
CLINIPACE
WORLDWIDE
ENCOURAGING SUCCESS IN
IMMUNO-ONCOLOGY
CLINICAL TRIALS
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INTRODUCTION

Background

Cancer remains the second most common cause of death in the US, accounting for nearly 1 in every 4 deaths.[1] In 2015, approximately 1,658,370 new cancer cases are expected to be diagnosed and approximately 589,430 Americans are expected to die of cancer (~1,615 people per day).[1] The estimated direct medical costs for cancer in the US in 2011 were $88.7 billion.[1] While a number of treatments are available, considerable research focus is being placed on the development of immunotherapies for cancer (immuno-oncology), both preventive and therapeutic, to help reduce both the economic and patient burdens of disease.

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Basis of immuno-oncology

The recent focus on immuno-oncology is based on a long history of clinical and preclinical observations that suggest there is an immune response to cancer.

Coley's toxin

Perhaps the earliest well-documented clinical observations are those that underpin Coley's toxin.[2] In 1891, William B. Coley found that surgery for soft tissue sarcoma was ineffective; in his review of the literature to find a suitable treatment, he discovered that concurrent infection leads to regression and even cure of underlying malignancy. As a result, Coley speculated that infection around a tumor induced a direct cytotoxic reaction and commenced administering local injections of streptococcal cultures for tumors. The clinical response varied from patient to patient, with a correlation between the tumor response and the severity of the patient's response to the infection. Coley's toxin eventually consisted of a combination of *Serratia marcescens* and streptococci because the former enhances the virulence of the latter. Additional findings were that a remote injection also elicited a response and tumor destruction; therefore, a systemic response to infection was also effective for tumor treatment.

This toxin was used for more than 45 years, and the best response was observed in sarcomas, but carcinomas responded poorly. These observations suggest that an immunologic host response may influence the biologic behavior of some malignant tumors, and some manipulation of the immune system balance is necessary to recognize the tumor, initiate a response, and kill the tumor.[2] Some propose that Coley's work was abandoned too soon with the introduction of modern chemotherapy, radiotherapy, and surgical techniques.

Spontaneous regression of some cancers

The observation that some cancers, such as melanoma and renal cell carcinoma, spontaneously regress, either partially or completely without evidence of remaining metastases, is not fully understood. Although melanomas induce immune responses, most tumors exceed the ability of the immune system to destroy it. With spontaneous regression, it is believed that the immune system finally "wins" in its efforts to destroy the tumor. A response to a preceding febrile infection has also been proposed as a stimulant for the immune system.[3]

Abscopal effect

The abscopal effect, seen with radiation therapy, supports the existence of an immune response to cancer. Following local radiation of tumors, malignant masses at distant sites can regress.[4] This has been attributed to the induction and enhancement of the endogenous anti-tumor innate and adaptive immunity. Radiation activates DNA repair pathways and cell cycle checkpoints, resulting in recovery or cell death. While the mechanism of the abscopal effect is not known in detail, the antigens released by the dying cells along with the inflammation that accompanies necrosis could lead to an antigen-specific immune response targeting malignant cells throughout the body.[4]

Cytokines also play an important role in this effect, with demonstrated effects of tumor necrosis factor-α (TNF-α) and interferon-β (IFN-β), which might result from inflammation following the localized radiation of the tumor. Furthermore, chemokine administration after local radiation therapy can result in enhanced killing of tumors at distal sites, further supporting the immune cell mediation. Therefore, radiation boosts a tumor-specific immune response via multiple pathways, making these pathways therapeutic targets to enhance tumor cell immunogenicity while reducing overall toxicity.

Preclinical observations

There is vast preclinical literature documenting the role of immunity in tumor growth and control. Better-known examples include the immunogenicity of tumor transplantation and transfer of immunity with thoracic duct cells.

Experimental tumor transplantation in cancer research began in the early 1900s. An early use showed that cancers could be transmitted by infectious agents[5] and that immunization to that agent was possible. Another finding, this time in mice, was that an implanted tumor graft could stimulate the immune system against the tumor, resulting in disease response.[6] However, the results have been inconsistent, potentially explained by differences between the exogenous and endogenous tumors as well as histocompatibility. For example, the grafted tumor can evoke antibodies against itself and regress if the antigenic alleles on the tumor are not those present in the host, but not if both the tumor and host have the same antigenic alleles.[7] However, the findings of these studies did help us to understand that cancer-specific antigens exist.

Intravenous administration of thoracic duct cells in mice conferred protection against subsequently administered tumor cells, existing fibrosarcomas, and previously deposited intradermal tumors.[8] In these studies, it is likely that the cells were immunologically activated before they were transferred and then continued to function in the host.

Spectacular observations, limited success

Despite occasional brilliant success, there was a failure to obtain consistent results with immune therapies. A limited understanding of the immune system resulted in an inability to effectively and reproducibly manipulate the human immune system and to translate success in animal models to clinical practice.

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Immuno-oncology

However, there has been an abiding interest in harnessing the immune response as treatment for many types of cancers based on evidence of efficacy and the potential for long-lasting protection from disease. Immuno-oncology aims to manipulate the immune system to treat malignancy. Many approaches have been tried over more than 100 years of research, all of which, until recently, have failed.

Prophylactic immuno-oncology

Prophylactic immuno-oncology, or vaccination, is intended to prevent or decrease the incidence of cancer, in the absence of a prior history of the disease. The goal is to prevent infection by organisms closely linked to malignant transformation by activating specific B-lymphocytes and creating a strong and sustained antibody response.[9] Cancers known to be linked to infections represent approximately 18% of the global cancer burden, primarily from the bacterium *Helicobacter pylori*, human papilloma viruses (HPVs), hepatitis B and C viruses, Epstein-Barr virus, and human immunodeficiency virus (HIV) (Table 1).[10,11] Other sources include parasites such as liver flukes, which are primarily found in raw or undercooked fish in Asian countries, and *Schistosoma haematobium*, which primarily affects people in developing countries.

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PARASITE/BACTERIA/VIRUS	ASSOCIATED CANCER	VACCINE
Liver flukes *(Opisthorchis viverrini, Clonorchis sinensis)*	Bile duct cancer	No
Schistosoma haematobium	Liver, bladder, and gallbladder cancers	No
Helicobacter pylori	Stomach and gastric cancers; gastric lymphoma	No
HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66	Cervical cancer	Yes
HPV 16 and 18	Vulva, vagina, penis, anus, oral cavity, and oropharyngeal cancer	Yes
Hepatitis B	Liver cancer	Yes
Hepatitis C	Liver cancer	No
Epstein-Barr virus	Burkitt lymphoma, non-Hodgkin lymphoma in immunosuppressed subjects, sinonasal angiocentric T-cell lymphoma, Hodgkin lymphoma, and nasopharyngeal carcinoma	No
HIV/human herpesvirus 8	Kaposi sarcoma, non-Hodgkin lymphoma	No

Table 1. Parasitic, bacterial, and viral causes of cancer[10,11]

The vaccines for HPV and hepatitis B are considered successful, although they have not been available long enough to document reduction in the incidence of cancer associated with these viral infections.[12] However, convincing evidence exists that Gardasil (Merck), licensed by the FDA in 2006, provides protection from infection by HPV types 6, 11, 16, and 18[12], and Cervarix (GSK) protects against HPV types 16 and 18.[12]

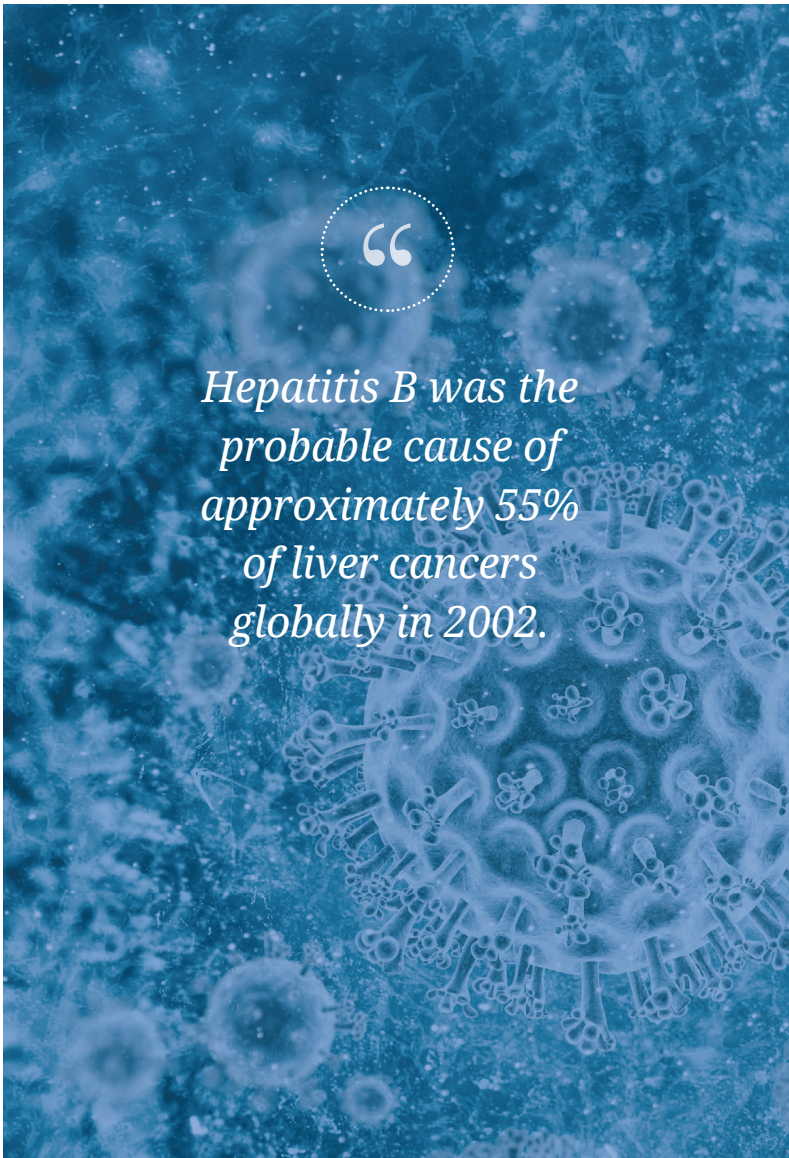
A randomized, double-blind phase 2b-3 trial of investigational 9-valent vaccine against HPV types 6, 11, 16, and 18, which are included in the quadrivalent HPV vaccines, as well as 5 additional oncogenic types (31, 33, 45, 52, and 58) published in February 2015 demonstrated that the antibody responses to 6, 11, 16, and 18 were non-inferior to the quadrivalent vaccine.[13] Over the 4.5-year follow-up with the 9-valent vaccine, the incidence of high-grade cervical epithelial neoplasia, adenocarcinoma in situ, and cervical cancer related to the additional HPV types (31, 33, 45, 52, and 58) was 0.1 per 1000 person-years, compared with 1.5 per 1000 person-years with the quadrivalent vaccine, while the incidences of persistent infection (≥6 months) with the same 5 types were 2.1 per 1000 person-years and 52.4 per 1000 person-years, respectively. Therefore, the 9-valent vaccine prevented cervical, vulvar, and vaginal disease and persistent infection of the 5 additional HPB types.

