Immune Checkpoint Blockade in Cancer Therapy

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INTRODUCTION

The idea of using the immune system to fight cancer has been around for decades, with multiple false starts along the way. The field of cancer immunotherapy had largely been focused entirely on ways in which to turn T cells on, with implementation of therapies such as cytokines, for example IL-2, or antigenic vaccines. However, our understanding of T cells at the time was limited. Our work, together with that of a cadre of immunologists dedicated to understanding the fundamental mechanisms involved in regulating T cell responses, showed that the process was more complicated. These fundamental studies also revealed inhibitory pathways that could be modulated to generate powerful T cell responses with subsequent tumor elimination. This led to the successful development of immune checkpoint blockade as a potential curative cancer therapy.

My love for T cells took root during an undergraduate immunology course in the 1960s. I was majoring in biochemistry with my thesis project being biochemical and serologic characterization of anti-neoplastic bacterial asparaginases, which at the time were showing promise in treating childhood leukemias. Professor Bill Mandy, who was primarily a B cell/antibody guy, taught the course, and he gave one lecture on T cells, which in 1965 had been shown by Max Cooper and Robert Good to be a

lineage distinct from antibody generating B cells (1). While B cells and antibodies are certainly fascinating, T cells were new and little was known about them beyond the fact that they had the ability to travel all over the body and recognize and eliminate cells with foreign features, including viral, transplantation, and possible tumor antigens. I was hooked and determined to spend my career delving into the secrets of T cells.

With the help of Bill Mandy and Barrie Kitto, my dissertation advisors in 1974, I secured a postdoctoral position in Ralph Reisfeld's laboratory at the (then) Scripps Clinic and Research Foundation in La Jolla, California. Scripps was a hotbed of immunological research. My main project in the Reisfeld lab was to bring my background in protein biochemistry to bear on structural studies of human histocompatibility antigens. While I was fairly productive and obtained some of the first amino acid sequence data on both Class I and Class II antigens, I was somewhat frustrated in that I was not able to take full advantage of the opportunities available in T cell biology at Scripps.

THE SCIENCE PARK YEARS

In 1978, as a newly minted assistant professor with a small lab in a pine forest near Smithville, Texas, at the Science Park campus of the University of Texas M. D. Anderson Cancer Center, I remained fascinated by the complexity of the T cell response, which involved moving through the body to sample different antigens and then making decisions about when to proliferate in order to amass an army of cells that would eradicate any foreign entity. The super hero of our immune system! But, how did T cells make such complicated decisions? What were the signals that regulated T cell responses?

Throughout the 1970s and early 1980s there were remarkable advances in our understanding of T cell biology, including the clonal nature and MHC restriction of antigen recognition, and the role of a variety of cell surface molecules and cytokines in regulation of T cell responses. However, although many theories existed regarding the nature of the T cell receptor (TCR), its identification remained elusive and began to be regarded as the "holy grail" of immunology.

My first set of experiments to identify the TCR stemmed from a lecture I heard by Irv Weissman and led me to use a biochemical approach in identification of the protein structure of the TCR. I should point out that I was abetted by my relative ignorance of the field and the relative isolation of the Science Park.

The basic assumptions were: (1) the T cell antigen receptor, like the individual idiotypes associated with the B cell receptor, should be detectable in a clonotypic fashion as individually specific antigens, which could

be identified by monoclonal antibodies; (2) the structure detected by these antibodies should be on all T cell tumors and normal T cells but not on B cells; and (3) the structure from different clones should have both tumor specific and shared peptide structures. Thus, I made a monoclonal antibody, 124-40, against C6XL, which was in the panel of lymphomas that I used in my thesis project on anti-tumor activity of asparaginase. The activity of the antibody with C6XL could be detected by flow cytometry and radioimmune assay. None of the other lymphomas in the panel reacted with 124-40, nor did normal splenic T cells. Working with Brad McIntyre, a summer undergraduate intern, then a research technician and ultimately a doctoral student, we carried out a series of immunochemical tests of the assumptions. Radioimunoprecipitation using the 124-40 monoclonal on the original C6XL lymphoma yielded a disulfide-bonded heterodimer with 39 and 41 kDa components. The antibody did not precipitate anything from other T cell lymphomas, again indicating that the antigen was clonally-specific (2). Taking the antigen eluted from that antibody, I generated a rabbit polyclonal antibody that interacted with all T cells. After reduction, the protein eluted from the antibody could be seen clearly on a 2D blot and consisted of α and β heterodimers. Peptide mapping showed that each consisted of both shared and clonally distinct peptides. We ran the whole cell lysate out on a gel and saw that the rabbit polyclonal reacted with the same protein on all T cells. The clonally-specific candidate receptor was also common to all T cells (3).

