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Immune Checkpoint Inhibition in Advanced Cancer

Faculty Presenter
Michael Postow, MD, Assistant Attending Physician, Melanoma-Sarcoma Oncology Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Scholars' Summaries

*Authored by **Meghan Campo, MD,** Dana-Farber Cancer Institute, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA*

Breakthroughs in immunotherapy have revolutionized the treatment of patients with advanced cancer. Dr. Michael Postow's lecture highlighted the current landscape of immunotherapy with a focus on the use and development of combination therapies.

Following the success of single agent CTLA-4 and PD-1 inhibition, focus has shifted to the study of novel combinations of immune therapeutics with the goal of improving efficacy. A major breakthrough was seen in CheckMate 067 as dual PD1/CTLA4 blockade demonstrated robust and often durable responses. However, this efficacy came at the cost of considerable toxicity, as ≥ 50% of patients on combination therapy experienced grade 3/4 adverse events. When discussing toxicities, Dr. Postow made an important point regarding the need to critically evaluate the clinical implications of the toxicity data reported. For example, in patients treated with combination ipi/nivo, grade 3/4 elevations in amylase and/or lipase were seen in 30 patients; however only 2 developed clinically significant pancreatitis.

Dr. Postow then reviewed emerging treatment options focusing on alternative combinatorial strategies. The enzyme indoleamine 2, 3-dioxygenase (IDO) is thought to be upregulated in tumor cells and myeloid-derived suppressor cells. IDO acts to converts tryptophan to kynurenine, leading to immune suppression in the tumor microenvironment and suppressive activity on T cells. While monotherapy with IDO inhibition has failed to demonstrate significant clinical activity, promising results have been seen with the combination of the IDO inhibitors and checkpoint blockade. A recent study explored the use of the IDO inhibitor epacadostat in combination with pembrolizumab. In this phase I/II study, treatment was well tolerated across cancer types (no grade 4 AE, only 5% of patients discontinuing therapy), with promising efficacy data reported in the 19 patients with metastatic melanoma (ORR of 53% and DCR of 74%).

In addition to combination immune therapies, we discussed the role of combined checkpoint inhibition and radiation therapy (RT). Of growing interest in the treatment of advanced malignancies (especially melanoma) is the combination of immune therapy and RT due to the possible role RT plays in immune modulation. The abscopal effects of RT and check point inhibition with both ipilimumab and PD-1 inhibitors have been reported. These case reports suggest that the increased antigenicity with radiation acts additively with immune therapy and thereby improves patient outcomes. Though this proposed synergism is an exciting therapeutic prospect, it has yet to be prospectively established. Further clinical investigation into the use of these modalities will be critical in understanding the full benefits of a multi-modal approach.

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*Authored by **Russell W. Jenkins, MD, PhD,** Dana-Farber Cancer Institute, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA*

Dr. Michael Postow gave an excellent talk discussing immune checkpoint inhibition in advanced cancer. Starting with an overview of the scientific rationale behind reinvigorating exhausted T lymphocytes, he transitioned to a review of the foundational clinical evidence demonstrating improved response rates and overall survival with single-agent checkpoint

blockade. He provided additional background regarding the hypothesized role for PD-1 signaling at the level of the tumor microenvironment and CTLA-4 within lymph nodes, while also discussing a nuanced view of the uncertainties in this model including reported activity of anti-CTLA-4 therapies against regulatory T cells (Tregs) in the tumor microenvironment. He then transitioned to discussion of dual checkpoint blockade with anti-PD-1 (nivolumab) and anti-CTLA-4 (ipilimumab) therapies, using this as a jumping off point to emphasize three major unanswered questions in the field of immunotherapy: (1) combination immunotherapies, (2) immune-mediated toxicity, and (3) the role of radiation. He also presented some interesting data using proliferating CD8 T cells as a surrogate for action of immune checkpoint inhibitors and discussed the need for better markers of toxicity and opportunities to evaluate checkpoint blockade in combination with radiation.

