

# MELANOMA IN FOCUS

Current Developments in the Management of Melanoma

Section Editor: Sanjiv S. Agarwala, MD

## The Future of Combination Treatment With Checkpoint Inhibitors in Melanoma



Ryan J. Sullivan, MD  
Assistant Professor of Medicine  
Harvard Medical School  
Boston, Massachusetts

**H&O** What dual checkpoint blockade regimens have been approved for use in metastatic melanoma?

**RS** So far, the only approved option is the combination of the anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) agent ipilimumab (Yervoy, Bristol-Myers Squibb) and the anti-programmed death 1 (PD-1) agent nivolumab (Opdivo, Bristol-Myers Squibb). The regimen consists of intravenous (IV) nivolumab at 1 mg/kg and ipilimumab at 3 mg/kg every 3 weeks for up to 4 doses, followed by single-agent nivolumab at 3 mg/kg every 2 weeks until progression or unacceptable toxic effects.

The change that we are most likely to see in the foreseeable future regards dosing, on the basis of data from CheckMate 511 (A Study of Two Different Dose Combinations of Nivolumab in Combination With Ipilimumab in Subjects With Previously Untreated, Unresectable or Metastatic Melanoma) presented recently by Dr Celeste Lebbé at the European Society for Medical Oncology (ESMO) 2018 Congress. The data demonstrated that when the dosing of ipilimumab and nivolumab was flipped—so that ipilimumab was given at 1 mg/kg and nivolumab at 3 mg/kg—the treatment was just as efficacious and the toxicity profile was different; the rate of high-grade toxicities was lower (33.9% vs 48.3%) than with standard dosing.

The other ipilimumab-based regimen consists of pembrolizumab (Keytruda, Merck) plus ipilimumab. Dr Georgina Long recently presented phase 1b/2 data from the KEYNOTE-029 study (Safety and Tolerability of

Pembrolizumab + Pegylated Interferon Alfa-2b and Pembrolizumab + Ipilimumab in Participants With Advanced Melanoma or Renal Cell Carcinoma) at the 2018 Society for Melanoma Research Congress. This single-arm study included approximately 153 patients, all of whom received pembrolizumab and low-dose ipilimumab as frontline treatment. Limitations of the study were its small size,

The primary advantage of dual checkpoint blockade is a more rapid response to treatment.

single-arm design, and specific patient population—the trial was conducted in a sunny area where many people have sun-damaged skin. Dr Long reported response rates higher than 60%, in addition to remarkably durable progression-free and overall survival data (3-year rates of 59% and 73%, respectively).

**H&O** What are the advantages of dual checkpoint blockade over monotherapy?

**RS** The primary advantage of dual checkpoint blockade is a more rapid response to treatment. Although this rapid response does not translate to an immediate improve-

ment in survival, it is highly useful for patients with brain metastases. The brain is an organ in which quick control of disease is advantageous; you may be able to spare your patient radiation or even death.

The usefulness of this approach has been shown in 2 studies: ABC (Anti-PD 1 Brain Collaboration for Patients With Melanoma Brain Metastases) by Dr Georgina Long and colleagues, which appeared in *Lancet Oncology* in early 2018, and CheckMate 204 (An Investigational Immuno-therapy Study to Evaluate Safety and Effectiveness in Patients With Melanoma That Has Spread to the Brain, Treated With Nivolumab in Combination With Ipilimumab, Followed by Nivolumab by Itself) by Dr Hussein Tawbi and colleagues, which appeared in the *New England Journal of Medicine* later in 2018.

Most of the patients in ABC and all in CheckMate 204 had asymptomatic brain metastases, although none of them was large enough that corticosteroids or immediate resection was required. The response rate was greater than 50% in both trials and the progression-free survival was also very high, so these are excellent results. Virtually all of the melanoma experts at academic medical centers now favor dual checkpoint blockade in patients with brain metastases.