We published these data and proposed that the protein we had identified was the elusive TCR. Unfortunately, we had no functional data and there was initially skepticism. Luckily, at about the same time, John Kappler and Pippa Marrack, at the National Jewish Hospital in Denver, had developed a clonotypic monoclonal antibody that caused IL-2 release by an antigen-specific hybridoma, which was an indication of activation. I sent them our antibody and they confirmed that the protein identified by both our labs had the same heterodimeric structure (4).

There were other laboratories with similar antibodies, and others with molecular cloning techniques, so there was an intense race to clone the genes for the TCR. I decided to go to Irv Weissman's lab and work with Tom St. John to clone the genes, but we were ultimately beaten on that front by excellent work from Mark Davis and Steve Hedrick, along with Tak Mak, who cloned the beta chain of mouse and human TCR (5–7).

THE BERKELEY YEARS

While I was at Stanford trying to clone the TCR genes, I was invited to present a seminar on my work at the University of California, Berkeley and meet some of the faculty. A few weeks later, I was asked if I was inter-

ested in a faculty position. In 1984, after much encouragement by Marion "Bunny" Koshland, who was the leader of Immunology at Berkeley, and who also became a close friend and mentor, I decided to accept the offer and moved to Berkeley. After eight years in the bucolic environment of Science Park, UC Berkeley was a revelation and initially somewhat scary. The campus teemed with intellectual and scientific fervor, and new ideas could be welcomed, but subjected to a healthy and helpful degree of skepticism.

By the late 1980s, it became clear that the TCR was not the whole story in T cell activation. For T cell tumors and hybridomas, engagement of the TCR alone was sufficient for activation. However, as it became possible to grow and study clones of normal T cells, it was found that TCR engagement alone was not sufficient for T cell activation. Several labs, including notably that of Ronald Schwartz at the National Institute for Allergy and Immunological Diseases, showed that additional signals were required (8). The Schwartz group showed that while antigen presenting cells (APCs) pulsed with the appropriate antigenic peptide could fully activate T cell clones, treatment of the pulsed APCs with certain chemical fixatives resulted in loss of T cell activation. Furthermore, T cells exposed to antigen in this manner were unresponsive when re-exposed to antigen on unfixed APCs. Thus, the T cells had been rendered anergic. However, if T cells were exposed to chemically fixed peptide-pulsed APCs in the presence of unfixed APCs that had not been pulsed with antigen, the T cells were fully activated. This led to the 2-signal model for T cell activation by APCs. Signal 1 is provided upon recognition of antigen/MHC complexes by the T cell antigen receptor. Signal 2, the costimulatory signal, was provided by an antigen-independent signal engaging an unknown costimulatory receptor on the T cell. The race was on to determine the identity of the receptor/ligand pair that mediated costimulation.

In the mid 1980s, Hansen, Ledbetter, June, and others in Robert Nowinski's group had produced an antibody to human T cells named 9.3 and showed that it elevated IL-2 production from T cells (9). The target of 9.3 was later shown to be CD28 (10). Enhancement of IL-2 production seemed to be a property consistent with costimulation but, unfortunately, the mouse homolog was not known. With the help of Brian Seed at MIT and Jane Gross, a graduate student in my lab, we succeeded in cloning the mouse CD28 gene and went on to produce a monoclonal antibody to mouse CD28 (11). Fiona Harding, a postdoc in the lab, in collaboration with my colleague, David Raulet, at Berkeley, used this antibody to show that engagement of CD28 by the antibody was sufficient and necessary to prevent the induction of anergy in T cell clones by fixed antigen-pulsed APCs. In addition, we showed that the CD28 antibody, in combination with antibodies to the T cell antigen receptor, allowed for full activation

of naïve T cells (12). Thus, CD28 met the criteria for an essential costimulatory receptor.

