biotech has just scooped up an extra 12-acre complex in its home town of Foster City, CA. And the central view comes with room enough for an extra 800,000 square feet of space to accommodate a fast-growing staff.

The developers of the site struck an agreement with local officials last year to expand on the parcel. Gilead, which makes a point of never explaining or complaining, has remained customarily tight-lipped, notes the hometown newspaper, *The Daily Journal*. The *Journal* reports that Gilead paid $120 million for the central location.

Gilead had 5,000 staffers at the end of 2012 and 6,100 a year later, according to its SEC filings. By the end of last January, the full-time head count had grown to 7,000. The company has been doing a makeover of its Foster City campus, razing old buildings and constructing 17 new ones. And just last spring the company said it would add researchers and other staff as it doubled down on its development plans in Alberta, Canada.

Gilead is a prime example of an explosive growth biotech, one of several which have been offsetting big layoffs at giants like Amgen ($AMGN) and GlaxoSmithKline ($GSK). The company's fortunes were built around its blockbuster suite of HIV drugs, but the approval of its new drugs for hepatitis C--which have revolutionized the way hep C is cured--has added much, much more to the bottom line.

The big biotech has been a lightning rod for critics, though, pricing its therapies in a way that drew an outraged response from patient groups and physicians and prompted payers like Express Scripts ($ESRX) to start playing hardball in formulary negotiations. None of that, though, has blunted its meteoric growth.

At last count, Gilead's market cap rests at $155 billion. And it clearly wants a headquarters campus that reflects the company's global domination in select drug markets.

- here's the report

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The big question for Gilead: Who are you going to buy?
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5. Acadia finally delivers long-delayed application for 'breakthrough' Parkinson's drug

By John Carroll

Acadia CEO Steve Davis

The long wait at San Diego-based Acadia is over. Six months after disappointing investors with the latest delay in their FDA application for a new Parkinson's drug, the biotech says it's handed over the package to regulators and decided to give interim CEO Steve Davis the top job on a permanent basis.

Back in mid-March Acadia worked out a $616,000 going-away package for longtime CEO Uli Hacksell, as Davis moved up from the CFO's office to run the company as the board sorted out a permanent replacement. The latest delay for pimavanserin--to be sold as Nuplazid if it reaches the market--was attributed to manufacturing concerns, while last fall the company said the application simply wasn't ready on time.

The delays and the change at the top came after the biotech had whipped up considerable enthusiasm for pimavanserin, which won the FDA's hotly sought breakthrough drug designation, a category that is intended to help grease the skids to a quick regulatory decision.

With all late-stage assets getting careful attention on Wall Street in light of the current frenzy of buyouts and product deals, Acadia came in for an extra round of buyout rumors earlier in March after it canceled a pair of presentations at investor conferences.

"We are building on our momentum as we prepare for the expected launch of Nuplazid in the United States and continue our efforts to explore the full potential of Nuplazid to treat patients suffering from additional CNS disorders," Davis noted in a statement.

Davis got off to a solid start today, with the company shares trading up 9% in early trading. But those shares have been on a roller coaster ride for more than two years, dating back to the spring of 2013 when the company said the FDA would allow a straight shot at a marketing approval, bypassing a confirmatory study.

Acadia investors had cheered when investigators reported that they hit the primary

endpoint in the first Phase III, demonstrating highly significant antipsychotic efficacy on a reduced 9-item SAPS-PD scale. Pimavanserin also scored well on key secondary endpoints. The drug arm was significantly less likely to suffer from hallucinations and delusions than the placebo arm and was twice as likely to rate as "very much improved" or "much improved."

CNS has been making something of a comeback in recent years. New startups and some long-term survivors in the field have been pushing programs ahead, relying on new research insights as well as better delivery tech.

- here's the release on Nuplazid
- here's the release on Davis' new job

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Acadia craters as takeover buzz is silenced by (another) NDA delay, CEO exit
Acadia's shifting calendar spurs market-moving takeout rumors
Acadia surges after nabbing 'breakthrough' title for late-stage Parkinson's drug

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Also Noted

SPOTLIGHT ON... Amgen swings for EU approval with its new kidney drug

Amgen ($AMGN) filed a European application for etelcalcetide, an intravenous drug for kidney dialysis that the company believes can usurp its own Sensipar. Formerly AMG 416, etelcalcetide is designed to relieve symptoms of secondary hyperparathyroidism (SHPT), a disorder that affects patients with chronic kidney disease receiving hemodialyis. In three Phase III trials presented earlier this year, the drug met its primary goals by significantly reducing parathyroid hormone levels. Amgen has said it plans to file etelcalcetide for FDA approval later this year. Release

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> Former Targacept CEO Stephen Hill has taken the top spot at Faraday Pharmaceuticals, a biotech upstart developing treatments for critical care. More

> Pfizer ($PFE) is pushing back against investors calling for the company to release full trial results from past studies, arguing that doing so would provide little benefit to patients. Story

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Sent: Wednesday, September 09, 2015 9:55 AM
To: 'Arie Belldegrun'
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Cc: David Chang; Jeff Wiezorek
Subject: Fwd: Industry News - September 3, 2015

Hi Steve,

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Thanks,

Arie

Arie Belldegrun, MD FACS

President and CEO, Chairman

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> **From:** Alex Gray <agray@burnsmc.com>
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INDUSTRY NEWS – September 3, 2015

GENERAL HEALTH

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GENERAL HEALTH

Wall Street Journal

Seven VA Home Residents in Illinois Die of Legionnaires'

By Ben Kesling

September 2, 2015

Seven elderly veterans have died from Legionnaires' disease, and dozens more have contracted the ailment at a group home in Illinois, according to state Veterans' Affairs officials, who have yet to determine the cause of the outbreak.

By Wednesday, 45 veterans had tested positive for the disease, which can cause pneumonia,

according to a spokesman for the state's Department of Veterans Affairs. The veterans all live at the Illinois Veterans' Home in Quincy. No further veterans have been admitted to local hospitals with symptoms in the past 48 hours, the spokesman said Wednesday afternoon.

Those who have died all had underlying health problems and an average age of 88, according to the state VA spokesman, Ryan Yantis.

Legionella bacteria, which cause Legionnaires', often thrive in lukewarm water, according to Justin DeWitt, chief engineer with the state's Department of Public Health. The disease spreads through inhaling bacteria-laden misted water, like from a shower or hot tub, or when misted water blows onto people in public places like near fountains or commercial cooling towers. It is not transmitted person-to-person.

Late summer can be the perfect growing season for bacteria, said Mr. DeWitt, because temperature shifts can make cold water just warm enough to harbor them and slight temperature changes can upset commercial water systems and cause a spike in bacterial growth. Legionella is always present in water systems, he said, and engineers can never really purge it from systems. "Trying to eliminate it, it's a false hope," he said.

The Quincy home is in compliance with state and federal health codes, according to the state VA spokesman. The facility houses about 400 residents on a 200-acre campus with 40 buildings, some of which date back to the 19th century, though Mr. DeWitt said the age and configuration of pipes doesn't affect water safety as much as proper maintenance.

The facility is run by the Illinois Department of Veterans' Affairs, not by the federal VA, which declined to comment on the Illinois outbreak.

In 2011-12, the federal VA saw a high-profile outbreak of Legionnaires' at its Pittsburgh health-care facility; nearly two dozen people were infected and five died. The outbreak prompted congressional hearings, internal investigations and policy re-evaluations at the VA. That hospital now has a more robust water-treatment system.

Illinois first confirmed the most recent outbreak last week and requested aid from the U.S. Centers for Disease Control and Prevention in determining the cause. Facilities test results take up to two weeks, according to state health officials.

The Illinois outbreak comes as state officials in California work to determine the cause of a Legionnaires' outbreak at the San Quentin State Prison, which has six confirmed cases of the disease and more than 80 possible cases, according to prison officials.

Earlier this summer, New York City was hit by dozens of cases of the disease traced to mist produced by a hotel cooling tower.

Between 8,000 and 18,000 people are infected with Legionnaires' each year, according to the CDC, though only about 3,000 report the illness. The bacteria are common and people often come into contact with them, according to the CDC, though it typically only infects the very young, very old or others with compromised immune systems.

New York Times

Polio Paralyzes 2 Children in West Ukraine Outbreak

By Donald McNeil Jr.

September 2, 2015

Two children in western Ukraine have been paralyzed by polio, in the first cases of the disease seen in Europe in five years, the World Health Organization announced Wednesday.

Although the infections are a setback in the global drive against polio, the W.H.O.'s director of polio eradication, Dr. Hamid Jafari, said that the outbreak appeared to be small and that similar ones had been quickly snuffed out.

The two children, an infant and a 4-year-old, were not paralyzed by the "wild-type virus" that is now known to be circulating only in Pakistan and Afghanistan, but by a strain derived from the oral polio vaccine itself.

The oral vaccine contains three strains of weakened live virus, and very occasionally — the W.H.O. estimates it as once in a million vaccinations — one mutates to become more virulent. Then, like wild virus, it can be shed in feces and spread to others in sewage.

Outbreaks of vaccine-derived virus are usually limited and can be stopped by immunizing children in areas around all known cases. Ukraine has a large supply of polio vaccine on hand and is preparing a vaccination drive, Dr. Jafari said.

The two new cases occurred in villages only about 30 miles apart, and sewage sampling suggests the outbreak is not widespread. Polio thrives in hot weather, and Ukraine's cold winter should slow any spread.

The challenge, Dr. Jafari said, is that half of Ukraine's children are not fully immunized against polio and many other diseases.

That shortfall is not related to the struggles with Russia in the eastern part of the country, he said. The outbreak is in the west, near the borders with Romania, Slovakia, Hungary and Poland.

Rather, many Ukrainian parents resist vaccines because of a 2008 case in which a high school student died, apparently of sepsis, shortly after getting a shot for measles, mumps and rubella.

The Health Ministry and the United Nations Children's Fund, which supplied the vaccine, insisted then that the death was a coincidence and that the vaccine was safe. But panic spread, and nearly 100 students went to hospitals complaining of headaches, fevers and sore throats.

The president at the time, Viktor A. Yushchenko, ordered all measles immunizations halted while officials investigated. Since then, about a third of Ukrainian parents have told pollsters that they fear vaccines, and vaccination rates have plummeted.

The incidence of measles rose from 100 cases in 2010 to 12,700 two years later. In 2013, Unicef warned that Ukraine was at risk of a polio outbreak.

"How Ukraine's officials handle communications strategy will be important," Dr. Jafari said.

Forbes

Hospitals Say Aetna-Humana Deal Endangers Medicare Advantage

By Bruce Japsen

September 2, 2015

The nation's powerful hospital lobby, the American Hospital Association, urged the U.S. Justice Department to closely scrutinize the proposed $37 billion acquisition by Aetna (AET) of Humana (HUM), saying it threatens competition in the business of providing health benefits to seniors in the growing privately run portion of the Medicare program.

Specifically, the AHA, which represents some 5,000 U.S. hospitals, says the combination of the two health insurance giants would give a larger Aetna too much power to potentially raise prices and end choices for seniors who buy Medicare Advantage plans, which contract with the government to provide traditional Medicare coverage plus extras that include wellness care, preventive screenings and prescription drugs.

Enrollment in Medicare Advantage plans has soared in recent years and hospitals fear insurers with too much control in this growing market.

"The deal will not just eliminate current competition between Humana and Aetna, it will eliminate future competition between them," Melinda Hatton, senior vice president and general counsel at the AHA said in her letter this week to Assistant U.S. Attorney General William Baer in the Justice Department's antitrust division and U.S. Secretary of Health and Human Services Sylvia Burwell. "Humana is the second largest insurer of Medicare Advantage lives in the country. Aetna is the fourth largest."

The hospital industry appears to be the first among health care providers to aggressively challenge health plan mergers. Providers are also expected to launch a legal and political assault on the proposed merger between Anthem (ANTM) and Cigna (CI).

Hospitals say almost one in three Medicare beneficiaries, or nearly 17 million Americans, obtain coverage through an Advantage plan and the combined Humana and Aetna would lead to market dominance in more than 1,000 markets that would "become highly concentrated."

Aetna and Humana and supporters of the deal say the larger insurer would allow the plans to extract price cuts from doctors and hospitals, which would be a good thing. Health plans also say they need to consolidate to reduce overhead and comply with rules under the Affordable Care Act that demand more dollars be spent on medical care rather than administrative costs.

But while the hospitals admit that the larger insurer could reduce prices but overall it would "materially may harm competition in multiple ways" in large part because there would be an enormous barrier of entry for any new health plans to enter Medicare Advantage.

"It may create monopsony power and enable the merged firm to exploit small, relatively powerless providers," AHA's Hatton said in her letter to the justice department. "Second, the merger may create downstream market power, which could offset the desirable effects of countervailing power and raise premiums to consumers. Finally, the merger might create countervailing power but the merged firm might exercise it in anticompetitive ways, harming consumers or small providers."

For their part, Aetna and Humana say a larger entity would invest more in benefits and health programs that benefit seniors saying they already score well on Medicare's five-star quality ratings system. They also say there have been more than 30 new parent companies that have entered the Medicare Advantage market in the last four years including providers of medical care.

"Aetna and Humana have the greatest number of plans rated four stars and higher in this highly competitive environment," Aetna said in a statement. "Because of this, Medicare beneficiaries will experience strong quality and value with our plans."

INDUSTRY NEWS

Wall Street Journal

Court Decision Could Allow Novartis to Sell Copy of Amgen's Neupogen

By Peter Loftus

September 2, 2015

A federal appeals court in Washington denied Amgen Inc.'s request for a temporary injunction to block Novartis AG from selling a copycat version of the blockbuster drug Neupogen in the U.S.

The decision by the U.S. Court of Appeals for the Federal Circuit could clear the way for Novartis to begin selling Zarxio, a knockoff version of Neupogen that was approved by the U.S. Food and Drug Administration in March. The U.S. market accounted for more than 70% of Amgen's $1.16 billion in global sales last year of Neupogen, a drug prescribed to chemotherapy patients.

Zarxio was the first biosimilar—a copy of a biotechnology drug—approved by the FDA under abbreviated criteria enabled by a provision of the 2010 Affordable Care Act. But the product's introduction has been held up by a legal dispute between Amgen and Novartis.

The drug industry and its lawyers are closely watching the Neupogen biosimilar case because the outcome could shape the path to market for a coming wave of biosimilar drugs that are expected to cost less than the original brands.

A Novartis spokesman said the company welcomed Wednesday's decision, but didn't provide plans for selling Zarxio. An Amgen spokeswoman said the company will "compete effectively" but declined to comment directly on the court decision.

The same appeals court issued a ruling in July that largely sided with Novartis, but ordered an injunction on Zarxio's sale until Wednesday. Amgen subsequently asked for a temporary injunction that would bar the sale of Zarxio beyond Wednesday, while Amgen pursues further legal options. The court denied Amgen's request without explanation in an order issued Wednesday.

Novartis hasn't announced a price for Zarxio. In Europe, where biosimilars have been available for several years, they typically cost 15% to 30% less than the original brands.

The dispute began when Amgen filed a lawsuit in federal court in San Francisco last year, accusing Novartis of failing to disclose certain information about its copycat product to Amgen, which Amgen said was required under the new criteria for FDA approval of biosimilars. Amgen also alleged Zarxio would infringe upon a patent for Neupogen. Novartis denies the allegations.

Wall Street Journal

Lannett to Acquire UCB's Kremers Urban Pharmaceuticals Unit for $1.23 Billion

By Maria Armental

September 2, 2015

Lannett Company Inc. has agreed to buy UCB SA's Kremers Urban Pharmaceuticals Inc. for $1.23 billion.

The deal, with tax benefits expected to top $100 million, also calls for potential contingency payments under sales and timing thresholds. Lannett said it expects the deal to close in the fourth quarter.

Lannett's shares, up 15% this year, rose nearly 18% to $58.25 in late trading.

Philadelphia-based Lannett, which is borrowing up to $1.29 billion, in part to fund the transaction, estimated a mid- to high-single-digit increase in adjusted profit in fiscal 2016 and 20% to 25%

increase in fiscal 2017.

On a pro forma basis, Lannett said the deal will leave it with about $225 million left in its credit line.

"KU brings considerable manufacturing capacity, a first class research and development team and the potential for advancing our active pharmaceutical ingredients business," Lannett Chief Executive Arthur Bedrosian said.

Kremers Urban, based in Princeton, N.J., is a specialty generic-drug maker. Its main drug is a generic form of Johnson & Johnson's Concerta, used to treat attention deficit hyperactivity disorder.

Belgian pharmaceutical company UCB, which acquired Kremers Urban when it bought Schwarz Pharma in 2006, tried to sell it last year to private-equity firms Advent International and Avista Capital Partners for $1.53 billion. The deal was called off when the Food and Drug Administration changed the ratings for two Concerta generics and requested additional information showing bioequivalency to Concerta.

The contingency payments in the Lannett deal are tied to the FDA's restoring the rating. Kremers Urban submitted the final results of new bioequivalence studies in June. Under the current rating, its methylphenidate hydrochloride extended-release tablets can be prescribed but may not be automatically substituted for Concerta at pharmacy counters.

Wall Street Journal

Medtronic Results to Provide Checkup on Covidien Deal

By Charley Grant

September 2, 2015

Multibillion-dollar acquisitions can be thrilling for investors. What happens next, though less exciting, can be just as important.

Medtronic PLC on Thursday reports first-quarter results for its fiscal 2016 year ending in April. This will mark the second round of results since the device manufacturer's $50 billion acquisition of Covidien PLC closed in January.

Analysts see Medtronic posting $7.1 billion in sales and $1.01 in adjusted earnings per share. The legacy Covidien business, now known as the minimally invasive therapies group, is expected to contribute about a third of total revenue.

The Covidien purchase allowed Medtronic to complement its existing cardiac, spinal and diabetes products with surgical offerings. Plus, Medtronic expects to achieve $850 million in annual cost savings through the first three years of the deal, including $300 million to $350 million in fiscal 2016. Importantly, the deal allowed Medtronic to relocate its headquarters to Ireland and reduce its tax rate to about 16% to 18%.

And the story could get more attractive. For instance, cost synergies could be realized sooner than expected, and revenue gains within Medtronic's product line that weren't forecast could yet be achieved.

Meanwhile, the negative effects of the strong dollar are baked into the full-year guidance for adjusted earnings. Medtronic said in June that it expects to earn $4.30 to $4.40 a share this year, which reflects a negative currency impact of 40 to 50 cents. That could prove conservative if the dollar's recent fall against the euro were to pick up steam.

All this made the purchase a hit with investors. The stock rose by 25% between the deal's announcement in June 2014 and its completion.

Still, the transaction came at a cost to Medtronic's balance sheet, adding $16 billion in new debt. And the early glow has worn off: The stock is down 6% since the deal closed.

The problem is that Medtronic needs to deliver on the deal's promise and exceed expectations. Its market value adjusted for net debt now exceeds 11 times forward earnings before interest, taxes, depreciation and amortization. That is well above the pre-acquisition valuation of about nine times.

With the stock market starting to wobble, Medtronic has to show that there is proof in this deal pudding.

PHARMA/BIOTECH NEWS

New York Times

Insurer Says Clients on Daily Pill Have Stayed H.I.V.-Free

By Donald McNeil Jr.

September 2, 2015

Demonstrating that taking a daily pill to prevent H.I.V. infection can work in the real world, San Francisco's largest private health insurer announced Wednesday that not one of its 657 clients receiving the drug had become infected over a period of more than two years.

That outcome contradicted some critics' predictions that so-called pre-exposure prophylaxis, or PrEP, would lead to less condom use and more H.I.V. infections.

A study published in Clinical Infectious Diseases found that the San Franciscans on PrEP, almost all of whom were gay men, did use fewer condoms — and contracted several other venereal diseases as a result. But none got H.I.V.

Most other sexual infections, while potentially dangerous, can be cured with antibiotics. H.I.V. cannot, though it can be controlled with antiretroviral drugs taken for life.

"This is very reassuring data," said Dr. Jonathan E. Volk, an epidemiologist for the insurer, Kaiser Permanente of San Francisco, and the study's lead author. "It tells us that PrEP works even in a high-risk population."

Observational studies like this one are not considered as scientifically rigorous as randomized clinical trials in which some participants receive a placebo.

But Dr. Volk and his colleagues followed a large number of men engaged in very risky behavior from mid-2012, when the Food and Drug Administration approved the use of a two-drug combination called Truvada for prevention of H.I.V. infection, through February of this year.

That amounts to 388 "person years" of observation.

By contrast, in a 2014 clinical trial among gay men in England, participants who received a placebo instead of Truvada had nine infections for every 100 person years of observation, said Dr. Anthony S. Fauci, the director of the National Institute for Allergy and Infectious Diseases.

That trial, nicknamed the Proud study, was one of several that were stopped early because researchers decided it was unethical to keep some participants on a placebo once it had become abundantly clear that PrEP worked.

"This shows that the effectiveness of PrEP is really strikingly high," Dr. Fauci said. "And this study takes it out of the realm of clinical trials and into the real world."

The newest study "fills in a critical gap by showing that PrEP can prevent infections in a real-world public health program," said Mitchell J. Warren, the executive director of AVAC, an organization lobbying for AIDS prevention.