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*Authored by **Konstantinos Leventakos, MD,** Mayo Clinic College of Medicine, Rochester, MN, USA*

Novel immunotherapy agents are revolutionary in the treatment of cancer. Three agents that target the PD1/PDL1 pathway (pembrolizumab, nivolumab, and atezolizumab) have been approved for the treatment of certain cancer types, and many others are investigated in clinical trials. Combination treatments are also underway. There are direct methods of combination modalities that include “turning on” T cells or “turning off” certain tumor checkpoints. Indirect methods include radiotherapy and chemotherapy, oncolytic viral therapy, and targeted therapy. The combination of ipilimumab with nivolumab showed a response rate of 61% compared to 11% with nivolumab alone, but combination has more side effects than either drug alone. Interestingly, we can continue to see high response rates among patients who discontinue early. That raises the question of stopping ipilimumab after achieving a response; indeed, a protocol testing adaptively-dosed combination immunotherapy is underway. Indoleamine 2,3-dioxygenase (IDO) is a oxidoreductase that catalyzes the degradation of the essential amino acid tryptophan to N formyl-kynurenine and has been recognized as another intratumoral enzyme “checkpoint”. Recent focus has been given to the immunologic changes that can be monitored in order to predict who is going to respond to immunotherapy or what the effect of combination therapies would be. For example, T-cell receptor (TCR) diversity can shed light into the diversity and clonality of the cell population. For example, TCR diversity was associated with ipilimumab benefit in a study, and radiation was found to increase intratumoral diversity of T cells in non-irradiated tumors. Clearly, as immunotherapy is entering clinical practice in a robust way, studies of immunotherapy biomarkers will be of pivotal importance in order to define the best immunotherapy combinations and the best patient selection.

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*Authored by **Tomohiro Nishijima, MD,** University of North Carolina Hospitals, Chapel Hill, NC, USA*

Anti-CTLA-4 and PD-1/PD-L1 monoclonal antibodies have been the best studied immunotherapies so far and have been shown to improve survival outcomes in various randomized controlled trials. The mechanism of action of CTLA-4 inhibitors involves abrogation of immune tolerance leading to increases in the number and repertoire of activated T cells. PD-1/PD-L1 inhibitors, on the other hand, re-stimulate previously primed T cells that have lost effector and proliferative function during the course of an immune response. These immune checkpoint inhibitors have shown significant improvement in progression-free survival (PFS) and overall survival compared with standard care in different advanced solid tumors. Recently, improvement in response rate (61% vs. 11%) and PFS (11 vs 2.9 months) was observed with the combination of ipilimumab and nivolumab compared with ipilimumab alone in patients with metastatic melanoma. Ipilimumab and nivolumab combination also appears to have greater efficacy than nivolumab alone. The major downside of ipilimumab and nivolumab combination is a high (55%) risk for grade 3 or 4 treatment-related adverse events (colitis 17%, diarrhea 11%, increased ALT 11%, and increased lipase 9%). Even though high-grade elevation of lipase is relatively common, Dr. Michael Postow’s group has found that clinical pancreatitis is rare at 1-2%.

Based on the success of ipilimumab and nivolumab combination, combination immunotherapy is actively studied pre-clinically and clinically. Intratumoral enzyme Indoleamine 2,3 Dioxygenase (IDO) depletes tryptophan, produces toxic kynurenine, and induces immune tolerance by suppressing T-cell response. Epacadostat is a potent, selective, oral inhibitor of IDO1 that has demonstrated antitumor synergistic with PD-1 blockade. The overall response rate was 58% in 19 untreated melanoma patients treated with epacadostat and pembrolizumab in a phase I study. Not only the immune checkpoints, but also immune activating receptors such as OX40, and CD137 are targeted and tested as a component of combination immunotherapy.

Anecdotal reports suggest a benefit of combining radiation with immunotherapy, as radiation enhances multiple inflammatory pathways by killing the tumor with immunogenic stimulus. Preclinical data showed synergistic antitumor responses with combination of CTLA-4 inhibitor + PD-1 inhibitor + radiation. Radiation and immunotherapy combination is investigated in clinical trials.

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*Authored by **Daniel S. Shin, MD,** University of California, Los Angeles, CA, USA*

Immune check point blockade is currently a very hot topic in oncology drug development. Many clinical trials are trying to address how we can improve the clinical outcome by combining existing conventional chemotherapy, targeted therapy, or other checkpoint blockades or checkpoint agonists. Dr. Michael Postow summarized his work in developing double checkpoint blockade with nivolumab and ipilimumab. Although it comes with significant toxicity, it has demonstrated an impressive response rate that has resulted in significant improvement of progression free survival. (Overall survival data is not yet mature.) Dr. Postow is also conducting translational studies to better understand the response and resistance from this promising therapeutic approach. There are many opportunities for us to participate in the rapidly-evolving field of tumor immunology as fellows or junior faculty. It is such an exciting time to be an oncologist.