Peter Linsley demonstrated that a molecule called B7, which was originally found on B cells but also expressed by dendritic cells and other hematopoietic cells, was a ligand for CD28 (13). A few years later, several groups showed that a second molecule, B7-2, was also a ligand for CD28. Thus, it appeared that when a T cell received contemporaneous signals through the TCR and CD28 from antigen/MHC complexes and B7 molecules on an APC, such as a dendritic cell, a program initiated in the T cell allows rapid proliferation and acquisition of effector function, which results in generation of a T cell army from a small number of relevant T cells.

It was at this point that that there was an unexpected twist to the story. In 1988 Pierre Golstein (Marseille) cloned a gene for a T cell molecule he named cytotoxic lymphocyte antigen-4 (CTLA-4) (14). Little was known of it except that it was highly homologous to CD28, but was only found on T cells after activation. Peter Linsley made a recombinant form of CTLA-4 and showed that, like CD28, it bound to both B7-1 and B7-2, albeit with much higher avidities. While CTLA-4 was initially thought to be another costimulatory molecule, the evidence remained inconclusive. Finally, in the mid 1990s both Jeff Bluestone's lab and Max Krummel, an excellent postdoc in my lab, using an antibody that blocked CTLA-4, showed conclusively that CTLA-4 negatively regulates T cell activation by opposing CD28-mediated costimulation (15, 16). It was a paradigm-shifting finding, revealing CTLA-4 as the first immune checkpoint. Subsequently, it was shown that mice in which the *ctla-4* gene had been inactivated suffer from a rapid T cell lymphadenopathy and die about 3 weeks after birth (17–19). Basically, the T cells in CTLA-4 knockout mice cannot stop dividing. This suggests that CTLA-4 is a crucial downregulator of the proliferative phase that follows activation of T cells by antigen regulation and costimulation. Thus, activation of T cells results in not only the proliferative phase, but also induction of expression the CTLA-4 gene and subsequent events which will terminate proliferation.

One additional observation that we had made contributed to the development of immune checkpoint therapy. In a series of experiments designed with the goal of developing a new strategy for therapeutic vaccination, we engineered mouse tumor cell lines to express the CD28 ligand B7. Sarah Townsend, a postdoc in my lab, showed that tumor cell lines that normally grew in mice did not grow after transfection with the B7-1 gene unless T cells were depleted (20). Thus, the tumors expressed sufficient antigens for rejection, but were unable to initiate an effective T cell response because of the lack of ability to provide the B7 costimulatory signal required by CD28. This suggested that arising tumor cells might be

invisible to T cells, allowing them to grow uninhibited by immune responses until reaching a size that results in tumor cell death to cause inflammation and accumulation of antigen presenting which can phagocytize dying tumor cells and presenting tumor antigens in the context of costimulation and cross-prime naïve T cells. This would lead to T cell activation and proliferation. This would result in induction of the CTLA-4 pathway, which would perform its normal function of limiting the T cell response.

Based on our new data regarding the signals that regulate T cell responses, I wondered how we could use the information to treat cancer. I surmised that tumor cells, which do not express B7 molecules, have a head start against the immune system because T cells could not recognize the tumor cells initially; however, as tumors got bigger and a few tumor cells died, APCs would take up the dead tumor cells by phagocytosis and then present mutated tumor antigens via MHC to T cells. T cells would interact with APCs, in the context of T cell receptor plus MHC with antigen (signal 1) and CD28 plus B7, which would lead to T cell activation consisting of proliferation and cytokine production, and forming an army of activated T cells focused on eradicating tumors. But, this process would be limited by CTLA-4 (Figure 1). CTLA-4 would halt the T cell response in order to prevent T cells from continuous proliferation and cytokine production, which would have pathologic consequences including autoimmunity and death. In my mind, it became a race; if CTLA-4 halted T cell responses too soon, before all tumor cells were eradicated, the tumor would win and the cancer would persist. I considered the possibility that an antibody to block CTLA-4 would enable T cell responses to persist long enough to eradicate all tumor cells and perhaps cure at least some cancers (Figure 2).