Cervical cancer is the second leading cause of cancer deaths in women worldwide;[14] the high levels of seroconversion observed with the cervical cancer vaccines is expected to reduce the incidence of cervical cancer caused by these infectious strains. This is particularly true given the findings of the most recent study regarding the 9-valent vaccine that clearly demonstrated efficacy against infections and cancers within the follow-up period. Furthermore, the increasing incidence of oropharyngeal cancers starting in the late 1980s has been attributed to HPV-16 infection,[15] and these vaccines might prove beneficial in prevention of these head and neck cancers. These vaccines are based on synthetic particles that mimic the natural viral capsid structure and do not contain oncogenic viral DNA; therefore, the risks of side effects are reduced.[9]

The hepatitis B vaccine, approved by the FDA in 1981, was originally developed to protect against viral hepatitis but is expected to decrease the incidence of hepatocellular carcinoma associated with hepatitis B infection.[16] Hepatitis B was the probable cause of approximately 55% of liver cancers globally in 2002.

Therapeutic immuno-oncology

In contrast, therapeutic immunotherapies are intended for patients who have an active malignancy or are at high risk of relapse from a prior cancer. Such agents must eradicate or reduce an existing tumor mass or any residual disease after primary treatment. Despite decades of work and sporadic evidence of activity, therapeutic immunotherapy has only recently gone "mainstream." This lack of success is believed to be the result of the cancer cells' natural ability to avoid recognition by the immune system and block a cytotoxic T lymphocyte (CTL) response,[9,17] either in a non-antigen-specific manner or an antigen-specific manner.



Non-antigen-specific therapeutic immunotherapies. Non-antigen-specific therapies, or non-specific immune stimulators,[9] enhance the immune response generally or decrease the immunosuppression present in the tumor environment[17] by various mechanisms. These include an iatrogenic infection (e.g., Coley's toxin), a cytokine that is part of the immune cascade (e.g., interleukin [IL]-2,[17] IL-4,[18] IFN, TNF), or Toll-like receptor agonists. Other methods include vaccination with inactivated whole cells that eliminates the need to identify key antigens.[19] Such non-specific vaccine therapies rely on the patients' endogenous dendritic cells for their uptake and effective antigen presentation to tumor-specific T cells.

In 1957, Drs. Alick Isaacs and Jean Lindenmann first demonstrated the existence of IFN, the first cytokine. They showed that a heat-inactivated influenza virus interfered (hence, interferon) with active virus;[20] although virus interference was a known phenomenon, the mechanism was unknown at that time. It was later discovered that one virus can interfere with the growth of a number of unrelated viruses and that there was not just one IFN, but multiple types (i.e., α, β, γ), each with a specific action. These findings led to the understanding that IFN did not kill cells, but stopped them from multiplying without harming the host cell.

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In the 1960s, Kari Cantell and coworkers developed a method to prepare crude IFN from white blood cells in volumes that could be used to treat patients. These early preparations were used in clinical trials for several types of malignancies, and acceptable response rates were observed in the early clinical trials when compared with the available chemotherapy at the time.[21] These early IFN preparations were crude extracts, and some 20 different IFNs have been identified, each with different specificities and functions. IFNs can enhance the immune response by activating natural killer cells and dendritic cells. Despite early hopes that IFN would be the treatment for cancer, its limitations are now better understood, particularly related to the varying response based on cancer type and the debilitating and often dose-limiting adverse reactions of fever, chills, fatigue, myalgia, thyroid problems, pulmonary hypertension, and hypotension in addition to anorexia, nausea, vomiting, and/or diarrhea.[21,22]

Another group of cytokines, the interleukins, also have a role in immune signaling. One of these interleukins, IL-2, was first identified in 1976.[23] IL-2 is a regulator of the immune system and acts as a growth factor that stimulates proliferation and differentiation of many immune cells, including T cells. The anti-tumor activity is mediated by the proliferation of cytotoxic cells, including natural killer cells and lymphokine-activated killer cells. It has proven particularly effective in metastatic melanomas and metastatic renal cell carcinoma, with a recent study reporting an overall survival at 2 years of 60.6% in 91 patients.[24] However, severe toxic effects are common because of the systemic stimulation of profound lymphocytosis, eosinophilia, and thrombocytopenia[25] and include pulmonary edema, capillary leak syndrome, hypotension, impaired liver function, fever, and chills. For this reason, when administered at high doses, a hospital stay is required during treatment. Furthermore, the overall cure rate is only 6%.[25]

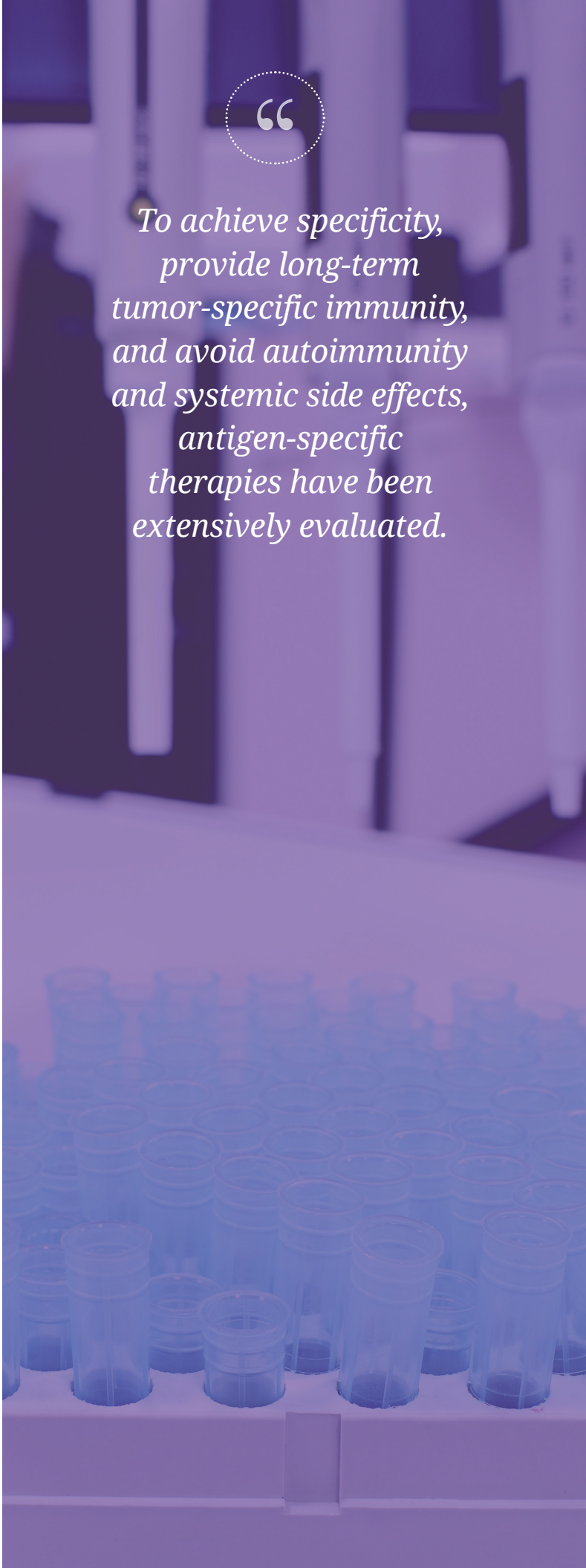
Because it was not possible to select antigens at the time, the first cancer vaccine therapies consisted of whole tumor cells derived from the patient to be treated and inactivated to prevent growth. Often, these

were injected with immune adjuvants such as bacillus Calmette-Guérin (BCG) or a growth factor such as granulocyte macrophage colony-stimulating factor (GM-CSF) to create an inflammatory environment to attract antigen-presenting cells. This approach has proved successful in mouse models but never in humans and has the risk of autoimmunity.[26,27] Because these vaccines are personalized, it is difficult to individually prepare the vaccines.[27]

To achieve specificity, provide long-term tumor-specific immunity, and avoid autoimmunity and systemic side effects, antigen-specific therapies have been extensively evaluated.

