

# Cancer Immunotherapy:

## Immune Checkpoint Inhibitors, Cancer Vaccines, and Adoptive T-cell Therapies

Allan B. Haberman. Ph.D.

**T**his report focuses on the rising potential for the newest and most promising of cancer treatments: cancer immunotherapy. Cancer immunotherapy was once just a dream in the minds of physicians, clinicians and patients, but only recently (2010s era) has it actually been within reasonable reach. Cancer Immunotherapy: immune checkpoint inhibitors, cancer vaccines, and adoptive T-cell therapies covers three principle therapies that have been in the works for cancer patients.

One principle therapy that has been on the rise is checkpoint inhibitors. Checkpoint inhibitors are a class of monoclonal antibodies that inhibit pathways responsible for blocking the response of T-cells to antigens. Not only have results from clinical trials of these therapeutics been promising, but treatments have already been approved both in the U.S. and Europe for metastatic melanoma. There are several agents and targets covered in this section, including the September 5, 2014 approval of Merck's PD-1 inhibitor: pembrolizumab (Keytruda), as well as the future outlook of potential combination checkpoint inhibitor therapies.

Another principle therapy under investigation are anticancer vaccines. This is another major strategy surfacing in cancer therapeutics and, unlike traditional vaccines which are given to prevent illness (i.e. smallpox, measles, and pertussis), these vaccines are given to patients who already have cancer and are designed to elicit an antitumor response to even the most aggressive of cancers. Though this is a theoretically good approach to combat cancer, there have been an unfortunate number of clinical failures and the industry has gained only one U.S. approved anticancer vaccine. Combination therapies are also a possible route these vaccines will take in the future.

Finally, the last therapy addressed in this report is adoptive cellular immunotherapy. Adoptive cellular immunotherapy is when syngeneic activated T-cells are infused in patients to attack their cancers. There are a few types of cellular immunotherapies including: tumor infiltrating lymphocyte (TIL) therapy, genetically engineered T cells bearing chimeric antigen receptors (CARs), and recombinant TCR technology. Improving these therapies is the goal over the next few years and researchers have been working heavily to commercialize these products and technologies.

The report is further coupled with an in-depth introduction and history as well as with data for market outlook. Also featured in this report are exclusive interviews with three high-end professors, researchers and CEOs:

- Adil Daud, MD, Clinical Professor, Department of Medicine (Hematology/Oncology), University of California at San Francisco (UCSF); Director, Melanoma Clinical Research, UCSF Helen Diller Family Comprehensive Cancer Center.
- Matthew Lehman, Chief Executive Officer, Prima BioMed (a therapeutic cancer vaccine company with headquarters in Sydney, Australia).
- Marcela Maus, MD, PhD, the Director of Translational Medicine and Early Clinical Development, Translational Research Program, Abramson Cancer Center, University of Pennsylvania in Philadelphia.

Furthermore, Insight Pharma Reports also conducted and analyzed survey data representing a population sample from the R&D industry. This survey depicts market outlook, and portrays industry opinions and perspectives.



## Executive Summary

**T**he regular use of immunotherapy for treatment of cancer, which had been an elusive dream for over 100 years, has very recently become within the grasp of researchers, physicians, and patients. As of the early-to-mid 2010s, cancer immunotherapy has become a “hot” area, with intense competition between biotechnology and pharmaceutical companies to be the first to market the newest, most effective therapies.

This report focuses on the three principal types of therapeutics that have become the major focuses of research and development in cancer immunotherapy (which is often called “immuno-oncology”) in recent years:

Checkpoint inhibitors (discussed in Chapter 2)

- Therapeutic anticancer vaccines (discussed in Chapter 3)
- Adoptive cellular immunotherapy (discussed in Chapter 4)
- The report also includes a survey on adoptive immunotherapy for cancer, which was conducted by Insight Pharma Reports in conjunction with this report, and is discussed in Chapter 5.

Also included are three expert interviews with the following people:

- Adil Daud, MD, Clinical Professor, Department of Medicine (Hematology/Oncology), University of California at San Francisco (UCSF); Director, Melanoma Clinical Research, UCSF Helen Diller Family Comprehensive Cancer Center.
- Matthew Lehman, Chief Executive Officer, Prima BioMed (a therapeutic cancer vaccine company with headquarters in Sydney, Australia).
- Marcela Maus, MD, PhD, the Director of Translational Medicine and Early Clinical Development, Translational Research Program, Abramson Cancer Center, University of Pennsylvania in Philadelphia.

Chapters 2-5 are preceded by an introductory Chapter 1, which focuses on the history of cancer immunotherapy, and the use of cytokines as immunotherapies for cancer. Although the use of high-dose interleukin-2 as an immunotherapy for advanced melanoma and kidney cancer has fallen out of favor in recent years due to the toxicity of the agent and the need for specialized treatment centers, there are researchers who are attempting to revive and improve this treatment. This is because IL-2 is the only drug (as opposed to cellular therapies) so far that has produced any durable complete responses in patients with metastatic melanoma or metastatic RCC. Moreover, the type of specialized treatment centers needed for IL-2 therapy may also constitute the best solution for delivery of certain types of cellular therapies. Researchers are also working to develop novel types of cytokine-based immunotherapies for cancer, such as OncoSec’s locally administered IL-12-based gene

therapy. Thus the field of cytokine-based immunotherapies is far from dead.

Nevertheless, cytokine-based immunotherapies have limited utility, and do not command the excitement of the three more recently developed modes of therapy discussed in Chapters 2, 3, and 4.

## Checkpoint inhibitors

Most of the current excitement over cancer immunotherapy is focused on the field of immune checkpoint inhibitors, a class of monoclonal antibodies (MAbs) that inhibit pathways that block the response of T cells to antigens. Checkpoint inhibitors work to overcome mechanisms by which tumors co-opt certain immune checkpoint pathways, and thus resist T cell-mediated antitumor immunity.

One checkpoint inhibitor, ipilimumab (Medarex/ BMS's Yervoy) was approved by the FDA for the treatment of metastatic melanoma in March 2011, and in the European Union for second line treatment of metastatic melanoma in 2012.