Then, along with Max Krummel and Dana Leach in my lab, I designed experiments in tumor-bearing mice to test whether anti-CTLA-4 antibody would lead to tumor rejection. These studies were initially conducted in 1994 and then reproduced in multiple other tumor models before we published our findings in 1996. The data were clear and convincing, in the presence of a CTLA-4-blocking antibody, after a short delay while the immune system ramped up, tumors simply melted away (21) (Figure 3). Not only that, those animals then mounted a strong immune response to rechallenge the same tumors, often completely rejecting them.

My lab conducted many successful experiments in murine models over the next several years; however, I desperately wanted to translate my idea to the clinic. I approached many different pharmaceutical companies but they were resistant to the idea of developing an immunotherapy agent to treat cancer. The field of cancer immunotherapy had many failures, and companies were not interested in pursuing another potential failure.

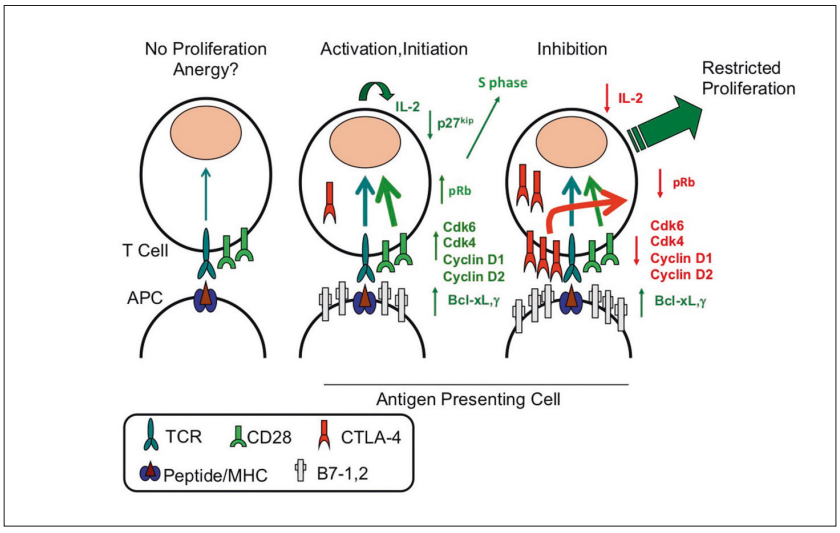

Figure 1. Dynamic Integration of TCR and Costimulatory Signals (circa 1996). Cartoon illustrates the primary cell surface signaling receptors involved in antigen-specific T cell activation and cognate ligands on APCs. T cells that are primed through the interaction of the TCR with antigen-bound MHCs enter a state of anergy in the absence of co-stimulation. Interaction of CD28 with B7 on the APC surface fully activates the T cell and initiates proliferation, while CTLA-4 on the T cell surface disrupts co-stimulation and inhibits T cell proliferation. (represents work performed in my laboratory by Jane Gross, Fiona Harding, Max Krummel, Cynthia Chambers, Monika Brunner, Egen and Kuhns).

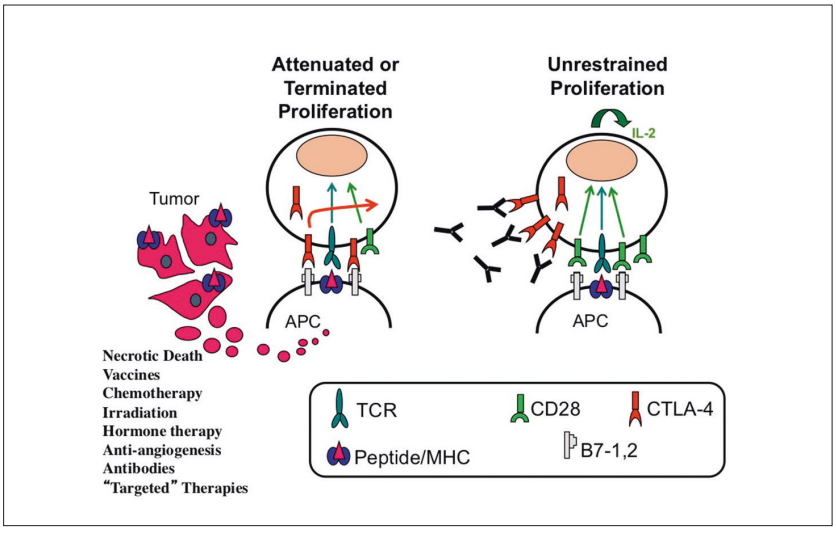

Figure 2. CTLA-4 Blockade Enhances Tumor-Specific Immune Responses. CTLA-4 on the T cell surface inhibits effective tumor-immune response by reducing T cell proliferation. Blockade of CTLA-4 removes inhibition of T cell proliferation and increases the antitumor response.

