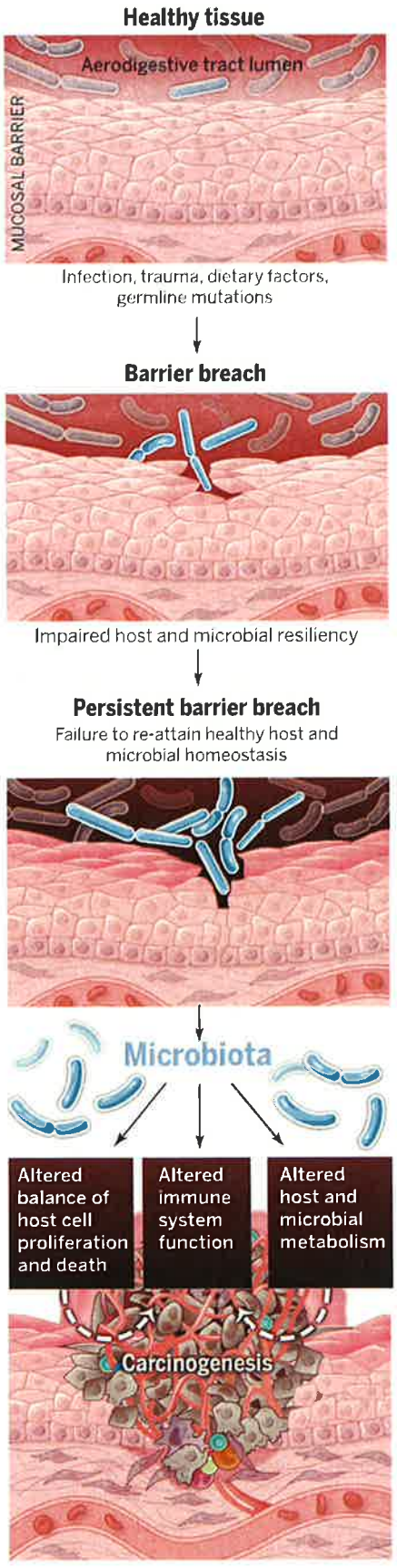

group *Escherichia coli* (*10*) as well as by other Enterobacteriaceae (*11*)], *Bacteroides fragilis* toxin (Bft) produced by enterotoxigenic *B. fragilis*, and cytolethal distending toxin (CDT) produced by several ε- and γ-proteobacteria. Colibactin has emerged as a molecule of interest in colorectal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

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

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

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

The immune system, microbes, microbiota, and cancer

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

Proinflammatory responses can be procarcinogenic

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

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

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

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

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

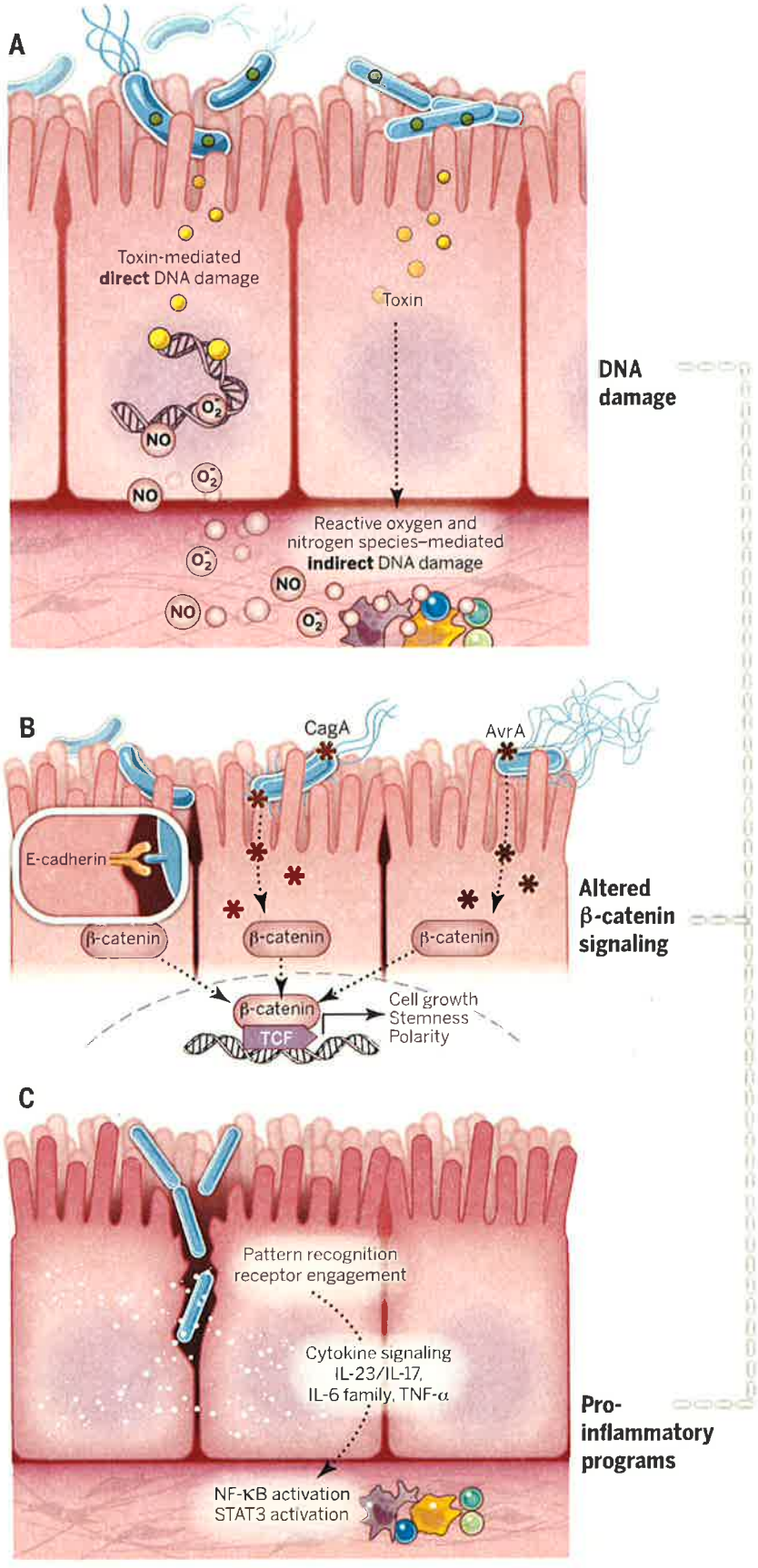

Fig. 2. Mechanisms by which microbes influence cancer development and progression. (**A**) Bacterial toxins can directly damage host DNA. Bacteria also damage DNA indirectly via host-produced reactive oxygen and nitrogen species. When DNA damage exceeds host cell repair capacity, cell death or cancer-enabling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

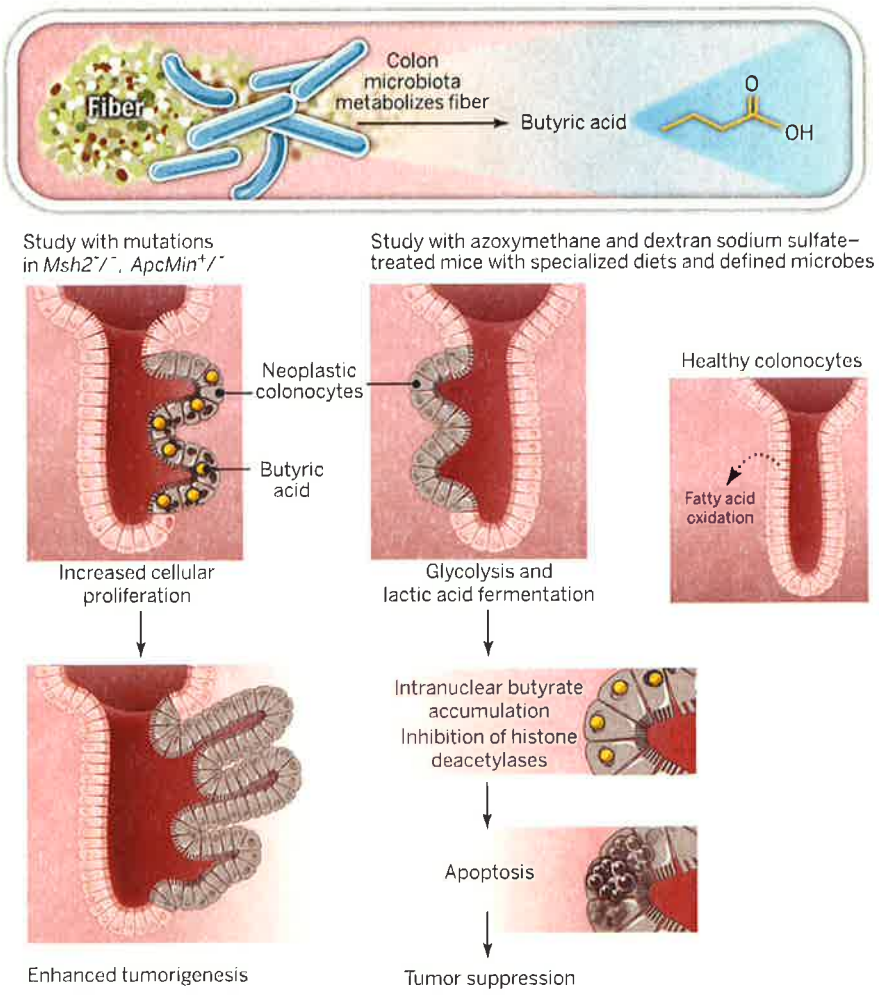

Fig. 3. Dietary fiber, microbiota, butyrate, and tumorigenesis. Metabolism of fiber by colonic microbes results in generation of butyric acid. When genetic mutations in *Msh2* and *Apc* are present, butyrate increases cell proliferation and enhances tumorigenesis. Data from another model of colorectal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

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

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

Immune-dampening responses can be cancer-permissive

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

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

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

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

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

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

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

Microbes, metabolism, and cancer

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

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

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

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

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

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

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

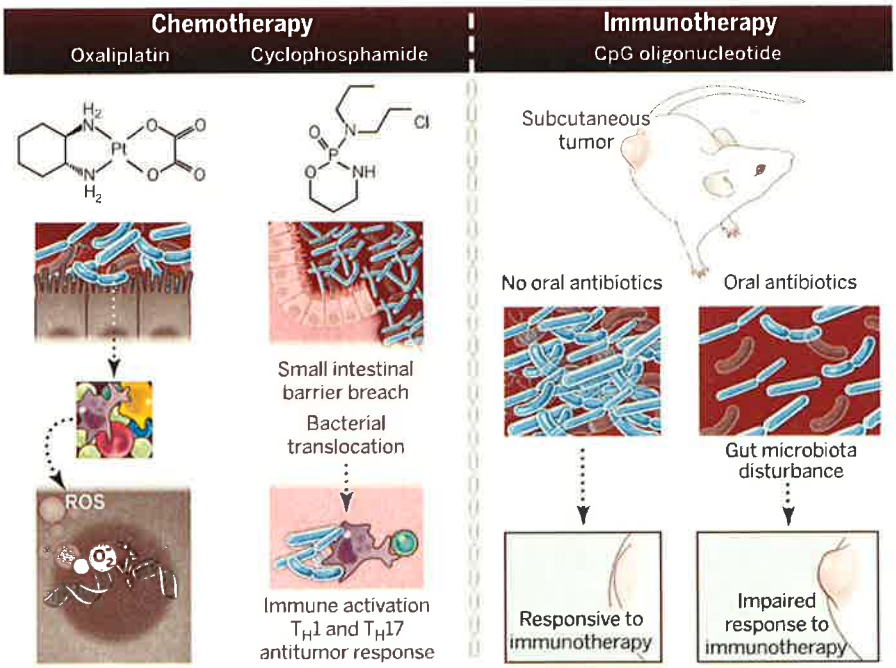

Fig. 4. How the microbiota modulate chemotherapy and immunotherapy efficacy in mouse models. The gut microbiota stimulate immune cells to produce reactive oxygen species (ROS). ROS enhance DNA damage caused by oxaliplatin, blocking DNA replication and transcription and resulting in cell death. Cyclophosphamide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

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

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

Drugs, bugs, and cancer

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

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

The microbiota and immunotherapy: Friend or foe?

