

## 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 Jeanette Muniz Kovtun, MD, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA*

Ipilimumab was the first monoclonal antibody immune checkpoint inhibitor and targets CTLA-4, a negative regulator of T cells. Subsequently, several agents have been developed which target PD-1, including nivolumab, pembrolizumab, atezolizumab, avelumab and durvalumab. PD-1/PDL-1 is another important negative stimulatory interaction both in the tumor's interaction with T cell and also in earlier dendritic and T cell interactions.

There are several areas in need of further investigation in immunotherapy including: 1. Studying combinations of drugs, 2. correlative studies or deeper understanding of clinical data, and 3. understanding toxicities.

Strategies to enhance immune checkpoint inhibition may include increasing the visibility of the tumor via identification and targeting of neoantigens, which can distinguish tumor from self. Additionally there are studies to enhance T cells in the tumor microenvironment via bispecific T cell engagers targeting M2 macrophages/tumor suppressors.

The potential synergy between radiation therapy (RT) and immunotherapy is another active area of investigation. Preclinical models have demonstrated that radiation enhances multiple inflammatory pathways. Postow et al. NEJM 2012 showed patient examples of tumor regression with radiation even after prior progression. Radiation was shown to increase intratumoral diversity of T cells in non-irradiated tumor and TCR clones (Twyman-Saint Victor et al. Nature 2015), and TCR diversity was associated with ipilimumab benefit (Postow J Immunother Cancer 2015). Maximizing potential synergy between RT and immunotherapy with respect to drug combinations, timing of therapies, and RT fractionation are also currently unclear.

Other areas of investigation are the durability of response after discontinuation of immunotherapy. Schadendorf and Postow JCO 2017 showed durable responses after discontinuation due to side effects. Of note, this was a retrospective study, and PFS and OS were not significantly different in those who continued vs discontinued due to toxicity. A Phase 2 protocol (MSKCC IRB 17-162) is testing adaptively dosed combination immunotherapy with ipilimumab and nivolumab. If a 6 week scan shows favorable anti-tumor effect, then patients receive maintenance nivolumab. Otherwise patients without favorable response will receive 2 more doses of combination ipilimumab and nivolumab. All patients will have a 12 week scan.

Dr. Postow discussed the importance of accurately characterizing immunotherapy side effects, such as pneumonitis (Naidoo et al. JCO 2017). He also stressed that not all grade 3 toxicities may be clinically

relevant (e.g. elevated lipase only associated with clinical pancreatitis in 1% patient per Friedman et al. JNCI 2017.) Whether toxicity is associated with efficacy or outcome is unclear. For example, studies have shown association of development of vitiligo with improved immunotherapy response.

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*Authored by **Angel Qin, MD**, Fellow, Division of Hematology/Oncology, University of Michigan, Ann Arbor, MI, USA*

The immune checkpoint (PD-1/PD-L1, CTLA4) inhibitors block interactions between tumor cells and T cells that would otherwise result in T cell energy. The mechanism of action of these drugs is therefore allowing cytotoxic T cells to recognize and kill tumor cells. Checkpoint inhibitors are now approved in a multitude of solid tumors and have been evaluated in many different settings, i.e. in metastatic disease, as maintenance therapy, and in combination with other cytotoxic and targeted agents. Instead of discussing the current numerous approvals of checkpoint inhibitors, Dr. Michael Postow focused his talk on how fellows and young investigators can contribute in what has already become a crowded space of immunotherapy research. He highlighted three research voids, including:

- 1) Providing data or a concept to justify a novel combination
- 2) Taking data from a clinical trial and examining it more deeply to generate hypotheses, and
- 3) Improving the understanding of toxicities associated with these agents.

As a young investigator, I found his talk to be very thought-provoking. It helped generate ideas on how to augment my own research interest in this area.

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*Authored by **Sheng Yang, MD**, Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Immunotherapy with checkpoint inhibitors is revolutionizing the management of cancer. With his expertise and experience, Dr. Michael Postow presented a fascinating lecture geared towards fellows. He explained the notion of immune checkpoint inhibition, the rationale for its utility in cancer, and current status in this field. Subsequently, he devoted most of the talk to a discussion of potential research opportunities for fellows.

He suggested that we provide data or propose a concept to justify a combination therapy. He used as an example radiation plus immunotherapy. It has been known that radiotherapy can increase the level of multiple cytokines with enhancing effects on dendritic cell migration to lymph nodes and subsequent antigen cross presentation, resulting in enhanced CD8+ T-cell proliferation and increased chemokine production to attract CD8+ CTLs. In addition, there have

been anecdotal clinical reports of abscopal effect after radiotherapy and checkpoint inhibitors. In one case, serologic antigen screening revealed 10 antigenic targets with significantly increased antibody response, supporting the theory that radiation may boost anti-cancer immunity. Unfortunately, radiation plus ipilimumab yielded suboptimal efficacy in a clinical trial. However, when turning to preclinical data, evidence indicated that the addition of PD-1 antibody to this combination would improve outcome. Moreover, a correlative study demonstrated that radiotherapy can increase intratumoral diversity of T cells in non-irradiated tumor and peripheral blood TCR clones of greatest TIL frequency. Now clinical trials combining radiotherapy and checkpoint inhibitors are ongoing. Also, various treatment approaches have the potential to improve the efficacy of immunotherapy by increasing antigenicity, including vaccines (peptide, DNA), or “in vivo” vaccines (for instance, oncolytic viral therapy), some oncogenic directed targeted therapy, certain chemotherapy, and histone deacetylase inhibitors.

The second approach was to study data (correlatively or clinically) deeper than previous studies and reports have done. For instance, dual checkpoint blockade with ipilimumab plus nivolumab has dramatically improved the efficacy in melanoma compared with ipilimumab single agent. Correlative studies showed that both CTLA-4 inhibitor and PD-1 blocker can increase Ki-67+ T cells, and the combination of the two agents exerts the most potent effects. Another example is that of patients with response who stopped immunotherapy because of toxicities. Most of these patients’ responses were sustained, and their PFS and OS seemed comparable with that of patients who received continuous drug administration. Based on this observation, a phase 2 study is investigating adaptive dosed combination immunotherapy.

Last, but not least, immune checkpoints have distinct toxicity profiles, and raised a new study domain. It is important to keep a critical view on reported data, and not all grade 3-4 events are clinically important. Experience from MSKCC showed 20% of the patients treated with ipilimumab and nivolumab had grade 3 increased lipase, ~8% have grade 3-4 increased lipase and amylase, but only ~1% developed clinical pancreatitis. Also, by reviewing the clinical data of two institutions, a cooperative study characterized pneumonitis in patients treated with PD-1 monoclonal antibody. Moreover, the mechanisms underlying immunotherapy related toxicities may be organ-specific, and correlative studies may further guide toxicity management.