Cancer Immunotherapy:
Building on Initial Successes to Improve Clinical Outcomes

Allan B. Haberman. Ph.D.
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Cancer Immunotherapy:
Building on Initial Successes to Improve Clinical Outcomes

Allan B. Haberman, Ph.D.

Published in April 2017 by Cambridge Healthtech Institute

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Publisher: Lisa Scimemi  
781-972-5446, lscimemi@healthtech.com

Marketing: Dan Miller  
781-972-5492, dmiller@healthtech.com

Corporate Subscriptions: Dan Miller  
781-972-5492, dmiller@healthtech.com

Customer Service: Adriana Randall  
781-972-5402, arandall@healthtech.com

Production: Thomas Norton  
781-972-5440, tnorton@healthtech.com  
Ann Marie Handy  
781-972-5493, ahandy@healthtech.com
Executive Summary

Cancer Immunotherapy: Building on Initial Successes to Improve Clinical Outcomes

This new report builds on our 2014 Insight Pharma Report, Cancer Immunotherapy: Immune Checkpoint Inhibitors, Cancer Vaccines, and Adoptive T-cell Therapies. In the 2014 report, we focused on the major classes of cancer immunotherapy drugs that were then emerging from academic and corporate research: immune checkpoint inhibitors, cancer vaccines, and adoptive T-cell therapies. This new report includes an updated discussion of approved and clinical stage agents in immuno-oncology, including recently-approved agents. It also addresses the means by which researchers and companies are attempting to build on prior achievements in immuno-oncology to improve outcomes for more patients. Some researchers and companies refer to this approach as “immuno-oncology 2.0.” The American Society of Clinical Oncology (ASCO), in its 12th Annual Report on Progress Against Cancer (2017), named “Immunotherapy 2.0” as its “Advance of the Year.”

As discussed in our 2014 report and still true in early 2017, the most successful class of immunotherapeutics has been the checkpoint inhibitors (discussed in Chapter 2). Checkpoint inhibitors and other immuno-oncology agents represent a significant advance in cancer treatment beyond the traditional modalities of chemotherapy, radiation therapy, and surgery. Moreover, treatment of advanced melanoma (the cancer for which the largest amount of data on immunotherapy has been amassed) with checkpoint inhibitors has in some cases produced spectacular results. For example, data released at the May 2016 ASCO Annual Meeting indicate that 40% of metastatic melanoma patients who received pembrolizumab (Merck’s Keytruda) in a large clinical trial are still alive three years later. This represents a substantial improvement over just a few years ago, when the average survival time for patients with advanced melanoma was measured in months.

Nevertheless, metastatic melanoma remains incurable. Furthermore, in many studies in advanced melanoma and other cancers, only a minority of patients have benefited from immunotherapy treatments. Researchers and companies are therefore looking for ways to build on the initial successes of the immuno-oncology field to improve outcomes for more patients, hence the need for an “immuno-oncology 2.0.” Agents that are intended to improve the results of treatment with agents like checkpoint inhibitors may also be referred to as “second-wave” immuno-oncology agents.

As discussed in this report, researchers have found that checkpoint inhibitors produce tumor responses by reactivating TILs (tumor infiltrating...
lymphocytes)—especially CD8+ cytotoxic T cells. This key observation is perhaps the most important factor driving development of second-wave immuno-oncology strategies. As a result, researchers have been developing biomarkers that distinguish inflamed (i.e. TIL-containing) tumors—which are susceptible to checkpoint inhibitor therapy—from “cold” tumors, which are not. They have also been working to develop means to render “cold” tumors inflamed, via treatment with various conventional therapies and/or development of novel agents. These studies are the major theme of “second-wave” immuno-oncology, or “immuno-oncology 2.0.”

**Approvals of checkpoint inhibitors**

As discussed in Chapter 2, researchers are continuing to conduct clinical trials designed to gain approval for new checkpoint inhibitors and for new indications for already-approved agents. Notable recent developments include the 2016 approval of atezolizumab (Roche/Genentech's Tecentriq), the first PD-L1 (programmed death-ligand 1) inhibitor to be approved. On May 18, 2016 atezolizumab was approved by the FDA for treatment of advanced or metastatic urothelial carcinoma that has worsened during or following platinum-containing chemotherapy or within 12 months of receiving platinum-containing chemotherapy, either before or after surgical treatment. Later, on October 18, 2016, the FDA approved atezolizumab for use in patients with metastatic NSCLC (regardless of PD-L1 expression) who have progressed during or after treatment with a platinum-based chemotherapy or appropriate targeted therapy.