ABC, which was an open-label phase 2 trial, randomly assigned 63 patients with asymptomatic brain metastases to either nivolumab/ipilimumab or nivolumab alone. After a median follow-up of 17 months, an intracranial response was observed in 46% of those in the nivolumab/ipilimumab group and 20% of those in the nivolumab group. Intracranial complete responses occurred in 17% of the patients in the nivolumab/ipilimumab group and 12% of those in the nivolumab group.

Grade 3 or 4 treatment-related adverse events occurred in 54% of the patients in the nivolumab/ipilimumab group and 16% of those in the nivolumab group. Of note, a third cohort of patients was enrolled whose disease had failed to respond to local therapy (ie, surgery or radiation); these patients had symptomatic brain metastases or leptomeningeal disease and were treated with single-agent nivolumab. Only 2 patients were progression-free at 6 months.

CheckMate 204, which included 94 patients with a median follow-up of 14.0 months, found an intracranial clinical benefit rate from nivolumab/ipilimumab of 57%, a complete response rate of 26%, a partial response rate of 30%, and a rate of stable disease for at least 6 months of 2%. The extracranial clinical benefit rate was 56%. Treatment-related grade 3 or 4 adverse events were reported in 55% of patients, including events involving the central nervous system in 7%.

Another advantage to the combination is that

patients are less likely to need additional therapy afterward. Patients in the early trials evaluating this combination were not allowed, per protocol, to transition to maintenance nivolumab in the setting of certain side effects, yet have remained in response.

### H&O What are the disadvantages of dual checkpoint blockade?

**RS** The main disadvantage is toxicity. Dual checkpoint blockade is a highly toxic regimen that requires a ton of support to get through. The rate of grade 3 or 4 treatment-related adverse events was as high as 54% in the ABC study, depending on the cohort, and was 55% in CheckMate 204. One patient died of immune-related myocarditis.

This does not mean the regimen is not worth using in certain situations. However, in the absence of dramatic improvements in certain outcomes, little justification exists for using the combination in most patients.

### H&O What are the specific situations in which dual checkpoint blockade is the preferred option for first-line treatment?

**RS** Beyond patients with brain metastases, we might choose dual checkpoint blockade for 3 other types of patients: those who have rapidly progressing disease, very widespread disease, or disease that is threatening a critical spot in the body. In these 3 scenarios, the question I ask is, If this patient doesn't respond in the next 3 months, will we have the opportunity to use ipilimumab as salvage therapy down the road? The use of ipilimumab as salvage therapy may be one reason why long-term progression-free survival and overall survival do not differ that much between single and dual checkpoint blockade. The use of ipilimumab later in treatment is not inferior to its use as frontline treatment, so when a patient has a good response to a single agent, we are able to spare him or her the toxicity of dual checkpoint inhibition. However, if a patient is not likely to survive 3 months after starting single-agent anti-PD-1 therapy, then I use the combination.

### H&O Does programmed death ligand 1 (PD-L1) status affect the treatment decision at all?

**RS** As is elaborated on in the most recent publication of CheckMate 067 (Phase 3 Study of Nivolumab or Nivolumab Plus Ipilimumab Versus Ipilimumab Alone in Previously Untreated Advanced Melanoma), by Wolchok and colleagues, PD-L1 status should not be used for this purpose.

## H&O What are the causes of primary and secondary resistance to checkpoint inhibitors?

**RS** One of the key drivers of primary resistance is a lack of immune cells in the tumor. A tumor in which the microenvironment is devoid of the appropriate immune elements is often referred to as a “cold” tumor, and the evidence suggests that tumors without the right immune cells will not respond to treatment—that is what happens in many cases of primary resistance. Also, because the tumor can adapt to evade the immune system either before or after immunotherapy is given, anything that can cause secondary resistance can also be a cause of primary resistance.

