Tumors use a variety of mechanisms to inhibit anti-tumor immune response and checkpoint blockade offers new avenues for treating cancer by blocking pathways used by tumors to inhibit anti-tumor immunity. Interactions between T cells and tumor antigens involve recognition of the MHC bound antigen by the T cell receptor (TCR) with additional positive and negative co-stimulatory signals. Binding of the MHC-bound tumor antigen to the TCR leads to up-regulation of PD-1 ligand (PD-L1) on the tumor cell or antigen presenting cells (APCs). This results in an immune-inhibitory feedback loop as PD-L1’s interaction with PD-1 on the T cell leads to inhibition of T cell activation. A similar interaction between B7 expressed on APCs with CTLA4 on the T cells also inhibits T cells and terminates anti-tumor immune response. Tumor-infiltrating T cells behave like “exhausted” T cells where PD-1 levels continue to stay high, and multiple other immuno-inhibitory receptors are expressed.

PD-L1 is expressed on the surface of many solid tumors and hematologic malignancies, and inhibits anti-tumor immune responses. Antibodies that block PD-1 or PD-L1 can increase anti-tumor T cell activity, and several such antibodies are being developed and evaluated in clinical trials. In addition, the anti-PD-1 antibodies pembrolizumab and nivolumab have recently received FDA-approval for advanced melanoma and lung cancer. Checkpoint inhibitors have also shown anti-tumor activity in other cancers such as Hodgkin’s disease, non-Hodgkin’s lymphoma, renal, and breast cancer. Response rates of 20-50% have been observed in trials and durable responses lasting for years have also been observed. Highly mutated tumors, or tumors with genetically amplified PD-L1 and PD-L2, or those with viral antigens appear to respond well to these therapies. As PD-L1 expression in tumor increases the likelihood of response to PD-1/PD-L1 blockade, developing predictive clinical biomarkers that can accurately assess PD-L1 expression are key to identifying which patients may benefit most from these agents. PD-1 or PD-L1 inhibitors have an overall good safety profile with serious adverse effects such as autoimmune pneumonitis and colitis observed in less than 10% of patients.

As tumor infiltrating lymphocytes can express many immune-inhibitory receptors in addition to PD-1, combination therapies blocking the PD-1 pathway and other immune-inhibitory signals can improve outcomes. These therapies may be more effective as they can target the cancers at different sites such as inhibiting CTLA-4 in the lymph node in addition to PD-1 inhibition in the tumors.

Developing checkpoint blockade therapies will require different trial endpoints, as overall survival assesses the activity of these agents more accurately than progression free survival. Additional research is required to identify which patients will respond to PD-1 blockade, identify mechanisms of resistance, and help develop immunotherapies to treat non-responders.
however, serious side effects can occur. The most serious adverse events observed are autoimmune related, such as pneumonitis and colitis. In general, response rates to these agents are moderate (20-50% response rates across clinical trials), however, several that have response are able to achieve durable remissions. The development of predictive biomarkers for PD-1 and PD-L1 inhibitors has been a challenge. PD-L1 expression in the tumor increases the likelihood of response to these agents, but this is not absolute. Recent studies have suggested that perhaps high mutational burden, and thus high tumor neoantigen burden, is a predictor of response to PD-1, PD-L1 inhibitor therapy. While PD-1/PD-L1 blockade is a promising strategy, it has also become evident that inhibition of TILs is caused by more than just the PD-1 pathway. TILs express multiple immunoinhibitory receptors, which may be druggable targets in the future. In fact, the combination of PD-1 blockade and CTLA-4 blockade, another immunoinhibitory pathway, has been shown to be more effective than CTLA-4 blockade alone in patients with advanced melanoma. Another challenge remains determining the most appropriate measure of efficacy for immunotherapy drugs, as responses are often slower to occur than traditional cytotoxic agents, but may provide more durable clinical benefit for a proportion of patients. In the future, research efforts will focus on the development of biomarkers to predict response to PD-1/PD-L1 blockade as well as determination of the mechanism by which tumor cells fail to respond to these agents.