Ipilimumab is a CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) blocking agent that overcomes blockage of the “second signal” that is required in addition to TCR (T cell receptor) recognition of MHC/ antigen for activation of naïve T cells. In metastatic melanoma, ipilimumab gives about a 10% response rate. However, it gives a 20-30% rate of adverse effects, including serious autoimmune toxicities in about 10-15% of patients. The adverse effects of ipilimumab can be overcome via treatment with high-dose steroids.

Autoimmune toxicities associated with ipilimumab treatment appear to be due to the fact that the drug targets CTLA-4 on all T cells in the body that express this protein. It is not specific for antitumor T cells. Thus ipilimumab treatment can give rise to autoimmune-related adverse effects in sites other than tumors. Ipilimumab treatment may also uncover autoreactive T cells via blockage of CTLA-4.

The other immune checkpoint pathway that is being targeted by researchers and companies developing immuno-oncology agents is the PD-1 (programmed cell death protein 1) receptor pathway. PD-1 is a receptor on the surface of activated T lymphocytes. Like CTLA-4, PD-1 is a negative regulator of T-cell receptor signals. However, the physiological role of the PD-1 pathway is to limit the activity of effector T cells in peripheral tissues at the time of an inflammatory response (for example, in infection), and thus to limit autoimmunity. Tumor cells—like inflamed tissue cells—may express PD-L1 (programmed death-ligand 1), a ligand that binds PD-1 on T cells and sends a negative signal to the T cells. This PD-1-PD-L1 interaction blocks the ability of tumor-infiltrating T cells, or endogenous TILs (tumor infiltrating lymphocytes), to carry out an anti-tumor immune response. Thus agents that inhibit the PD-1 pathway are designed to reactivate endogenous TILs at the tumor site, without activating autoreactive T cells at other sites in the body.



The most advanced anti-PD-1 MAb drugs in development are Medarex/BMS' nivolumab and Merck's pembrolizumab (also known as MK-3475). Both of these experimental therapeutics are in Phase 3 clinical trials in advanced melanoma, NSCLC, and head and neck cancer, and in Phase 2 trials in other cancers. In Phase 1 trials in advanced melanoma, a PD-1 inhibitor such as pembrolizumab gives a 30%-50% response rate, and about a 10% incidence of adverse effects. These early results appear to confirm the greater degree of specificity for unblocking T cell activity at the tumor site rather than in normal tissues for PD-1 inhibitors, as compared to CTLA-4 inhibitors. Researchers are confident that this difference will hold up in Phase 2 and Phase 3 clinical trials, but the results are not yet in.

There is fierce competition between Merck and BMS in the PD-1 inhibitor field, to determine whether nivolumab or MK-3475 will be first to market, and which shall command the greatest market share. In June 2014, BMS announced that its randomized blinded comparative Phase 3 study evaluating nivolumab versus the standard of care dacarbazine (DTIC) in advanced melanoma was stopped early, because an independent Data Monitoring Committee found evidence of superior overall survival in patients receiving nivolumab compared to those receiving DTIC. BMS says its study is the first randomized Phase 3 trial of a PD-1 inhibitor to show an overall survival benefit as compared to standard of care.

Nivolumab was approved in July 2014 for treatment of unresectable melanoma in Japan, where it will be manufactured and marketed by Ono. Ono gained Japanese rights to nivolumab via an agreement with Medarex, prior to the acquisition of Medarex by BMS.

Meanwhile, as of April 2013, Merck's pembrolizumab has been designated as a Breakthrough Therapy for the treatment of advanced melanoma. In May 2014, the FDA accepted for review Merck's Biologics License Application (BLA) for pembrolizumab, for the treatment of advanced melanoma in patients who have been previously treated with ipilimumab. On September 5, 2014, the FDA granted accelerated approval to pembrolizumab (with the trade name Keytruda) for treatment of patients with advanced or unresectable melanoma who are not responding to other drugs. Pembrolizumab is thus the first anti-PD-1 agent to reach the U.S. market. In July 2014, the European Medicines Agency (EMA) accepted Merck's Marketing Authorization Application filing, putting pembrolizumab into contention to be the first immune checkpoint inhibitor for treatment of cancer to reach the EU market.

In February 2014, Merck formed collaborations with Pfizer, Amgen and Incyte to test combination therapies of pembrolizumab with drugs owned by the latter three companies in a variety of types of cancer. Pembrolizumab may be considered as not just a single experimental drug, but also a drug portfolio. The pembrolizumab program now includes studies in 30 types of tumors, both as a monotherapy and in combination with various drugs developed by other companies. By the end of 2014, Merck projects that there will be 24 clinical trials underway

with 6,000 patients, including four new Phase 3 trials. Meanwhile, BMS has been testing a combination therapy between nivolumab and ipilimumab in melanoma.

PD-L1 inhibitors constitute another type of checkpoint inhibitor that blocks the PD-1 receptor pathway. The most advanced PD-L1 in development is Genentech/Roche's MPDL3280A. Genentech researchers hypothesize that anti-PD-L1 agents may have fewer adverse effects than anti-PD-1 agents. That is because anti-PD-L1 agents would target tumor cells while leaving T cells free to participate in immune networks that work to prevent autoimmune reactions. MPDL3280A is in Phase 2 trials in renal cell carcinoma and urothelial bladder cancer, and in Phase 1 trials in several other types of cancer.

In May 2014, the FDA granted MPDL3280A Breakthrough Therapy status for treatment of bladder cancer. Early Phase 1 results suggest that MPDL3280A has greater efficacy against smoking-related NSCLC than in NSCLC in never-smokers. MPDL3280A is expected to be competitive with PD-1 blockers, especially in NSCLC and bladder cancer.

Another PD-L1 inhibitor in development is MedImmune/AstraZeneca's MEDI4736. Based on Phase 1 safety and efficacy data in NSCLC and other cancers, AZ has accelerated development of MEDI4736 to Phase 3 development. It is thus in a Phase 3 clinical trial in NSCLC.