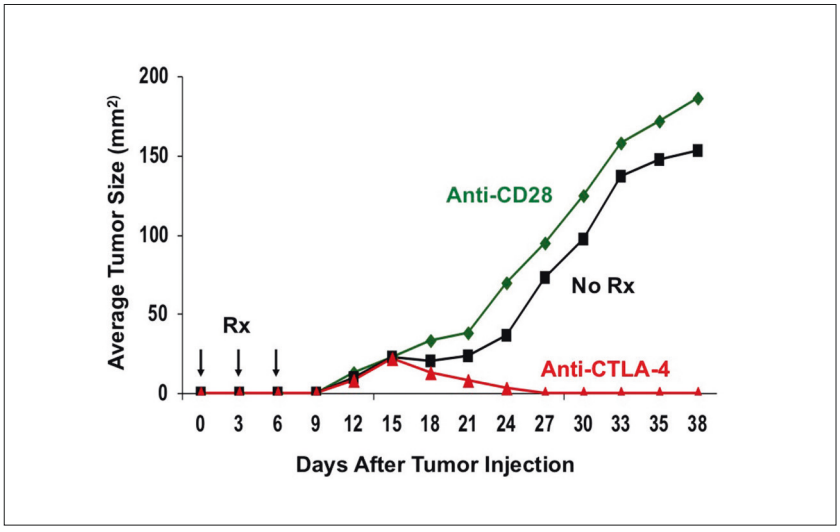

Figure 3. Anti-CTLA-4 Induces Regression of Transplantable Murine Tumor. Addition of CTLA-4 inhibitory antibody results in complete tumor rejection in BALB/c mice injected with V51BLim10 colon carcinoma cells (21).

Luckily, my friend Alan Korman was interested in my idea and, with the encouragement of Nils Lonberg and others, his new job at Medarex provided him with the opportunity to develop a humanized anti-CTLA-4 antibody in a novel murine model that had been genetically engineered to express human immune genes.

The new humanized anti-CTLA-4 antibody was initially called MDX-CTLA-4 and then was referred to as MDX-010. Medarex designed a Phase I clinical trial with MDX-CTLA-4 based on input from multiple investigators, including world-renowned immunologist, Dr. Lloyd Old, and his post-doctoral fellow at the time, Dr. Padmanee (Pam) Sharma. I had very little knowledge regarding clinical trials at the time, but I was determined to learn everything possible.

A pilot clinical trial with the anti-CTLA-4 antibody at a single dose of 3mg/kg was initiated in patients with metastatic prostate cancer and reported for the first time at the American Society of Clinical Oncology (ASCO) in May 2002, with subsequent publication in 2007, which demonstrated decline in the prostate-specific antigen (PSA) tumor marker by greater than or equal to 50% in 2 of 14 treated patients (22). In another clinical trial, MDX-CTLA-4 antibody was given as a single dose of 3mg/kg to patients with different tumor types, including patients with metastatic

non-small cell lung cancer, patients with metastatic ovarian cancer, patients with acute myelogenous leukemia, and patients with metastatic melanoma. Preliminary data from the patients with metastatic melanoma, who were enrolled on this clinical trial between November 2000 and October 2002, were encouraging based on tumor biopsies demonstrating tumor necrosis and T cell infiltration into tumors (23). These data quickly led to multiple clinical trials for patients with metastatic melanoma. Another clinical trial with MDX-010 in 14 patients with metastatic melanoma reported 3 patients, who either had complete (2 patients) or partial regression (1 patient) of their tumors, including regression of brain metastasis (24).