About a third of all San Franciscans with private health insurance use Kaiser Permanente, which has its own hospitals, doctors and pharmacies and tracks all of its patients in one electronic records system.

About a third of all San Franciscans on PrEP receive the drug through Kaiser, and its doctors urge all their clients who are at risk to ask if PrEP is right for them, Dr. Volk said.

All but four of the 657 participants in the Kaiser study were gay men, and 84 percent of them reported multiple sexual partners.

After starting PrEP, half of them became infected with syphilis, gonorrhea or chlamydia within a year.

After the participants had six months of PrEP use, Dr. Volk's team surveyed 143 about their sexual behavior.

More than 40 percent said that their use of condoms had decreased.

The vast majority, 74 percent, said that their number of sexual partners had remained the same.

Previous studies have shown that PrEP is highly effective at preventing infection when participants take all or most of their daily pills.

The Kaiser study did not take blood samples to see whether its clients were taking the Truvada regularly, but all the men were on PrEP specifically because they had asked their primary care doctors for it and so presumably intended to take it, Dr. Volk said.

Although it is possible that PrEP contributed to higher rates of syphilis, gonorrhea and chlamydia, rates of those infections had begun climbing among gay men even before PrEP became available, Dr. Volk said.

The authors of the English study noted the same phenomenon.

The infections may have begun rising, Dr. Volk said, as some gay men began "sero-sorting" — choosing to have condomless sex only with men of the same H.I.V. status as themselves — or because H.I.V.-negative men agreed to have condomless sex with infected men who were taking their antiretroviral drugs so regularly that their blood levels of H.I.V. were undetectable, meaning they almost certainly could not pass that infection on.

"PrEP is another line of defense," Dr. Volk said. "This is exciting news."

Forbes

UK Study Indicates that the Cardiovascular Risk of Celebrex No Different from Other Pain Drugs

By John LaMattina

September 2, 2015

An important, yet underpublicized, study among the hundreds presented at this week's European Society of Cardiology conference held in London was "The Standard Care versus Celecoxib Outcome Trial" (SCOT). As you may recall, Merck took Vioxx, its COX-2 inhibiting pain reliever, off the market in 2004 for concerns over increased cardiovascular events such as heart attacks and strokes. Shortly thereafter, the FDA held a three day Advisory Committee meeting in Washington,

DC, to assess the potential that this was a class effect of COX-2 inhibitors and not just specific to Vioxx. A major revelation at this meeting was that ALL non-steroidal anti-inflammatory drugs (NSAIDs) – including popular drugs such as ibuprofen and diclofenac, not just COX-2 inhibitors — have the potential of increasing cardiovascular events. As a result of these deliberations, Celebrex remained on the market, but the labels of these drugs were changed to reflect this risk.

Physicians, however, were left in a bit of a quandary. After all, most arthritic patients tend to have characteristics that make them prone to cardiovascular events: >65 years old, overweight, high blood pressure, high cholesterol, etc. Should they avoid using COX-2 inhibitors in these types of patients, even if the patients appear free of cardiovascular disease?

To answer this question, "The Standard Care versus Celecoxib Outcome Trial" (SCOT) was undertaken. This was a pragmatic trial designed to mimic the real world setting of the situations that doctors face daily in treating their patients with pain. The study was sponsored by the University of Dundee and funded via an investigator initiated research grant from Pfizer , the manufacturer of celecoxib (generic name for Celebrex). This study was required by the European Medicines Agency (EMA) as a post-approval commitment for Celebrex. Using primary care practices across the UK, Denmark, and the Netherlands, 7,297 patients were recruited for the study. They were all over 60 years old, were free of cardiovascular disease, and were already chronically taking NSAIDs (predominantly diclofenac and ibuprofen). In SCOT, half of these patients were switched to Celebrex while the other half stayed on the NSAID that they had already been taking. These patients were then followed on average for 3.2 years (the study itself took almost 10 years to run). The patients were monitored during this period with the primary endpoints being hospitalization for non-fatal MI, non-fatal stroke, or cardiovascular death. Cardiovascular events were adjudicated by an independent monitoring committee.

The first surprise was that, on treatment, there was on average about 1 primary event per 100 patient years. One might have expected more than that given the characteristics of this patient population. Furthermore, the event rate was no different between the two groups. The study also monitored adverse GI events as COX-2 inhibitors were designed to minimize this adverse effect. Here a statistically significant benefit was indeed observed as there were 38 serious adverse gastrointestinal reactions with Celebrex versus 66 with the traditional NSAIDs although here, too, there were fewer GI events than expected.

The authors of the SCOT study concluded that:

"In patients with arthritis, without known cardiovascular disease, CV event rates were low and serious ulcer-related complication rates very low, and neither outcome differed significantly between NSAIDs and celecoxib. In the study population, NSAIDs and celecoxib both appeared acceptably safe. In patients who get significant symptomatic relief from these medicines, the benefit/risk balance appears positive."

Of course, SCOT was conducted in patients without cardiovascular disease. But what about those with heart disease who also suffer from arthritis or other chronic pain conditions? To answer that question, the "Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen and Naproxen" (PRECISION) trial was initiated in 2006 by the Cleveland Clinic. Funded by Pfizer, and likely costing upwards of $300 million, this study has been fully recruited and, according to Clinicaltrials.com (NCT00346216), should be completed next March. The results of this trial, in combination with the SCOT results, will be invaluable to physicians and patients as they seek optimal ways of controlling their pain. But for those free of cardiovascular disease, Celebrex appears to offer no increased cardiovascular risk compared to traditional NSAIDs like ibuprofen and diclofenac. Many would have bet against such an outcome 10 years ago.

Fierce Biotech

Novartis Team Tracks Remissions of 4-Plus Years in a Pioneering CAR-T study

By John Carroll

September 3, 2015

Five years after the University of Pennsylvania began recruiting a small group of 14 patients with hard-to-treat chronic lymphocytic leukemia, researchers are still tracking three of them who are still alive with no signs of their cancer returning after being treated with a first-generation CAR-T therapy.

The study offers a glimpse into the promise of a durable response for reengineered T cells--in this case taking the T cells out of patients and then adding a chimeric antigen receptor for a treatment called CTL019, which is owned by Novartis-while outlining the challenges involved in keeping patients safe from a severe and common reaction and devising new approaches to overcome some of the personalized treatment's limitations as the first of these drugs move closer to a possible marketing approval.

Out of the 14, four experienced complete remissions, meaning their cancer was no longer detectable. One of those four later died of other causes. Four patients had partial responses, with two of them dying after 10 months and 27 months of therapy. One of the partial-response patients died from a pulmonary embolism, and the other was switched to a different therapy after 13 months and died after three years.

Six of the patients did not respond to the therapy. And of the three patients still alive, two were treated more than four years ago, making them the longest running remissions in the CAR-T field.

The key takeaway:

"Importantly, our tests of patients who experienced complete remissions showed that the modified cells remain in patients' bodies for years after their infusions, with no sign of cancerous or normal B cells," said the study's senior author, Dr. Carl June, one of the pioneers in immunotherapy, which is emerging as a multibillion-dollar market. "This suggests that at least some of the CTL019 cells retain their ability to hunt for cancerous cells for long periods of time."

All of the patients who responded to the therapy experienced a potentially life-threatening case of cytokine release syndrome, sometimes called a cytokine storm, with the drug triggering high fevers and in several cases difficulty with breathing and low blood pressure. Doctors responded with the antibody drug tocilizumab and steroids, and all of the patients survived.

In a small study like this, investigators can learn as much from failure as they can from success. Testing the 6 patients who did not respond, the scientists said that their customized T cell

populations did not expand as aggressively as in the patients who were first flattened by a cytokine storm in their first response to the solo treatment.

The Novartis/Penn team as well as rivals Juno and Kite and a whole pack of companies jumping into the game have been studying new technology that can be used to amp up the T-cell attack on cancer cells. A whole host are also tackling the challenge of moving past B cells to solid tumors and off-the-shelf therapies, which represent a big challenge--and a much bigger market.

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Thursday, September 10, 2015 3:56 AM
To: Linda Barnes
CC: Rosenberg, Steven A. (NIH/NCI) [E]; Jeff Wiezorek
Subject: RE: NCI-Kite Mtg. re: CD27L-41BBz & KRAS Update [LARGE GRP]

Hi Linda,

I am supposed to land by that time and be in the car on the way to the hotel. Please connect me to the call.

Arie Belldegrun, MD FACS
President and CEO, Founder
Chairman, Board of Directors
Kite Pharma

2225 Colorado Ave
Santa Monica, CA 90404
Tel:310-622-9093
www.kitepharma.com

From: Jeff Wiezorek
Sent: Wednesday, September 9, 2015 2:56 PM
To: William Go <WGo@KitePharma.com>; Marc Better <MBetter@KitePharma.com>; Tony Polverino <TPolverino@KitePharma.com>; Kerr Clark <kerrclark@kitepharma.com>; Jim Economou <jeconomou@conet.ucla.edu>; Allan Pantuck <apantuck@mednet.ucla.edu>; Owen Witte <owenwitte@mednet.ucla.edu>; Antoni Ribas MD PhD <aribas@mednet.ucla.edu>; Adrian Bot <ABot@KitePharma.com>; Rajul Jain <RJain@KitePharma.com>; Arie Belldegrun <Arie@kitepharma.com>; James Kochenderfer <kochendj@mail.nih.gov>; Robert Somerville <robert.somerville@nih.gov>; Dr. Paul Robbins <PaulRobbins@mail.nih.gov>; Steven A. Rosenberg <sar@mail.nih.gov>; Mary Ann Toomey <toomeym@mail.nih.gov>; Steven Feldman <Feldmanst@mail.nih.gov>; Shell, Linda (NIH/NCI) [E] <chilesl@mail.nih.gov>; David Chang <DChang@KitePharma.com>; Rizwana Sproule <RSproule@KitePharma.com>; Margo Roberts <MRoberts@KitePharma.com>; Zachary Roberts <ZRoberts@kitepharma.com>; David Chang <DChang@KitePharma.com>
Cc: Chantel Cox <ccox@kitepharma.com>; Linda Barnes <LBarnes@KitePharma.com>; Katae Long-Phelps <klongphelps@kitepharma.com>
Subject: RE: NCI-Kite Mtg. re: CD27L-41BBz & KRAS Update [LARGE GRP]

The agenda for tomorrow's meeting and associated slides are attached.
Please let me know if there are additional items for discussion.

Jeff << File: NCI-KITE Team Agenda 9-10-15.docx >> << File: Kite meeting 9-10-15.ppt >>

-----Original Appointment-----
From: Patricia Lettner **On Behalf Of** Jeff Wiezorek
Sent: Tuesday, April 7, 2015 10:19 AM
To: Jeff Wiezorek; William "Will" Go MD PhD (wgo@kitepharma.com); Marc Better; Tony Polverino; Kerr Clark; Jim Economou; Allan Pantuck; Owen Witte; Antoni Ribas MD PhD; Adrian Bot; Rajul Jain; Arie Belldegrun; James Kochenderfer; Robert Somerville; Dr. Paul Robbins; Steven A. Rosenberg; Mary Ann Toomey; Steven Feldman; Shell, Linda (NIH/NCI) [E]; David Chang; Rizwana Sproule; Margo Roberts (mroberts@kitepharma.com); Arianne Perez; Jed Wiltzius; Armen Mardiros; Ruben Rodriguez; Roy Doumani; Donald Kohn; Salah D. Kivlighn (SKivlighn@kitepharma.com);

Zachary Roberts; Rizwana Sproule (rsproule@kitepharma.com); Margo Roberts; David D. Chang, M.D., Ph. D. (dchang@kitepharma.com)
Cc: Chantel Cox (CCox@kitepharma.com); Linda Barnes; Katae Long-Phelps; Cynthia Butitta; Sean Yoder; Scott Bernstein; Marianna Sabatino; Prentice Curry; Helen Kim; Cary Freeny; baanderson@mednet.ucla.edu; jpalaganas@mednet.ucla.edu; Mary Jo Spaulding; Samantha
Subject: NCI-Kite Mtg. re: CD27L-41BBz & KRAS Update [LARGE GRP]
When: Thursday, September 10, 2015 12:30 PM-2:00 PM (UTC-08:00) Pacific Time (US & Canada).
Where: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Thursday, September 10, 2015 3:56 AM
To: Linda Barnes
CC: Rosenberg, Steven A. (NIH/NCI) [E]; Jeff Wiezorek
Subject: RE: NCI-Kite Mtg. re: CD27L-41BBz & KRAS Update [LARGE GRP]

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Cc: Chantel Cox <ccox@kitepharma.com>; Linda Barnes <LBarnes@KitePharma.com>; Katae Long-Phelps <klongphelps@kitepharma.com>
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Cc: Chantel Cox (CCox@kitepharma.com); Linda Barnes; Katae Long-Phelps; Cynthia Butitta; Sean Yoder; Scott Bernstein; Marianna Sabatino; Prentice Curry; Helen Kim; Cary Freeny; baanderson@mednet.ucla.edu; jpalaganas@mednet.ucla.edu; Mary Jo Spaulding; Samantha
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PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

From: David Chang [DChang@KitePharma.com]
Sent: Thursday, September 10, 2015 12:25 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]; Justin Jackson
CC: Chu, Keting (National Office); Greenberger, Lee (National Office)
Subject: Re: Steve Rosenberg

Dear Steve,

I am following on this request from LLS, and also to connect you directly with Keting and Lee.

As previously discussed (and Keting can confirm) the topic will not include any product specific ones.

Thanks,

David

David D. Chang, M.D., Ph.D.
office: (310) 622-9094
PERSONAL INFORMATION,REDACTED PER AGREEMENT

www.kitepharma.com

Sent from my iPhone

On Sep 10, 2015, at 9:49 AM, Chu, Keting (National Office) <Keting.Chu@lls.org> wrote:

> Hi David,
> Good morning.
> As discussed, We would like to video tap Steve at the Immunotherapy conference in NYC on Sept 16-18th where he is giving a keynote speech. I would appreciate if you can email connect us with Steve as discussed.
> Thank you in advance for your help
> Regards
> keting
>
> **:: keting Chu, MD. PhD | VP, Research Therapy Acceleration Program**
> :: The Leukemia & Lymphoma Society | 1311 Mamaroneck Ave., Suite 310, White Plains, NY 10605
> :: Tel: 914-821-8843 | VOIP 8843 | Fax: 914-821-3343| www.lls.org | keting.chu@lls.org

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Monday, September 14, 2015 8:52 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Fwd: Kite Pharma Expands Collaboration With Netherlands Cancer Institute (NKI)

Hi Steve,

Just FYI.

Shana Tova!

Arie Belldegrun, MD, FACS
Chairman, CEO, Founder
Kite Pharma
Santa Monica, CA 90404

Begin forwarded message:

From: "Kite Pharma, Inc." <jjackson@burnsmc.com>
Date: September 14, 2015 at 14:07:52 GMT+2
To: <Arie@kitepharma.com>
Subject: Kite Pharma Expands Collaboration With Netherlands Cancer Institute (NKI)

Logo

Kite Pharma Expands Collaboration With Netherlands Cancer Institute (NKI)

Kite and NKI Sign Master Services Agreement and Kite Obtains From NKI Exclusive Option to License T Cell Receptor (TCR) Cancer Immunotherapy Product Candidates

SANTA MONICA, Calif., Sept. 14, 2015 (GLOBE NEWSWIRE) -- Kite Pharma, Inc. (Kite) (Nasdaq:KITE) today announced that it has expanded its collaboration with the Netherlands Cancer Institute (NKI). Kite and the NKI have entered into an agreement under which Kite will receive from the NKI the exclusive option to license multiple T cell receptor (TCR) gene sequences for the development and commercialization of cancer immunotherapy candidates targeting solid tumors. Kite has also expanded its access to additional resources and research facilities through a master services agreement with the NKI.

"We are excited with the progress of the TCR research programs with Kite and look forward to further advancements of the programs and our collaboration," said Professor René Medema, Director of NKI. "NKI believes that TCR technologies hold great potential for cancer care, and we are committed to making these new therapies a reality for patients."

Kite Pharma EU, based in Amsterdam, will be conducting preclinical research related to candidates under the agreement with NKI. Kite Pharma EU is comprised of a leading team of immuno-oncology

researchers and collaborators, including Professor Dr. Ton N. M. Schumacher, who serves as Chief Scientific Officer of Kite Pharma EU. Professor Dr. Schumacher, a pioneer in T cell biology and gene therapy, is a developer of Kite's proprietary TCR-GENErator™ discovery platform, an industry-leading R&D engine for rapid, high-throughput identification of TCR-based product candidates.

"With Kite Pharma EU, we have established a central hub of cancer immunotherapy efforts in Europe, attracting leading scientific experts, researchers and collaborators in this field," said Arie Belldegrun, M.D., FACS, Chairman, President and Chief Executive Officer of Kite. "Kite's relationship with the NKI, an internationally renowned cancer research and clinical institution, provides an important operational platform, as we advance TCR-based immuno-oncology product candidates."

About Kite Pharma, Inc.

Kite Pharma, Inc., is a clinical-stage biopharmaceutical company engaged in the development of novel cancer immunotherapy products, with a primary focus on engineered autologous cell therapy (eACT™) designed to restore the immune system's ability to recognize and eradicate tumors. Kite is based in Santa Monica, CA. For more information on Kite Pharma, please visit www.kitepharma.com.

Kite Pharma, Inc. Forward-Looking Statements

This press release contains forward-looking statements for purposes of the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. The press release may, in some cases, use terms such as "predicts," "believes," "potential," "proposed," "continue," "estimates," "anticipates," "expects," "plans," "intends," "may," "could," "might," "will," "should" or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. Forward-looking statements include statements regarding intentions, beliefs, projections, outlook, analyses or current expectations concerning, among other things: the ability to advance, and the success of, TCR-based product candidates. Various factors may cause differences between Kite's expectations and actual results as discussed in greater detail in Kite's filings with the Securities and Exchange Commission, including without limitation in its Form 10-Q for the quarter ended June 30, 2015. Any forward-looking statements that are made in this press release speak only as of the date of this press release. Kite assumes no obligation to update the forward-looking statements whether as a result of new information, future events or otherwise, after the date of this press release.

CONTACT: Kite Pharma
Cynthia M. Butitta
Chief Financial Officer and Chief Operating Officer
310-824-9999

For Media: Justin Jackson
For Investor Inquiries: Lisa Burns
Burns McClellan
212-213-0006
jjackson@burnsmc.com
lburns@burnsmc.com

Source: Kite Pharma, Inc.

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Monday, September 28, 2015 10:35 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Fwd: Cellular Biomedicine Group announces positive results from CAR-T EGFR immunotherapy in ph.1/II trial

FYI

Arie Belldegrun, MD FACS
President and CEO, Chairman
Kite Pharma

www.kitepharma.com

From: FactSet_Alerts@factset.com
Sent: Monday, September 28, 2015 5:59:30 AM
To: PERSONAL INFORMATION,REDACTED PER AGREEMENT
Subject: Cellular Biomedicine Group announces positive results from CAR-T EGFR immunotherapy in ph.1/II trial

28 Sep '15 8:59 AM **CBMG-US** StreetAccount

Cellular Biomedicine Group announces positive results from CAR-T EGFR immunotherapy in ph.1/II trial
Monday, September 28, 2015 12:59:28 PM (GMT)

FACTSET | streetaccount

- CBMG announced results from an expanded Phase I/II clinical trial evaluating the safety, feasibility and anti-tumor activity of its Chimeric Antigen Receptor-Modified T-Cells (CAR-T) immunotherapy (CBM-EGFR.1) targeting wild type EGFR (Epidermal Growth Factor Receptor) for the treatment of patients with EGFR expressing advanced relapsed/refractory solid tumors.
- Based on the results from 24 patients treated with CBM-EGFR.1 (17 patients with non-small cell lung cancer (NSCLC), 5 patients with cholangiocarcinoma, 1 patient with pancreatic cancer and 1 patient with renal cell carcinoma (RCC)), the early results showed that CBM-EGFR.1 immunotherapy was safe, well tolerated, and had positive signal of clinical activity in several indications.
- The data was selected for a late-breaking oral presentation entitled EGFR-Targeted Chimeric Antigen Receptor-Modified T Cells Immunotherapy for Patients With EGFR-Expressing Advanced or Relapsed/Refractory Solid Tumors at the 5th World Congress on Cancer Therapy in Atlanta, Georgia on 28-Sep-15. The abstract can be viewed online here.
- The results from the first 11 NSCLC patients in the trial outlined in the abstract, entitled Chimeric Antigen Receptor-Modified T-Cells for the Immunotherapy of Patients with HER-1 Expressing Advanced Relapsed/Refractory Non-Small Cell Lung Cancer was presented at the 2015 European Cancer Congress' (ECCO) annual meeting held in Vienna, Austria from 25-Sep-29, 2015. The abstract can be viewed online here.