Antigen-specific therapies. The discovery of tumor-associated antigens resulted in the development of antigen-specific therapies that aim to induce immune cells that target cancer cells expressing a particular antigen or set of antigens. The antigens may be administered with or without stimulants/adjuvants (e.g., aluminum-based salts or squalene-oil-water emulsion [MF59][26]) in addition to GM-CSF or other effectors. Antigens can be presented in viruses along with GM-CSF or other vectors.[28] These include peptide-based, protein-based, cancer cell-based, viral vector, DNA, messenger RNA, and carbohydrate vaccines that promote local inflammation.[17]

To elicit strong immunity, tumor-cell vaccines must include substances that activate dendritic cells because they rely on the endogenous dendritic cells for uptake and antigen presentation.[26] Unfortunately, with the possible exception of sipuleucel-T (see below), antigen-specific therapies have failed to prove effective. A review of 440 individuals (422 with melanoma) treated with peptide-based cancer vaccines at the NCI between February 1995 and April 2004 resulted in partial responses in 9 patients and complete responses in 2 patients (2.9% objective response rate).[28] A further review of 35 cancer vaccine (peptide-based, viral, tumor cells, dendritic cells, or heat shock proteins) trials in 765 patients resulted in a cumulative response rate of 3.8% in various types of metastatic cancer (melanoma, prostate, breast, cervical, colorectal, lung, or kidney).



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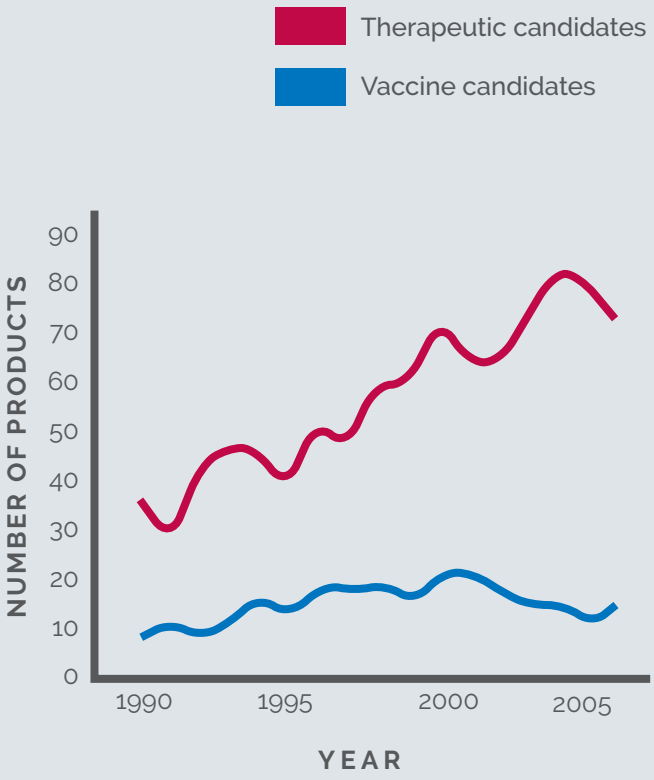


Figure 1. The number of therapeutic candidates under investigation has continued to increase

Possible reasons for the many failed trials include an inadequate scientific understanding of cancer immunology, excess zeal in going from phase II to phase III trials, lack of specificity of tumor-associated antigens, and the patients' limited immune response.[29]

Why is failure so common?

Possible reasons for the many failed trials have been discussed previously and include an inadequate scientific understanding of cancer immunology, excess zeal in going from phase II to phase III trials (both often underpowered), lack of specificity of tumor-associated antigens, and the patients' limited immune response.[29]

Despite this poor showing, an online search of clinicaltrials.gov (accessed 9 February 2015) showed 1604 trials for "cancer vaccines," including 402 open trials, and the number of therapeutic vaccine products showed continued growth through 2006 (last year reported) (Figure 1).[29] Over the years, a small number of cancer immunotherapies have been approved by the FDA, some of which are highlighted in the following paragraphs (Table 2).

Examples of approved therapeutic immunotherapies for cancer

Intravesicular infusions of BCG, which is a weakened form of a bacterial pathogen and used as a vaccine for *Mycobacterium tuberculosis*, results in an inflammatory process that attracts antigen-presenting cells that detect tumor antigens released by the tumor cells that have been damaged by the bacterial infection. This can result in an anti-tumor response, which was initially investigated in the 1950s. Currently, this treatment is limited to superficial bladder cancer, and approximately 30% of these cancers do not respond to the treatment. The mechanism underlying this activity had not previously been understood; however, a recently published study indicated that particular mutations of a component that suppresses tumor cell proliferation, survival, and growth might increase the cells' susceptibility to the infection.[30]

IL-2 (aldesleukin) therapy is an FDA-approved immunotherapy option for melanoma and kidney cancer and was initially approved in 1992. It is a human recombinant IL-2 produced using a genetically engineered *E. coli* strain containing an analog of the human IL-2 gene. As with native human IL-2, this version of IL-2 activates cellular immunity with enhanced lymphocyte cytotoxicity, induction of killer cell activity, and induction of IFN-gamma production. Although inhibition of tumor growth has been demonstrated, the exact mechanism remains unknown. The FDA-approved use involves high doses

(600,000 IU/kg) administered as a bolus intravenously over 15 minutes every 8 hours for a maximum of 14 doses. This is repeated after 9 days of rest, for a total maximum of 28 doses. Doses may need to be withheld for toxicity, as described earlier in this paper. The treatment can be provided again after a rest period of at least 7 weeks from hospital discharge. Because of the high risk of toxicity with IL-2, medical supervision in a hospital setting is required for its administration and throughout treatment.[25]

IFN was first approved by the FDA in 1986 to treat cancer and has subsequently been approved and used via subcutaneous or intramuscular injections for hairy cell leukemia, malignant melanoma, non-Hodgkin lymphoma, AIDS-related Kaposi sarcoma, hepatitis C infection, and hepatitis B infection.[22]

Sipuleucel-T was the first cell-based cancer immunotherapy approved by the FDA (2010) for treatment of asymptomatic metastatic castrate-resistant prostate cancer (Figure 2). It consists of antigen-presenting cells from autologous peripheral blood mononuclear cells, extracted during leukapheresis that are activated *ex vivo* by the fusion protein PA2024 that combines recombinant GM-CSF, which is the immune cell activator, and recombinant prostatic acid phosphatase (PAP), a tissue antigen expressed by prostate cancer cells in more than 95% of prostate adenocarcinomas.[31] Once re-infused into the patient, the activated (by GM-CSF) antigen-presenting cells can recognize and kill PAP-positive prostate cancer cells.

In practice, the patient is administered three treatment cycles over four weeks. Each treatment cycle requires two visits. The patient is leukopheresed in the first, and the treated cells are reinfused in the second, which occurs 3 days later. Variations in the number of activated cells and cellular composition are observed between each of the 3 treatment cycle doses for the same patient.[17,32] The first dose primes the immune system, and the following 2 doses provide a booster, similar to a classical vaccine-mediated memory response.

AGENT	PURPOSE/MECHANISM	INDICATION
Non-antigen-specific therapies		
Interferon (IFN)	Systemic immune response by activating natural killer cells and dendritic cells	Hairy cell leukemia, malignant melanoma, non-Hodgkin lymphoma, AIDS-related Kaposi sarcoma, hepatitis C infection, and hepatitis B infection
Low-dose interleukin-2 (IL-2)	Systemic immune response by proliferation of cytotoxic cells	Renal cell carcinoma, melanoma
High-dose interleukin-2 (IL-2) or aldesleukin	Systemic immune response by proliferation of cytotoxic cells	Metastatic renal cell carcinoma, metastatic melanoma
Bacillus Calmette-Guérin (BCG)	Systemic immune response to infection	Superficial bladder cancer
Antigen-specific therapies		
Sipuleucel-T	Recognition and destruction of prostatic acid phosphatase-positive cells	Asymptomatic metastatic castrate-resistant prostate cancer