Prior to anti-CTLA-4 therapy, patients with metastatic melanoma had poor long-term prognosis, with approximately 75% of patients surviving less than one year and 5-year mortality rate of 90% (25). The median overall survival at the time was approximately 8 months for patients with metastatic melanoma (26), and there was typically shorter life span for patients with brain metastases (27). At the time, approved therapies for patients with metastatic melanoma consisted of the chemotherapeutic agent dacarbazine (DTIC) or its oral analogue temozolamide or fotemustine chemotherapy or biochemotherapy regimens that included cytokine therapies with IL-2 or IFN-α, which led to reported responses but, the increased response rates observed with these agents did not translate to improved overall survival for patients (26–31). In fact, prior to anti-CTLA-4 therapy, no agent approved for the treatment of metastatic melanoma had been shown to improve the overall survival of patients in a randomized, phase III clinical trial.

The initial studies with anti-CTLA-4 in patients with metastatic melanoma led to multiple phase I and phase II clinical trials with various monotherapy or combination therapy studies, including combination studies with IL-2, gp-100 peptide vaccine, or chemotherapy (32). These studies identified toxicities, termed immune-related adverse events (irAEs), which were associated with anti-CTLA-4 therapy and confirmed to be inflammatory in nature, with increased infiltration of immune cells into affected tissues, which was documented by histopathology studies. The irAEs were found to be reversible in most cases, especially with cessation of anti-CTLA-4 therapy and administration of steroid therapy. Another key finding from these clinical trials was related to the unique kinetics of responses observed after treatment with anti-CTLA-4. Some patients had clinical responses that could be categorized as responding to therapy as per the previously established Response Evaluation Criteria in Solid Tumors (RECIST) for evaluation of tumor response to therapy, which required tumor shrinkage (at least a 30% decrease) without any associated growth (defined as greater than or equal to 20% increase in the sum of diameters

and at least 5 mm increase) in the existing tumor lesions designated as target lesions or any development of new tumor lesions (33). However, some patients had disease progression (with increase in size of the tumors or development of new tumor lesions) before they eventually had response to anti-CTLA-4 therapy. According to RECIST criteria, these patients would not be counted as having had a response to anti-CTLA-4 therapy, which would imply that the drug did not work. The clinical terminology and endpoints were foreign to me. I needed to learn more.

Like in the animal models, it takes some time for patients to initiate a strong immune response after anti-CTLA-4 checkpoint blockade, and as such, even in the best responders, tumors often continued to progress for some time before shrinking and disappearing, which we published in our animal studies in 1996 (21). Because of this, the traditional RECIST criteria, which rely on definitions that were used for evaluating responses to chemotherapy agents that directly target tumor cells, as opposed to immunotherapy agents, which target immune cells to enable activation and proliferation for subsequent attack on tumor cells, many early studies underestimated the clinical benefit of anti-CTLA-4 therapy.

THE MSKCC YEARS

Our goal, based on our animal studies, was to eliminate the disease. When examining overall survival (a more appropriate metric for immunotherapy), we saw that patients treated with anti-CTLA-4 were surviving longer than expected. These observations led me to become involved with the clinical development of anti-CTLA-4, which meant that I needed to be working with the clinical teams that were developing the clinical trials. In 2004, I moved from the University of California at Berkeley to Memorial Sloan-Kettering Cancer Center (MSKCC), which was leading the phase III clinical trials for anti-CTLA-4 therapy. I took a faculty position as Chair of Immunology at MSKCC and became collaborators with the clinical investigators and the pharmaceutical company, Bristol-Myers Squibb (BMS), which had entered into collaboration with Medarex to lead the phase III clinical trials with anti-CTLA-4.

I quickly learned that clinical trials comprised 3 phases: phase I trials represented safety studies to evaluate how a drug affected humans, with various doses and/or schedules of a drug being tested; phase II trials represented efficacy studies to determine whether an established dose and schedule of drug could elicit clinical responses in patients; and phase III trials represented studies comparing the new drug to an established standard-of-care treatment in order to determine whether the new drug will become the new standard-of-care treatment. The phase I and phase II studies highlighted the safety issues and potential clinical benefit of

anti-CTLA-4 but, the reported response rates as per defined RECIST criteria were less than 10%, which was not sufficient to lead to FDA approval. In addition, a second pharmaceutical company, Pfizer, had launched their own anti-CTLA-4 program and their phase III clinical trial was declared a failure in 2008.