Industries: Biotechnology & Drugs
Primary Identifiers: CBMG-US
Related Identifiers: CBMG-US
Reference Links:
- Cellular Biomedicine Group Announces Positive Results From CAR-T EGFR Immunotherapy in Advanced Relapsed/Refractory Patients With Solid Tumors

FactSet News Alert for: Craig Gordon MD

***Please do not reply to this e-mail.*

From: Rosenberg, Steven A. (NIH/NCI) [E]
Sent: Monday, September 28, 2015 5:03 PM
To: 'Arie Belldegrun'
Subject: RE: Cellular Biomedicine Group announces positive results from CAR-T EGFR immunotherapy in ph.1/II trial

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Steven A. Rosenberg M.D., Ph.D.
Chief, Surgery Branch
National Cancer Institute
10 Center Drive MSC 1201
CRC Room 3-3940
Bethesda, MD 20892
301-496-4164
sar@nih.gov

From: Arie Belldegrun [mailto:Arie@kitepharma.com]
Sent: Monday, September 28, 2015 10:35 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Fwd: Cellular Biomedicine Group announces positive results from CAR-T EGFR immunotherapy in ph.1/II trial

FYI

Arie Belldegrun, MD FACS
President and CEO, Chairman
Kite Pharma

www.kitepharma.com

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To: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT
Subject: Cellular Biomedicine Group announces positive results from CAR-T EGFR immunotherapy in ph.1/II trial

28 Sep '15 8:59 AM **CBMG-US** StreetAccount

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Monday, September 28, 2015 12:59:28 PM (GMT)

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Primary Identifiers: CBMG-US
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- Cellular Biomedicine Group Announces Positive Results From CAR-T EGFR Immunotherapy in Advanced Relapsed/Refractory Patients With Solid Tumors

FactSet News Alert for: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

***Please do not reply to this e-mail.*

From: David Chang [DChang@KitePharma.com]
Sent: Wednesday, September 30, 2015 10:38 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT
Attachments: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Hi Steve,

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Thanks,
David

David D. Chang, MD, PhD
Executive Vice President of R&D
and Chief Medical Officer
Kite Pharma, Inc
office: 310-622-9094
PERSONAL INFORMATION,REDACTED PER AGREEMENT

www.kitepharma.com

MICROTECHNOLOGY

CRISPR-Cas9 delivery to hard-to-transfect cells via membrane deformation

10.1126/sciadv.1500454

Xin Han,[1,2] Zongbin Liu,[1,2] Myeong chan Jo,[1,2] Kai Zhang,[1,2] Ying Li,[1,2] Zihua Zeng,[3] Nan Li,[4] Youli Zu,[3] Lidong Qin[1,2,5]*

The CRISPR (clustered regularly interspaced short palindromic repeats)–Cas (CRISPR-associated) nuclease system represents an efficient tool for genome editing and gene function analysis. It consists of two components: single-guide RNA (sgRNA) and the enzyme Cas9. Typical sgRNA and Cas9 intracellular delivery techniques are limited by their reliance on cell type and exogenous materials as well as their toxic effects on cells (for example, electroporation). We introduce and optimize a microfluidic membrane deformation method to deliver sgRNA and Cas9 into different cell types and achieve successful genome editing. This approach uses rapid cell mechanical deformation to generate transient membrane holes to enable delivery of biomaterials in the medium. We achieved high delivery efficiency of different macromolecules into different cell types, including hard-to-transfect lymphoma cells and embryonic stem cells, while maintaining high cell viability. With the advantages of broad applicability across different cell types, particularly hard-to-transfect cells, and flexibility of application, this method could potentially enable new avenues of biomedical research and gene targeting therapy such as mutation correction of disease genes through combination of the CRISPR-Cas9–mediated knockin system.

INTRODUCTION

The CRISPR (clustered regularly interspaced short palindromic repeats)–Cas (CRISPR-associated) nuclease system is an easy-to-use, highly specific, efficient, and multiplexable genome editing tool that has been used in various organisms, including human and mouse cell lines (*1*–*3*). In the two-component system, a single-guide RNA (sgRNA) directs Cas9 nuclease to introduce sequence-specific targeted loss-of-function mutations into the genome (*3*, *4*). Cas9 can be easily programmed to induce DNA double-strand breaks through RNA guides, which can generate insertions and deletions (indels) and stimulate genome editing at specific target genomic loci (*5*, *6*). The ability to perturb the genome in a precise and targeted manner is crucial to understanding genetic contributions to biology and disease (*3*, *7*).

Successful delivery of sgRNA and Cas9 into cells guarantees efficient genome editing. Typical intracellular delivery techniques use liposomes or polymeric nanoparticles to induce cell membrane poration or endocytosis (*8*–*11*), and recently, cell-penetrating peptide-mediated delivery of sgRNA and Cas9 has been used for gene disruption (*12*). In these methods, delivery efficiency is often dependent on cell type and the structure of the target molecule. Electroporation is an attractive alternative for many applications and allows highly efficient RNA-guided genome editing via delivery of purified Cas9 ribonucleoprotein (*13*–*15*). However, this method can cause cell damage and generate a high cell death rate. Moreover, commonly used virus (adeno-associated virus, retrovirus, or lentivirus)–mediated delivery of sgRNA and Cas9 is often associated with uncontrolled chromosomal integration (*16*, *17*), limiting its clinical potential.

Rapid mechanical deformation of cells can produce transient membrane disruptions that facilitate passive diffusion of material into the cytosol. Using physical constriction to deform and shear cells for delivery has achieved high efficiency with low cell death rate. This method has the advantage of high-throughput delivery of almost any macromolecule into almost any cell type (*18*). Membrane deformation–based microfluidic devices have been used in the delivery of a range of materials such as carbon nanotubes, proteins, and short interfering RNAs (siRNAs). They have been used for delivering transcription factors for cell reprogramming (*18*). Microfluidic membrane deformation has the potential to serve as a broad-based universal delivery platform and boasts the advantages of precise control over treatment conditions at the single-cell level, with macroscale throughput. Here, we optimized the physical constriction in a microfluidic setup, considering both delivery efficiency and cell viability. Through this, we successfully delivered single-stranded DNA (ssDNA), siRNAs, and large-sized plasmids into different cell types, including adherent and non-adherent cells, hard-to-transfect lymphoma, and embryonic stem cells. Sequence analysis, together with biochemical and functional analyses, demonstrated highly efficient genome editing and successful generation of gene-knockout cell lines, using our delivery device in different cell types. To the best of our knowledge, this is the first demonstration of membrane deformation for CRISPR/Cas9 gene editing. Thus, we expect that our new microfluidic delivery method will facilitate RNA-guided genome editing and gene loss-of-function analysis across different cell types, especially difficult-to-transfect cells. Achievement of high genome editing efficiency in non-adherent lymphoma cells suggests that the approach also has potential for clinical use.

[1]Department of Nanomedicine, Houston Methodist Research Institute, Houston, TX 77030, USA. [2]Department of Cell and Developmental Biology, Weill Medical College of Cornell University, New York, NY 10065, USA. [3]Department of Pathology and Genomic Medicine and Cancer Pathology Laboratory, Houston Methodist Hospital and Houston Methodist Research Institute, Houston, TX 77030, USA. [4]Department of Experimental Radiation Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX 77030, USA. [5]Department of Molecular and Cellular Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX 77030, USA.
*Corresponding author. E-mail: lqin@houstonmethodist.org

RESULTS

Delivery principle and chip design

When a cell passes through a constriction smaller than the cell diameter, it undergoes rapid mechanical deformation, causing transient membrane

disruption or holes. The shear and compressive forces imposed on the cell during passage through the constriction determine the degree of disruption and the size and frequency of the holes. Macromolecules small enough to pass through the holes can diffuse into the cytosol from the surrounding medium and may remain and function in the cell after the membrane recovers from the deformation (Fig. 1, A and B). To apply this principle, we designed a family of microfluidic devices with a series of constrictions of different dimensions formed by structures of different shapes (fig. S1A).

Devices were fabricated with standard polydimethylsiloxane (PDMS) microfluidics technology. Each chip consists of 14 identical cell-scattering and deformation zones, and each zone contains 10 arrays of structures forming microconstrictions (Fig. 1C). The scatter zone is designed to prevent device collapse and also disperse or "scatter" the cell suspension. The deformation zone is where cells pass through microconstrictions, becoming deformed and generating transient membrane holes that ensure delivery of the macromolecule(s) of interest. Interconnected channels enable high throughput of treated cells by preventing clogging. To optimize the microconstriction design, we first prepared constrictions using structures of several different shapes, including circle, ellipse, and diamond (fig. S1A). Suspended cells were applied to the chip through a Tygon tube connected to the inlet, and fluid flow was controlled by a syringe pump. To optimize the design, we did a series of test deliveries of fluorescein isothiocyanate (FITC)–labeled ssDNA into human embryonic kidney 293T (HEK293T) cells. The smallest constriction width of the three designs, 4 μm, was chosen for further experiments. Of the three designs, the diamond pattern showed nearly identical delivery efficiency at a range of flow rates from 50 to 250 μl/min, with much higher cell viability than the circle or ellipse patterns (fig. S1, B and C), and so this pattern was chosen for further experiments. To maximize the functional area, we minimized the length of the diamond edge to 10 μm (Fig. 1C). The parallel chip design (fig. S1D) was generated by arranging multiple devices side by side to demonstrate that delivery can be multiplexed. The cell recovery rate after delivery for both HEK293T and SUM159 cell lines was close to 100% (fig. S1E). Movie S1 shows cells passing through microconstrictions formed by the diamond pattern at a flow rate of 30 μl/min. Cell stress simulation (Fig. 1D and fig. S2) and flow velocity simulation (fig. S3) were applied to the diamond pattern design at the time point when a cell began to penetrate the microconstriction. Movie S2 shows the flow velocity simulation. With this chip design, we expect to successfully deliver plasmids encoding different sgRNAs and Cas9 into different types of cells and achieve precise genome editing and perform specific gene loss-of-function analysis, as depicted in Fig. 1B.

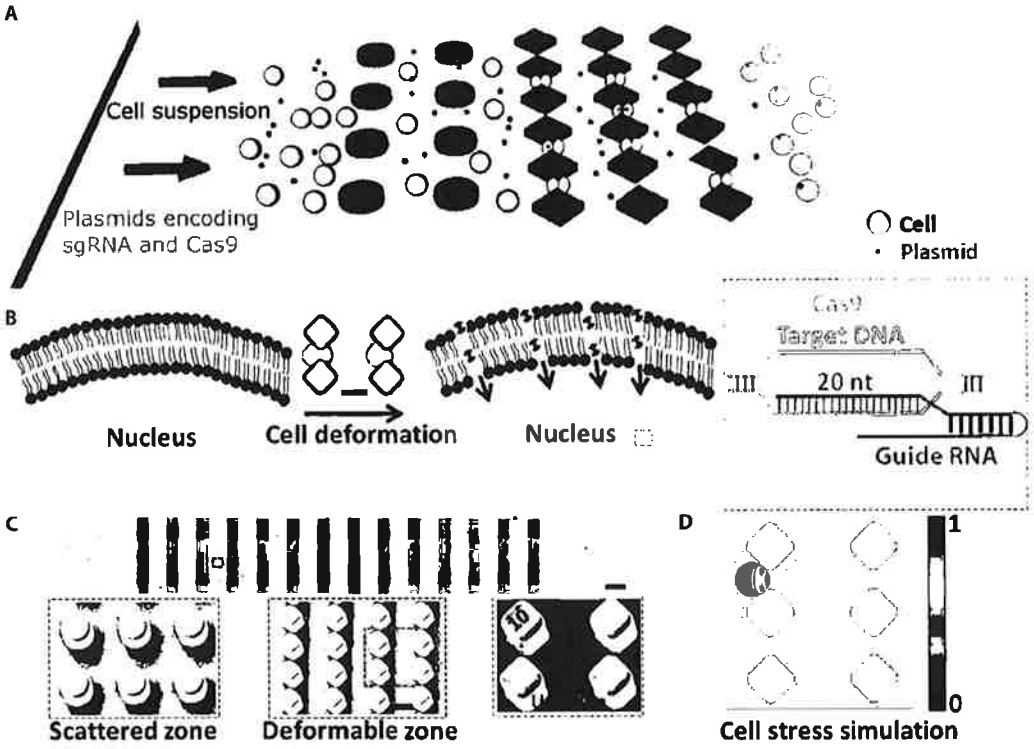

Fig. 1. Delivery mechanism and device design. (**A**) Illustration of the delivery process wherein cells pass through the microconstriction and experience deformability. Plasmids encoding sgRNA and Cas9 protein are mixed with the cells to flow through the chip. (**B**) Illustration of the delivery mechanism whereby transient membrane holes are generated when cells pass through the microconstriction and specific genome editing is conducted after plasmids encoding sgRNA and Cas9 protein are delivered into the cell. Cell deformation was shown by microscopy when cells passed through the microconstriction. Scale bar, 15 μm. nt, nucleotide. (**C**) Microscopy of the whole device structure. Scale bar, 0.5 mm. Scanning electron microscopy (SEM) of scattered and deformable zones in the device is also shown. Scale bar, 15 μm. One diamonded microconstriction of 15-μm depth and 4-μm width is indicated by the red arrow. The length of the diamond edge is 10 μm. (**D**) Cell stress simulation was applied on the diamonded microconstriction design with 15-μm depth and 4-μm width when a cell began to penetrate the constriction. A graphical representation of the cell stress gradient that forms across the membrane is shown.

Optimization of the delivery chip specifications

To optimize the delivery performance of the chip, we took into consideration constriction dimensions, fluid flow rates, and duration of cell passage through the chip as three key parameters. In the diamond design, the constriction depth was 15 μm, and the width varied from 4 to 5 μm (Fig. 1C). In pursuit of high delivery efficiency coupled with high cell viability, we did a series of testing deliveries of FITC-labeled ssDNA into HEK293T cells (Fig. 2A). Our data showed that delivery efficiency increased with increasing flow rate across design patterns (Fig. 2B). The 4-μm constriction width presented higher delivery efficiency than the 5-μm width at all flow rates, with minimal effect on cell viability. Increasing the number of operational cycles with the same chip allowed multiple cell passaging times, which would also enhance the delivery efficiency; however, the operation clearly decreased cell viability (Fig. 2, B and C). The data for the 0 μl/min flow rate represents a control whereby the cells were treated exactly as the other samples but were not applied with the membrane deformation, thus ruling out the possibility that cell FITC positivity was the result of any endocytotic or surface binding events.

Broad applicability

To investigate the adaptability of this technique, we first tried siRNA delivery for gene knockdown. Considering both delivery efficiency and cell viability, we chose a microconstriction width of 4 μm, a fluid flow rate of 250 μl/min, and single passage of the cells through the chip for all subsequent experiments. When we delivered three siRNAs specific for Akt1 into PC-3 cells, all of the oligos achieved >70% knockdown efficiency in 48 hours after delivery (Fig. 2D). Moreover, depletion of Akt1 by all three siRNAs suppressed cell growth, which is consistent with previous research (Fig. 2E), indicating that our technique is reliable for cell phenotype analysis and gene function study (*19*).

To further assess the delivery ability of the chip across different cell types, we used plasmids encoding green fluorescent protein (GFP) to measure the delivery efficiency. We successfully delivered plasmids encoding GFP with high efficiency into HEK293T cells, human luminal-like MCF7 and basal-like SUM159 breast cancer cells, human SU-DHL-1 anaplastic large cell lymphoma cells, and mouse AB2.2 embryonic stem cells (Fig. 2F), all with minimal cell death. Using our method, we achieved nearly the same percentage of GFP-expressing cells as

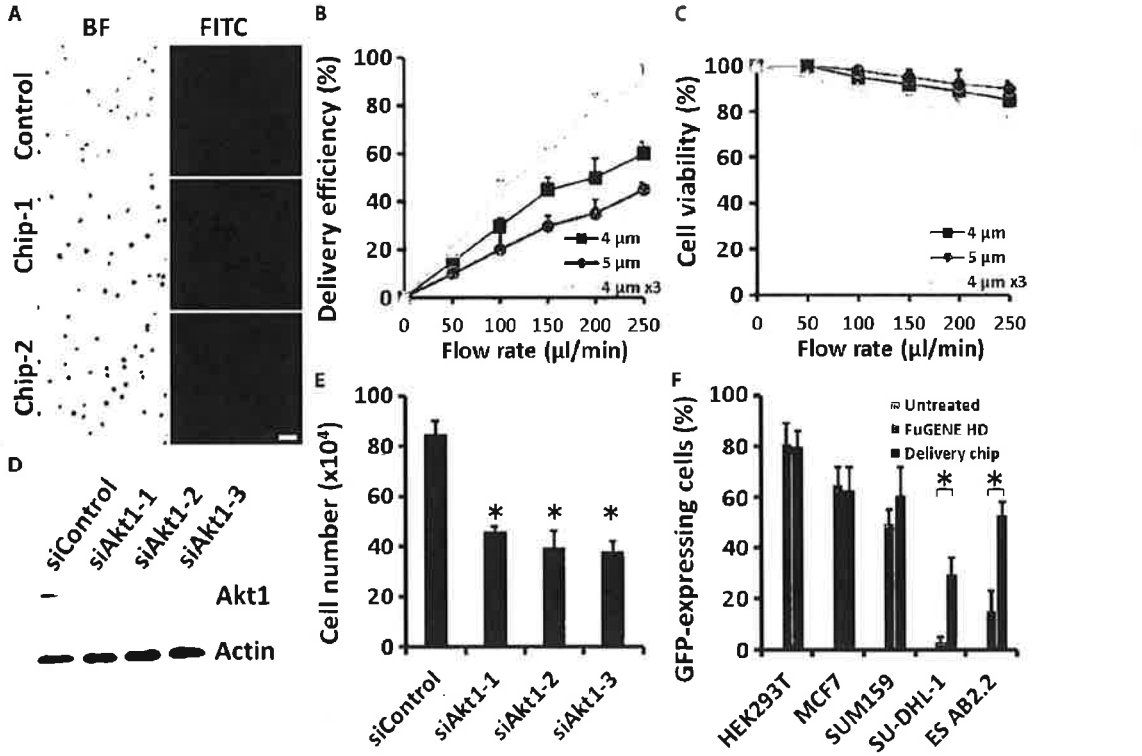

Fig. 2. Governing parameters and broad applicability. (**A**) Microscopy of HEK293T cells into which FITC-labeled ssDNA was delivered through our chip. Results shown are from two independent chips. Control indicated all the same treatments for the cells except passing through the chip. Scale bar, 50 μm. BF, bright field. (**B** and **C**) Delivery efficiency (B) and cell viability (C) 16 hours after treatment were calculated for (A) as a function of fluid speed at different parameter designs; 4 or 5 μm indicates the constriction width, and 4 μm ×3 indicates cells passing through the same device three times. Error bars indicate SEM ($n = 3$). (**D**) Western blotting of PC-3 cells 48 hours after delivery with three different siRNA oligos targeting Akt1. Actin is showed as a loading control. (**E**) Cells from (D) were seeded in complete medium and, after 6 days, were recovered and trypsinized to count the numbers with a Countess II FL Automated Cell Counter (Life Technologies). Error bars indicate SEM ($n = 3$). *$P < 0.005$ determined by Student's t test. (**F**) Delivery efficiency in different cell lines. HEK293T cells, human luminal-like MCF7 and basal-like SUM159 breast cancer cells, human SU-DHL-1 anaplastic large cell lymphoma cells, and mouse AB2.2 embryonic stem cells were delivered with plasmids encoding GFP. Untreated serves as a negative control and FuGENE HD serves as a positive control. Error bars indicate SEM ($n = 3$). *$P < 0.005$ determined by Student's t test.

obtained with traditional FuGENE HD transfection (Fig. 2F and fig. S4, A to E). Our delivery method achieved even higher efficiency than FuGENE HD transfection in human anaplastic large cell lymphoma cells and mouse embryonic stem cells without inducing stem cell differentiation (Fig. 2F and fig. S4F), suggesting potential application in difficult-to-transfect cells. Device designs have not been optimized for different cell types, indicating that we can expect further improvement in delivery efficiency, with the goal of cell-specific delivery protocols, in future applications.

EGFP knockout via chip

We used cells stably expressing enhanced GFP (EGFP) to illustrate the potential application of this method in CRISPR-Cas9–mediated genome editing. EGFP was introduced into cells with lentivirus, and the EGFP encoding sequences were integrated into chromosomal DNA. Plasmids encoding Cas9 only or sgRNAs targeting EGFP (sgEGFP-1 and sgEGFP-2) and Cas9 were delivered into adherent MDA-MB-231 cells and non-adherent SU-DHL-1 lymphoma cells. To enhance delivery efficiency, cells were passed through the same chip three times. After delivery, cells were allowed to recover in culture for 7 days. Bright-field and fluorescence microscopic (Fig. 3A) and flow cytometric analyses (Fig. 3B and fig. S5A) showed that plasmid delivery was efficient and genome editing was successful in MDA-MB-231 cells, achieving >90% EGFP knockout efficiency with both sgRNAs targeting different EGFP coding sequences. In SU-DHL-1 lymphoma cells, bright-field and fluorescence microscopic analyses (Fig. 3C) and flow cytometric analyses (Fig. 3D and fig. S5B) showed >70% EGFP knockout efficiency, which was satisfactory for this difficult-to-transfect lymphoma cell line and could not be achieved by current transfection methods. As expected, EGFP expression was not affected in the negative control cells, which were delivered with plasmids encoding Cas9 only.

