

MELANOMA IN FOCUS

Current Developments in the Management of Melanoma

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Future Directions for Checkpoint Inhibition in Melanoma



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H&O What are the limitations of checkpoint inhibition in melanoma?

OH The limitations at this point are based on our inability to clearly understand who will benefit from checkpoint inhibitors, and who will not. If we knew which patients would not benefit from single-agent immunotherapy, we would begin with combination treatment. If we knew which patients would benefit from single-agent treatment, we could spare them the toxicity of combination immunotherapy.

We are taking more steps toward understanding which category a patient falls into through tissue and blood biopsies. Certain biomarkers—biological properties or molecules in tissue or blood that can indicate the presence or severity of a disease—can help us know how people are going to respond. For example, Paul Tumei and colleagues have shown us that tumors in an inflamed environment respond better to checkpoint inhibitors than tumors not in an inflamed environment.

H&O What other limitations to the use of checkpoint inhibitors exist?

OH Another limitation is toxicity. We can combine an anti-cytotoxic T-lymphocyte-associated antigen 4 (anti-CTLA-4) agent with an anti-programmed death 1 (anti-PD-1) agent to increase the response rate, but this leads to a 50% rate of toxicity. Approximately 30% of patients are unable to continue therapy, which is a big limitation.

H&O What are some new approaches to dealing with these limitations?

OH We have been testing checkpoint inhibitors in combination with other agents in an effort to produce the same efficacy with less toxicity. For example, Dr Georgina Long and I presented data at the Society for Melanoma Research 2015 Congress showing high response rates to pembrolizumab (Keytruda, Merck) and the investigative indoleamine dioxygenase (IDO) inhibitor epacadostat, which acts as an immunosuppressant in the tissue microenvironment. Another combination is pembrolizumab and talimogene laherparepvec, commonly called T-VEC (Imlygic, Amgen), which is an oncolytic viral therapy that was approved by the US Food and Drug Administration (FDA) in October of 2015. Although these combinations have not been shown to improve overall survival, they have produced initially high response rates in phase 1 trials, and the toxicities are only negligibly greater than those seen with single-agent pembrolizumab.

H&O What makes the existing checkpoint inhibitors different from one another?

OH The anti-CTLA-4 drugs include ipilimumab (Yervoy, Bristol-Myers Squibb), which was approved by the FDA for metastatic melanoma in 2011 and in the adjuvant setting in 2015, and the experimental agent tremelimumab. Agents that target the PD-1/programmed death ligand 1 (PD-L1) pathway include pembrolizumab and nivolumab (Opdivo, Bristol-Myers Squibb). Pembrolizumab and

nivolumab are both approved for use in melanoma and lung cancer, and nivolumab was recently approved for use in renal cell carcinoma. Nivolumab also has been approved in combination with ipilimumab for melanoma and has a breakthrough designation in Hodgkin disease.

A number of additional anti-PD-1/PD-L1 agents are being evaluated in solid tumors, including atezolizumab, avelumab, and durvalumab. Atezolizumab has received breakthrough designation in lung cancer and bladder cancer, avelumab has received breakthrough designation in Merkel cell carcinoma, and durvalumab is being looked at in multiple solid and liquid tumors.

There are multiple differences between anti-CTLA-4 agents and anti-PD-1/PD-L1 agents. For starters, the targets are different. Anti-CTLA-4 agents primarily act between the antigen-presenting cell and the T cell, and anti-PD-1/PD-L1 agents primarily act in the tumor microenvironment where the T cell and the tumor interact. We also know more about how the anti-CTLA-4 agents work. We know that they can move T cells into tumors.

Another difference is in the response to treatment. Our experience has been that patients whose tumors respond to anti-CTLA-4 treatment tend to have durable responses. We now have 10-year data showing a long-term survival benefit with anti-CTLA-4 agents. We also have seen durable responses in the subset of patients whose tumors respond to anti-PD-1/PD-L1 agents, but the tumors ultimately cease to respond in some of these patients. We are trying to figure out why that is so.

Finally, the toxicity spectra of anti-CTLA-4 agents and anti-PD-1/PD-L1 agents are different. The incidence of grade 3 or 4 toxicity is higher with anti-CTLA-4 therapy than with anti-PD-1/PD-L1 therapy, and the toxicities are different. We tend to see colitis, panhypopituitarism, autoimmune hepatitis, and rash with anti-CTLA-4 agents, whereas hypothyroidism, hyperthyroidism, and inflammatory conditions such as hepatitis and meningitis are associated with anti-PD-1/PD-L1 agents.

H&O What new checkpoint inhibitors are in development?

OH Multiple agents that stimulate or inhibit multiple checkpoints beyond CTLA-4 and PD-1/PD-L1 are being evaluated at this point. These include agents that target CD40, OX40, glucocorticoid-induced tumor necrosis factor receptor (TNFR)-related protein (GITR), T-cell immunoglobulin and mucin protein 3 (TIM3), and lymphocyte activation gene 3-encoded protein (LAG3). Multiple phase 1 trials are investigating the use of these experimental agents both singly and as part of combination therapy. At the Angeles Clinic and Research Institute, we are going to be looking at OX40, GITR, and LAG3.

H&O What other immune targets are being investigated?

OH Another area to target is the tumor microenvironment. This is why we have been so interested in the idea of using inhibitors of IDO and colony-stimulating factor 1 receptor (CSF1R) in combination with checkpoint inhibitors.

Another type of immunotherapy is interleukin 2, which has shown a long-term benefit in those patients who experience a complete response. Although this is still in early trials, researchers are hoping to combine interleukin 2 with checkpoint inhibition in order to improve response rate and durability.

We are also putting more effort into investigating T-cell adoptive therapy both as single-agent treatment and in combination with checkpoint inhibition. We recently heard data at the Society for Melanoma Research 2015 Congress from Dr Mark Middleton about a bi-specific antibody from Immunocore, called IMCgp100, that simultaneously targets CD3 on T cells and gp100 on melanoma cells, creating an immune synapse. What is important about bi-specific antibodies is that they avoid cross-toxicity, so someone who experiences significant toxicity with checkpoint inhibitors may be able to avoid that toxicity with a bi-specific antibody.

H&O What should oncologists be doing to ensure that their patients benefit from checkpoint inhibition when it is warranted?

OH I am pleased to see that patients and investigators are now insisting on tumor biopsy before therapy, during therapy, and at disease progression in order to better understand the mechanisms of response and failure. Also, referral of these patients for participation in a clinical trial is important.

H&O What should the next step in research be?

OH The most important point is that certain patients are not immune-activated, and our biggest challenge is to understand who they are. Should we treat them with other types of therapies, or can we drive T cells into their tumors to allow these patients to benefit from immunotherapy? Our next step is looking at how to do that.

Suggested Readings

Hamid, O. Preliminary data from a phase 1/2 study of epacadostat (INCB024360) with pembrolizumab (pembro) in patients with advanced/metastatic melanoma. SMR 2015 International Congress.

Middleton MR, Corrie P, Steven N, et al. Safety and efficacy of IMCgp100, a soluble HLA-A2 restricted gp100-specific T cell receptor-CD3 therapeutic, in patients with advanced uveal melanoma. SMR 2015 International Congress.

Tumeh PC, Harview CL, Yearley JH, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. *Nature*. 2014;27;515(7528):568-571.