Sweeney, Timothy (NIH/NCI) [E]

From: Rosenberg, Steven A. (NIH/NCI) [E]
Sent: Thursday, April 02, 2015 4:57 PM
To: Lovoy, Liz (NIH/NCI) [E]
Cc: David Chang MD PhD (dchang@kitepharma.com)
Subject: Intrexon press release
Attachments: Intrexon Signs Cooperative Research and Development Agreement.pdf

Liz

I am distressed by the Intrexon Press Release (attached). Although the explanatory paragraph is accurate the title of the press release states that we will be "...using T cell Receptors (TCR) Derived from Peripheral Blood".

This is wrong and clearly misleading. TCRs are specifically excluded from the CRADA.

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

INTREXON®

Intrexon Signs Cooperative Research and Development Agreement (CRADA) with the National Cancer Institute (NCI) for RheoSwitch® Controlled IL-12 Cancer Therapies Using T cell Receptors (TCR) Derived from Peripheral Blood

GERMANTOWN, MD, April 1, 2015 – Intrexon Corporation (NYSE: XON), a leader in synthetic biology, today announced that Intrexon has signed a Cooperative Research and Development Agreement (CRADA) with the National Cancer Institute (NCI), part of the National Institutes of Health, for the development of adoptive T cell therapies utilizing the RheoSwitch Therapeutic System® (RTS®) platform for the treatment of solid tumor malignancies. The principal goal of the CRADA is to develop and evaluate improved adoptive cell transfer-based immunotherapies (ACT) using NCI proprietary methods for the identification of autologous peripheral blood lymphocytes (PBL) possessing naturally occurring anti-tumor activity combined with Intrexon's RTS® gene switch for introducing spatially and temporally controlled interleukin-12 (IL-12) expression.

RTS® technology enables transcriptional regulation of a wide variety of therapeutic genes upon dosing of an oral activator ligand veledimex, including *in vivo* modulation of IL-12 gene expression with a broad dynamic range. As the first gene switch employed in the clinic to enable dose-dependent cytokine expression and offer the ability to administer or withdraw veledimex for continued treatment cycles, the RheoSwitch® platform provides the opportunity to tailor solutions for patient-specific therapeutic effects. Intrexon will genetically modify PBL using vectors that encode IL-12 under RTS® inducible control. Lead anti-tumor ACT/PBL/IL-12 cell therapy candidates will then be clinically evaluated by NCI in patients with metastatic cancer.

Under the CRADA, Steven A. Rosenberg, M.D., Ph.D., Chief of the Surgery Branch in the Center for Cancer Research at the NCI, will be the Principal Investigator for the study, and Gregory Frost, Ph.D., Senior Vice President and Head of Intrexon's Health Sector, will serve as co-investigator.

"Dr. Rosenberg and his colleagues at the NCI Surgery Branch have extensive experience in the clinical translation of tumor-targeting peripheral blood products for cancer treatment," said Dr. Frost. "Together with our molecular and cell engineering capabilities, we believe the research programs under this CRADA have the potential to accelerate development of targeted and controllable adoptive therapies for patients suffering with advanced stage malignancies."

About Intrexon Corporation

Intrexon Corporation (NYSE: XON) is a leader in synthetic biology focused on collaborating with companies in Health, Food, Energy, Environment, and Consumer sectors to create biologically-based products that improve the quality of life and the health of the planet. Through the Company's proprietary UltraVector® platform and integrated technology suite, Intrexon provides its partners with industrial-scale design and development of complex biological systems delivering unprecedented control, quality, function, and performance of living cells. We call our synthetic biology approach Better DNA®, and we invite you to discover more at www.dna.com.

Trademarks
Intrexon, UltraVector, RheoSwitch, RheoSwitch Therapeutic System, RTS, and Better DNA are trademarks of Intrexon and/or its affiliates. Other names may be trademarks of their respective owners.

Safe Harbor Statement
Some of the statements made in this press release are forward-looking statements. These forward-looking statements are based upon our current expectations and projections about future events and generally relate to our plans, objectives and expectations for the development of our business. Although management believes that the plans and objectives reflected in or suggested by these forward-looking statements are reasonable, all forward-looking statements involve risks and uncertainties and actual future results may be materially different from the plans, objectives and expectations expressed in this press release.

###

For more information contact:
Intrexon Corporation contacts:
Corporate Contact:
Marie Rossi, Ph.D.
Senior Manager, Technical Communications
Tel: +1 (301) 556-9850
publicrelations@intrexon.com

Investor Contact:
Christopher Basta
Vice President, Investor Relations
Tel: +1 (561) 410-7052
Investors@intrexon.com

Sweeney, Timothy (NIH/NCI) [E]

From: Rosenberg, Steven A. (NIH/NCI) [E]
Sent: Friday, April 03, 2015 11:35 AM
To: Gregory Frost Ph. D. (gfrost@intrexon.com)
Cc: Lovoy, Liz (NIH/NCI) [E]
Subject: FW: Intrexon press release
Attachments: Intrexon Signs Cooperative Research and Development Agreement.pdf

Greg

Please call me. (I have left you several messages). The title of the Intrexon press release is clearly wrong and misleading and needs to be corrected.

The title says we will be "...using T cell Receptors (TCR) Derived from Peripheral Blood".

We discussed this extensively and the CRADA document (see page 2 of the Research Plan) specifically excludes the use of T cell receptors in our work with Intrexon.. We will be working with IL-12 only **in endogenous anti-tumor T cells in the circulation** - NOT with TCRS.

This press release must be corrected since it incorrectly announces work not included in the CRADA [redacted] always take pride in being sure that we accurately portray our work and agreements.

Please call me today with plans to correct this error.

Steve

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: Rosenberg, Steven A. (NIH/NCI) [E]
Sent: Thursday, April 02, 2015 4:57 PM
To: Lovoy, Liz (NIH/NCI) [E]
Cc: David Chang MD PhD (dchang@kitepharma.com)
Subject: Intrexon press release

Liz

I am distressed by the Intrexon Press Release (attached). Although the explanatory paragraph is accurate the title of the press release states that we will be "...using T cell Receptors (TCR) Derived from Peripheral Blood".

This is wrong and clearly misleading. TCRs are specifically excluded from the CRADA. Do we have any recourse concerning this misleading title on the press release?

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

INTREXON®

Intrexon Signs Cooperative Research and Development Agreement (CRADA) with the National Cancer Institute (NCI) for RheoSwitch® Controlled IL-12 Cancer Therapies Using T cell Receptors (TCR) Derived from Peripheral Blood

GERMANTOWN, MD, April 1, 2015 – Intrexon Corporation (NYSE: XON), a leader in synthetic biology, today announced that Intrexon has signed a Cooperative Research and Development Agreement (CRADA) with the National Cancer Institute (NCI), part of the National Institutes of Health, for the development of adoptive T cell therapies utilizing the RheoSwitch Therapeutic System® (RTS®) platform for the treatment of solid tumor malignancies. The principal goal of the CRADA is to develop and evaluate improved adoptive cell transfer-based immunotherapies (ACT) using NCI proprietary methods for the identification of autologous peripheral blood lymphocytes (PBL) possessing naturally occurring anti-tumor activity combined with Intrexon's RTS® gene switch for introducing spatially and temporally controlled interleukin-12 (IL-12) expression.

RTS® technology enables transcriptional regulation of a wide variety of therapeutic genes upon dosing of an oral activator ligand veledimex, including *in vivo* modulation of IL-12 gene expression with a broad dynamic range. As the first gene switch employed in the clinic to enable dose-dependent cytokine expression and offer the ability to administer or withdraw veledimex for continued treatment cycles, the RheoSwitch® platform provides the opportunity to tailor solutions for patient-specific therapeutic effects. Intrexon will genetically modify PBL using vectors that encode IL-12 under RTS® inducible control. Lead anti-tumor ACT/PBL/IL-12 cell therapy candidates will then be clinically evaluated by NCI in patients with metastatic cancer.

Under the CRADA, Steven A. Rosenberg, M.D., Ph.D., Chief of the Surgery Branch in the Center for Cancer Research at the NCI, will be the Principal Investigator for the study, and Gregory Frost, Ph.D., Senior Vice President and Head of Intrexon's Health Sector, will serve as co-investigator.

"Dr. Rosenberg and his colleagues at the NCI Surgery Branch have extensive experience in the clinical translation of tumor-targeting peripheral blood products for cancer treatment," said Dr. Frost. "Together with our molecular and cell engineering capabilities, we believe the research programs under this CRADA have the potential to accelerate development of targeted and controllable adoptive therapies for patients suffering with advanced stage malignancies."

About Intrexon Corporation

Intrexon Corporation (NYSE: XON) is a leader in synthetic biology focused on collaborating with companies in Health, Food, Energy, Environment, and Consumer sectors to create biologically-based products that improve the quality of life and the health of the planet. Through the Company's proprietary UltraVector® platform and integrated technology suite, Intrexon provides its partners with industrial-scale design and development of complex biological systems delivering unprecedented control, quality, function, and performance of living cells. We call our synthetic biology approach Better DNA®, and we invite you to discover more at www.dna.com.

Trademarks
Intrexon, UltraVector, RheoSwitch, RheoSwitch Therapeutic System, RTS, and Better DNA are trademarks of Intrexon and/or its affiliates. Other names may be trademarks of their respective owners.

Safe Harbor Statement
Some of the statements made in this press release are forward-looking statements. These forward-looking statements are based upon our current expectations and projections about future events and generally relate to our plans, objectives and expectations for the development of our business. Although management believes that the plans and objectives reflected in or suggested by these forward-looking statements are reasonable, all forward-looking statements involve risks and uncertainties and actual future results may be materially different from the plans, objectives and expectations expressed in this press release.

###

For more information contact:
Intrexon Corporation contacts:
Corporate Contact:
Marie Rossi, Ph.D.
Senior Manager, Technical Communications
Tel: +1 (301) 556-9850
publicrelations@intrexon.com

Investor Contact:
Christopher Basta
Vice President, Investor Relations
Tel: +1 (561) 410-7052
Investors@intrexon.com

Sweeney, Timothy (NIH/NCI) [E]

From: Rosenberg, Steven A. (NIH/NCI) [E]
Sent: Thursday, April 16, 2015 11:54 AM
To: David Chang MD PhD (dchang@kitepharma.com)
Subject: FW: SOP

FYI

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: Miettinen, Markku (NIH/NCI) [E]
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

Hi Steve,

Proprietary Information,Redacted Per Agreement

Mark

On 2/15/15 11:36 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
>
>
>
>-----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
>
>Hi Steve, Mary,
>Here are the conditions for the
>Mark
>

Proprietary Information,Redacted Per Agreement

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
>>
>

Sweeney, Timothy (NIH/NCI) [E]

From: Rosenberg, Steven A. (NIH/NCI) [E]
Sent: Monday, April 20, 2015 4:55 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
Attachments: AACR 4-15 final.ppt

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

From: Arie Belldegrun [mailto: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

The view of the street of CARs for solid tumors. 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
[redacted]
arie@kitepharma.com

www.kitepharma.com

Personal Information,Redacted Per Agreement

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.

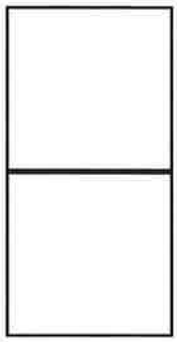
Data demonstrated no responses in solid tumor: UPenn presented updates on their CAR-T meso program (n=6) in mesothelioma (n=2), pancreatic (n=2) and ovarian carcinoma (n=2) that did not show any responses. Six subjects treated with UPenn's CART-meso construct achieved limited cell expansion at 2x below 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.



The Curative Potential of T Cell Immunotherapy for Human Cancer

AACR

March, 2015

Steven A. Rosenberg, M.D., PhD.
Surgery Branch, National Cancer Institute

THREE MAIN APPROACHES TO CANCER IMMUNOTHERAPY

---

1. **Nonspecific stimulation of immune reactions**
   a) **Stimulate effector cells**
      IL-2 (melanoma and renal cancer)
   b) **Inhibit regulatory factors**
      anti-CTLA4 (melanoma)
      anti-PD-1 (melanoma, lung cancer)

2. **Active immunization to enhance anti-tumor reactions (cancer vaccines)**

3. **Passively transfer activated immune cells with anti-tumor activity (adoptive immunotherapy)**

ADVANTAGES OF CELL TRANSFER THERAPY

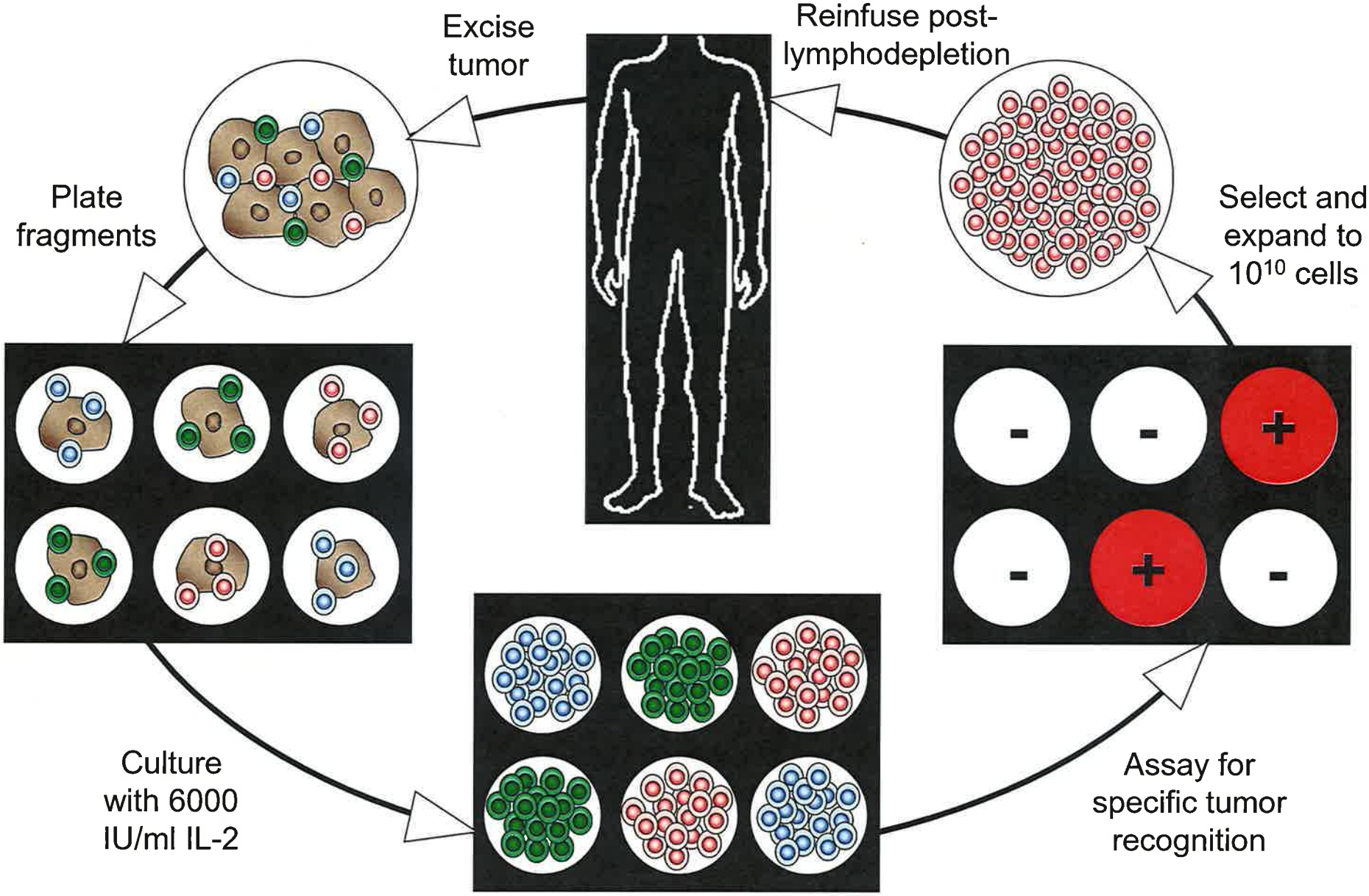
1. Administer large numbers of highly selected cells with high avidity for tumor antigens.

2. Administer cells activated ex-vivo to exhibit anti-tumor effector function.

3. Potentially identify exact cell subpopulations and effector functions required for cancer regression in vivo.

4. Manipulate host prior to cell transfer to provide altered environment for transferred cells.

Adoptive transfer of tumor infiltrating lymphocytes (TIL)



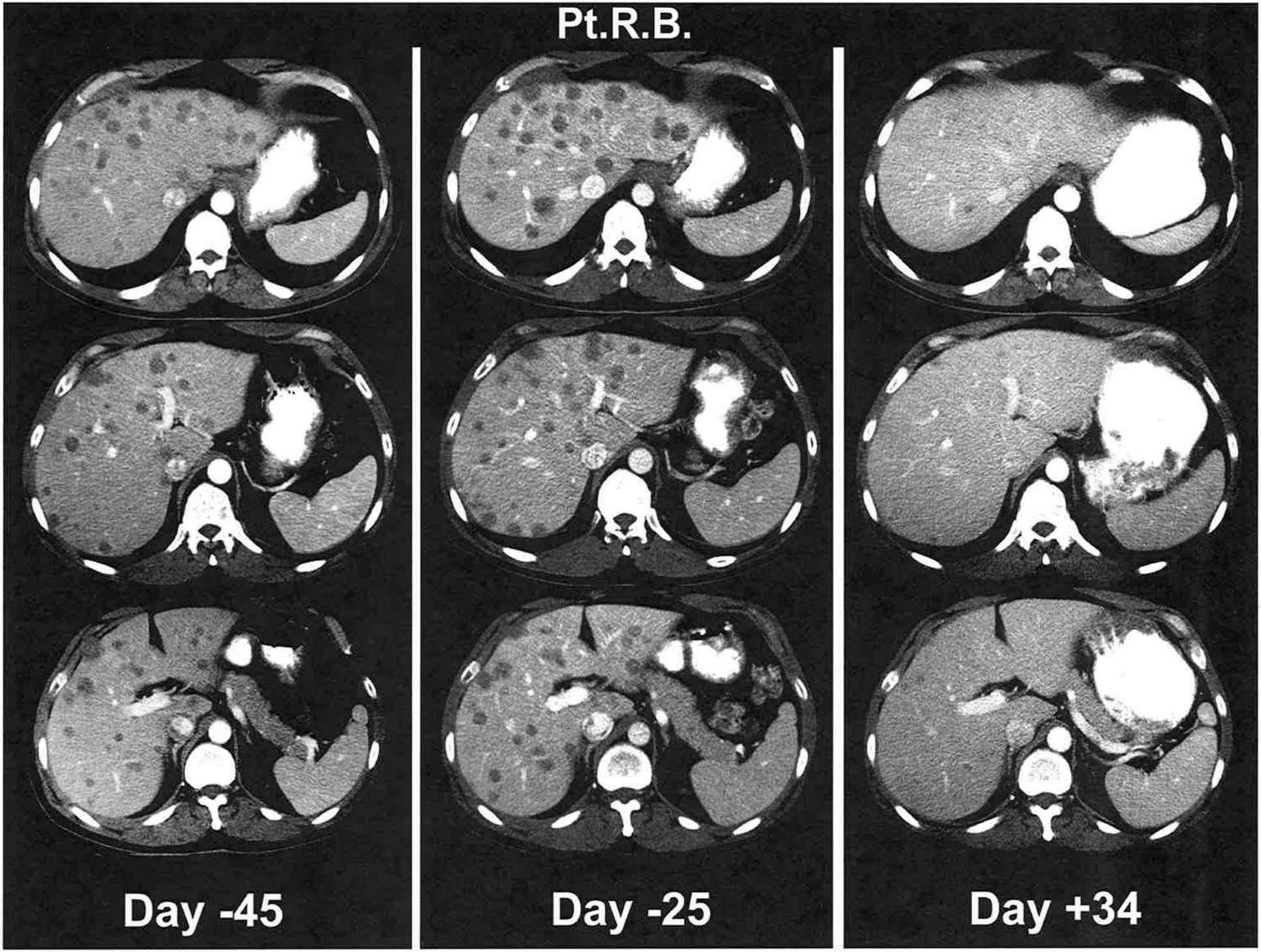
Summary of Cell Transfer Protocols for the Treatment of Patients with Metastatic Melanoma*

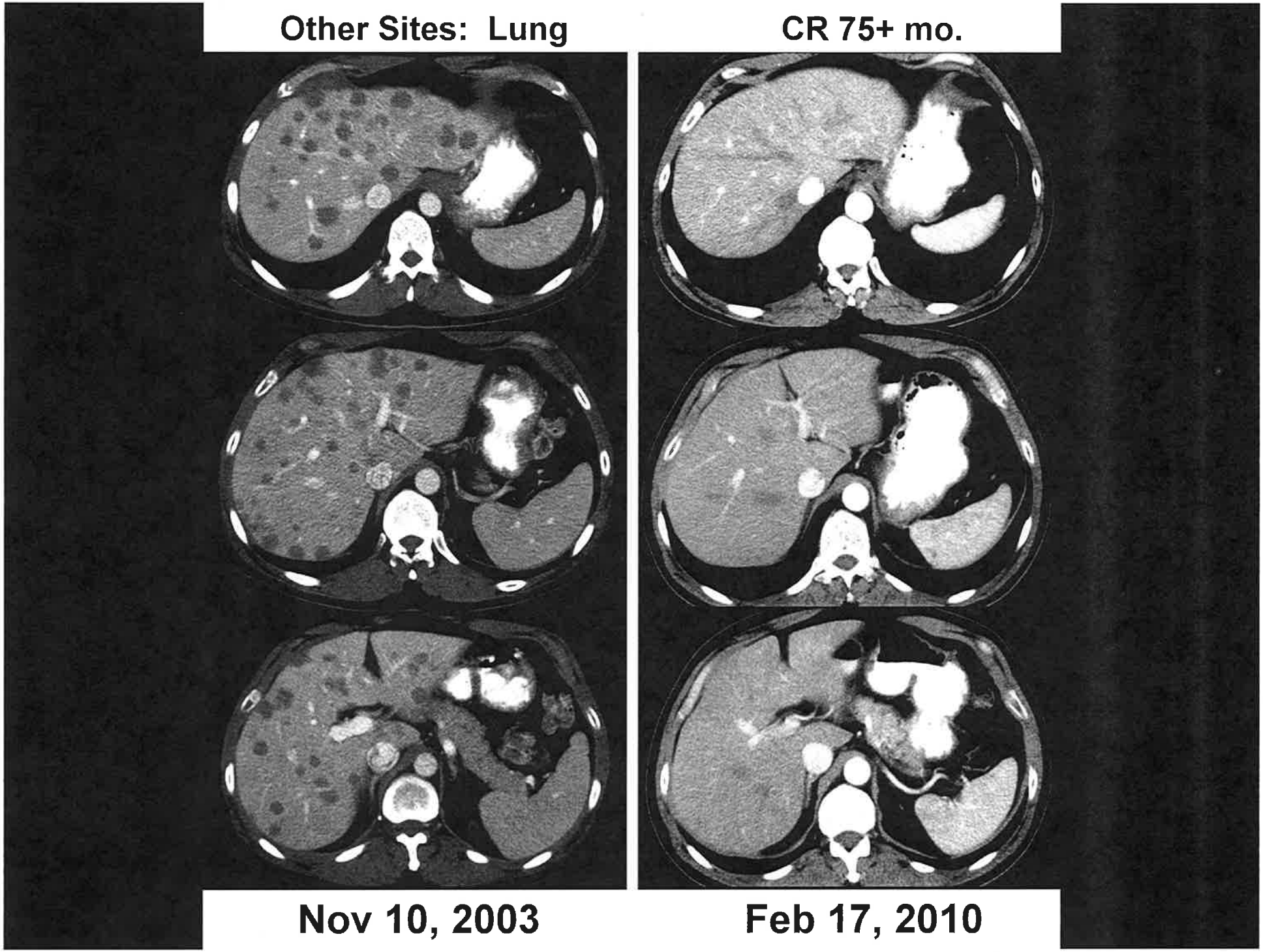
(median potential followup 8.8 years) (4/1/14)

Total	PR	CR	OR
	number of patients (duration in months)		
93	32 (34%)	20 (22%)	52(56%)
	(84, 36, 29, 28, 21, 14, 14, 13, 12, 11, 9, 7, 7, 7, 7, 7, 6, 6, 6, 6, 5, 5, 4, 4, 4, 3, 3, 3, 2, 2, 2, 2)	(124+, 122+, 121+, 111+, 108+, 107+, 103+, 100+, 96+, 91+, 88+, 87+, 82+, 82+, 81+, 81+, 80+, 80+, 80+, 19)	

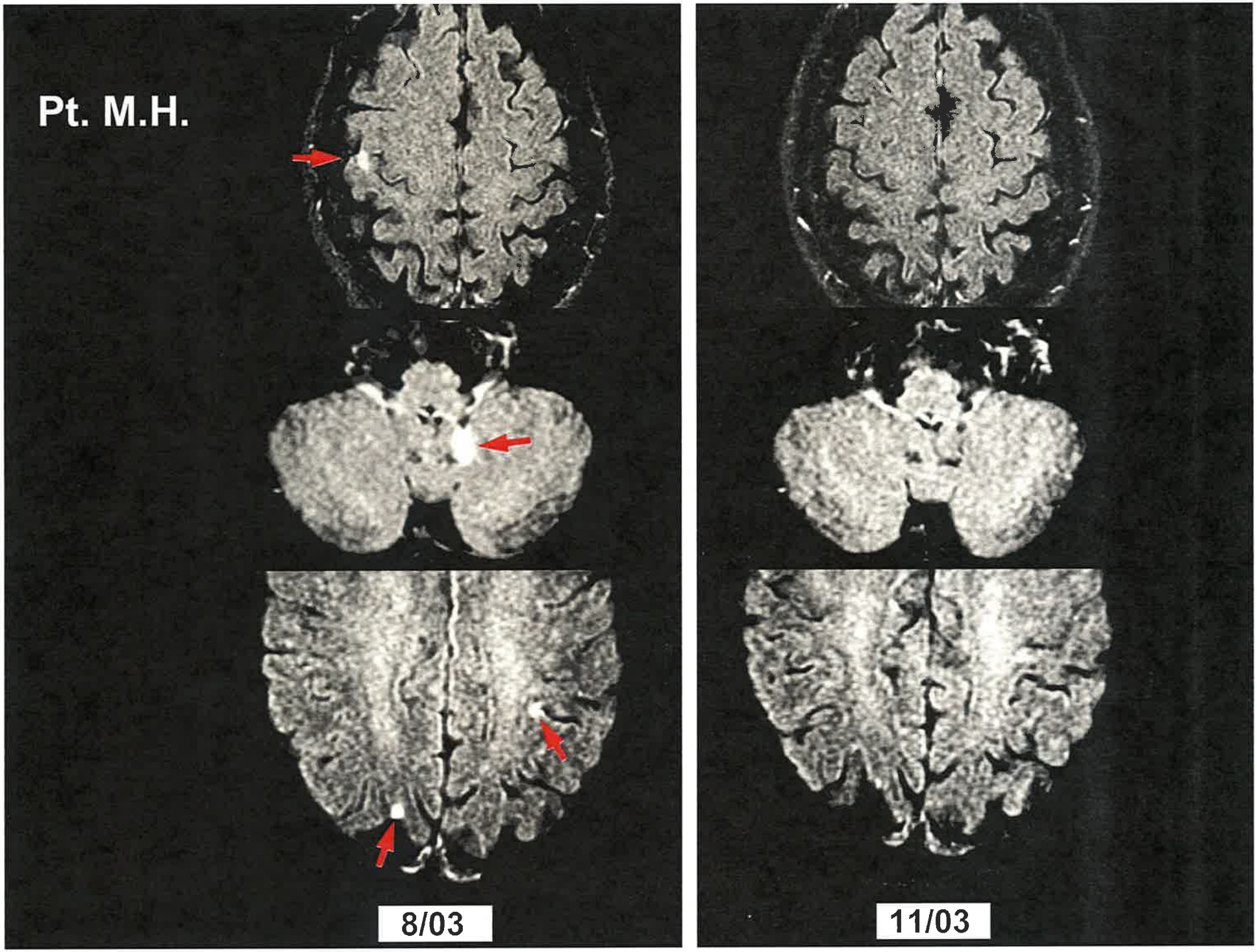
*from 3 consecutive trials using different lymphodepleting regimens

19 of 20 complete responders are ongoing at 80 to 124 months.