To analyze the indels at the EGFP locus generated by CRISPR-Cas9–mediated genome editing, we amplified the specific sgEGFP-1 target regions by polymerase chain reaction (PCR) and conducted TA cloning of the products in SU-DHL-1 lymphoma cells (fig. S5C). The results of sequence analysis showed that delivery of plasmids encoding sgRNA targeting EGFP and Cas9 via our chip caused different types of mutations in the EGFP locus (Fig. 3E). These data indicate that we successfully delivered plasmids encoding sgRNAs and Cas9 into different human cell lines using our chip and achieved highly efficient genome editing.

Gene disruption platform

To determine whether our delivery platform could be used for gene disruption and function analysis, we carried out further delivery of plasmids encoding Cas9 and sgRNAs targeting different genes in different types of cell lines. Plasmids encoding sgRNA targeting the endogenous *AAVS1* locus and Cas9 were delivered into MCF7 cells. The cells were allowed to recover in culture for 7 days, followed by PCR amplification of the specific sgRNA target region. The results of TA cloning and sequence analysis showed that the delivery of plasmids encoding Cas9 and sgRNA targeting *AAVS1* resulted in mutations, including indels, at the specific genomic loci (Fig. 4A). Surveyor mutation detection assay revealed substantial cleavage at the *AAVS1* locus, with indels occurring at a frequency of about 18 to 46% when delivery was optimized by passage of the cells through the chip three times (Fig. 4B).

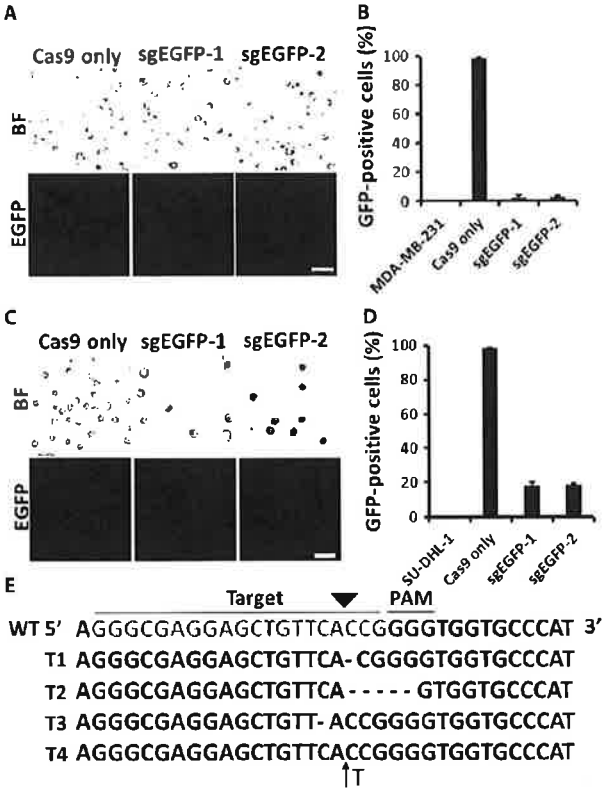

Fig. 3. EGFP knockout via a microfluidic method. (**A**) Microscopy of MDA-MB-231 cells stably expressing EGFP 7 days after being delivered with plasmids encoding only Cas9 protein or both sgEGFP and Cas9 protein. Scale bar, 20 μm. (**B**) Percentage of cells displaying EGFP fluorescence from (A) was quantified by flow cytometry. MDA-MB-231 serves as a negative control for EGFP fluorescence signal. Error bars indicate SE ($n = 3$). (**C**) Microscopy of SU-DHL-1 lymphoma cells stably expressing EGFP 7 days after being delivered with plasmids encoding only Cas9 protein or both sgEGFP and Cas9 protein. Scale bar, 20 μm. (**D**) Percentage of cells displaying EGFP fluorescence from (C) was quantified by flow cytometry. SU-DHL-1 serves as a negative control for EGFP fluorescence signal. Error bars indicate SE ($n = 3$). (**E**) PCR product sequencing data for the sgEGFP-1 targeting region in SU-DHL-1 lymphoma cells. The 20–base pair (bp) target sequence is shown in red; the PAM sequence is shown in blue. Representative sequences for indels are shown. Short black lines denote different deletions. Black arrow denotes an insertion. WT, wild type.

We designed an sgRNA targeting the first exon of the *NUAK2* gene and cloned it into a vector for coexpression with sgRNA and Cas9 (Fig. 4C). Plasmids encoding Cas9 and sgRNA targeting NUAK2 were delivered into HeLa cells via our membrane deformation method, and the cells were allowed to recover in culture for 7 days. PCR amplification of the sgRNA target region followed by TA cloning and sequence analysis showed deletion mutations at the specific genomic loci (Fig. 4D). Mutation detection assay revealed substantial cleavage at the *NUAK2* gene locus, with indels occurring at a frequency of about 30% (Fig. 4E). The indel mutation frequencies could be optimized in a few ways such as passaging cells multiple times through the deformation chip, increasing the concentration of the plasmids, and using a selective drug to kill the nontransfected cells.

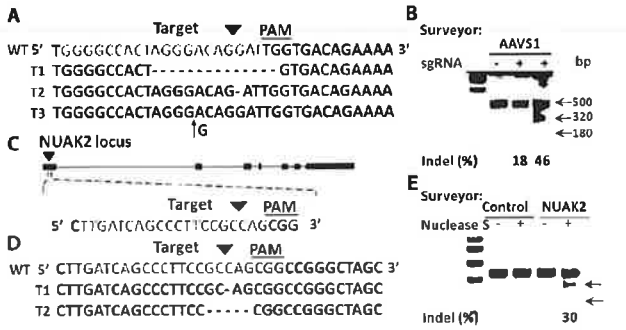

Fig. 4. Gene disruption via chip. Plasmids encoding both sgRNA targeting *AAVS1* locus or NUAK2 and Cas9 protein were delivered into MCF7 and HeLa cells, respectively. After 7 days of cell culture, genomic DNA was extracted. PCR product sequencing for specific targeting regions was performed. (**A**) PCR product sequencing data for the sgAAVS1 targeting region. The 20-bp target sequence is shown in red; the PAM sequence is shown in blue. Representative sequences for indels are shown. Short black lines denote different deletions. Black arrow denotes an insertion. (**B**) Surveyor mutation detection assay for sgAAVS1- and Cas9 protein–mediated indels via chip. Arrows indicate the expected positions of DNA bands cleaved by Surveyor Nuclease S. The symbol * indicates the cleavage lane of DNA bands after cells went through the same chip three times. (**C**) Illustration of sgNUAK2 targeting region at the first exon. The 20-bp target sequence is shown in red; the PAM sequence is shown in blue. (**D**) PCR product sequencing data for the sgNUAK2 targeting region. Representative sequences for deletions are shown. Short black lines denote different deletions. (**E**) Surveyor mutation detection assay for sgNUAK2- and Cas9 protein–mediated indels via chip. Arrows indicate the expected positions of DNA bands cleaved by Surveyor Nuclease S.

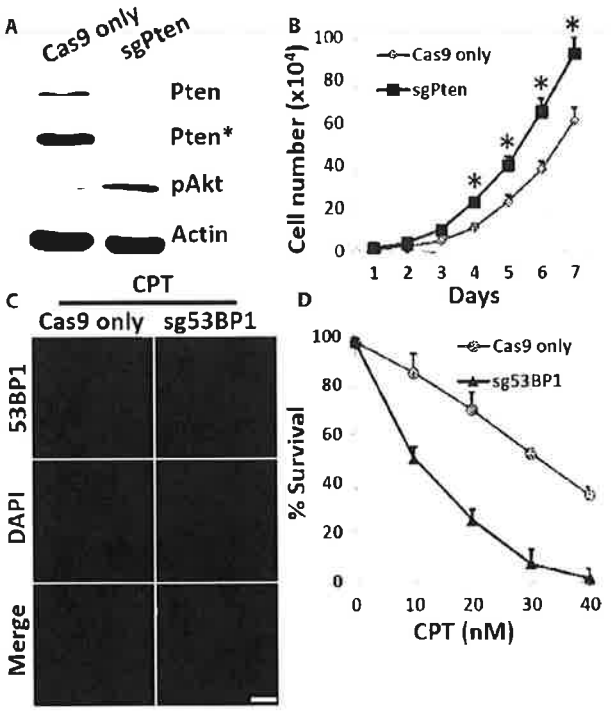

Fig. 5. Microfluidic platform for cell phenotype and gene function analysis. (**A**) MCF7 cells delivered with plasmids encoding only Cas9 protein or both sgPten and Cas9 protein were cultured for 7 days and then analyzed by Western blotting with the indicated antibodies. Actin was used as a loading control. The symbol * indicates long exposure. (**B**) Cells (5×10^4) from (A) were seeded in 60-mm dishes in complete medium and cultured for 7 days. Cells were trypsinized and collected for cell count in a Countess II FL Automated Cell Counter (Life Technologies) daily for 7 days. Error bars indicate SEM ($n = 3$). *$P < 0.005$ determined by Student's t test. (**C**) HeLa cells delivered with plasmids encoding only Cas9 protein or both sg53BP1 and Cas9 protein were cultured 7 days. Then, the cells were treated with 1 μM CPT for 2 hours and then examined by immunostaining with anti-53BP1 antibodies (red). Scale bar, 10 μm. DAPI, 4′,6-diamidino-2-phenylindole. (**D**) Survival rate of HeLa cells from (C) after control or CPT treatment was assessed by colony survival assay. Error bars indicate SEM ($n = 3$).

Next, we explored gene function and cell phenotype via our delivery chip. Plasmids encoding Cas9 and sgRNA targeting phosphatase and tensin homolog (Pten) (fig. S6A) were delivered into MCF7 cells, followed by culture for 48 hours and puromycin selection. More than 80% of the cells survived the selection process, indicating the high delivery efficiency of our method. Cells were allowed to recover for 7 days and then analyzed by Western blotting. The results of Western blotting analysis showed that endogenous Pten expression was abolished compared with expression in control cells transfected only with plasmid encoding Cas9. Moreover, the level of Akt phosphorylation increased with Pten depletion, consistent with activation of Akt by loss of Pten (Fig. 5A). Cells were immunostained to further confirm successful knockout of Pten and Akt activation (fig. S6B). Cell proliferation was also increased in MCF7 cells after Pten knockout (Fig. 5B), which is consistent with a previous study (*20*).

Tumor suppressor p53 binding protein 1 (53BP1) is required for DNA damage response and tumor suppression (*21*–*23*). We designed an sgRNA targeting a 53BP1 gene locus and delivered plasmids encoding both sg53BP1 and Cas9 via our chip into HeLa cells (fig. S6C). Cells were cultured for 48 hours and then selected with puromycin. Similar to Pten knockout, more than 80% of 53BP1 knockout cells survived the selection process. Western blotting analysis showed the clear absence of 53BP1 expression compared with control cells (fig. S6D). Camptothecin (CPT) causes DNA strand breaks mediated by transcription and induces clear 53BP1 foci in the nuclei. Here, we showed that CPT treatment resulted in clear 53BP1 foci formation in the nuclei of control cells, but not in the cells treated with plasmids encoding both sg53BP1 and Cas9 (Fig. 5C). Consistent with this, cell survival was also greatly decreased in the cells delivered with plasmids encoding both sg53BP1 and Cas9 after CPT treatment (Fig. 5D). Together, these data show that our chip-mediated delivery is a rapid, efficient, and high-throughput method for CRISPR-Cas9–mediated genome editing and gene knockout analysis and may provide a multiplexable and integrated platform for gene phenotype and functional analysis.

DISCUSSION

Our delivery method uses the mechanical deformability of cells to generate transient holes in the cell membrane, permitting diffusion of biomaterials in the extracellular milieu into the cytoplasm. We achieved high delivery efficiency and high cell viability with delivery of siRNAs and plasmids. On the basis of the delivery principle, this method also has the potential to deliver other materials, such as proteins and nanoparticles. Moreover, the delivery method can be applied across different

types of cells, including hard-to-transfect cells, such as immune cells and stem cells, to address clinical needs. In the future, with a better understanding of the nature of the deformation experienced by cells passing through a microconstriction and optimization of device parameters, one can expect to achieve better performance in a range of cell types and applications.

The mechanical deformability–based principle provides a new solution for delivery and has advantages over some existing methods. To our knowledge, this is the first application of this microfluidic deformation method to the delivery of the CRISPR-Cas9 system to achieve genome editing and gene disruption. Similar to microinjection, the method does not rely on cell type or the structure of the target molecule (*24*, *25*); however, it is easier to use with higher throughput than microinjection. Electroporation has been successfully applied to CRISPR-Cas9 delivery and allows highly efficient RNA-guided genome editing. However, unlike our microfluidic method of delivery, electroporation damages cells and often affects cell viability. The high delivery efficiency and associated high cell viability of our method guarantee efficient genome editing and precise gene functional analysis. To increase genome editing activity, we may apply the cells multiple times through the deformation chip times, increase the concentration of the plasmids, and/or use a selective drug to kill the nontransfected cells. Using stable Cas9-expressing cells for sgRNA delivery or Cas9 protein/sgRNA co-complexes may also be helpful to increase the indel frequencies. Given our achieved capability of the deformation-based CRISPR/Cas9 gene editing, we expect to expand the work to many other cells and model systems.

Microfluidics as a basic research tool has the advantage that it is capable of integration and incorporation into a larger system including multiple posttreatment modules. This enables potential integration of our CRISPR-Cas9 system delivery and gene loss-of-function or mutation correlation analysis. For example, the device could be integrated with the single-cell protrusion microfluidic chip developed in our laboratory for screening genes potentially involved in cell protrusion mechanics (*26*). Use of our device would generate large quantities of CRISPR-Cas9–mediated knockout or knockin cells for high-throughput cell phenotypic screening.

CRISPR-Cas9–mediated delivery for gene therapy has been reported recently for correction of some mutations associated with disease (*7*, *27*–*30*). Our technique enables novel approaches to this type of gene therapy. We have achieved high delivery efficiency compared with traditional liposome-mediated delivery in SU-DHL-1 lymphoma cells, and successful application in anaplastic large cell lymphoma cells provides the possibility of delivery in primary patient cells. For example, a patient's target cells could be isolated from blood or other tissue, treated with the device to deliver the CRISPR-Cas9 knockin system with wild-type template to correct the disease gene mutation, and then reintroduced into the patient. The enhanced delivery efficiency of our method would increase the likelihood of correcting disease mutation genes by gene targeting therapy.

MATERIALS AND METHODS

Materials and reagents

SPR 220-7 photoresist was purchased from Rohm and Haas Electronic Materials. PDMS (GE 615 RTV) was purchased from Fisher Scientific. Tygon tubing was purchased from Saint-Gobain. Flat steel pins were purchased from New England Small Tube. Fetal bovine serum (FBS), trypsin, and penicillin-streptomycin were purchased from Fisher Scientific. Dulbecco's modified Eagle's medium (DMEM), Ham's F-12 medium, RPMI 1640 and F-12K medium, insulin, hydrocortisone, and phosphate-buffered saline (PBS) were purchased from Life Technologies. FITC-labeled ssDNA DNA was purchased from Integrated DNA Technologies. SiRNAs targeting Akt1 (siAkt1-1 SASI_Hs01_00105952, siAkt1-2 SASI_Hs01_00105953, and siAkt1-3 SASI_Hs01_00105954) were used previously and purchased from Sigma-Aldrich (*31*). Plasmids encoding sgRNA and Cas9 were purchased from Addgene, and specific sgRNA target sequences were cloned into the CRISPR v2 vector (Addgene plasmid #52961). The 20-bp target sequences of sgRNAs targeting EGFP, AAVS1, and Pten were used previously (*4*–*6*). The 20-bp target sequences of the indicated sgRNAs were as follows: sgEGFP-1, GGGCGAGGAGCTGTTCACCG; sgEGFP-2, GAGCTGGACGGCGACGTAAA; sgAAVS1, GGGGCCACTAGGGACAGGAT; sgNUAK2, TTGATCAGCCCTTCCGCCAG; sgPten, AGATCGTTAGCAGAAACAAA; sg53BP1, CATAATTTATCATCCACGTC. The primers used for PCR amplification of sgRNA target regions were as follows: EGFP-FP, ATGGTGAGCAAGGGCGAGGA; EGFP-RP, TTACTTGTACAGCTCGTCCA; AAVS1-FP, CCCCGTTCTCCTGTGGATTC; AAVS1-RP, ATCCTCTCTGGCTCCATCGT; NUAK2-FP, GCTTTACTGCGCGCTCTGGTACTGC; NUAK2-RP, CAGGCGCCCCGAGCTCTCCC.

Chip design and fabrication

The microchip pattern was designed with AutoCAD (Autodesk). Each chip consists of 14 identical cell-scattering and deformation zones, and each zone contains 10 arrays of constrictions. The constriction depth is 15 μm, and the width varies from 4 to 5 μm. The parallel chip design was generated by arranging multiple devices side by side. The microfluidic chip was fabricated using standard photolithography and soft lithography procedures. The negative photoresist SU8-3025 (MicroChem) was used to fabricate patterns on a silicon wafer. The silicon wafer was then silanized using trimethylchlorosilane (Thermo Scientific) for 30 min to facilitate PDMS mold release. PDMS prepolymer (10A:1B, Sylgard 184 silicone elastomer kit, Dow Corning) was poured onto the silicon wafer and cured at 80°C for 1 hour. Holes were then punched in the PDMS for the inlets and outlets, and oxygen plasma treatment was used to chemically bond the PDMS mold to a glass slide.

Finite element method

The flow velocity distribution, cell trajectory, and stress on the cell were simulated using the finite element method. To perform the temporal simulation, the fluidic dynamics equation (incompressible Navier-Stokes equations) and solid mechanics equation (Newton's second law of motion) were coupled and implemented by fluid-solid interactions. This combined the spatial frame interface for fluid flow and the material frame for the cell. The mesh geometry was continuously moved and deformed by applying the arbitrary Lagrangian-Eulerian method. The dimensions of model geometries and mechanical properties were identical to the actual experiment. The stress on the cell was computed as the von Mises stress, which is a scalar value determined from the stress tensor of a particle under the pressure in fluid flow.

Cell culture

HEK293T, MCF7, MDA-MB-231, and HeLa cells were grown in DMEM supplemented with 10% FBS and 1% penicillin-streptomycin

in a humidified atmosphere of 5% CO_2/95% air at 37°C. PC-3 cells were grown in F-12K medium supplemented with 10% FBS and 1% penicillin-streptomycin. SUM159 cells were grown in Ham's F-12 medium supplemented with 5% FBS, 1% penicillin-streptomycin, insulin (5 μg/ml), and hydrocortisone (1 μg/ml). Human SU-DHL-1 anaplastic large cell lymphoma cells were cultured in RPMI 1640 supplemented with 10% FBS and 1% penicillin-streptomycin. Mouse AB2.2 embryonic stem cells were maintained on a 0.1% gelatin (Sigma-Aldrich)–coated tissue culture dish in high-glucose DMEM, supplemented with 15% FBS, 55 μM β-mercaptoethanol (Life Technologies), and 0.01% mouse leukemia inhibitory factor (Millipore) under feeder-free conditions.

Delivery procedure and puromycin selection

The channels in the device were wetted with PBS and blocked with 1% bovine serum albumin in PBS for 10 min. Cells were first suspended in the desired volume of Opti-MEM medium (Life Technologies) and then mixed with the desired amount of delivery material (ssDNA, siRNA, or plasmid) and loaded into plastic Tygon tubing with a 5-ml syringe. The tubing was then connected to the device inlet reservoir by a flat steel pin. During the flow experiments, a syringe pump controlled the fluid flow through the device. Treated cells were incubated in a 37°C incubator for 20 min to recover before further treatment.

Plasmids encoding both Cas9 and sgRNA targeting Pten or 53BP1 were delivered into MCF7 or HeLa cells, respectively, via our chip. After 48 hours of culture, the cells were grown in DMEM supplemented with 10% FBS, 1% penicillin-streptomycin, and puromycin (2 μg/ml; Sigma) for 2 to 3 days to kill the undelivered cells.

Immunostaining, Western blotting, and flow cytometry

Cells grown overnight on coverslips were fixed in 4% paraformaldehyde and then permeabilized with 0.5% Triton X-100 plus 300 mM sucrose. Cells were then immunostained and visualized under an Olympus FV1000 confocal microscope. The primary antibodies used were anti-53BP1 (NB100-304, Novus Biologicals), anti-Oct4 (ab18976, Abcam), anti-Pten (ab130224, Abcam), and anti–phospho-Akt (Ser^{473}) (ab81283, Abcam). The secondary antibodies used were Alexa Fluor 488–conjugated goat anti-mouse (A-11001, Life Technologies) and Texas red–conjugated goat anti-rabbit (T-2767, Life Technologies).

For Western blotting after siRNA-mediated knockdown or sgRNA-Cas9–mediated knockout, cells were allowed to recover in culture for 2 or 7 days, respectively. The primary antibodies used were anti-Akt1 (ab32505, Abcam), anti-53BP1 (ab21083, Abcam), and anti-actin (A3853, Sigma-Aldrich). For flow cytometric analysis after sgEGFP-mediated knockout, cells were allowed to recover in culture for 7 days followed by analysis of EGFP fluorescence with a BD LSRFortessa cell analyzer.