Despite researchers' enthusiasm for anti-PD-1 agents, they believe that it is too early to tell whether anti-PD-L1 agents may or may not be superior to anti-CTLA-4 and anti-PD-1 agents, in terms of efficacy and safety, for any particular type of cancer. Confirmatory Phase 2 and Phase 3 studies are needed.

Researchers believe that checkpoint inhibitors are likely to be tested in combination with each other and with other agents in the next 3-5 years. As mentioned previously, some such studies are in progress. The goal of such combination therapies will be to "go to the cure point", or at least to take response rates from 30-50% (as with PD-1 drugs) up to 60-70%.

### **Therapeutic anticancer vaccines**

The second major immunotherapy strategy that is being pursued by researchers and companies is development of anticancer vaccines. Unlike the prophylactic vaccines to prevent such diseases as influenza, measles, mumps, polio, smallpox, and pertussis that are familiar to most people, cancer vaccines are therapeutic vaccines that are given to patients who already have cancer. They are designed to elicit an antitumor immune response.

The cancer vaccine field has been characterized by a long series of clinical failures, beginning in the 1990s and continuing to the present day. Failures in early cancer vaccine research appear to be due to an over-reliance on



surrogate endpoints, as opposed to objective clinical responses. This was coupled with a lack of understanding of the role of dendritic cells in immunization.

However, despite researchers' greater understanding of dendritic cell biology, and despite improved design of vaccines, clinical cancer vaccine studies have continued to experience failure, even to the present day. Researchers hypothesize that a key factor in the continuing failures in the cancer vaccine field is immune suppression in the tumor environment. Since checkpoint inhibitors appear to work in part by overcoming immunosuppression in the tumor environment, this suggests that administering the vaccines in combination with immune checkpoint inhibitors may overcome this source of vaccine failure.

Currently, there is only one approved and marketed anticancer vaccine, sipuleucel-T (Dendreon's Provenge). It is approved in the U.S. and in Europe to treat asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (formerly known as hormone-refractory prostate cancer). Sipuleucel-T is a personalized dendritic cell vaccine, prepared by treating a patient's autologous PBMCs (peripheral blood mononuclear cells) with a recombinant fusion protein, consisting of prostatic acid phosphatase (PAP) (an antigen present in prostate cancer cells) fused to the dendritic cell activator GM-CSF (granulocyte-macrophage colony-stimulating factor).

Sipuleucel is the only cancer vaccine so far to demonstrate improvement in overall survival (by 4.1 months) and to gain marketing approval. However, it has suffered from high manufacturing costs and competition with two newer, less-expensive small-molecule oral agents.

Some industry experts have voiced doubt about the viability of dendritic cell vaccines in general, especially the difficulties and expense of manufacturing personalized therapeutic vaccines. Other classes of vaccines now under development are manufactured similarly to most biologics, and are thus not "personalized" in the sense that dendritic cell vaccines are. The need to develop and carry out processes for manufacturing personalized cellular therapeutics also applies to adoptive cellular immunotherapies.

However, despite these doubts, Matthew Lehman, the CEO of Prima BioMed (Sydney, Australia), whom we interviewed for this report, is confident that Prima BioMed can produce its dendritic cell vaccine for ovarian cancer, CVac, with an acceptably low cost of goods sold (COGS). Moreover, as discussed in Chapter 4, such companies as Novartis (which purchased a former Dendreon manufacturing plant and retained most of its experienced staff) and Lonza are engaged in developing viable manufacturing strategies for cellular therapies. Thus the logistical and cost issues associated with manufacturing personalized cellular vaccines may be largely overcome in a few years.

Meanwhile, Dendreon is sponsoring clinical trials of combinations of sipuleucel-T and various agents, including the checkpoint inhibitor ipilimumab and both of its recently approved oral-drug competitors. If any of these trials

show that the combination therapies give greater overall survival (with acceptable safety) than either single drug alone, that will boost the prospects for sipuleucel-T and will suggest that the therapeutic cancer vaccine field may have a brighter future than that foreseen by many industry experts today.

Chapter 3 discusses several cancer vaccines in clinical trials, including recombinant viral vaccines, peptide vaccines, and personalized dendritic cell vaccines. Two of these agents failed in previous trials, and are being tested using different strategies than in the original trials (in one case, as a combination therapy, and in the other case, being tested in a subpopulation in which the vaccine appeared to give statistically significant overall survival despite failing to do so in the overall population).

In Phase 2 studies Celldex' rindopepimut (a peptide vaccine for EGFRvIII-positive glioblastoma, now in Phase 3 clinical trials) appeared to give a substantial and continuing survival benefit in comparison to independent control datasets. Patients who developed humoral and cellular immune responses to the vaccine experienced significantly increased overall survival as compared to patients who did not develop such responses (47.7 months versus 22.8 months).

Despite the failures and minimal responses that have characterized the cancer vaccine field, these agents may find their place as components of combination therapies, especially if paired with checkpoint inhibitors. In some cases (such as Prima BioMed's CVac, the focus of the Lehman interview), cancer vaccines may be applied to increasing survival in certain specific populations of cancer patients who have been previously treated with more conventional therapies. Demonstration of improved overall survival by such vaccines may also serve as a launching platform for combining the vaccine with a checkpoint inhibitor, in order to increase survival further or even to produce long-term complete remissions.

### **Adoptive immunotherapy for cancer**

The third major immunotherapy strategy that is being pursued by researchers and companies is adoptive immunotherapy. In this class of therapies, autologous or syngeneic activated T cells (which may or may not be genetically modified) are infused into patients in order to attack their cancers. Adoptive immunotherapy is also known as adoptive cell transfer (ACT).

#### **TIL therapy**

ACT, especially therapies involving adoptive transfer of autologous TILs, was pioneered by Dr. Steven Rosenberg (NCI). Most studies with TIL therapy have been in advanced melanoma. In recent years, Dr. Rosenberg and



his colleagues have obtained improved results with TIL therapy by use of preparative lymphodepletion with chemotherapy, in some cases combined with total body irradiation. Following this treatment, patients were treated with autologous TILs that had been selected for antitumor activity, followed by treatment with high-dose IL-2.