For example, if immune cells bombard a tumor, significant clonal selection can occur—pruning of the sensitive cells and growth of the more resistant cells. In

A lot of interest has been shown in combining checkpoint inhibitors with other agents.

checkpoint inhibition, the T cells do the work, rather than the monoclonal antibody against PD-1. If the immune system that once was functioning robustly is no longer doing so, the reason could be that the tumor microenvironment is keeping things at bay by using immune checkpoints, like PD-L1, to prevent tumor destruction. In this situation, one would expect immune checkpoint inhibitors to work. Alternatively, the tumor microenvironment may no longer be using immune checkpoints to protect itself. Instead, the tumor cells that have grown out may have lost antigen expression, which is what allows the immune system to recognize tumor cells for destruction, or may have crippled the interferon machinery that is required for the immune system to destroy tumor cells. The published mechanisms of resistance that are beginning to emerge include beta-2 macroglobulin mutations, other antigen presentation machinery defects, and JAK1 and JAK2 aberrations that lead to dysfunctional interferon signaling. Additional resistance mechanisms include expression of the phosphoinositide 3-kinase (PI3K) pathway, the acquisition of mutations or aberrations that drive a cell cycle process such as cyclin D or cyclin-dependent kinase 4 (CDK4), and loss of the regulatory protein CDKN2A. But outside the cold tumor scenario, every other potential

mechanism of immune system resistance that a tumor adapts can be primary or secondary.

## H&O Is there reason to think that adding an agent from a class other than checkpoint inhibitors could be useful?

**RS** A lot of interest has been shown in combining checkpoint inhibitors with other agents. The goal, of course, is to find the right other agent. In the world of lung cancer and now breast cancer, and other diseases in which chemotherapy is effective, researchers are looking at the combination chemotherapy with immune checkpoint inhibitor therapy, which has produced some success.

Altering the tumor microenvironment, whether with cytotoxic chemotherapy, with targeted therapies such as dabrafenib (Tafinlar, Novartis) and trametinib (Mekinist, Novartis) in patients who have *BRAF*-mutant melanoma, or with radiation, has the potential to work in concert with the immune checkpoint inhibitor toward creating a more robust response and thus improve outcomes.

## H&O What agents have been studied with checkpoint inhibitors so far?

**RS** One combination is ipilimumab with or without the granulocyte-macrophage colony-stimulating factor (GM-CSF) sargramostim (Leukine, Partner Therapeutics). A phase 2/3 study is looking at ipilimumab/nivolumab with or without sargramostim; this is a cooperative trial that currently is on hold (NCT02339571). Another cooperative group study that is currently on hold is looking at ipilimumab with or without the vascular endothelial growth factor (VEGF) agent bevacizumab (Avastin, Genentech) as second-line treatment (NCT01950390). In addition, KEYNOTE-034 (Pembrolizumab With or Without Talimogene Laherparepvec or Talimogene Laherparepvec Placebo in Unresected Melanoma) is looking at pembrolizumab with or without the intra-tumoral injectable talimogene laherparepvec (T-VEC; Imlygic, Amgen) as frontline melanoma therapy. This trial has completed accrual.

It was hoped that a combination of pembrolizumab and the indoleamine 2,3-dioxygenase 1 (IDO1) inhibitor epacadostat would lead to an augmented response, but it did not, and the KEYNOTE-252 trial (A Phase 3 Study of Pembrolizumab + Epacadostat or Placebo in Subjects With Unresectable or Metastatic Melanoma) was halted in April 2018. A phase 2/3 trial is looking at nivolumab with or without a lymphocyte activation gene 3 (LAG3) inhibitor (NCT03470922). In addition, a phase 1b study suggested some interesting activity with a combination of nivolumab and the engineered cytokine NKTR-214,

which is a polyethylene glycol–modified (pegylated) interleukin 2 (IL-2) agent. Data from the melanoma cohort, presented by Dr Saul Kivimae at the Society for Immunotherapy of Cancer (SITC) 33rd Annual Meeting, showed a complete response rate of 25%. At least several hundred checkpoint inhibitor combinations are being evaluated right now, many of which are specifically investigating or including patients with melanoma.

**H&O** Can you speculate as to why results with the combination of pembrolizumab and epacadostat were so negative?

**RS** The pharmacokinetic and pharmacodynamic endpoints of the dose that was used in the trial were reasonable and were met in the tumor microenvironment and in the blood, so I think that was fine.