Pt.R.B.
Day -45
Day -25
Day +34


Other Sites: Lung
CR 75+ mo.
Nov 10, 2003
Feb 17, 2010

Personal Information
3 pages redacted

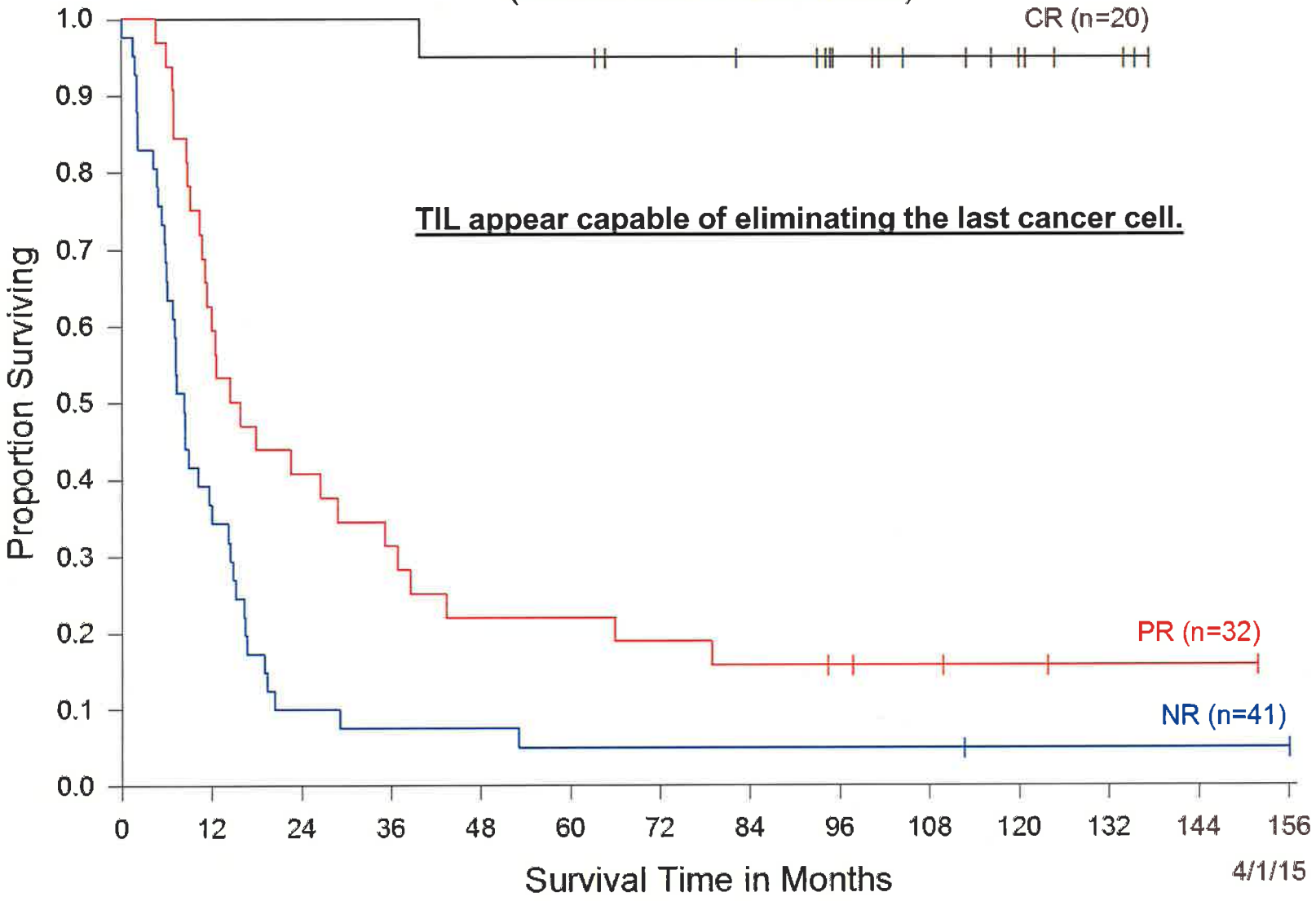

Pt. M.H.
8/03
11/03

Effect of Prior Vemurafenib, IL-2, Ipilimumab, Anti-PD1 on Response to ACT with TIL

	evaluable	Objective Response (number of patients %)
Any VEM	7	3 (43%)
Any IL-2	32	20 (63%)
Any ipi	37	20 (54%)
Any PD1	10	5 (50%)
None	39	21 (54%)

Survival of Patients with Metastatic Melanoma
Treated with Autologous Tumor Infiltrating Lymphocytes and IL-2

(Deaths due to melanoma)



TIL appear capable of eliminating the last cancer cell.

4/1/15

Conclusion

Adoptive cell therapy can mediate complete, durable, and likely curative, regression of metastatic melanoma.

The Puzzle of Melanoma Immunogenicity

Melanoma, among the many cancer histologies appears to be unique in:

1. **susceptibility to treatment with immune modulators**
   e.g. IL -2
   anti-CTLA4
   anti-CD40
   anti-PD1

2. **generating infiltrating lymphocytes (TIL) that recognize cancer-associated antigens**

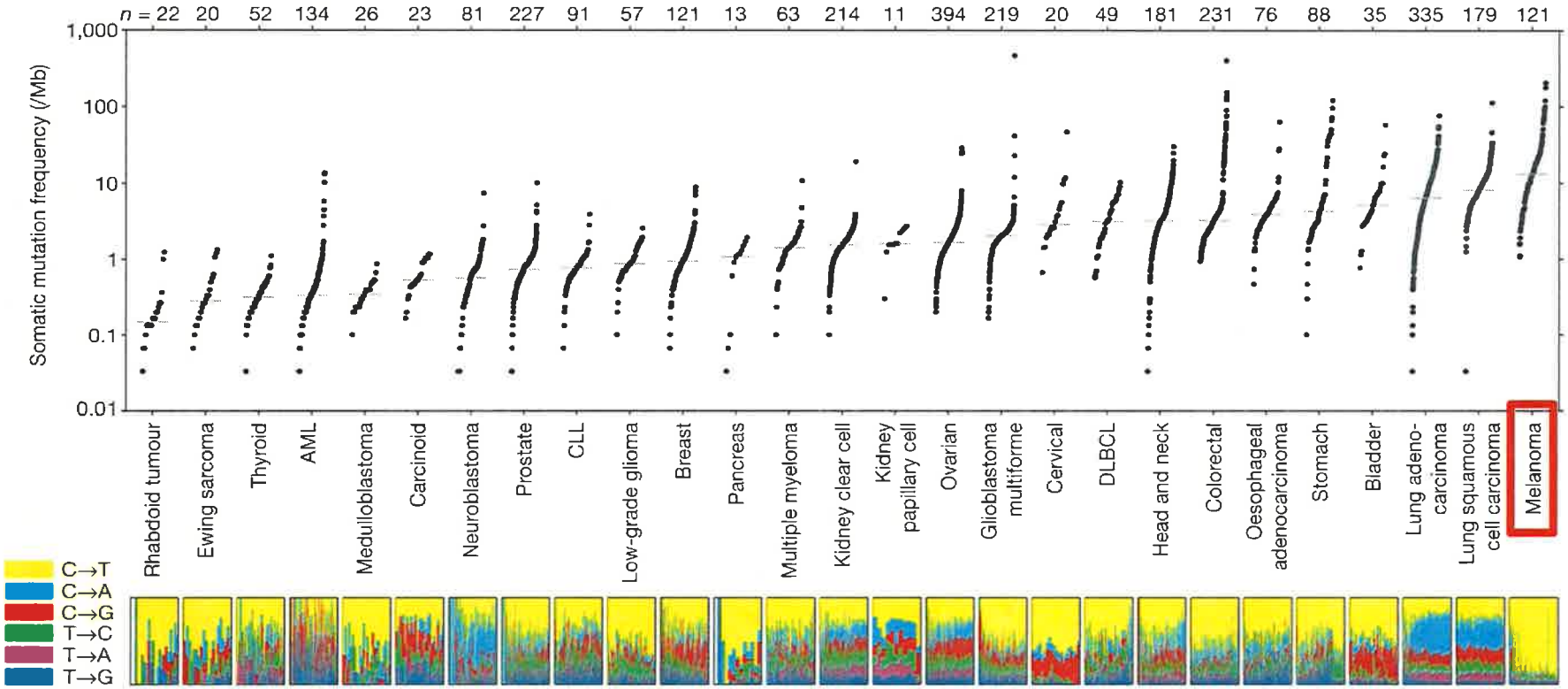
<u>Questions:</u>

Why is melanoma uniquely immunogenic?

What do TIL recognize that enables the in vivo destruction of the last cancer cell?

Can the study of melanoma provide insights for the immunotherapy of common epithelial cancers?

Somatic mutation frequencies observed in exomes from 3,083 tumour–normal pairs



MS Lawrence *et al. Nature* 1-5 (2013) doi:10.1038/nature12213

Wide variation in # of non-synonymous mutations detected in melanomas

Tumor	Date	Patient	# of Nonsynonymous mutations
TC 1477	11/2/1994	BA	142
TC 2589	8/17/2005	TB	308
TC 3309-3	7/8/2009	RC	303
TC 2098	12/12/2002	BC	279
TC 2167a	4/30/2003	PD	415
TC 2265	12/16/2003	ED	32
TC 2555-2	11/16/2005	GJ	1,637
TC 2202	7/22/2003	EG	121
TC 2224	8/28/2003	AH	105
TC 2159	4/1/2003	KH	95
TC 2272	1/22/2004	DH	114
TC 2427	12/29/2004	AH	5839
TC 2598	10/16/2006	JS	234
TC 2146	3/20/2003	AK	83
TC 2197	7/16/2003	JK	578
TC 2535-2a	9/23/2005	DL	579
TC 1946-3	7/10/2001	MM	108
TC 2479-2	5/26/2005	LN	234
TC 2531	9/16/2005	LN	182
TC 2183	6/10/2003	CP	646
TC 3338	8/12/2009	LP	337
TC 3396	11/16/2009	LP	302
TC 2614-1	3/15/2006	JR	306
TC 2232-L	9/16/2003	MR	350
TC 2650-2	6/30/2006	ER	219
TC2359	9/8/2004	DS	552
TC 2698	10/11/2006	SS	124
TC 2199	7/21/2003	TT	110
TC 2238	9/30/2003	AW	107
TC 2133-1	2/25/2003	EW	139
TC 2244	10/23/2003	CW	157
TC2591	2/8/2006	DW	235
TC 2207	7/24/2003	SW	116

Non-synonymous mutations

Average – 457 (289 w/o AH)
Median – 234
(n=33)

Mining the Cancer Exome to Identify Immunogenic Cancer Mutations

---

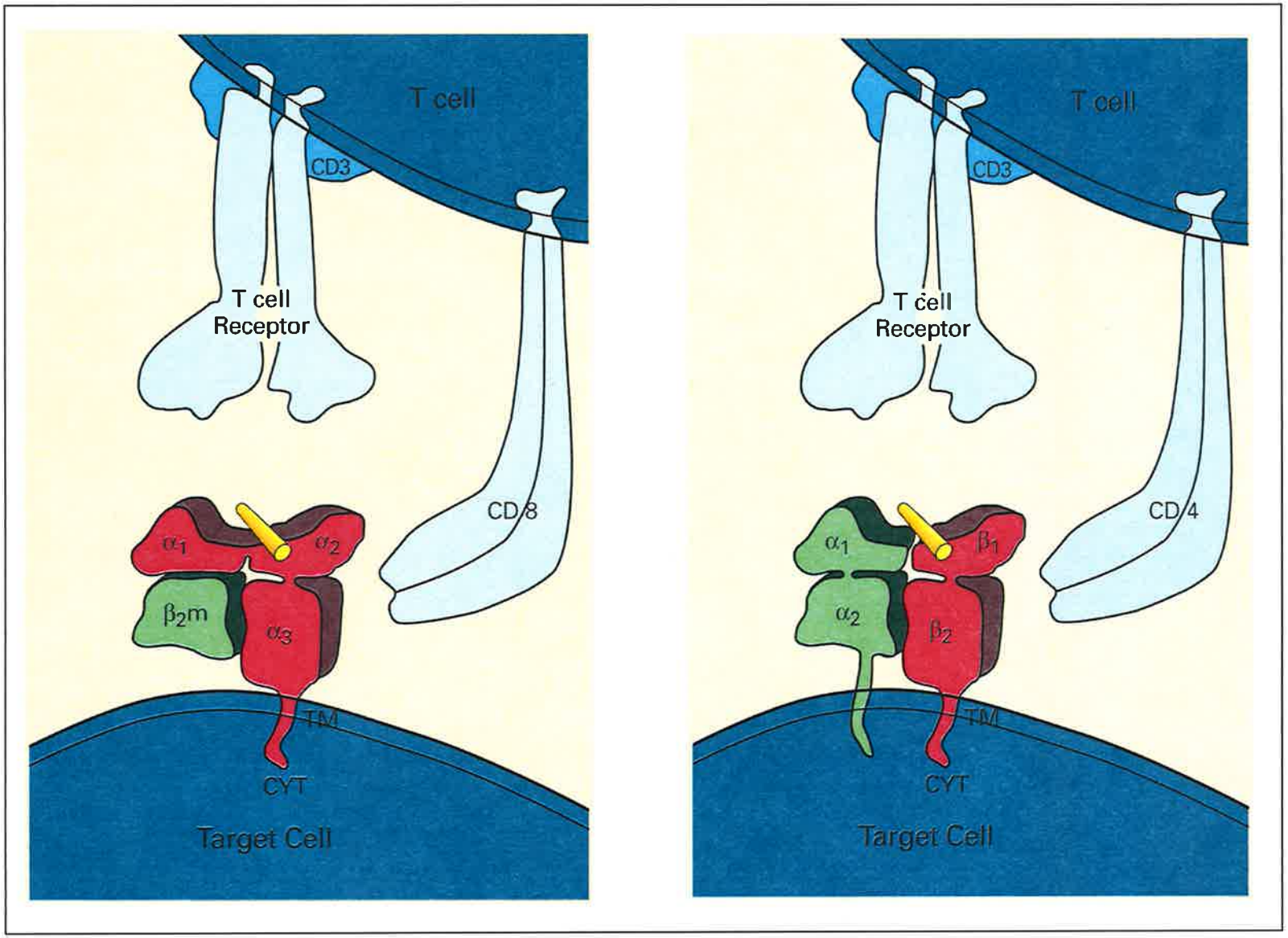
For a mutation to be a cancer antigen it has to:

1) be processed intracellularly into a 9-11 amino acid peptide

2) the peptide must fit and be presented in the groove of on one of the patient's surface MHC molecules

Thus, only some mutations will be antigenic.

Antigen recognition by $CD4^+$ and $CD8^+$ T lymphocytes



Strategy for identifying cancer mutations that are immunogenic

---

Whole exome sequence autochthonous tumor to identify all nonsynonymous mutations

In silico list all 21-mer peptides containing the mutated aa flanked by the natural 10 aa on either side

Use prediction algorithms to identify and the 20 candidate peptides with the highest affinity to the patient's MHC

Screen peptides for in vitro recognition by TIL that mediated complete cancer regression

(Nature Med 19:747-53,2013)

Patient D.S. (TIL 2369)

---

32 year old male with metastatic melanoma

Jan. 1996: excision of neck melanoma; positive lymph nodes
Feb. 1996: 1 year alpha interferon
July 2004: liver and brain metastases
Oct. 2004: High-dose IL-2; progressive disease
Jan. 2005: SRS to brain met; then excision
July 2005: TIL/200TBI/IL-2 with lymphodepletion

Complete regression ongoing as of Feb. 2014

(Exomic analysis revealed 595 nonsynonomous mutations)

Listing of the 21-mer peptides flanking the central mutated amino acid (#2369)

Gene	cDNA change	protein change	nM	ref aa	var aa
C22orf33	c.G349A	p.G117S	2.3497	SSVFSDYYDLGYNMRSNLFRG	SSVFSDYYDL**S**YNMRSNLFRG
PLEKHM2	c.C3013T	p.H1005Y	3.206	VLTDDRLFTCHEDCQTSFFRS	VLTDDRLFTC**Y**EDCQTSFFRS
GRIN3B	c.A1861G	p.N621D	4.7952	STVFSYSSALNLCYAILFRRT	STVFSYSSAL**D**LCYAILFRRT
PLCB1	c.C2062T	p.L688F	5.2812	LSVKIISGQFLSDKKVGTYVE	LSVKIISGQFFSDKKVGTYVE
HEG1	c.C1807T	p.H603Y	5.9497	SSHSEYSSFFHAQTERSNISS	SSHSEYSSFFYAQTERSNISS
BAI3	c.C251T	p.S84L	6.9239	SKKDLSCSNFSLLAYQFDHFS	SKKDLSCSNFLLLAYQFDHFS
MPP4	c.T994C	p.F332L	7.2822	EETFESDKEEFVGYGQKFFIA	EETFESDKEELVGYGQKFFIA
OR4C46	c.C571T	p.H191Y	8.0429	PLLNLACTDTHMLELFIAANS	PLLNLACTDTYMLELFIAANS
UEVLD	c.C178T	p.P60S	12.364	KDLLNFTGTIPVMYQGNTYNI	KDLLNFTGTISVMYQGNTYNI
COL9A1	c.C467T	p.S156L	13.3332	INGQTQSVVFSYKGLDGSLQT	INGQTQSVVFLYKGLDGSLQT
LST-3TM12	c.C1066T	p.L356F	14.0447	LLHMSSYIASLTYIIKMVEQQ	LLHMSSYIASFTYIIKMVEQQ
OR4C46	c.C571T	p.H191Y	21.9828	PLLNLACTDTHMLELFIAANS	PLLNLACTDTYMLELFIAANS
OR2T2	c.G350A	p.G117D	22.418	TLIGGEFFLLGLMAYDRYVAV	TLIGGEFFLLDLMAYDRYVAV
MEOX2	c.G530A	p.G177E	23.3779	RKSDSSDSQEGNYKSEVNSKP	RKSDSSDSQEENYKSEVNSKP
OR8B3	c.C364T	p.R122C	31.391	CYMLTSMAYDRYVAICNPLLY	CYMLTSMAYDCYVAICNPLLY
PPP1R3B	c.C527A	p.P176H	48.7889	FDTWKSYTDFPCQYVKDTYAG	FDTWKSYTDFHCQYVKDTYAG
LRP2	c.G10030A	p.A3344T	51.034	YLYWADWGHRAYIGRVGMDGT	YLYWADWGHRTYIGRVGMDGT
LRRC3B	c.C656T	p.S219L	53.9571	TMFGWFTMVISYVVYYVRQNQ	TMFGWFTMVILYVVYYVRQNQ
C15orf2	c.C1583T	p.S528F	71.4286	SMCVDSPPPLSFLTLLPVPST	SMCVDSPPPLFFLTLLPVPST
RNPEP	c.C592T	p.P198S	85.0666	KYKYSALIEVPDGFTAVMSAS	KYKYSALIEVSDGFTAVMSAS
MIRO-2	c.C799T	p.R267W	86.0664	QWTLVTYLDVRSCLGHLGYLG	QWTLVTYLDVWSCLGHLGYLG
PPP1R3B	c.C527A	p.P176H	100.1711	FDTWKSYTDFPCQYVKDTYAG	FDTWKSYTDFHCQYVKDTYAG
BCR	c.C2546T	p.S849F	103.6965	RNGKSYTFLISSDYERAEWRE	RNGKSYTFLIFSDYERAEWRE
ABCA12	c.C172T	p.P58S	124.4896	LNISANSPYIPYLACVRNVTD	LNISANSPYISYLACVRNVTD
KIAA1211	c.C2386T	p.P796S	125.3308	TEGCKFAKDLPSFLVPSLPYP	TEGCKFAKDLSSFLVPSLPYP
SYPL2	c.C374T	p.S125F	126.6517	AEFFVTLGIFSFFYTMAALVI	AEFFVTLGIFFFFYTMAALVI
PLCB1	c.C2062T	p.L688F	134.0483	LSVKIISGQFLSDKKVGTYVE	LSVKIISGQFFSDKKVGTYVE
PPP4R4	c.G953A	p.G318E	165.2447	SILISLSFHLGKLCHGLYGIF	SILISLSFHLEKLCHGLYGIF
FLRT2	c.C1330T	p.L444F	167.9839	DTSIQVSWLSLFTVMAYKLTW	DTSIQVSWLSFFTVMAYKLTW
HHLA2	c.C806T	p.S269F	171.8293	TWSRMKSGTFSVLAYYLSSSQ	TWSRMKSGTFFVLAYYLSSSQ
HHLA2	c.C806T	p.S269F	172.6459	TWSRMKSGTFSVLAYYLSSSQ	TWSRMKSGTFFVLAYYLSSSQ
CDH5	c.C1106T	p.P369L	180.1531	VIINITDVDEPPIFQQPFYHF	VIINITDVDELPIFQQPFYHF