Authored by Diwakar Davar, MBBS, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Following initial interaction between antigens and antigen-specific T-cell receptor (TCR), T-cell activation is regulated by a plethora of positive and negative immune checkpoints – the aggregate of which decides the fate of the T-cell response. By expressing ligands that interact with negative regulatory checkpoints, tumors are able to subvert antitumor immunity. Development of monoclonal antibodies against either receptors or ligands can restore effective antitumor immunity – an approach first validated by the success of cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) blocking antibody ipilimumab in advanced melanoma, the first immune checkpoint modulator to be approved by the US Food and Drug Administration (FDA) for the treatment of advanced cancer1.

Although ipilimumab improved survival in advanced melanoma patients including previously both treated and treatment-naïve patients, it is only effective in 20-23% of patients and is not particularly effective in other malignancies. Programmed cell death protein 1 (PD1) is an inhibitory cell surface receptor found on T-cells and pro-B cells that binds two ligands - PD-L1 and PD-L2. PD-1/PD-L1 activation promotes apoptosis in antigen-specific T-cells and suppresses apoptosis in regulatory T-cells resulting in suppression of T-cell activation – reversed by blocking antibodies directed against PD-1/PD-L1. PD-1/PD-L1 blocking antibodies have a greater response rate – 30-50% - than ipilimumab and are effective in ipilimumab-refractory melanoma patients2. Further, these features have demonstrated efficacy in a broad range of tumor types besides melanoma including non-small cell and small cell lung cancer, Hodgkin’s lymphoma, microsatellite unstable (MSI-H) colorectal carcinoma, renal cell carcinoma, and bladder carcinoma – resulting in FDA approving both nivolumab and pembrolizumab for non-small cell lung cancer recently3-8.

Although our understanding of the interplay between the various positive and negative regulatory checkpoints is as yet evolving, investigators have already considered combinatorial strategies to see if added benefit can be derived by adding various agents to PD-1/PD-L1. Combinations involving multiple checkpoints (PD-1/CTLA-4, PD-1/LAG-3, anti-KIR) and checkpoint/vaccine (PD-1/sipuleucel-T, PD-1/Vigil, PD-1/peptide vaccine, PD-1/GVAX, PD-1 DC vaccine, PD-1/GM.CD-40L vaccine) aim to increase the intensity of the immune response to PD-1 therapy alone. Combinations of checkpoint inhibitors with either chemotherapy (PD-1/gemcitabine) or radiation (PD-1/SRS) aim to increase breadth of the T-cell repertoire by increasing the fraction of immunogenic antigens presented following use of cytotoxic therapy. Further, PD-1 inhibitors are being combined with various agents aimed at targeting mediators of resistance within the tumor microenvironment including tryptophan metabolism (IDO inhibitors - PD-1/epacadostat), M2 macrophages (PD-1/PLX3397), PI3K signaling (PD-1/INCB050465), TGFβ signaling (PD-1/galunisertib) and epigenetic modulation (PD1/RRx-001, PD-1/azacitadine). Besides providing treatment options for patients with refractory malignancies, such combinations have the capacity to transform our understanding of tumor immunology by shedding further light on tumor-mediated immune escape.

Predictive biomarkers of response to immune checkpoint modulators remain elusive. Initial work focused on PD-L1 expression (as determined by IHC) and mutational burden (defined as number of nonsynonymous mutations in exons)9–11. Each of these has singular advantages and disadvantages - well described in other publications. In the studies primarily in non-small cell lung cancer that utilized PD-L1 expression as an integrated biomarker – biomarker-positive patients (high PD-L1 status) had high response rates with PD-1 directed therapy but biomarker-negative patients (low/absent PD-L1 status) had response rates equivalent (and in some cases greater) than control populations treated with chemotherapy – suggesting that the biomarker predicts benefit to PD-1 directed therapy but did not capture the entire spectrum of responders. In a study of advanced melanoma, response to CTLA-4 inhibitor ipilimumab was associated with elaboration of immunogenic
Similar analyses in patients with non-small cell lung cancer treated with PD-1 inhibitors drew identical conclusions – providing a putative link between cigarette smoking and higher rate of response to PD-1 inhibition seen in active/heavy smokers with lung cancer. However, subsequent work by Gajewski TF et al suggests that although mutated tumors are associated with T-cell infiltrate which ipso facto predicts for response to CTLA-4 and PD-1 inhibition, non-T-cell infiltrated tumors are equally mutated implying that an alternative mechanism besides somatic hypermutation mediates T-cell exclusion.