From a mechanistic standpoint, it made sense that this combination would produce good results, but perhaps IDO1 is just an auxiliary player in human melanoma. However, the spectacular failure of this combination provides an excellent lesson in how we need to do a better job of vetting the combinations that move forward in development. Before we move ahead with a combination, we should identify whether any of the following scenarios occur: (1) Are responses seen in the population with refractory disease? (2) Do responses occur with each agent when used singly? (3) Are we seeing an odd toxicity signal that is clearly associated with an on-target effect? (4) Do we have randomized data from smaller cohorts suggesting that this combination is more effective than a single agent? (5) Can we define a cohort of patients who are more likely to benefit?

If we had focused on these 5 criteria, the epacadostat/pembrolizumab trial would not have moved forward—the combination did not meet any of them. With whatever combination moves forward next, we should be able to check at least one of the boxes next to these 5 questions.

### Disclosure

*Dr Sullivan has consulted for or served on the advisory boards of Merck, Amgen, Compugen, Syndax, Array, Novartis,*

*Roche/Genentech, and Replimune. His institution has received research funding from Merck, Amgen, Sanofi, Neon, Roche/Genentech, Compugen, Moderna, Immunocore, Aeglea BioTherapeutics, Adaptimmune, Asana, Astex, Tesaro, Lilly, Novartis, and BioMed Valley Discoveries.*

### Suggested Readings

ClinicalTrials.gov. Ipilimumab with or without bevacizumab in treating patients with stage III-IV melanoma that cannot be removed by surgery. <https://clinicaltrials.gov/ct2/show/NCT01950390>. Identifier: NCT01950390. Accessed December 13, 2018.

ClinicalTrials.gov. A study of relatlimab plus nivolumab versus nivolumab alone in participants with advanced melanoma. <https://clinicaltrials.gov/ct2/show/NCT03470922>. Identifier: NCT03470922. Accessed December 13, 2018.

ClinicalTrials.gov. Nivolumab and ipilimumab with or without sargramostim in treating patients with stage III-IV melanoma that cannot be removed by surgery. <https://clinicaltrials.gov/ct2/show/NCT02339571>. Identifier: NCT02339571. Accessed December 10, 2018.

ClinicalTrials.gov. Pembrolizumab with or without talimogene laherparepvec or talimogene laherparepvec placebo in unresected melanoma. <https://clinicaltrials.gov/ct2/show/NCT02263508>. Identifier: NCT02263508

Hodi FS, Chiarion-Sileni V, Gonzalez R, et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. *Lancet Oncol*. 2018;19(11):1480-1492.

Kivimae S, Hennessy M, Pena R, et al. Systemic anti-tumor immunity and immune memory formation by a novel TLR7/8 targeting agent NKTR-262 combined with CD122-biased immunostimulatory cytokine NKTR-214. Presented at: Society for Immunotherapy of Cancer Annual Meeting; November 7-11, 2018; Washington, DC. Abstract P364.

Lebbé C, Meyer N, Mortier L, et al. Initial results from a phase IIIb/IV study evaluating two dosing regimens of nivolumab (NIVO) in combination with ipilimumab (IPI) in patients with advanced melanoma (CheckMate 511) [ESMO abstract LBA47]. *Ann Oncol*. 2018;29(suppl)(8).

Liu D, Jenkins RW, Sullivan RJ. Mechanisms of resistance to immune checkpoint blockade [published online September 26, 2018]. *Am J Clin Dermatol*. doi:10.1007/s40257-018-0389-y.

Long GV. Long-term follow-up of standard-dose pembrolizumab (pembro) plus reduced-dose ipilimumab (ipi) in 153 patients (pts) with advanced melanoma (MEL): KEYNOTE-029 1B. Presented at: the 15th annual congress of the Society for Melanoma Research; October 24-27, 2018; Manchester, United Kingdom.

Long GV, Atkinson V, Lo S, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. *Lancet Oncol*. 2018;19(5):672-681.

Tawbi HA, Forsyth PA, Algazi A, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. *N Engl J Med*. 2018;379(8):722-730.

Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med*. 2017;377(14):1345-1356.