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

Hematopoietic transplants, complications, and the microbiota

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

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

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

Back to the future: Perspectives and directions for cancer bacteriotherapy

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

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

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

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

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

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CANCER IMMUNOLOGY

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

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

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

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

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

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

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

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

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

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

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

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

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

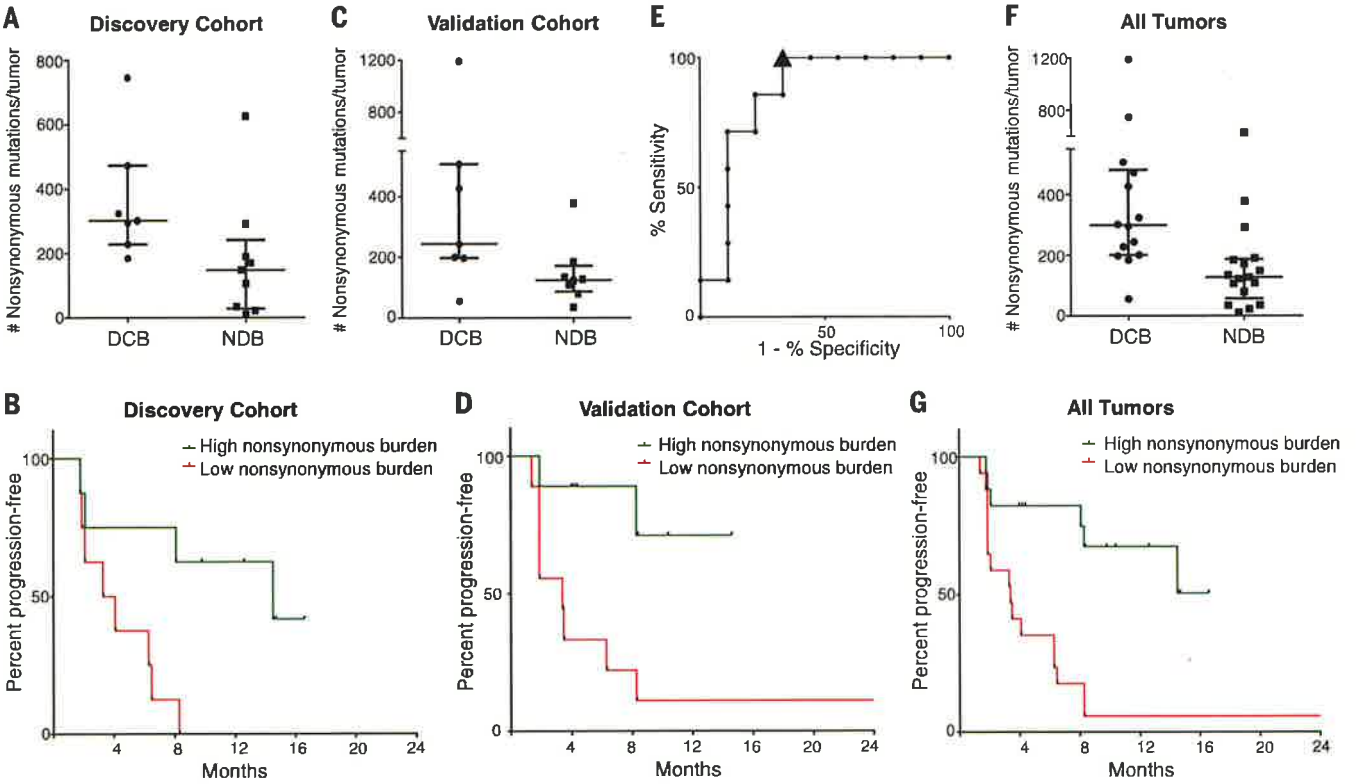

Fig. 1. Nonsynonymous mutation burden associated with clinical benefit of anti–PD-1 therapy. (**A**) Nonsynonymous mutation burden in tumors from patients with DCB ($n = 7$) or with NDB ($n = 9$) (median 302 versus 148, Mann-Whitney $P = 0.02$). (**B**) PFS in tumors with higher nonsynonymous mutation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

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

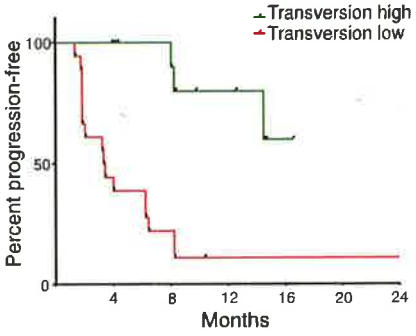

Fig. 2. Molecular smoking signature is significantly associated with improved PFS in NSCLC patients treated with pembrolizumab. PFS in tumors characterized as TH by molecular smoking signature classifier (n = 16) compared to TL tumors (n = 18) (HR 0.15, 95% 0.06 to 0.39, log-rank P = 0.0001).

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

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

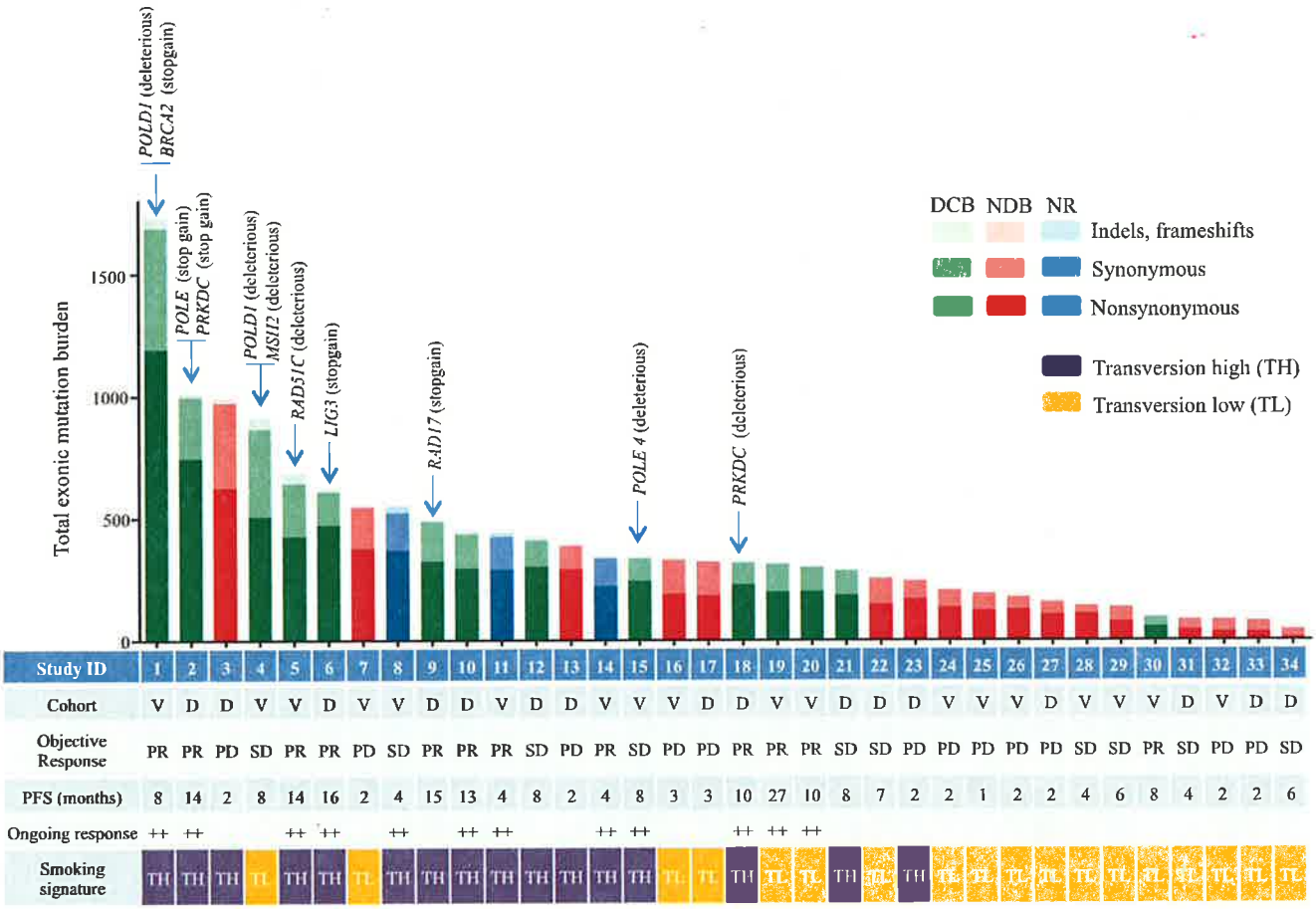

Fig. 3. Mutation burden, clinical response, and factors contributing to mutation burden. Total exonic mutation burden for each sequenced tumor with nonsynonymous (dark shading), synonymous (medium shading), and indels/frameshift mutations (light shading) displayed in the histogram. Columns are shaded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

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

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

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

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

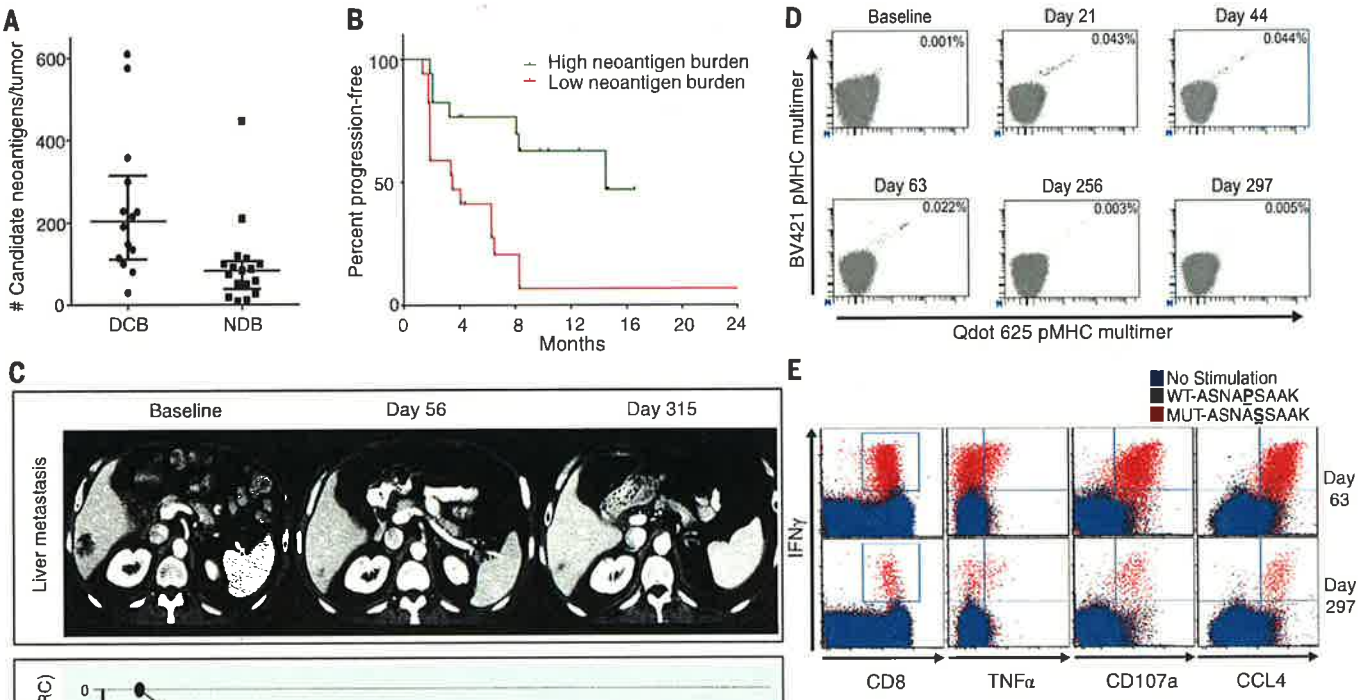

Fig. 4. Candidate neoantigens, neoantigen-specific T cell response, and response to pembrolizumab. (**A**) Neoantigen burden in patients with DCB (n = 14) compared to NDB (n = 17) across the overall set of sequenced tumors (median 203 versus 83, Mann-Whitney P = 0.001). (**B**) PFS in tumors with higher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

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

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

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

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SUPPLEMENTARY MATERIALS

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

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GENE EXPRESSION

MicroRNA control of protein expression noise

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

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

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

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

Naiyer A. Rizvi *et al.*

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Neoantigens in cancer immunotherapy

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

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

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

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

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

Exome-guided neoantigen identification: Process considerations

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

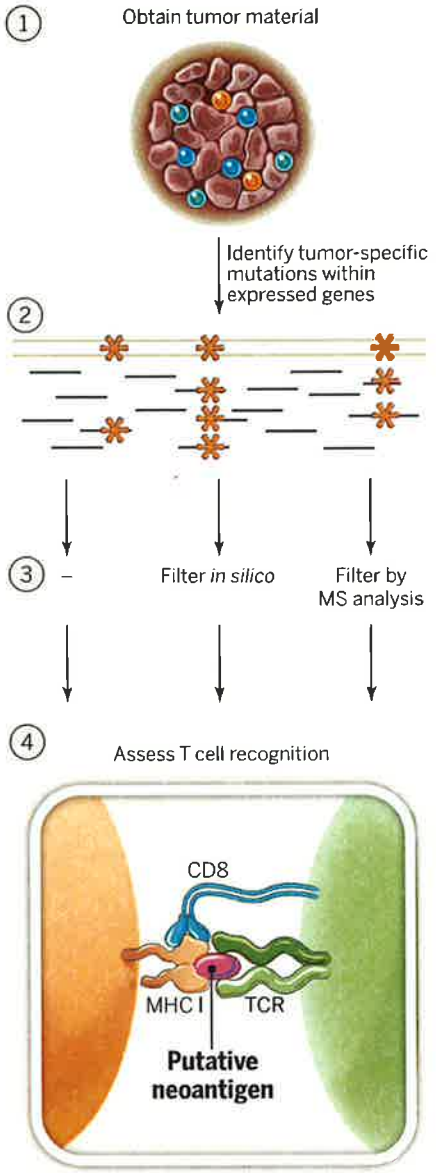

Fig. 1. Cancer exome–based identification of neoantigens. Tumor material is analyzed for nonsynonymous somatic mutations. When available, RNA sequencing data are used to focus on mutations in expressed genes. Peptide stretches containing any of the identified nonsynonymous mutations are generated in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