Also in October 2016, the FDA approved the PD-1 (programmed cell death protein 1) inhibitor pembrolizumab as a monotherapy for first-line treatment of patients with advanced NSCLC whose tumors expressed PD-L1 at ≥50%. This was after this agent met its primary endpoint of progression-free survival in patients with previously untreated advanced NSCLC whose tumors expressed PD-L1 at ≥50%. In contrast, monotherapy with the competing PD-1 inhibitor nivolumab (Bristol-Myers Squibb’s Opdivo) did not meet its primary endpoint of progression-free survival in patients with previously untreated advanced NSCLC whose tumors expressed PD-L1 at ≥50%. This result is affecting the competition between BMS' nivolumab and Merck's pembrolizumab.

In Merck’s KEYNOTE-024 trial, the patient population that was treated with either pembrolizumab or chemotherapy consisted of individuals with previously untreated advanced NSCLC whose tumors expressed PD-L1 at ≥50%. In contrast, BMS’ CheckMate 026 trial of nivolumab as a monotherapy evaluated the drug in patients with previously untreated advanced NSCLC whose tumors expressed PD-L1 at ≥50%. This difference in trial design may explain the divergent results of the two trials, rather than a potential superior efficacy of pembrolizumab over nivolumab. Nevertheless, the results of the KEYNOTE-024 trial advance the prospects of Merck’s pembrolizumab for first-line treatment of advanced NSCLC with high levels of PD-L1 expression, while BMS must conduct an evaluation of its study and decide what to do next.

In addition to the discussions of approved checkpoint inhibitors, Chapter 2 also includes discussions of clinical stage agents in this class. These include Novartis’ PD-1 inhibitor PDR001, AstraZeneca’s PD-L1 inhibitor durvalumab, and Merck-Serono/Pfizer’s PD-L1 inhibitor avelumab. Notably, avelumab has been under evaluation in a pivotal Phase 2 trial in Merkel cell carcinoma, with favorable results reported in the 2016 ASCO annual meeting. Merck-Serono and Pfizer plan to submit the drug to regulatory authorities based on these results.
Biomarkers for checkpoint inhibitor treatments

The later sections of Chapter 2 discuss the role of biomarkers in checkpoint inhibitor treatments, especially in the context of “immuno-oncology 2.0.” “Immuno-oncology 2.0” may involve development of novel agents, such as those discussed in this and other chapters of the report. It may also involve combining different immunotherapies, combining immunotherapies with older types of treatments and/or with new experimental treatments, or other novel approaches. The development and use of biomarkers will be key to the progress of “immuno-oncology 2.0.” Biomarkers will help researchers and physicians predict responses to immunotherapy treatments. Such tests may not only spare patients the costs and adverse effects of treatments that may not help them, but may also help researchers to design optimal, “personalized” treatments.

Several classes of biomarkers are in use and/or development for cancer immunotherapy, and especially for use in combination with checkpoint inhibitors. A target biomarker is a biomarker that reflects the presence of a specific molecular drug target. In the case of PD-1 inhibitors, the direct target is PD-1, and the downstream target (i.e. the ligand of PD-1 that is affected by its binding) is PD-L1. In the case of PD-L1 inhibitors, the direct target is PD-L1. Recent results from studies of first-line treatment of advanced NSCLC with either nivolumab or pembrolizumab as a monotherapy demonstrate the potential value of PD-L1 as a biomarker in treatment of patients with PD-1 inhibitors.

PD-L1 expression might still respond to the drug, the greater efficacy of atezolizumab in those classified as positive for PD-L1 expression suggests that the level of PD-L1 expression in tumor-infiltrating immune cells may help identify patients more likely to respond to treatment with the agent.

Target biomarkers—especially PD-L1—are being used to define patient subsets that can productively be treated with a checkpoint inhibitor, especially in clinical trials and in approval decisions by regulatory agencies. However, these tests imperfectly discriminate between patients who can benefit from these therapeutics and those who cannot. Moreover, they are of little use in designing improved therapies that build on current checkpoint inhibitor therapies to improve patient outcomes.

Genetic biomarkers are also under investigation for use in cancer immunotherapy. In immuno-oncology, genetic biomarkers are generally used to determine the likelihood that a patient’s tumors possess a sufficient somatic mutation load to support a large and diverse population of CD8+ TILs, which are specific for mutation-associated neoantigens. Treatment with checkpoint inhibitors can then reactivate these TILs, resulting in effective antitumor immune responses. Examples of genetic biomarkers discussed in this report include mismatch repair (MMR) deficiency and mutation load, as determined by whole-exome sequencing.