In a study of this treatment that was first reported in 2008, with a follow-up report in 2011, of 93 patients treated, objective response rates ranged from 49% to 72%, depending on the type of preparative lymphodepletion received. Twenty of the 93 patients (22%) achieved complete regression, and 19 of these had ongoing complete regressions beyond 3 years. The 3- and 5-year survival rates for the entire group were 36% and 29%, respectively, but for the 20 complete responders were 100% and 93%. The likelihood of achieving a complete response was not dependent on the prior therapies received by the patients.

The results of TIL therapy after preparative lymphodepletion appear to be superior to the results of other treatments available for metastatic melanoma, including chemotherapy, targeted therapies, high-dose IL-2, and even checkpoint inhibitors such as ipilimumab and PD-1 inhibitors. However, the results of Phase 3 trials of PD-1 inhibitors and of PD-L1 inhibitors are not in yet, so this conclusion could be premature. Moreover, patients need to be treated for the toxicities associated with preparative lymphodepletion and TIL therapy (which involves high-dose IL-2). This therapy must therefore be given in specialized centers.

Despite its apparent high degree of efficacy and curative potential, TIL therapy cannot be given to all advanced melanoma patients. Patients must have resectable tumors from which sufficient numbers of TILs can be cultured and expanded in vitro. Dr. Rosenberg and his colleagues estimate that approximately 45% of advanced melanoma patients could receive TIL therapy.

Dr. Rosenberg's group has recently been working to identify specific immunodominant mutations that are the targets of TIL therapy in melanoma patients who achieve durable complete remissions. They have been using the strategies and technologies involved in these studies to design TIL-based therapies for other types of cancer. Notably, they recently reported on a TIL-based treatment of a patient with an epithelial cancer, cholangiocarcinoma (a type of epithelial bile duct cancer), which resulted in a tumor regression that has continued for two years post-treatment. Epithelial cancers (e.g., lung, breast, colorectal, pancreatic) constitute over 80% of all human malignancies. Research on extending TIL therapy to this class of cancers is thus potentially important.

Despite the success of TIL therapy in advanced melanoma, and despite recent research in extending this therapy to other cancers, this therapy has been difficult to commercialize and to make accessible to greater numbers of patients. An example for why TIL therapy has been difficult to commercialize is that the therapy has lacked a clearly defined claim to intellectual property, since the patient's own cells are not a "drug" to be patented.

However, recently Lion Biotechnologies (Woodland Hills, CA) has been pursuing commercialization of TIL

therapy. Lion is working with Dr. Rosenberg and his colleagues at the NCI under a Cooperative Research and Development Agreement (CRADA) to develop and commercialize TIL therapy. Under the CRADA with the NCI, Lion will gain exclusive rights to new adoptive cell therapy technologies for the treatment of metastatic melanoma, and access to all clinical data, manufacturing data and standard operating procedures. The company may also conduct clinical trials at the NCI.

Lion also has a licensing agreement with the Moffitt Cancer Center. The company licensed from Moffitt the rights to develop and commercialize new technologies to enhance TIL production for melanoma, which may be applicable to other tumor types. Lion is also developing next generation more potent TILs, which are projected to allow for lower cost of goods and a shorter manufacturing process. It is also developing “designer T cells” that incorporate such features as cytokine production and checkpoint inhibition, and is working to extend TIL therapies to cancers other than melanoma. Lion estimates that the peak sales for its TIL therapy for metastatic melanoma will be \$1 billion.

#### **Adoptive immunotherapy with genetically engineered T cells bearing chimeric antigen receptors (CARs)**

Several academic research groups and companies have recently been developing genetically engineered T cells for use in adoptive immunotherapy, as an alternative to TILs. The most advanced of these in development involves engineering T cells with retroviral vectors carrying chimeric antigen receptors (CARs). Dr. Carl June’s group at the University of Pennsylvania and Dr. Michel Sadelain’s group at the Memorial Sloan Kettering Cancer Center (MSKCC) have been the leaders in developing these technologies. Novartis has entered into an exclusive global research and licensing agreement with Penn to study and commercialize cellular immunotherapies based on CAR technologies developed at Penn. Juno Therapeutics (Seattle WA) is a private, commercial venture that was launched by an academic consortium including the Fred Hutchinson Cancer Research Center, MSKCC, and the Seattle Children’s Research Institute in December 2013. So far, Juno has raised over \$300M in venture capital funding. The company focuses on development and commercialization of adoptive T-cell immunotherapies, including those based on CAR technologies developed at MSKCC, and on genetically engineered T cells with high-affinity TCRs.

CARs are synthetic, engineered receptors that are designed to target molecules on the surface of target tumor cells in their native conformation. Unlike TCRs, CARs bind to their target molecules independent of antigen processing by the target cell and independent of MHC restriction. This in principle allows CAR-engineered T cells to address a broader range of target molecules and cells than natural T cells. T cells for use in autologous CAR-based therapy are usually derived from peripheral blood T cells from the patient to be treated. Thus CAR T-cell therapy does not require isolating and culturing T cells from tumors. This makes derivation of T cells for therapy, as well as manufacturing of autologous T-cell cultures, much easier in CAR therapy than in TIL therapy.



Nor does treatment with the leading CAR T-cell therapies require administration of exogenous IL-2.

CARs typically engage their target molecules via single-chain variable fragments (scFvs) derived from an antibody. The scFv-based extracellular moiety of a CAR is attached via a hinge and a transmembrane region to intracellular signaling moieties. Thus, when a CAR engages its target molecule on the surface of a tumor cell via the scFv moiety, it sends activating signals to the T cell, resulting in cytokine expression and antitumor responses. Most researchers use retroviral or lentiviral vectors to insert the DNA that encodes for the CAR into T cells.

The most advanced products in the CAR T-cell therapy field are Penn/Novartis' CTL019 (formerly known as CART19) and MSKCC/Juno's 19-28z. Both target the cell surface protein CD19, which is expressed on all malignant and normal B-cells. Both are in Phase 2 clinical studies in several B-cell malignancies, especially B-cell ALL (acute lymphocytic leukemia) and CLL (chronic lymphocytic leukemia).