String together all mutated 21-mers

AEYKKSKDEKRGTPLKKDSKK
AGLVSLDLPLNPLWEFPRDRL
ALREPMREYPEMDHSEANSLG
ALTLRTLAASNVTKHYELVRE
ALTSALRLHQSLPHFQLSRAF
APSRVPPLFVSQGTSERKDSS
AQAAAERLGYLVLVRAAFALG
AQQFLTFLSHCGEETGNIRGS
ARVLAAHGSDREQVSLRLNGH
ASNEAGSSSCLATVTVREPPS
ASTNSDDVRDKKVKVLKCISE
ATGESDELLGETDPLEMEIKL
AVTDFLVAVLMMPFSIVYIVR
AYFHINVHDSREGNIYPELVL
CCQAGMVLGGQKFKKFNKVRV
CDALCGGYIQGKSGTVLSPGF
CEMLSILALVRVLHPFYRSNN
CISPKPQKPWNKDAWEIPRES
CKFGMNDKIVFEKQGKGTADE
CKKSHQSKKWWIQAQENFAKK
CMEKFDKKRFCYIILKQKFLE
CPMDLKNFPMNVQTCIMQLES
DAREKKKPKKHSSLSAVLNSI
DAVDSAQSSAFCPSLAVVGSD
DDMVTVPKSPSAYARSSDMYS
DEILLNPNNKGFKPGIIEKFR
DEYYTEGDGEDETYYYEYPYY
DIYLKVQQELSHLPQSEINKK
DSLWFSLQKKIDTTEIETLLL
DVQTWQESKMVCAAQNASLLK
DYGLPFMCHAEVSTAYIILQL
EKENQTWNLQQKKNLEVTIVP
EKHREQKDQEKKPRPQLDLKA
ELRRAQMTEGLNTAPPNFSHT
EMETQSSDFPLSLTQPAPDQS
EPAGALDLTGIRPESQLACCD
EQQQLQLRPEYEAMCKHRKLN
ERRPPETKNRANDVDFSTSSF
ERRRGLVIVTKLCTEELLERI
ESILTDKKNSTKNPWQEYNYL
ESQVPDQPSSFHVRPQTNCII
ETESLLVGRVSLQLESPHEER
EVELQKLTEISWLYYILHPNE
EVIKVERPGASDDTRTWGPPF
EVLSCDHNGGFPRIPFSTFQF
EVQRNFIELSNSTKATSHYKP
EVSTNTAMIQISKTEITELRR
EYFMKQMNDARHGGWTTKMDW
FAVCTKHRGVFLQALNDKDMN
FFCQDGDLMKSYPGTEEESFI
FLKVKMHTMSFSHLFYLALCL
FMESGVLVATTFDRYVAICDP
FPDTLLGDPGWRVRFFDPLRN
FSDDMLFLRFCYIILKQKFLE
FSNATFQSEKKTGDRNYAIGY
FSTECRMPDITLPSQFVVPAN
FYPGYYPDDNAIYNQKFPFKT
FYTVISHYSVVKQSTARAIGP
GADMDIVHPQKRMMESDYIVM
GALRTFSSSLLYLMFL*FNLH
GCSECGKTFSYNSSLFRHQRV
GENQKKPKKGSPDEERKRQEM
GEVDKVGKFGFGFNSVYHITD
GGKELLADQNFKFIDPFCKIA
GKDACKGDSGSPLSCKHNEVW
GKGILLTWHYNPNMTCDYVIK
GKVNALNIEVKQNGKPSLVDL
GLDPREVFCPKTRRLKTGEES
GNRGETGPSGLVGPAGAVGPR
GNVAPKTPAGHLFCVFYGLFG
GPPGPHGPPGSMGPHGLPGPK
GSAFRLEAAA*PGWFLCGPAE
GVVGSDVALRKLMKLAPRYKL
GYPATQSMTQVVIQGAFTSDD
HEYLPESRDKSALQNQSQRVD
HLCMALASMA*LSGIATTLVQ
HMDTFQVARITYCTADHNVSP
HTGTALLIAHRNERSPAFTDQ
ICFAPYHFSFSLDFLVKSNEI
ICLPGTSSDYHLMDGDLGLIS
IDTSTSVTYDS
IEKVIYTGKEEKSSRGCPIAK
IGLLAAATQSSSMPASLGRMN
IIEAAPRQCIKLYFDEKYSIE
IITQAGATGVISSPGIKSPIT
INMAHLCVIGFHAVNGVARIH
IPEFYVGSILCVTTADPYASG
IRRKAGASWQGETRWSDSSVT
IWGDTVNVEIPAEDAGQEDVI
IYPSEDDIEKLIIFNQDGTMT
KAFIRVAYLT*HEKIHGEKHY
KAVHQIDQLQ*EQRHLKRQLE
KEAEKNLTDLEKFCGLCVCPC
KELRAQQGLASEPRAPGTLPE
KESQDKFLWQTAFIGKETLKD
KFIQTDAPKEINLDFHTKEVI
KGQHLGSSSK*ERDRQKQKSM
KKAEKKERE REKRDEEKAKLR
KLVFYLHRVGGGVSIGTTCLL
KNKARFSIPSITQHHAGRYRC
KNLTEEMAGLNETIAKLTKEK
KNQTCERTLDSYRNEVSQLYS
KPTSTTVGKQIIFTGPDYIKD
KRYGFTFLGN*NGYMRVENQR
KSGGVARDVASQGKDMPPAAN
KSPTENMLAT*RVSLSPSPPE
KTHVLLHRMSEKGLAAHYFFP
KWSAPQQNFLLGKTSSVVEM
KWSAPQQNFLLGKTSSVVEME
KWSAPQQNFLLGKTSSVVEMS
KWSAPQQNFLLGKTSSVVEMV
KYPSRKECTWKISATPGHRIK
LAFVDPDDCTLLKTITRFYNH
LDGALNRVPVEFYQKVWKVLQ
LDPLSNPDAIRHSDDELLNA*
LEKCGHLCPASCHDQALIKQT
LEKERMEQQR*QLSKKEKKAT
LEMYGEMLAVFKLYPTYSTKS
LEPVQRIPRYKLLLKDYLLKL
LEQVQPLIRRNCNYSNLEKIL
LFSCSVVDVFFQLNQSFEIIK
LGDPSSDPACFQSGPMEAEED
LGESRGTKDLLPVKDPGALSR
LHDFGLDGYREYSLADWVCLA
LINKGQACFCNHYAWTQWTSC
LIRKSKRFRVCYDGIHYLDIV
LLANYFEVDILKIDVYHYEVD
LLKVAIDNARPQEKQVQLEKT
LLQKLQMQIGNHEHFNSWNQG
LMVDGDKVATESYRFTWSSSH
LNKQLIQRVEFLGFKALVITL
LPSKYLYGFGKTEHRSYRRDL
LPVLKEPEPEKPEDVLESAKH
LQLPLFCLFLEIYTVTVVGNL
LRRSRSHSKNLKR*VYYIRQV
LRRSRSHSKNLKRSRSREHRR
LSLEDSESVKEAESEDIQGSS
LSLNLPCRFSSMYPTASASIE
LTFHAFAETMNIPSTHIAKTL
LTTAFFRDAMSFLLMFDLTSQ
MASIKAEADKAYTFTDNAPSP
MFFKDIEEQYLTSLACVEIVN
MLDYEQAPNI*LSIGVKNQAD
MNFFFFFSVGQKFKKFNKVRV
MNMVKRIMGRSRQEECSPQDN
MQELILMKFIHTSQYDNCLTY
MVGVNSRTNTSVETWKGSKGK
NGIPAEYTAPYPHPAPEYTGQ
NGSSSCEGRVQFQVQGSWAPL
NIICDLLELSSEETPAGAWAR
NILSAFPFLQKYTVKLSNIPT
NKTDILEEKISTSHLATYFPS
NNIGDNIFFSLLSLLYALSMV
NQRTTLILHMIIHDGKEILDC
NRGLAITRKLEFPDVIMPGDI
NRGPAYMFSDCSTSLSIEEER
NSNKNLQTSDDDINNIDFDNN
NVTVNGLVLSVILPKELKRIS
PAKAITSSRVLGEDGTLPPTQ
PDEAPNPPSSNEESTGSWTQL
PGAESVSMGPMPGVSSLGACW
PGGRRAGESGLTVADYLKFKD
PGQSLEPHPESPQRLRSDPGP
PNAWMSDSGTRLTYWKLEEKD
PPESASHSTLSLDTSTTLSQG
PPGRCLCGPTINVNNPSYGES
PPLTPRPQPPSPESCCALPPR
PPRAKVDFILFKYGLVGGEGG
PSEELALNELGTLTCLARGFS
PSEETDIISKRDFPLEESFST
PSTSGRRKTFFTCGSHLAVVT
PTFAASPFSDLFQLDNPDPQP
PYIDSFDEEPLLLEDKTWNPF
PYIDSFDEEPLLLELGIHFDH
QDNDQLEQRQKNQNNLLSHVK
QKAIEGHTKSEVQLRPPLASF
QKWNDPRLKLSSDFRGSDALT
QLNELVNSHGHSQEQLIRLQG
QLPVLKEPEPDEPEDVLESAK
QLTKESEPSACTKFYFEQSW*
QMIAVILGSLLLIASVTWLLW
QMTTFIGEGEHEAQITYIDSK
QNTDADTASPFNGTHNNSVLP
QPEGPGPTQVRKPAAPTLTVN
QPLPETEPPTLEPGPKTPPRT
QQPQEESSPQFDIPAPPSSKA
QRTLITGMASDSIVAFNIDFN
QSQGILNAMIAKISNELQALT
QSTLHSLSTSLSSVTLLLALM
QTIKSKKDFSRPKSKKAHETK
QTKEALLKILRDMQPGDYFDL
RAIPAMVVPNVTLLEKLLEKY
RALGTLLHTNVRIKRDSQGEL
RDSSTEKLLQQLNGWYMEKEE
REWHLRKQAKKENSAIIIQSW
RGRPAVCQPQERFSTQCQYQG
RLAEVWMDEFNNFFYIISPGV
RLGLMATPLDKCLRPFPDPMV
RLLGLPFIAGSVDIRHFFTGL
RPSKVLSLQDHCCRAVVSCTP
RQAGDDFVESFILDAVQRVDS
RQRVPDNPERLDSQPCVLGWE
RSSASAIHPPRPITTATSLYS
RVGEIVVFRIKGREIPIVHRV
SANKAFDVLGKVEAYLKLLKS
SEGKPYVTKEKLYQNLTREQA
SEPVIIGITIDSVVGLLVIFS
SFYPVIMYCFFGTSRHISIGP
SGFFANAARFYSTGAYRTIRD
SKFDREIWSNKLSPVLNLWKK
SKLETALLPTALIKKMAQWRH
SKPGSSSSLSPRERWTVFKGL
SKPGSSSSLSPRERWTVFKVR
SLKMETETSASGEQPQFLGVR
SLSLAPLSPRVPSEDVFAFDL
SLTTAFFRDAIGFLLMFDLTS
SLVCEAYSYPLATITWFKDGT
SPEYLKVKYL*EYSRYLHAHL
SPSLLSEKCEKPQANPSTFYD
SPVFLFEDHTEKPAPEDYPLF
SQWSSSTSVIRLSKDVDSQEK
SRAASASPYTSEHAASVPTHS
SSFPAQVGLLEIQMIWTRDSE
SSGNLKFVQD*VGSGLLYSRW
TAFSTIKSSVLTKPHGCLLPP
TEASPQQKKGEEDEDMPAAGM
TEVVVALLMCLLPLNSNGAEM
TGLGRLGVSLFKGLHHKAVLA
TIIEGRITATSKESPNPPNPS
TIIFDNFPDPFDTWEITETIG
TKLELEKQVFCSRSLPRGPDS
TLNIYLDELIRNTQTYTFTIS
TNKSTTPQSPIEGKNKLLKSG
TPTVKMHTMSFSHLFYLALCL
TTKSPSDVNIFAQPALSNFIS
TVSINDKPLWCYSYDLNGNLH
TVTVETMEPS*DEARTTDNNV
TVWSAPNYCYCCGNIASIMVF
VAKSHSFFSLPKKNGRSENGK
VAPRSKISPQVYGRRRRRSLP
VDLAITICIV*NTLFMAMEHY
VELSSGKVKMTKSLKEPLKAE
VEVLPENLHLNESETSEEDHG
VHQKIHGGEKFYECNECGKTF
VIENEMADSPVFTSIPACYWW
VISKLLPTNTNIFGLKISNSL
VITYPHEHHAFKSSRFYLLLL
VKFNAPSLLYRALRDYQKIGL
VKIGDFGLATEKSRWSGSHQF
VKQPCQPPPQKPCIPKTKEPC
VLLLGSVDGRPLLRTLSRAKF
VLPVKTKWSNFGFHILLFDLE
VNLKDLSKIRERKRGKPGTRF
VPDSVNLFANKVAAKIMNLTE
VRTISALAIAPLAEAATPYGI
VSIDYRNIQMITREHLAKAQR
VSKVTFFNLNKTKPRGKFTYD
VTCSHVGHVFWKATPYTFPGG
VTYKNLKFQV*DLGGQTSIRP
VVVNALVGAISSIMNVLLVCL
WISSPPNGWEKISGLDENYTP
WKEDNALWERNRNLLQEDKAL
WPLPQPSQHNLRSSYHNITDV
WSFRELGSLSQKAANVLTKPC
WVFINCLIENSTFDSQTKENM
YCPRNCMQANSHYARVIGTRV
YFTVAEKGSFSDIIIYEYPSL
YICTYCGKAYCFLSQFKQHIK
YILKKEDELQKMMVKDSRTEE
YIPCTLEPVFRKMFELTCTLP
YLIPCYFDAIIIGAYTTLLDT
YPVLDLLSYICTEKLLLHTCT
YQRGHLPTGGRLAVCHFPCLL
YQYNTDVVFDFQGKLLARYHK
YRLIGSSSATYIISGDTVIWD
YRVVLCINHREEHVGGCNPQL
YSMIVMFTAL*PQRQCSVCRQ
YVAICKPLHYVAIMSNKVCKT

Coculture with TIL of 20 highest binding mutated peptides (pt.2369)

	Peptide	Mutation	Affinity (nM)	Gene
1	FSDYYDLSY	117 G to S	2	C22orf33
2	LTDDRLFTCY	1005 H to Y	3	PLEKHM2
3	YSSALDLCY	621 N to D	5	GRIN3B
4	FSDKKVGTY	688 L to F	5	PLCB1
5	HSEYSSFFY	603 H to Y	6	HEG1
6	CSNFLLLAY	84 S to L	7	BAI3
7	ESDKEELVGY	332 F to L	7	MPP4
8	CTDTYMLELF	191 H to Y	8	OR4C46
9	FTGTISVMY	60 P to S	12.	UEVLD
10	QTQSVVFLY	156 S to L	13	COL9A1
11	MSSYIASFTY	356 L to F	14	LST-3TM12
12	CTDTYMLEL	191 H to Y	22	OR4C46
13	LLDLMAYDRY	117 G to D	22	OR2T2
14	SSDSQEENY	117 G to E	23	MEOX2
15	LTSMAYDCY	122 R to C	31	OR8B3
16	YTDFHCQYV	176 P to H	49	PPP1R3B
17	WADWGHRTY	3344 A to T	51	LRP2
18	FTMVILYVVY	219 S to L	54	LRRC3B
19	CVDSPPPLFF	528 S to F	71	C15orf2
20	VSDGFTAVM	198 P to S	85	RNPEP

Coculture with TIL of 20 highest binding mutated peptides (pt.2369)

	Peptide	Mutation	Affinity (nM)	Gene	IFN-γ (pg/ml)
1	FSDYYDLSY	117 G to S	2	C22orf33	<30
2	LTDDRLFTCY	1005 H to Y	3	PLEKHM2	10400
3	YSSALDLCY	621 N to D	5	GRIN3B	<30
4	FSDKKVGTY	688 L to F	5	PLCB1	<30
5	HSEYSSFFY	603 H to Y	6	HEG1	<30
6	CSNFLLLAY	84 S to L	7	BAI3	<30
7	ESDKEELVGY	332 F to L	7	MPP4	<30
8	CTDTYMLELF	191 H to Y	8	OR4C46	<30
9	FTGTISVMY	60 P to S	12	UEVLD	<30
10	QTQSVVFLY	156 S to L	13	COL9A1	<30
11	MSSYIASFTY	356 L to F	14	LST-3TM12	<30
12	CTDTYMLEL	191 H to Y	22	OR4C46	<30
13	LLDLMAYDRY	117 G to D	22	OR2T2	<30
14	SSDSQEENY	117 G to E	23	MEOX2	<30
15	LTSMAYDCY	122 R to C	31	OR8B3	<30
16	YTDFHCQYV	176 P to H	49	PPP1R3B	13400
17	WADWGHRTY	3344 A to T	51	LRP2	<30
18	FTMVILYVVY	219 S to L	54	LRRC3B	<30
19	CVDSPPPLFF	528 S to F	71	C15orf2	<30
20	VSDGFTAVM	198 P to S	85	RNPEP	<30

Mutated Antigens in Autologous Tumor Recognized by TIL 2369

PLEKHM2: Pleckstrin homology domain – containing family member M2

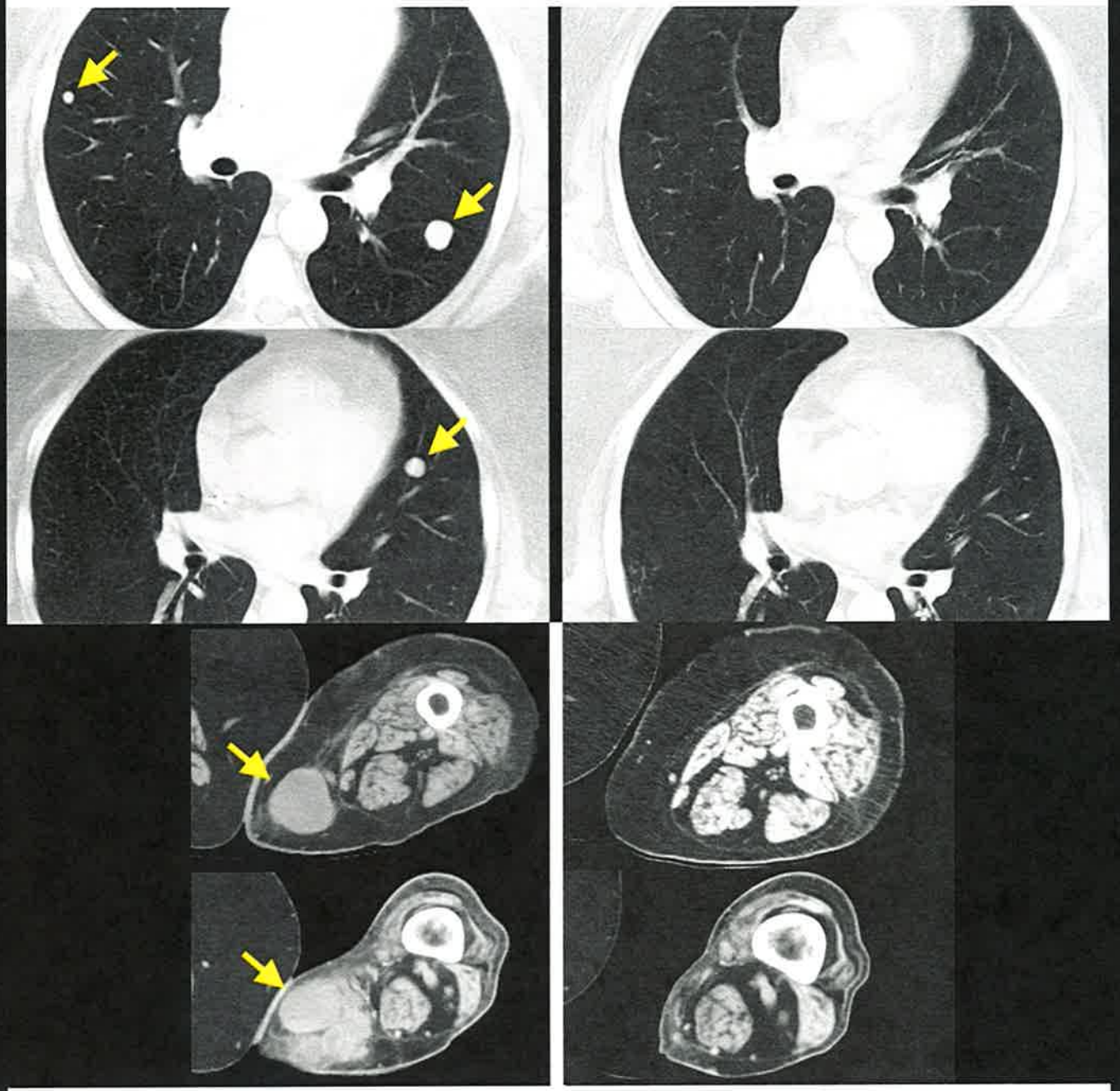
interacts with kinesin and plays a role in microtubule formation

PP1R3B: Protein phosphatase 1 regulating subunit Ga protein

regulates glycogenesis in myotubes

Other Sites: Pancreas, subcutaneous

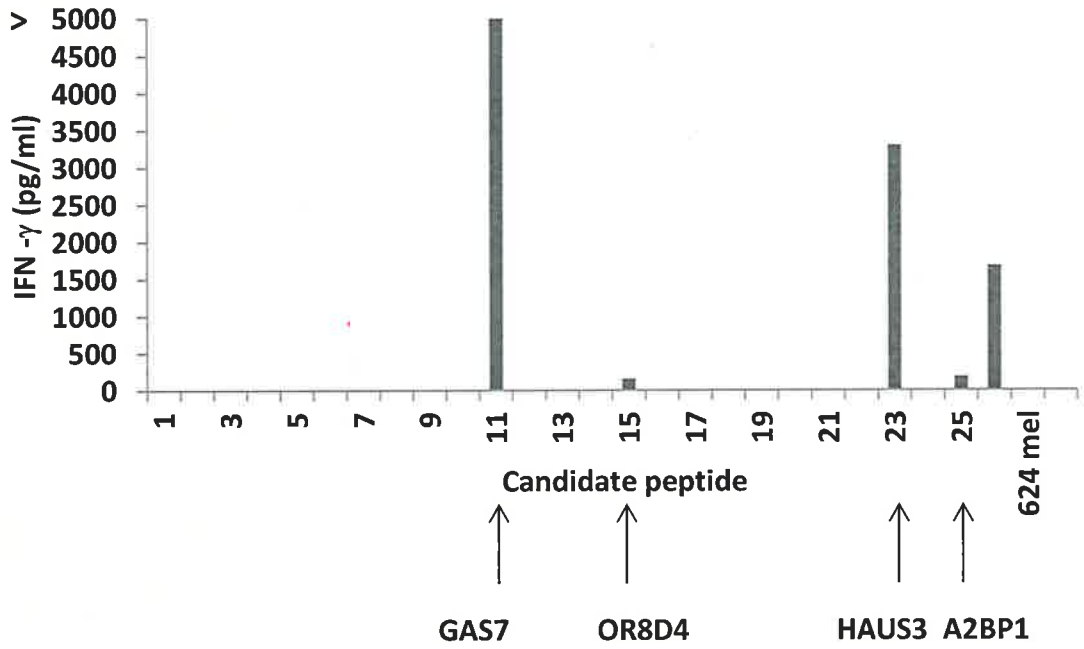
CR 58+ mo.



Jan 27, 2003

Dec 10, 2007

Screening of #2098 TIL (A2)
Peptide pulsed T2



No.	Peptide	Sub.	Predicted affinity (nM)	Gene	IFN-γ (pg/ml)
1	FLLGKTSSV	136 Q to L	4	ZNF559	<30
2	YMFSDCSTSL	91 R to C	4	TRPC6	<30
3	SLLSLLYAL	32 S to L	4	SERPINB11	<30
4	LMMPFSIVYI	76 V to M	4	HTR1F	<30
5	FQLNQSFEI	1281 S to F	6	UNC13A	<30
6	FILDAVQRV	613 S to F	6	PXDNL	<30
7	SLAPLSPRV	310 A to V	7	CNKSR1	<30
8	LLGDPGWRV	72 R to W	11	KCNA6	<30
9	FSFSLDFLV	251 P to S	11	GPR174	<30
10	MLFLRFCYI	55 R to C	12	WDR47	<30
11	SLADEAEVYL	229 H to Y	12	GAS7	47288
12	FLQKYTVKL	183 E to K	13	GSTA4	<30
13	CLFLEIYTV	33 G to E	13	OR8D4	<30
14	TMSFSHLFYL	13 S to F	16	IGF1	<30
15	FLEIYTVTV	33 G to E	17	OR8D4	156
16	YLTSLACVEI	1039 P to L	17	BRCA2	<30
17	LLADQNFKFI	190 L to F	20	RRP1B	<30
18	SLSTSLSSV	1084 S to L	21	CNTN5	<30
19	AMIAKISNEL	160 T to A	22	C4orf15	<30
20	ALGTLLHTNV	1577 L to V	23	NOTCH2	<30
21	SVVDVFFQL	1281 S to F	28	UNC13A	<30
22	MLSILALVRV	65 G to R	31	C15orf32	<30
23	ILNAMIAKI	160 T to A	34	HAUS3	3300
24	GLNETIAKL	990 D to N	35	MYH4	<30
25	YTAPYPHPA	45 H to Y	36	A2BP1	181

Mutated Antigens in Autologous Tumor Recognized by TIL 2098

GAS7: Member of the Pombe Cdc 15 homology protein family

expressed primarily in growth arrested cells

HAUS3: augmin-like complex, subunit 3

plays a role in microtuble formation within the mitotic spindle

Problems with prediction approaches for the identification of immunogenic epitopes

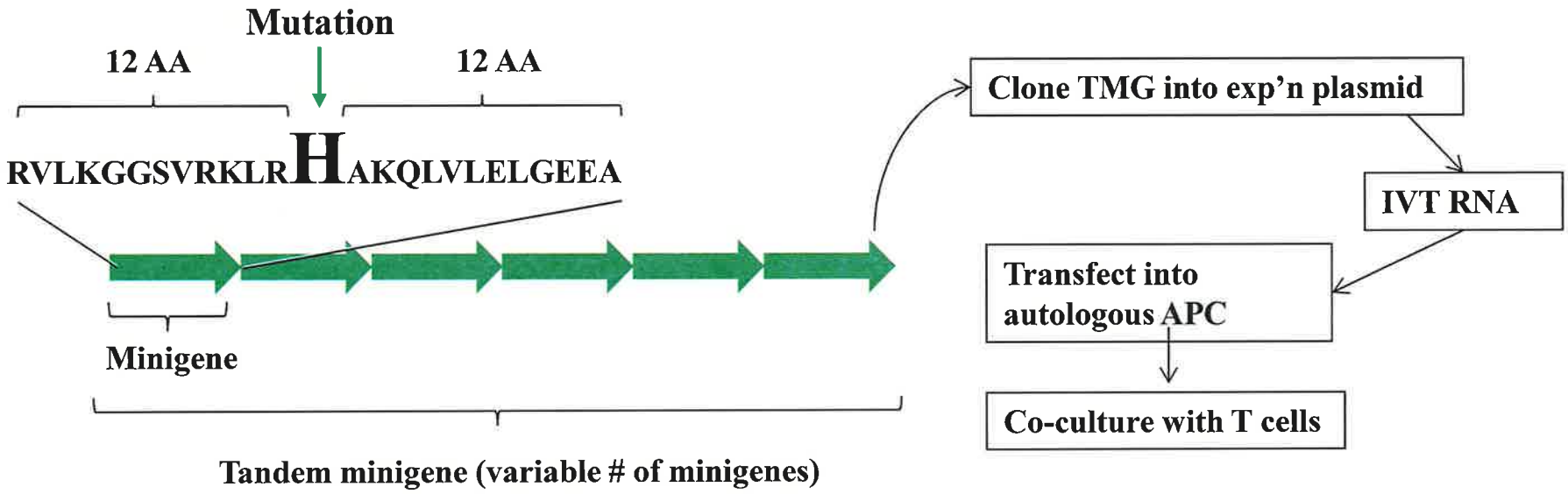
---

There are hundreds of Class I and Class II MHC molecules that can present mutated peptides; many are rare and thus prediction algorithms are inaccurate.

<u>Tandem minigene approach:</u>

A method to simultaneously evaluate mutated peptide binding by all of the patients MHC using autologous antigen presenting cells; no predictions needed.

Tandem minigene (TMG):
String of minigenes encoding the mutated AA flanked by 12 AA



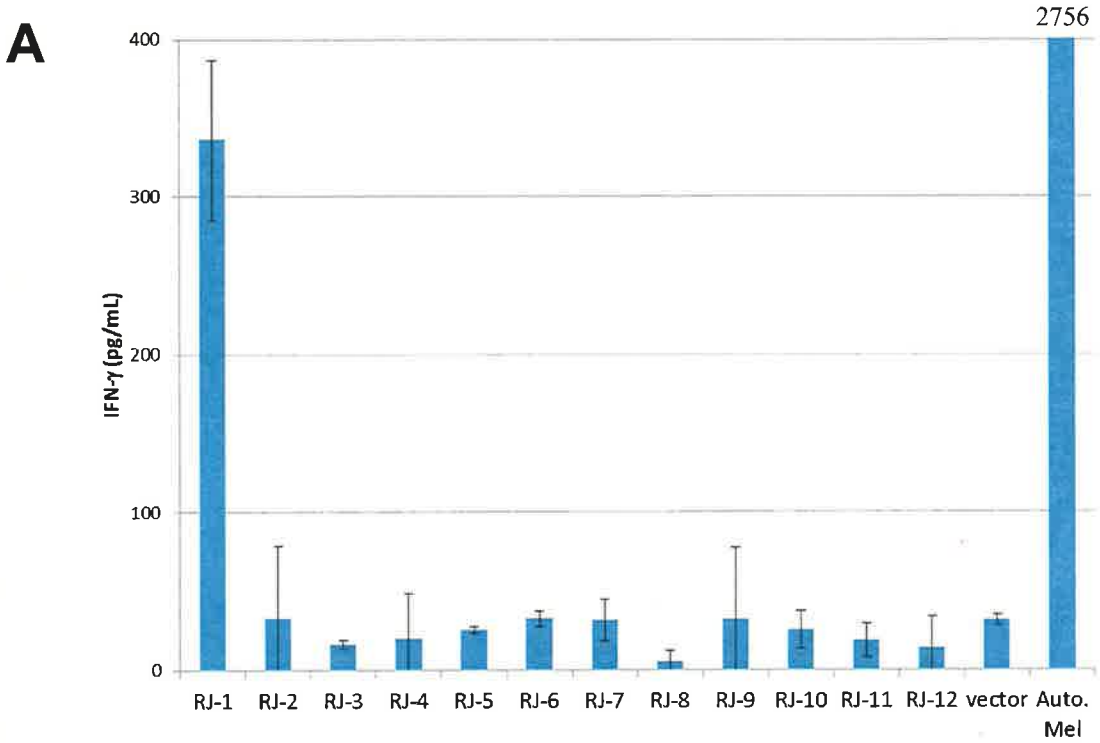
Advantages of this approach:

No need to predict peptide binding to MHC.

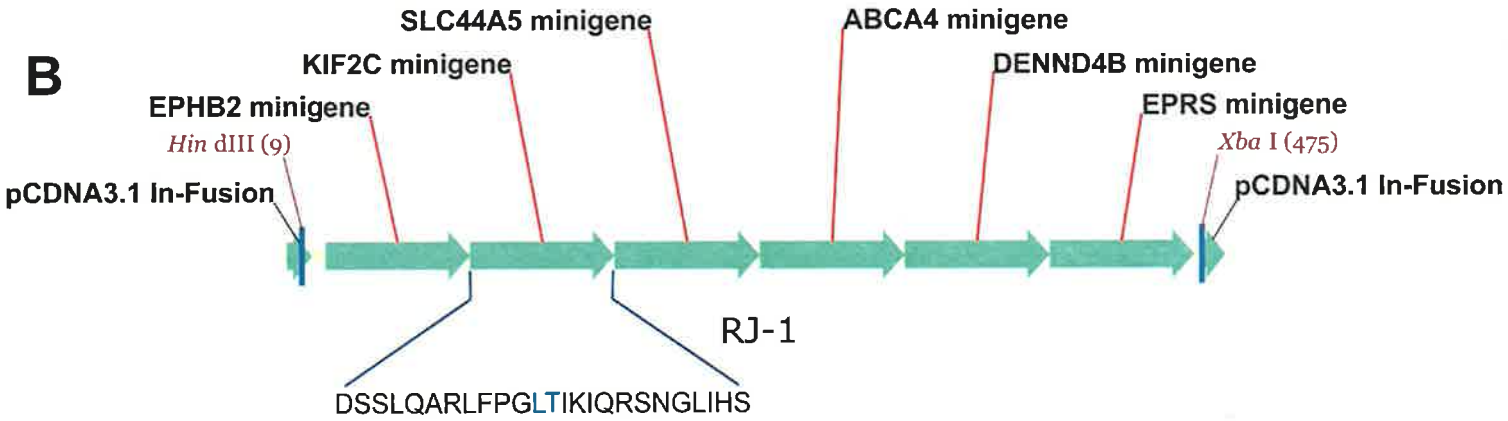
All candidate peptides and all MHC loci are included in the screen.

No tumor cell line necessary.