Immunological biomarkers enable direct testing to determine whether a patient’s tumors contain sufficient TILs to enable successful treatment with a checkpoint inhibitor. In particular, researchers have found that CD8+ TILs located at the invasive margin of a tumor (as determined, for example, by quantitative immunohistochemistry) appear to be necessary for successful treatment with checkpoint inhibitors. In one study, researchers found that pre-existing CD8+ T cells located at the
invasive margins of tumors from patients with metastatic melanoma may predict response to therapy with the anti-PD-1 inhibitor pembrolizumab. Patients who responded to therapy showed proliferation of the intratumoral CD8+ T cells that directly correlated with reduction in tumor size. The researchers established a predictive model based on CD8 expression at the invasive margin and validated the model in an independent group of 15 patients.

Another type of immunological biomarker is the “Immunoscore”—a method of characterizing the nature and function of immune cell infiltrates into tumors based on measuring the densities of CD3+ and CD8+ cells in the tumor core and the invasive margin using immunohistochemistry. The Immunoscore was developed by Jérôme Galon, Ph.D. [Institut National de la Santé et de la Recherche Médicale (INSERM)] and his colleagues for use in studies of colorectal cancer. According to Dr. Galon’s findings, use of checkpoint inhibitors is the logical strategy for patients with high Immunoscores. In contrast, for patients with low Immunoscores, effective immuno-oncology treatments will need to focus on getting immune cells into the tumor in the first place (e.g. by treatment with a “second-wave” immunotherapy agent) before checkpoint inhibitors can be used.

Genetic and immunological biomarkers may be combined with target biomarkers and other parameters to move toward better discrimination between patients who are likely to benefit from checkpoint inhibitor treatments and those who are not. Specifically, biomarkers can be used to discriminate between “cold” and inflamed tumors. Genetic and immunological biomarkers can also be used to design therapies that can turn “cold” tumors into inflamed tumors, thus improving responses to checkpoint inhibitor therapy and other immunotherapies. For example, these biomarkers might be used to design combinations of treatments that induce immune infiltration of tumors with checkpoint inhibitors that activate or reanimate infiltrating immune cells, such as TILs. Novel agents that might induce immune infiltration of tumors are discussed in several chapters of this report.

More immediately, combination therapies involving the use of older treatments or agents, followed by administration of checkpoint inhibitors, are under clinical investigation to determine whether any of these older agents might render “cold” tumors inflamed, making them susceptible to checkpoint inhibitor therapy. Among these older treatments (discussed in Chapter 2) are radiation therapy (especially stereotactic body radiation therapy (SBRT), targeted therapies, and cytotoxic chemotherapies.

**Approved and clinical-stage immunotherapy biologics other than checkpoint inhibitors**

Various chapters of this report focus on approved and clinical-stage biologics other than the checkpoint inhibitors. Most of these agents may be used as “immuno-oncology 2.0” agents, i.e. agents that promote T-cell infiltration of tumors, thus rendering them susceptible to successful treatment with checkpoint inhibitors.

In addition to serving as an introduction to the report as a whole and discussing the early history of cancer immunotherapy, Chapter 1 focuses on cytokines as cancer immunotherapeutics. Interleukin-2, interferon-alpha-2a, and interferon alpha-2b have long been approved for treatment of various cancers. To this day, despite the introduction of newer immunotherapies, such as checkpoint inhibitors, high-dose recombinant IL-2 (Novartis/Prometheus Laboratories’ Proleukin) is the only drug so far that has produced durable, long-term responses in patients with metastatic melanoma or metastatic renal cell carcinoma. According to Patrick Ott, M.D., Ph.D. (Dana-Farber Cancer Institute, Boston, MA),
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Introduction

In our 2014 Insight Pharma Report, Cancer Immunotherapy: immune checkpoint inhibitors, cancer vaccines, and adoptive T-cell therapies, we focused on the major classes of cancer immunotherapy drugs that were emerging from academic and corporate research – immune-checkpoint inhibitors, cancer vaccines, and adoptive T-cell therapies.

At the time of the September 2014 report’s publication, there was particular excitement over the emergence onto the market of checkpoint inhibitors, which are agents that inhibit immune checkpoints, i.e., inhibitory pathways in the immune system, especially those that block the response of T cells to antigens. So far, all checkpoint inhibitors that have been approved by regulatory agencies are monoclonal antibodies (mAbs). We shall discuss checkpoint inhibitors in greater detail in Chapter 2 of this report.