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

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

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

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

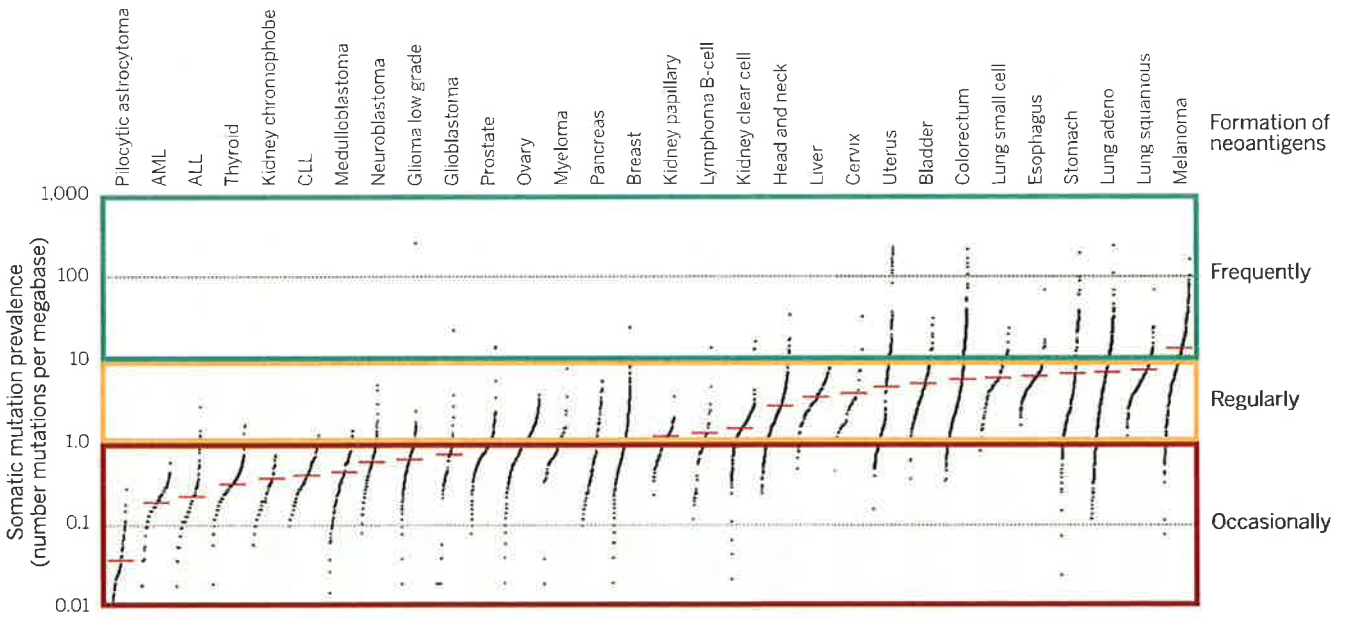

Fig. 2. Estimate of the neoantigen repertoire in human cancer. Data depict the number of somatic mutations in individual tumors. Categories on the right indicate current estimates of the likelihood of neoantigen formation in different tumor types. Adapted from (*50*). It is possible that the immune system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

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

Size and nature of the neoantigen repertoire

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

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

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

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

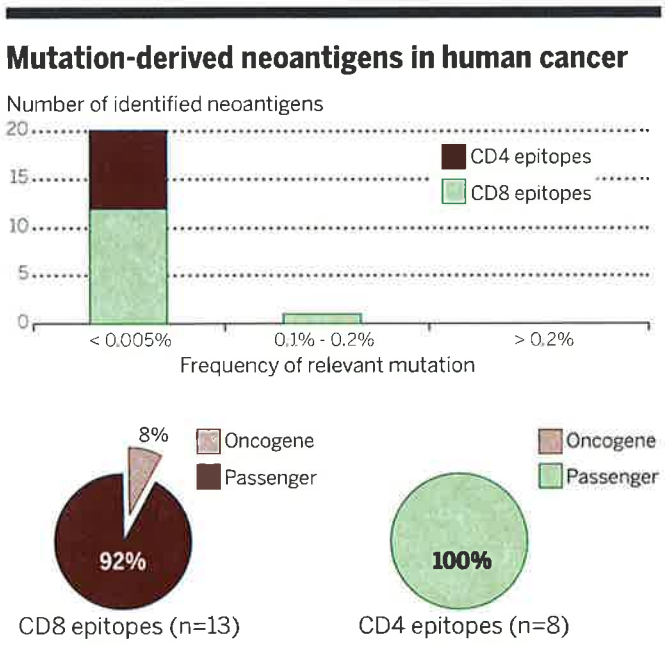

Fig. 3. Characteristics of melanoma neoantigens. (**Top**) For a group of CD4+ T cell neoantigens (8 epitopes) and CD8+ T cell neoantigens (13 epitopes) identified by cancer exome–based screens, the frequency of mutation of that residue in a cohort of ~20,000 human tumor samples (*51*) is depicted. (**Bottom**)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

Extrinsic influences on the tumor antigenic landscape

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

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

Role of neoantigens in cancer immunotherapy

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

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

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

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

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

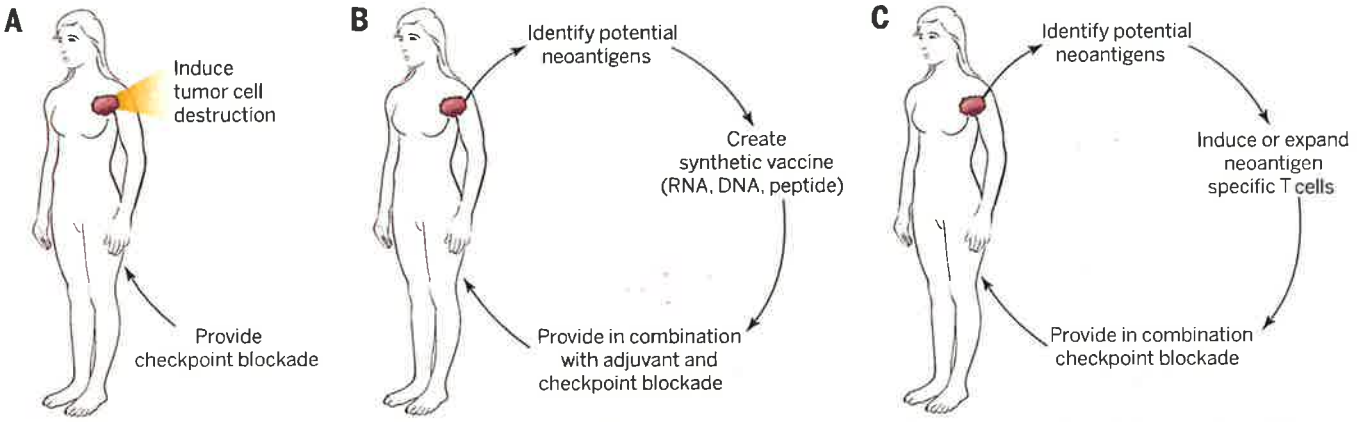

Fig. 4. Strategies to target the patient-specific neoantigen repertoire. (**A**) Immunotherapy is given in combination with interventions such as radiotherapy that enhance exposure to autologous neoantigens. (**B**) Potential neoantigens are identified as in Fig. 1 steps 1 to 3, a patient-specific vaccine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

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

Therapeutic use of the patient-specific neoantigen repertoire

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

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

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

Concluding remarks

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

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REVIEWS

T cell exclusion, immune privilege, and the tumor microenvironment

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

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

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

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

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

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Sweeney, Timothy (NIH/NCI) [E]

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

Hi Steve,

The attendees from Kite will be :

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

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Look forward to seeing you next Thursday.

David

David D. Chang, MD, PhD
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From: David Chang <DChang@KitePharma.com>
Sent: Tuesday, April 14, 2015 7:17 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Cc: Arie Belldegrun
Subject: RE: Kite: NCI visit on April 23

Dear Steve,

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Thanks

David

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

Hi Steve,

The attendees from Kite will be :

- Adrian Bot
- Jeff Wiezorek
- Tony Polverino (VP, Research)
- Margo Roberts
- Myself
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Sweeney, Timothy (NIH/NCI) [E]

From: David Chang <DChang@KitePharma.com>
Sent: Thursday, April 16, 2015 8:28 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: RE: SOP

Steve,

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Thanks you.

David

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

FYI

Steven A. Rosenberg M.D., Ph.D.
Chief, Surgery Branch
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10 Center Drive MSC 1201
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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

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

Markku

Could you please call me about this?

Steve

Steven A. Rosenberg M.D., Ph.D.
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Bethesda, MD 20892
301-496-4164
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-----Original Message-----
From: Raffeld, Mark (NIH/NCI) [E]
Sent: Sunday, February 15, 2015 6:31 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Re: SOP

Hi Steve,

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Mark

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

>Mark

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>Steve
>
>Steven A. Rosenberg M.D., Ph.D.
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>10 Center Drive MSC 1201
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>-----Original Message-----
>From: Toomey, Mary Ann (NIH/NCI) [E]
>Sent: Thursday, February 12, 2015 5:13 PM
>To: Rosenberg, Steven A. (NIH/NCI) [E]
>Subject: FW: SOP
>

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

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

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>>Steve
>>
>>
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>>Chief, Surgery Branch
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>

Sweeney, Timothy (NIH/NCI) [E]

From: David Chang <DChang@KitePharma.com>
Sent: Thursday, April 16, 2015 10:01 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: RE: SOP

Steve - Proprietary Information,Redacted Per Agreement Thanks, David

-----Original Message-----
From: David Chang
Sent: Thursday, April 16, 2015 5:28 PM
To: 'Rosenberg, Steven A. (NIH/NCI) [E]'
Subject: RE: SOP

Steve,

Proprietary Information,Redacted Per Agreement

Thanks you.

David

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

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

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,

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

FYI

Proprietary Information,Redacted Per Agreement

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

2225 Colorado Avenue
Santa Monica, CA 90404
Tel: 310-622-9093

Personal Information,Redacted Per Agreement

arie@kitepharma.com

www.kitepharma.com

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

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

GUGGENHEIM People. Ideas. Success

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

SECTOR: Biopharmaceuticals April 20, 2015

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

CLICK HERE TO ACCESS THIS REPORT

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

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

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

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

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

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

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

Sweeney, Timothy (NIH/NCI) [E]

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

Proprietary Information,Redacted Per Agreement

Thank you for all your help.

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

2225 Colorado Ave
Santa Monica, CA 90404

310 824-9999 x102
arie@kitepharma.com

www.kitepharma.com

From: Rosenberg, Steven A. (NIH/NCI) [E] [mailto:sar@mail.nih.gov]
Sent: Monday, April 20, 2015 1:55 PM
To: Arie Belldegrun

Subject: RE: Pressure on CAR-T Stocks Overdone; More to Come on CAR-T Cell Therapies Tomorrow at AACR - Guggenheim Securities, LLC

Arie

Proprietary Information,Redacted Per Agreement

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

Steve

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

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Sent: Monday, April 20, 2015 2:15 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
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Tel: 310-622-9093

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arie@kitepharma.com

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Sent: Monday, April 20, 2015 10:56 AM
To: Arie Belldegrun; Cynthia Butitta
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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

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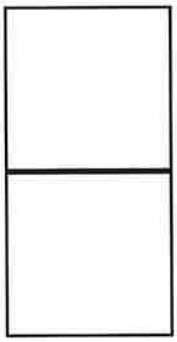

Sweeney, Timothy (NIH/NCI) [E]

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

Proprietary Information,Redacted Per Agreement

All the best,
David

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

Personal Information,Redacted Per Agreement

www.kitepharma.com

Proprietary Information,Redacted Per Agreement,Redacted Through Page 7

Sweeney, Timothy (NIH/NCI) [E]

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

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

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

2225 Colorado Avenue
Santa Monica, CA 90404
Tel: 310-622-9093
Personal Information,Redacted Per Agreement
arie@kitepharma.com

www.kitepharma.com

-----Original Message-----
From: Proprietary Information,Redacted Per Agreement
Sent: Tuesday, April 21, 2015 2:44 PM
To: Arie Belldegrun; David Chang; Cynthia Butitta; Helen Kim; Margo Roberts; Ton Schumacher
Cc: Rubino, Stephen
Subject: Thank you

Dear Arie, David, Cynthia , Helen and Ton Thanks for making time today

Proprietary Information,Redacted Per Agreement

Thanks

Proprietary Information,Redacted Per Agreement

Sweeney, Timothy (NIH/NCI) [E]

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

Hi Steve,

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

Thanks,
David

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

Dear Steve,

Proprietary Information,Redacted Per Agreement

Thanks

David

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

Hi Steve,

The attendees from Kite will be :

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

Meetings we would like to have:

Proprietary Information,Redacted Per Agreement

Look forward to seeing you next Thursday.

David

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

Personal Information,Redacted Per Agreement

www.kitepharma.com

Sweeney, Timothy (NIH/NCI) [E]

From: Arie Belldegrun <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
Attachments: mime-attachment.png

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

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

Rating BUY
Price Target $84.00
Price $57.56
Key Takeaway

Novartis/UPenn will be presenting preliminary data from its pilot study on the first 3 patients that have been treated w/ its autologous CAR-T towards the 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: David Chang <DChang@KitePharma.com>
Sent: Thursday, April 23, 2015 4:20 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Kite

Steve,

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

Proprietary Information,Redacted Per Agreement

David

David D. Chang, M.D., Ph.D.
office: (310) 622-9094

Personal Information,Redacted Per Agreement

www.kitepharma.com

Sent from my iPad

Sweeney, Timothy (NIH/NCI) [E]

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

FYI.