Table 2. Approved therapeutic cancer immunotherapies in the US

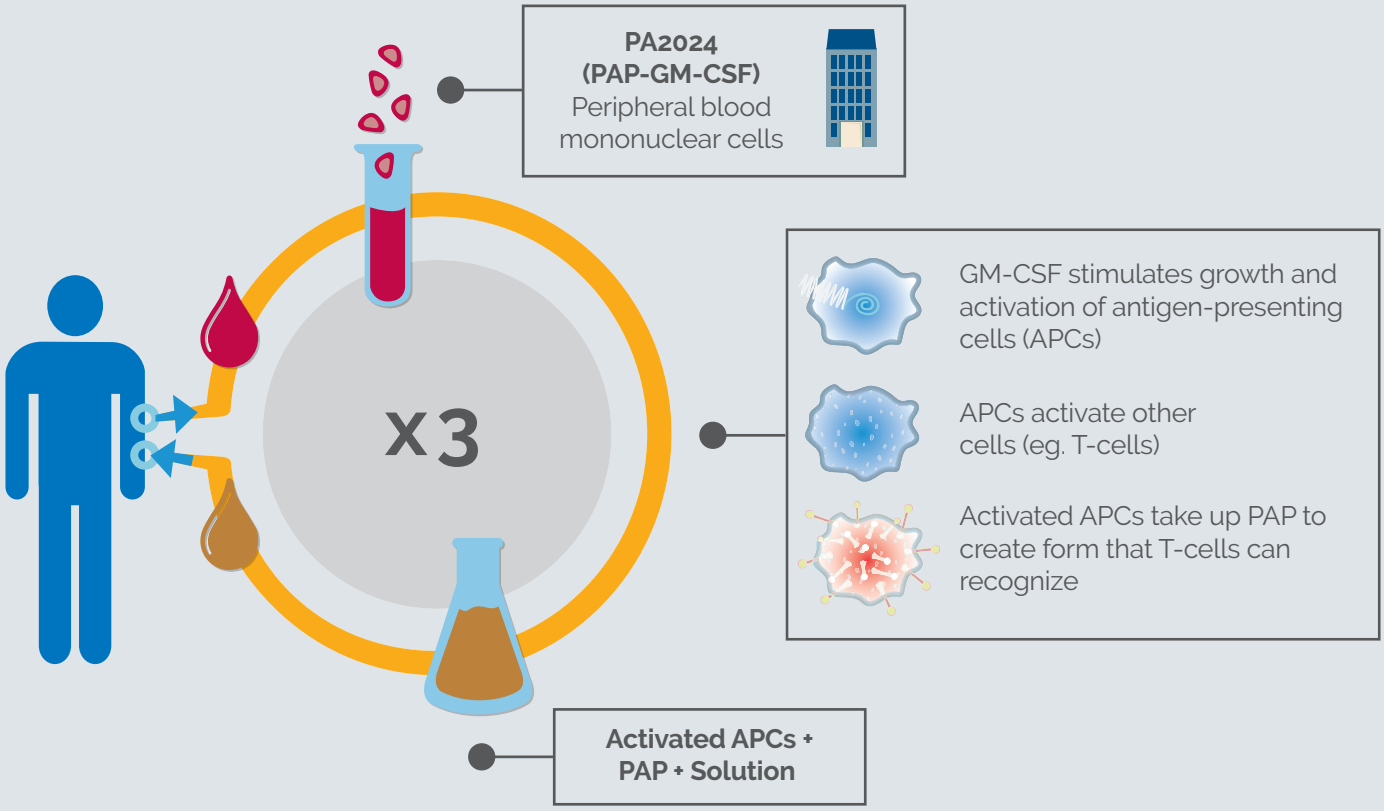


Figure 2. Sipuleucel-T in the treatment of asymptomatic metastatic castrate-resistant prostate cancer[32]

In 2 different randomized, placebo-controlled, double-blind clinical trials, an increase in median survival of 4.1–4.5 months was observed,[33,34] compared to a median survival benefit of 2.4 months with the previous standard therapy of docetaxel.[35] In addition, the risk of death was reduced by 1/3[34] or 1/5,[33] with fewer side effects.[33] However, a disadvantage of a therapy such as sipuleucel-T is that cell culture processing is required for each patient, which limits the number of treatments available. Sipuleucel-T has proved far from a commercial success with the parent company, Dendreon, filing for bankruptcy in November of 2014.[36]

The number of immunotherapies currently approved (prior to the advent of immune checkpoint agents) and their limited efficacy shows the difficulty of effectively harnessing the immune system as a cancer therapeutic. However, research continues to identify more effective and safer therapeutics, including checkpoint inhibitors and chimeric antigen receptor-modified (CAR) T-cell therapy, and a number of cancer immunotherapies have been approved in other countries (Figure 3).

In 2 different randomized, placebo-controlled, double-blind clinical trials for Sipuleucel-T, an increase in median survival of 4.1–4.5 months was observed.[33,34]

Figure 3. Approved cancer immunotherapies in other countries, as of 2008[27]

*Fast track status granted by US FDA

Promise of immune checkpoint inhibitors

At this time, probably the most promising area of cancer research is that of immune checkpoint inhibitors. Immune checkpoints act to prevent excessive activity of T cells under normal conditions (Figure 4). Inappropriate T cell activation can cause autoimmune diseases. However, in cancer, these checkpoint pathways can be modified to inhibit the adaptive immunity. The new checkpoint agents target the signaling between the antigen-presenting cells and T effector cells, tipping the balance from tolerance of the tumor to targeting of the tumor.

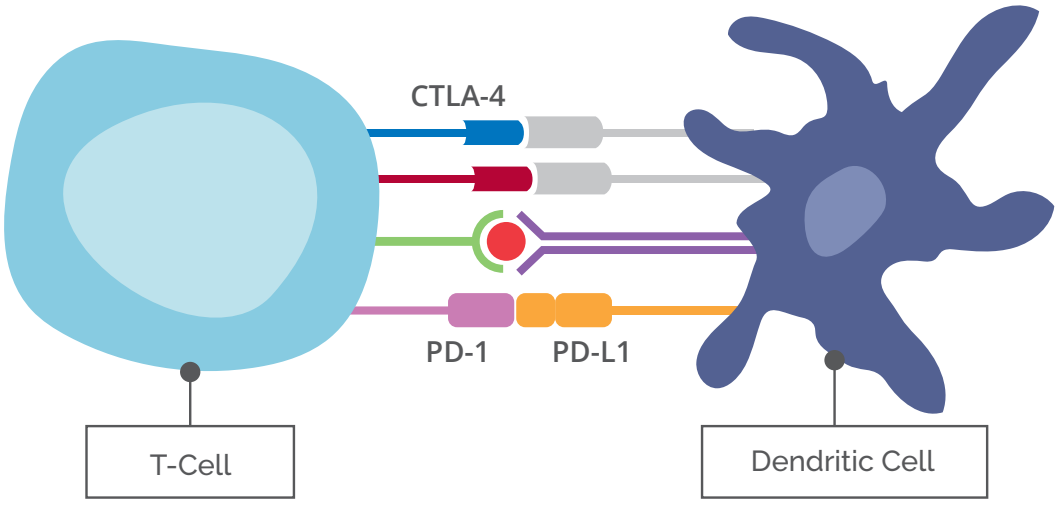


Figure 4. Basic illustration of immunologic synapses between T cells and dendritic cells

To date, the blockade of 2 elements of the synapse have undergone extensive clinical testing, and multiple agents have been approved for use or are in late-stage testing (Table 3).

PURPOSE	AGENT	STATUS	INDICATION
Inhibit CTLA-4 checkpoint	Ipilimumab (Yervoy®)	Approved (March 2011)	Melanoma
	Tremelimumab	Phase 3	Malignant mesothelioma, hepatocellular carcinoma, melanoma, glioblastoma, metastatic pancreatic cancer
Inhibit interaction between PD-1 checkpoint and ligands	Nivolumab (anti-PD-1; Opdivo®)	Approved (December 2014)	Metastatic or unresectable melanoma
		Phase 1	Melanoma, breast cancer, pancreatic cancer, non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma, NSCLC, glioblastoma, solid tumors, B-cell non-Hodgkin lymphoma
		Phase 2	Nasopharyngeal carcinoma, kidney cancer, myeloid leukemia, pancreatic cancer, colorectal cancer, head and neck cancer, ovarian cancer, anal cancer, solid tumors, Hodgkin lymphoma, NSCLC
		Phase 3	NSCLC, renal cell carcinoma, renal cell carcinoma, gastric cancer
	Pembrolizumab (anti-PD-1; previously lambrolizumab; MK-3475; Keytruda®)	Approved (September 2014)	Metastatic or unresectable melanoma
		Phase 1	NSCLC, melanoma, colon carcinoma, rectal carcinoma, renal cell cancer, ovarian cancer, pancreatic cancer, multiple myeloma
		Phase 2	Recurrent head and neck cancer, malignant glioma, brain tumor, glioblastoma, melanoma, solid tumors, thymic carcinoma, pancreatic cancer, prostate cancer, Hodgkin lymphoma, SCLC, multiple myeloma, colorectal cancer
		Phase 3	Advanced melanoma, urothelial cancer
	MPDL3280A (RG7446; anti-PD-L1)	Phase 1	Malignant melanoma, solid cancers, NSCLC, B-cell lymphoma
		Phase 2	Renal cell carcinoma, bladder cancer, NSCLC, colorectal cancer
		Phase 3	NSCLC, bladder cancer