Ipilimumab (Medarex/Bristol-Myers Squibb’s [BMS’] Yervoy), which was approved by the FDA for treatment of advanced melanoma in 2011, was the first checkpoint inhibitor to be approved. Just at the time our report was published, the FDA approved pembrolizumab (formerly known as MK-3475 or Merck’s Keytruda) also for the treatment of advanced melanoma. A third checkpoint inhibitor, nivolumab (BMS/Ono’s Opdivo) had been approved for treatment of unresectable melanoma in Japan in July 2014 and was in preregistration in the US. The FDA granted accelerated approval to nivolumab for treatment of unresectable or metastatic melanoma on December 22, 2014.

Since the initial approvals of these three checkpoint inhibitors, the use of these drugs has been expanded to other types of cancer, especially non-small cell lung cancer. And in May 2016, an additional checkpoint inhibitor discussed in our 2014 report, atezolizumab (Roche/Genentech’s Tecentriq, which was previously known as MPDL3280A), was approved by the FDA for treatment of urothelial carcinoma, which is the most common type of bladder cancer.

Moreover, a few additional immunotherapeutic drugs have reached the market, and companies and researchers have been hard at work developing additional immuno-oncology treatments, some of which appear to be promising.

Immuno-oncology agents such as checkpoint inhibitors represent a significant advance in cancer treatment beyond the traditional modalities of chemotherapy, radiation therapy, and surgery. Moreover, treatment of advanced melanoma (the type of cancer for which the largest amount of data on immunotherapy treatment has been amassed) with checkpoint inhibitors has in some cases resulted in spectacular results. For example, data released on May 18, 2016, before the annual meeting...
of the American Society of Clinical Oncology (ASCO), indicate that 40% of metastatic melanoma patients who received pembrolizumab in a large clinical trial are still alive three years later. This is a very significant improvement over just a few years ago when average survival time for patients with advanced melanoma was measured in months.

One case of successful use of immunotherapy in treatment of a cancer patient that has made the news is the treatment of former President Jimmy Carter. President Carter, aged 91, was diagnosed with metastatic melanoma in August 2015. A small mass was surgically removed from his liver, but metastases were found in his liver and his brain. He then was treated with a combination of stereotactic radiation therapy and the checkpoint inhibitor pembrolizumab. In December 2015, President Carter announced that his most recent diagnostic scans did not reveal any signs of cancer. As of that date, he was to continue to receive regular three-week treatments with pembrolizumab. At this point, it is not clear whether immunotherapy, radiation, or surgery – or some combination of these modalities – was responsible for President Carter’s favorable results. However, according to experts such as Jedd Wolchok, M.D., Ph.D. (Memorial Sloan-Kettering Cancer Center), if his cancer continues to be in remission over the long term, it is likely that immunotherapy played an important role. According to Dr. Wolchok, around 10 years ago, melanoma patients with brain metastases had life expectancies measured in weeks and months. Now, there are similar patients in his practice who have been alive for years. Immunotherapy is an important factor in this advancement.

Despite these promising results, metastatic melanoma remains incurable. In many studies in advanced melanoma and in other cancers, only a minority of patients have benefited from immunotherapy treatments. Researchers and companies are, therefore, looking for ways to build on the initial successes of the immuno-oncology field to improve outcomes for more patients. In addition to developing novel immuno-oncology agents, these means include combining different immunotherapies, combining immunotherapies with older types of treatments and/or with new now-experimental treatments, and starting immunotherapy earlier in the course of the disease. Researchers are also looking for biomarkers and other means to predict responses to immunotherapy treatments. These tests may not only spare patients the costs and adverse effects of treatments that may not help them, but may also help oncologists to design more optimal, “personalized” treatments. Moreover, longer follow-up of patients who have received immunotherapies in clinical trials will help assess the true clinical benefit of these approaches.

This report will focus on means by which researchers and companies are attempting to build on what has been achieved in immuno-oncology up to 2014 to improve outcomes for more patients. One young cancer immunotherapy company, Jounce Therapeutics (Cambridge, MA; http://jouncetx.com), calls this approach “immuno-oncology 2.0.” Its version of immuno-oncology 2.0 involves using a set of technologies to understand the tumor micro-environment across solid tumors, and thus to identify discrete patient populations defined by biomarkers. This information is then to be used to target a specific patient population with immuno-oncology agents (including currently approved agents and novel drugs) that are likely to benefit patients in that population. It also includes developing novel agents that may be used in the “immuno-oncology 2.0” setting.