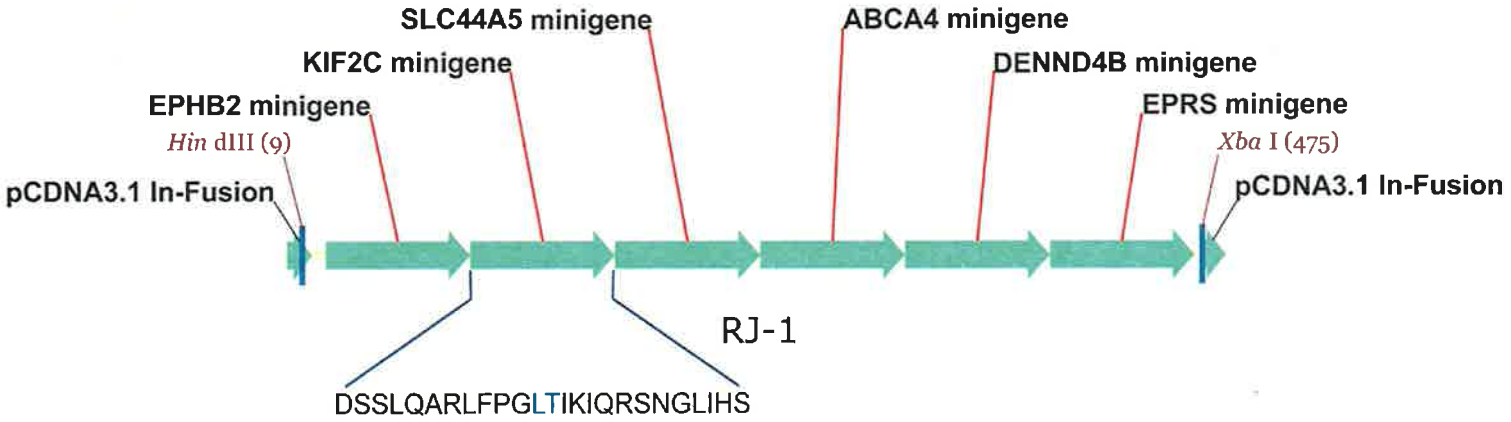
Minigene approach: J. bulk TILs recognize tandem minigene RJ-1

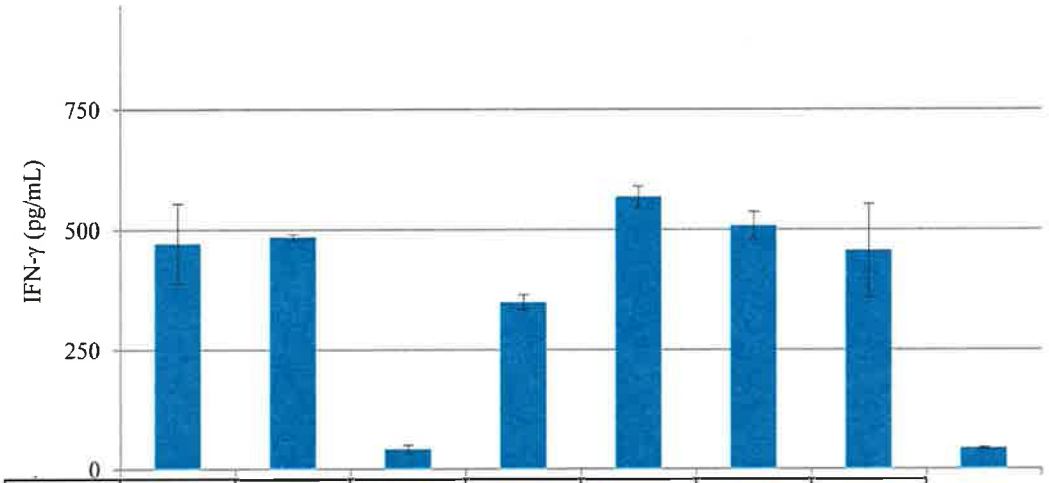


71 non-synonymous mutations
12 tandem minigene constructs
HLA-A*0205



Mutated antigen KIF2C (kinesin family member 2C) recognized by R. J. TILs

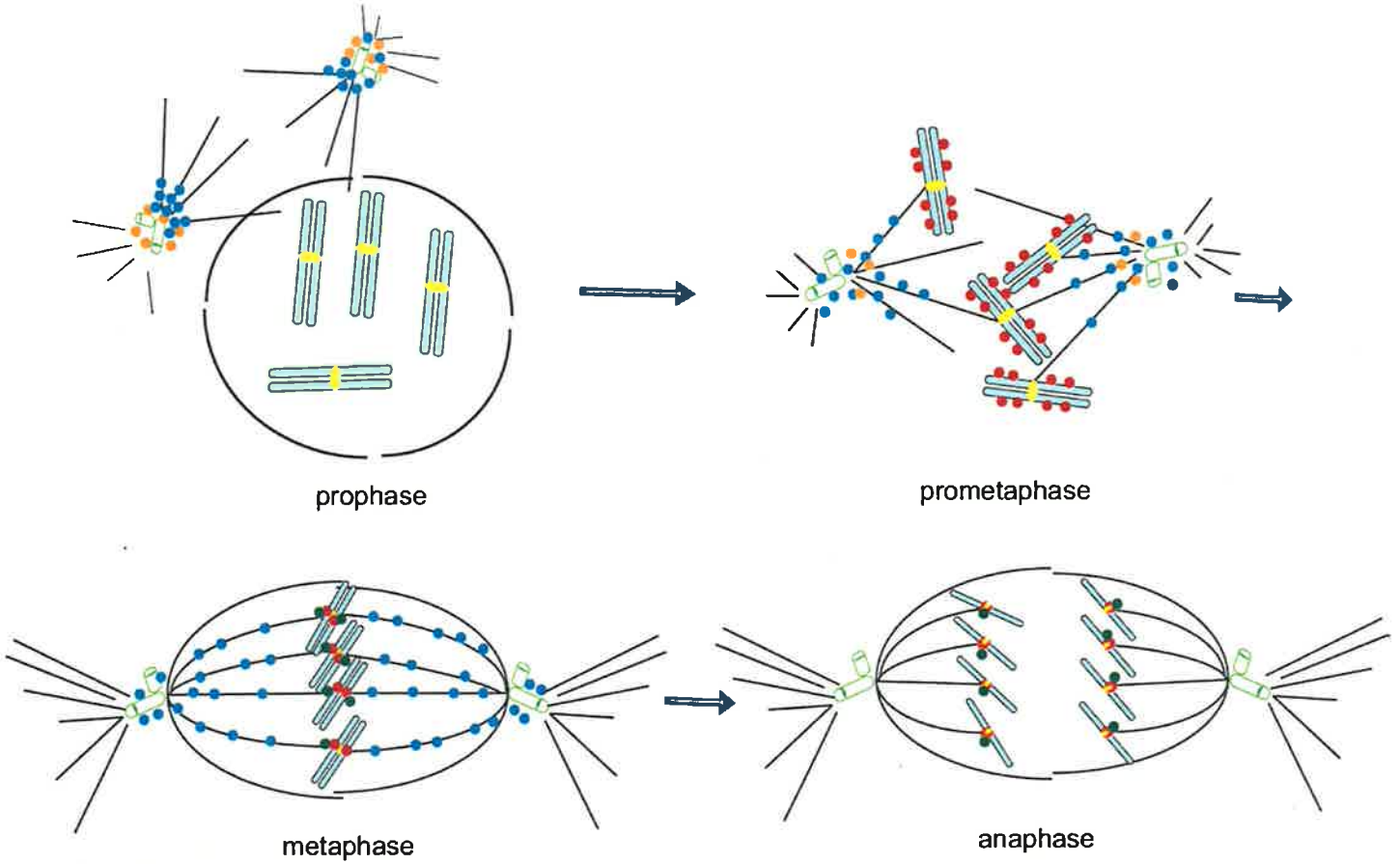




EPHB2	mut	wt	mut	mut	mut	mut	mut
KIF2C	mut	mut	wt	mut	mut	mut	mut
SLC44A5	mut	mut	mut	wt	mut	mut	mut
ABCA4	mut	mut	mut	mut	wt	mut	mut
DENND4B	mut	mut	mut	mut	mut	wt	mut
EPRS	mut	mut	mut	mut	mut	mut	wt

vector

Kinesin family member 2C (KIF2C)
also known as mitotic centromere-associated Kinesin (MCAK)



Sanhaji M et al, *Oncotarget* (2011)

Mutated antigens recognized by melanoma TIL

Tumor type	sample ID	Gene	HLA-RE
Melanoma	1290	β-catenin	A*2402
Melanoma	1290	Ki-67	DRβ1*1502
Melanoma	1290	NOP-56	A*0201
Melanoma	1913	HLA-A*11	-
Melanoma	1913	p14ARF/p16	A*11
Melanoma	3713	CENPL	A*29:02
Melanoma	3713	HELZ2	A*29:02
Melanoma	3713	PRDX3	A*29:02
Melanoma	3713	GCN1L1	A*29:02
Melanoma	3713	AFMID	A*29:02
Melanoma	3713	PLSCR4	A*29:02
Melanoma	3713	SEC22C	A*29:02
Melanoma	3713	WDR46	A*02:01
Melanoma	3713	AHNAK	A*02:01
Melanoma	3713	SRPX	A*02:01
Melanoma	3466	COL18A1	A*02:01
Melanoma	3466	TEAD1	A*02:01
Melanoma	3466	ERBB2	A*02:01
Melanoma	3466	PDZD8	B*44:02
Melanoma	3466	PXMP4	B*39:01
Melanoma	3466	KHSRP	B*39:01
Melanoma	3868	GANAB	A*02:01
Melanoma	3903	PKHA1	B*38:01
Melanoma	3903	KIAA1279	B*38:01
Melanoma	3919	TRIP12	A*01:01
Melanoma	2556	MYH14	A*01:01
Melanoma	2556	RAC1	A*02:01
Melanoma	3703	NSHDL	A*02:01
Melanoma	2098	CSNK1A1	A*02:01
Melanoma	2098	GAS7	A*02:01
Melanoma	2098	HAUS3	A*02:01
Melanoma	2098	GAPDH	A*02:01
Melanoma	3309	MATN2	A*11:01
Melanoma	3309	CDK12	A*11:01
Melanoma	2369	PLEHHM2	A*01:01
Melanoma	2369	PPP1R3B	A*01:01
Melanoma	2359	KIF2C	A*02:05
Melanoma	2591	POLA2	C*07:01
Melanoma	2224	KPNA5	A*02:01
Melanoma	1362	MART-2	A*0101
Melanoma	1558	TPI	DRβ1*0101
Melanoma	1363	LDLR-FUT	DRβ1*0101
Melanoma	1359	CDC-27	DRβ1*0401
Melanoma	1087	neo-PAP	DRβ1*0701
Melanoma	164	ARTC1	DRβ1*0101

45 different mutations unique to each patient

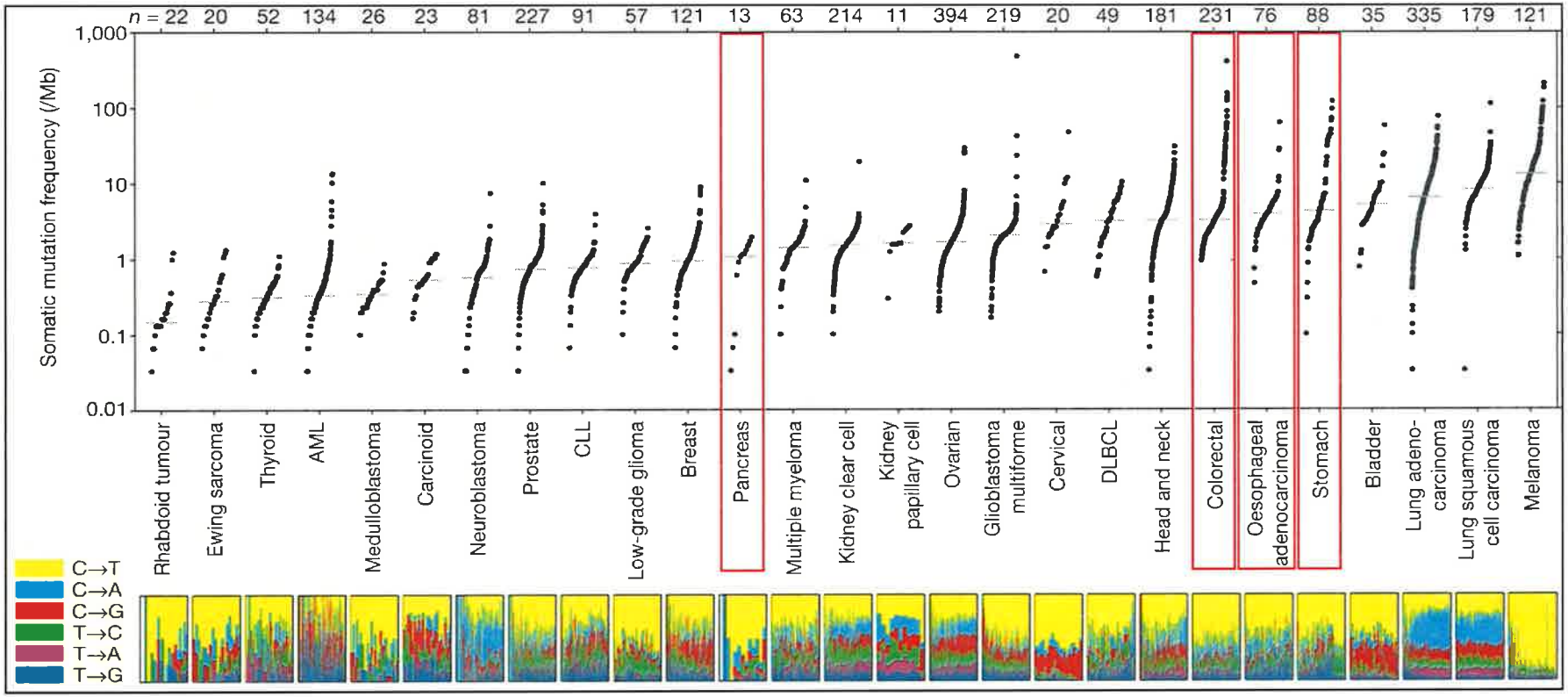
Preliminary Conclusion

Adoptive cell therapy mediates complete, durable, and likely curative, regressions of metastatic melanoma based on the recognition of unique immunogenic cancer mutations.

(These mutations are likely the targets of IL-2, anti-CTLA4 and anti-PD1 as well.)

Can we utilize this approach to treat common epithelial cancers by targeting the unique immunogenic mutations expressed by that cancer?

Somatic mutation frequencies observed in exomes from 3,083 tumour–normal pairs



MS Lawrence *et al. Nature* 1-5 (2013) doi:10.1038/nature12213

Patient M.B.

---

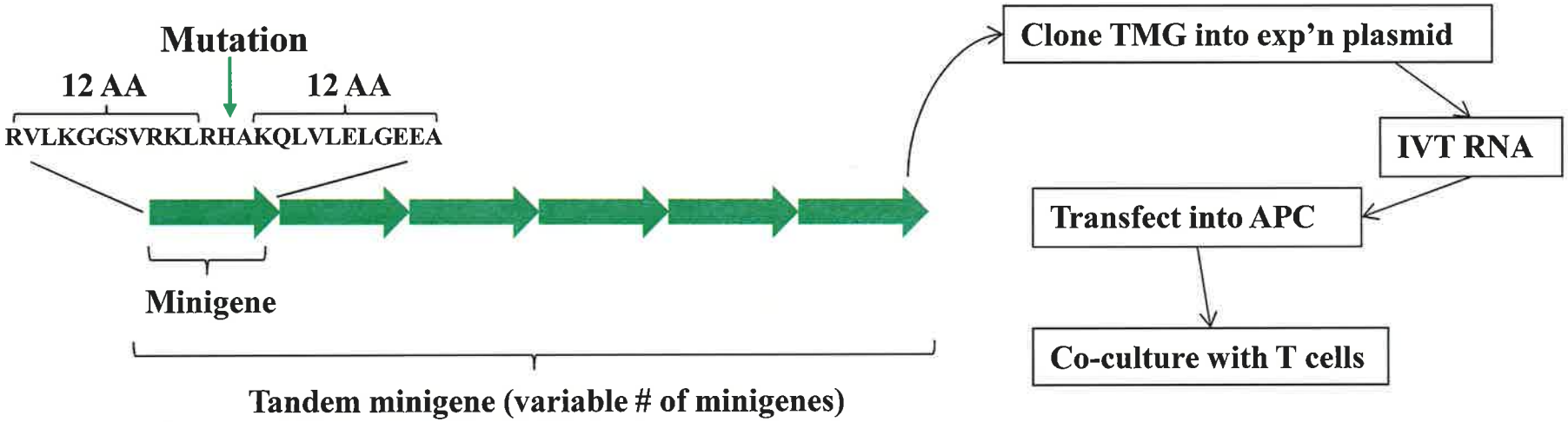
45 y.o. female with metastatic cholangiocarcinoma

12/2009	**Right hepatectomy for cholangiocarcinoma**
4/2010	**Multiple lung and liver metastases** **Received cisplatin and gemcitabine: PD**
5/2011	**Taxotere chemotherapy: PD**
3/2012	**Lung lesion resected for TIL; TIL infused; minimal response (not PR) then PD**
10/2013	**TMG approach to target unique cancer mutations**

Whole exome sequencing identifies 26 mutations in a lung metastasis

Gene Symbol	Mutation Position		Mutation Type	Consequence
	Nucleotide (genomic)	Amino Acid (protein)		
ALK	chr2_29996620-29996620_C_T	137R>H	Substitution	Nonsynonymous coding
AR	chrX_66858483-66858483__C	NA	Insertion	Frameshift
CD93	chr20_23012929-23012929_C_T	634R>Q	Substitution	Nonsynonymous coding
DIP2C	chr10_365545-365545_C_T	NA	Substitution	Splice site acceptor
ERBB2IP	chr5_65385316-65385316_A_G	805E>G	Substitution	Nonsynonymous coding
FCER1A	chr1_157544227-157544227_G_C	219D>H	Substitution	Nonsynonymous coding
GRXCR1	chr4_42590102-42590102_C_T	21A>V	Substitution	Nonsynonymous coding
HLA-DOA	chr6_33085209-33085209_C_T	NA	Substitution	Splice site donor
KIF9	chr3_47287859-47287859_T_C	155T>A	Substitution	Nonsynonymous coding
KLHL6	chr3_184692410-184692413_CAGA_	NA	Deletion	Frameshift
LHX9	chr1_196164923-196164923_A_	NA	Deletion	Frameshift
LONRF3	chrX_118007666-118007666_A_C	NA	Substitution	Splice site donor
NAGS	chr17_39440355-39440355_G_A	412R>H	Substitution	Nonsynonymous coding
NLRP2	chr19_60186650-60186650_G_T	591S>I	Substitution	Nonsynonymous coding
PDZD2	chr5_32124833-32124833_A_	NA	Deletion	Frameshift
POU5F2	chr5_93102847-93102847_A_C	60V>G	Substitution	Nonsynonymous coding
RAC3	chr17_77584690-77584690_C_A	125T>N	Substitution	Nonsynonymous coding
RAP1GDS1	chr4_99532209-99532209_C_A	198L>I	Substitution	Nonsynonymous coding
RASA1	chr5_86703757-86703757_C_T	589R>C	Substitution	Nonsynonymous coding
RETSAT	chr2_85424308-85424308_C_T	553R>K	Substitution	Nonsynonymous coding
SEC24D	chr4_119872085-119872085_A_G	901M>T	Substitution	Nonsynonymous coding
SENP3	chr17_7408824-7408824_A_G	292M>V	Substitution	Nonsynonymous coding
SLIT1	chr10_98753840-98753840_G_C	1280N>K	Substitution	Nonsynonymous coding
TARBP1	chr1_232649342-232649342_C_A	655G>V	Substitution	Nonsynonymous coding
TGM6	chr20_2332325-2332325_G_A	398D>N	Substitution	Nonsynonymous coding
TTC39C	chr18_19966475-19966475_A_C	503N>T	Substitution	Nonsynonymous coding

Tandem minigene (TMG):
String of minigenes encoding the mutated AA flanked by 12 AA

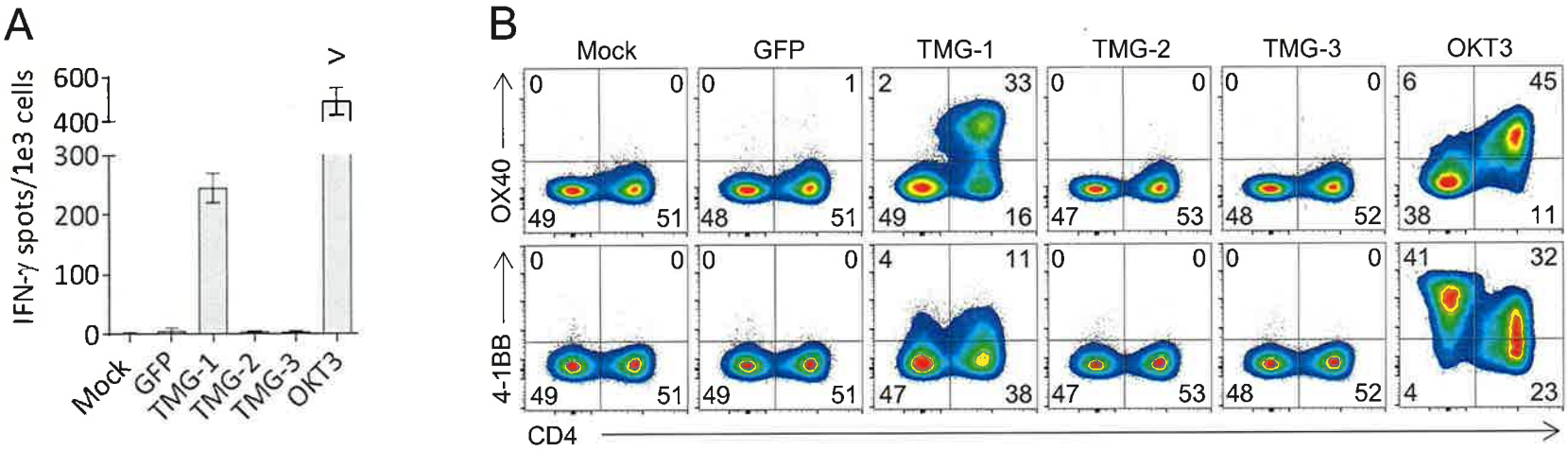


Three Tandem Mini-Genes (TMGs) generated

TMG-1	TMG-2	TMG-3
ALK	RAP1GDS1	SENP3
CD93	RASA1	LHX9
ERBB2IP	RETSAT	KLHL6
FCER1A	SEC24D	AR
GRXCR1	SLIT1	PDZD2
KIF9	TARBP1	HLA-DOA
NAGS	TGM6	LONRF3
NLRP2	TTC39C	
RAC3	POU5F2	

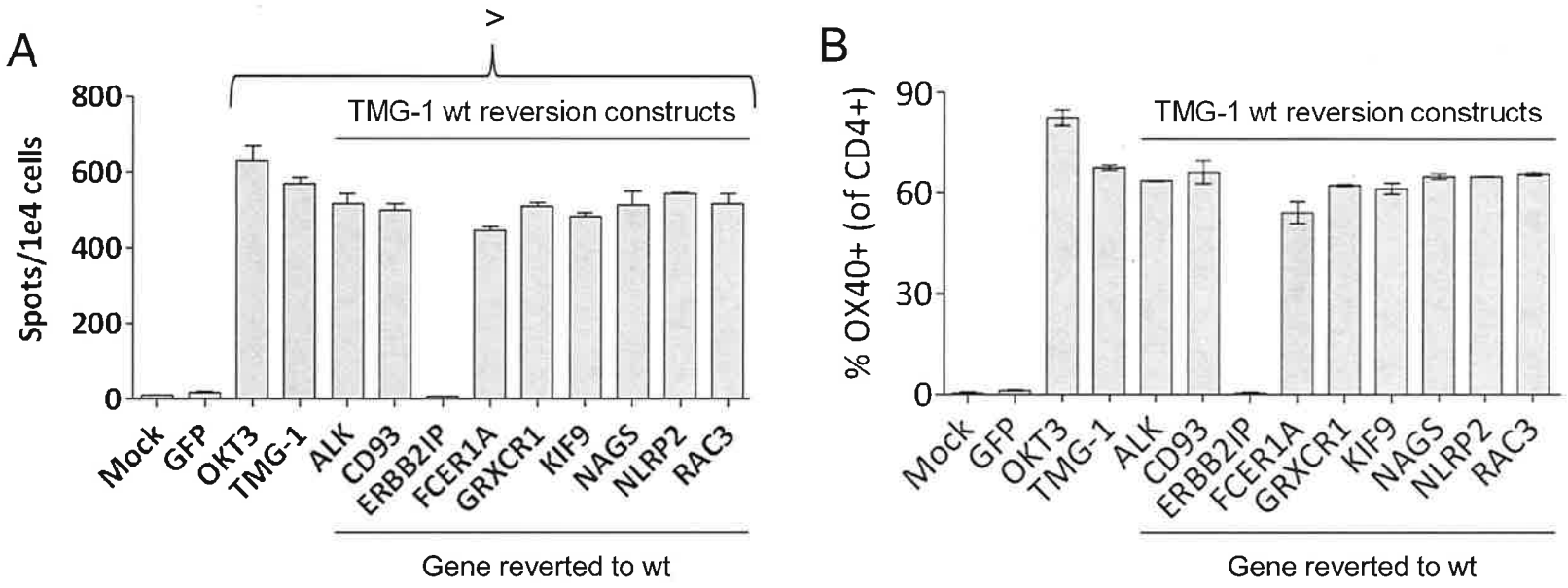
Only TMG-1 is recognized by CD4+ T cells in MB-3737 infusion bag