PURPOSE	AGENT	STATUS	INDICATION
	Pidilizumab (CT-011; anti-PD-1)	Phase 2	Multiple myeloma, malignant gliomas, lymphomas, metastatic melanoma
	AMP-514 (MEDI0680; anti-PD-1)	Phase 1	Solid tumors, advanced malignancies, B-cell lymphomas
	MEDI4736 (anti-PD-L1)	Phase 1	Solid tumors, myelodysplastic syndrome
		Phase 2	Solid tumors, NSCLC, colorectal cancer, head and neck cancer
		Phase 3	NSCLC
	AMP-224 (recombinant PD-L2-Fc fusion protein)	Phase 1	Solid tumors, colorectal cancer
	rHIgM12B7 (anti-PD-L2)	Phase 1	Melanoma
	BMS-936559 (anti-PD-L1)	Withdrawn at phase 1	Melanoma
Inhibit LAG-3 checkpoint	BMS-986016	Phase 1	Leukemias, lymphomas, multiple myeloma, solid tumors,
	IMP321	Phase 1	Breast cancer, renal cell carcinoma, melanoma
Inhibit TIM-3 checkpoint	None		
Inhibit adenosine A2A receptor	None		
Dual treatments			
Inhibit CTLA-4 + PD-1	Ipilimumab + nivolumab	Phase 3	Melanoma
		Phase 1/2	Renal cell cancer, colon, NSCLC, triple-negative breast cancer, gastric cancer, pancreatic cancer, SCLC
	Ipilimumab + pembrolizumab	Phase 1	Melanoma, renal cell cancer, NSCLC, gastric cancer
Inhibit CTLA-4 + PD-L1	Tremelimumab + MEDI4736	Phase 1	NSCLC, solid tumors, head and neck cancer, solid malignancies, B-cell lymphomas
		Phase 2	Head and neck cancer
Inhibit PD-1 + LAG-3	Nivolumab + BMS-986016	Phase 1	Solid tumors
Inhibit PD-1 and PD-L1	AMP-514 + MEDI4736	Phase 1	Advanced malignancies

Table 3. Checkpoint inhibitors approved for use or in late-stage testing[37], www.clinicaltrials.gov (February 2015)

Within the immune checkpoint pathway, the cell surface receptor cytotoxic T-lymphocyte antigen-4 (CTLA-4) is expressed by a cytotoxic T cell when it becomes active. CTLA-4 competes with other molecules that share ligands on the antigen-presenting cell, which helps to appropriately regulate cytotoxic activity. However, in some cancers, CTLA-4 is abnormally expressed, which allows the malignant cells to go unnoticed by T cells.[38]

Another important therapeutic target is the programmed death-1 (PD-1)/PD-1 ligand (PD-L1) pathway; PD-1 is also a surface receptor expressed on many cell types, including activated T cells, B cells, and natural killer cells.[38] PD-L1 is the ligand to PD-1 on antigen presenting cells; together, they work to induce T-cell tolerance. Abnormal expression of PD-L1 can occur on malignant cells inhibiting the recognition of tumor antigens by antigen-presenting cells. Drugs that can either block the PD-1 protein (on the surface of T cells) or the PD-L1 protein (on the surface of cancer cells) can increase cancer antigen recognition.[16]

Immune-related adverse events (irAEs) resulting from immune modulation are of concern with these treatments. These can manifest as autoimmunity to any organ or organ system with anti-CLTA-4.[39] In a review of 14 phase I-III trials for NSCLC , 64.2% of 1,498 patients experienced irAEs of any grade.[40] However, these events appear to be associated with dose, the antitumor response, and survival. Corticosteroids for immunosuppression appear to be the best management of these irAEs.

There are approximately 900 active clinical trials currently investigating PD-1/PD-L1 listed on clinicaltrials.gov (accessed February 2015) and approximately 50 active clinical trials investigating CLTA-4 for melanoma, leukemias, lymphomas, prostate cancer, adenocarcinomas, liver cancer, and lung cancers.

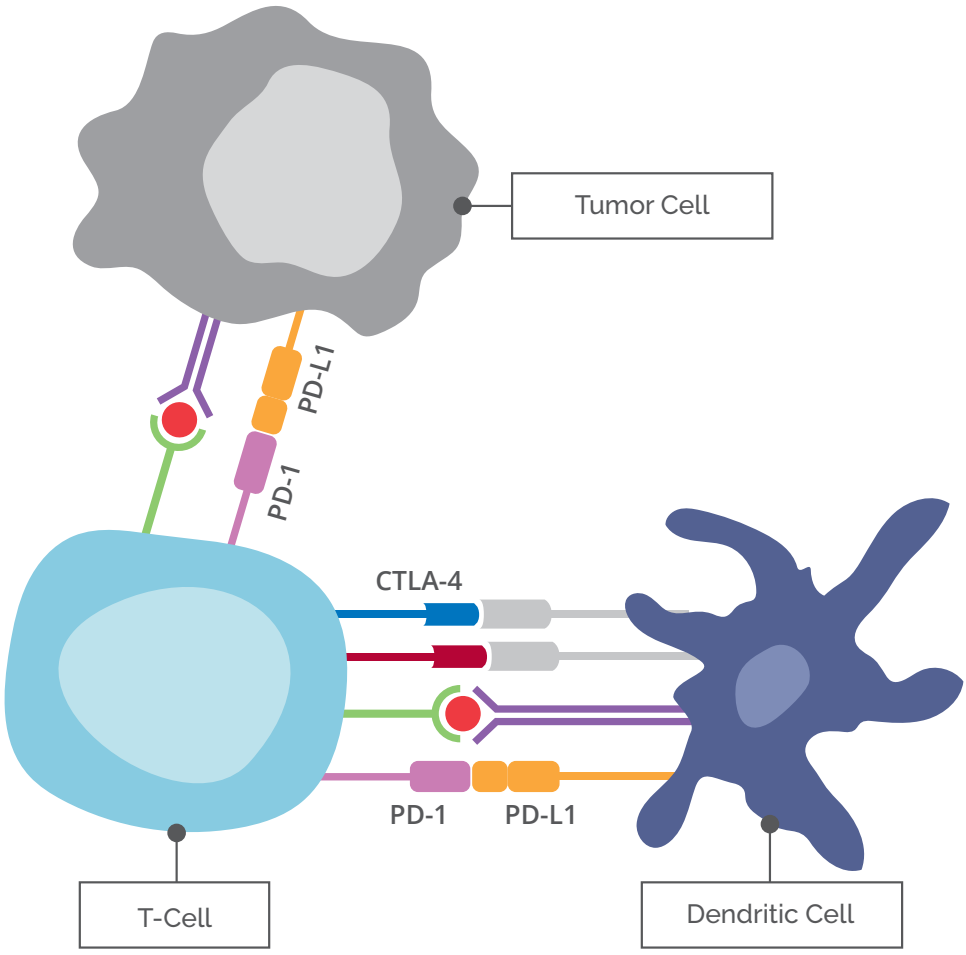


Figure 5. Abnormal expression of receptors on malignant cells can occur

Examples of approved checkpoint inhibitors for cancer

Ipilimumab binds to and inhibits CTLA-4 on T cells;[16] it was approved by the FDA in 2011 for the treatment of advanced melanoma. In an earlier stage of melanoma, it reduced the relative risk of recurrence by 25% compared with placebo, but approximately half of the patients had to stop therapy early because of adverse effects that were possibly related to autoimmunity, including inflammation of the colon, thyroid, and pituitary gland as well as skin rash.[16] In addition, it is being investigated for use in NSCLC in combination with chemotherapy with promising results particularly for squamous lung cancers, which have had few therapeutic advances.[38]

Pembrolizumab was the first PD-1-targeted drug to receive FDA approval (September 4, 2014). It was approved for the treatment of unresectable or metastatic melanoma and disease progression after treatment with ipilimumab and, if the person is positive for BRAF V600 mutation, progression after the use of a BRAF inhibitor.[16,17] In a clinical trial, approximately 24% of the patients who received pembrolizumab at the recommended dose of 2 mg/kg experienced tumor regression.

Nivolumab is a fully human PD-1-targeted drug that was also approved by the FDA (December 2014) for the treatment of unresectable or metastatic melanoma and disease progression after treatment with ipilimumab and, if the person is positive for BRAF V600 mutation, progression after the use of a BRAF inhibitor.[41] At the recommended dose of 3 mg/kg (60-minute intravenous infusion) every 2 weeks in 120 patients that met these criteria, the objective response rate at 6 months was 32%, 4 patients experienced complete remission, and 34 patients experienced partial remission. At this same dose, the overall survival was 72.9%, and the median progression-free survival was 5.1 months in patients with previously untreated melanoma without BRAF mutation in a recent study.[42] Similar durable responses have also been demonstrated in NSCLC and renal cell carcinoma.[43]

The US FDA granted a breakthrough therapy designation for the investigational cancer immunotherapy MPDL3280A by Genentech of the Roche Group, which is a PD-L1 inhibitor, for PD-L1 positive NSCLC with disease progression during or after platinum-based chemotherapy (February 2015). This follows the designation of a breakthrough therapy for metastatic bladder cancer in 2014.[44]

In an earlier stage of melanoma, Ipilimumab reduced the relative risk of recurrence by 25% compared with placebo.[16]