On July 19, 2016, Jounce entered into an immuno-oncology partnership with Celgene, which could be worth up to $2.6 billion. This agreement involves development of Jounce’s lead agent, JTX-2011, and also includes up to four early-stage programs. JTX-2011 is only in the late preclinical stage. It is a monoclonal antibody that specifically targets ICOS (inducible T-cell costimulator), which is a protein found on the surface of some activated T cells. Studies in mice indicate that
an ICOS-targeting mAb that provides an agonistic signal through the ICOS pathway synergizes with the immune checkpoint ipilimumab in antitumor activity against established melanoma and prostate cancer.\(^7\) JTX-2011 is a mAb that was developed to carry out human clinical studies based on these studies in mice.

Jounce’s strategy represents one of many approaches to achieving “immuno-oncology 2.0,” i.e., building on the initial success of the cancer immunotherapy field to improve outcomes for more patients. In our report (as in the original 2014 cancer immunotherapy report), we shall focus on agents that are already in the clinic rather than preclinical agents such as those in the Jounce pipeline.

The early history of cancer immunotherapy – Coley’s toxins

Despite the perception in the scientific and medical communities of cancer immunotherapy as a “hot new area” that has suddenly appeared on the scene, the field actually has a long history, going back about 125 years.

In 1891, William B Coley, M.D., a surgeon at the New York Cancer Hospital (now Memorial Sloan-Kettering Cancer Center, New York, N.Y.) observed that patients who experienced infections after cancer surgery often had a better outcome than those who had not suffered post-surgery infections.\(^8,9\) He hypothesized that mobilization of the immune system to fight the infection counteracted the spread or reappearance of cancer as well. Coley therefore developed preparations of inactivated bacteria, known as “Coley’s toxins.” He injected these preparations into tumors. Occasionally – over the following 40 years – this treatment resulted in significant responses. However, these successes were sporadic and difficult to reproduce. Physicians largely abandoned the use of Coley’s toxins. They continued to rely on surgery, and increasingly, on effective newer methods, such as radiation therapy and ultimately chemotherapy.

The one exception to the sporadic and largely ineffective results of treatment of cancer with bacterial preparations has been superficial bladder cancer. Beginning in the 1950s and 1960s, and especially after a definitive study in 1980, researchers developed the use of a vaccine for tuberculosis, bacillus Calmette-Guérin (BCG), for treatment of recurrent superficial bladder cancer.\(^10\) BCG is an attenuated form of Mycobacterium bovis. BCG, infused directly into the bladder, has been used as a treatment for bladder cancer since the 1980s, and it remains the most effective treatment for early, noninvasive (carcinoma in situ) bladder cancer. In that use, BCG is essentially a more modern version of a Coley’s toxin. BCG does not target a specific antigen in bladder cancer cells, and its exact mechanism of action is poorly understood. Recent studies suggest that urothelial cells (including bladder cancer cells themselves) and cells of the immune system (e.g., T cells, natural killer cells, granulocytes, macrophages, and dendritic cells) mediate the antitumor effects of BCG.\(^11\)

A high percentage of bladder cancer patients treated with BCG experience long-term remission, and BCG treatment is more effective than chemotherapy in establishing long-term remission and preventing disease progression.

Despite the limited success of BCG treatment of bladder cancer, the development and clinical application of immunotherapy for treatment of cancer did not advance further until the late 20th and early 21st century.

Although Coley’s toxins have been largely superseded by other therapies – including more modern and reliable immunotherapies – a few researchers are reinvestigating these preparations in preclinical and clinical studies.\(^12\) In a Phase 1 study published in 2012, researchers developed a new, biochemically well-defined and current good
As we discussed in Chapter 1 and in our September 2014 Cancer Immunotherapy Report, most of the excitement over cancer immunotherapy has been focused on emergence of checkpoint inhibitors into the market. Checkpoint inhibitors are agents that block inhibitory pathways in the immune system. So far, all checkpoint inhibitors that have been approved by regulatory agencies are monoclonal antibodies (mAbs).

Immune checkpoints refer to a large number of inhibitory pathways in the immune system, especially those that block the response of T cells to antigens. The normal physiological functions of immune checkpoints are to maintain self-tolerance (and thus prevent autoimmunity) and to limit tissue damage when the immune system responds to infection by a pathogen. However, tumors can co-opt certain immune checkpoint pathways in order to resist T cell-mediated antitumor immunity.

This chapter will focus on the immune checkpoint pathways that are targeted by leading marketed and clinical-stage checkpoint inhibitor agents. We will not cover the entirety of immune checkpoints, which are quite complex and are by no means completely understood. Moreover, only a small number of immune checkpoints are currently a major focus for researchers and companies developing checkpoint inhibitors for cancer immunotherapy. The products discussed in this chapter are listed in Table 2-1.