Besides the usual characteristics of predictive biomarkers (sensitivity, specificity, reproducibility and well-characterized cutoffs), putative biomarkers to checkpoint inhibition need additional characteristics including the ability to capture atypical responses and accurately depict the dynamic state of the immune microenvironment. Development of validated predictive biomarkers to PD-1 and CTLA-4 inhibitors would greatly improve the therapeutic index of these agents and in an era of increasing cost-consciousness permit providers and patients the ability to select therapies with the greatest cost-benefit ratio.

Bibliography


Authored by Thomas A. Longo, MD, Duke University Medical Center, Durham, NC, USA

Dr. Freeman’s narrative traced the development of immunotherapy through history. This method of discussion was an entertaining way to display the information, but it held an even greater value. It showed the scientific process of trial and error, which is fertile ground for my own experimental design. The discovery of each step of the pathway helped to crystallize my own understanding as we walked through the work involved; how anomalies in one experiment lead to a different design and the revelation of a costimulant or other factor. Seeing it from the lens of history also provides hope that a more profound understanding of nature is certain to develop as we compile small gains in knowledge.

Following the pathway discussion, Dr. Freeman launched into checkpoint inhibitor immunotherapy. He went over the early trials, and as part of an overarching theme of the forum, he mentioned biomarkers. His thoughts on the development of cell lines from the patient’s own cancer, versus a genetically engineered cell line (with a solitary mutation) were an area beyond my own knowledge. As such, it was all news to me, and something that I will consider going forward in my own research,
and in the evaluation of others.

The concept of T cell fatigue is something that I had heard of, but it had never been so thoroughly explained as it was during the forum. This insight of the interplay between acute versus chronic immune response invaluable; it was one of those thoughts that seems so obvious once it has been voiced aloud. The idea of stimulating the immune system has fallen short until it was discovered that removing the inhibition of the immune system is of equal or greater importance.

Combination therapy is now coming to the forefront and is proving to be greater than the sum of its parts. These combinations are working on different mechanisms, and in different locations to produce profound results. Indeed, these results are being measured in traditional ways (OS, PFS,...) but almost demand a new metric, such as a tumor immunoevasion score, or sequencing the cancer genome. Certainly, a lot of work remains to determine who the nonresponders are, and how we can manipulate them to become responders. It is also unclear what the best measure of efficacy is for this burgeoning field of therapy. Dr. Freeman ended on a bright note, that “It’s a wonderful time to be an oncologist or researcher.” STOFF reinforced this sentiment, and I am grateful I had the opportunity to attend and learn.

Author by John T. Lucas, Jr., MD, MS, St. Jude Children’s Research Hospital, Memphis, TN, USA

In Dr. Gordon Freeman’s lecture on Immune Checkpoint Inhibition in Advanced Cancer we learned about how blockade of pathways used by tumors to inhibit anti-tumor immunity functions to achieve tumor responses in patients.

The history of anti-tumor response really goes back decades to a time when BCG was used to facilitate or act as an adjuvant locally to trigger an immune response. Other more modern approaches have used adjuvants such as IL-1 or GM-CSF. The most successful approaches in immunotherapy have focused on PD-1-PD-L1 and CTLA4 and B7-1 interactions. PD-L1 seems to be expressed on the cell-surface of as much as 30% of solid tumors. The therapeutic effect of PD-1 seems to abrogate the “tuning down” of the immune response after tumor clearance and reduces the tolerance to self.

Numerous agents are currently in development but started back with a compound called MDX-1106, now known as Nivolumab. The relatively high response rates in early studies were very encouraging and seem to be related to the degree of genetic disarray in tumors. Some patients may have short lived responses while other patients can have durable responses that last for years and border on “cure”. This is not without cost as some patients can develop autoimmune mediated adverse events such as pneumonitis, colitis, etc.

Selection of patients for immunotherapy: not all patients will respond but it appears that patients with increased PD-L1 expression do have a higher response rate in most studies. More anecdotal literature demonstrates that patients with somatic mutation frequencies greater than 10/Mb have an increased response rate to immunotherapy. This mirrors what we have seen in tobacco associated malignancies like SCC of the lung, and UV light associated DNA damage related malignancies like Melanoma, higher grade malignancies like some renal cell carcinoma and MSI colorectal and MSI uterine tumors.

The next steps appear to be exploring combinations of immunotherapy like Nivolumab and Ipilimumab, determining whether radiotherapy can act as an antigen release mechanism for facilitating immune response and better clarifying who might benefit from immunotherapy.