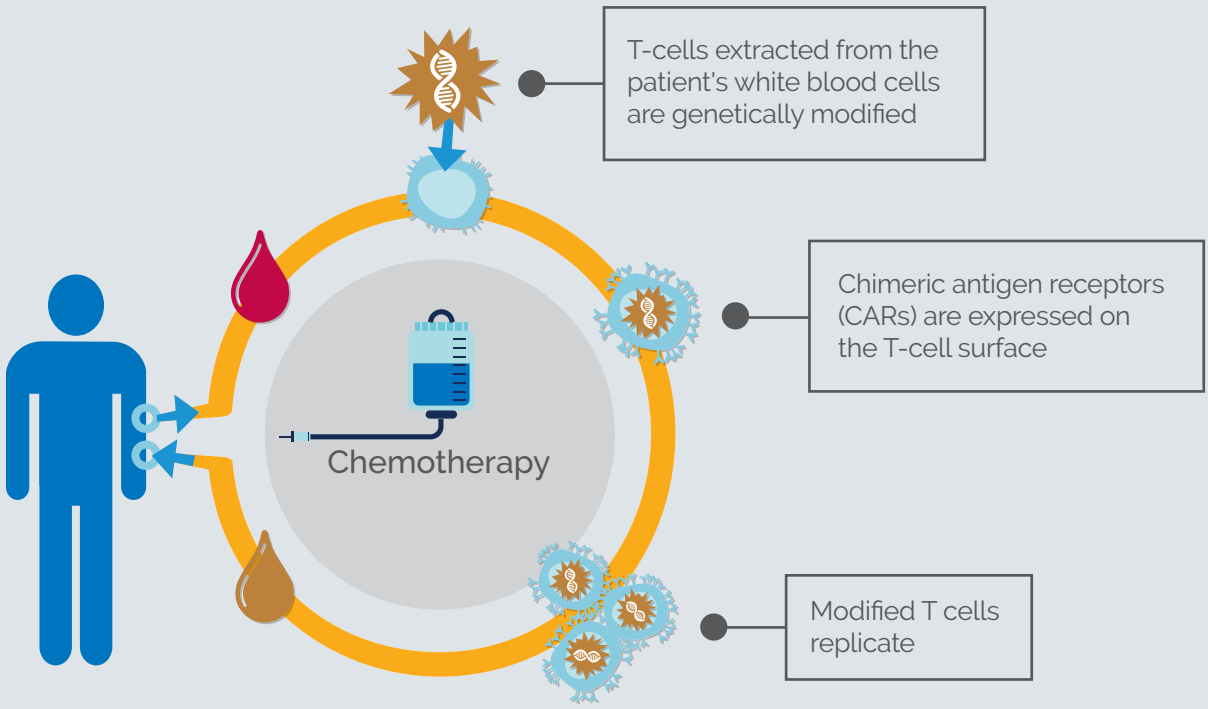


Figure 6. CAR-T therapy

Chimeric antigen receptor-modified (CAR) T-cell therapy

CAR-T therapy utilizes the patient's own immune cells to recognize and attack their tumors, following genetic modification to produce the chimeric antigen receptors (CARs) on the T cell surface.

T cells are isolated from the patient's blood and genetically modified *ex vivo* with the CARs (Figure 6). Chemotherapy is administered while the T cells are being treated. Following infusion into the patient, the reprogrammed T cells attach to specific antigens on the cancer cells and continue to multiply thousands of times[16] in the presence of the target antigen; as the target antigen declines, the T cells decrease. Upon binding with the tumor antigen, the CAR sends an intracellular signal to the effector T cell, prompting destruction of the malignant cell.

CAR-T therapy differs from checkpoint inhibition in that it is generated on an individual basis; therefore, it has the logistic disadvantages of sipuleucel-T. However, unlike sipuleucel-T, it causes complete responses for some patients with advanced disease with the possibility of long-term disease control. Two small studies have been successful for relapsed acute lymphoblastic leukemia (ALL) in both children and adults. In adults with chemotherapy-resistant B-cell ALL, complete remissions occurred in 88% of the patients, with a response as early as 7-10 days after CAR-T infusion. CTL019, which is a CAR-T therapy for refractory leukemia, was granted breakthrough therapy status in July 2014 and showed a 92% complete remission rate in pediatric relapsed/refractory ALL. CAR-T therapy remains experimental at this time and is only available through clinical trials.

In adults with chemotherapy-resistant B-cell ALL, complete remissions occurred in 88% of the patients, with a response as early as 7-10 days after CAR-T infusion.

Concerns with CAR-T therapy are the side effects of neurotoxicity and cytokine release syndrome (cytokine storm), which probably result from large-scale T-cell activation. A rapid and massive release of cytokines in the bloodstream can lead to dangerously high fevers and precipitous drops in blood pressure. Because the patients that experienced severe reactions had particularly high levels of IL-6, which is secreted in response to inflammation, drugs to treat inflammatory conditions might help to manage toxicity. It has been suggested that the FDA will not approve CAR-T therapy that does not include a safety feature for the risk of toxicity.[45]

There are approximately 40 active trials listed in clinicaltrials.gov (accessed February 2015) for CAR-T therapies for a wide range of cancers, including leukemias, lymphomas, breast cancers, pancreatic cancer, neuroblastomas, lung cancer, gastric cancer, colorectal cancer, ovarian cancer, and brain cancers.

To date, only immunotherapies offer the prospect of long-term cancer control in metastatic solid tumors. Unlike surgery, chemotherapy, or radiation in this setting, they have the potential to be curative rather than palliative and to provide lifelong rather than temporary control of disease.

Immune therapy development

The evaluation of immunological cancer therapies can differ from that of conventional cytotoxic therapies, such as chemotherapy or radiation. Because there can be an initial increase in the apparent size of a tumor on imaging, new criteria for the response to cancer immunotherapies are now used to account for the initial inflammatory response to active immune treatment. In addition, the side effect profile of some immunotherapies differs from that seen with other, more traditional cancer therapies. For example, checkpoint inhibitors can elicit autoimmunity to normal tissues as well as malignant tissues, while CAR cells have their own side effect spectrum, including cytokine storm.

Determinants for success of immunotherapies in cancer

Given the seemingly poor success rate for immuno-oncology agents in the past, it is understandable to have a pessimistic view of the future of these therapies. For example, a review published in 2004 indicated that the overall response rate to cancer immunotherapies was only 3.3%; however, 96% of the patients had melanoma.[28]

Supporters of the potential applications of immunotherapies in cancer have taken advantage of the long history of research and the data provided by both failed and successful trials to identify the factors that might improve their success in the future. One common theme throughout the literature is the lack of a consistent result, which could be explained by the following:

DEFINITIONS OF RESPONSE TO TREATMENT[46]

HETEROGENEITY WITHIN AND BETWEEN CANCERS, TUMORS, AND MUTATIONS

AVAILABILITY OF INFRASTRUCTURE TO UNDERSTAND, IDENTIFY, AND MONITOR TARGETS[47,48]

SAMPLING AND HANDLING PROCESS

These are discussed in more detail in the following paragraphs.

FDA guidance

There is increasing recognition that the considerations for the development of a cancer immunotherapy are different than those for a more traditional biological product or cytotoxic drug for the treatment of cancer; as a result, the FDA developed specific guidance for vaccine and immunotherapy trials (antigen-specific therapeutic only).[49] In this guidance document, clinical considerations of particular interest are highlighted.

First, therapies are traditionally first tested in patients with advanced cancers who have failed multiple treatment regimens with potential detriment to the immune system. In addition to minimizing the potential responsiveness to the cancer vaccine, the vaccine may be more effective with low disease burden in the first place.[17,26,49] Furthermore, the time to develop an anti-tumor immune response to a cancer immunotherapy is typically 2-3 months, compared with shorter times for traditional cytotoxic therapy.

The kinetics of tumor growth rates differ, and this can present as shrinkage in all baseline lesions, stable disease followed by a slow decline in tumor burden, increase in tumor burden followed by response, or presence of new lesions.[17,39] A delayed response is also often observed, and inflammation and tumor enlargement (pseudoprogression) from cytotoxic T lymphocytes and immune cells can be difficult to differentiate from tumor progression.[39]

Because of this, the criteria traditionally used to estimate the response to typical cytotoxic agents (e.g., Response Evaluation Criteria in Solid Tumors [RECIST] or World Health Organization [WHO] criteria) might underestimate the response with immunologic agents and result in treatment cessation in patients that might respond given enough time.[46] Therefore, new criteria for immune-related response have been developed (Table 4). However, these criteria have not been fully validated, and modified RECIST and modified WHO are also being evaluated in clinical trials. Regardless, an appropriate length of time is necessary to observe an effect.

Similarly, appropriate endpoints should be identified. Therapeutic immunotherapies do not directly target the tumor, but instead target the immune system. As mentioned, adequate time is required for the immune system to develop, and booster treatments might also be required. Instead of immediate and significant reduction in tumor burden, the resulting effects might be related to slower tumor growth rate. Therefore, overall survival (OS) might be a better endpoint than the traditional endpoints of response or progression-free survival.[39] For example, in the trials of Sipuleucel-T, the primary objective of time to disease progression was not different between the intervention and control groups; however, the risk of death was lower, overall survival time was higher, and time to first opioid analgesic was longer with sipuleucel-T, which indicated a delayed treatment effect that was likely from active immunotherapy.[50]

Overall survival (OS) might be a better endpoint than the traditional endpoints of response or progression-free survival.[39]

CLASSIFICATION	CRITERIA
Immune-related complete response (irCR)	Complete disappearance of all lesions (regardless of being measurable) and no new lesions
	Confirmation by repeat, consecutive assessment at least 4 weeks from the first documented date
Immune-related partial response (irPR)	Decrease in tumor burden ≥50% relative to baseline
	Confirmation by repeat, consecutive assessment at least 4 weeks from the first documented date
Immune-related stable disease (irSD)	In the absence of irPD, without meeting criteria for irCR or irPR
Immune-related progressive disease (irPD)	Increase in tumor burden ≥25% relative to nadir (minimum recorded tumor burden)
	Confirmation by repeat, consecutive assessment at least 4 weeks from the first documented date

Table 4. Criteria for tumor response with immunotherapy[46]