CTL019 was granted Breakthrough Therapy status for treatment of relapsed and refractory ALL by the FDA in July 2014. In pilot and Phase 1 clinical trials, infused autologous CTL019 T cells (derived via transduction of patient's autologous peripheral blood T cells) expanded 1,000-fold in vivo without the use of exogenous IL-2, and trafficked to bone marrow. In one Phase 1 trial of CTL019, 15 of 32 adult patients with CLL (47 percent) responded to CTL019 therapy, with seven of those experiencing a complete remission. In another Phase 1 trial, 19 of 22 pediatric patients with relapsed or refractory ALL (86 percent) experienced complete remissions. Five patients have relapsed, including one whose tests revealed new tumor cells that do not express CD19, the protein targeted by CTL019. All five adult ALL patients treated so far in this study experienced complete remissions, the longest of which continues six months after treatment. Another patient underwent a bone marrow transplant after achieving remission with CTL019 treatment (the standard of care for ALL patients who achieve remission), and remains in remission. Another patient relapsed after three months with disease that also tested negative for CD19. Overall, 89 percent of ALL patients who did not respond to conventional therapies experienced complete remission after receiving CTL019. CTL019 appears to work better in ALL than in CLL.

In a Phase 1 study published in February 2014, researchers showed that adoptive immunotherapy with autologous T cells transduced with the 19-28z CAR induced complete responses in 88% of 16 patients with relapsed or refractory B cell ALL. This allowed the researchers to transition seven of the 16 patients (44 percent) to standard-of-care allogeneic hematopoietic stem cell transplantation. This study (in 16 patients) confirmed the results of an earlier 5-patient study. The researchers found that all 5 of these ALL patients experienced rapid tumor eradication and achieved minimal residual disease-negative complete remissions.

Thus, the results of treatment of B-cell ALL with autologous 19-28z T-cell therapy appear to closely resemble those seen in the same disease with autologous CTL019 therapy.

In terms of adverse effects, treatment with either CTL019 or 19-28z can result in potentially dangerously high levels of cytokines in vivo, especially in patients with high tumor burdens. High-level cytokine release occurs at the same time as the lysis of large amounts of tumor in these patients, and also coincides with peak T-cell expansion. It is associated with the ability of CAR T cells to give significant tumor responses, without the need for administering exogenous IL-2 as with TILs. However, patients may experience cytokine release syndrome (CRS), with fever, myalgias, nausea, and/or anorexia. Some patients require treatment for CRS with the IL-6-receptor antagonist tocilizumab (Roche's Actemra, approved for the treatment of rheumatoid arthritis and other conditions) and/or high-dose corticosteroids.

The issue of CRS-related toxicity associated with treatment with 19-28z T-cells has received a great deal of attention due to two patient deaths that occurred in clinical trials at MSKCC of this therapy, as reported on April 6, 2014. This resulted in a clinical hold on the trial at MSKCC. However, on April 24, 2014, the FDA lifted the clinical hold. Moreover, there does not appear to be any significant difference between the two anti-CD19 CARs with respect to safety, and CRS that results from either therapy can be treated via the same protocol.

Both MSKCC and Penn researchers are conducting studies to investigate how and whether their respective CAR T-cell technology platforms can be applied to other types of cancer, as are other researchers. Initial studies suggest that it may be possible to develop CAR-based therapies for at least some solid tumors.

Other companies developing CAR-based T-cell therapies include bluebird bio in collaboration with Celgene, and Kite Pharma, via a CRADA with the NCI.

### **Recombinant TCR technology**

Other researchers and companies are developing autologous T-cell therapies based on recombinant TCRs. Adaptimmune is the leader in this field. It is conducting Phase 1 and Phase 2 clinical trials in multiple myeloma and other cancers with autologous T-cells engineered with increased affinity recombinant TCR that target cancer testis antigens, especially NY-ESO-1 (New York esophageal squamous cell carcinoma 1). Unlike CAR T-cells, recombinant TCR-engineered T cells must recognize target antigens complexed with specific HLA proteins. Thus patients enrolled in each study need to express the specific HLA/antigen combination for which each recombinant TCR was designed.

In June 2014, Adaptimmune and GlaxoSmithKline (GSK) entered into a strategic collaboration and licensing agreement for the development and commercialization of a recombinant TCR therapy that targets NY-ESO-1. Adaptimmune's U.S. clinical trials of its recombinant TCR-based therapy that targets NY-ESO-1 have generated



encouraging results in multiple myeloma, melanoma, sarcoma and ovarian cancer, and European trials are set to begin shortly.

Other companies with early-stage recombinant TCR programs include Juno and Kite. Steven Rosenberg's group at the NCI has also been investigating recombinant TCR therapies.

### **The future of adoptive immunotherapy for cancer**

The field of adoptive cellular immunotherapy is maturing, with improvements in TIL therapies, development of next-generation technologies such as CARs and recombinant TCR technology, and evidence that cancers other than melanoma and CD19<sup>+</sup> B-cell malignancies may be treatable with ACT. Efforts to commercialize these technologies and products have also been advancing, with the entry of Big Pharmas Novartis and GSK into the field, and the involvement of manufacturing specialists such as Lonza and those in the former Dendreon plant purchased by Novartis. Moreover, at least several ACT therapies continue to exhibit the extraordinary degree of efficacy seen in earlier studies of TIL therapy.

These factors indicate that ACT may well take its place beside checkpoint inhibitor therapies as an important modality of immunotherapy for cancer within the next several years.

### **Outlook for cancer immunotherapy**

The regular use of immunotherapy for treatment of cancer, which had been an elusive dream for over 100 years, has very recently become a "hot" area, with intense competition between biotechnology and pharmaceutical companies to be the first to market the newest, most effective therapies.

The great majority of the excitement the immuno-oncology field is due to the development of novel immune checkpoint inhibitors. For example, in a March 24, 2014 *FierceBiotech* article (based on a *Wall Street Journal* analysis), analysts predicted that the anti-PD-1 agents nivolumab and Merck's pembrolizumab, as well as the anti-PD-L1 agent MPDL3280A, might be approved by the FDA before the end of 2015. They also projected that the three drugs would peak at about \$12.5 billion a year.