A) IFN-g ELISPOT assay; B) Flow cytometry



Only mutated ERBB2IP is recognized by CD4+ T cells in MB-3737 infusion bag

Co-culture exp't (transfected DCs + Infusion bagy;
A B) Flow cytometry



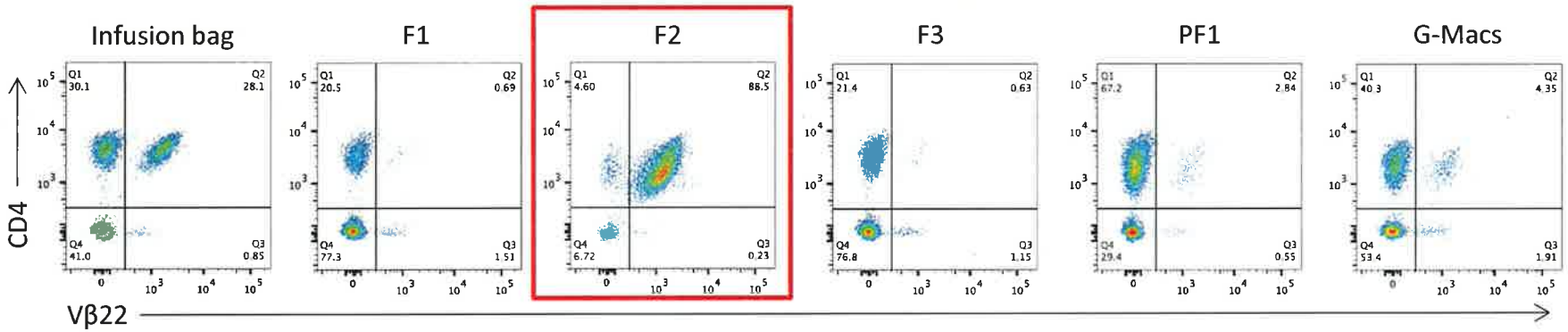
ERBB2IP

Tumor suppressor that binds to ERBB2

Attenuates downstream RAS/ERK signaling

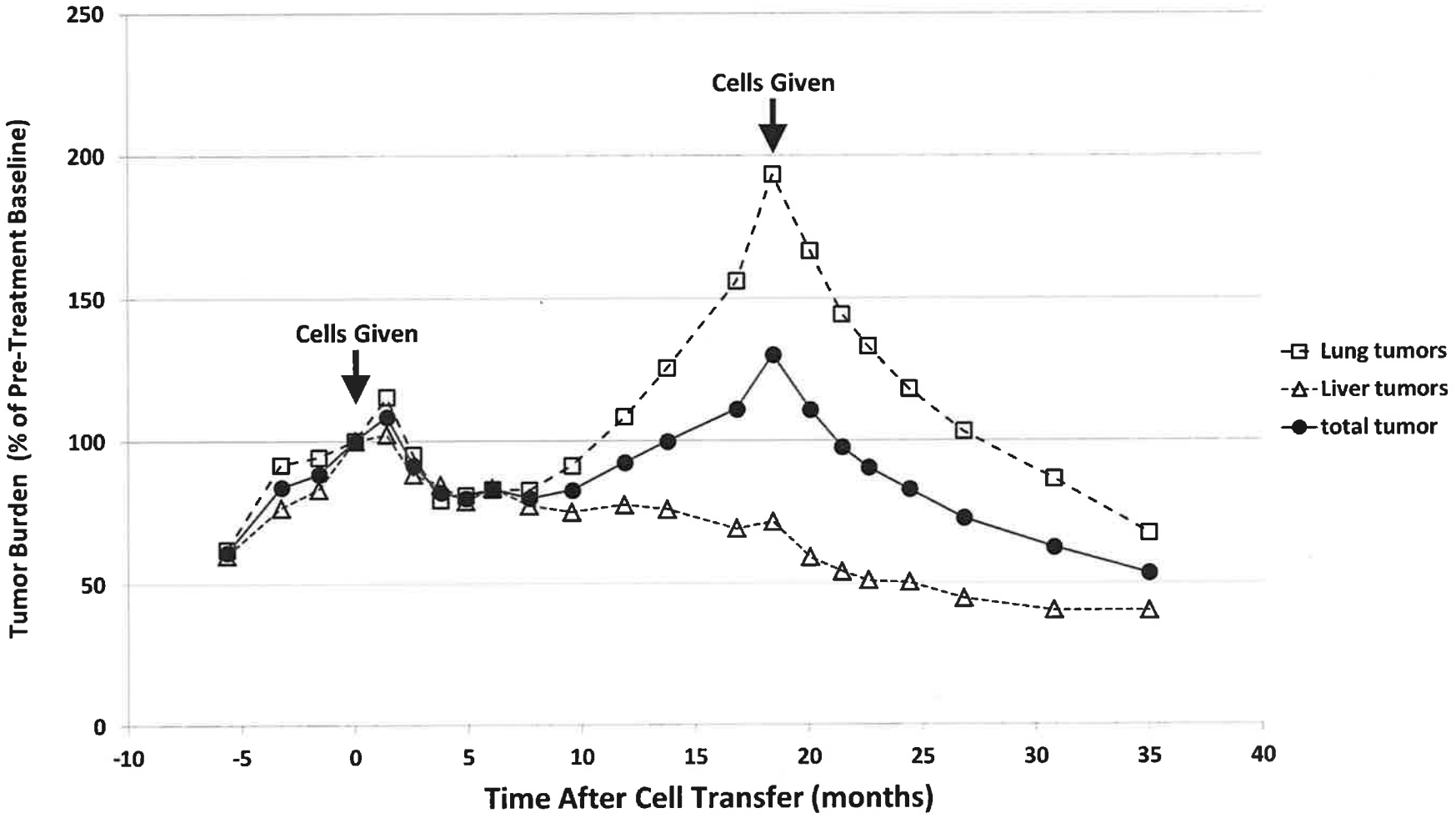
Likely is a “driver” mutation

Isolation of ERBB2IP reactive cells

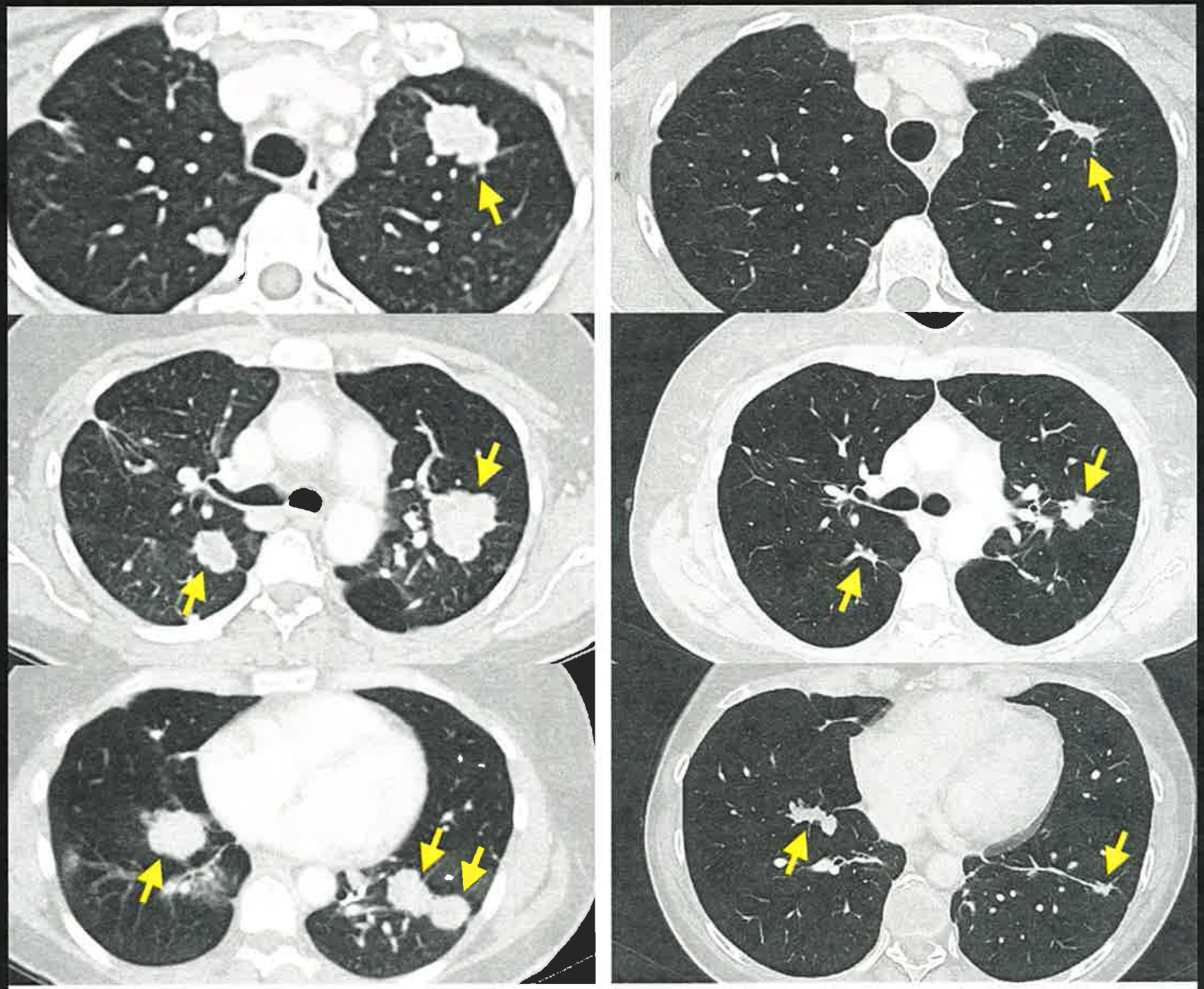


Use purified ERBB2IP autologous lymphocytes for treatment

Second Adoptive Therapy with Mutation-Specific Cells: 16 month FU



Tumor regression after ACT of ERBB2IP-mutation-reactive Th1 cells

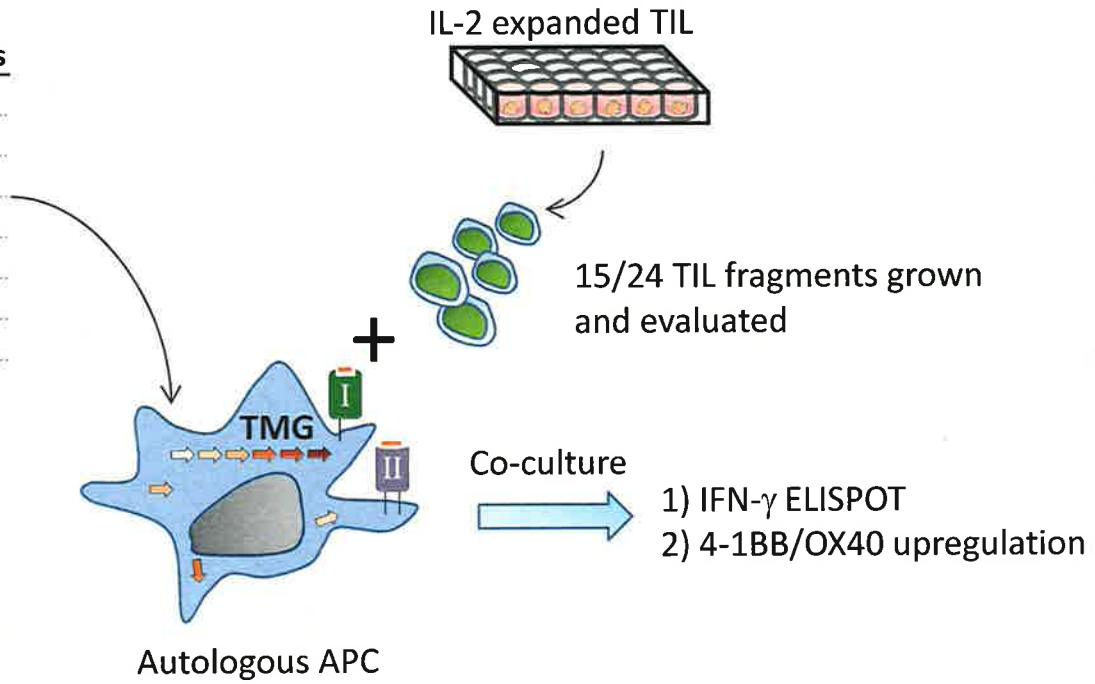


October 2013 Feb 2015

Patient BB (4069)

- 57-year old male with pancreatic cancer metastatic to the liver and lung
- Segment VII liver resection for TIL harvest
  - 15/24 TIL cultures grown and evaluated
- Whole-exome sequencing performed on FFPE primary tumor
  - 10 mutations called (PGDx, stringent), relaxed filters (in-house) 97 putative mutations evaluated
  - 7 TMGs constructed

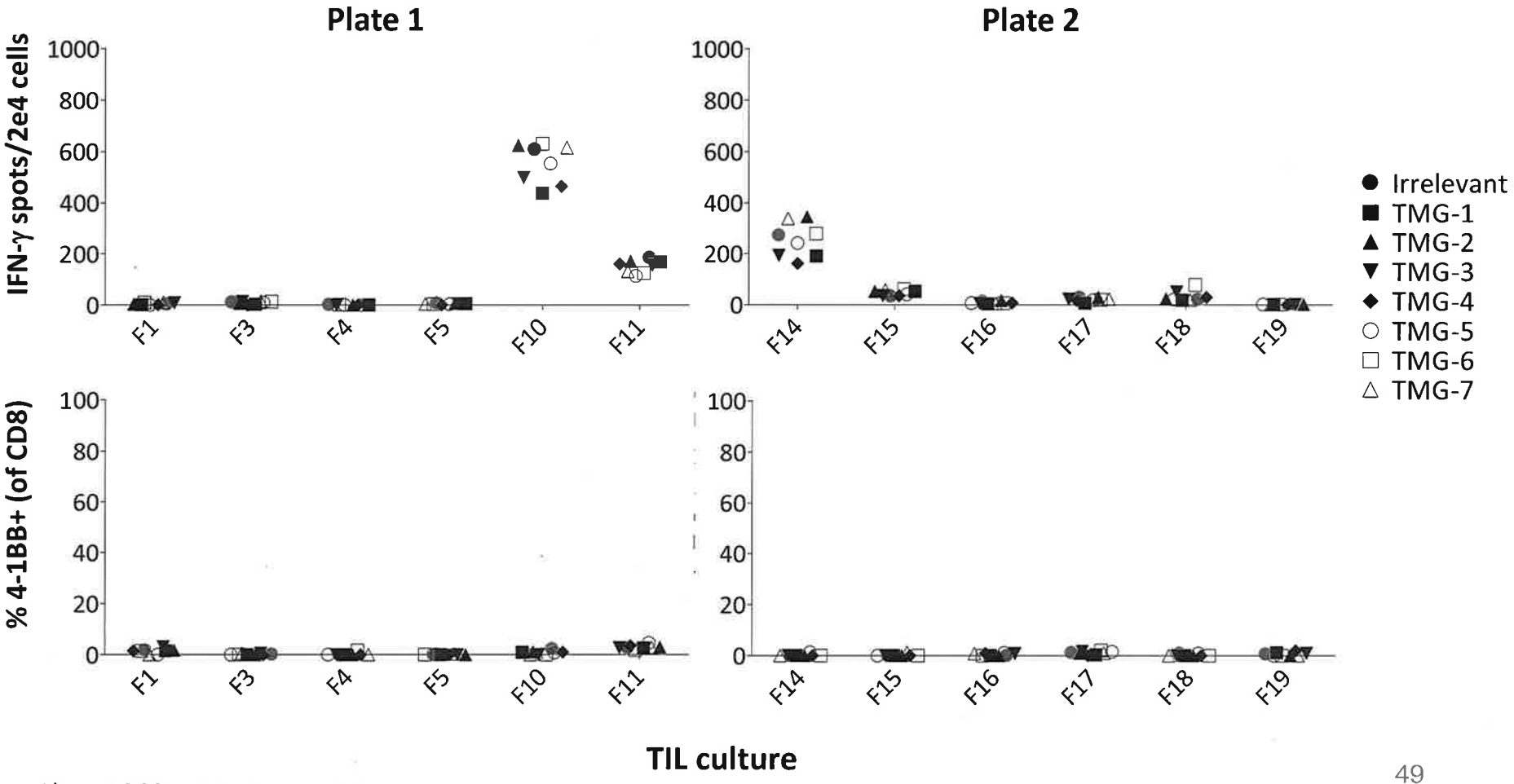
TMG	# minigenes
1	16
2	13
3	17
4	13
5	11
6	15
7	12



One out of fifteen TIL cultures display reactivity against TMG-1

Co-culture: TIL fragments with TMG RNA transfected DCs

IFN-γ ELISPOT (top); 4-1BB upregulation by flow cytometry (bottom)

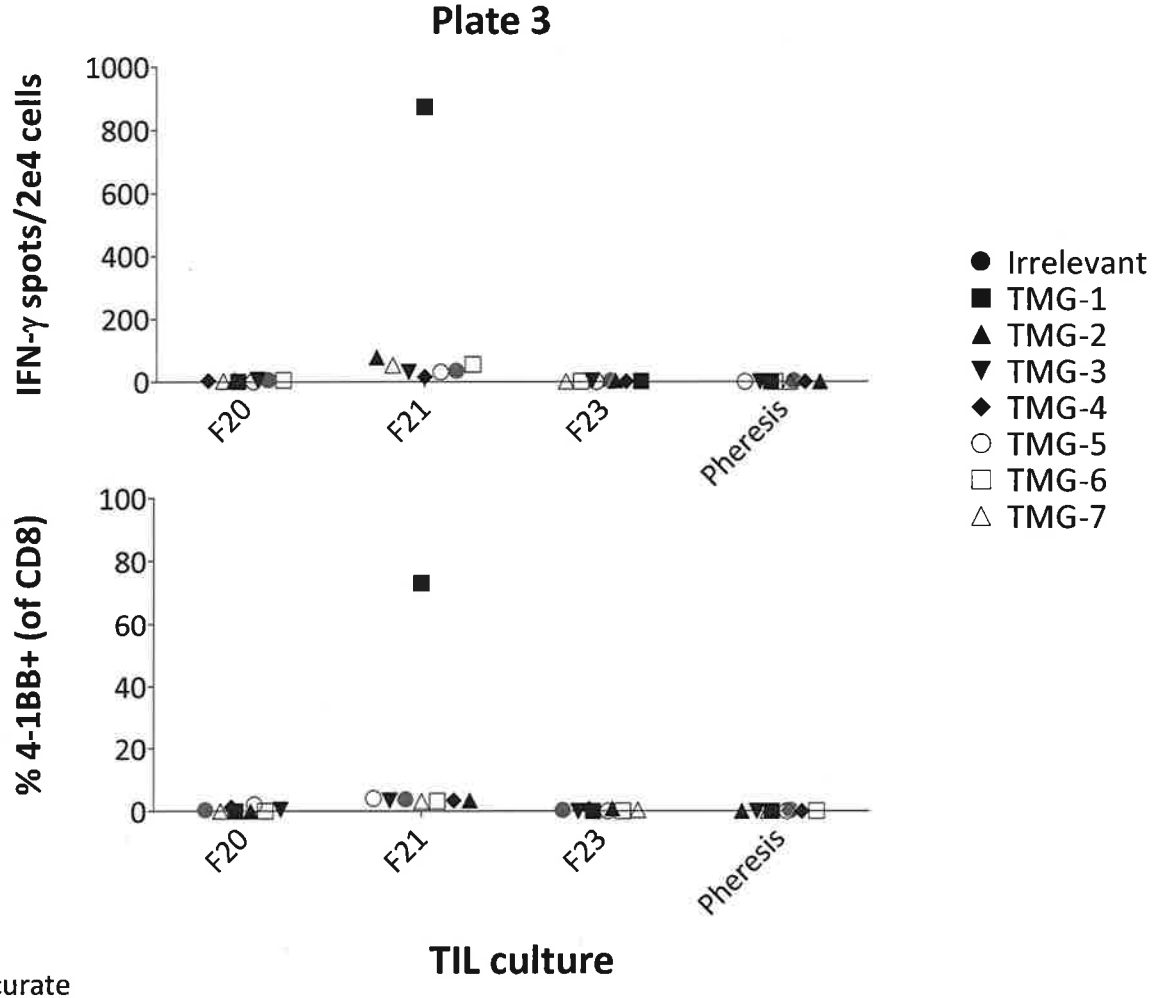


Above ~500 spots not accurate

One out of fifteen TIL cultures display reactivity against TMG-1

Co-culture: TIL fragments with TMG RNA transfected DCs

IFN-γ ELISPOT (top); 4-1BB upregulation by flow cytometry (bottom)



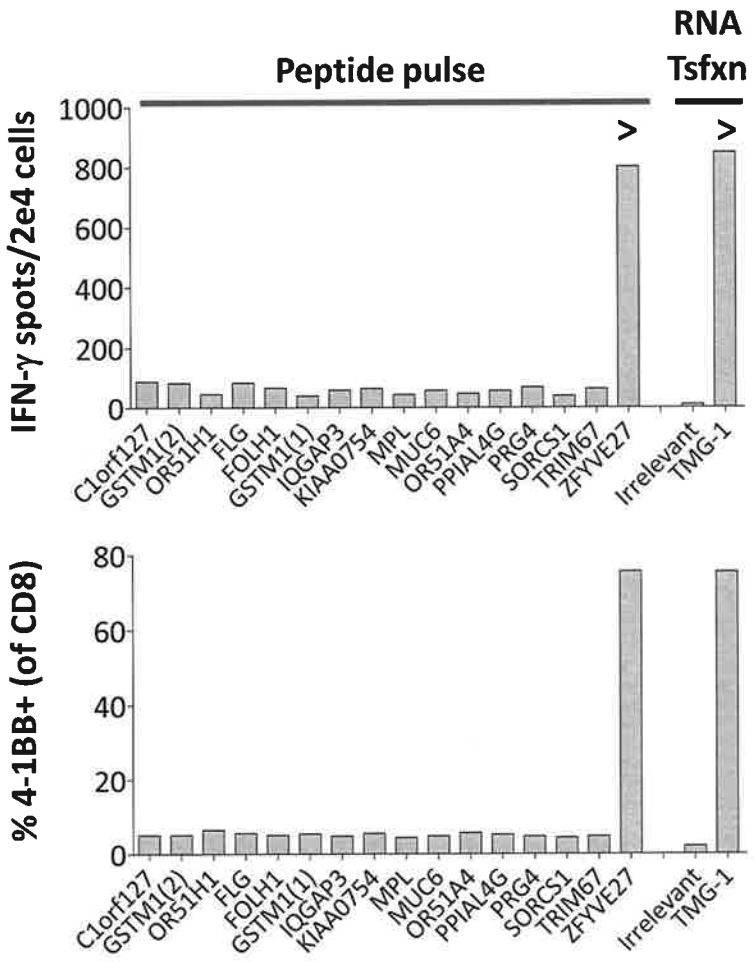
Above ~500 spots not accurate

F21 TIL recognize mutated ZFYVE27

Co-culture: F21 + DCs pulsed with long peptides or transfected with TMG RNA

TMG-1

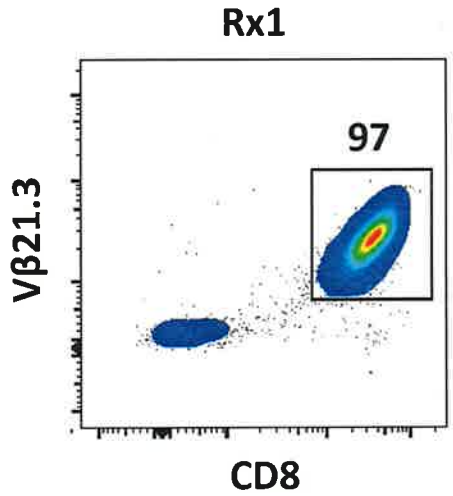
Mutated gene	Long peptide AA sequence
C1orf127	WTVESFFQCVGSETESPASTAALRT
GSTM1(2)	FPNVGRQKRRRFLWTFWRTRPRTTI
OR51H1	LSPVVHMVMADISLLLPPVLNPIVY
FLG	SERWSGSASRNHHGSAWEQSRDGSR
FOLH1	NYARTEDFFKLEWDMKINCSGKIVI
GSTM1(1)	HNLCGETEEEKILVDILENQTTDNH
IQGAP3	TAAQLLEKGVLVKIEDLPASHFRNV
KIAA0754	AVPTPEESASAAAAVPTPEESASPA
MPL	RPRQAGDWRWTRGSRRPVNRHSWFA
MUC6	QTRTTTEYTTPQPPHTTHSPPTAGS
OR51A4	IAVSYTLILKTVPGIASKKEQLKAL
PPIAL4G	MANAGPNTNGSQLFICTAKTEWLDG
PRG4	APTTPKEPTPTTTKEPAPTTKEPAP
SORCS1	ALLAGAGLLILCTPGVCGGGSCCPS
TRIM67	PSRGPFAKHRLVQPPPPPPPAEAAS
ZFYVE27	MQTSEHEGSGPELSPSVM



ZFYVE27: protein potentially involved in neurite formation

Adoptive transfer with a highly enriched population of ZFYVE27-mutation reactive T cells

- F21 selected for rapid expansion and treatment (Rx1)
- Rx1: ~97% CD8+Vβ21.3+ cells



- Infusion of ~9e10 total cells (~8.7e10 mutation-reactive) on March 6, 2015

Mutation-reactive TIL identified in 10 out of 12 patients with metastatic gastrointestinal cancers

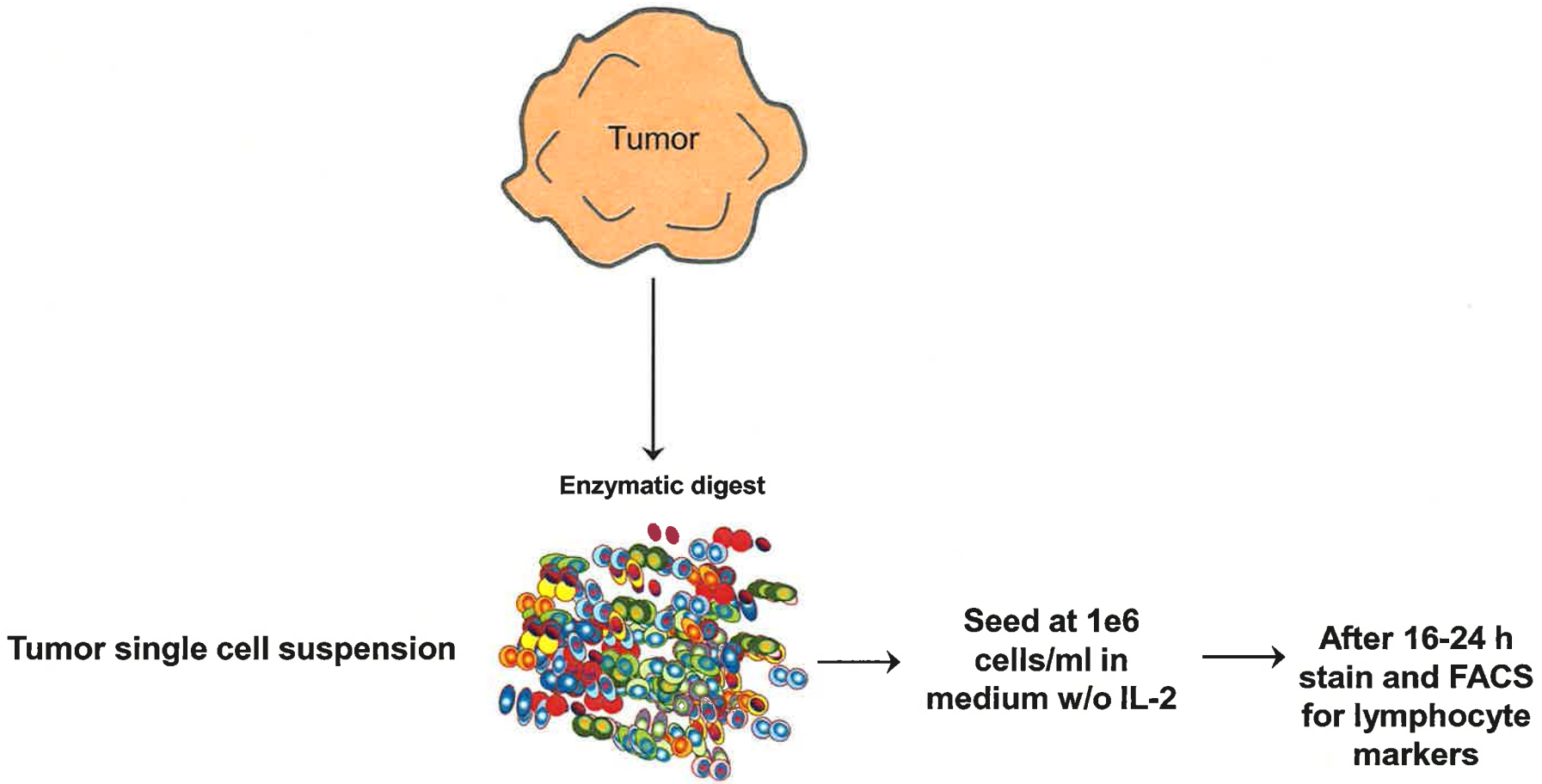
Patient	Cancer type	# of putative mutations assessed	Mutated gene recognized	T cell	Notes
3737	Cholangio	25	ERBB2IP	CD4	Multiple clonotypes; TCRs isolated
3812	Cholangio	179	-------	-------	High background in TIL
3942	Rectal	140	NUP98 KARS GPD2	CD8 CD8 CD4	TCRs isolated
3948	Esophageal	210	PLEC ASTN2	CD4 CD4	
3971	Colon	119	CASP8	CD8	TCR isolated
3978	Cholangio	37	ITGB4	CD4	Preferential reactivity against mut vs wt
3995	Colon	154	TUBGCP2 RNF213 KRAS	CD8 CD8 CD8	4th reactivity in progress; KRAS G12D reactive TCR isolated
4007	Colon	265	SKIV2L H3F3B KLHDC7A	CD8 CD8 CD4	Two clonotypes for SKIV2L; TCRs isolated
4032	Colon	222	API5 RNF10 PHLPP1	CD8 CD8 CD8	Two clonotypes for API5
4060	Colon	315	-------	-------	
4069	Pancreatic	97	ZFYVE27	CD8	
4071	Colon	285	In progress	CD8	At least 2 different reactivities