Tumor heterogeneity is the next important consideration in the FDA guidance document.[49] The inherent heterogeneity of tumors (among patients, among different tumors from the same patient, and among different regions of the same tumor)[48] affects the ability to respond to vaccines, resulting in difficulties in interpreting trial results and the risk of not achieving trial objectives. Specifically, the tumor/mutation type should be considered because only a small number of mutations are of biological relevance and therapeutic benefit.[48] Predicted immunoreactivity and high levels of tumor infiltrating lymphocytes (TILs) can provide some insight;[47,51] the presence of a high number of TILs might identify tumors that are more immunogenic, with a failed endogenous immune response that has already occurred, and less likely to respond to immunotherapy.[52] In these cases, the use of a vaccination might not be appropriate, while first-line immunotherapy involving checkpoint inhibition might be more appropriate.[52]

Identification of subtypes or groups that respond to a treatment in an ongoing trial is often used to continue the trial in only those specific groups, with greater success. For example, in a trial of anti-PDL1 as first line therapy for NSCLC, delayed disease progression without serious adverse effects was observed more in patients with PD-L1-positive tumor cells (response rate of 67%) than patients with PD-L1-negative tumors or unknown status (no response). Another example trial with belagenpumatucel-L, an allogeneic genetically modified NSCLC tumor cell therapy, did not find significantly increased median survival; however, those that received the therapy within 12 weeks of chemotherapy did have a significant improvement, and the study is continuing with this subgroup.[53]

The FDA also recommends the development of an assay or mechanism to measure the target antigen expression to help with patient selection and to monitor response.[49] Because a clinically effective anti-tumor response is often a multi-component process, multiple assays may be required. Personalized therapies based on immune type and mutation profile would help to counteract tissue heterogeneity, but markers are needed to identify patients that will respond. The most common biomarker is the immune response to the tumor-associated antigen following vaccination, compared with before the vaccination. However, a T cell's cytokine production is not always associated with its lytic ability, and no study has identified a surrogate for clinical response.[54] For example, in the clinical trials of sipuleucel-T, responses to PAP were present in only approximately 30% of the patients, despite demonstrated benefits in survival.[33,34] However, markers that have been shown to correlate with clinical outcome include antigen-specific T-cell response based on IFN-gamma enzyme-linked ImmunoSpot (ELISPOT) assays, cytokine expression levels, reduction in regulatory T-cells,[55-58] and eosinophil count.[59]

Other considerations

An effective therapeutic cancer vaccine must induce a high number of antigen-specific T-cells against an established tumor that can then migrate to the tumor to perform their effector functions.[9,17] The first challenge is achieving high numbers of antitumor T-cells in the presence of an ongoing, dysfunctional immune response. Second, the therapy might be recognized as tumor cells in the periphery and eliminated; if the therapeutic agent does reach the tumor, it has to overcome the immune evasion techniques used by the tumor to support tumor growth and metastatic spread. To overcome these difficulties, adequate drug delivery through encapsulation techniques[60] might be useful. In addition, *ex vivo*-generated dendritic cells might help to overcome the need for endogenous dendritic cells, which are often dysfunctioning because of tumor-related suppressive factors, to uptake the antigens; these *ex vivo* dendritic cells can mature in the absence of tumor-related immunosuppression, allowing more control of this process.[17]

The first challenge of an effective therapeutic cancer vaccine is achieving high numbers of antitumor T-cells in the presence of an ongoing, dysfunctional immune response.

The next challenge to overcome is the lack of the proinflammatory signals required to promote effective tumor responses because they are replaced by tumor-induced immunosuppressive/anti-inflammatory signals that predominate in cancer patients. The immunosuppressive tumor microenvironment must also be overcome in order to kill the tumor cells; this microenvironment consists of regulatory T cells, suppressor cells, and natural killer cells, which can then release soluble immunosuppressive factors such as TGF-beta, IL-10, and VEGF.[17,54] A combination approach that alters the tumor to reduce the secreted immunosuppressive factors using cytokines such as IL-2, IL-15, IL-7, GM-CSF, and IFN in addition to the immunotherapy could be useful.[9,17,54]

Combination therapies

Some cancer immunotherapies might not suffice on their own to adequately induce or augment the immune response.[61] The use of adjuvants can enhance the immunogenicity of vaccines by activating antigen-presenting cells to stimulate T cells more efficiently, activating natural killer cells or other cells of the innate system to produce cytokines, or promoting the survival of antigen-specific T cells. These can include aluminum-based salts; a squalene-oil water emulsion; cytokines such as IL-2, GM-CSF, IL-12, IL-4, and others; and bacterial products such as lipopolysaccharide from gram-negative bacteria and monophosphoryl lipid A from Salmonella.[26]

The combination of immunotherapies and cytotoxic therapies might result in both tumor regression (cytotoxic therapy) and reduced tumor growth rate (immunotherapy). Chemotherapy, radiation, and small-molecule targeted therapeutics can alter the tumor cell phenotype.[54] In addition, immunotherapy-mediated killing of T cells by chemotherapeutic agents might occur as a result immune-related tumor cell death and enriched ratios of effector and regulator cells.[54]

It has been suggested that combination therapies with immune checkpoint inhibitors and any of the above adjuvants or cytotoxic therapies are particularly promising.[37,38,54]

However, combination therapies require the assessment of each component, which can prolong the development.

The combination of immunotherapies and cytotoxic therapies might result in both tumor regression (cytotoxic therapy) and reduced tumor growth rate (immunotherapy).

Trial logistics

Certain aspects of the trial logistics for cancer immunotherapies can differ from or require greater attention than other clinical trials. The combination of experience and enabling technology is key to successful implementation of these trials.

Clinipace Worldwide has experience with immuno-oncology clinical trials for ovarian cancer (phase 3), Ewing's sarcoma (phase 2), colon cancer (phase 3), metastatic colorectal cancer (phases 1 and 2), acute myeloid leukemia (phase 2), glioblastoma multiforme (phase 2), renal cell carcinoma (phase 3), and non-small cell lung cancer (phase 3) in the US, Asia, South America, and Europe, and some of the learnings from these trials are provided here.

First, investigators must have access to the specific types of patients needed, and a considerable number of inclusion and exclusion criteria typically have to be fulfilled owing to the specific set of patient characteristics. Common eligibility criteria include specific disease state, age, gender, prior therapies, lab results, activity levels, and current and previous medications. More stringent eligibility criteria make it harder to enroll appropriate numbers of participants, especially in a population where many patients have undergone intense treatments and may be reluctant to undergo a clinical trial. When tissue staging is critical to the study design, eligibility criteria must specify that patients either have previous tissue samples or be willing to undergo a biopsy prior to enrollment.[62]

Cooperation from many departments of the hospital is also required (e.g., pathology, surgical, oncology), which can be a large challenge. Access to a well-qualified pathologist may be important, and access to a radiology department is essential for timely and consistent tumor size evaluations. Interaction with ancillary units such as a cryolab and the shipping department might be required for storage and transport.

Distribution of the samples and therapies can also be particularly challenging. Specialized containers might be required. Airline access and scheduling options are critical if tissue samples for autologous vaccines need to be processed within 48 hours after collection. This might restrict the countries that can be involved in a global study given international flight schedules and custom requirements. If the products are shipped prior to final release by quality control, action plans for positive sterility might need to be developed.

Specialized methods for product receipt, storage, and thaw are needed that do not deviate from site standard procedures; if they do deviate, enough time is required to negotiate study-specific procedures with the applicable site departments. Furthermore, a specific clean room might be required to handle the therapies and/or adjuvants (e.g., BCG) at the sites. In some cases, this can mitigated with changes in packaging or the thaw procedure.

Cold chain management during transport and storage is important and requires particular consideration. Continuous temperature devices can be required for shipment, and the site has to check the devices immediately after arrival and store all of the therapies in certified refrigerators or liquid nitrogen freezers, which also require special cartridges. Each refrigerator is typically certified by the sponsor following the review of a temperature log over a 1-week period, including one weekend, which must be completed prior to shipment and maintained on a monthly basis. Every temperature deviation must be recorded. Therefore, the requirements for continuous monitoring, certificate of validation, and documentation by the sites for the refrigerators are considerable. If the sites are not able to comply with these requirements, a sponsor-provided device should be considered; however, this still requires a certain level of maintenance.

Careful tracking of all samples and therapies from the patient to off-site handling facilities back to the patient is required. Often, this process occurs within a short period of time (~72 hours). A central database is instrumental in monitoring this process. TEMPO™, which is a proprietary, cloud-based e-clinical software platform developed by Clinipace Worldwide, not only provides the general collection and storage of all study-related data but also includes specialized modules for these types of situations. Moreover, the central platform enables appropriate management and reporting of the large volumes of data, including medications and irAEs, that are part of these trials.

None of these issues are insurmountable, but significant time must be spent in the trial planning stages to make sure that these considerations are included in the study protocol and subsequent discussions with the sites. A highly qualified site, with experience in handling these types of products, can help to minimize significant issues. It is useful to have the insight of an experienced contract research organization, such as Clinipace Worldwide, who can help to mitigate the risks that are inherent to this type of study, identify qualified sites, and address any issues that occur as the study is implemented.

The central platform enables appropriate management and reporting of the large volumes of data, including medications and irAEs, that are part of these trials.