**CTLA-4 blocking agents**

The initial focus of researchers and companies developing checkpoint inhibitor agents has been on modulating T-cell co-stimulation, i.e. the “second signal” that is required, in addition to T cell receptor signaling, to activate naïve T cells. The role of the “second signal” in regulation of T cell activation, as well as how checkpoint inhibition blocks this step, is illustrated in Figure 2-1.

**Figure 2.1: T Cell Costimulation by CD28 and Checkpoint Control by CTLA-4**

Source: Haberman Associates

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**Table 2-1: Products Discussed in This Chapter**

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Development of immune agonists constitutes another approach to cancer immunotherapy that is complementary to targeting immune checkpoints. Immune agonist therapeutics—most of which are antibodies, as in the case of checkpoint inhibitors—target specific cell surface proteins on T cells, resulting in stimulation of T cell activity. This mechanism contrasts with that of checkpoint inhibitors, which are designed to overcome blockages to T cell activity mediated by immune checkpoints.

Leading immune agonists that are under development for use in immuno-oncology are discussed in this chapter and are listed in Table 3-1.

**Celldex Therapeutics’ Varililumab (CDX-1127)**

Celldex Therapeutics (Hampton, NJ) is developing varililumab (CDX-1127), a fully human mAb agent that targets CD27. As discussed in Chapter 2, the Insight Pharma Reports’ cancer immunotherapy report, activation of naïve T cells requires both T-cell receptor (TCR) signaling and costimulation by a “second signal.” In Chapter 2 and in Figure 2-1, we discussed the example of CD28 (present on the surface of T cells) interacting with B7 (present on the surface of antigen-presenting cells [APCs], such as dendritic cells) as a means to deliver a “second signal.” Similarly, CD27 interacts with CD70 on antigen-presenting cells to deliver “second signal.”

Varililumab can function as a substitute for CD70 by delivering a costimulatory signal to CD27-bearing T cells with engaged TCRs. This signal can change a weak immune response into a strong, prolonged response. In preclinical models, immunostimulation by varililumab has been shown to mediate antitumor effects. These preclinical models have demonstrated that in addition to its costimulatory activity on effector T cells, varililumab treatment can also decrease the numbers of Tregs in a tumor.

Varililumab may also exert direct therapeutic effects against tumors that express CD27 at high levels, including a subset of human B and T cell lymphomas. It has shown potent anti-tumor activity against these lymphomas in preclinical models. In this setting, varililumab may exert its therapeutic activity both via “second-signal” immune activation and via direct antitumor activity against CD27-bearing lymphoma cells.
Bispecific antibodies

Marketed bispecific antibody agents

A bispecific Ab (bsAb) is a type of monoclonal antibody (mAb). Whereas standard mAbs target and bind to a single antigen, bsAbs are designed with two different variable domains, enabling the Ab to bind simultaneously to two different targets. For example, one variable domain can bind to a target on a tumor cell, while the other binds to a target on a cytotoxic immune cell. Researchers have produced different types of bsAbs, but all are designed to bind simultaneously to two different targets. Those used in cancer immunotherapy generally bind one target on a tumor cell and another target on a cytotoxic immune system cell, thus bringing the two cell types into close proximity so that the immune system can act against the tumor cell.

Figure 4-1 provides an illustration showing how bsAbs can be utilized in immuno-oncology.
Introduction

In previous chapters of this report, we have examined immune checkpoint inhibitors, immune agonists, cytokine-based immunotherapies, and bispecific antibodies. Of these cancer immunotherapy modalities, immune checkpoint inhibitors have been the most successful. However, immune checkpoint inhibitors tend to be effective only for a subset of patients with certain types of cancers, and responding patients eventually succumb to their diseases. Immune agonists and a subset of cytokines are under investigation for use in combination therapies with checkpoint inhibitors in order to improve their efficacy. These therapies may, therefore, be mainly considered as adjuncts to immune checkpoint inhibitor immunotherapy. Bispecific antibodies (Chapter 4) are under investigation as alternatives to CAR-T cell therapy, which will be discussed in Chapter 6, along with other cellular immunotherapies. Therefore, other than bispecific antibodies, the major focus of the report thus far has been on checkpoint inhibitors and their potential adjuncts.