Proprietary Information,Redacted Per Agreement

Thanks,

David

David D. Chang, M.D., Ph.D.
office: (310) 622-9094
Personal Information,Redacted Per Agreement
www.kitepharma.com

Sent from my iPad

Begin forwarded message:

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

Proprietary Information,Redacted Per Agreement

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

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

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

Steve,

Proprietary Information,Redacted Per Agreement

Thanks,

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

2225 Colorado Avenue
Santa Monica, CA 90404
Tel: 310-622-9093
Personal Information,Redacted Per Agreement
arie@kitepharma.com

www.kitepharma.com

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

Arie

Proprietary Information,Redacted Per Agreement

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

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

Rating BUY
Price Target $84.00
Price $57.56

Key Takeaway

Novartis/UPenn will be presenting preliminary data from its pilot study on the first 3 patients that have been treated w/ its autologous CAR-T towards the 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.

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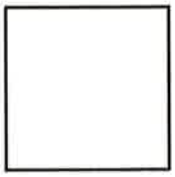
(212) 284-2535 svempati@jefferies.com

Timothy Chou *, Equity Associate
(212) 284-2571 tchou@jefferies.com

*** Jefferies LLC**



Sweeney, Timothy (NIH/NCI) [E]

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

Dear Steve,

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

Proprietary Information,Redacted Per Agreement

All the best,
David

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

Sweeney, Timothy (NIH/NCI) [E]

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

Hi Steve,

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

Thanks for everything!

Arie

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

www.kitepharma.com

Begin forwarded message:

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

LINK TO FULL REPORT & DISCLOSURES

Biotechnology

Kite Pharma

Equity Research | Quick Take: Company Update

May 6, 2015

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

OUTPERFORM (1)

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

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

Key Data

Symbol	NASDAQ: KITE
Market Cap (MM)	$2,430.3

Leading The Way In DLBCL And So Much More

The Cowen Insight

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

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

While much investor attention has been focused on Kite and its competitors' CD19 directed CAR therapies, Kite has quietly assembled what it believes is (1) the best platform from which new CAR/TCR based therapies can be developed and (2) the broadest pipeline of engineered T cell therapies. Kite has worked with the NCI to optimize T cell production methods, completed tech transfer to an external CMO, and is now the only company with an FDA cleared, corporately held CAR T cell IND (KTE-C19). Kite is also in the process of building commercial scale (5000 patients/yr capacity) and clinical scale (300 patients/yr capacity) manufacturing facilities in Los Angeles from which to rapidly move promising preclinical product candidates into the clinic and ultimately market without the need for external tech transfer. This will also form a platform to quickly test emerging engineered T cell technologies (e.g. gene editing, switches, etc.) as needed. Through its CRADA with the National Cancer Institute (NCI), Kite has active clinical programs utilizing two CAR constructs (CD19 and EGFRvIII) and four TCR constructs (NY-ESO-1, MAGE A3, MAGE A6, and HPV-16 E6). NCI is also working on additional clinical and preclinical constructs to which Kite has development rights including a mesothelin CAR and HPV-16 E7, SSX2, and personalized neo-antigen TCRs. In addition, Kite has gained access to multiple oncology targets through a 50:50 partnership with Amgen. Finally, the recent acquisition of T Cell Factory (TCF) has given Kite a proprietary high-throughput method for identifying and cloning rare TCR sequences from patient samples. Following this acquisition, Kite possesses many of the

leading minds in engineered T cells and immune-therapy as internal employees (Drs. Margo Roberts and Ton Schumacher), collaborators (Dr. Steven Rosenberg), or scientific advisors (Drs. Ron Levy, Toni Ribas, and Owen Witte). Presentations from many of these people will be featured when Kite reviews its platform, pipeline, and future directions at an R&D day in NYC on June 23, 2015.

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

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

2014 Was And 2015 Is All About Execution

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

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

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

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

engineered T cell therapy in solid tumors (NY-ESO-1 TCR) utilized a preconditioning regimen.

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

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

Sweeney, Timothy (NIH/NCI) [E]

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

Proprietary Information,Redacted Per Agreement

David

David D. Chang, M.D., Ph.D.
office: (310) 622-9094
mobile: (805) 469-4362

www.kitepharma.com

Sent from my iPad

Begin forwarded message:

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

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

LINK TO FULL REPORT & DISCLOSURES

Biotechnology

Fate Therapeutics

Company Update

May 6, 2015

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

OUTPERFORM (1)

Boris Peaker, Ph.D., CFA
646.562.1377
boris.peaker@cowen.com

Joseph Catanzaro, Ph.D.
646.562.1387
joseph.catanzaro@cowen.com

George Chen
646.562.1306
george.chen@cowen.com

Key Data

Symbol	NASDAQ: FATE
52-Week Range	$8.78 - 3.50
Market Cap (MM)	$149.4
Net Debt (MM)	$(29.5)
Cash/Share	$2.39
Dil. Shares Out (MM)	20.6
Enterprise Value (MM)	$119.9
ROIC	NA
ROE (LTM)	NA
BV/Share	$1.38
Dividend	NA

FY (Dec)	2014A	2015E	2016E
Earnings Per Share			
Q1	$(0.34)	$(0.39)	-
Q2	$(0.30)	$(0.32)	-
Q3	$(0.30)	$1.15	-
Q4	$(0.30)	$(0.31)	-
Year	$(1.27)	$0.45	$(1.32)
P/E	NM	16.1x	NM
Consensus EPS	$(1.27)	$(1.29)	$(1.26)

Consensus source: Thomson Reuters

Revenue (MM)			
Year	$0.0	$50.0	$0.0

CAR-T Partnership and Positive PUMA Data Update

The Cowen Insight

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

Deal Terms Highly Favorable For Fate and Juno

Juno agreed to pay Fate $5MM to develop a cocktail of small molecules to enhance the therapeutic profile of CAR-T cells. Fate will receive $50MM in milestones and a low single digit royalty on each product developed under the agreement. Juno also agreed to fund all mutual collaboration activities for an exclusive four year period and will purchase 1MM shares of Fate at $8/share (6' premium). The terms of the deal are highly favorable for Fate but also for Juno a the agreement will give Juno an edge in the highly competitive CAR-T space. W believe the deal underscores both the discount in the shares and potential of Fate's ex-vivo hematopoietic cell modulation platform to enhance other immuno-oncology cell therapies.

Ex Vivo Modulation May Enhance CAR-T Therapies

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

PROHEMA Continues To Perform In PUMA Study

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

EV/S	-	2.4x	-

Please see addendum of this report for important disclosures.

Sweeney, Timothy (NIH/NCI) [E]

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

Nick - Proprietary Information,Redacted Per Agreement Thanks! David

David D. Chang, M.D., Ph.D.
office: (310) 622-9094
Personal Information,Redacted Per Agreement
www.kitepharma.com

Sent from my iPad

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

Hi David,

Thank you for sending this interesting analysis from the Cowen Group.

Proprietary Information,Redacted Per Agreement

Nick

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

Proprietary Information,Redacted Per Agreement

David

David D. Chang, M.D., Ph.D.

office: (310) 622-9094

[redacted]

Personal Information,Redacted Per Agreement

www.kitepharma.com

Sent from my iPad

Begin forwarded message:

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

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

LINK TO FULL REPORT & DISCLOSURES

[redacted]

Biotechnology

Fate Therapeutics

Company Update

May 6, 2015

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

OUTPERFORM (1)

Boris Peaker, Ph.D., CFA
646.562.1377
boris.peaker@cowen.com

Joseph Catanzaro, Ph.D.
646.562.1387
joseph.catanzaro@cowen.com

George Chen

CAR-T Partnership and Positive PUMA Data Update

The Cowen Insight

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Deal Terms Highly Favorable For Fate and Juno

Juno agreed to pay Fate $5MM to develop a cocktail of small molecules to

646.562.1306
george.chen@cowen.com

Key Data

Symbol	NASDAQ: FATE
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Cash/Share	$2.39
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ROE (LTM)	NA
BV/Share	$1.38
Dividend	NA

FY (Dec)	2014A	2015E	2016E
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Q2	$(0.30)	$(0.32)	-
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P/E	NM	16.1x	NM
Consensus EPS	$(1.27)	$(1.29)	$(1.26)

Consensus source: Thomson Reuters

Revenue (MM)			
Year	$0.0	$50.0	$0.0
EV/S	-	2.4x	-

enhance the therapeutic profile of CAR-T cells. Fate will receive $50MM in milestones and a low single digit royalty on each product developed under tl agreement. Juno also agreed to fund all mutual collaboration activities for ar exclusive four year period and will purchase 1MM shares of Fate at $8/shar premium). The terms of the deal are highly favorable for Fate but also for Ju the agreement will give Juno an edge in the highly competitive CAR-T spac believe the deal underscores both the discount in the shares and potential o Fate's ex-vivo hematopoietic cell modulation platform to enhance other imm oncology cell therapies.

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

PROHEMA Continues To Perform In PUMA Study

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

Please see addendum of this report for important disclosures.

Sweeney, Timothy (NIH/NCI) [E]

From: Arie Belldegrun <Arie@kitepharma.com>
Sent: Thursday, May 21, 2015 10:58 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Fwd:

HinSteve,

Please see below from Ton, Proprietary Information,Redacted Per Agreement

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

www.kitepharma.com

Begin forwarded message:

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

Dear Arie,

Proprietary Information,Redacted Per Agreement

Sent from mobile

Sweeney, Timothy (NIH/NCI) [E]

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

Fresh from ASCO...

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

www.kitepharma.com

Begin forwarded message:

> **From:** Lisa Burns <LBurns@burnsmc.com>
> **Date:** June 1, 2015 at 01:57:07 CDT
> **To:** Arie <arie@kitepharma.com>, C Butitta <cbutitta@kitepharma.com>, "David Chang M.D. D. Ph. D. (dchang@kitepharma.com)" <dchang@kitepharma.com>
> **Cc:** "Linda Barnes " <lbarnes@kitepharma.com>, "Catherine Bechtold (kbechtold@kitepharma.com)" <kbechtold@kitepharma.com>, Kite Team <Kite_Team@burnsmc.com>
> **Subject: FW: QUICK TAKE - KITE - KTE-C19 Heading Into Open Waters, Much More Below The Surface - Cowen and Company**
>
> **From:** Eric Schmidt, Ph.D. [mailto:eric.schmidt@cowen.com]
> **Sent:** Monday, June 01, 2015 2:35 AM
> **To:** Lisa Burns
> **Subject:** QUICK TAKE - KITE - KTE-C19 Heading Into Open Waters, Much More Below The Surface - Cowen and Company

LINK TO FULL REPORT & DISCLOSURES

Biotechnology

Kite Pharma

Equity Research | Quick Take: Company Update

June 1, 2015

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

OUTPERFORM (1)

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

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

Key Data

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

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

The Cowen Insight

In conjunction with ASCO we hosted a dinner with senior Kite management. KTE-C1 is enrolling patients into a potentially pivotal Phase I/II trial. Management indicates its solid tumor pipeline has generated responses and is set for further expansion. We continue to view Kite as a leader in immune oncology and remain at Outperform.

Laying The Foundation To Be A Major Player In IO

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

Long-Term Persistence Not Required For Durable DLBCL Responses

Management reviewed the results of a correlative analysis that was presented in poster session at ASCO. Kite conducted an in-depth analysis of samples from 2 DLBCL patients treated with CD19-CAR T cells at the NCI. Among these patient 22 responses (11 CRs and 11 PRs) were observed. Responders were divided in two groups. The first representing those with responses lasting <1yr (n=10) and the second representing ongoing responses of at least 1yr (n=11). Both patient groups had median peripheral CD19 CAR T cell persistence of 29 days. In fact, t responder with the longest T cell persistence (184 days) experienced a response lasting <1yr. Conversely the responder with the least persistency (11 days) has a ongoing response of >1yr. In addition, 7/11 long-term responders have experienced B cell recovery and are no longer using prophylactic immunoglobuli therapy. This further indicates that long-term maintenance of a peripheral CD19 CAR population is not necessary for a durable response in DLBCL. Kite's data ir DLBCL stands in contrast to statements from Juno and Novartis' collaborators at Penn regarding their datasets in ALL. It is not clear if the disparate conclusions regarding persistency is due to (1) differences in cellular therapies, (2) difference in the indications studied, or (3) the limited size of the datasets.

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

First Corporate CAR T Cell Trial Now Enrolling.

In May, Kite announced that the Phase I portion of its Phase I/II trial on KTE-C19 for refractory diffuse large B cell lymphoma (DLBCL) had enrolled its first patient The Phase I lead-in is designed to ensure that T cell production outside of NCI is generating similar efficacy and safety data as that previously reported from the NCI. Management intends to present data from this n=6 patient cohort at ASH 2015. The company will also press release the start of the Phase II portion of the

trial. In the meantime, no news from the study is good news as any major safety efficacy challenges that might merit a change in strategy would need to be disclosed. For competitive reasons, management is not disclosing the chemotherapy conditioning regimen or cell dose, but Kite did say that T cells expanded for six days appear to have optimal properties for transplantation, so where possible (assuming enough T cells can be collected) we assume Kite is employing a six day T cell expansion process. Management noted that enrollmer does not appear to be an issue as centers are highly interested in participating. Nonetheless the company will limit the pace of the study to ensure logistics are smooth and protocols are followed closely.