Detection of Immunogenic Mutations in Various Cancer Types

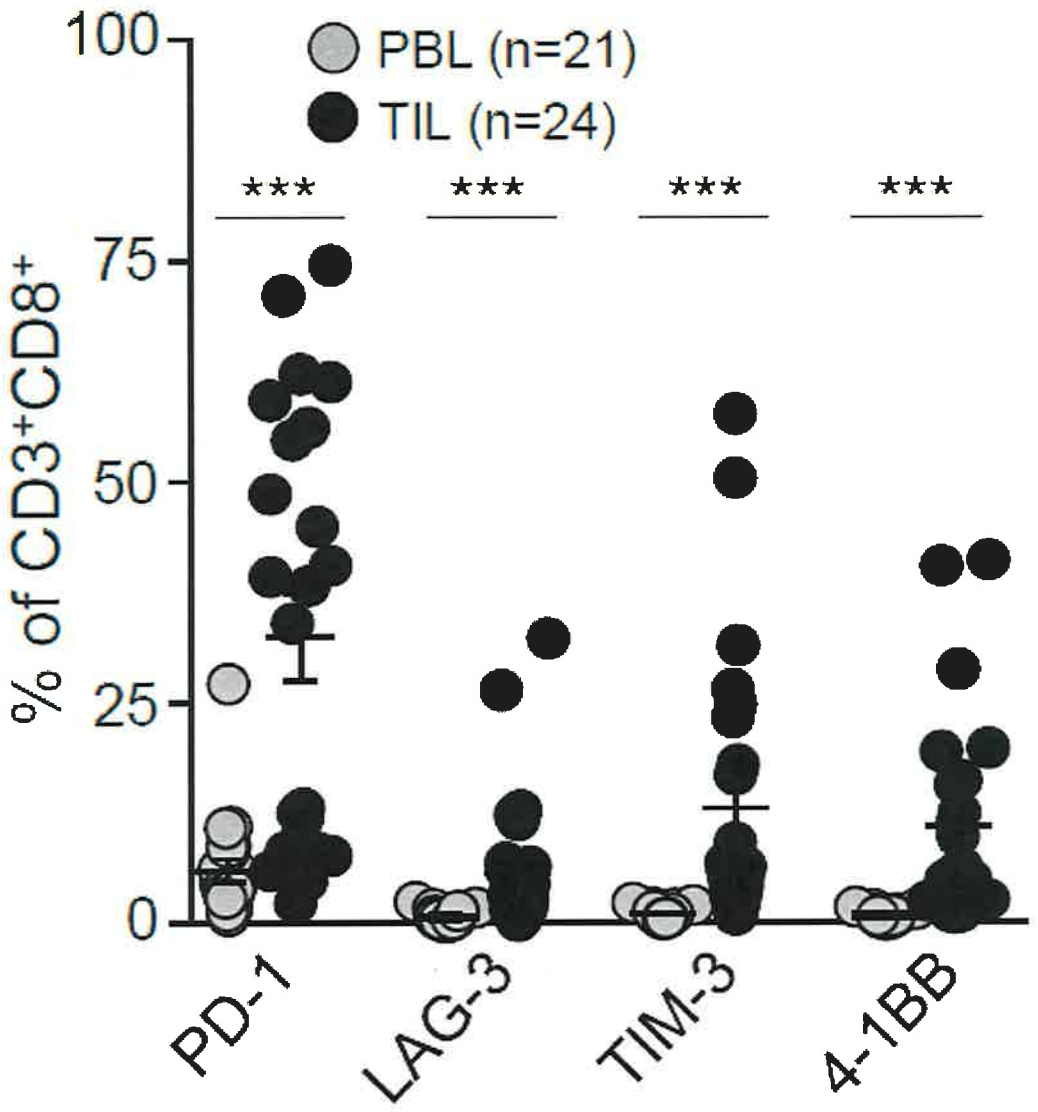
Cancer Type	# patients evaluated	# mutations analyzed	# immunogenic mutations
Ovarian	2	280	1
		122	0
Lung	2	313	4
		108	7
Cervical	1	222	3
Bladder	1	242	1
Breast	2	20	0
		72	2
Bile duct	3	26	1
		179	0
		37	1
Colorectal	7	140	3
		119	1
		154	4 (including Kras)
		265	3
		222	3
		315	0
		285	2
Esophageal	1	210	2
Pancreatic	1	97	1

(16 of 20 patients with metastatic epithelial cancers expressed immunogenic mutations – all unique)

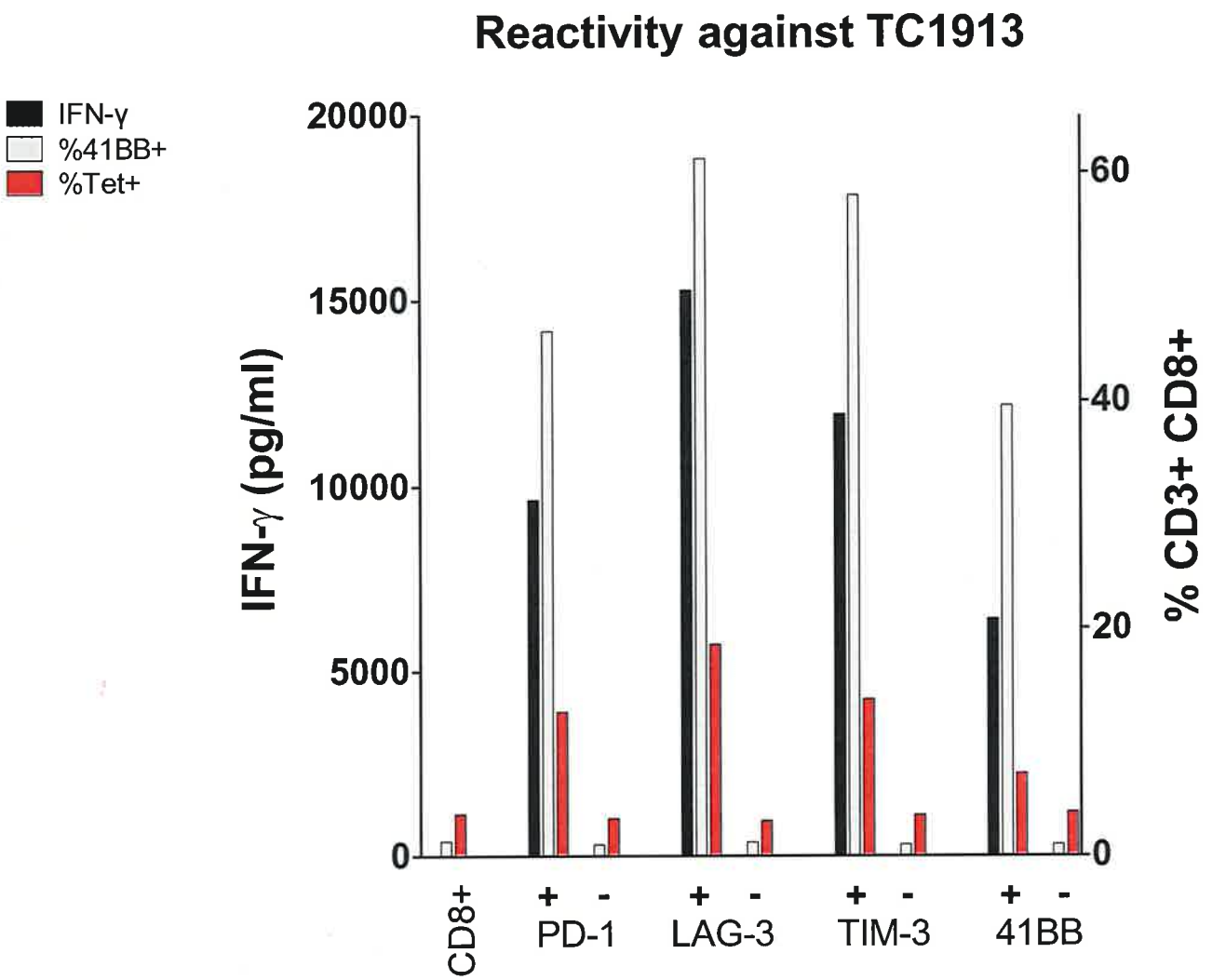
Can fresh TIL be enriched for mutation reactive T cells?



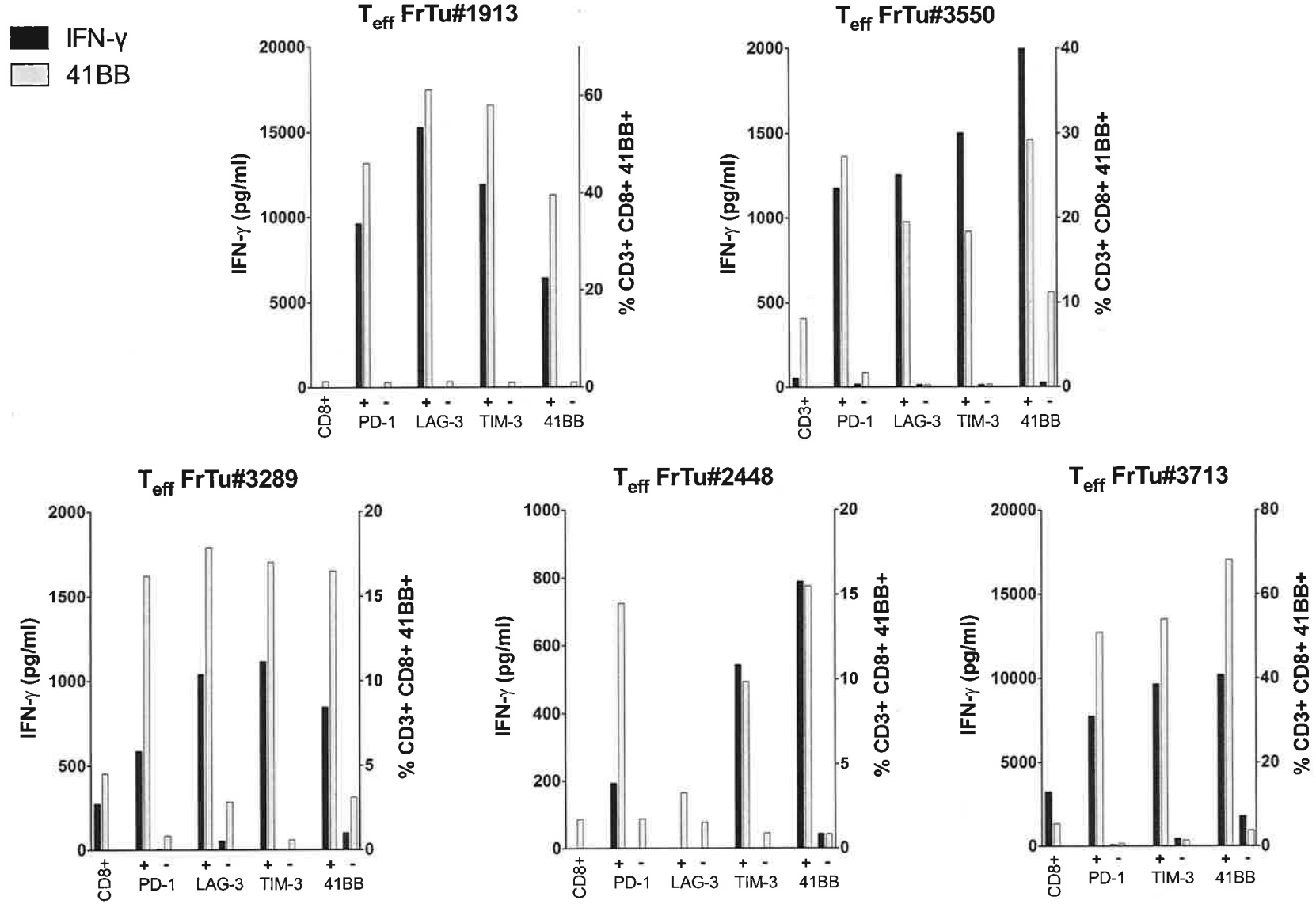
CD8+ melanoma TIL express variable levels of PD-1, LAG-3, TIM-3 and 4-1BB in the fresh tumor



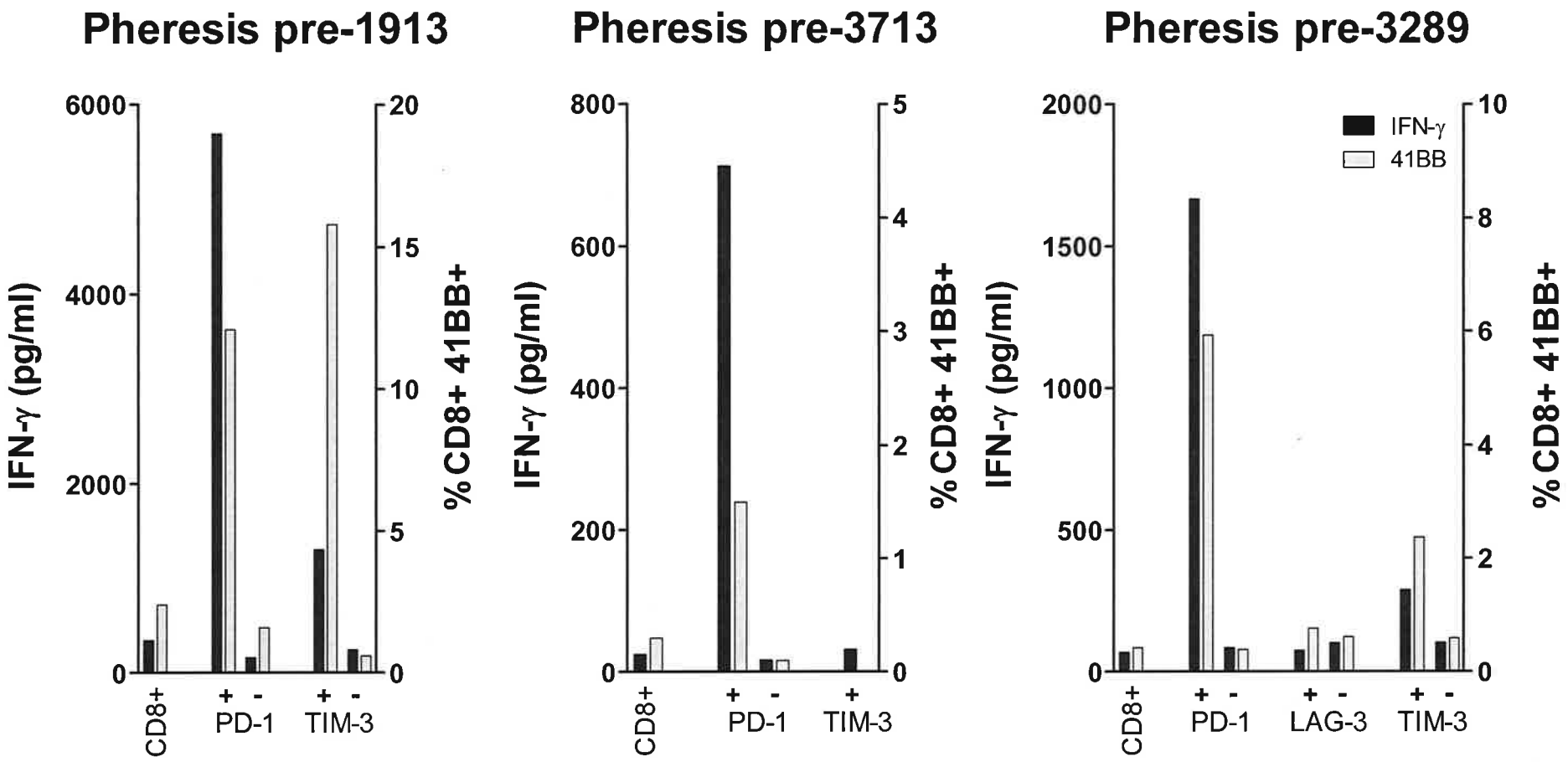
Lymphocytes reactive with autologous tumor are highly enriched in subsets expressing PD-1, LAG-3, TIM-3 and 41BB



Cells reactive with autologous tumor are enriched in subsets expressing PD-1, LAG-3, TIM-3 and 41BB



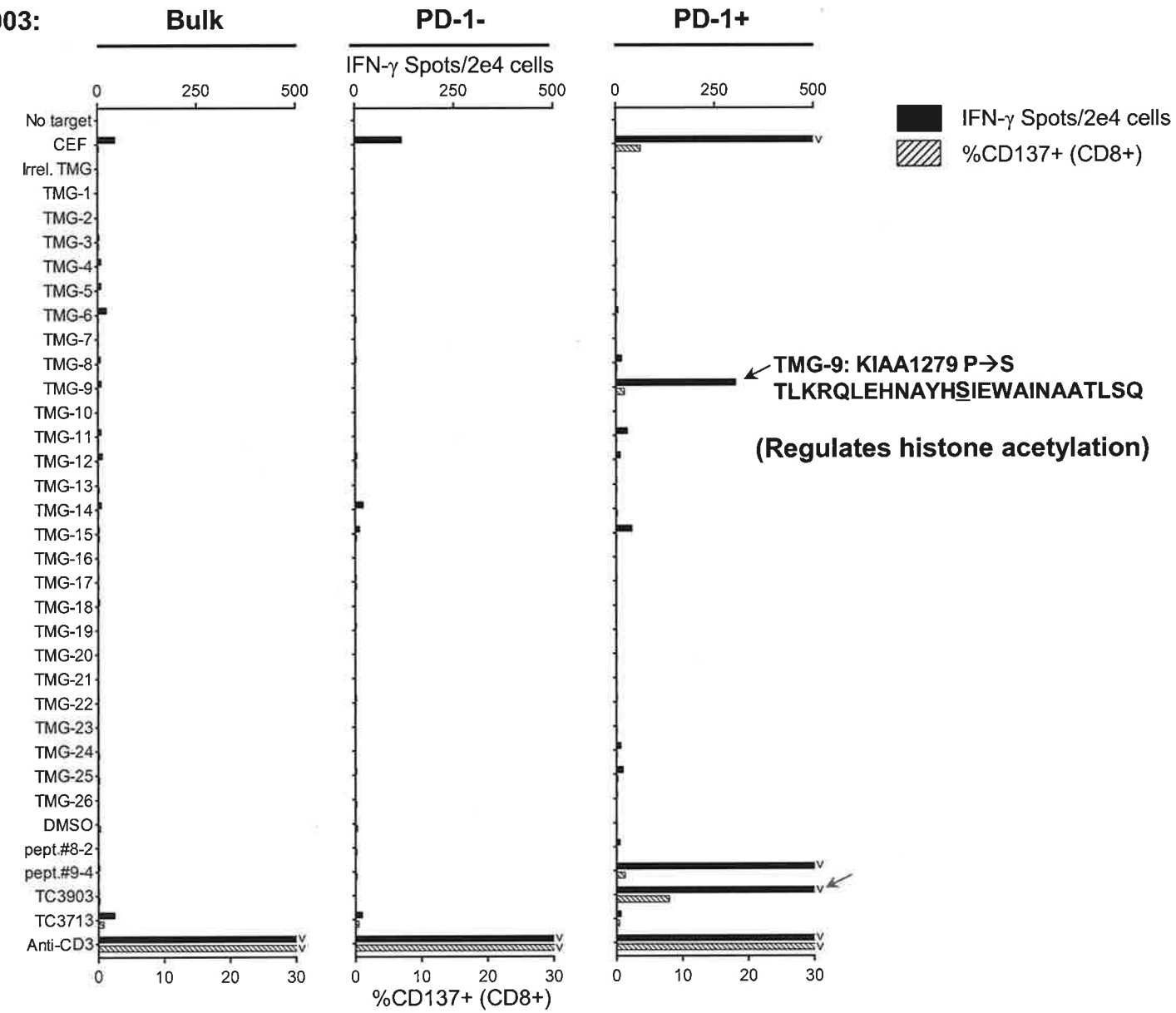
Enrichment of tumor-reactive cells from peripheral blood



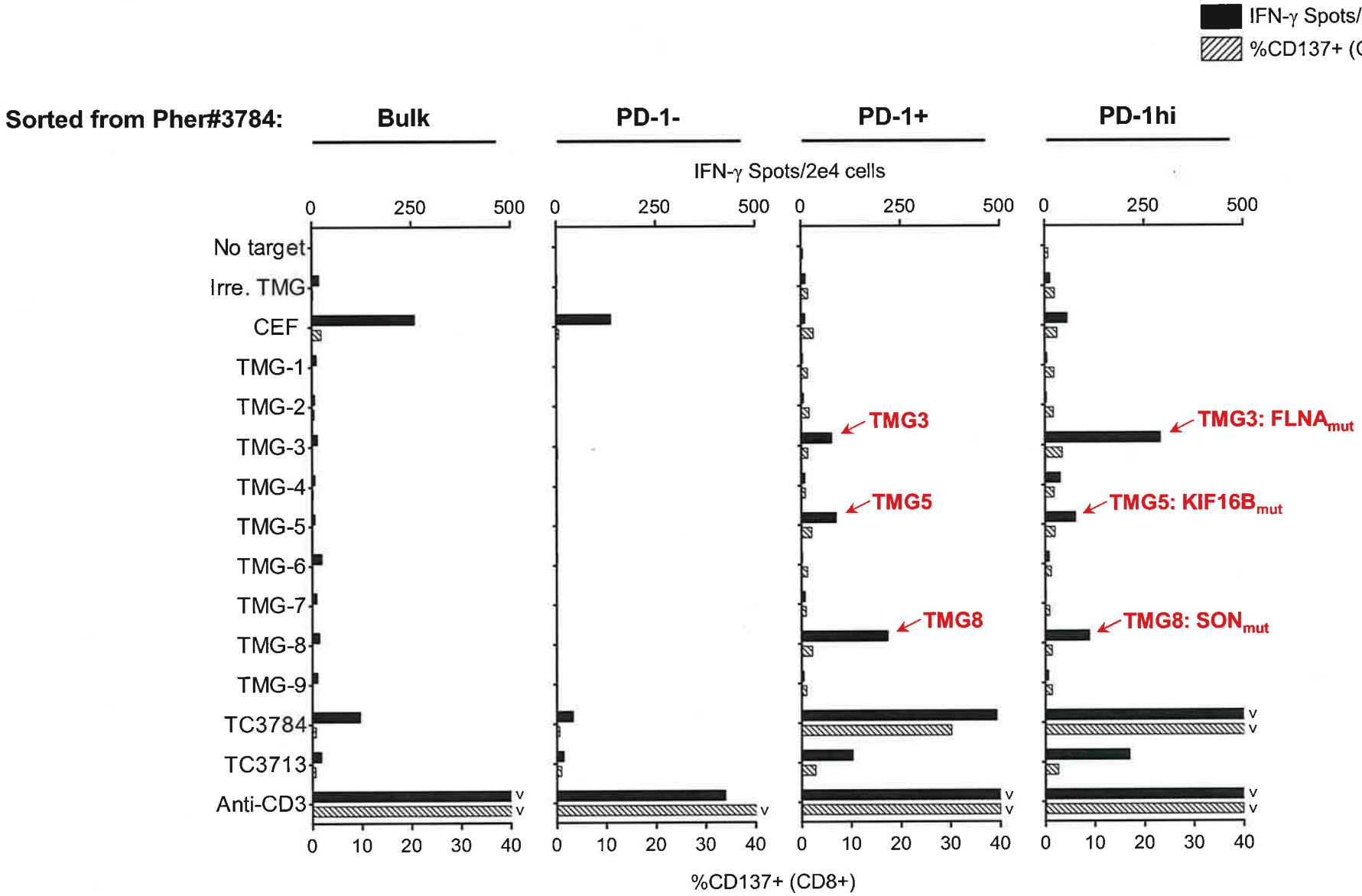
❖ Enrichment of tumor-reactive cells was possible from 3/3 pheresis samples pre-treatment by selecting PD-1+ cells

Selection of peripheral blood CD8+PD-1+ cells enriches for tumor-reactive and mutation-specific cells

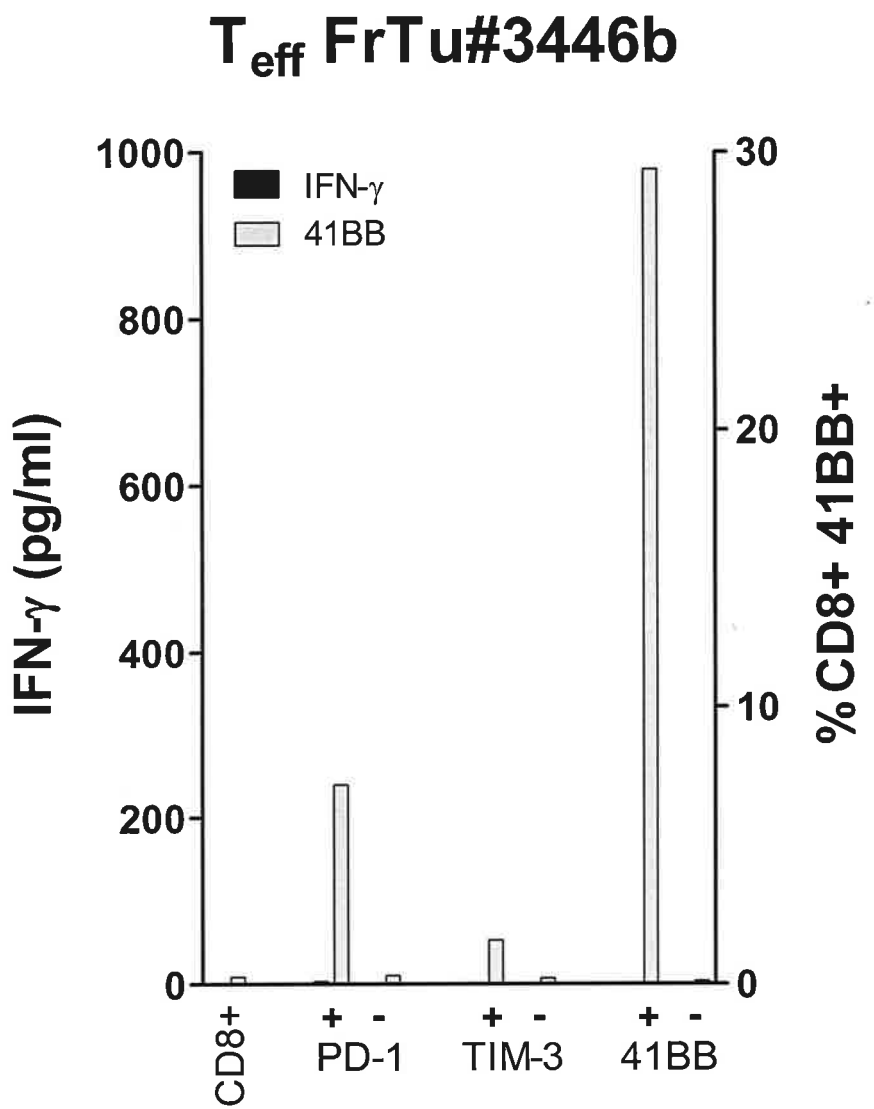
Sorted from Pheresis 3903:



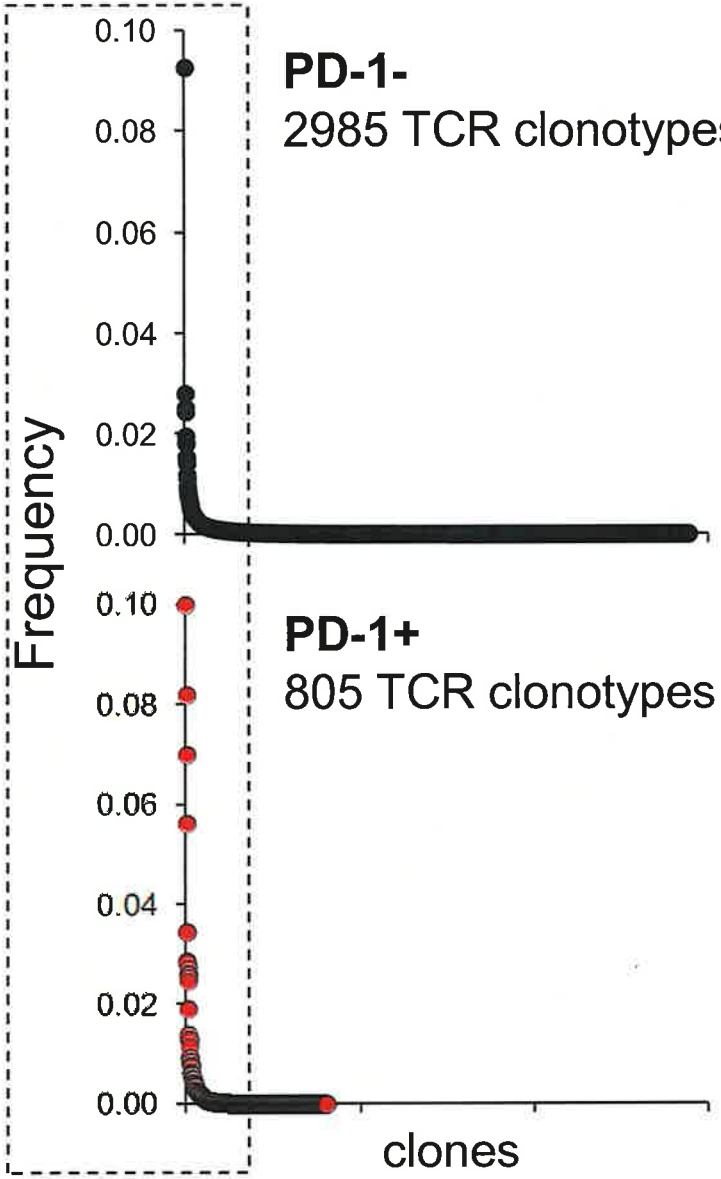
Mutations-specific cells are more prevalent in the circulating CD8+PD-1+ and PD-1hi subsets