In addition to the strategies noted above, development of anticancer vaccines and oncolytic viruses represents an important area of research and development in immuno-oncology and will be the focus of this chapter. Most vaccines familiar to both the biotechnology/pharmaceutical industry and the general public are prophylactic, or preventive, vaccines. These vaccines are designed to induce immunologic memory for a pathogen in order to prevent disease in individuals deemed to have little or no immunity to that pathogen. Familiar prophylactic vaccines include those designed to prevent such infectious diseases as influenza, measles, mumps, polio, smallpox, and pertussis. Vaccination against smallpox ultimately resulted in the eradication of this once devastating disease. Similarly, polio vaccination has eradicated this disease in all but a few small regions of the world. Large numbers of people are vaccinated every fall against the flu strains that are expected to be prevalent in the coming flu season, and such vaccination is generally effective in preventing or ameliorating influenza in susceptible populations. Prophylactic vaccination has thus been a very successful strategy, with the exception of a few important diseases (e.g. HIV/AIDS, malaria), which so far have been resistant to vaccine-targeting.

In the case of cancers caused by two specific viruses—hepatitis B virus and human papillomavirus (HPV)—prophylactic vaccines have been developed using strategies similar to those used to develop vaccines for non-cancer diseases of viral etiology. However, the vast majority of human cancers are not caused by viruses, or at least have no known viral
etiology. Therefore, as an alternative vaccine-based strategy for cancer immunotherapy, researchers and companies have been attempting to develop therapeutic vaccines—i.e. vaccines designed to elicit an antitumor immune response in patients with existing cancers.

Efforts to develop therapeutic cancer vaccines began in the 1990s. Cancers express a host of antigens that are absent or rare in adult human tissues. These antigens include products of the many mutated genes that arise in cancerous tumors, products of non-mutated genes that are preferentially expressed by cancer cells (such as cancer-testis antigens), or differentiation-associated antigens associated with the cancer’s tissue of origin (e.g. melanosome-associated proteins in melanoma). Furthermore, patients can harbor CD8+ and CD4+ T cells specific for these tumor-expressed antigens.

Based on these data, researchers hypothesized that they might develop vaccines capable of amplifying the frequency and strength of these endogenous responses, or perhaps capable of inducing novel antitumor T-cell populations. Moreover, various studies demonstrated strong associations between prolonged patient survival and the presence of intratumoral cytotoxic T cells (i.e. TILs) and interferon-gamma (IFNγ) expression. Thus, researchers hypothesized, they might be able to induce these types of T-cell responses through vaccination, resulting in a clinical benefit. Meanwhile, Steven Rosenberg (National Cancer Institute, Bethesda, MD) and his colleagues were reporting tumor regression in advanced melanoma patients treated with adoptive immunotherapy consisting of in vitro-expanded autologous TILs. (We will discuss adoptive cellular immunotherapies in Chapter 6.) Despite these exciting findings, many other researchers preferred to focus on development of therapeutic vaccines for solid tumors.

Cancer vaccines—a field rife with clinical failures

The vast experience of researchers with prophylactic vaccines for the prevention of infectious diseases provided a framework for initiating vaccine-based approaches for cancer immunotherapy, despite the substantial differences between the two settings (e.g. inducing immunologic memory to prevent a viral disease versus inducing an antitumor immune response against a large tumor burden in patients with existing advanced disease). Unlike adoptive immunotherapy, vaccines are usually easily administered on an outpatient basis and generally have only mild adverse effects. However, despite these advantages, the cancer vaccine field has been characterized by a long series of clinical failures, beginning in the 1990s and continuing to the present day.

One important reason for clinical failure in early cancer vaccine research is that researchers were overly reliant on surrogate endpoints, such as lymphocyte infiltration or histological evidence of tumor necrosis, rather than relying on objective measures of tumor regression and survival. Therefore, despite the absence of significant clinical responses in early vaccine studies, researchers reported the “success” of these trials based on surrogate endpoints. Then they often persisted in their clinical studies until it became clear that the studies had failed.

In their 2004 Nature Medicine article on cancer vaccines, Dr. Rosenberg and his colleagues described their early clinical research on cancer vaccines. Together with their academic and industry partners, Dr. Rosenberg and colleagues at the Surgery Branch of the National Cancer Institute (NCI) performed clinical studies of more than 500 cancer vaccines from 1995 to 2004. They evaluated the results of these studies using standard oncological criteria based on objective clinical responses,
based, neoantigen/neoeptope cancer vaccines, based on the IVAC Mutanome technology platform. Together, the two companies will develop personalized cancer immunotherapies against a broad range of cancers.

There are several other neoantigen-vaccine specialist companies that have been founded and have research and/or preclinical stage programs using largely undisclosed technologies. Among these is Gritstone Oncology (Emeryville, CA and Cambridge, MA). Gritstone was launched in October 2015 with a Series A financing of $102 million\(^ {229}\) and is in the preclinical stage. On May 9, 2016, Gritstone entered into a collaboration with Immune Design (Seattle, WA) to develop novel, personalized immunotherapies combining both companies’ leading technologies.\(^ {231}\) The likely focus of the two companies’ collaborative efforts will be in NSCLC. The first clinical trial (which is expected to involve combining novel personalized neoantigen vaccines with a checkpoint inhibitor) is expected to commence in 2017.