Other analysts recently projected that the cancer immunotherapy market will increase to nearly \$9 billion across the world's major pharmaceutical markets by 2022. They also projected that taken together, BMS' ipilimumab (Yervoy), BMS/Ono's nivolumab, Merck's pembrolizumab, Genentech/Roche/Chugai's MPDL3280A and MedImmune/AZ's MEDI4736 will dominate the immuno-oncology market and capture an 85% market share in 2022.

Both of these market analyst groups predict that nivolumab will be the sales-leading agent among checkpoint inhibitors. We believe that it is too early to make such predictions. Prior to the aggressive strategic moves that

have positioned Merck's pembrolizumab in first place in the race to commercialize an anti-PD-1 agent, it was easy to anoint nivolumab as the expected leader in immuno-oncology sales. However, now the outcome of the race between nivolumab, MK-3475, and MPDL3280A will depend on the results of clinical trials, and on FDA and EMA action. Nivolumab will face direct and intense competition from pembrolizumab (especially in malignant melanoma and NSCLC)—and, perhaps from MPDL3280A in non-small-cell lung cancer. Especially if the results on the efficacy of MPDL3280A in NSCLC in smokers hold up in later clinical trials, the competition by MPDL3280A in NSCLC may be greater than expected.

Experts in the immuno-oncology market show much less enthusiasm for cancer vaccines than for checkpoint inhibitors. Analysts project that the cancer therapeutic vaccines segment of the market will have sales of \$1.2 billion in major pharmaceutical market countries in 2022. However, this projection is based on the prediction that five specific vaccine products will join sipuleucel-T (Dendreon's Provenge) as marketed products by 2022.

These five vaccines include two that failed in Phase 3 clinical trials, and which the companies that are developing them are trying to revive. The clinical data on the efficacy of a third vaccine is still too preliminary to draw any conclusions. Given these factors, and other uncertainties such as manufacturing difficulties for personalized dendritic vaccines, the degree of accuracy of any projections for the cancer vaccine market is likely to be very low. It is a safe bet, however, that the size of the cancer vaccine market will not approach that of the checkpoint inhibitor market by the 2020-2022 period.

As discussed earlier, T-cell based adoptive immunotherapy for cancer has been difficult to commercialize, and has thus remained in the hands of the NCI and other academic cancer centers. As a result, patient access has also been difficult—for example, TIL therapy is not reimbursed by third-party payers. And the market for ACT has received scant attention from analysts.

However, as ACT technologies and development efforts have matured in the last several years, the potential for commercialization of these therapies has grown. For example, we have identified several leading adoptive T-cell therapies in commercial development.

The ACT market for cancer should be worth billions of dollars within the next 5-10 years. For example, Lion Biotechnologies estimates that its TIL therapy for melanoma will have peak sales of \$1 billion. This is before development of next-generation TIL therapies.

One analyst estimates that Novartis' CAR-based therapy CTL019 has the potential to reach \$10 billion a year, if approved to treat multiple forms of CD19<sup>+</sup> cancer, and if Novartis can overcome the manufacturing challenges associated with all cellular immunotherapies. Other analysts are more skeptical, citing the complexity of manufacturing and administering CTL019, as well as the potential emergence of competitive treatments. Competition has already been emerging in CLL. Based on these factors, one analyst believes that CTL019 is likely



to be used as a salvage treatment, and that it will have limited commercial potential.

However, CTL019 is only one of at least several adoptive immunotherapy products in the clinic. Thus, provided that adoptive immunotherapy developers can overcome the manufacturing, administration, and distribution challenges that affect the field as a whole, ACTs should constitute a multi-billion dollar market by 2020. The high degree of efficacy seen with several adoptive immunotherapies, with the potential for long-term durable responses and cures not seen with other types of therapies, should drive commercial interest in the field.

In conclusion, immuno-oncology is expected to be a game-changing approach to treating cancer. It may well constitute a new mode of cancer treatment, alongside surgery, chemotherapy (including treatment with cytotoxic and/or targeted drugs), and radiation therapy. Immunotherapies may eventually be used in as many as 60% of cases of advanced cancer, and are likely to see their first applications in melanoma, NSCLC, and B-cell malignancies. Either alone or in combination therapies, immunotherapies may produce long-term remissions and even cures (especially if TIL and recombinant T-cell therapies can be successfully developed and commercialized) for cancers that have been uniformly fatal until very recently. Thus immuno-oncology is an important and rapidly emerging field, which deserves the attention it has been receiving in recent years.

# Report Contents

## Executive Summary

### Checkpoint inhibitors

### Therapeutic anticancer vaccines

### Adoptive immunotherapy for cancer

#### TIL therapy

#### Adoptive immunotherapy with genetically engineered T cells bearing chimeric antigen receptors (CARs)

#### Recombinant TCR technology

#### The future of adoptive immunotherapy for cancer

### Outlook for cancer immunotherapy

## CHAPTER 1

### Introduction

### The early history of cancer immunotherapy

### Cytokines as immunomodulatory drugs

#### Interleukin-2

#### Alpha-interferons

#### Interleukin-12

#### Interleukin-12 as a bridge between innate and adaptive immunity

#### Investigation of interleukin-12 as an anticancer therapeutic

## CHAPTER 2

### Checkpoint Inhibitors

### What are immune checkpoints?

### CTLA-4 blocking agents

#### Ipilimumab

#### Tremelimumab

### PD-1 blocking agents

#### Nivolumab

#### Nivolumab in NSCLC

#### Combination therapy of nivolumab plus ipilimumab in melanoma

#### Pembrolizumab (Merck's Keytruda)

#### PD-L1 expression as a biomarker for response to pembrolizumab in melanoma and in NSCLC

#### Merck's strategy for development and approval of pembrolizumab

#### Other anti-PD-1 agents

### PD-L1 blocking agents

#### Roche/Genentech's MPDL3280A

#### MPDL3280A in NSCLC

#### MPDL3280A in urothelial bladder cancer

#### MedImmune/AstraZeneca's MEDI4736

#### Medarex/BMS's MDX-1105

### Are there other clinical-stage checkpoint inhibitors on the horizon?

### Discussion of the Adil Daud interview

### Conclusions

### Interview with Adil Daud, MD

## CHAPTER 3

### Therapeutic anticancer vaccines

### Introduction

### Cancer vaccines—a field rife with clinical failures

#### Why has the cancer vaccine field been so prone to clinical failure?



## Marketed and selected late-stage cancer vaccines in development

Dendreon's sipuleucel-T (APC8015, Provenge)  
 Talimogene laherparepvec (Amgen's T-Vec)  
 Celldex' rindopepimut (CDX-110)  
 Tecemotide (Oncothyreon/Merck Serono)  
 PROSTVAC-VF (Bavarian Nordic)  
 AGS-003 (Argos Therapeutics)  
 CVac (Prima BioMed)  
 Cancer vaccine failure the result of poor clinical trial design?