Mutation detection assay, TA cloning, and sequencing

Genomic DNA was extracted using the PureLink Genomic DNA Mini Kit (K1820-00, Life Technologies) according to the manufacturer's instructions. PCR amplicons of nuclease target sites were generated and analyzed for the presence of mismatch mutations using the Transgenomic Surveyor Mutation Detection Kit (Integrated DNA Technologies) according to the manufacturer's instructions. Briefly, PCR amplicons of sgRNA target regions were denatured by heating for 10 min at 95°C, annealed to form heteroduplex DNA using a thermocycler from 95° to 25°C at −0.3°C/s, digested with Surveyor Nuclease S for 2 hours at 42°C, and separated by 1% agarose gel electrophoresis. For sequence analysis, PCR products corresponding to genomic modifications were cloned into pCR4-TOPO vector using the TOPO TA Cloning Kit (Life Technologies). Cloned products were sequenced using the M13 primer.

Cell proliferation assay, CPT treatment, and sensitivity assay

After chip-mediated delivery and recovery in culture for siRNA knockdown or sgRNA-Cas9–mediated knockout, cells (5×10^4) were seeded in 60-mm dishes in complete medium and cultured for 7 days. Cells were harvested by trypsinization daily and counted in a Countess II FL Automated Cell Counter (Life Technologies).

To assess CPT sensitivity, cells were treated with 1 μM CPT for 2 hours and immunostained with anti-53BP1 or treated with 10, 20, 30, or 40 nM CPT for sensitivity assay. CPT sensitivity was assessed by colony survival assay. Briefly, CPT-treated cells (500 to 1000) were plated in 60-mm dishes in complete medium and incubated for 2 to 3 weeks to form clones. Clones were stained with Coomassie blue, and survival rate was calculated.

SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/1/7/e1500454/DC1

Fig. S1. Performance of chip with different designs.
Fig. S2. Cell stress simulation.
Fig. S3. Flow velocity simulation.
Fig. S4. Comparison of FuGENE HD transfection and delivery via chip.
Fig. S5. Flow cytometric analysis of EGFP knockout cells.
Fig. S6. Pten and 53BP1 knockout mediated by delivery via chip.
Movie S1. Cells passing through the diamonded microconstrictions.
Movie S2. Flow velocity simulation in the diamonded microconstriction chip.

REFERENCES AND NOTES

1. P. Mali, L. Yang, K. M. Esvelt, J. Aach, M. Guell, J. E. DiCarlo, J. E. Norville, G. M. Church, RNA-guided human genome engineering via Cas9. *Science* **339**, 823–826 (2013).
2. L. Cong, F. A. Ran, D. Cox, S. Lin, R. Barretto, N. Habib, P. D. Hsu, X. Wu, W. Jiang, L. A. Marraffini, F. Zhang, Multiplex genome engineering using CRISPR/Cas systems. *Science* **339**, 819–823 (2013).
3. P. D. Hsu, E. S. Lander, F. Zhang, Development and applications of CRISPR-Cas9 for genome engineering. *Cell* **157**, 1262–1278 (2014).
4. W. Xue, S. Chen, H. Yin, T. Tammela, T. Papagiannakopoulos, N. S. Joshi, W. Cai, G. Yang, R. Bronson, D. G. Crowley, F. Zhang, D. G. Anderson, P. A. Sharp, T. Jacks, CRISPR-mediated direct mutation of cancer genes in the mouse liver. *Nature* **514**, 380–384 (2014).
5. T. Wang, J. J. Wei, D. M. Sabatini, E. S. Lander, Genetic screens in human cells using the CRISPR-Cas9 system. *Science* **343**, 80–84 (2014).
6. O. Shalem, N. E. Sanjana, E. Hartenian, X. Shi, D. A. Scott, T. S. Mikkelsen, D. Heckl, B. L. Ebert, D. E. Root, J. G. Doench, F. Zhang, Genome-scale CRISPR-Cas9 knockout screening in human cells. *Science* **343**, 84–87 (2014).
7. K. High, P. D. Gregory, C. Gersbach, CRISPR technology for gene therapy. *Nat. Med.* **20**, 476–477 (2014).
8. F. Heitz, M. C. Morris, G. Divita, Twenty years of cell-penetrating peptides: From molecular mechanisms to therapeutics. *Br. J. Pharmacol.* **157**, 195–206 (2009).
9. A. Verma, O. Uzun, Y. Hu, Y. Hu, H. S. Han, N. Watson, S. Chen, D. J. Irvine, F. Stellacci, Surface-structure-regulated cell-membrane penetration by monolayer-protected nanoparticles. *Nat. Mater.* **7**, 588–595 (2008).
10. J. Zabner, Cationic lipids used in gene transfer. *Adv. Drug Deliv. Rev.* **27**, 17–28 (1997).
11. H. Duan, S. Nie, Cell-penetrating quantum dots based on multivalent and endosome-disrupting surface coatings. *J. Am. Chem. Soc.* **129**, 3333–3338 (2007).
12. S. Ramakrishna, A. B. Kwaku Dad, J. Beloor, R. Gopalappa, S. K. Lee, H. Kim, Gene disruption by cell-penetrating peptide-mediated delivery of Cas9 protein and guide RNA. *Genome Res.* **24**, 1020–1027 (2014).

13. M. B. Fox, D. C. Esveld, A. Valero, R. Luttge, H. C. Mastwijk, P. V. Bartels, A. van den Berg, R. M. Boom, Electroporation of cells in microfluidic devices: A review. *Anal. Bioanal. Chem.* **385**, 474–485 (2006).
14. S. Li, Electroporation gene therapy: New developments in vivo and in vitro. *Curr. Gene Ther.* **4**, 309–316 (2004).
15. S. Kim, D. Kim, S. W. Cho, J. Kim, J. S. Kim, Highly efficient RNA-guided genome editing in human cells via delivery of purified Cas9 ribonucleoproteins. *Genome Res.* **24**, 1012–1019 (2014).
16. Y. C. Hu, Baculoviral vectors for gene delivery: A review. *Curr. Gene Ther.* **8**, 54–65 (2008).
17. R. Waehler, S. J. Russell, D. T. Curiel, Engineering targeted viral vectors for gene therapy. *Nat. Rev. Genet.* **8**, 573–587 (2007).
18. A. Sharei, J. Zoldan, A. Adamo, W. Y. Sim, N. Cho, E. Jackson, S. Mao, S. Schneider, M. J. Han, A. Lytton-Jean, P. A. Basto, S. Jhunjhunwala, J. Lee, D. A. Heller, J. W. Kang, G. C. Hartoularos, K. S. Kim, D. G. Anderson, R. Langer, K. F. Jensen, A vector-free microfluidic platform for intracellular delivery. *Proc. Natl. Acad. Sci. U.S.A.* **110**, 2082–2087 (2013).
19. T. Sasaki, K. Nakashiro, H. Tanaka, K. Azuma, H. Goda, S. Hara, J. Onodera, I. Fujimoto, N. Tanji, M. Yokoyama, H. Hamakawa, Knockdown of Akt isoforms by RNA silencing suppresses the growth of human prostate cancer cells in vitro and in vivo. *Biochem. Biophys. Res. Commun.* **399**, 79–83 (2010).
20. J. Zhang, P. Zhang, Y. Wei, H. L. Piao, W. Wang, S. Maddika, M. Wang, D. Chen, Y. Sun, M. C. Hung, J. Chen, L. Ma, Deubiquitylation and stabilization of PTEN by USP13. *Nat. Cell Biol.* **15**, 1486–1494 (2013).
21. S. Panier, S. J. Boulton, Double-strand break repair: 53BP1 comes into focus. *Nat. Rev. Mol. Cell Biol.* **15**, 7–18 (2014).
22. J. R. Chapman, P. Barral, J. B. Vannier, V. Borel, M. Steger, A. Tomas-Loba, A. A. Sartori, I. R. Adams, F. D. Batista, S. J. Boulton, RIF1 is essential for 53BP1-dependent nonhomologous end joining and suppression of DNA double-strand break resection. *Mol. Cell* **49**, 858–871 (2013).
23. I. Rappold, K. Iwabuchi, T. Date, J. Chen, Tumor suppressor p53 binding protein 1 (53BP1) is involved in DNA damage–signaling pathways. *J. Cell Biol.* **153**, 613–620 (2001).
24. Y. Zhang, L. C. Yu, Microinjection as a tool of mechanical delivery. *Curr. Opin. Biotechnol.* **19**, 506–510 (2008).
25. D. Luo, W. M. Saltzman, Synthetic DNA delivery systems. *Nat. Biotechnol.* **18**, 33–37 (2000).
26. K. Zhang, C. K. Chou, X. Xia, M. C. Hung, L. Qin, Block-Cell-Printing for live single-cell printing. *Proc. Natl. Acad. Sci. U.S.A.* **111**, 2948–2953 (2014).
27. Y. Wu, H. Zhou, X. Fan, Y. Zhang, M. Zhang, Y. Wang, Z. Xie, M. Bai, Q. Yin, D. Liang, W. Tang, J. Liao, C. Zhou, W. Liu, P. Zhu, H. Guo, H. Pan, C. Wu, H. Shi, L. Wu, F. Tang, J. Li, Correction of a genetic disease by CRISPR-Cas9-mediated gene editing in mouse spermatogonial stem cells. *Cell Res.* **25**, 67–79 (2015).
28. H. Yin, W. Xue, S. Chen, R. L. Bogorad, E. Benedetti, M. Grompe, V. Koteliansky, P. A. Sharp, T. Jacks, D. G. Anderson, Genome editing with Cas9 in adult mice corrects a disease mutation and phenotype. *Nat. Biotechnol.* **32**, 551–553 (2014).
29. Y. Wu, D. Liang, Y. Wang, M. Bai, W. Tang, S. Bao, Z. Yan, D. Li, J. Li, Correction of a genetic disease in mouse via use of CRISPR-Cas9. *Cell Stem Cell* **13**, 659–662 (2013).
30. G. Schwank, B. K. Koo, V. Sasselli, J. F. Dekkers, I. Heo, T. Demircan, N. Sasaki, S. Boymans, E. Cuppen, C. K. van der Ent, E. E. Nieuwenhuis, J. M. Beekman, H. Clevers, Functional repair of CFTR by CRISPR/Cas9 in intestinal stem cell organoids of cystic fibrosis patients. *Cell Stem Cell* **13**, 653–658 (2013).
31. X. Han, D. Liu, Y. Zhang, Y. Li, W. Lu, J. Chen, Z. Songyang, Akt regulates TPP1 homodimerization and telomere protection. *Aging Cell* **12**, 1091–1099 (2013).

Funding: We acknowledge funding support from the Cancer Prevention and Research Institute of Texas (CPRIT-R1007), NIH-CA180083, NIH-U54CA143837, and Golfers Against Cancer Foundation. **Author contributions:** X.H. and L.Q. designed the experiments and developed the method. X.H. and Z.L. performed the experiments. M.C.J. assisted with flow velocity simulation. K.Z. and Y.L. assisted with device optimization. N.L. assisted with the CPT sensitivity assay. Z.Z. and Y.Z. provided SU-DHL-1 lymphoma cells and helpful suggestions for improved user-friendliness. X.H. and L.Q. wrote the paper. All co-authors reviewed and approved the manuscript. **Competing interests:** The authors declare that they have no competing interests.

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From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Thursday, October 01, 2015 10:42 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Fwd: Press Release
Attachments: 15-0929 Neon Launch Press Release.docx; ATT00001.htm

FYI Neon. The neon company PROPRIETARY INFORMATION, has been launched, focusing on neoantigens. See the PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

On a separate e mail I will send you the correspondence with Ton, which we agreed to before he joined us.

It is amazing to see how the whole scientific community is following your ideas, something that is often being lost from their memory.....I do not forget!!!

Arie Belldegrun, MD FACS
President and CEO, Chairman
Kite Pharma

www.kitepharma.com

Begin forwarded message:

> **From:** David Chang <DChang@KitePharma.com>
> **Date:** September 30, 2015 at 15:35:42 PDT
> **To:** Arie Belldegrun <Arie@kitepharma.com>, Cynthia Butitta <CButitta@KitePharma.com>, Helen Kim <HKim@KitePharma.com>
> **Subject: FW: Press Release**
>
> FYI. This is the new Neoantigen company.
>
> > Neon Therapeutics is building a product engine poised to take full advantage of neoantigen biology. The company is developing multiple programs in therapeutic vaccines and T cell modalities, targeting both neoantigens that are specific to individual patients as well as neoantigens that are shared across patients and tumor types.
>
> **From:** David Chang
> **Sent:** Wednesday, September 30, 2015 3:32 PM
> **To:** 'Sharma,Padmanee' <PadSharma@mdanderson.org>
> **Cc:** Kate Bechtold <kbechtold@kitepharma.com>
> **Subject:** Press Release
>
> PROPRIETARY INFORMATION,REDACTED PER AGREEMENT
>
> PS I owe you a draft of the collaboration plan – will get it to you by the weekend.
>
> Thanks, David
>
> David D. Chang, MD, PhD
> Executive Vice President of R&D
> and Chief Medical Officer
> Kite Pharma, Inc
> office: 310-622-9094
> PERSONAL INFORMATION,REDACTED PER AGREEMENT
>
> www.kitepharma.com

Neon Therapeutics Launches with $55 Million Series A to Develop Neoantigen-based Cancer Immunotherapies

Third Rock Ventures Leads Investment with Additional Financing from Clal Biotechnology Industries and Access Industries

Company Assembles World Experts to Develop Therapies that Leverage the Power of Neoantigens to Attack Tumors

Cambridge, Mass. – October 1, 2015 – Third Rock Ventures, LLC today announced the formation of Neon Therapeutics, an immuno-oncology company developing neoantigen-based therapeutic vaccines and T cell therapies to treat cancer. Neon Therapeutics is focused on unlocking the full potential of the immune system to recognize and attack cancer via targeting proteins known as neoantigens. By leveraging neoantigen biology to elicit a potent immune attack on tumors, Neon Therapeutics' pipeline has the potential to significantly influence the course of cancer and provide durable responses to patients in need. Clal Biotechnology Industries and Access Industries joined Third Rock Ventures in the $55 million Series A financing.

Neoantigens result from mutations occurring during tumor growth, are recognized as foreign and differ from native antigens to which the immune system is tolerant. Mounting evidence suggests that immune rejection of tumors, for example that which is seen with checkpoint modulators, may be mediated by recognition of neoantigens. Neon Therapeutics is building a product engine poised to take full advantage of neoantigen biology. The company is developing multiple programs in therapeutic vaccines and T cell modalities, targeting both neoantigens that are specific to individual patients as well as neoantigens that are shared across patients and tumor types. Neon Therapeutics is committed to advancing the field of cancer immunotherapy by investing in research to improve identification and delivery of the most effective neoantigens in order to optimize neoantigen-directed T cell activity and to monitor patients treated with immunotherapies.

"Recent advances in immuno-oncology place us at a point that is unprecedented in the history of cancer drug development," said Cary Pfeffer, M.D., interim chief executive officer of Neon Therapeutics. "We have a completely new understanding of the immune system's role in unlocking powerful mechanisms to induce immune attack of tumors, representing an enormous opportunity for precision therapies for cancer patients. These insights enable Neon Therapeutics to develop therapies that are complementary to current immunomodulatory therapies and may significantly enhance the specificity and potency of existing approaches."

"There is mounting evidence that supports the role of neoantigens in tumor rejection," said Robert Tepper, M.D., Neon Therapeutics' interim chief scientific officer. "Neon

NEON
THERAPEUTICS

Therapeutics aspires to be the leading company focused on neoantigen targeting for therapeutic applications, and we have assembled the world's best experts to tackle this problem to provide new treatments for patients facing life-threatening cancers."

Neon Therapeutics was founded by globally-recognized experts in neoantigen biology, tumor immunology, vaccinology and personalized therapeutics. These founders have already made significant contributions to the Neon Therapeutics' plan and strategy, and bring complementary expertise to guide the future of the company. Founders include:

- James Allison, Ph.D., MD Anderson Cancer Center
- Ed Fritsch, Ph.D., Neon Therapeutics
- Nir Hacohen, Ph.D., Broad Institute and Massachusetts General Hospital
- Eric Lander, Ph.D., Broad Institute of MIT and Harvard
- Robert Schreiber, Ph.D., Washington University
- Ton Schumacher, Ph.D., Netherlands Cancer Institute
- Catherine Wu, M.D., Broad Institute and Dana-Farber Cancer Institute

Neon Therapeutics' lead program, NEO-PV-01, is a personalized neoantigen vaccine that builds upon initial clinical trials developed collaboratively by the Broad Institute and Dana-Farber Cancer Institute. The company will build upon ongoing research by initiating a company-sponsored clinical development program. In addition, Neon Therapeutics will also develop personalized T cell therapies that leverage the strengths of its platforms in epitope prediction and immune monitoring. The contributions from world-leading experts in core scientific advances in neoantigen biology have paved the way for the founding of Neon Therapeutics, and the company plans to work closely with them moving forward to bring new therapies to patients.

About Neon Therapeutics
Neon Therapeutics is an immuno-oncology company focused on developing novel therapeutics leveraging neoantigen biology to treat cancer. A neoantigen-based product engine will allow Neon to develop further treatment modalities including next-generation vaccines and T cell therapies targeting both personalized as well as shared neoantigens. Neon Therapeutics' lead program is a personalized neoantigen vaccine that builds upon years of research and development at the Broad Institute and Dana-Farber Cancer Institute, and is already in multiple clinical trials. For more information, please visit www.neontherapeutics.com.

About Clal Biotechnology Industries
Clal Biotechnology Industries (TASE: CBI) is a specialized holding company, which identifies and supports promising biotechnology companies with proprietary solutions to unmet medical needs, approaching large potential markets. Holding and managing an international portfolio of some twenty promising companies, Clal Biotechnology Industries undertakes significant investments and applies diverse models of strategic cooperation. For more information, please visit www.cbi.co.il.

NEON
THERAPEUTICS

About Access Industries
Access Industries is a privately held industrial group with long-term holdings worldwide. The company's industrial focus spans four primary sectors: Natural resources and chemicals, media and telecommunications, real estate, and technology and e-commerce. Founded in 1986 by Len Blavatnik, an American entrepreneur and philanthropist, Access is an international industrial concern with strategic investments in the United States, Europe and South America. Over the years, Mr. Blavatnik and the Blavatnik Family Foundation have provided significant support for cancer vaccine research and development at the Broad Institute and Dana-Farber Cancer Institute. The company has corporate offices in New York, London and Moscow. For more information, please visit www.accessindustries.com.

About Third Rock Ventures
Third Rock Ventures is the leading healthcare venture firm focused on disruptive areas of science and medicine to discover, launch and build companies that make a dramatic difference in people's lives. By combining our team's scientific vision, strategic leadership, operational expertise and innovative deal-making capabilities, we nurture bold ideas that translate into successful business enterprises. Recognizing that the best way to create value for our investors is to create value for patients, our companies are built on a solid foundation of science, medicine, people and business strategy. For more information, please visit www.thirdrockventures.com.

About the Broad Institute of MIT and Harvard
The Eli and Edythe L. Broad Institute of MIT and Harvard was launched in 2004 to empower this generation of creative scientists to transform medicine. The Broad Institute seeks to describe all the molecular components of life and their connections; discover the molecular basis of major human diseases; develop effective new approaches to diagnostics and therapeutics; and disseminate discoveries, tools, methods and data openly to the entire scientific community. Founded by MIT, Harvard and its affiliated hospitals, and the visionary Los Angeles philanthropists Eli and Edythe L. Broad, the Broad Institute includes faculty, professional staff and students from throughout the MIT and Harvard biomedical research communities and beyond, with collaborations spanning over a hundred private and public institutions in more than 40 countries worldwide. For more information, please visit broadinstitute.org.

About Dana-Farber Cancer Institute
Dana-Farber Cancer Institute, a principal teaching affiliate of Harvard Medical School, is world-renowned for its leadership in adult and pediatric cancer treatment and research. Designated as a comprehensive cancer center by the National Cancer Institute (NCI), it is one of the largest recipients among independent hospitals of NCI and National Institutes of Health grant funding. For more information, please visit www.dana-farber.org.

###

Media Contact:
Katie Engleman
Pure Communications, Inc.
910-509-3977
Katie@purecommunicationsinc.com

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Thursday, October 01, 2015 10:42 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Fwd: Neon press release

Here is the correspondence with Tom.

Arie Belldegrun, MD FACS
President and CEO, Chairman
Kite Pharma

www.kitepharma.com

Begin forwarded message:

From: David Chang <DChang@KitePharma.com>
Date: September 30, 2015 at 15:38:07 PDT
To: "t.schumacher@nki.nl" <t.schumacher@nki.nl>
Cc: Arie Belldegrun <Arie@kitepharma.com>
Subject: RE: Neon press release

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

-----Original Message-----
From: t.schumacher@nki.nl [mailto:t.schumacher@nki.nl]
Sent: Wednesday, September 30, 2015 8:26 AM
To: David Chang <DChang@KitePharma.com>
Subject: Neon press release

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

From: Rosenberg, Steven A. (NIH/NCI) [E]
Sent: Thursday, October 01, 2015 3:26 PM
To: David Chang MD PhD (dchang@kitepharma.com); 'arie@kitepharma.com'
Subject: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Steven A. Rosenberg M.D., Ph.D.
Chief, Surgery Branch
National Cancer Institute
10 Center Drive MSC 1201
CRC Room 3-3940
Bethesda, MD 20892
301-496-4164
sar@nih.gov

From: David Chang [DChang@KitePharma.com]
Sent: Thursday, October 01, 2015 4:14 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
CC: Arie Belldegrun
Subject: Re: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Steve,

We just signed the paperwork. I really appreciate your support.