Figure 7. Survival with sipuleucel-T (Provenge) compared with placebo (control)[31,32,48]

Case study

The commercial failure of Dendreon (sipuleucel-T/Provenge)

As described earlier in this paper, sipuleucel-T (Provenge) is an autologous cellular immune therapy that involves harvesting of the patient's peripheral white cells by leukapheresis at an approved cell collection center and incubation with a recombinant construct of PAP and GM-CSF at a central processing facility, which is then reinfused into the patient.[31] The complex administration process, over multiple visits and multiple treatment cycles, in practice means that not all patients can actually be treated. In addition, sipuleucel-T is indicated only for asymptomatic or minimally symptomatic patients with castrate-resistant (hormone-refractory) prostate cancer (FDA package insert), and the benefits are limited. Only a 4.1–4.5-month improvement in overall survival was observed in two randomized controlled trials compared with a placebo (Figure 7).[33,34] Furthermore, it does not decrease tumor size or prolong time to progression; therefore, it should not be used in patients with rapidly progressing metastatic castrate-resistant prostate cancer.[31]

In addition to being difficult to administer and of limited benefit, the estimated cost of sipuleucel-T is $93,000 USD per treatment course,[35] and a single estimated economic analysis resulted in a 96.5% certainty that it is not cost-effective.[31]

Finally, since the initial approval of sipuleucel-T in 2010, abiraterone (CYP17 inhibitor approved in 2011 in combination with prednisone) and enzalutamide (androgen-receptor inhibitor approved in 2012) have become available. Both are oral, off-the-shelf drugs administered once daily, approved for men with metastatic hormone-refractory prostate cancer regardless of symptom status, and associated with a median survival of 35.3 months for men without prior cytotoxic treatment (abiraterone),[63] 18.4 months in those with prior docetaxel treatment (enzalutamide),[64] and 32.4 months, with an 81% reduced risk of radiographic progression, in chemotherapy-naïve patients (enzalutamide).[65]

However, research continues with sipuleucel-T, and a recent focus is its use in combination therapy with chemotherapy, with radiation, with checkpoint inhibitors, or as an adjuvant to surgery.[31] All patients ultimately develop castrate-resistant (hormone-refractory) prostate cancer, with a median survival of only 1–2 years.[35,66]

The estimated cost of sipuleucel-T is $93,000 USD per treatment course.[35]

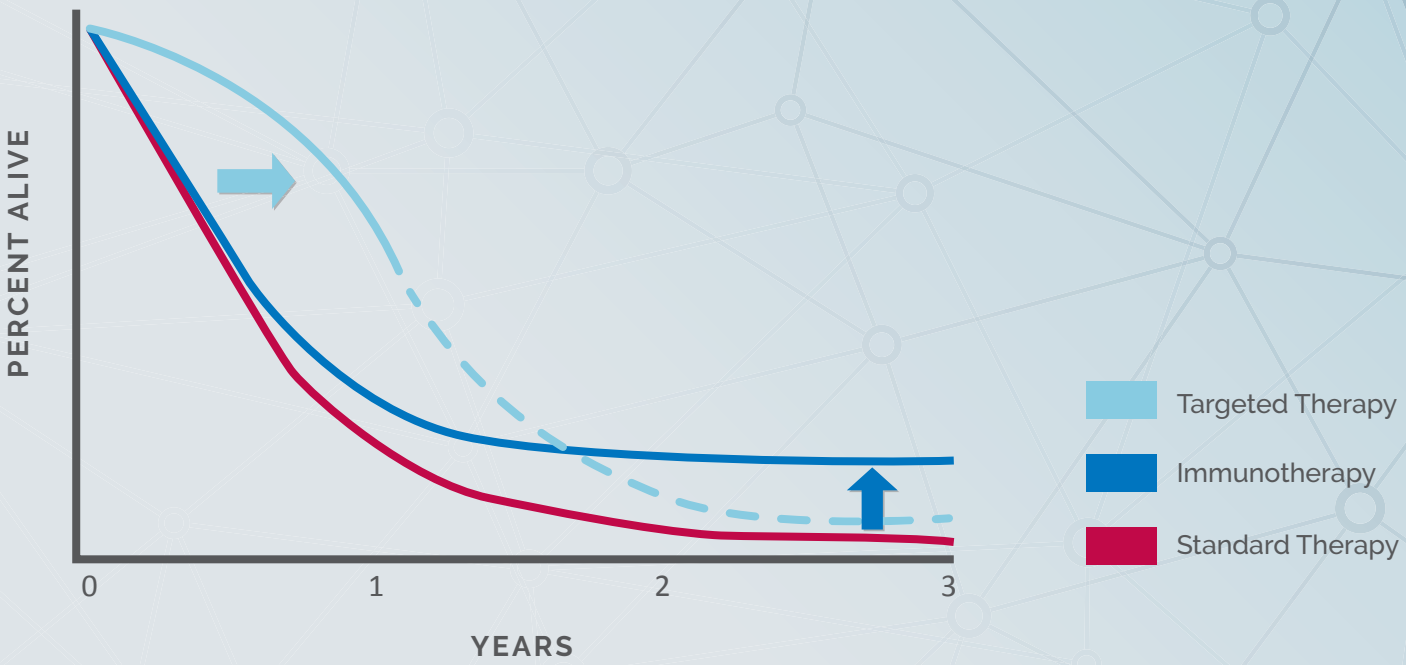


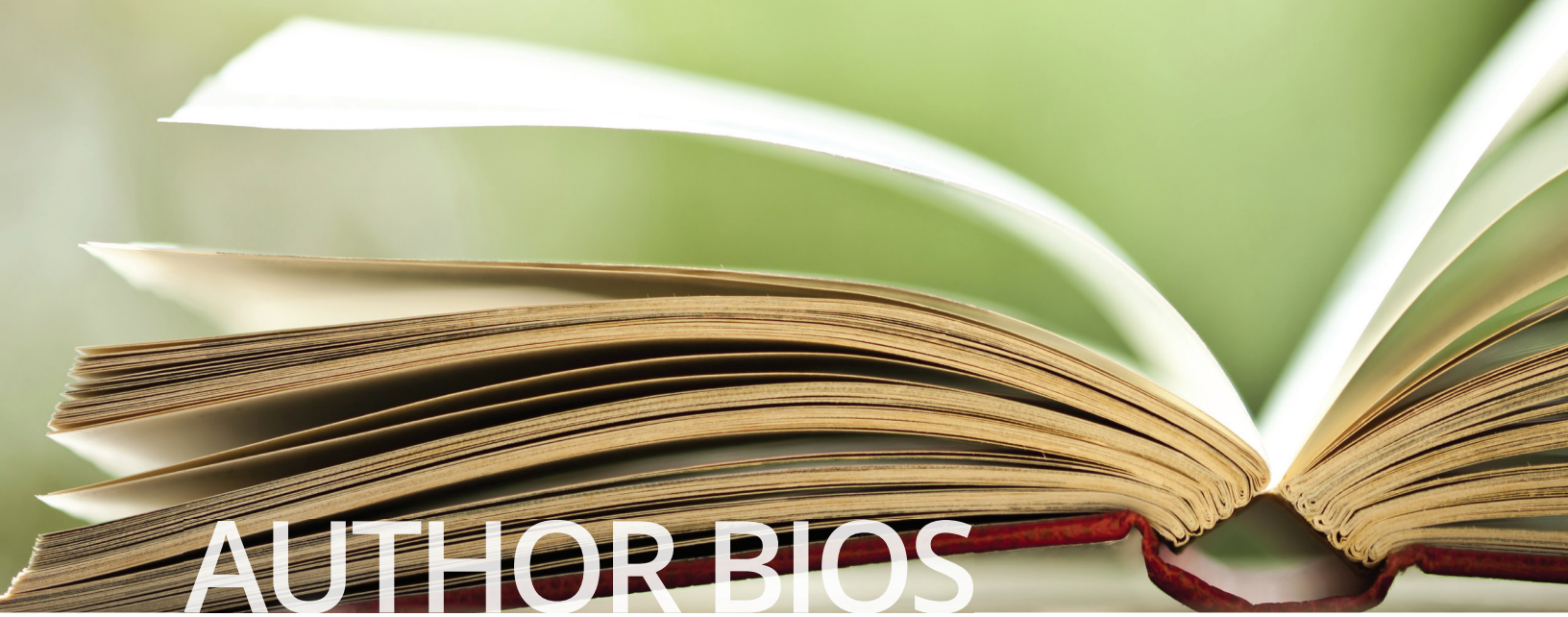
Figure 8. Survival with immunotherapy compared with targeted and standard therapy

Critical lessons

1. **AN OFF-THE-SHELF AGENT** is preferable to one that must be custom manufactured.
2. **SURVIVAL BENEFIT** must be commensurate with difficulty of treatment.
3. **COST MUST BE IN LINE** with the benefit.
4. **IF THE BENEFIT IS RESTRICTED TO A RELATIVELY SMALL SUBSET OF PATIENTS,** it must be substantial in that group.
5. **NEW COMPETING TREATMENTS**—either immune, hormonal, or targeted—can quickly supplant a marginally effective therapy.
6. **IT IS IMPORTANT TO FOCUS ON THE POTENTIAL ADVANTAGE** of immunotherapy in advanced cancer, the potential for long-term disease control, and even the potential to cure, rather than a small improvement in overall or progression-free survival. (Figure 8)

Conclusion

After over 120 years of basic and clinical research, immunotherapy has become a true part of the anti-cancer armamentarium in the last decade. The dissection of immune regulation and response has made effective therapy possible. Although therapeutic vaccines remain to be proven, the new insights into and the ability to affect the immune synapse may open the door to effective vaccines, whether personalized or off the shelf. Furthermore, our definitions of success might need to change and different criteria for efficacy used. Immunotherapy, especially vaccines, has the potential of greatly reduced toxicity and, most importantly, durable disease control.



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