## Conclusions

## Interview with Matthew Lehman

## CHAPTER 4

## Adoptive Immunotherapy for Cancer

### Introduction

### Adoptive immunotherapy with tumor infiltrating lymphocytes (TILs)

A specific immunodominant mutation in a melanoma patient who had a durable complete remission due to TIL therapy  
 Adoptive immunotherapy based on mutation-specific CD4<sup>+</sup> T cells in an epithelial cancer  
 Commercializing TIL therapy  
 Adoptive immunotherapy with genetically engineered T cells bearing chimeric antigen receptors (CARs)  
 University of Pennsylvania/Novartis' CD19-targeting CAR T-cell therapy CTL019 (formerly CART19)  
     Pilot studies of CTL019  
     Later studies of CTL019  
     Commercialization of CTL019 therapy  
     The Marcela Maus interview and CTL019  
 Juno Therapeutics' 19-28z CD19-targeting CAR T-cell therapy

Serum cytokine levels and safety of 19-28z CAR T-cell immunotherapy  
 Efficacy of 19-28z CAR T-cell therapy in patients with CD19<sup>+</sup> malignancies

Can CAR T-cell therapy be applied to treatment of solid tumors?  
 CAR T-cell therapy targeting mesothelin on malignant pleural mesothelioma and pancreatic cancer

CAR T-cell therapy targeting GD2 on neuroblastoma

Other companies developing CAR-based immunotherapies

## Recombinant TCR technology

Adaptimmune

Autologous recombinant TCR therapies under investigation in Dr. Steven Rosenberg's group at the NCI

## Market issues

Marcela Maus, MD, PhD

## CHAPTER 5

## Summary and Conclusions

### Checkpoint inhibitors

### Therapeutic anticancer vaccines

### Adoptive immunotherapy for cancer

TIL therapy

Adoptive immunotherapy with genetically engineered T cells bearing chimeric antigen receptors (CARs)

Recombinant TCR technology

The future of adoptive immunotherapy for cancer

## Insight Pharma Reports survey on cancer immunotherapy

## Outlook for cancer immunotherapy

## References

## TABLES

- Table 1.1:** Cytokines in cancer immunotherapy
- Table 2.1:** Select checkpoint inhibitors—approved and in development
- Table 3.1:** Types of cancer vaccines that have been developed by academia and industry
- Table 3.2:** Select cancer vaccines—approved and in development
- Table 4.1:** Select adoptive T-cell therapies in commercial development
- Table 5.1:** What Best Describes Your Organization?
- Table 5.2:** Do You Work in Any Aspect of Discovery and Development of Cancer Immunotherapies?
- Table 5.3:** What types of agents do you work on?\*
- Table 5.4:** What aspect(s) of the drug development process do you work in?\*
- Table 5.5:** What is your role in developing and/or using cancer immunotherapy agents?\*
- Table 5.6:** Efficacy of PD-1 inhibitors vs. CTLA-4-targeting drugs in future clinical studies
- Table 5.7:** Do you believe, as predicted in a recent FierceBiotech article, that the PD-1 inhibitor class may reach \$12.5 billion in peak sales?
- Table 5.8:** Do you believe that anti-PD-L1 agents will prove to be superior to both anti-CTLA-4 and anti-PD-1 agents, in terms of efficacy and safety?..
- Table 5.9:** Do you believe that researchers will be able to find means to overcome the severe adverse effects seen in some patients treated with checkpoint inhibitors?
- Table 5.10:** Do you believe that researchers will be able to develop biomarkers that will enable clinicians to identify which cancer patients will benefit from treatment with checkpoint inhibitors?
- Table 5.11:** Do you believe that the intense competition in the checkpoint inhibitor field will result in lowering the costs to patients and payers of these expensive therapies?
- Table 5.12:** Do you believe that the expected high cost of combination therapies for cancer will limit their use?
- Table 5.13:** Impact of regulatory agencies
- Table 5.14:** CAR to adoptive immunotherapy
- Table 5.15:** Do you believe that these groups (mentioned in previous question) can make adoptive immunotherapy reimbursable and commercially viable?
- Table 5.16:** Future of commercializable adoptive immunotherapies
- Table 5.17:** Do you believe that researchers will be able to find means to overcome the severe adverse effects seen in some patients treated with adoptive immunotherapy?
- Table 5.18:** Do you believe that companies such as Novartis and Juno will be able to successfully manufacture T cells for use in personalized adoptive immunotherapies?