Thanks,

David

David D. Chang, M.D., Ph.D.
office: (310) 622-9094
PERSONAL INFORMATION,REDACTED PER AGREEMENT

www.kitepharma.com

Sent from my iPhone

On Oct 1, 2015, at 12:25 PM, Rosenberg, Steven A. (NIH/NCI) [E] <sar@mail.nih.gov> wrote:

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Steven A. Rosenberg M.D., Ph.D.
Chief, Surgery Branch
National Cancer Institute
10 Center Drive MSC 1201
CRC Room 3-3940
Bethesda, MD 20892
301-496-4164
sar@nih.gov

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Monday, October 05, 2015 9:04 PM
To: Patty Lettner; Kite Pharma US; Bianca Weissbrich; Bo Schrikkema; Carsten Linnemann; Gavin Bendle; Georg Dossinger; Laura Bies; Manon Freriks; Markwin Velders; Ton Schumacher
CC: HR Support; Owen Witte (owenwitte@mednet.ucla.edu); Barbara Anderson [Asst: Owen Witte] (baanderson@mednet.ucla.edu); jeconomou@mednet.ucla.edu; Professor Zelig Eshhar (zelig.eshhar@weizmann.ac.il); Ron Levy; Allan Pantuck (apantuck@mednet.ucla.edu); Antoni Ribas MD PhD (aribas@mednet.ucla.edu); Inder verma; Beth Coyne [Asst: Inder Verma, Kite SAB Member] (coyne@salk.edu); Kohn, Donald; Rosenberg, Steven A. (NIH/NCI) [E]; Shell, Linda (NIH/NCI) [E]; Cary Freeny (cfreeny@mednet.ucla.edu); bmueller@mednet.ucla.edu; JoAnn Palaganas (jpalaganas@mednet.ucla.edu); Mary Jo Spaulding (mspaulding@conet.ucla.edu); vamaya82@stanford.edu
Subject: RE: Organizational Announcement - Jeff S Wiezorek, MD

Jeff,

We are all indebted to you. Your leadership in building the best clinical team in the industry and spearheading the most innovative trials is not only transforming Kite but also the lives of many desperate patients and revolutionizes the practice of oncology.

Thank you,

Arie Belldegrun, M.D.,FACS
President and CEO
Chairman, Board of Directors; Founder
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Tel: 310-622-9093
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Sent: Monday, October 5, 2015 11:38 AM
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Cc: HR Support <HRsupport@kitepharma.com>; Owen Witte (owenwitte@mednet.ucla.edu) <owenwitte@mednet.ucla.edu>; Barbara Anderson [Asst: Owen Witte] (baanderson@mednet.ucla.edu) <baanderson@mednet.ucla.edu>; jeconomou@mednet.ucla.edu; Professor Zelig Eshhar (zelig.eshhar@weizmann.ac.il) <zelig.eshhar@weizmann.ac.il>; Ron Levy <levy@stanford.edu>; Allan Pantuck (apantuck@mednet.ucla.edu) <apantuck@mednet.ucla.edu>; Antoni Ribas MD PhD (aribas@mednet.ucla.edu) <aribas@mednet.ucla.edu>; Inder verma <verma@salk.edu>; Beth Coyne [Asst: Inder Verma, Kite SAB Member] (coyne@salk.edu) <coyne@salk.edu>; Kohn, Donald <DKohn1@mednet.ucla.edu>; sar@nih.gov; Shell, Linda (NIH/NCI) [E] <chilesl@mail.nih.gov>; Cary Freeny (cfreeny@mednet.ucla.edu) <cfreeny@mednet.ucla.edu>; bmueller@mednet.ucla.edu; JoAnn Palaganas (jpalaganas@mednet.ucla.edu) <jpalaganas@mednet.ucla.edu>; Mary Jo Spaulding (mspaulding@conet.ucla.edu) <mspaulding@conet.ucla.edu>; vamaya82@stanford.edu
Subject: Organizational Announcement - Jeff S Wiezorek, MD

Importance: High

Message from David Chang:

I am delighted to announce that Jeff has been promoted to Senior Vice President, Clinical Development.

Jeff joined Kite in April, 2014 as Vice President, Clinical Development, Jeff has made several significant contributions, including building the clinical development organization and advancing KTE-C19 and other eACT programs. Under his leadership, the clinical development organization has made key hires in Jeff Aycock, Will Go, Lynn Navale, Rajul Jain, and Zack Robert, and achieved key milestones including the successful submission of Kite's first IND and the initiation of KTE-C19 Phase 1/2 study in refractory aggressive non-Hodgkins lymphoma. Jeff will continue to report to me.

Prior to joining Kite Pharma, Dr. Wiezorek held roles of increasing responsibility over 9 years at Amgen. In his most recent position as Executive Medical Director, Global Development, he had global oversight of the clinical strategy for the immunotherapy, angiogenesis, and denosumab oncology product areas. He received his B.A. degree in biophysics from the University of Pennsylvania and his M.D. degree from Columbia University. Dr. Wiezorek trained in internal medicine at Stanford University and also completed a fellowship in oncology at UCLA. Prior to joining Amgen, he investigated the role of nuclear factor-kappaB in cellular proliferation and cancer pathogenesis in the laboratory of Dr. David Baltimore at the California Institute of Technology.

Please join me in congratulating Jeff on his promotion.

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Monday, October 05, 2015 9:04 PM
To: Patty Lettner; Kite Pharma US; Bianca Weissbrich; Bo Schrikkema; Carsten Linnemann; Gavin Bendle; Georg Dossinger; Laura Bies; Manon Freriks; Markwin Velders; Ton Schumacher
CC: HR Support; Owen Witte (owenwitte@mednet.ucla.edu); Barbara Anderson [Asst: Owen Witte] (baanderson@mednet.ucla.edu); jeconomou@mednet.ucla.edu; Professor Zelig Eshhar (zelig.eshhar@weizmann.ac.il); Ron Levy; Allan Pantuck (apantuck@mednet.ucla.edu); Antoni Ribas MD PhD (aribas@mednet.ucla.edu); Inder verma; Beth Coyne [Asst: Inder Verma, Kite SAB Member] (coyne@salk.edu); Kohn, Donald; Rosenberg, Steven A. (NIH/NCI) [E]; Shell, Linda (NIH/NCI) [E]; Cary Freeny (cfreeny@mednet.ucla.edu); bmueller@mednet.ucla.edu; JoAnn Palaganas (jpalaganas@mednet.ucla.edu); Mary Jo Spaulding (mspaulding@conet.ucla.edu); vamaya82@stanford.edu
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Cc: HR Support <HRsupport@kitepharma.com>; Owen Witte (owenwitte@mednet.ucla.edu) <owenwitte@mednet.ucla.edu>; Barbara Anderson [Asst: Owen Witte] (baanderson@mednet.ucla.edu) <baanderson@mednet.ucla.edu>; jeconomou@mednet.ucla.edu; Professor Zelig Eshhar (zelig.eshhar@weizmann.ac.il) <zelig.eshhar@weizmann.ac.il>; Ron Levy <levy@stanford.edu>; Allan Pantuck (apantuck@mednet.ucla.edu) <apantuck@mednet.ucla.edu>; Antoni Ribas MD PhD (aribas@mednet.ucla.edu) <aribas@mednet.ucla.edu>; Inder verma <verma@salk.edu>; Beth Coyne [Asst: Inder Verma, Kite SAB Member] (coyne@salk.edu) <coyne@salk.edu>; Kohn, Donald <DKohn1@mednet.ucla.edu>; sar@nih.gov; Shell, Linda (NIH/NCI) [E] <chilesl@mail.nih.gov>; Cary Freeny (cfreeny@mednet.ucla.edu) <cfreeny@mednet.ucla.edu>; bmueller@mednet.ucla.edu; JoAnn Palaganas (jpalaganas@mednet.ucla.edu) <jpalaganas@mednet.ucla.edu>; Mary Jo Spaulding (mspaulding@conet.ucla.edu) <mspaulding@conet.ucla.edu>; vamaya82@stanford.edu
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Importance: High

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Please join me in congratulating Jeff on his promotion.

From: David Chang [DChang@KitePharma.com]
Sent: Wednesday, October 07, 2015 2:39 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT
Attachments: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Dear Steve,

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

have any interest, please feel free to contact [redacted] directly.

Thanks,
David

From: PERSONAL INFORMATION,REDACTED PER AGREEMENT
Sent: Tuesday, October 6, 2015 2:33 PM
To: David Chang <DChang@KitePharma.com>
Subject: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Thanks for your time today David.

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Thanks again for the intros.
--

PERSONAL INFORMATION,REDACTED PER AGREEMENT

Email attachment

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT,WITHHELD THROUGH THE NEXT 24 pages

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Wednesday, October 07, 2015 10:55 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: FW: Kite Pharma Commends Steven A. Rosenberg, M.D., Ph.D., on the Prestigious Medal of Honor Award From the American Cancer Society

Congratulations!!

Arie Belldegrun, M.D., FACS
President and CEO
Chairman of the Board; Founder
Kite Pharma Inc.

2225 Colorado Ave
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310 824-9999 x102
arie@kitepharma.com

www.kitepharma.com

From: Kite Pharma, Inc. [mailto:jjackson@burnsmc.com]
Sent: Wednesday, October 07, 2015 5:04 AM
To: Arie Belldegrun <Arie@kitepharma.com>
Subject: Kite Pharma Commends Steven A. Rosenberg, M.D., Ph.D., on the Prestigious Medal of Honor Award From the American Cancer Society

Logo

Kite Pharma Commends Steven A. Rosenberg, M.D., Ph.D., on the Prestigious Medal of Honor Award From the American Cancer Society

– In addition, Dr. Rosenberg Recently Received the Service to America Medal for Career Achievement and the Betty Ford Lifetime Achievement Award

SANTA MONICA, Calif., Oct. 7, 2015 (GLOBE NEWSWIRE) -- Kite Pharma, Inc. (Kite) (Nasdaq:KITE) today announced that Steven A. Rosenberg, M.D., Ph.D., Chief of Surgery at the National Cancer Institute (NCI) and a special advisor to Kite, has received three significant awards for his achievements and career dedicated to advancing cancer research. The American Cancer Society (ACS), the largest voluntary health organization in the United States, awarded Dr. Rosenberg its Medal of Honor for his pioneering leadership in cancer immunotherapy. The Medal of Honor is the ACS' highest honor and was presented to Dr. Rosenberg at a ceremony held in Washington, DC, on September 30, 2015. Additional recent awards include:

- Dr. Rosenberg has been awarded the Samuel J. Heyman Service to America Medal for career achievement by the Partnership for Public Service. The "Sammies" are bestowed upon individuals to highlight excellence in the federal workforce and inspire other talented and dedicated individuals to go into public service. Dr. Rosenberg will receive his award during a gala and ceremony that is taking place tonight, October 7, in Washington, DC.
- Susan G. Komen, the world's largest breast cancer organization, awarded Dr. Rosenberg the Betty Ford Lifetime Achievement Award for his four decades of work in fighting cancer at the NCI. This award recognizes individuals who have committed their lives to engaging the public in the fight against breast cancer, advocating for meaningful change, and educating communities to support women and men facing the disease. Dr. Rosenberg was recognized during the Honoring the Promise gala, which took

place in Washington, DC, on September 24, 2015.

In 2012, Kite partnered with Dr. Rosenberg and the NCI under a Cooperative Research and Development Agreement (CRADA) to further the research and development of multiple chimeric antigen receptor (CAR) and T cell receptor (TCR) based product candidates for the treatment of advanced solid and hematological malignancies. Many of these product candidates are now being assessed in clinical trials and Kite has since exclusively licensed intellectual property related to certain of these product candidates.

"We have always appreciated the great honor of being able to advance cancer therapies with Steve and are thrilled that three of the most prominent awards in medicine and public service have been made in recognition of the pivotal role Steve has played in cancer care and research on the national stage," said Arie Belldegrun, M.D., FACS, Chairman, President and Chief Executive Officer of Kite. "During his long and successful career, Steve's insights time and again have had an astounding impact on the direction of cancer research. His contributions, including to the exciting field of cancer immunotherapy, have been immense, and we are elated for Steve to receive these awards."

About Kite Pharma, Inc.

Kite Pharma, Inc., is a clinical-stage biopharmaceutical company engaged in the development of novel cancer immunotherapy products, with a primary focus on engineered autologous cell therapy (eACT™) designed to restore the immune system's ability to recognize and eradicate tumors. Kite is based in Santa Monica, CA. For more information on Kite Pharma, please visit www.kitepharma.com.

CONTACT: Kite Pharma:
Cynthia M. Butitta, Chief Financial Officer and Chief Operating Officer
310-824-9999

For Media: Justin Jackson
For Investor Inquiries: Lisa Burns
Burns McClellan
212-213-0006
jjackson@burnsmc.com
lburns@burnsmc.com

Source: Kite Pharma, Inc.

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Tuesday, October 20, 2015 2:09 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: FW: Gritsone - neoantigen cancer vaccine

Hi Steve ,

PROPRIETARY INFORMATION, please see today's article discussing Gritstone and Neon and the massive recent efforts around a field you have created, the Neoantigen.

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Arie Belldegrun, M.D.,FACS
President and CEO
Chairman, Board of Directors; Founder
Kite Pharma Inc.

2225 Colorado Avenue
Santa Monica, CA 90404
Tel: 310-622-9093
PERSONAL INFORMATION,REDACTED PER AGREEMENT
arie@kitepharma.com

www.kitepharma.com

Subject: Gritsone - neoantigen cancer vaccine

October 20, 2015
By Mark Terry, BioSpace.com Breaking News Staff

San Francisco-based **Gritstone Oncology announced** today that it had closed on a Series A financing round worth $102 million. Co-leading the round were **Versant Ventures** and **The Column Group**, with **Clarus Ventures** alongside. Additional investors included **Frazier Healthcare Partners**, **Redmile Group**, **Casdin Capital**, and **Transformational Healthcare Opportunity**.

Andrew Allen, Co-Founder, President and CEO of Gritstone Oncology

Gritstone was co-founded by **Andrew Allen**, who will act as president and chief executive officer. Allen co-founded Boulder, Colo.-based **Clovis Oncology (CLVS)**.**Patrick Mahaffy**, chief executive officer of **Clovis**, will act as **Gritstone**'s chairman.

The company will focus on cancer vaccines based on what are being called neoantigens. Allen founded the company after reading a 2014 paper in the **New England Journal of Medicine** that discussed why some patients don't seem to respond to immune checkpoint inhibitors. Tumors create molecules that prevent the immune system from identifying and attacking them. So blocking those molecules allows the immune system to find and kill those tumor cells. But cancer cells are constantly mutating, creating so-called **neoantigens**.

"This is, to me, a massive, massive advance," Allen **told** Xconomy. "[It's a] completely rational, totally understandable, and potentially exploitable insight into how tumors can be cleared by the human immune system."

Earlier this month, Boston-based **Third Rock Ventures**, along with Israel-based **Clal Biotechnology Industries** and New York-based **Access Industries**, **formed Neon Therapeutics** with $55 million in Series A financing. **Neon** is working on neoantigens as well, with a lead candidate, NEO-PV-01, which is a vaccine that will be individually programmed to respond to each patient's unique neoantigens, and will be combined with a checkpoint inhibitor.

Gritstone's **approach** will be slightly different. In newly diagnosed lung cancer patients, it will take tumor samples, sequence their DNA in order to identify specific mutations, then choose the markers that will hopefully act as the best antigens to be identified by the immune system. They will then become part of the vaccine. In other words, although Neon is looking for common neoantigens across all tumors, **Gritstone** plans to customize the vaccine for each individual patient.

One of the industry's concerns over this approach is the need to essentially customized each vaccine and treatment for the patient. Although neoantigens show a great deal of promise, it's not entirely clear how to mass produce such a vaccine and make it affordable. The technology will also need to lean on sequencing technology and bioinformatics, and face a time factor in preparing drugs for seriously ill patients.

"We're going to learn from every patient," Allen told Forbes. "Every product is unique to the patient."

The nascent company indicated it believes it could acquire a tumor sample at its central laboratory, identify and evaluate the neoantigens, and customize the vaccine in approximately four weeks.

Gritstone's other co-founders are **Tim Chan** and **Naiyer Rizvi**, both physicians at **Memorial Sloan-Kettering Cancer Center**. Additional co-founders include **Jean-Charles Soria** of the **Institut Gustave Roussy** in Paris, **Graham Lord** of **King's College London**, and **Mark Cobbold** of **Massachusetts General Hospital**.

"The scientific community doesn't yet know how to transition from individual tumor-mutation data to a short list of neoantigens that are therapeutically relevant to each patient," said **Peter Svennilson**, founder and managing partner of **The Column Group** in a statement, "but the **Gritstone** team's expertise and approach made us confident that they will be the ones to successfully tackle this scientific challenge."

Allen and Mahaffy's pedigree with **Clovis Oncology (CLVS)** is worth considering. The company has had

some **recent success** with its drug, roceletinib, for the treatment of non-small cell lung cancer, as well as positive Phase II results from two studies in ovarian cancer for the drug rucaparib. Analysts think the company is ripe for an acquisition, often citing **Gilead Sciences, Inc.** (**GILD**) and **Roche** (**RHHBY**) as potential buyers. It's clear they have experience in driving successful research programs, although **Gritstone** may present a different set of challenges.

"There's some work to be done," Allen told Xconomy. "But sample collection from lung cancer doctors is obviously something that we at **Clovis** did many times. This is our bread and butter."

From: David Chang [DChang@KitePharma.com]
Sent: Thursday, October 22, 2015 3:21 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
CC: Arie Belldegrun
Subject: Fwd: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT
Attachments:

Dear Steve,

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

David

David Chang, MD, PhD
office: (310) 622-9094
PROPRIETARY INFORMATION,REDACTED PER AGREEMENT
www.kitepharma.com

Sent from my iPad

Begin forwarded message:

All,

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Thanks,

Edmund

Edmund Kim, Ph.D.
Senior Director, Business Development
Kite Pharma, Inc.
2225 Colorado Avenue
Santa Monica, CA 90404
Office: 310.742.2842
PERSONAL INFORMATION,REDACTED PER AGREEMENT
Email: ekim@kitepharma.com


Kite Icon

EMAIL Attachment

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT,WITHHELD THROUGH THE NEXT 20 pages

From: arie@addthis.com on behalf of arie@kitepharma.com
Sent: Thursday, October 22, 2015 5:29 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Moderna joins the personalized cancer vaccine rush with third new venture

see the Neoantigen newCo rin by Tal Zaks.....

http://www.fiercebiotech.com/story/moderna-joins-personalized-cancer-vaccine-rush-third-new-venture/2015-10-22?utm_campaign=+SocialMedia

From: Aric Belldegrun [Aric@kitepharma.com]
Sent: Friday. October 23. 2015 1:50 PM
To: Yoram Reiter; Rosenberg, Steven A. (NIH/NCI) [E]
CC: danz@tx.technion.ac.il
Subject: RE: CAR-T cell therapy

Steve,

Please see below. PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Thanks,

Arie Belldegrun, M.D.,FACS
President and CEO
Chairman, Board of Directors; Founder
Kite Pharma Inc.

2225 Colorado Avenue
Santa Monica, CA 90404
Tel: 310-622-9093
PERSONAL INFORMATION,REDACTED PER AGREEMENT
arie@kitepharma.com

www.kitepharma.com

From: Yoram Reiter [mailto:yoramreiter@gmail.com]
Sent: Friday, October 23, 2015 10:09 AM
To: Arie Belldegrun <Arie@kitepharma.com>
Cc: danz@tx.technion.ac.il
Subject: Fwd: CAR-T cell therapy

Dear Arie,
I hope all is well.
Please take a look at the e mail below. Is it possible to help in this case ?
I thank you in advance and hope to see you soon for science.
Thanks and warm regards,
Yoram Reiter

נשלח מה-iPhone שלי

תחילת ההודעה שהועברה:

מאת: "danz@bi.technion.ac.il" <danz@bi.technion.ac.il>
תאריך: 23 19:41:21 באוקטובר 2015 בשעה GMT+3
אל: Reiter Yoram <reiter@tx.technion.ac.il>
נושא: FW: CAR-T cell therapy

Yoram,
Can you help with the enclosed?
Danny

eng_DanZ

From: PERSONAL INFORMATION,REDACTED PER AGREEMENT
Sent: Friday, October 23, 2015 7:34 PM

To: Dan Zilberstein <danz@techunix.technion.ac.il>
Subject: CAR-T cell therapy

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Thanks for your help,

PERSONAL INFORMATION,REDACTED PER AGREEMENT

From: David Chang [DChang@KitePharma.com]
Sent: Monday, October 26, 2015 3:58 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
CC: Shell, Linda (NIH/NCI) [E]; Patty Lettner
Subject: Visit to NCI: Nov 2

Dear Steve,

I would like to visit NCI next Monday (Nov 2) to join in during the Monday lab meeting and meet with you, Christian, Jim, Nick, and Paul. Please let me know if your schedule permits this.