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

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

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

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

Beyond its CRADA with the NCI, management indicates that its Amgen collaboration is also progressing according to plan. Under this collaboration Kite and Amgen will work together on CAR constructs in pairs. Each CAR pair will consist of one Kite-owned program (with a single-digit Amgen royalty) and one Amgen-owned candidate (with a high single to double-digit royalty to Kite). The collaboration is expected to result in its first IND filing within 18 months of it beinç signed. Therefore, the first Kite:Amgen IND should occur around mid-2016. A steady stream of INDs is expected to follow with programs alternating between tl Kite and Amgen pipelines.

KITE Also Holds A Leadership Position In Neo-antigens.

Termed the "ultimate personalized therapy" neo-antigen T cell therapy refers to autologous T cells that have been engineered to recognize neo-antigens within a specific patient's tumor cells. At ASH 2014, Dr. Rosenberg presented an initial proof-of-concept for how the NCI can conduct the neo-antigen sequencing, TCR isolation, and T cell production required to deliver such a therapy within 10 week Kite believes that in order for this approach to be commercially viable, turn arour times will need to be shortened to 4-6 weeks, The company believes the scientif progress in this field is rapid, and it is now just a matter of time before neo-antige based TCR therapy becomes a reality. It believes clinical trials might be possible

within 3-5 years. By virtue of its association with Dr. Rosenberg and Ton Schumacher (Kite Europe), we believe Kite is far and away the leader in this cutting edge area of immune oncology,

Sweeney, Timothy (NIH/NCI) [E]

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

Hi steve,

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

Thanks,

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

www.kitepharma.com

Begin forwarded message:

> **From:** Cynthia Butitta <CButitta@KitePharma.com>
> **Date:** June 1, 2015 at 09:59:29 CDT
> **To:** Arie Belldegrun <Arie@kitepharma.com>, David Chang <DChang@KitePharma.com>
> **Cc:** Justin Jackson <JJackson@burnsmc.com>
> **Subject: Fwd: Current Status of ASCO data release review at NCI**
>
> Our PR is waiting for Rosenberg's approval. If this doesn't get out today, it will be stale news.
>
> Cindy
>
> Sent from my iPhone
>
> Begin forwarded message:
>
> > **From:** Justin Jackson <JJackson@burnsmc.com>
> > **Date:** June 1, 2015 at 7:56:21 AM PDT
> > **To:** C Butitta <cbutitta@kitepharma.com>
> > **Cc:** David Chang <DChang@KitePharma.com>, Kate Bechtold <kbechtold@kitepharma.com>, Veer Bhavnagri <veer@kitepharma.com>, Lisa Burns <LBurns@burnsmc.com>, Carol Werther <cwerther@burnsmc.com>, Rebecca Cohen <rcohen@burnsmc.com>, Ilana Portner <iportner@burnsmc.com>
> > **Subject: RE: Current Status of ASCO data release review at NCI**
> >
> > Thanks, Cindy.

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

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

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

Thx!

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

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

Justin,

We need to get this out.

Cindy

Sent from my iPhone

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

Good morning, all.

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

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

Thank you!

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

Hello, I hope the conference is going very well!

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

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

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

Thank you!

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

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

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

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

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

About Kite Pharma

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

Cautionary Note on Forward-Looking Statements

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

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

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

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

Cindy and Kate,

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

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

Thanks!

Justin W. Jackson
Executive Vice President
Burns McClellan, Inc.
257 Park Avenue South
15th Floor

New York, NY 10010
212-213-0006, ext. 327

Sweeney, Timothy (NIH/NCI) [E]

From: Arie Belldegrun <Arie@kitepharma.com>
Sent: Monday, June 22, 2015 8:56 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Fwd: Kite Pharma and bluebird bio Announce Strategic Collaboration to Advance Second Generation TCR Cell Therapy Products to Treat HPV-Associated Cancers

FYI from this morning.

Proprietary Information,Redacted Per Agreement

See you tomorrow.

Arie

Sent from my iPad

Begin forwarded message:

From: "Kite Pharma, Inc." <jjackson@burnsmc.com>
Date: June 22, 2015 at 8:04:22 AM EDT
To: <Arie@kitepharma.com>
Subject: Kite Pharma and bluebird bio Announce Strategic Collaboration to Advance Second Generation TCR Cell Therapy Products to Treat HPV-Associated Cancers

Kite Pharma and bluebird bio Announce Strategic Collaboration to Advance Second Generation TCR Cell Therapy Products to Treat HPV-Associated Cancers

Collaboration Combines bluebird bio's Gene Editing and Lentiviral Gene Delivery Technologies and Kite's TCR Capabilities and Exclusive Rights to a TCR Directed Against the HPV-16 E6 Oncoprotein

Exclusive Worldwide Co-Development and Co-Commercialization Collaboration

NEWSWIRE) -- Kite Pharma, Inc. (Nasdaq:KITE) and bluebird bio, Inc. (Nasdaq:BLUE) today announced that they have entered into a collaboration agreement to co-develop and co-commercialize second generation T cell receptor (TCR) product candidates directed against the human papillomavirus type 16 E6 (HPV-16 E6) oncoprotein incorporating gene editing and lentiviral technologies. bluebird bio has a platform comprised of lentiviral gene delivery and gene editing capabilities, with a focus on rare diseases and cancer immunotherapies. Kite has a broad existing pipeline of TCR product candidates and will continue to develop its existing and wholly-owned TCR programs directed against high-risk HPV, which are unaffected by this collaboration, including HPV-16 E6 TCR, currently in a Phase I study, and HPV-16 E7 TCR. The collaboration brings together the powerful technologies and capabilities of these two leading immunotherapy companies.

Under the terms of the agreement, both companies will jointly develop and commercialize second generation TCR product candidates directed against the HPV-16 E6 oncoprotein, incorporating gene editing to efficiently modify certain genes to enhance T cell function. In addition, the companies will explore using lentiviral vectors to optimize delivery of HPV-16 E6 TCRs into patient T cells.

Kite will lead the program in the U.S., and bluebird bio will have the option to lead the program in the European Union. Both companies will share overall costs, including research and development and sales and marketing expenses, and profits will be equally split between the companies. Additionally, Kite will have a co-promotion option in the European Union, and bluebird will have a co-promotion option in the U.S.

"As we continue to build a differentiated immuno-oncology portfolio, we are delighted to partner with Kite in a collaboration that combines their leadership in T cell-based immunotherapies with our expertise in gene editing and industry-leading lentiviral vector platform," said Nick Leschly, chief bluebird. "We believe partnering with Kite will allow us to deliver game-changing T cell therapies to patients through great science and great capabilities."

"This partnership is a natural fit with our mission to develop and deliver novel immunotherapies for cancer patients, and collaborating globally with bluebird bio will allow us to benefit from the strengths and capabilities of both companies in immuno-oncology. Through this collaboration, we will have access to our partner's strong science expertise and enabling technologies to further enhance one of our key TCR programs and to evaluate gene editing technology in the context of T cell therapy," said Arie Belldegrun, M.D., FACS, Kite's Chairman, President and Chief Executive Officer.

Kite will discuss further details of this collaboration at its upcoming Investor Day event on June 23rd that will be webcast at www.kitepharma.com.

About HPV-Associated Cancers

reproductive tract, with two viral strains, HPV type 16 and type 18, believed to cause 70% of cervical cancers and precancerous cervical lesions, as well as other urogenital cancers.[1] There were over 500,000 new cases and about 270,000 deaths attributable to cervical cancer worldwide in 2012.[2]

Additionally, HPV infection has become established as an etiologic risk factor for oropharyngeal head and neck cancers. The incidence of HPV-associated oropharyngeal cancers has been increasing for at least the past decade, and recent studies show that about 70 percent of oropharyngeal cancers may be linked to HPV[3,4]. According to the CDC, there are over 12,000 new cases of oropharyngeal cancers in the U.S., of which an estimated 7,500 new cases are attributable to HPV-16.[4]

About Kite Pharma, Inc.

Kite Pharma, Inc., is a clinical-stage biopharmaceutical company engaged in the development of novel cancer immunotherapy products, with a primary focus on eACT™ designed to restore the immune system's ability to recognize and eradicate tumors. Kite is based in Santa Monica, CA. For more information on Kite Pharma, please visit www.kitepharma.com.

About bluebird bio, Inc.

With its lentiviral-based gene therapy and gene editing capabilities, bluebird bio has built an integrated product platform with broad potential application to severe genetic diseases and T cell-based immunotherapy. bluebird bio's clinical programs include Lenti-D™, currently in a Phase 2/3 study, called the Starbeam Study, for the treatment of childhood cerebral adrenoleukodystrophy, and LentiGlobin®, currently in three clinical studies: a global Phase 1/2 study, called the Northstar Study, for the treatment of beta-thalassemia major; a single-center Phase 1/2 study in France (HGB-205) for the treatment of beta-thalassemia major or severe sickle cell disease; and a separate U.S. Phase 1 study for the treatment of sickle cell disease (HGB-206). bluebird bio also has ongoing preclinical CAR T immuno-oncology programs, as well as discovery research programs utilizing megaTALs/homing endonuclease gene editing technologies.

bluebird bio has operations in Cambridge, Massachusetts, Seattle, Washington, and Paris, France. For more information, please visit www.bluebirdbio.com.

Kite Pharma, Inc. Forward-Looking Statements

This press release contains forward-looking statements for purposes of the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. The press release may, in some cases, use terms such as "predicts," "believes," "potential," "proposed," "continue," "estimates," "anticipates," "expects," "plans," "intends," "may," "could," "might," "will," "should" or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. Forward-looking statements include statements regarding intentions,

other things: the success of the collaboration between Kite and bluebird; the ability to research and develop existing and new therapeutic candidates, including TCR products directed against HPV antigens; and the expectations regarding the clinical effectiveness and safety of T cell therapies. Various factors may cause differences between Kite's expectations and actual results as discussed in greater detail in Kite's filings with the Securities and Exchange Commission, including without limitation in its Form 10-Q for the quarter ended March 31, 2015. Any forward-looking statements that is made in this press release speak only as of the date of this press release. Kite assumes no obligation to update the forward-looking statements whether as a result of new information, future events or otherwise, after the date of this press release.

bluebird bio, Inc. Forward-Looking Statements

This release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, including statements regarding the research, development and advancement of bluebird bio's immuno-oncology product candidates and research programs. Any forward-looking statements are based on management's current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to, the risk that bluebird bio's immuno-oncology research programs, including those shared with Kite will be unsuccessful and not identify any viable product candidates or will not be safe or effective in clinical trials, the risk of cessation or delay of any of the planned clinical studies and/or our development of our immuno-oncology product candidates, the risk of a delay in the enrollment of patients in bluebird's clinical studies, the risk that our collaboration with Kite around HPV-16 E6 product candidates will not continue or will not be successful, and the risk that any one or more of our product candidates will not be successfully developed and commercialized. For a discussion of other risks and uncertainties, and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, see the section entitled "Risk Factors" in our most recent quarterly report on Form 10-Q, as well as discussions of potential risks, uncertainties, and other important factors in our subsequent filings with the Securities and Exchange Commission. All information in this press release is as of the date of the release, and bluebird bio undertakes no duty to update this information unless required by law.

[1] World Health Organization, Human papillomavirus (HPV) and cervical cancer, Fact sheet N°380, accessed 6/10/15.

[2] GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012 (http://globocan.iarc.fr/Default.aspx), accessed 6/10/15.

[3] Human papillomavirus and rising oropharyngeal cancer incidence in the United States, Journal of Clinical Oncology, 2011: 29(32):4294-4301.

(http://www.cdc.gov/cancer/hpv/statistics/cases.htm), accessed 6/10/15.

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

Media:
Justin Jackson
Burns McClellan
212-213-0006
jjackson@burnsmc.com

bluebird bio, Inc.
Investor Relations:
Manisha Pai, 617-245-2107
mpai@bluebirdbio.com
or
Media:
Pure Communications
Dan Budwick, 973-271-6085

Source: Kite Pharma, Inc.

Sweeney, Timothy (NIH/NCI) [E]

From: Arie Belldegrun <Arie@kitepharma.com>
Sent: Tuesday, June 23, 2015 10:05 AM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: Fwd: NVS
Attachments: image001.jpg

Please see from today. That have timed it around your talk today!! Questions will follow from analysts!

Arie

Begin forwarded message:

From: Ran Nussbaum <ran@pontifax.com>
Date: June 23, 2015 at 08:49:24 EDT
To: David Chang <DChang@KitePharma.com>, Arie Belldegrun <Arie@kitepharma.com>, Helen Kim <HKim@KitePharma.com>, Margo Roberts <mroberts@kitepharma.com>
Cc: Jeff Rowbottom <jeff@pontifax.com>, Cynthia Butitta <CButitta@KitePharma.com>
Subject: NVS

Novartis Institute For Biomedical Research (NIBR)
CART
NVS's pivotal Phase III trial in pediatric r/r ALL started in March and initiation of the pivotal DLBCL trial is expected to start in H2:15. Filing in these indications is expected for late 2016 (ALL) and 2017 (DLBCL). CART targeting EGFRvIII to treat glioma has entered the clinic with early data presented at ASCGT. Additional CARTs targeting MM and AML are expected to enter the clinic in H2:15. Despite the enthusiasm around CART in hematological malignancies, Novartis cautioned that finding a safe target in solid tumors is challenging. Most targets overexpressed in solid tumors have some levels of expression in normal tissue and their targeting can lead to severe side effects. For example, HER2 is expressed at low levels in the lining of the lungs and a CART approach against HER2 in breast cancer led to severe respiratory toxicity. CTL019 sales are forecast at $500MM in 2020.