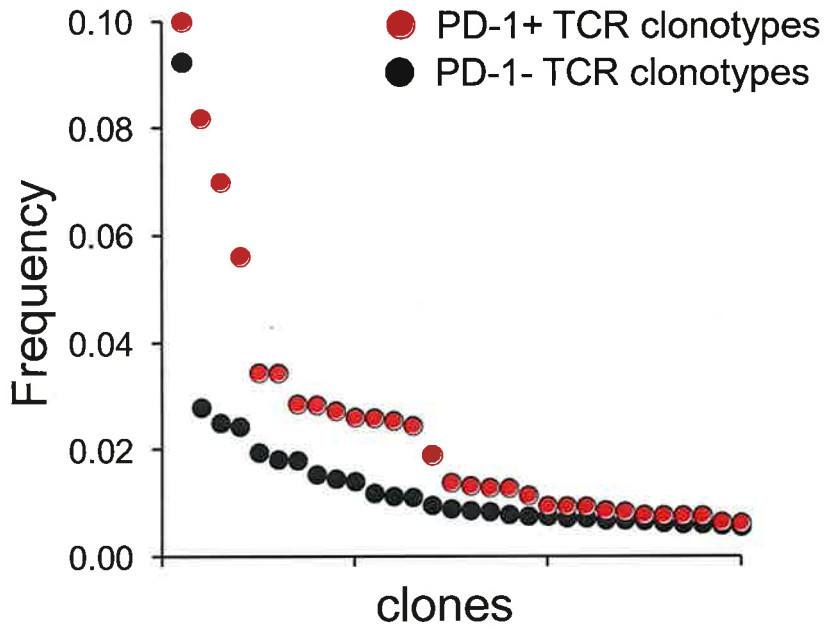


Selection of PD1+ or 41BB+ cells enriches for tumor-reactive cells from GI tract tumors

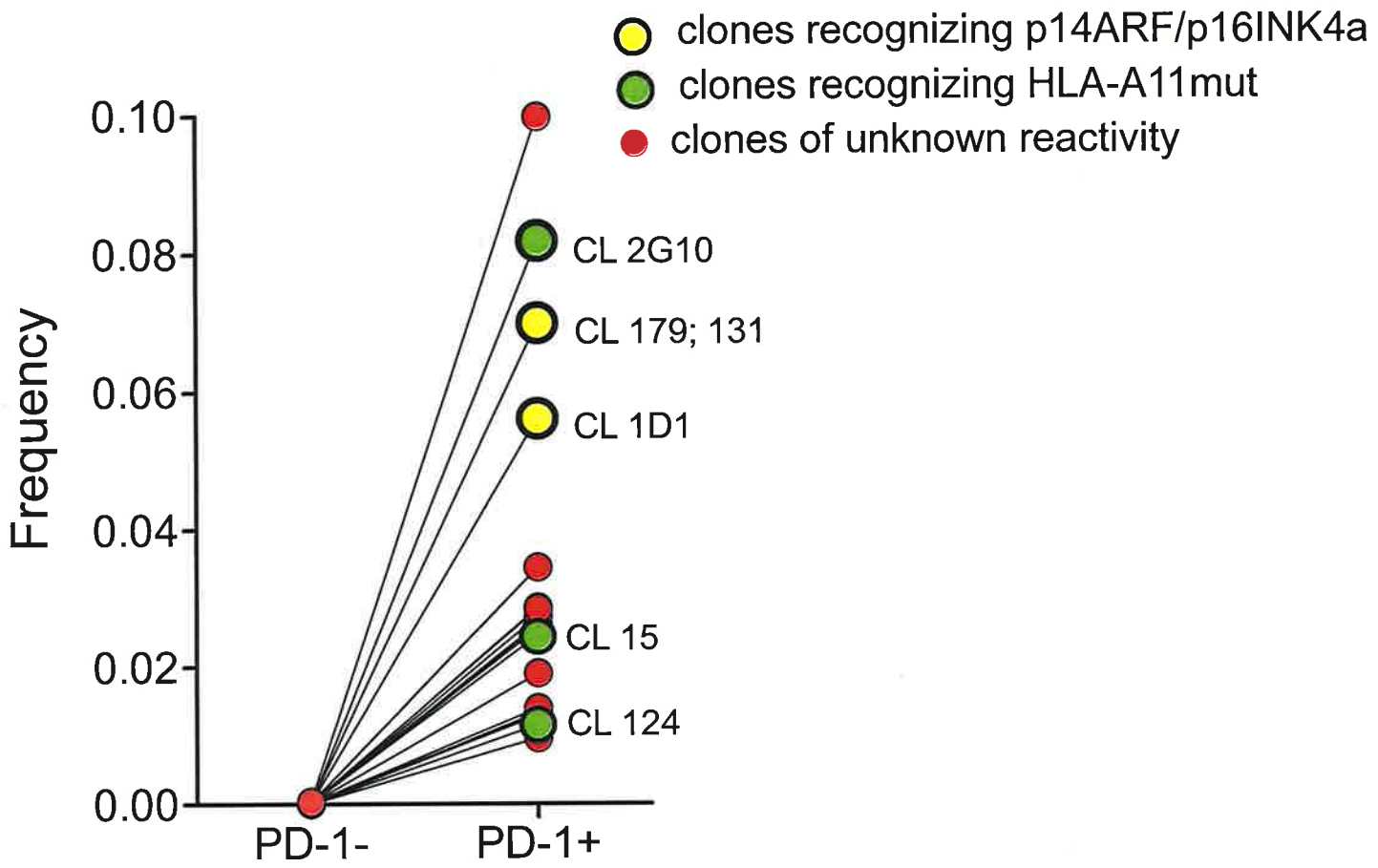


PD-1+ derived cells are more oligoclonal than PD-1- derived cells





Clones targeting mutated epitopes in the 20 most frequent clones in the expanded PD-1+ derived population (1913)



Ongoing development of a simplified approach to identify anti-tumor TCRs for cancer gene therapy

---

Is the tumor reactivity of PD1+ enriched lymphocytes in the fresh tumor related to the frequency of individual TCRs in PD1+ cells?

Approach:

Perform deep sequencing of the beta chain of all TCRs in isolated PD1+ cells.

Match the beta chain with its corresponding alpha chain.

Transduce the TCR chains into the patient's normal lymphocytes and test for tumor reactivity.

Anti-Cancer Activity of T-cell Receptors is Related to their Rank Frequency in PD1^{+} Cells in the Resected Metastatic Cancer

Patient	Rank frequency of TCRs that recognize cancer (of top 10 most frequent TCRs)*
1913	2, 4
3713	2, 3, 4, 5, 6, 8, 10
3759	1, 2, 6
3922	1
3926	3, 5, 7
3977	1, 6
3998	4, 6, 7, 8

*not all of the top 10 TCRs tested because of ongoing work to match the α & β chains

CONJECTURE

The identification and selective targeting of mutated antigens unique to each patient's cancer may be a means to apply cell transfer immunotherapy to common epithelial cancers.

(ultimate "personalized therapy")

A lesson learned the hard way concerning immunotherapy targets

---

T cells can recognize as few as 5 molecules on the cell surface

Thus even minimal expression of the target on normal cells can lead to serious toxicity.

anti-CEA:	acute colitis
melanocyte antigens:	uveitis and hearing loss
Her2:	lung toxicity

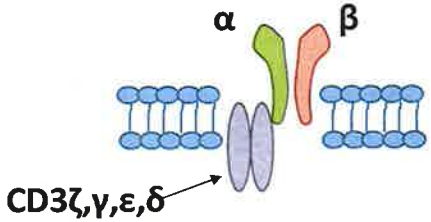
Categories of antigens to target using cell therapy

1. Mutations unique to each individual cancer
2. Antigens expressed on cancers and on non-essential normal tissues (CD19, thyroglobulin)
3. Shared antigens unique to cancer (cancer-testes antigens)

Construction of T-cell Receptors (TCR) and Chimeric Antigen Receptors (CAR)

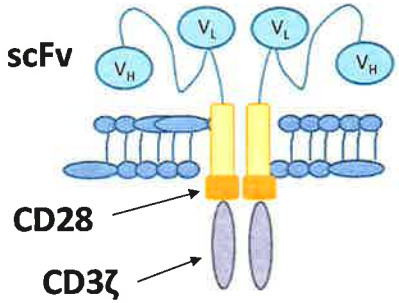
TCR Vector (eg, mutations, NY-ESO-1)

TCR receptor



CAR Vector (eg, CD19)

CAR receptor



T cells can be genetically engineered to express an anti-CD19 chimeric antigen receptor

DNA encoding an anti-CD19 CAR was ligated into the MSGV gammaretroviral backbone and used to transduce lymphocytes from patients with B cell lymphomas.

Anti-CD19 CAR

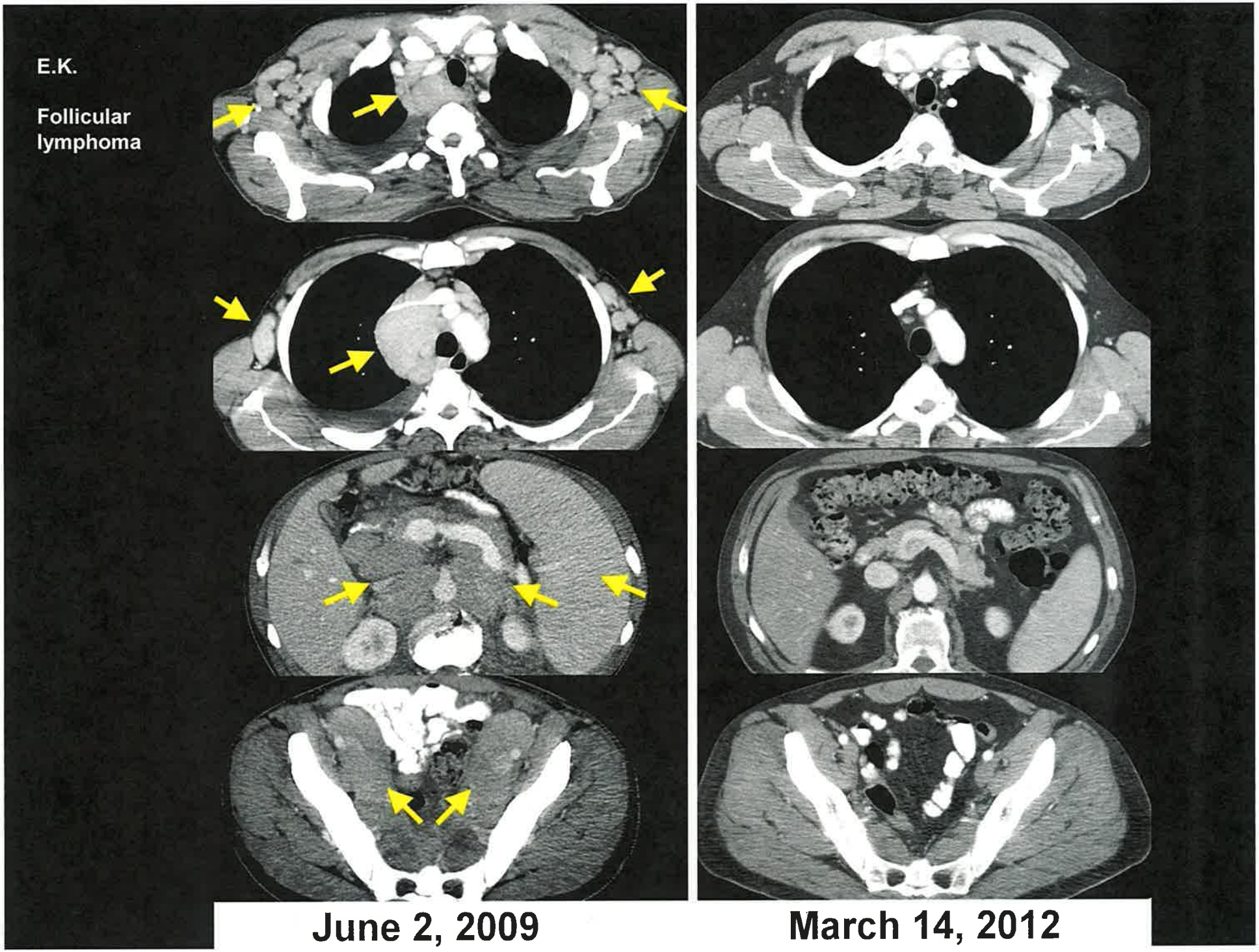
Patient E.K.

48 year old male with follicular non-Hodgkin lymphoma

Aug. 2002	diagnosed with stage IV lymphoma 7 cycles PACE chemotherapy (cisplatin, doxorubicin, cyclophosphamide, etoposide)
April 2004	idiotypic/KLH vaccine (5 doses)
Sept. 2007	ipilimumab
Nov. 2007	6 cycles EPOCH-R chemotherapy (etoposide, predisone, vincristine, cyclophosphamine, rituximab)
May 2009	To NCI for treatment with autologous anti-CD19 CAR transduced T cells

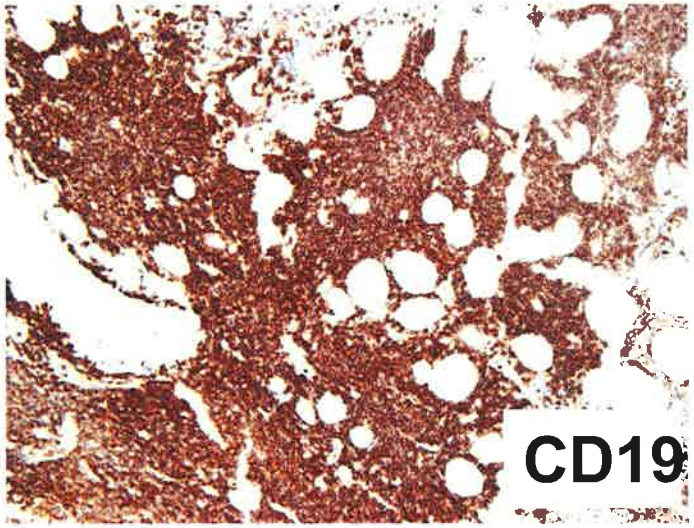
In ongoing progression-free regression as of February, 2014 (57+ months).

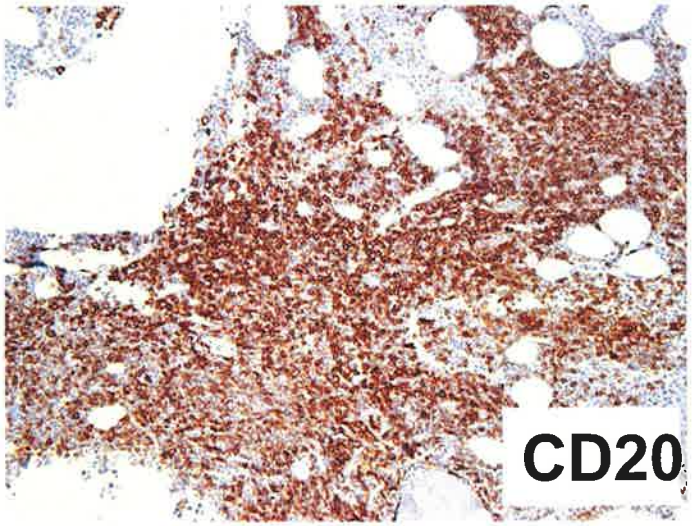
(Blood 116:3875-86, 2010; 119:2709-20, 2012)


E.K.
Follicular lymphoma
June 2, 2009
March 14, 2012

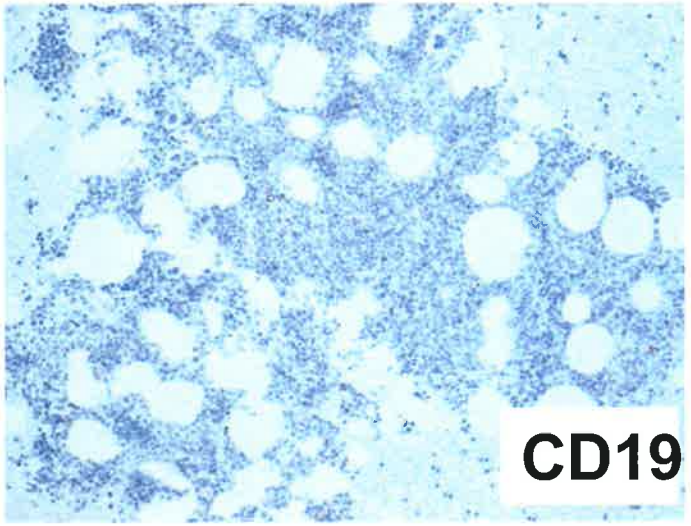
Bone marrow biopsies showed extensive CLL before treatment and nearly absent B-lineage cells after treatment

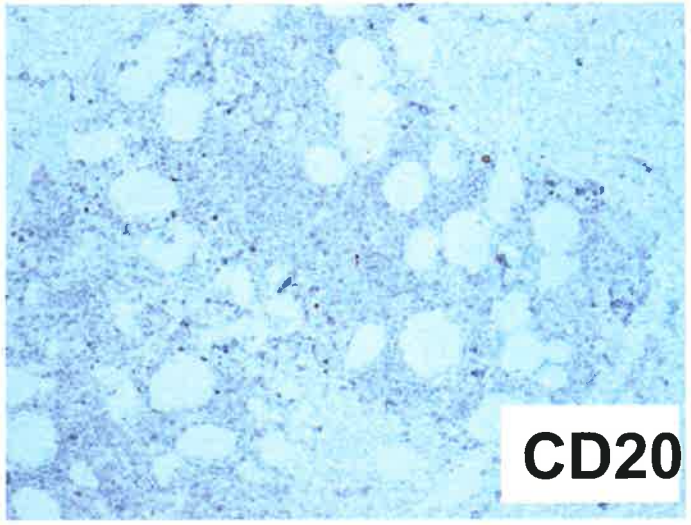
Before treatment



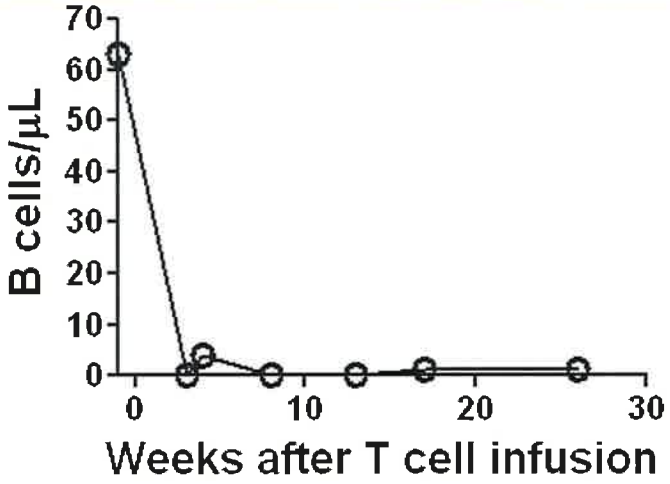


3 months after treatment

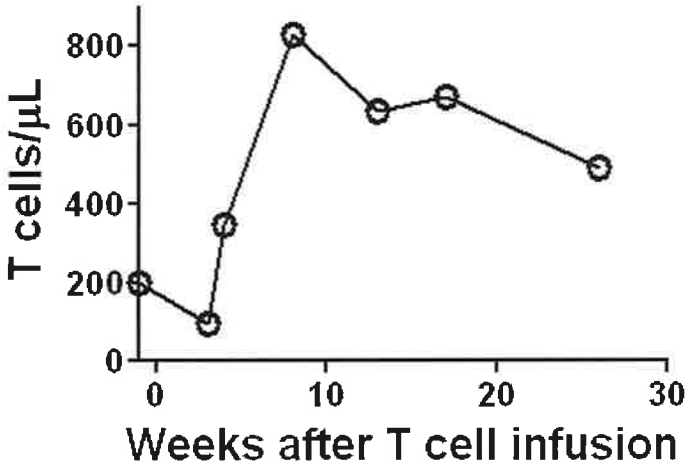


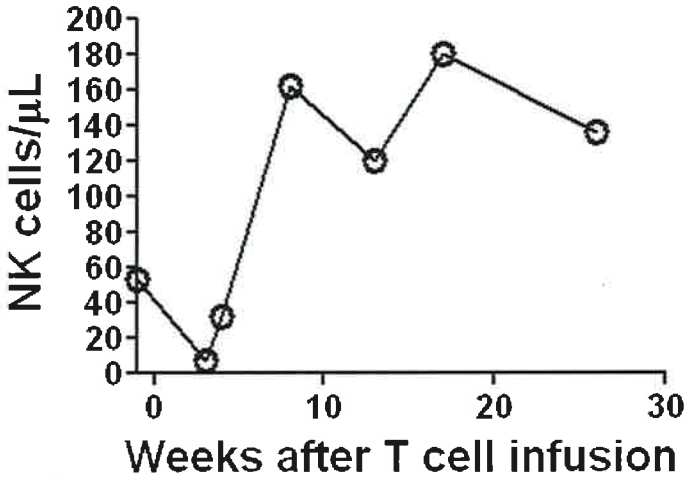


In Patient 8, normal blood B cells were eliminated after CAR-transduced T cell infusion



In contrast, T and NK cell counts rapidly recovered after treatment





Five of six patients with indolent B-cell malignancies have ongoing CRs

Patient	Malignancy type	Number of prior therapies	Infused CAR+ T cells/kg	Response (duration in months)
1	SMZL	4	$5x10^6$	CR (35+)
2	CLL	2	$4x10^6$	CR (28+)
3	CLL	4	$2.5x10^6$	CR (23+)
4	CLL	1	$2.5x10^6$	CR (18+)
5	Low-grade lymphoma	4	$1x10^6$	CR (17+)
6	CLL	4	$1x10^6$	PR (4)

SMZL=Splenic Marginal Zone Lymphoma
CLL=Chronic lymphocytic leukemia

(F/U 11/15/14)

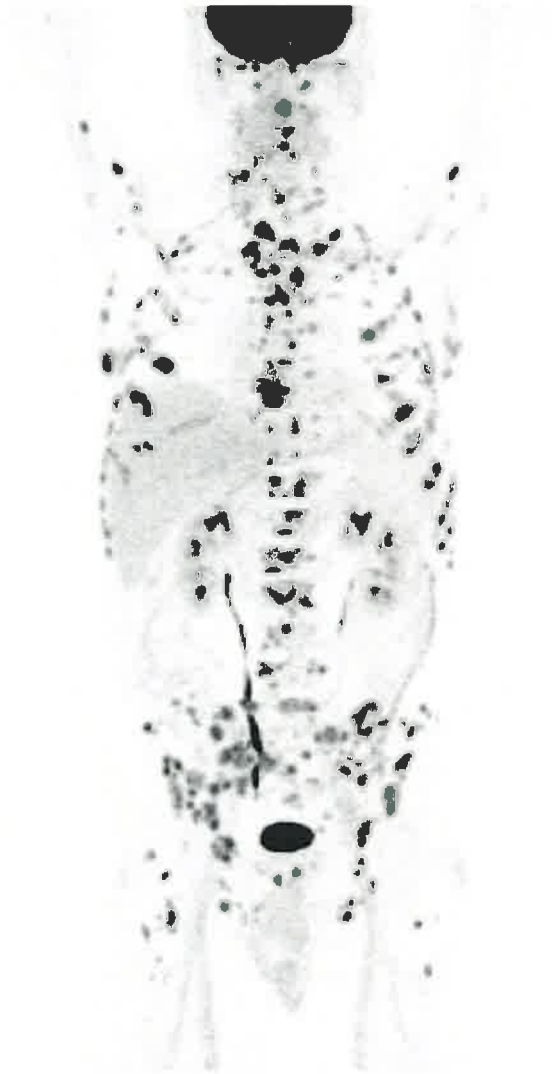
Five of nine large-cell lymphoma patients obtained CRs

Patient	Lymphoma type	Number of prior therapies	Infused CAR+ T cells/kg	Response (duration in months)
1	PMBCL	4	$5x10^6$	CR (30+)
2	PMBCL	3	$2.5x10^6$	NE, death
3	DLBCL, NOS	5	$2.5x10^6$	CR (16+)
4	PMBCL	10	$2.5x10^6$	CR (21+)
5	PMBCL	3	$2.5x10^6$	SD (1)
6	DLBCL, transformed from CLL	13	$1x10^6$	PR (1)
7	DLBCL, NOS	3	$1x10^6$	NE
8	DLBCL, NOS	2	$1x10^6$	CR (6)
9	DLBCL, NOS	3	$1x10^6$	CR (14+)

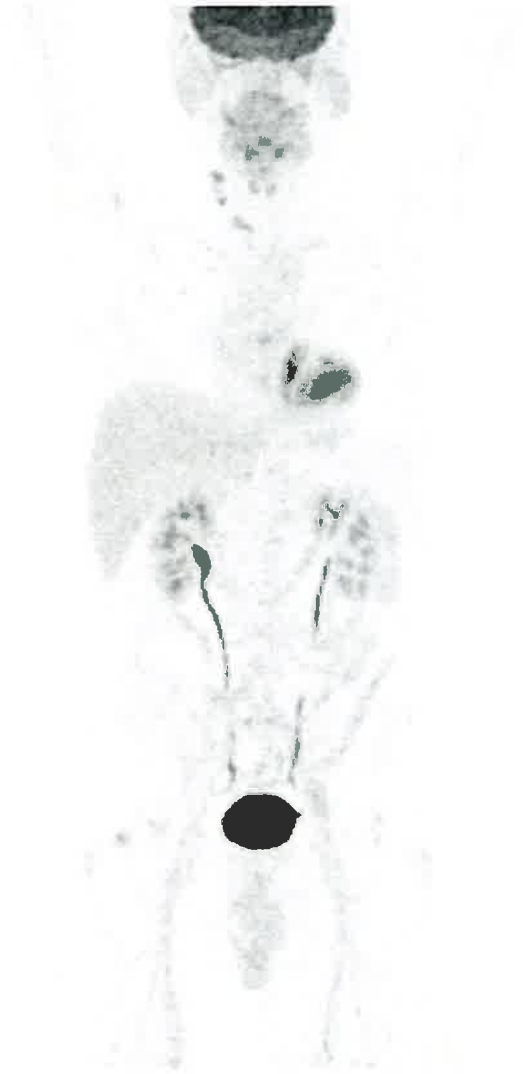
All but Patient 9 refractory to their last chemotherapy regimen prior to enrollment. Patient 9 had relapsed after auto stem cell transplant.
F/U 11/15/14