Thanks,
David

David D. Chang, MD, PhD
Executive Vice President of R&D
and Chief Medical Officer
Kite Pharma, Inc
office: 310-622-9094
PERSONAL INFORMATION,REDACTED PER AGREEMENT

www.kitepharma.com

From: Rosenberg, Steven A. (NIH/NCI) [E]
Sent: Tuesday, October 27, 2015 11:29 AM
To: 'David Chang'
Subject: RE: Visit to NCI: Nov 2

David

I regret that Nov 2 will not work for your visit.

We already have a group from Israel visiting on that day as well as a group of people from another company that I work with who will be visiting as well.

Nov. 9, 16, or the 23rd would be ok for your visit.

Steve

Steven A. Rosenberg M.D., Ph.D.
Chief, Surgery Branch
National Cancer Institute
10 Center Drive MSC 1201
CRC Room 3-3940
Bethesda, MD 20892
301-496-4164
sar@nih.gov

From: David Chang [mailto:DChang@KitePharma.com]
Sent: Monday, October 26, 2015 3:58 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Cc: Shell, Linda (NIH/NCI) [E]; Patty Lettner
Subject: Visit to NCI: Nov 2

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David

David D. Chang, MD, PhD
Executive Vice President of R&D
and Chief Medical Officer
Kite Pharma, Inc
office: 310-622-9094
PERSONAL INFORMATION,REDACTED PER AGREEMENT

www.kitepharma.com

From: David Chang [DChang@KitePharma.com]
Sent: Tuesday, October 27, 2015 11:56 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Re: Visit to NCI: Nov 2

Dear Steve,

It was a late request - also I seemed to have picked a day that did work.

Among the other dates below, I would like to visit NCI on Nov 16.

Look forward to seeing you.

Thanks,

David

David D. Chang, M.D., Ph.D.
Executive Vice President of R&D
and Chief Medical Officer
Kite Pharma, Inc
office: (310) 622-9094
PERSONAL INFORMATION,REDACTED PER AGREEMENT

www.kitepharma.com

Sent from my iPhone

On Oct 27, 2015, at 10:29 AM, Rosenberg, Steven A. (NIH/NCI) [E] <sar@mail.nih.gov> wrote:

> David
>
> I regret that Nov 2 will not work for your visit.
>
> We already have a group from Israel visiting on that day as well as a group of people from another company that I work with who will be visiting as well.
>
> Nov. 9, 16, or the 23rd would be ok for your visit.
>
> Steve
>
> Steven A. Rosenberg M.D., Ph.D.
> Chief, Surgery Branch
> National Cancer Institute
> 10 Center Drive MSC 1201
> CRC Room 3-3940
> Bethesda, MD 20892
> 301-496-4164
> sar@nih.gov
>
> ---
>
> **From:** David Chang [mailto:DChang@KitePharma.com]

Sent: Monday, October 26, 2015 3:58 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Cc: Shell, Linda (NIH/NCI) [E]; Patty Lettner
Subject: Visit to NCI: Nov 2

Dear Steve,

I would like to visit NCI next Monday (Nov 2) to join in during the Monday lab meeting and meet with you, Christian, Jim, Nick, and Paul. Please let me know if your schedule permits this.

Thanks,
David

David D. Chang, MD, PhD
Executive Vice President of R&D
and Chief Medical Officer
Kite Pharma, Inc
office: 310-622-9094
PERSONAL INFORMATION,REDACTED PER AGREEMENT

www.kitepharma.com

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Thursday, November 05, 2015 8:28 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Fwd: Adaptimmune announces data from clinical study of NY-ESO affinity enhanced T-cell therapy in synovial sarcoma

FYI. hot from the ASH abstracts. Will send more...

Arie Belldegrun, MD FACS
President and CEO, Chairman
Kite Pharma

www.kitepharma.com

Begin forwarded message:

From: PERSONAL INFORMATION,REDACTED PER AGREEMENT
Date: November 5, 2015 at 08:21:20 EST
To: Arie Belldegrun <Arie@kitepharma.com>, "Helen Kim (HKim@kitepharma.com)" <HKim@kitepharma.com>
Subject: FW: Adaptimmune announces data from clinical study of NY-ESO affinity enhanced T-cell therapy in synovial sarcoma

From: FactSet_Alerts@factset.com [mailto:FactSet_Alerts@factset.com]
Sent: Thursday, November 05, 2015 5:21 AM
To: PERSONAL INFORMATION,REDACTED PER AGREEMENT
Subject: Adaptimmune announces data from clinical study of NY-ESO affinity enhanced T-cell therapy in synovial sarcoma

5 Nov '15 8:20 AM **ADAP-US** StreetAccount

<!--[if !vml]--><!--[endif]-->**Adaptimmune announces data from clinical study of NY-ESO affinity enhanced T-cell therapy in synovial sarcoma**
Thursday, November 05, 2015 01:20:30 PM (GMT)

FACTSET streetaccount

- The data presented are the following:
    - In the primary efficacy analysis, 50% of synovial sarcoma patients receiving Adaptimmune's affinity enhanced T-cell therapy targeting NY-ESO responded, and 75% remain alive and on long term-follow up. Sixty (60) percent of patients receiving the target dose responded, and 90% remain alive and on long term-follow up;
    - qAdaptimmune's affinity enhanced T-cell therapy targeting NY-ESO in multiple myeloma generated responses that were better than expected for autologous stem cell transplant (ASCT) alone, despite the patients having advanced stage disease with 60% of patients having tumor chromosomal abnormalities; and
    - Adaptimmune's platform technology enables the generation of multiple TCRs to a large number of cancer targets. Once affinity engineered, these TCRs are subjected to an extensive preclinical safety and efficacy package.

- In the synovial sarcoma poster presentation the company is providing an update on Adaptimmune's NY-ESO-1 synovial sarcoma study, including all patients in the original cohort (n=12), and longer follow-up and time-to-event, as well as updated correlative and safety data, and characterization of the product pre- and post-infusion. All patients enrolled in the study had metastatic or relapse

inoperable synovial sarcoma, and failed prior ifosfamide and/or doxorubicin therapy. The authors of the poster conclude:

- Adaptimmune's affinity enhanced T-cell therapy targeting NY-ESO demonstrated robust clinical responses in synovial sarcoma, including a 50% (6/12) overall response rate (ORR) in patients receiving T-cells, and a 60% (6/10) response rate in a subset of patients who received the target dose of one to six billion total engineered T-cells. Two patients received below the target dose, and neither responded. This compares favorably to a historical partial response rate of approximately four percent observed with pazopanib, which is the only approved drug in this patient population.
- Seventy-five (75) percent (9/12) of all subjects who received any dose of NY-ESO-1 T cells - and 90% (9/10) of subjects who received the minimum intended cell dose - are alive and on long term follow-up. Forty-two (42) percent (5/12) of patients who received any dose have survival data beyond one year.
- NY-ESO-1 T-cells durably persist and maintain function without accumulation of exhaustion markers; persistence detected at up to 21 months in those receiving the minimum intended cell dose. Poor persistence was observed in subjects receiving less than 1B NY-ESO-1 T-cells, with no detectable cells beyond day 25.
- The encouraging anti-tumor activity considered in the context of a generally manageable safety profile is supportive of a favorable benefit:risk for NY-ESO-1 T-cells in this patient population. Most treatment related adverse events resolve within 30 days of treatment. The most common adverse events include: nausea, anemia, pyrexia, lymphopenia, and neutropenia. There were no treatment related deaths. Cytokine release syndrome was seen in 4 subjects; Grade 3 cytokine release syndrome was observed in 2/4 subjects, no grade 4 events were observed.
- The evidence of relapse seen in some patients provides rationale for testing of combination approaches or second generation T-cells designed to overcome the immune suppressive environment of selected tumors.

- See attached press release for additional poster presentation information:

Industries: Biotechnology & Drugs
Primary Identifiers: ADAP-US
Related Identifiers: ADAP-US
Reference Links:
- Adaptimmune Announces Data From Clinical Study of NY-ESO Affinity Enhanced T-Cell Therapy in Synovial Sarcoma at the 2015 Annual Meeting of the Society of Immunotherapy for Cancer (SITC)

FactSet News Alert for: PERSONAL INFORMATION,REDACTED PER AGREEMENT

***Please do not reply to this e-mail.*

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Friday, November 20, 2015 9:33 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Fwd: Kite - Arie on CNBC Squawk Box Europe

Steve,

Sorry I could not join the call yesterday. I was in london speaking at a Goldman Sachs healthcare conference. Earlier that day I gave an interview to CNBC and mentioned your work. Please watch towards the end.

Best,

Arie Belldegrun, MD, FACS
Chairman, CEO, Founder
Kite Pharma
Santa Monica, CA 90404

Begin forwarded message:

> **From:** Linda Barnes <LBarnes@KitePharma.com>
> **Date:** November 19, 2015 at 20:40:22 EST
> **To:** "David Bonderman - Tarrant Capital IP, LLC (dbonderman@tpg.com)" <dbonderman@tpg.com>, "Farah Champsi - Alta Partners (fchampsi@altapartners.com)" <fchampsi@altapartners.com>, "Humer, Franz B." <franz_b.humer@roche.com>, "Josh Kazam (jak@tworiver.com)" <jak@tworiver.com>, "Jonathan M. Peacock" <jon.peacock@bellerophon.com>, "roy@doumani.net" <roy@doumani.net>, "Ran Nussbaum - Pontifax (ran@pontifax.com)" <ran@pontifax.com>, "Steve Ruchefsky (sruchefsky@caremipartners.com)" <sruchefsky@caremipartners.com>
> **Cc:** Arie Belldegrun <Arie@kitepharma.com>
> **Subject: RE: Kite - Arie on CNBC Squawk Box Europe**
>
> Hello everyone,
>
> Please accept my apologies—the link I sent yesterday contained only a portion of Arie's CNBC interview, and I understand some of you weren't able to access it at all.
>
> Here is a link to the full CNBC interview from yesterday morning:
>
> CNBC World 11-18-15 with Dr. Belldegrun
>
> If you have any trouble accessing this version, please let me know.
>
> I'm so sorry for the inconvenience!
>
> Best wishes,
> Linda
>
> **From:** Linda Barnes
> **Sent:** Wednesday, November 18, 2015 9:40 AM

To: David Bonderman - Tarrant Capital IP, LLC (dbonderman@tpg.com) <dbonderman@tpg.com>; Farah Champsi - Alta Partners (fchampsi@altapartners.com) <fchampsi@altapartners.com>; 'Humer, Franz B.' <franz_b.humer@roche.com>; Josh Kazam (jak@tworiver.com) <jak@tworiver.com>; 'Jonathan M. Peacock' <jon.peacock@bellerophon.com>; roy@doumani.net; Ran Nussbaum - Pontifax (ran@pontifax.com) <ran@pontifax.com>; Steve Ruchefsky (sruchefsky@caremipartners.com) <sruchefsky@caremipartners.com>
Cc: Arie Belldegrun <Arie@kitepharma.com>
Subject: Kite - Arie on CNBC Squawk Box Europe

Dear BOD members,

Hope you're doing well.

In case you've not seen it, Arie was live from London early this morning on CNBC's Squawk Box Europe. The main part of the interview can be viewed here:

http://video.cnbc.com/gallery/?video=3000455714&play=1

Best wishes,
Linda

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Friday, December 04, 2015 8:33 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Fwd: PR in Review at NCI

Hi Steve,

Any chance you can approve this press release of the poster before Monday??

We are at ASH and the poster is on Sunday.

Thanks,

Arie Belldegrun, MD FACS
President and CEO, Chairman
Kite Pharma

www.kitepharma.com

Begin forwarded message:

> **From:** Cynthia Butitta <CButitta@KitePharma.com>
> **Date:** December 3, 2015 at 14:40:58 EST
> **To:** Kate Bechtold <kbechtold@kitepharma.com>, Arie Belldegrun <Arie@kitepharma.com>, David Chang <DChang@KitePharma.com>
> **Cc:** Veer Bhavnagri <veer@kitepharma.com>, David Tanen <DTanen@KitePharma.com>, Linda Barnes <LBarnes@KitePharma.com>, Justin Jackson <JJackson@burnsmc.com>
> **Subject: RE: PR in Review at NCI**
>
> PROPRIETARY INFORMATION,REDACTED PER AGREEMENT
>
> **From:** Kate Bechtold
> **Sent:** Thursday, December 3, 2015 11:35 AM
> **To:** Arie Belldegrun <Arie@kitepharma.com>; Cynthia Butitta <CButitta@KitePharma.com>; David Chang <DChang@KitePharma.com>
> **Cc:** Veer Bhavnagri <veer@kitepharma.com>; David Tanen <DTanen@KitePharma.com>; Linda Barnes <LBarnes@KitePharma.com>; Justin Jackson <JJackson@burnsmc.com>
> **Subject:** PR in Review at NCI
>
> Arie, Cindy, David,
>
> PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Thank you,
Kate

From: Rosenberg, Steven A. (NIH/NCI) [E] [sar@mail.nih.gov]
Sent: Saturday, December 05, 2015 6:23 PM
To: Arie Belldegrun
Subject: Re: PR in Review at NCI

Arie

Ok with me

Good luck

Warm regards

Steve

Sent from my iPhone

On Dec 4, 2015, at 8:32 PM, Arie Belldegrun <Arie@kitepharma.com> wrote:

> Hi Steve,
>
> Any chance you can approve this press release of the poster before Monday??
>
> We are at ASH and the poster is on Sunday.
>
> Thanks,
>
> Arie Belldegrun, MD FACS
> President and CEO, Chairman
> Kite Pharma
>
> www.kitepharma.com
>
> Begin forwarded message:
>
> > **From:** Cynthia Butitta <CButitta@KitePharma.com>
> > **Date:** December 3, 2015 at 14:40:58 EST
> > **To:** Kate Bechtold <kbechtold@kitepharma.com>, Arie Belldegrun <Arie@kitepharma.com>, David Chang <DChang@KitePharma.com>
> > **Cc:** Veer Bhavnagri <veer@kitepharma.com>, David Tanen <DTanen@KitePharma.com>, Linda Barnes <LBarnes@KitePharma.com>, Justin Jackson <JJackson@burnsmc.com>
> > **Subject: RE: PR in Review at NCI**
> >
> > PROPRIETARY INFORMATION,REDACTED PER AGREEMENT
> >
> > **From:** Kate Bechtold
> > **Sent:** Thursday, December 3, 2015 11:35 AM
> > **To:** Arie Belldegrun <Arie@kitepharma.com>; Cynthia Butitta <CButitta@KitePharma.com>; David Chang <DChang@KitePharma.com>
> > **Cc:** Veer Bhavnagri <veer@kitepharma.com>; David Tanen <DTanen@KitePharma.com>; Linda Barnes <LBarnes@KitePharma.com>; Justin Jackson <JJackson@burnsmc.com>

Subject: PR in Review at NCI

Arie, Cindy, David,

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Thank you,
Kate

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Monday, December 07, 2015 7:27 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Fwd: Kite Pharma Receives FDA Breakthrough Therapy Designation for KTE-C19 for the Treatment of Refractory, Aggressive Non Hodgkin Lymphoma (NHL)

Arie Belldegrun, MD, FACS
Chairman, CEO, Founder
Kite Pharma
Santa Monica, CA 90404

Begin forwarded message:

From: "Kite Pharma, Inc." <jjackson@burnsmc.com>
Date: December 7, 2015 at 06:31:49 EST
To: <Arie@kitepharma.com>
Subject: Kite Pharma Receives FDA Breakthrough Therapy Designation for KTE-C19 for the Treatment of Refractory, Aggressive Non Hodgkin Lymphoma (NHL)


Logo

Kite Pharma Receives FDA Breakthrough Therapy Designation for KTE-C19 for the Treatment of Refractory, Aggressive Non Hodgkin Lymphoma (NHL)

SANTA MONICA, Calif., Dec. 7, 2015 (GLOBE NEWSWIRE) -- Kite Pharma, Inc. (Nasdaq:KITE) today announced that the U.S. Food and Drug Administration (FDA) has granted Breakthrough Therapy Designation status to the Company's lead product candidate, KTE-C19, for the treatment of patients with refractory diffuse large B cell lymphoma (DLBCL), primary mediastinal B cell lymphoma (PMBCL), and transformed follicular lymphoma (TFL). KTE-C19 is an investigational therapy in which a patient's T cells are genetically modified to express a chimeric antigen receptor designed to target the antigen CD19, a protein expressed on the cell surface of B cell lymphomas and leukemias.

"The FDA's designation of KTE-C19 as a breakthrough therapy recognizes the potential for KTE-C19 to address the unmet need for patients with refractory DLBCL, PMBCL, and TFL," noted Arie Belldegrun, M.D., FACS, Chairman, President, and Chief Executive Officer. "We are pleased to receive this designation and look forward to working more closely with the FDA as we continue to advance our program for KTE-C19."

Breakthrough Therapy Designation is granted by the FDA to expedite the development and review of new therapies to treat serious or life-threatening conditions. The criteria for Breakthrough Therapy Designation require preliminary clinical evidence that demonstrates the therapy may have substantial improvement on at least one clinically significant endpoint over available therapy. This designation conveys all fast track program features, as well as more intensive FDA guidance on an efficient drug development program and eligibility for rolling review and priority review.

About Kite's ZUMA Clinical Programs

Study	Phase	Indication	Status
ZUMA-1 NCT02348216	Phase 2 Pivotal (N=112)	Refractory DLBCL, PMBCL, TFL	Phase 2 enrolling
ZUMA-2 NCT02601313	Phase 2 Pivotal (N=70)	Relapsed/refractory MCL	Phase 2 enrolling
ZUMA-3 NCT02614066	Phase 1/2 Pivotal (N=75)	Relapsed/refractory Adult ALL	Phase 1/2 enrolling
ZUMA-4	Phase 1/2 Pivotal (N=75)	Relapsed/refractory Pediatric ALL	Phase 1/2 enrolling

DLBCL = diffuse large B cell lymphoma

PMBCL = primary mediastinal B cell lymphoma

TFL = transformed follicular lymphoma

MCL = mantle cell lymphoma

ALL = acute lymphoblastic leukemia

About Kite Pharma

Kite Pharma, Inc., is a clinical-stage biopharmaceutical company engaged in the development of novel cancer immunotherapy products, with a primary focus on engineered autologous cell therapy (eACT™) designed to restore the immune system's ability to recognize and eradicate tumors. Kite is based in Santa Monica, CA. For more information on Kite Pharma, please visit www.kitepharma.com. Sign up to follow @KitePharma on Twitter at www.twitter.com/kitepharma.

Cautionary Note on Forward-Looking Statements

This press release contains forward-looking statements for purposes of the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. We may, in some cases, use terms such as "predicts," "believes," "potential," "proposed," "continue," "estimates," "anticipates," "expects," "plans," "intends," "may," "could," "might," "will," "should" or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. Forward-looking statements include statements regarding our intentions, beliefs, projections, outlook, analyses or current expectations concerning, among other things: the ability to advance multiple

clinical trials of KTE-C19 and to obtain regulatory approval based on the studies of KTE-C19. Various factors may cause differences between Kite's expectations and actual results as discussed in greater detail in Kite's filings with the Securities and Exchange Commission, including without limitation in its Form 10-Q for the quarter ended September 30, 2015. Any forward-looking statements that we make in this press release speak only as of the date of this press release. We assume no obligation to update our forward-looking statements whether as a result of new information, future events or otherwise, after the date of this press release.

CONTACT: Kite Pharma
Cynthia M. Butitta
Chief Financial Officer and Chief Operating Officer
310-824-9999

For Media: Justin Jackson
For Investor Inquiries: Lisa Burns
Burns McClellan
212-213-0006
jjackson@burnsmc.com
lburns@burnsmc.com

Source: Kite Pharma, Inc.

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Thursday, December 17, 2015 11:46 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Fwd: Adaptimmune announces initiation of study to evaluate its new affinity enhanced T-Cell therapy targeting MAGE-A10

FYI

Regards

Arie Belldegrun, MD, FACS
Chairman, President and CEO
KITE PHARMA
Direct: 310.622.9093
Arie@kitepharma.com
www.kitepharma.com

Begin forwarded message:

From: PERSONAL INFORMATION,REDACTED PER AGREEMENT
Date: December 17, 2015 at 08:39:15 PST
To: Arie Belldegrun <arie@kitepharma.com>, Cynthia Butitta <CButitta@kitepharma.com>, Helen Kim <HKim@kitepharma.com>
Subject: FW: Adaptimmune announces initiation of study to evaluate its new affinity enhanced T-Cell therapy targeting MAGE-A10

PERSONAL INFORMATION,REDACTED PER AGREEMENT

From: FactSet_Alerts@factset.com
Sent: Thursday, December 17, 2015 8:31:53 AM
To: PERSONAL INFORMATION,REDACTED PER AGREEMENT
Subject: Adaptimmune announces initiation of study to evaluate its new affinity enhanced T-Cell therapy targeting MAGE-A10

17 Dec '15 11:31 AM **ADAP-US** StreetAccount

Adaptimmune announces initiation of study to evaluate its new affinity enhanced T-Cell therapy targeting MAGE-A10
Thursday, December 17, 2015 04:31:50 PM (GMT)

FACTSET streetaccount

- This will be the first study of Adaptimmune's unpartnered affinity enhanced T-cell therapy targeting MAGE-A10, a highly immunogenic member of the MAGE-A family of cancer testis antigens.