Best Regards,
Ran Nussbaum
Managing partner

Tel +97299725617
Fax +97299725618
Ran@pontifax.com

The message was checked by ESET NOD32 Antivirus.

http://www.eset.com

Sweeney, Timothy (NIH/NCI) [E]

From: Arie Belldegrun <Arie@kitepharma.com>
Sent: Tuesday, June 23, 2015 10:04 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]
Subject: FW: STIFEL: KITE ($62.72, Buy) - Kite Investor Day Update and Bluebird Bio Collaboration
Attachments: ATT00002.png; ATT00003.gif; ATT00001

Hi Steve,

Thank you so much for making the efforts to come to NY. I heard only raving reviews about your presence and presentation.

Here is the first report. The next ones will be sent to you separately.

Thanks,

Arie

Arie Belldegrun, MD FACS
President and CEO, Founder
Chairman, Board of Directors
Kite Pharma

2225 Colorado Ave
Santa Monica, CA 90404
Tel:310-622-9093
www.kitepharma.com

From: Lisa Burns [mailto:LBurns@burnsmc.com]
Sent: Tuesday, June 23, 2015 6:33 PM
To: Arie Belldegrun; Cynthia Butitta; David Chang
Cc: Linda Barnes; Kate Bechtold; Kite Team
Subject: Fwd: STIFEL: KITE ($62.72, Buy) - Kite Investor Day Update and Bluebird Bio Collaboration

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> **From:** Thomas Shrader <shradert@stifel.com>
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> **Reply-To:** "Thomas Shrader" <shradert@stifel.com>

[redacted]

June 23, 2015

Kite Pharma, Inc.
KITE – NASDAQ

Buy
Biotechnology

Company Update

CLICK HERE FOR FULL REPORT

Kite Investor Day Update and Bluebird Bio Collaboration

This afternoon we attended Kite Pharma's Investor Day where management provided a corporate overview and the company's key collaborator at the NCI (Steven Rosenberg) gave an overview of the field that hinted at some potentially earthshaking data to come (see below). Kite's recent collaboration with Bluebird was reviewed and looks like a high-level hand-holding exercise as both companies look to enter new areas without wasting time. As expected, the next IND will involve TCRs targeting HPV proteins which are increasingly being viewed as the best TCR target outside of neoantigens.

Rosenberg's Next Miracle? Steven Rosenberg delivered principally an overview of the field but also showed a slide of some patients where **his group at the NCI has isolated both neoantigens and their recognizing TCRs** from tumors other than melanoma – specifically gastrointestinal cancers. As a result, we expect he has treated these patients with TCR therapeutics and early data can't be far away (SR has been mentioning this program since ASH). We believe if these data are compelling and CRs are seen for neoantigen-based TCR therapeutics it will be viewed as a major proof-of-concept for Kite's focus on the neoantigen approach in solid tumors. As we have said in previous notes – the operational hurdles for this approach to treating solid tumors are non-trivial – but the approach puts cure on the table for as many as 50% of patients with solid tumors.

The Bluebird Collaboration. The two companies yesterday announced a collaboration agreement to co-develop second generation TCR products, specifically product candidates directed against the HPV-16 E6 oncoprotein. With Bluebird being a gene-editing focused company and Kite specializing in T-Cell therapeutics, the two will leverage each other's strengths to design next-generation T-Cell therapeutics. Kite is almost certainly looking to modify TCR therapeutics to combat the immunosuppressive tumor environment. As a result, we expect they are knocking out some of the receptors found on T-Cells that tumors use to put tumor-hunting TCRs to sleep. As reported at ASCO 2015, KTE019 T-Cells begin to express PD-1 after introduction into patients and tumor cells are expected to express PD-L1 and the resultant interaction potentially reduces efficacy. As a result, knocking out PD-1 in TCR (and CAR-T) therapeutics seems like an obvious things to try. The subsequent list of candidate genes to delete to stimulate TCR therapeutics is very long – probably spurring Kite's urge to find an expert partner.

Next IND – HPV. As was probably expected, Kite's second IND submission will be a TCR therapeutic targeting Human papillomavirus (HPV, a first generation

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We use a multiple of future earnings to derive our $83 target price for KITE. Specifically, to generate our valuation for

development-stage biotech companies, we use a 30x multiple of future earnings, which represents a discount to the 20-year average earnings multiple for profitable biotech companies of 37x. Kite's valuation is driven primarily by KTE-C19, currently in Phase I/IIa testing. We apply a 25% discount rate, which we feel reflects the degree of uncertainty surrounding KTE-C19. With a multiple of 30x, we calculate a $83 target price based on our 2022 diluted EPS estimate of $15.92, discounted back 7.5 years.

Development risk for KTE-C19 - If Kite is not able to successfully develop the experimental CAR-T technology, we would have to lower our revenue estimates.

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Regulatory risk for KTE-C19 - The FDA has never approved a CAR-T-based therapy before and there exists no precedent for the approval of a genetically engineered autologous cell product. If KTE-C19 is not approved on the timeline that we envision, we would have to reduce our estimates.

Changes	Previous	Current
Rating	—	Buy
Target Price	—	$83.00
FY15E EPS	—	$(1.49)
FY16E EPS	—	$0.02

Price (06/23/15):	$62.72
52-Week Range:	$89 – $21
Market Cap.(mm):	2,665.6
Dividend($ / %)	$0.00 / 0.0%

Thomas Shrader, PhD, CFA
shradert@stifel.com
(212) 271-3577

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One more- from top analyst and most respected- Eric Schmidt from Cowen.

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LINK TO FULL REPORT & DISCLOSURES

Biotechnology
Kite Pharma

June 23, 2015

Price: $62.72
(06/23/2015)
Price Target: NA

OUTPERFORM (1)

Depth Of Scientific Expertise Highlighted At Investor Day

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

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

Key Data

Symbol	NASDAQ: KITE
Market Cap (MM)	$2,700.7

The Cowen Insight

At yesterday's analyst day in NYC, Kite unveiled new technologies, reviewed its scientific foundation and aspirations, and provided a pipeline update. Kite's Phase I/II DLBCL trial continues to enroll patients and an ongoing HPV E6 TCR trial has generated responses in solid tumors. We continue to view Kite as the leader in engineered T cells and remain at Outperform.

Much Progress Has Been Made, But Kite Isn't Resting

Yesterday, Kite hosted an analyst event in New York. Management reviewed the significant progress it has made over the past year since its IPO. Kite has transitioned chimeric antigen receptor (CAR) T cell manufacturing outside of NCI, initiated a potentially pivotal program in DLBCL, begun construction of commercial manufacturing facilities, and significantly expanded its scientific expertise via the acquisition of T Cell Factory, a broadened CRADA with NCI, and collaborations with Amgen and bluebird bio. In addition, Kite set out its vision for the future of engineered T cell therapy. This vision includes new methods for manipulating the activation/inhibition of T

cells, a significant focus on T cell receptor (TCR) -based therapies for shared antigens, and ultimately TCRs specific for an individual patient's neo-antigens.

Kite Is Leading On The Science

There are three major approaches to cancer immunotherapy, (1) nonspecific activation of immune cells via stimulation (e.g. IL-2) or blocking inhibitory signals (e.g. PD-1), (2) immunization (e.g. Provenge, T-Vec), or (3) the transfer of *ex vivo* activated immune cells (eg. TILs, CAR T cells). Kite is focused on developing therapies belonging to the last category of immunotherapies. Specifically, Kite is developing engineered T cells that express CARs or TCRs specific for cancer antigens. Kite highlighted the immense depth of scientific experience in engineered T cells, immunology, oncology, and product development represented across the organization both through internal employees (Drs. Chang, Roberts, and Schumacher) and key external advisors/collaborators (Drs. Levy, Rosenberg, and Witte). Together these individuals were instrumental in the creation of the first CAR administered to humans (Dr. Roberts), the first successful cancer immunotherapy (Dr. Rosenberg), and multiple revolutionary cancer drugs including Rituxan (Dr. Levy) and Gleevec (Dr. Witte). Kite

and others have presented data indicating significant efficacy with CD19 CARs and NY-ESO-1 TCRs. We believe Kite has assembled the team required to make engineered T cells applicable to a broad portion of oncology. To accomplish this goal, Kite's efforts are focused on two primary methods to increase the breadth of tumors addressable by engineered T cells. First is identifying the appropriate cancer specific antigens to attack and second is developing secondary technologies to improve the activity of engineered T cells.

First Generation CARs Are Great But More Is Needed

Kite's collaborators discussed that CD19 is a nearly perfect antigen given its uniform expression across multiple tumor types and restriction to a healthy cell type (B cells) that can live without. Kite and its collaborators believe additional attractive antigens exist. One such antigen is EGFRvIII. Working with NCI, Kite has treated ~15 patients (GBM and head and neck cancers) at NCI using an EGFRvIII CAR construct. Dr. Rosenberg reported that dose escalation has just now reached the level where one could imagine seeing efficacy but that as of now no responses have been observed. Kite's collaboration with Amgen should provide additional attractive CAR candidates. This collaboration is directed at converting Amgen's library of antigen

targets and antibody sequences into CAR constructs for the treatment of AML, multiple myeloma, kidney, and lung cancers. The first IND from this collaboration is expected in H2:16. While hopeful for these efforts, Kite and its collaborators noted that 20+ years of antibody development had likely identified the few targets that fit the CD19-like expression criteria. Therefore, Kite is pursuing two mechanisms to broaden the list of potential tumor targets.

Second Generation CAR Therapies Bring Intelligence To The T Cell

First, Kite is working preclinically to develop second generation "logic gated" CAR therapies that require a targeted cell to either simultaneously express two antigens or perhaps more significantly express one antigen but not a second. These engineered T cells will simultaneously express two CAR constructs. In order to introduce an "and" operator the constructs will separately contain the primary stimulation (e.g. CD3) and secondary stimulation (e.g. CD28) signaling domains. Conversely, an "and not" operator can be introduced by using a traditional CAR construct containing both the primary and secondary stimulation domains in combination with a second CAR construct that contains an inhibitory domain. Consequently, if an off-target

cell expresses the target antigen but also the inhibitory antigen it will be spared whereas a tumor cell that only expresses the target antigen will be killed. Kite believes second generation CAR therapies are 2-3 years away from the clinic.

TCRs Triple The Potentially Addressable Antigens

Second, Kite is using T cell receptors to pursue the ~75% of proteins that are expressed intracellularly and are therefore inaccessible to antibody recognition. Kite currently has four TCR constructs (NY-ESO-1, MAGE A3/A6, MAGE A3. and HPV-16 E6) in the clinic and plans to initiate clinical trials on at least three additional constructs (HPV-16 E7, SSX2, and KRAS) within the next 18 months.
Kite acquired Dr. Ton Schumacher's T Cell Factory (TCF) to further expand the TCR pipeline. TCF's core TCR GENErator technology allows for the rapid isolation of high-affinity TCR sequences. Since TCR based therapies' target populations are restricted by MHC expression (ex. HLA-A2 is only expressed by ~50% of Caucasians) the TCF technology will be deployed to identify TCR sequences that utilize alternative MHC sequences to target the same antigen. Kite believes three TCR sequences per antigen are sufficient to cover >80% of the global population and approximately five sequences

can cover >90% of the global population. In addition, the TCR GENErator will be deployed to identify TCRs specific for neo-antigens being identified under the NCI CRADA. Dr. Rosenberg reports that his lab is able to complete exome sequencing of tumor samples within 48 hours of receiving the sample. Within an additional 48 hours Dr. Rosenberg's group is able to identify the subset of peptides that are actually presented on MHC molecules within the tumor. Dr. Rosenberg has now performed this protocol using samples from >25 melanoma and 16 GI cancer patients. Published data on the melanoma patients indicates that neo-antigens were presented universally, but each patient contained unique neo-antigens. Dr. Rosenberg disclosed that he has since found at least one melanoma patient with shared neo-antigens. Among the GI cancer patients, 15 were found to present neo-antigens. These neo-antigen profiles have not been published yet. With the TCR GENErator, Kite now possesses a high-throughput manner by which high-affinity TCRs specific to neo-antigen peptides can be isolated. Drs. Rosenberg and Schumacher believe that experience with TIL therapy indicates the simultaneous use of two to three neo-antigen TCR specificities should be sufficient to control many tumors. Kite has previously indicated that this ultimate in personalized medicine could

be ready for clinical trials in 3-5 years.

HPV E6 TCR Shows Efficacy In Solid Tumors

Human papilloma virus (HPV) is associated with numerous cancers including anal, head and neck, and the majority of cervical cancers. These cancers lead to ~15,000 deaths/yr in the U.S. Dr. Rosenberg recently published proof of concept data showing durable responses in two out of nine patients treated with HPV specific tumor infiltrating lymphocytes (TILs). Kite and Dr. Rosenberg have followed up these findings with an HPV E6 specific TCR product. Dr. Rosenberg disclosed for the first time that using this construct he has observed "multiple responses". As a result, Kite plans to transition the HPV-16 E6 program from an NCI held IND to a Kite held IND in early 2016.