## FIGURES

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

**Figure 3.1:** Structure of EGFRvIII, as Compared to Wild-type EGFR

**Figure 4.1:** Structures of Chimeric Antigen Receptors (CARs)

**Figure 5.1:** Growth of Immunotherapies

**Figure 5.2:** Impact of immunotherapy Inhibitors on NSCLC

**Figure 5.3:** The Future of Immunotherapy

**Figure 5.4:** Anti-cancer Vaccines as Anti-cancer Therapies

**Figure 5.5:** T-cell Based Adoptive Immunotherapy

**Figure 5.6:** Availability of CAR-based Adoptive Immunotherapies

## Report Pricing

<b>Academic</b>	\$1,595
<b>Single User</b>	\$2,495
<b>Single Site</b>	\$3,995
<b>Multi Site</b>	\$9,950

## To Order

**[InsightPharmaReports.com](http://InsightPharmaReports.com)**

**Phone:** 781.972.5402

**Email:** [arandall@healthtech.com](mailto:arandall@healthtech.com)

**Mail:** Cambridge Healthtech Institute  
Adriana Randall  
250 First Avenue, Suite 300  
Needham, MA 02494

For Corporate Subscriptions,  
Multi-Reports Orders, Discounts  
or Order Questions Contact:  
Kerri Kelley, at **781-972-1347** or  
by mail at:  
**Cambridge Healthtech Institute**  
**Adriana Randall**  
**250 First Avenue, Suite 300**  
**Needham, MA 02494**

## About Insight Pharma Reports

**CHI's Insight Pharma Reports** are written by experts who collaborate with CHI to provide a series of reports that evaluate the salient trends in pharmaceutical technology, business, and therapy markets.

Insight Pharma Reports are used by senior decision makers at life sciences companies to keep abreast of the latest advances in pharmaceutical R&D, their potential applications and business impacts. Our clients include the top 50 pharmaceutical companies, top 100 biotechnology companies, and top 100 vendors of life science products and services. Typical purchasers are managers, directors, and VPs in business development, discovery research, clinical development, strategic planning, portfolio management, new product planning, and marketing.

### Insight Pharma Reports offer:

- Current Information and analysis of R&D technologies, therapeutic markets, and critical business issues.
- Analysis of the probability of success for various applications of each technology.
- Expert insight based on interviews with key personnel in companies at the forefront of technological advances who share their views on their technology's current status, applications, future direction, and market environment.



## CHAPTER 2:

# Checkpoint Inhibitors

## What are immune checkpoints?

Most of the current excitement over cancer immunotherapy centers on a class of drugs known as “immune checkpoint inhibitors” or more simply “checkpoint inhibitors”. These are agents that inhibit immune checkpoints. Most of these agents 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.<sup>23</sup> The normal physiological function of immune checkpoints is to maintain tolerance of the organism toward self (and thus to 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, especially in order to resist T cell-mediated antitumor immunity.

This chapter will focus on the immune checkpoint pathways that are targets of the leading marketed and late-stage MAb agents. We shall not cover the universe of immune checkpoints, which is quite complex and is by no means completely understood.<sup>23</sup> Moreover, only a small number of immune checkpoints—and with respect to late-stage agents, only two checkpoints—are the major focus of researchers and companies developing checkpoint inhibitors for immunotherapy of cancer.

The products discussed in this chapter are listed in Table 2.1.

**Table 2.1: Select checkpoint inhibitors—approved and in development**

Name and company	Target	Cancer indication and stage	Comments
Ipilimumab (Medarex/BMS's Yervoy)	CTLA-4	Approved, advanced melanoma, 2011	First approved checkpoint inhibitor; clinical trials in progress for various indications
Tremelimumab (formerly known as ticilimumab; MedImmune/AstraZeneca/Pfizer)	CTLA-4	Phase 2, advanced malignant mesothelioma	Phase 3 trial in melanoma failed; not currently active in this indication

of the survey)] as compared to the CTLA-4-targeting drug ipilimumab (Bristol-Myers Squibb's Yervoy) will hold up in later clinical studies. (We discussed this issue in Chapter 2 and in the Adil Daud interview). Of the respondents, 21% answered yes, 3% answered no, and 57% answered “too early to tell”. The survey respondents are thus more cautious than Dr. Daud and other researchers as well as the FDA, who are enthusiastic about PD-1 inhibitors, and prefer to wait for Phase 3 results before forming an opinion on this issue.

**Table 5.6: Efficacy of PD-1 inhibitors vs. CTLA-4-targeting drugs in future clinical studies**

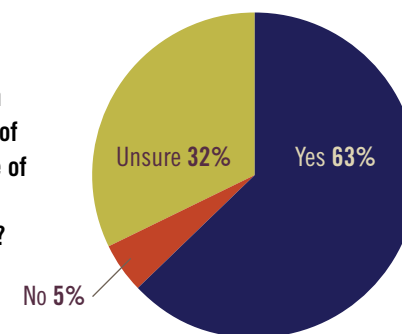
Do you believe that the apparent greater efficacy of PD-1 inhibitors (BMS' nivolumab and Merck's MK-3475) as compared to the CTLA-4-targeting drug ipilimumab (Bristol-Myers Squibb's Yervoy) will hold up in later clinical studies?

Total	N=99
Yes	21%
No	3%
Too early to tell	57%

Figure 5.2 depicts whether respondents believed that the encouraging early-stage results of treatment of non-small cell lung cancer (NSCLC) with PD-1 inhibitors herald the eventual use of immunotherapy in treating a wide range of cancers (beyond melanoma, kidney cancer, and hematologic malignancies). 63% said yes, 5% said no, and 32% were unsure.

**Figure 5.2: Impact of immunotherapy Inhibitors on NSCLC**

Do you believe that the encouraging early-stage results of treatment of non-small cell lung cancer (NSCLC) with PD-1 inhibitors herald the eventual use of immunotherapy in treating a wide range of cancers (not just melanoma, kidney cancer, and hematologic malignancies)?



Source: Insight Pharma Reports

**Table 5.7: Do you believe, as predicted in a recent FierceBiotech article, that the PD-1 inhibitor class may reach \$12.5 billion in peak sales?**

Total	N=99
Yes	36%
No	1%
Too early to tell	46%
Don't know/decline to answer	16%

In the question shown in Table 5.7, respondents were asked whether they believe, as predicted in a recent FierceBiotech article,<sup>34</sup> that the PD-1 inhibitor class may reach \$12.5 billion in peak sales. 36% answered yes, 1% answered no, and 46% answered “too early to tell”. The remaining 16% of respondents checked “don't know or declined to answer”. The answers to this question are consistent with the respondents' general caution about forming opinions on the efficacy of PD-1 inhibitor before the Phase 3 results are in. The respondents' answers shown in Table 5.8—whether anti-PD-L1 agents will prove to be superior to both anti-CTLA-4 and anti-PD-1 agents, in terms of