MAGE-A10 is expressed in a number of solid tumor cell types, and the immunogenicity of the MAGE-A10 antigen has been robustly established.

- The study is intended to enroll up to 32 patients in leading clinical centers located in the United States and Europe and will assess the safety and tolerability of Adaptimmune's affinity enhanced T-cell therapy targeting MAGE-A10.

Industries: Biotechnology & Drugs
Primary Identifiers: ADAP-US
Related Identifiers: ADAP-US
Reference Links:

- Adaptimmune Announces Initiation of Study to Evaluate its New Affinity Enhanced T-Cell Therapy Targeting MAGE-A10 in Patients With NSCLC, the Most Common Form of Lung Cancer

FactSet News Alert for: PERSONAL INFORMATION,REDACTED PER AGREEMENT

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Sunday, December 27, 2015 1:25 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Happy new year!

Hi Steve,

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Also, would you please send me Vince de Vita's e mail address please . I would like to congratulate him on his great book "the death of cancer".

I also noted that his daughter , Elisabeth, is a coauthor and a medical writer.

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Happy new year filled with health and great new ideas. This is going to be a huge year for us!!

Arie

Arie Belldegrun, MD, FACS
Chairman, CEO, Founder
Kite Pharma
Santa Monica, CA 90404

From: Rosenberg, Steven A. (NIH/NCI) [E]
Sent: Thursday, December 31, 2015 12:16 PM
To: 'Arie Belldegrun'
Subject: RE: Happy new year!

Arie

Thanks for your kind invitation for dinner. I will let you know when we visit LA so we can make plans.

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

I am totally committed to the success of Kite and am proud to be a part of this effort that will bring life-saving treatments to patients in need.

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

PERSONAL INFORMATION,REDACTED PER AGREEMENT

Warm wishes to you and your entire family for a happy, healthy and productive new year.

Steve

Steven A. Rosenberg M.D., Ph.D.
Chief, Surgery Branch
National Cancer Institute
10 Center Drive MSC 1201
CRC Room 3-3940
Bethesda, MD 20892
301-496-4164
sar@nih.gov

-----Original Message-----
From: Arie Belldegrun [mailto:Arie@kitepharma.com]
Sent: Sunday, December 27, 2015 1:25 PM
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Arie

Arie Belldegrun, MD, FACS
Chairman, CEO, Founder
Kite Pharma
Santa Monica, CA 90404

From: David Chang [DChang@KitePharma.com]
Sent: Thursday, January 07, 2016 3:02 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]; Shell, Linda (NIH/NCI) [E]; Marie Ferrier
CC: Arie Belldegrun
Subject: Jan 15, 2016

Steve,

Happy New Year.

I will be in Bethesda on Jan 15 and would like to have a short face time with you and also with Paul Robbins. Late morning or early afternoon will work the best for me. I will also be meeting with Jim K, whom I did not have a chance to meet when I visited NCI in Nov.

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Thanks,
David

David D. Chang, MD, PhD
Executive Vice President of R&D
and Chief Medical Officer
Kite Pharma, Inc
office: 310-622-9094| PERSONAL INFORMATION,REDACTED PER AGREEMENT

Kite Pharma
www.kitepharma.com

From: David Chang [DChang@KitePharma.com]
Sent: Sunday, January 17, 2016 12:58 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]; Yang, James C. (NIH/NCI) [E]
Subject: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT
Attachments: PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Dear Steve,

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Thanks,

David

David D. Chang, MD, PhD
Executive Vice President of R&D
and Chief Medical Officer
Kite Pharma, Inc
office: 310-622-9094| | mobile: PERSONAL INFORMATION,REDACTED PER AGREEMENT

Kite Pharma
www.kitepharma.com

Email Attachment

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT,WITHHELD THROUGH THE NEXT 1 Page

From: David Chang [DChang@KitePharma.com]
Sent: Wednesday, January 20, 2016 1:33 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
CC: Arie Belldegrun
Subject: FW: NCI Visit Sumary - Jan 15, 2016

Resending, the first one did not go through.

From: David Chang
Sent: Wednesday, January 20, 2016 10:30 AM
To: Steve Rosenberg (SAR@nih.gov) <SAR@nih.gov>
Cc: Arie Belldegrun <Arie@kitepharma.com>
Subject: NCI Visit Sumary - Jan 15, 2016

Dear Steve,

Thanks for the opportunity to spend time with you and Paul last Friday. As always such interaction is deeply appreciate. My takeaway from the meeting are:

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Sorry for a long email, but this is also my way of keeping Arie updated.

Thanks,
David

David D. Chang, MD, PhD
Executive Vice President of R&D
and Chief Medical Officer
Kite Pharma, Inc
office: 310-622-9094| | mobile: PERSONAL INFORMATION,REDACTED PER AGREEMENT

www.kitepharma.com

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Wednesday, February 03, 2016 4:33 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Fwd: QUICK TAKE - ADAP - NY-ESO-1 TCR Heading For Pivotal Trials - Cowen and Company

Steve,

FYI

Arie Belldegrun, MD, FACS
Chairman, President and CEO
KITE PHARMA
Direct: 310.622.9093
www.kitepharma.com

From: "Eric Schmidt, Ph.D." <eric.schmidt@cowen.com>
Date: 2 February 2016 at 1:10:17 pm GMT-5
To: <lburns@burnsmc.com>
Subject: QUICK TAKE - ADAP - NY-ESO-1 TCR Heading For Pivotal Trials - Cowen and Company
Reply-To: "Eric Schmidt, Ph.D." <eric.schmidt@cowen.com>

LINK TO FULL REPORT & DISCLOSURES

COWEN
AND COMPANY

Biotechnology
Adaptimmune

Equity Research
February 2, 2016

Price: $7.39 (02/1/2016)
Price Target: NA

OUTPERFORM (1)

Eric Schmidt, Ph.D.
646.562.1345
eric.schmidt@cowen.com

Marc Frahm, Ph.D.
646.562.1394
marc.frahm@cowen.com

Key Data

Symbol	NASDAQ: ADAP
Market Cap (MM)	$523.1

Quick Take: Company Update

NY-ESO-1 TCR Heading For Pivotal Trials

The Cowen Insight

Adaptimmune and GSK announced a revised partnership agreement that will accelerate their lead TCR candidate, directed against NY-ESO-1, into pivotal development for synovial sarcoma and support the accrual of earlier data in other cancers. We continue to believe TCRs will be a key component of future IO therapies and view Adaptimmune as a leader in the space. We reiterate our Outperform rating.

The News: This morning, Adaptimmune and GSK announced an amended partnership agreement covering the development of engineered T cells targeting NY-ESO-1 and up to four additional antigens. Recall that Adaptimmune has previously presented data demonstrating a 60% ORR (50% PR and 10% CR) among 10 synovial sarcoma patients receiving at least 1x10^9 NY-ESO-1 specific T cells (GSK3377794). Based upon this initial dataset, Adaptimmune signed a partnership agreement with GSK in 2014 that provided support for trials of NY-ESO-1 in additional tumor types (lung, melanoma, myeloma, and ovarian), development of additional antigen specificities, the refinement of Adaptimmune's manufacturing processes, and ultimately licensing options for GSK. Under the original partnership, GSK was able to opt into the NY-ESO-1 program following Phase II "proof-of-concept" data. Adaptimmune had expected to receive up to $350MM for development of NY-ESO-1 and two additional GSK programs from over the first seven years of the collaboration.

Under the new agreement, the partners will accelerate NY-ESO-1's development into a pivotal synovial cell sarcoma trial (to start by YE:16) in advance of GSK formally exercising its option on the program. This trial will be supported by funding from GSK and may

also include patients with NY-ESO-1 positive myxoid/round cell liposarcoma. GSK will continue to provide funding for Phase I/II trials of NY-ESO-1 in other tumor types both as a monotherapy and potentially in combination with other agents. Adaptimmune is now guiding that it could earn up to $500MM in development milestones for the NY-ESO-1 program alone. This assumes that NY-ESO-1 is successfully developed in at least two tumor types using TCRs specific for two HLA types. Adaptimmune is also entitled to undisclosed commercial milestones on NY-ESO-1 as well as significant development and commercial milestones for each of the four additional GSK programs. Finally, Adaptimmune reiterated its 2016 cash burn guidance of $80-100MM, and therefore it expects to exit 2016 with a cash balance of at least $150MM.

Our Take: Under the original partnership, GSK was not required to exercise its licensing options until Adaptimmune produced Phase II data. If GSK had opted in to a program, it would then have been responsible for running a Phase III trial. However, the evolving regulatory landscape for engineered T cells appears to have made Phase II "proof-of-concept" trials de facto pivotal programs. Therefore, the deal terms no longer appeared to fit the current regulatory landscape or effectively incentivized either party to aggressively pursue development in synovial cell sarcoma. In addition, the old partnership did not contemplate combination trials. By pulling forward GSK's financial responsibility to potentially pivotal Phase II trials and adding provisions for combination therapies we think this new agreement will serve both parties better. Across all five programs we believe Adaptimmune could be entitled to >$1B in development milestones. We think the scale of this GSK partnership is not fully appreciated by the investment community.

In addition, Adaptimmune's wholly owned pipeline candidates continue to progress with patients currently being dosed with a MAGE-A10 TCR construct and an IND soon to be filed for an AFP TCR. Importantly, the NIH's RAC did not require a public hearing prior to approving the AFP TCR. We think this is indicative of increased regulatory comfort with Adaptimmune's internally developed safety screening protocol for affinity enhanced engineered TCRs.

Upcoming Milestones: Adaptimmune expects to file an IND for its AFP specific TCR for hepatocellular carcinoma during Q1:16. During H1:16, Adaptimmune anticipates finalizing a development path for NY-ESO-1 TCRs in myeloma that may include combination with checkpoint inhibitors. Correlation studies using the existing NY-ESO-1 datasets will be presented at ASCO 2016. New/updated response data from ongoing NY-ESO-1 trials in melanoma, myeloma, NSCLC, ovarian, and/or synovial cell sarcoma will be presented in H2:16 (likely ESMO). Initial data from Adaptimmune's wholly owned MAGE-A10 program is also expected in H2:16.

From: Arie Belldegrun [Arie@kitepharma.com]
Sent: Sunday, February 07, 2016 12:47 PM
To: Restifo, Nicholas P. (NIH/NCI) [E]
CC: Rosenberg, Steven A. (NIH/NCI) [E]; Margo Roberts; David Chang; Tony Polverino
Subject: Re: Kite visit?

Hi Nick,

Thank you very much for the update. I am thrilled that your visit was successful and enjoyable , and I am looking forward to get the full update from the team on Monday.
All I know is that we find ourselves quoting your work so very often, that the anticipation for your visit was very high .

Again, I am sorry that I had to be out of town during your visit at Kite. We had a crucial 2 day board of directors meeting for TEVA in Tel Aviv , and I then had to complete few meetings in London on the way back.

All the best,

Arie

Arie Belldegrun, MD, FACS
Chairman, President and CEO
KITE PHARMA
Direct: 310.622.9093
Arie@kitepharma.com
www.kitepharma.com

On Feb 7, 2016, at 10:22, Restifo, Nicholas P. (NIH/NCI) [E] <restifon@mail.nih.gov> wrote:

> Hi Arie,
>
> PROPRIETARY INFORMATION,REDACTED PER AGREEMENT
>
> I am sure that Margo, Tony and the gang there can fill you in on our discussions.
>
> Sending best,
>
> Nick
>
> ---
>
> **From:** Arie Belldegrun [mailto:Arie@kitepharma.com]
> **Sent:** Wednesday, January 06, 2016 7:01 PM
> **To:** Katae Long-Phelps; Restifo, Nicholas P. (NIH/NCI) [E]; Margo Roberts
> **Cc:** David Chang; Tony Polverino; Marianna Sabatino; Linda Barnes
> **Subject:** RE: Kite visit?
>
> Hi Nick,
>
> So sorry to miss you in LA. I would have loved to be present at your UCLA talk and your visit at Kite.

Unfortunately, I have to be at a Teva Pharmaceutical Board of Directors on these 2 days.

Hope to see you back at the NCI or at another LA visit.

All the best,

<image001.png>
Arie Belldegrun, MD, FACS
Chairman, President & CEO
2225 Colorado Ave.
Santa Monica, CA 90404
310/622-9093
arie@kitepharma.com
www.kitepharma.com

From: Katae Long-Phelps
Sent: Wednesday, January 6, 2016 3:35 PM
To: Restifo, Nicholas P. (NIH/NCI) [E] <restifon@mail.nih.gov>; Margo Roberts <MRoberts@KitePharma.com>
Cc: Arie Belldegrun <Arie@kitepharma.com>; David Chang <DChang@KitePharma.com>; Tony Polverino <TPolverino@KitePharma.com>; Marianna Sabatino <msabatino@kitepharma.com>; Linda Barnes <LBarnes@KitePharma.com>
Subject: RE: Kite visit?

Hi Nick,

It was good to speak with you as well, thank you again for your call. I am discussing the details of your visit to our Kite offices on the afternoon of Feb 5th with Margo and Tony and will get back with you tomorrow.

In the meantime, please feel free to contact me with any other questions and we look forward to your visit!

Thank you,

Katae

<image002.jpg>

Katae Long-Phelps
Executive Assistant to CSO, VP of Research & VP of Translational Medicine

Kite Pharma
2225 Colorado Avenue, Santa Monica, CA 90404
Direct: 310.742.2893
klongphelps@kitepharma.com | www.kitepharma.com

From: Restifo, Nicholas P. (NIH/NCI) [E] [mailto:restifon@mail.nih.gov]
Sent: Wednesday, January 6, 2016 2:18 PM

To: Margo Roberts <MRoberts@KitePharma.com>
Cc: Arie Belldegrun <Arie@kitepharma.com>; David Chang <DChang@KitePharma.com>; Tony Polverino <TPolverino@KitePharma.com>; Katae Long-Phelps <klongphelps@kitepharma.com>
Subject: RE: Kite visit?

Hi Katae,

It was good to speak with you today about my upcoming visit for the UCLA Stem Cell Symposium on Thursday and Friday February 4th and 5th. My lecture at UCLA is first thing in the morning on February 5th, leaving other slots on Feb 4th or 5th as potentially good times for me to visit friends at Kite.

As I mentioned, I would like to see Arie if possible, and also Margo and David. It would be good to see my friend Marianna Sabatino on the schedule as well if possible. You asked about dinner but I am not yet sure about my availability.

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

My full contact info is below.

Sending best regards,

Nick

Nicholas P. Restifo, MD
Principal Investigator
National Cancer Institute, NIH
Bldg 10/CRC, Room 3-5762
Direct Line (301) 496-4904

From: Margo Roberts [mailto:MRoberts@KitePharma.com]
Sent: Friday, October 30, 2015 10:11 PM
To: Restifo, Nicholas P. (NIH/NCI) [E]
Cc: Arie Belldegrun; David Chang; Tony Polverino; Katae Long-Phelps
Subject: Re: Kite visit?

Nick,

That would be wonderful! Even if you can only make same day, we can make it work. I'm cc'ing Katae who can coordinate with you. Also, please let me know if you're free for dinner during your stay.

Margo

Sent from iPhone

On Oct 30, 2015, at 5:50 PM, Restifo, Nicholas P. (NIH/NCI) [E] <restifon@mail.nih.gov> wrote:

> Margo and Arie,

That would be great! There is much more for Kite! Will check my schedule but definitely will come by before or after the UCLA talk.

Nick

On Oct 30, 2015, at 7:46 PM, Margo Roberts <MRoberts@KitePharma.com> wrote:

> Hi Nick,
>
> Hope all is well! Arie brought to our attention that you will be giving a seminar at UCLA on Friday Feb 5th. If you could come out to LA earlier, we would love to host you at Kite on the Wed or Thurs before – or on the Monday if you have
>
> PROPRIETARY INFORMATION,REDACTED PER AGREEMENT
>
> Best,
> Margo

This e-mail contains information that may be confidential. If you are not the intended recipient, please delete the e-mail and notify the sender at Kite Pharma immediately.

From: David Chang [DChang@KitePharma.com]
Sent: Tuesday, February 09, 2016 2:55 AM
To: Restifo, Nicholas P. (NIH/NCI) [E]
CC: Arie Belldegrun; Rosenberg, Steven A. (NIH/NCI) [E]; Margo Roberts; Tony Polverino; Lovoy, Liz (NIH/NCI) [E]
Subject: Re: Talk at Kite

Nick,

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Best,
David

David Chang, MD, PhD
Executive Vice President of R&D
and Chief Medical Officer
Kite Pharma, Inc
office: (310) 622-9094
PERSONAL INFORMATION,REDACTED PER AGREEMENT

www.kitepharma.com

Sent from my iPad

On Feb 9, 2016, at 12:05 PM, Restifo, Nicholas P. (NIH/NCI) [E] <restifon@mail.nih.gov> wrote:

> Dear Arie and Colleagues at Kite,
>
> I am glad to hear that your visit to TEVA went well and that your travels home were safe.
>
> PROPRIETARY INFORMATION,REDACTED PER AGREEMENT
>
> Yours
> Nick
>
> ---
>
> **From:** Arie Belldegrun [mailto:Arie@kitepharma.com]
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> **Cc:** Rosenberg, Steven A. (NIH/NCI) [E]; Margo Roberts; David Chang; Tony Polverino
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All the best,

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Nick

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Sent: Wednesday, January 06, 2016 7:01 PM
To: Katae Long-Phelps; Restifo, Nicholas P. (NIH/NCI) [E]; Margo Roberts
Cc: David Chang; Tony Polverino; Marianna Sabatino; Linda Barnes
Subject: RE: Kite visit?

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<image001.png>

Arie Belldegrun, MD, FACS
Chairman, President & CEO
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Santa Monica, CA 90404
310/622-9093
arie@kitepharma.com
www.kitepharma.com

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Sent: Wednesday, January 6, 2016 3:35 PM
To: Restifo, Nicholas P. (NIH/NCI) [E] <restifon@mail.nih.gov>; Margo Roberts <MRoberts@KitePharma.com>
Cc: Arie Belldegrun <Arie@kitepharma.com>; David Chang <DChang@KitePharma.com>; Tony Polverino <TPolverino@KitePharma.com>; Marianna Sabatino <msabatino@kitepharma.com>; Linda Barnes <LBarnes@KitePharma.com>
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In the meantime, please feel free to contact me with any other questions and we look forward to your visit!

Thank you,

Katae

<image002.jpg>

Katae Long-Phelps
Executive Assistant to CSO, VP of Research & VP of Translational Medicine

Kite Pharma
2225 Colorado Avenue, Santa Monica, CA 90404
Direct: 310.742.2893
klongphelps@kitepharma.com | www.kitepharma.com

From: Restifo, Nicholas P. (NIH/NCI) [E] [mailto:restifon@mail.nih.gov]
Sent: Wednesday, January 6, 2016 2:18 PM
To: Margo Roberts <MRoberts@KitePharma.com>
Cc: Arie Belldegrun <Arie@kitepharma.com>; David Chang <DChang@KitePharma.com>; Tony Polverino <TPolverino@KitePharma.com>; Katae Long-Phelps <klongphelps@kitepharma.com>
Subject: RE: Kite visit?

Hi Katae,

It was good to speak with you today about my upcoming visit for the UCLA Stem Cell Symposium on Thursday and Friday February 4th and 5th. My lecture at UCLA is first thing in the morning on February 5th, leaving other slots on Feb 4th or 5th as potentially good times for me to visit friends at Kite.

As I mentioned, I would like to see Arie if possible, and also Margo and David. It would be good to see my friend Marianna Sabatino on the schedule as well if possible. You asked about dinner but I am not yet sure about my availability.

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

My full contact info is below.

Sending best regards,

Nick

Nicholas P. Restifo, MD
Principal Investigator
National Cancer Institute, NIH
Bldg 10/CRC, Room 3-5762
Direct Line (301) 496-4904

From: Margo Roberts [mailto:MRoberts@KitePharma.com]
Sent: Friday, October 30, 2015 10:11 PM
To: Restifo, Nicholas P. (NIH/NCI) [E]
Cc: Arie Belldegrun; David Chang; Tony Polverino; Katae Long-Phelps
Subject: Re: Kite visit?

Nick,

That would be wonderful! Even if you can only make same day, we can make it work. I'm cc'ing Katae who can coordinate with you. Also, please let me know if you're free for dinner during your stay.

Margo

Sent from iPhone

On Oct 30, 2015, at 5:50 PM, Restifo, Nicholas P. (NIH/NCI) [E] <restifon@mail.nih.gov> wrote:

> Margo and Arie,
>
> That would be great! There is much more for Kite! Will check my schedule but definitely will come by before or after the UCLA talk.

Nick

On Oct 30, 2015, at 7:46 PM, Margo Roberts <MRoberts@KitePharma.com> wrote:

Hi Nick,

Hope all is well! Arie brought to our attention that you will be giving a seminar at UCLA on Friday Feb 5th. If you could come out to LA earlier, we would love to host you at Kite on the Wed or Thurs before – or on the Monday if you have reason to stay over

PROPRIETARY INFORMATION,REDACTED PER AGREEMENT

Best,
Margo

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