Kite Is Also Working To Increase T Cell Activity

Beyond expanding the list of antigen targets, Kite is also developing methods by which it can make its T cells more potent. Preclinical studies have shown that IL-7 and IL-15 expression is vital for the engraftment and efficacy of CAR T cells. Working with NCI, Kite has conducted work to optimize the preconditioning regimen for among other parameters the generation of IL-7 and IL-15 expression. Preclinical work has also demonstrated that

engineered T cells that have undergone less *ex vivo* differentiation generate superior efficacy. Kite and NCI have developed a small molecule (KTE-SM01) that is capable of decoupling T cell proliferation and differentiation. The identity of KTE-SM01's target was not disclosed, but based upon a literature review we believe it to be an AKT kinase inhibitor. Using KTE-SM01, Kite hopes to generate T cell products that are skewed towards a stem cell memory phenotype. Kite is now working to include KTE-SM01 in its next generation T cell manufacturing protocol.

Kite is also pursuing strategies to combine engineered T cells with additional therapeutic manipulations including checkpoint inhibition and/or coexpression of cytokines. Kite intends to develop a second generation HPV E6 TCR therapy that contains an additional modification(s). Earlier this week, Kite signed a collaboration with bluebird bio for this project. Under the collaboration Kite and bluebird bio will develop an engineered T cell product using (1) Kite's HPV E6 TCR sequence, (2) bluebird's lentiviral delivery system and (3) bluebird's gene editing platform to modify activating/inhibitory pathways. Kite indicated that this project could result in clinical trials in 2-3 years.

KTE-C19's Pivotal DLBCL Trial Progressing

Kite has successfully transitioned production of KTE-C19 from NCI to its contract manufacturer (PTC). Last month, PTC produced cells were used to dose the first patient in Kite's potentially pivotal Phase I/II trial of KTE-C19 in DLBCL. For the Phase I portion, Kite is currently enrolling patients at four clinical sites. If no more than two dose limiting toxicities are observed among the first six patients, Kite will progress to the Phase II portion and enroll 50 patients from 20-25 clinical sites. This is expected to occur in H2:15. Data from the Phase I portion, including the trial's cell dose and preconditioning regimen will be presented at ASH 2015. Phase II data is expected to be released in 2016. Kite believes historical data indicates a <20% ORR and 4-5 month mOS would be expected. Therefore, an ORR of at least 40% with a mOS of at least 6 months is expected to be approvable. Simultaneous to beginning the Phase II portion of the DLBCL trial, Kite intends to initiate a Phase II trial of KTE-C19 in MCL. Also in H2:15, Kite plans to initiate a Phase I/II ALL trial and a Phase II CLL trial.

Sweeney, Timothy (NIH/NCI) [E]

From: David Chang <DChang@KitePharma.com>
Sent: Tuesday, June 23, 2015 11:25 PM
To: Owen N. Witte; Ron Levy; Rosenberg, Steven A. (NIH/NCI) [E]; Ton Schumacher
Cc: Margo Roberts; Marc Better; Jeff Wiezorek
Subject: Fwd: STIFEL: KITE ($62.72, Buy) - Kite Investor Day Update and Bluebird Bio Collaboration
Attachments: ATT00002.png; ATT00003.gif; ATT00001

FYI.

David Chang, MD, PhD
office: (310) 622-9094
Personal Information,Redacted Per Agreement
www.kitepharma.com

Sent from my iPad

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From: Lisa Burns <LBurns@burnsmc.com>
Date: June 23, 2015 at 9:32:59 PM EDT
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June 23, 20

Kite Pharma, I
KITE – NASD
B

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LINK TO FULL REPORT & DISCLOSURES

Biotechnology

Kite Pharma

Equity Research | Quick Take: Company Update

June 23, 2015

Price: $62.72 (06/23/2015)
Price Target: NA

OUTPERFORM (1)

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Second, Kite is using T cell receptors to pursue the ~75% of proteins that are expressed intracellularly and are therefore inaccessible to antibody recognition. Kite currently has four TCR constructs (NY-ESO-1, MAGE A3/A6, MAGE A3. and HPV-16 E6) in the clinic and plans to initiate clinical trials on at least three additional constructs (HPV-16 E7, SSX2, and KRAS) within the next 18 months.
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Human papilloma virus (HPV) is associated with numerous cancers including anal, head and neck, and the majority of cervical cancers. These cancers lead to ~15,000 deaths/yr in the U.S. Dr. Rosenberg recently published proof of concept data showing durable responses in two out of nine patients treated with HPV specific tumor infiltrating lymphocytes (TILs). Kite and Dr. Rosenberg have followed up these findings with an HPV E6 specific TCR product. Dr. Rosenberg disclosed for the first time that using this construct he has observed "multiple responses". As a result, Kite plans to transition the HPV-16 E6 program from an NCI held IND to a Kite held IND in early 2016.

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Sweeney, Timothy (NIH/NCI) [E]

From: Arie Belldegrun <Arie@kitepharma.com>
Sent: Wednesday, June 24, 2015 6:26 PM
To: Rosenberg, Steven A. (NIH/NCI) [E]; Ron Levy; Owen N. Witte MD; Ton Schumacher
Subject: Fwd: Investor Day Analyst Reports
Attachments: Kite June 23-24 analyst reports.docx; ATT00001.htm; CanaccordJune242015.pdf; ATT00002.htm; CowenJune232015.pdf; ATT00003.htm; GuggenheimJune242015.pdf; ATT00004.htm; JefferiesJune242015.pdf; ATT00005.htm; MizuhoJune242015.pdf; ATT00006.htm; StifelJune232015.pdf; ATT00007.htm

Steve, Ron, Owen, and Ton,

Thank you all for yesterday's stellar performance. You were truly a dream team!

I am sending you an unbiased report on the event yesterday, as perceived by the analysts who covered it, and the originals from the write ups so far.

Proprietary Information,Redacted Per Agreement

I started today at 6.30 AM at CNBC for a morning show and interview, and spent the rest of the day at the offices of WSJ (steve, Ron Winslow will call you for further interview), Bloomberg , and Forbes for additional interviews.
I am happy to be now on my way to LA!

Thanks again.

Arie

Begin forwarded message:

From: "Carol Werther" <cwerther@burnsmc.com>
To: "Arie Belldegrun" <Arie@kitepharma.com>, "David Chang" <DChang@KitePharma.com>, "Cynthia Butitta" <CButitta@KitePharma.com>, "Helen Kim" <HKim@KitePharma.com>, "Margo Roberts" <MRoberts@KitePharma.com>, "Marc Better" <MBetter@KitePharma.com>, "Jeff Wiezorek" <JWiezorek@KitePharma.com>, "Ton Schumacher" <tschumacher@kitepharma.com>, "Rajul Jain" <RJain@KitePharma.com>, "Kate Bechtold" <kbechtold@kitepharma.com>, "Linda Barnes" <LBarnes@KitePharma.com>
Cc: "Kite Team" <Kite_Team@burnsmc.com>
Subject: Investor Day Analyst Reports

Dear Arie, Cindy, David, Jeff, Marc, Margo, Ton, Helen, Rajul, Kate and Linda,

Proprietary Information,Redacted Per Agreement

Proprietary Information,Redacted Per Agreement

Sincerely,

BMC KITE team

Summary of Analyst Kite Comments:

Jefferies, Biren Amin: BUY, PT $83.00
Title: Kite Shares Its Vision at Analyst Day
Key Takeaways: KITE hosted an analyst day where it reiterated its clinical development plan for KTE-C19, plans to move add'l CAR/TCR targets to clinical trials, and pot'l new strategies to improve T-cell expansion and the introduction of a pot'l CAR to prevent off-target effects on healthy cells. The company is on track to disclosing topline data from the pilot trial enrolling patients with diffuse large B-cell lymphoma (DLBCL) at ASH '15.

Notes on Biren's Take:

Proprietary Information,Redacted Per Agreement

Stifel, Tom Shrader: BUY, PT $83.00
Title: KITE Investor Day Update and Bluebird Bio Collaboration
Summary: This afternoon we attended Kite Pharma's Investor Day where management provided a corporate overview and the company's key collaborator at the NCI (Steven Rosenberg) gave an overview of the field that hinted at some potentially earthshaking data to come (see below). Kite's recent collaboration with Bluebird was reviewed and looks like a high-level hand-holding exercise as both companies look to enter new areas without wasting time. As expected, the next IND will involve TCRs targeting HPV proteins which are increasingly being viewed as the best TCR target outside of neoantigens.

Notes on Tom's Take:

Proprietary Information,Redacted Per Agreement

Guggenheim, Tony Butler: BUY, PT $73.00
Title: KITE – BUY – Investor day 2015; Kite and Bluebird Soar Together into TCR's

Notes on Tony's Take:

Proprietary Information,Redacted Per Agreement

Proprietary Information,Redacted Per Agreement

Cowen, Eric Schmidt, No PT
Title: Depth of Scientific Expertise Highlighted At Investor Day
Summary: The Cowen Insight: At yesterday's analyst day in NYC, Kite unveiled new technologies, reviewed its scientific foundation and aspirations, and provided a pipeline update. Kite's Phase I/II DLBCL trial continues to enroll patients and an ongoing HPV E6 TCR trial has generated responses in solid tumors. We continue to view Kite as the leader in engineered T cells and remain at Outperform.

Notes on Eric's Take:

Proprietary Information,Redacted Per Agreement

Canaccord, John Newman: BUY, PT $90.00

Title: TCRs center stage at R&D day, KRAS , HPV-16 E7 enter clinic in 2015
Notes on John's Take:

Proprietary Information,Redacted Per Agreement

Mizuho, Peter Lawson; PT $90
Title: Investor Day – Under the Hood; No Near-Term Changes.
Notes on Peter's Take:

Proprietary Information,Redacted Per Agreement

carolwerther | Vice President, Investor Relations
Burns McClellan | 257 Park Ave South, 15 | New York, NY 10010 | T: 212.213.0006
cwerther@burnsmc.com | www.burnsmc.com

June 24, 2015

Dear Arie, Cindy, David, Jeff, Marc, Margo, Ton, Kate and Linda,

We are sending the original and our quick summary of 6 of your covering analysts.

Proprietary Information,Redacted Per Agreement

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Notes on Peter's Take:

Proprietary Information,Redacted Per Agreement

COWEN
AND COMPANY

Biotechnology

Kite Pharma

Equity Research

Quick Take: Company Update

June 23, 2015

Price: $62.72 (06/23/2015)
Price Target: NA

OUTPERFORM (1)

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

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

Key Data

Symbol	NASDAQ: KITE
Market Cap (MM)	$2,700.7

Depth Of Scientific Expertise Highlighted At Investor Day

The Cowen Insight

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Much Progress Has Been Made, But Kite Isn't Resting

Yesterday, Kite hosted an analyst event in New York. Management reviewed the significant progress it has made over the past year since its IPO. Kite has transitioned chimeric antigen receptor (CAR) T cell manufacturing outside of NCI, initiated a potentially pivotal program in DLBCL, begun construction of commercial manufacturing facilities, and significantly expanded its scientific expertise via the acquisition of T Cell Factory, a broadened CRADA with NCI, and collaborations with Amgen and bluebird bio. In addition, Kite set out its vision for the future of engineered T cell therapy. This vision includes new methods for manipulating the activation/ inhibition of T cells, a significant focus on T cell receptor (TCR) -based therapies for shared antigens, and ultimately TCRs specific for an individual patient's neo-antigens.

Kite Is Leading On The Science

There are three major approaches to cancer immunotherapy, (1) nonspecific activation of immune cells via stimulation (e.g. IL-2) or blocking inhibitory signals (e.g. PD-1), (2) immunization (e.g. Provenge, T-Vec), or (3) the transfer of *ex vivo* activated immune cells (eg. TILs, CAR T cells). Kite is focused on developing therapies belonging to the last category of immunotherapies. Specifically, Kite is developing engineered T cells that express CARs or TCRs specific for cancer antigens. Kite highlighted the immense depth of scientific experience in engineered T cells, immunology, oncology, and product development represented across the organization both through internal employees (Drs. Chang, Roberts, and Schumacher) and key external advisors/ collaborators (Drs. Levy, Rosenberg, and Witte). Together these individuals were instrumental in the creation of the first CAR administered to humans (Dr. Roberts), the first successful cancer immunotherapy (Dr. Rosenberg), and multiple revolutionary cancer drugs including Rituxan (Dr. Levy) and Gleevec (Dr. Witte). Kite and others have presented data indicating significant efficacy with CD19 CARs and NY-ESO-1 TCRs. We believe Kite has assembled the team required to make engineered T cells applicable to a broad portion of oncology. To accomplish this goal, Kite's efforts are focused on two primary methods to increase the breadth of tumors addressable by engineered T cells. First is identifying the appropriate cancer specific antigens to attack and second is developing secondary technologies to improve the activity of engineered T cells.

First Generation CARs Are Great But More Is Needed

Kite's collaborators discussed that CD19 is a nearly perfect antigen given its uniform expression across multiple tumor types and restriction to a healthy cell type (B cells) that can live without. Kite and its collaborators believe additional attractive antigens exist. One such antigen is EGFRvIII. Working with NCI, Kite has treated ~15 patients (GBM and head and neck cancers) at NCI using an EGFRvIII CAR construct. Dr. Rosenberg reported that dose escalation has just now reached the level where one could imagine seeing efficacy but that as of now no responses have been observed. Kite's collaboration with Amgen should provide additional attractive CAR candidates. This collaboration is directed at converting Amgen's library of antigen targets and antibody sequences into CAR constructs for the treatment of AML, multiple myeloma, kidney, and lung cancers. The first IND from this collaboration is expected in H2:16. While hopeful for these efforts, Kite and its collaborators noted that 20+ years of antibody development had likely identified the few targets that fit the CD19-like expression criteria. Therefore, Kite is pursuing two mechanisms to broaden the list of potential tumor targets.