There are other companies working on personalized neoantigen cancer vaccines that have not yet reached the clinic.\(^ {231}\) These include ISA Pharmaceuticals (Leiden, The Netherlands), Agenus (Lexington, MA), and Caperna (Cambridge, MA). Caperna (www.modernatx.com/our-business-model/ventures/caperna-llc) is a Moderna (Cambridge, MA) venture company. It is applying Moderna’s mRNA manufacturing technology to the development of RNA-based personalized neoantigen vaccines. In June 2016, Merck and Moderna announced a strategic collaboration and license agreement to develop and commercialize novel mRNA-based personalized neoantigen vaccines for cancer.\(^ {232}\) The two companies hypothesize that the mRNA-based personalized cancer vaccines will act synergistically with checkpoint inhibitor therapies, including Merck’s anti-PD-1 therapy, pembrolizumab.
been developing processes and systems for manufacturing of CAR T-cell therapeutics and other genetically engineered autologous T-cell therapies. The rationale for development of Cellectis’ “off-the-shelf” allogeneic CAR T-cells includes greater ease of manufacturing. With respect to TIL therapies, Lion Biotechnologies has agreements with cellular therapy manufacturing experts Lonza and WuXi AppTec.

**Insight Pharma Reports survey on cancer immunotherapy**

Insight Pharma Reports conducted a survey on immuno-oncology, in conjunction with this report. The results of this survey (conducted in the fall of 2016) are provided in chapter 8.

There were 100 qualified respondents to the survey. (Only results from qualified respondents are included in the survey results.) The first several questions assessed the nature of the respondents’ organizations and their own roles in the cancer immunotherapy field. The remaining questions asked for the respondents’ opinions on various aspects of cancer immunotherapy.

Of these respondents [See Q24], 54% were in industry, including 29% in pharmaceutical companies and 18% in biotech companies developing therapeutic products. Another 35% were in academia or in a government research center. Since these survey results include only responses from qualified participants, 100 (100%) of respondents work in some aspect of discovery or development of cancer immunotherapies. Another 35% were in academia or in a government research center. Since these survey results include only responses from qualified participants, 100 (100%) of respondents work in some aspect of discovery or development of cancer immunotherapies. Of these participants, 52% work on mAb checkpoint inhibitors, 24% work on small-molecule checkpoint inhibitors, 33% work on various types of anticancer vaccines (including dendritic cell, peptide or protein, neoantigen, or DNA plasmid vaccines), and 34% work on T cell-based adoptive cellular immunotherapies. Of those who work on other cancer immunotherapy agents, 21% work on cytokines, 23% work on other small-molecule immunomodulators, and 15% work on a variety of other types of agents. Note that respondents could give more than one response to this question. With respect to the respondents’ roles in developing and/or using cancer immunotherapy agents [q2], 59% work in laboratory research, 10% are clinicians, and 35% work in a wide variety of other capacities.

[q3] asks “According to a 2014 news article in *Nature*, immunotherapies may comprise a U.S. $35 billion market by 2024 and be used in 60% of cases of advanced cancer.” Do you agree? A total of 83 respondents said “Yes,” 4 said “No,” and 13 said “Don’t know” or declined to answer.

[q4] asks: “Recent clinical studies with checkpoint inhibitors that target PD-1 [BMS’s nivolumab (Opdivo) and Merck’s pembrolizumab (Keytruda)] and the CTLA-4-targeting drug ipilimumab (Yervoy) indicate that these drugs promote survival in an increasing number of types of previously untreatable advanced cancer.... However, these drugs do not benefit all patients with these cancers, nor do they induce long-term survival in all patients. Do you agree with the assessment that where we are with checkpoint inhibitor treatment in 2016 is similar to where we were with chemotherapy in the 1960s, when we were just beginning to use it? A total of 65 respondents said “Yes,” 24 said “No,” and 11 said “Don’t know” or declined to answer.

[q5] asks, “Do you believe that combining a checkpoint inhibitor with another checkpoint inhibitor; another immunotherapeutic (e.g. a cancer vaccine or T-cell therapy); with radiation, chemotherapy, or surgery; or with targeted therapies might give improved results?” Of the respondents, 38 said “Yes,” 1 said “No,” 50 said “It depends on the particular combination and the particular type of cancer,” 9 said “We need more data from the initial studies of this type,” and 2 said “Don’t know” or declined to answer.