BMS started their first phase III clinical trial with anti-CTLA-4 (MDX-010, which was subsequently named ipilimumab) in 2003. Based on available data at the time, many of us, including myself, Jedd Wolchok, Padmanee Sharma and Lloyd Old, felt strongly that the primary endpoint of the trial should be changed to overall survival (OS). We worked closely with Rachel Humphrey at BMS and she relayed our concerns to the leadership team at BMS, including Elliott Sigal, who was then Chief Scientific Officer and President of Research and Development. The phase III clinical trial was then amended to change the primary endpoint to OS. In 2010, the data was reported at the ASCO annual meeting and, for the first time, a randomized phase III clinical trial for patients with unresectable stage III or IV metastatic melanoma demonstrated an overall survival benefit, with ~45% of patients who received anti-CTLA-4 reported to be alive at 1 year and ~23% of patients who received anti-CTLA-4 reported to be alive at 2 years (34). Subsequent data reported from a cohort of about 5000 patients treated with anti-CTLA-4 (ipilimumab) on multiple clinical trials demonstrated 5-year survival for about 20% of patients (35) (Figure 4). The US FDA approved ipilimumab for the treatment of patients with metastatic melanoma in 2011.

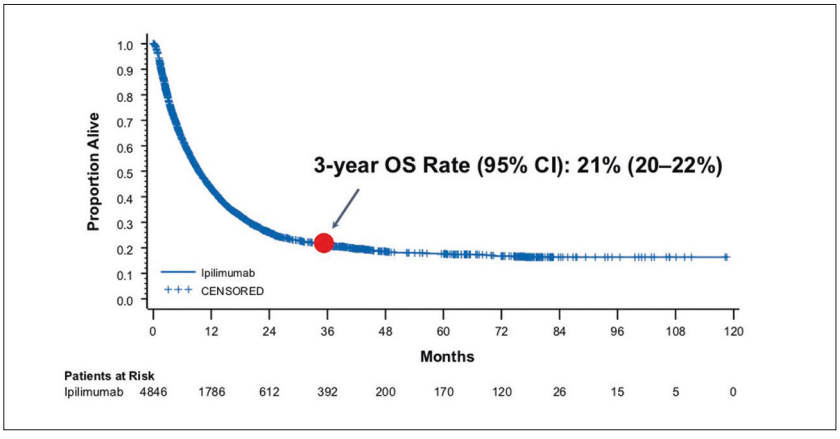

Figure 4. Ipilimumab induces lasting responses in 21% of patients with metastatic melanoma. Graph shows pooled data from 4846 patients with metastatic melanoma treated with ipilimumab. The group showed a 3-year overall survival (OS), and patients surviving 3 years remained tumor-free for 10 years and longer (35).

Clearly, the discovery of immune checkpoint inhibition had set into motion a line of work with the potential to cure all cancers. The success of anti-CTLA-4 in the clinic led to research work to identify other immune inhibitory pathways, with elegant work by other investigators, including Gordon Freeman, Arlene Sharpe, Lieping Chen and Tasuku Honjo in deciphering the inhibitory role of the PD-1/PD-L1 pathway and development of antibodies that block these inhibitory pathways to improve anti-tumor T cell responses and clinical outcomes (reviewed in Dr. Honjo's lecture). More recently, combination therapy with anti-CTLA-4 (ipilimumab) plus anti-PD-1 antibody (nivolumab) was US FDA-approved for the treatment of patients with metastatic melanoma (36) and for patients with metastatic renal cell carcinoma (37).

Since immune checkpoint therapy (anti-CTLA-4 and anti-PD-1/PD-L1 antibodies) targets immune cells, and specifically T cells, these treatments may theoretically provide clinical benefit for all cancer patients, regardless of tumor type. The clinical data supports this notion since multiple clinical trials have reported benefit for many different cancer types, which led the US FDA to approve immune checkpoint therapies for patients with diagnoses of: melanoma, renal cell carcinoma, bladder cancer, gastric cancer, head and neck cancer, non-small cell lung cancer, Hodgkin's disease, and even tumors defined by genetic mutations known as microsatellite instability (MSI) as opposed to tumors defined by anatomical location.