Second Generation CAR Therapies Bring Intelligence To The T Cell

First, Kite is working preclinically to develop second generation "logic gated" CAR therapies that require a targeted cell to either simultaneously express two antigens or perhaps more significantly express one antigen but not a second. These engineered T cells will simultaneously express two CAR constructs. In order to introduce an "and" operator the constructs will separately contain the primary stimulation (e.g. CD3) and secondary stimulation (e.g. CD28) signaling domains. Conversely, an "and not" operator can be introduced by using a traditional CAR construct containing both the primary and secondary stimulation domains in combination with a second CAR construct that contains an inhibitory domain. Consequently, if an off-target cell expresses the target antigen but also the inhibitory antigen it will be spared whereas a tumor cell that only expresses the target antigen will be killed. Kite believes second generation CAR therapies are 2-3 years away from the clinic.

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Valuation Methodology And Risks

Valuation Methodology

Biotechnology:

In calculating our 12-month target price, we employ one or more valuation methodologies, which include a discounted earnings analysis, discounted cash flow analysis, net present value analysis and/or a comparable company analysis. These analyses may or may not require the use of objective measures such as price-to-earnings or price-to-sales multiples as well as subjective measures such as discount rates.

We make investment recommendations on early stage (pre-commercial) biotechnology companies based upon an assessment of their technology, the probability of pipeline success, and the potential market opportunity in the event of success. However, because these companies lack traditional financial metrics, we do not believe there are any good methodologies for assigning a specific target price to such stocks.

Investment Risks

Biotechnology:

There are multiple risks that are inherent with an investment in the biotechnology sector. Beyond systemic risk, there is also clinical, regulatory, and commercial risk. Additionally, biotechnology companies require significant amounts of capital in order to develop their clinical programs. The capital-raising environment is always changing and there is risk that necessary capital to complete development may not be readily available.

Risks To The Price Target

Kite Pharma is unprofitable, has no approved products, and will likely need to raise additional capital from the public markets prior to turning profitable. There is limited clinical trial experience on lead candidate KTE-C19, and eACT's more broadly. Moreover, KTE-C19 faces a number of clinical, regulatory, and commercial hurdles prior to becoming successful, and projecting any future sales for KTE-C19 is inherently difficult.

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Addendum

Stocks Mentioned In Important Disclosures

Ticker	Company Name
KITE	Kite Pharma

Analyst Certification

Each author of this research report hereby certifies that (i) the views expressed in the research report accurately reflect his or her personal views about any and all of the subject securities or issuers, and (ii) no part of his or her compensation was, is, or will be related, directly or indirectly, to the specific recommendations or views expressed in this report.

Important Disclosures

Cowen and Company, LLC and or its affiliates make a market in the stock of Kite Pharma securities.

Kite Pharma has been client(s) of Cowen and Company, LLC in the past 12 months.

Kite Pharma is or was in the past 12 months a client of Cowen and Company, LLC; during the past 12 months, Cowen and Company, LLC provided IB services.

Cowen and Company, LLC and/or its affiliates received in the past 12 months compensation for investment banking services from Kite Pharma.

Cowen and Company, LLC and/or its affiliates managed or co-managed a public offering of Kite Pharma within the past twelve months.

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For important disclosures regarding the companies that are the subject of this research report, please contact Compliance Department, Cowen and Company, LLC, 599 Lexington Avenue, 20th Floor, New York, NY 10022. In addition, the same important disclosures, with the exception of the valuation methods and risks, are available on the Firm's disclosure website at https://cowen.bluematrix.com/sellside/Disclosures.action.

Price Targets: Cowen and Company, LLC assigns price targets on all covered companies unless noted otherwise. The price target for an issuer's stock represents the value that the analyst reasonably expects the stock to reach over a performance period of twelve months. The price targets in this report should be considered in the context of all prior published Cowen and Company, LLC research reports (including the disclosures in any such report or on the Firm's disclosure website), which may or may not include price targets, as well as developments relating to the issuer, its industry and the financial markets. For price target valuation methodology and risks associated with the achievement of any given price target, please see the analyst's research report publishing such targets.

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Cowen and Company, LLC. New York (646) 562-1000 **Boston** (617) 946-3700 **San Francisco** (415) 646-7200 **Chicago** (312) 577-2240 **Cleveland** (440) 331-3531 **Atlanta** (866) 544-7009 **London** (affiliate) 44-207-071-7500

COWEN AND COMPANY RATING DEFINITIONS

Cowen and Company Rating System effective May 25, 2013

Outperform (1): The stock is expected to achieve a total positive return of at least 15% over the next 12 months

Market Perform (2): The stock is expected to have a total return that falls between the parameters of an Outperform and Underperform over the next 12 months

Underperform (3): Stock is expected to achieve a total negative return of at least 10% over the next 12 months

Assumption: The expected total return calculation includes anticipated dividend yield

Cowen and Company Rating System until May 25, 2013

Outperform (1): Stock expected to outperform the S&P 500

Neutral (2): Stock expected to perform in line with the S&P 500

Underperform (3): Stock expected to underperform the S&P 500

Assumptions: Time horizon is 12 months; S&P 500 is flat over forecast period

Cowen Securities, formerly known as Dahlman Rose & Company, Rating System until May 25, 2013

Buy – The fundamentals/valuations of the subject company are improving and the investment return is expected to be 5 to 15 percentage points higher than the general market return

Sell – The fundamentals/valuations of the subject company are deteriorating and the investment return is expected to be 5 to 15 percentage points lower than the general market return

Hold – The fundamentals/valuations of the subject company are neither improving nor deteriorating and the investment return is expected to be in line with the general market return

Cowen And Company Rating Definitions

Distribution of Ratings/Investment Banking Services (IB) as of 03/31/15

Rating	Count	Ratings Distribution	Count	IB Services/Past 12 Months
Buy (a)	450	58.67%	103	22.89%
Hold (b)	302	39.37%	8	2.65%
Sell (c)	15	1.96%	0	0.00%

(a) Corresponds to "Outperform" rated stocks as defined in Cowen and Company, LLC's rating definitions. (b) Corresponds to "Market Perform" as defined in Cowen and Company, LLC's ratings definitions. (c) Corresponds to "Underperform" as defined in Cowen and Company, LLC's ratings definitions.

Note: "Buy", "Hold" and "Sell" are not terms that Cowen and Company, LLC uses in its ratings system and should not be construed as investment options. Rather, these ratings terms are used illustratively to comply with FINRA and NYSE regulations.

Kite Pharma Rating History as of 06/22/2015

powered by: BlueMatrix

Legend for Price Chart:

I = Initiation | 1 = Outperform | 2 = Market Perform | 3 = Underperform | UR = Price Target Under Review | T = Terminated Coverage | $xx = Price Target | NA = Not Available | S=Suspended

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FLASH NOTE

Company Update

USA | Healthcare | Biotechnology

June 24, 2015

Jefferies

Kite Pharma (KITE)

Kite Shares Its Vision At Analyst Day

BUY
Price target $83.00
Price $62.72

EQUITY RESEARCH AMERICAS

Key Takeaway

KITE hosted an analyst day where it reiterated its clinical development plan for KTE-C19, plans to move add'l CAR/TCR targets to clinical trials, and pot'l new strategies to improve T-cell expansion and the introduction of a pot'l CAR to prevent off-target effects on healthy cells. The company is on track to disclosing topline data from the pilot trial enrolling patients with diffuse large B-cell lymphoma (DLBCL) at ASH '15.

KTE-C19 Data At ASH '15: KITE has started enrolling pts in its pilot study with KTE-C19, a CD19 CAR-T in DLBCL this quarter with pivotal trial initiating in Q4. The company acknowledged that it is testing a new lymphodepletion regimen which falls btwn the NCI regimen and the "low" dose regimen presented at ASH '14. Based on data from the pilot study, KITE could modify the lymphodepletion regimen for the pivotal studies and the add'l PII studies evaluating KTE-C19. The company will be requiring all patients in the PII trial to enroll in the hospital for the 1st 7 days after infusion as a pre-cautionary measure and a req't similar to the NCI PI/II study. We think this is a prudent measure which may help address any pot'l toxicity issue(s) that may arise in the DLBCL trial. Based on learnings from this trial, the company may reduce/eliminate this req't longer-term. Interim data from the 1st 50 patients in the pivotal trial would drive a BLA filing by YE '16. KITE expects to complete patient enrollment by YE '16. The 1 EP is ORR with data expected in 2016. KITE also plans to initiate trials in acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL) which would initiate by YE '15.

Pipeline Programs Advance: The National Cancer Institute (NCI) has currently five ongoing trials with various targets with KITE having rights to the following cancer antigen targets - NY-ESO1 and HPV-16 E6 w/ KITE anticipating on filing an IND in 1H '16. The company announced NCI plans to initiate clinical testing w/ a KRAS TCR in pancreatic/ colorectal cancer and HPV-16 E7 TCR in cervical cancer in '15. We gained further insights into these programs from NCI's Chief of Surgery Branch, Dr. Steven Rosenberg, who provided his opinions into pot'l optimal targets for solid tumors. Rosenberg believes HPV-16 E6 is de-risked given data in 9 refractory cervical cancer patients treated with TIL therapy and observing 2 CRs and 1 PR with duration of response lasting 22, 15, and 3 mos, respectively (at end of April). Dr. Rosenberg believes EGFRviii could observe activity given the target resides on the tumor cell surface and could be targeted by CAR technology. A trial is currently ongoing evaluating EGFRviii in glioblastoma and have treated 15 patients to date in a slow dose escalation. NCI has not observed any clinical responses however the trial may be somewhat premature given patients have not been treated w/ therapeutic doses. The NCI is also evaluating NY-ESO1 TCR in various tumors and 4 patients have been treated, however, Dr. Rosenberg is less sanguine about the prospects of NY-ESO1 given less than 2% of all patients express the target at less than 50%. In comparison, MAGE A3 could be a better target given it is more commonly expressed. Lastly, Dr. Rosenberg also commented on the UPenn study at AACR evaluating 6 patients w/ mesothelin CAR-T and believes mesothelin may not be an appropriate target given it also is expressed in healthy tissues.

Next Gen Technologies Focused On Improving T Cell Expansion and Preventing Off-Target Effects: KITE introduced two concepts - one focused on generating T cells utilizing pharmacological molecules which may yield younger T cells w/ greater persistence. We think this technology is based on NCI research which focused on Akt inhibition (Crompton et al, Cancer Research 2015) leading to enhanced cell persistence of memory T cells. KITE is also developing a control CAR which at the presence of a healthy cell could signal the self-destruction of the CAR-T cell.

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Company Description

Kite Pharma, Inc. operates as a clinical stage biotechnology company which engages in the development of novel cancer immunotherapeutic products with focus on engineered autologous T cell therapeutics targeted to different tumor types. In addition, the company is advancing a novel therapeutic cancer vaccine aimed to trigger potent and specific immunity against multiple epithelial cancers, which has the potential to complement its eACT programs.

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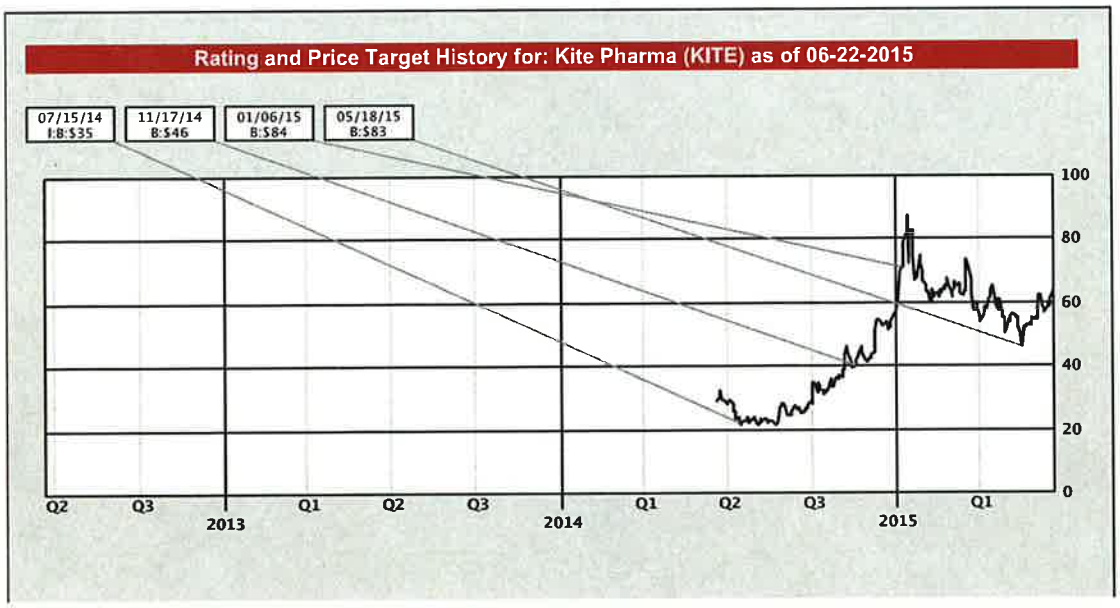

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HOLD	832	39.92%	161	19.35%
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