Patient with DLBCL after anti-CD19 T-cell infusion

Before treatment

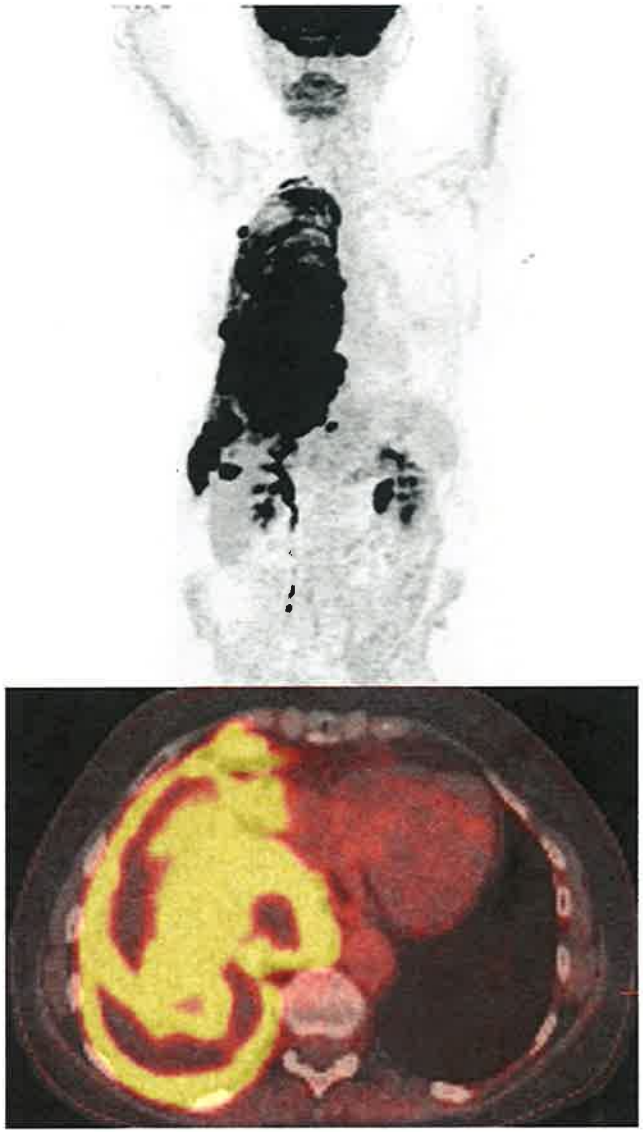


24 weeks after treatment

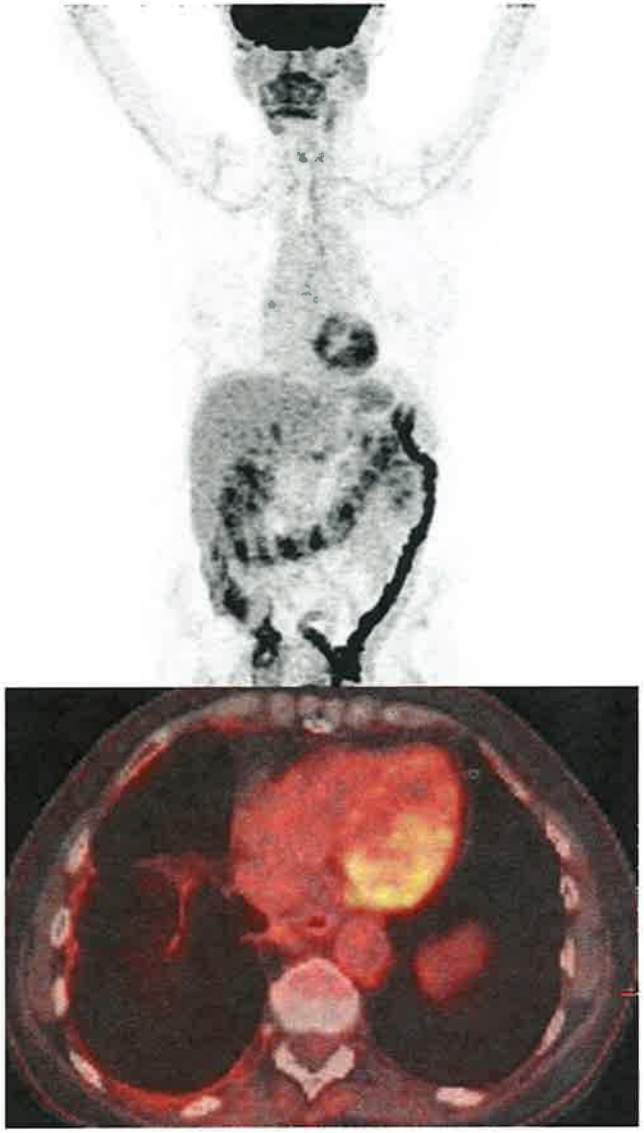


Patient with DLBCL after infusion of anti-CD19 CAR T cells

Before treatment

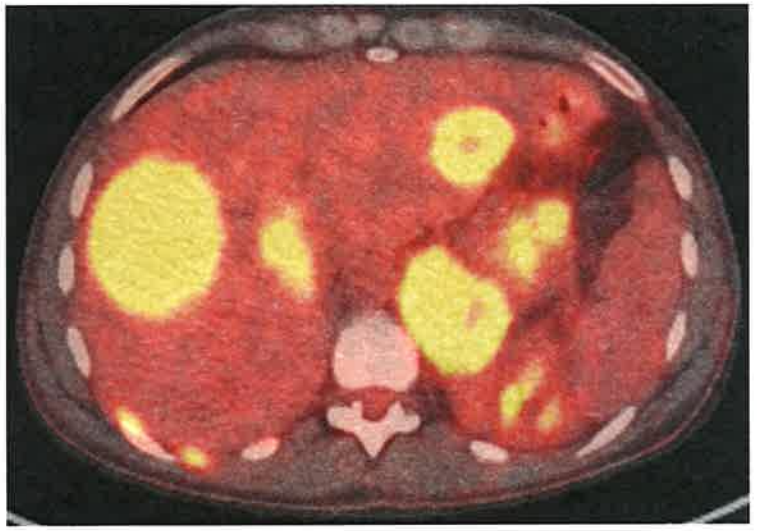


14 weeks after treatment

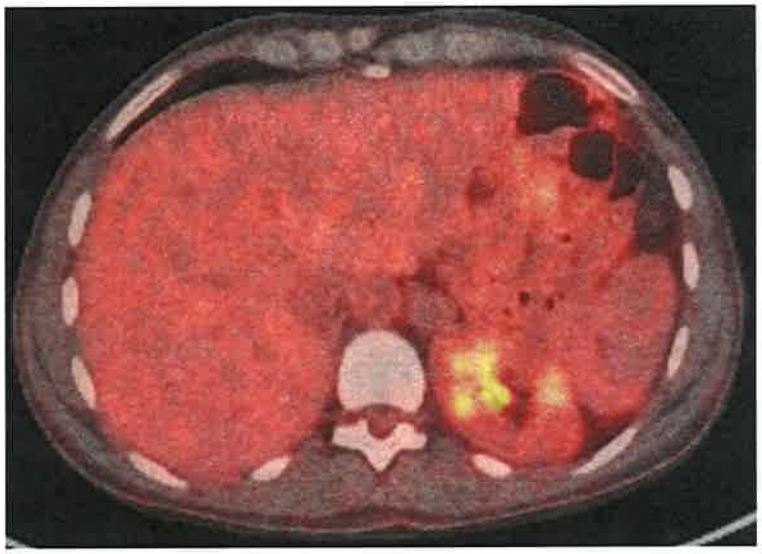


Complete remission of chemo-refractory primary mediastinal B-cell lymphoma ongoing 13 months after treatment

Before treatment



9 months after treatment



Treatment of Patient with Acute Lymphocytic Leukemia using anti-CD19 CAR*

(Pediatric Oncology Branch, CCR, NCI)

20 patients; Intention to treat analysis

14 (70%) complete response

12 (60%) MRD negative complete response

*Same Surgery Branch anti-CD19 retrovirus used in adults

(Lancet 385:517-28, 2015)

Categories of antigens to target using cell therapy

1. Mutations unique to each individual cancer
2. Antigens expressed on cancers and on non-essential normal tissues (CD19, thyroglobulin)
3. Shared antigens unique to cancer (cancer-testes antigens)

Cancer/Testes Antigens - Shared Tumor Specific Antigens

Expressed during fetal development

Restricted in their expression in adult normal tissues to germ cells

Up-regulated in 10-80% of cancers from multiple tissues

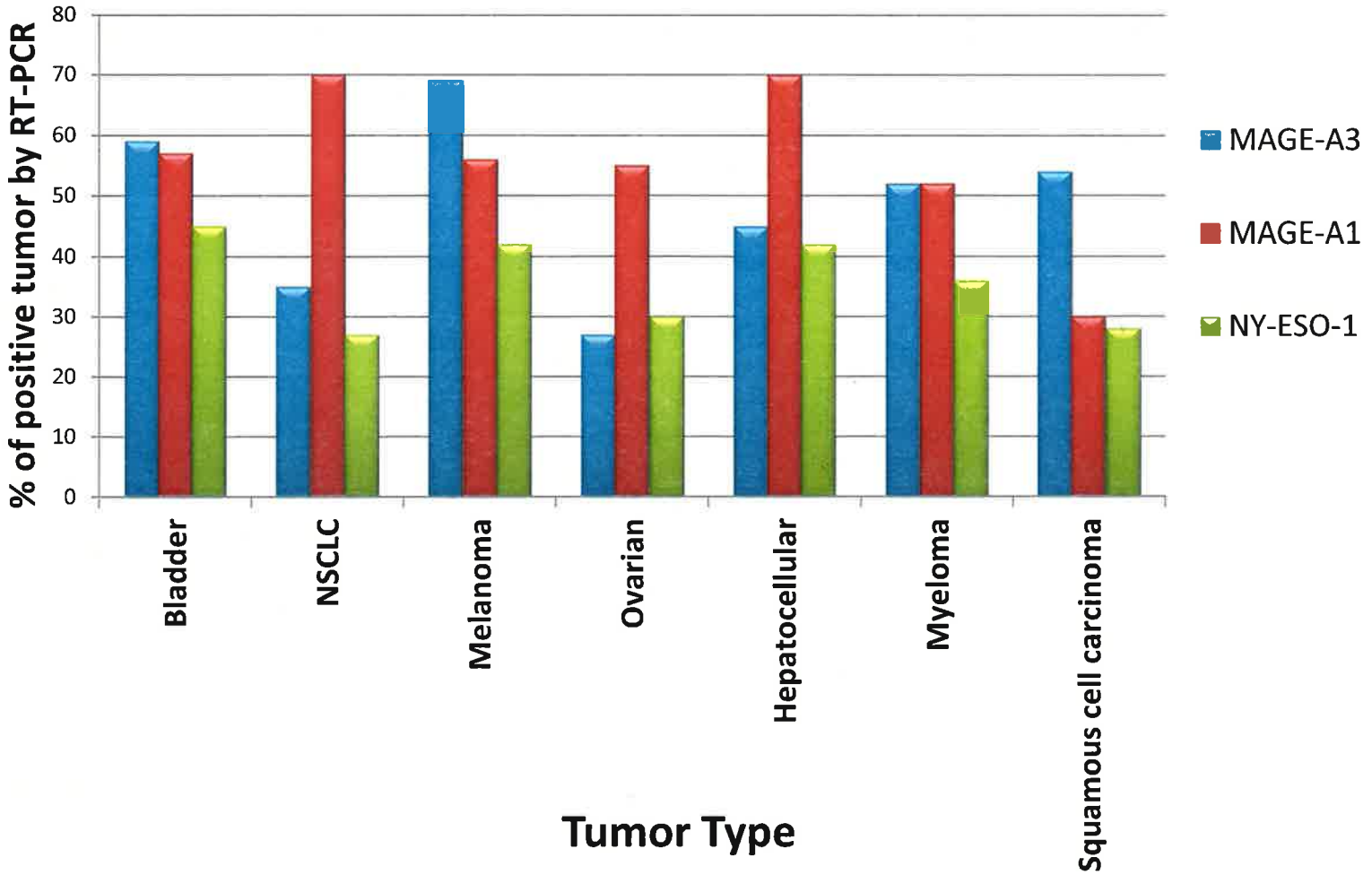
NY-ESO-1 Family

- **Small family of X-linked genes that includes NY-ESO-1 and LAGE-1**

MAGE Family

- **Family of ~ 45 X-linked genes**

Cancer/Testis Antigens Expressed in Multiple Tumor Types



Responses to Therapy with NY-ESO-1 TCR

	Total	PR	CR	OR
		number of patients (duration in months)		
Melanoma	19	6 (32%) (10**, 28, 8, 6+, 3, 3)	4 (21%) (58+, 54+, 28, 40+**)	10 (53%)
Synovial Cell Sarcoma	15	9 (60%) (47+**,18*, 12**,10, 8, 7, 5, 4, 3**)	1(7%) (20+)	10 (67%)

*treated twice

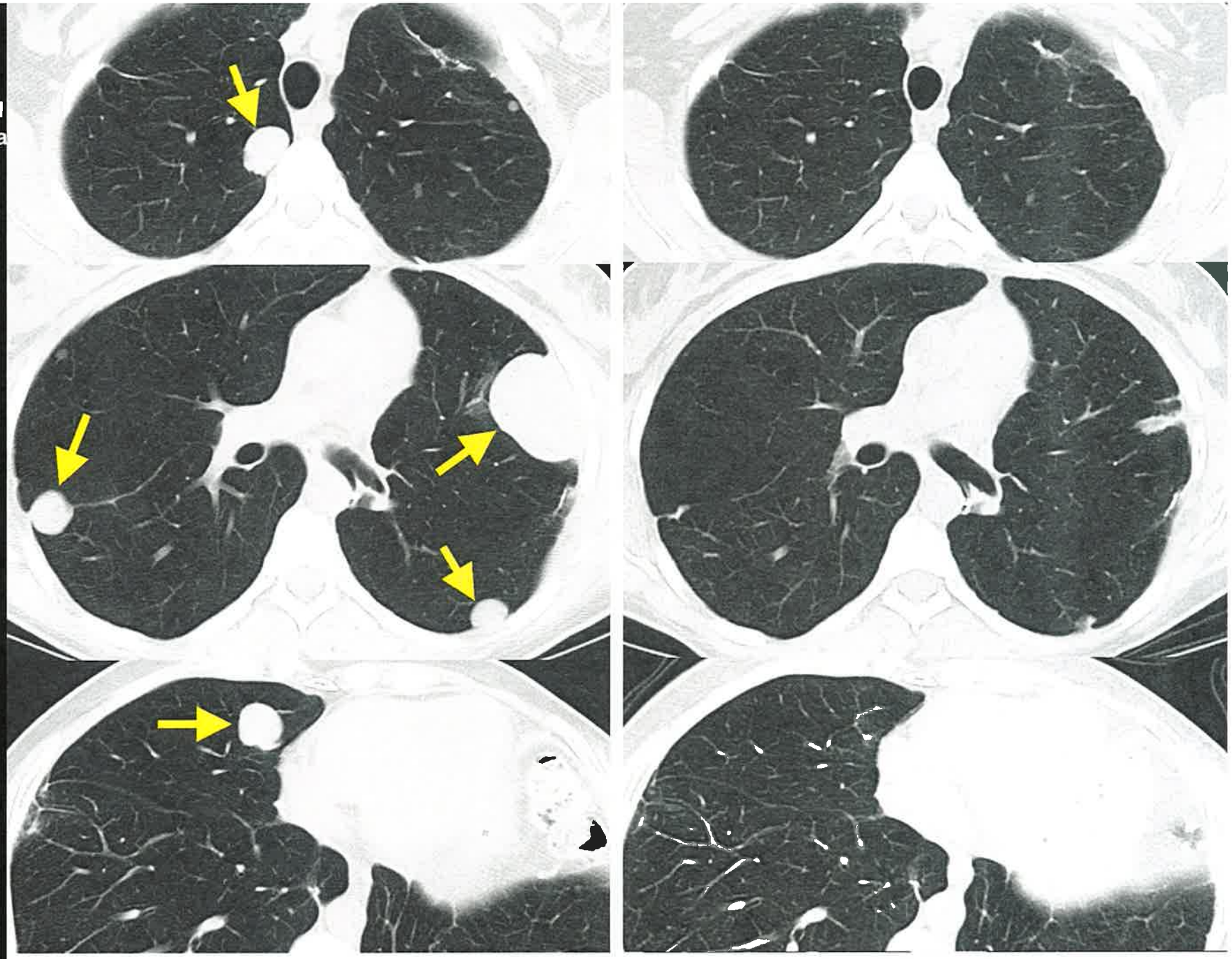
**plus ALVAC vaccine

(Robbins et al J Clin Oncol 29:917, 2011; Clin Cancer Res 21:1022,2015)

H.K.

Synovial Sarcoma

ESO TCR

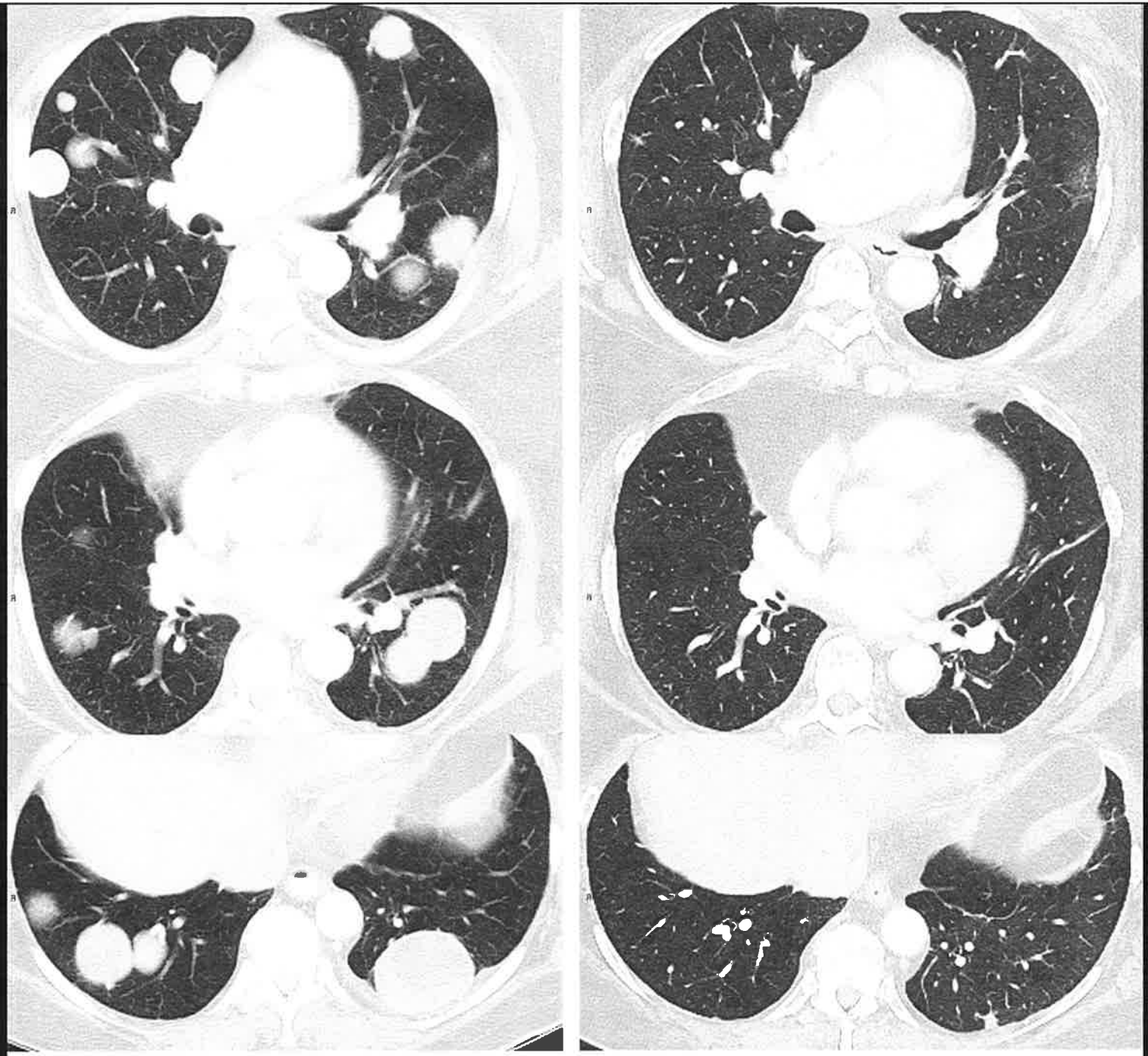


Pre-Treatment

14 Months

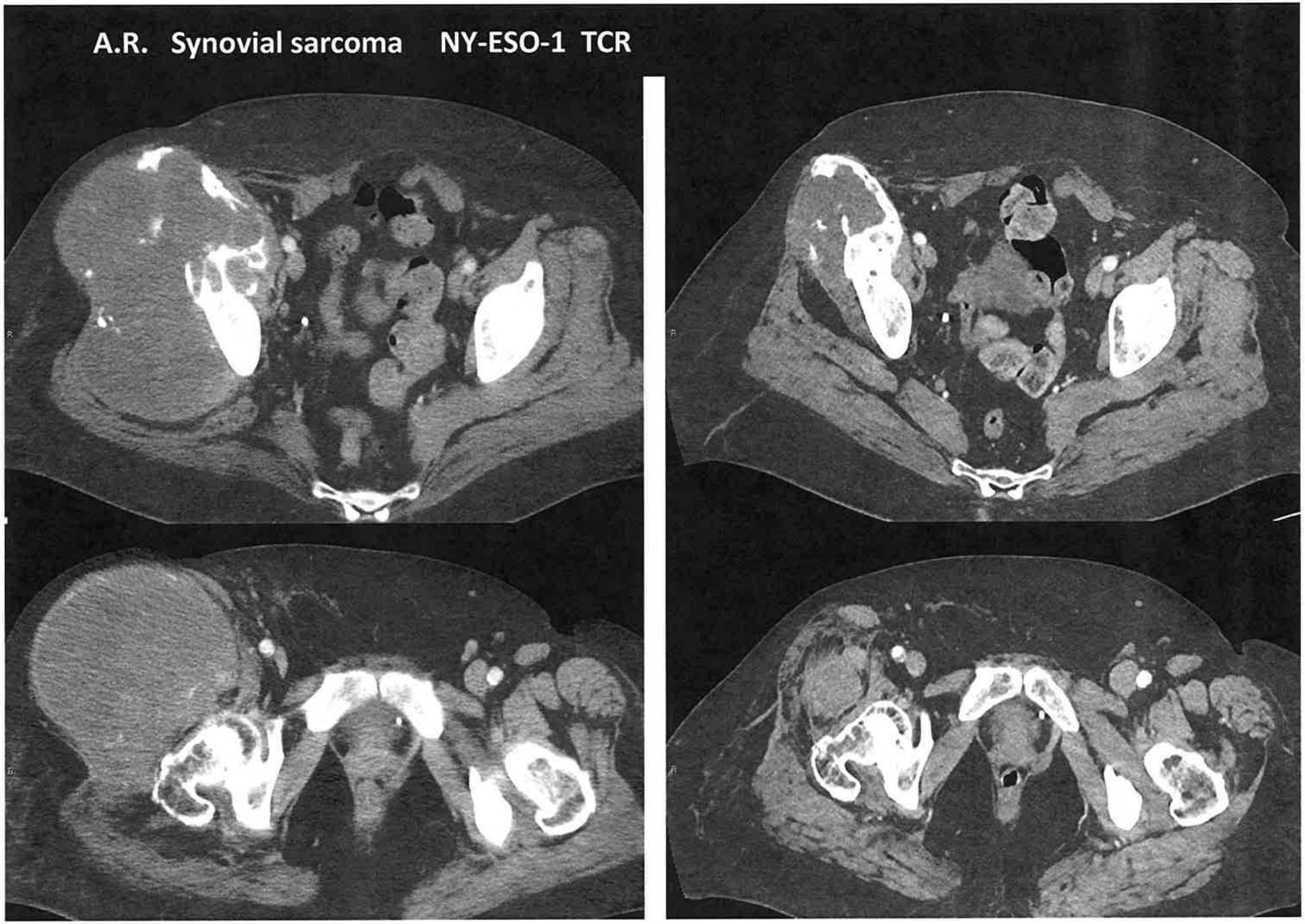
A.R.
Synovial
sarcoma

NY-ESO-1
TCR



August 2010

Feb 2015


A.R. Synovial sarcoma NY-ESO-1 TCR
August 2010
Feb 2015

Program for the Application of Cell Transfer GeneTherapy to a Wide Variety of Human Cancers

Targets	Type	Cancers	Status
MART-1	TCR	Melanoma	Closed
gp100	TCR	Melanoma	Closed
NY-ESO-1	TCR	Epithelial & Sarcomas	Accruing
CEA	TCR	Colorectal	Closed
CD19	CAR	Lymphomas	Accruing
VEGFR2	CAR	All cancers	Accruing
2G-1	TCR	Kidney	Accruing
IL-12	Cytokine	Adjuvant for all receptors	Accruing
MAGE-A3*	TCR	Epithelial	in development
EGFRvIII	CAR	Glioblastoma	Accruing
SSX-2	TCR	Epithelial	in development
Mesothelin	CAR	Pancreas & mesothelioma	Accruing
CSP4 (HMWAg)	CAR	Melanoma, Tnbreast, Panc	in development
Mutated Ag	TCR	All cancers	in development

Conclusions

Cell transfer therapy can mediate durable regressions in patients with metastatic cancer refractory to other treatments.

Autologous peripheral lymphocytes genetically modified to express anti-tumor T cell receptors can mediate cancer regression in vivo.

Identification and targeting of mutations unique to each cancer has the potential to extend cell therapy to patients with common epithelial cancers.

Sweeney, Timothy (NIH/NCI) [E]

From: Rosenberg, Steven A. (NIH/NCI) [E]
Sent: Thursday, April 23, 2015 11:33 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 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>
> **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>

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 w/ its autologous CAR-T towards the EGFRviii mutation at the ASGCT Meeting on Thurs, May 14. Given Novartis appears committed to moving the CART-EGFRviii program forward, we believe early data from this pilot trial may be informative on the outlook of KITE/NCI's EGFRviii CAR-T program.

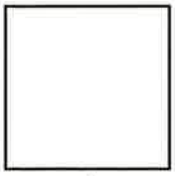
Novartis to Present Preliminary Data for EGFRviii CAR-T in First-In-Human Pilot Study at ASGCT Meeting in May: Novartis (NOVN VX, CHF100.20, Buy) will be presenting preliminary data from its first-in-human pilot study on the first three patients that have been treated w/ its autologous CAR-T directed towards the EGFRviii mutation at the 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 cells to be 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), and all three 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 as 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-EGFRviii in 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/ malignant gliomas expressing EGFRviii. Pts will receive a non-myeloablative but lymphocyte depleting preparative regimen (cyclophosphamide and fludarabine) followed by intravenous 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 will be to 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 established 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 treatment. We 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**



Sweeney, Timothy (NIH/NCI) [E]

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

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!

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

Sweeney, Timothy (NIH/NCI) [E]

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!

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

Sweeney, Timothy (NIH/NCI) [E]

From: Rosenberg, Steven A. (NIH/NCI) [E]
Sent: Thursday, June 18, 2015 11:36 AM
To: 'Jeff Wiezorek'; 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; Kochenderfer, James (NIH/NCI) [E]; Somerville, Robert (NIH/NCI) [E]; Robbins, Paul (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]
Attachments: Kite 3-18-15.ppt

Our studies of [redacted] for today's discussion.

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: Jeff Wiezorek [mailto:JWiezorek@KitePharma.com]
Sent: Wednesday, June 17, 2015 1:46 PM
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; 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]

The agenda for tomorrow's meeting is attached. Please let me know if there are additional items for discussion.

Jeff

-----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]

Proprietary Information,Redacted Per Agreement

Proprietary Information,Redacted Per Agreement,Redacted Through Page 6

Sweeney, Timothy (NIH/NCI) [E]

From: Rosenberg, Steven A. (NIH/NCI) [E]
Sent: Monday, August 10, 2015 4:20 PM
To: 'Adrian Bot'; Yang, James C. (NIH/NCI) [E]
Cc: David Chang; Jeff Wiezorek; Shell, Linda (NIH/NCI) [E]
Subject: RE: Next Kite-NCI call

Jim Yang will not be here and many are on vacation.

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: Adrian Bot [mailto:ABot@KitePharma.com]
Sent: Monday, August 10, 2015 4:01 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]; Yang, James C. (NIH/NCI) [E]
Cc: David Chang; Jeff Wiezorek; Shell, Linda (NIH/NCI) [E]
Subject: RE: Next Kite-NCI call
Importance: High

Hello Dr. Rosenberg,

I am following up on Jeff's email regarding the biweekly NCI Kite call on this Thursday.

Proprietary Information,Redacted Per Agreement

I hope that these topics are acceptable and we are looking forward to our call.

Many thanks in anticipation,

Adrian

Adrian Bot, M.D., Ph.D.
Vice President, Translational Medicine
Kite Pharma, Inc.
2225 Colorado Avenue
Santa Monica, CA 90404
Phone: (310)622 9105
Fax: (310)824 9994
Personal Information,Redacted Per Agreement
abot@kitepharma.com
www.kitepharma.com

From: Jeff Wiezorek
Sent: Friday, August 7, 2015 4:43 PM
To: Steven A. Rosenberg M.D., Ph.D. (sar@mail.nih.gov) <sar@mail.nih.gov>; Adrian Bot <ABot@KitePharma.com>
Subject: Next Kite-NCI call

Dr Rosenberg,

Proprietary Information,Redacted Per Agreement

Thanks,

Jeff

Jeff Wiezorek, MD
Vice President, Clinical Development
Kite Pharma
2225 Colorado Avenue
Santa Monica, CA 90404
(424) 322-1793 Office
Personal Information,Redacted Per Agreement
jwiezorek@kitepharma.com