MDACC AND THE FUTURE

Thousands of patients have benefitted from immune checkpoint therapy, but there are thousands of patients who do not respond to the treatments. We need dedicated research efforts to evaluate patients' immune responses within the tumor microenvironment, both before and while on treatment, in order to have a better understanding of why some patients respond to treatment while others do not. The first pre-surgical study to address this issue was conducted by Dr. Padmanee Sharma and published in 2006. She designed a clinical trial with anti-CTLA-4 in order to obtain entire cystectomy samples from patients with bladder cancer who received anti-CTLA-4 prior to surgery. She designed novel immune monitoring assays to evaluate the immune responses in the bladder tumors and identified T cells expressing inducible costimulator (ICOS) as a critical component of successful anti-tumor responses (38-41). Clinical trials are now underway to test the concept of targeting ICOS plus anti-CTLA-4 as a novel combination strategy to improve clinical responses for more patients. Dr. Sharma pioneered these types of reverse translational studies, which consist of innovative clinical trials focused on studying human

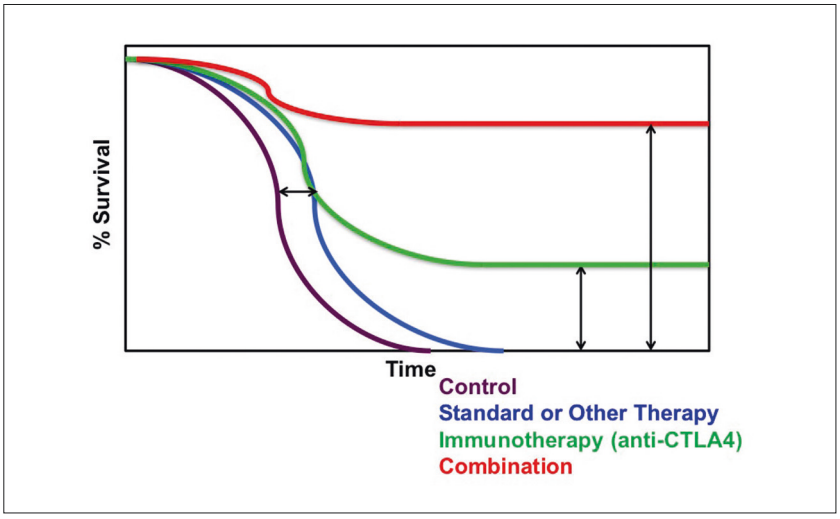

Figure 5. Improving Survival with Combination Therapy. Traditional cytotoxic therapies, seek to improve survival incrementally (horizontal arrow). Immunotherapies such as ipilimumab produce long-term responses, resulting in a 'tail' (above 1st vertical line) of patients that remain cancer-free. Combination therapies seek to 'raise the tail' (2nd vertical line), provided lasting responses to a larger number of patients.

immune responses with subsequent development of hypotheses that can be tested in the laboratory to generate new data for the next set of clinical studies. These studies are the foundation on which we built the Immunotherapy Platform at M. D. Anderson Cancer Center. The Immunotherapy Platform integrates both clinical trials and laboratory studies to develop novel treatments for cancer patients, with the hope of increasing overall survival for even more patients (Figure 5).

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In the course of the work described in this document I have benefited from interactions with a large number of individuals, both from the four Institutions with which I have had the privilege to be associated, and even more that I have encountered in my journey. It is not possible to overestimate my gratitude for these interactions, whether they be discussions, collaborations, arguments, or social interactions. Many of these, too many to name, have led to long lasting friendships. These include faculty, trainees, and laboratory staff. I have tried to mention those primarily responsible for aspects of the work, but it is not possible to mention all, and I apologize for any omissions.

I would like also to thank the National Cancer Institute, the Howard Hughes Medical Institute, and the Cancer Prevention and Research Insti-

tute of Texas, as well the Cancer Research Institute, the Prostate Cancer Foundation, the Melanoma Alliance, and the Parker Institute for Cancer Immunotherapy for supporting my research over the years.

I would also like to express my gratitude for Medarex and Bristol Myers-Squibb for having the courage in making it possible to bring my dream to the clinic, and most of all the patients involved in the clinical trials for the courage to take a chance on a new modality of cancer therapy.

Finally, I dedicate this Nobel Lecture and my Nobel Prize to my love and soulmate, Padmanee Sharma, my partner in life and science.

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