

MELANOMA IN FOCUS

Current Developments in the Management of Melanoma

Section Editor: John M. Kirkwood, MD

The Best Treatments to Use After Checkpoint Inhibition in Melanoma



Grant McArthur, MBBS, PhD
 Director, Melanoma and Skin Service and Cancer Therapeutics Program
 Peter MacCallum Cancer Centre
 Melbourne, Victoria, Australia

H&O Which patients with melanoma are candidates for checkpoint inhibition?

GM All patients with unresectable metastatic melanoma—stage IV and unresectable stage III disease—are candidates for checkpoint inhibition.

H&O How effective are checkpoint inhibitors in these patients?

GM We see impressive rates of response, progression-free survival, and overall survival, but not all patients benefit (Table). On average, monotherapy with a programmed death 1 (PD-1) inhibitor produces a 40% response rate. Combining the PD-1 inhibitor nivolumab (Opdivo, Bristol-Myers Squibb) with the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitor ipilimumab (Yervoy, Bristol-Myers Squibb) increases the response rate to 58%.¹ These are good response rates, but not as good as those achieved with targeted therapies in melanoma.

H&O What is the typical duration of response with checkpoint inhibitors?

GM These data are still emerging. The responses to PD-1 inhibitors seem to be fairly durable; 60% of responses last for at least 2 years. Although this rate is impressive, we would prefer to see 90% of responses lasting that long. The fact that the disease of many patients does not respond up front to checkpoint inhibitors, combined with the fact that too many patients acquire resistance, means that we

need to continue to focus on developing further therapies for advanced melanoma.

H&O With which of the checkpoint inhibitors have responses been longest?

GM The data with the longest follow-up are from patients treated with ipilimumab. Some of these patients have continued to experience benefit for more than 10 years. The interesting thing is that we sometimes see patients with no disease progression who still have signs of radiologic

Multiple clinical trials are looking at treatments for patients with primary or secondary resistance to checkpoint inhibitors.

abnormalities on scans, so it's not clear that we can use the term *cure*. Regarding PD-1 inhibitor monotherapy, we now have phase 1 data on 107 heavily pretreated patients with metastatic melanoma who received nivolumab. As Dr F. Stephen Hodi reported at the 2016 American Association for Cancer Research annual meeting, 34% of these

Table. Key Trials of Checkpoint Inhibition in Melanoma

Study	N	Patient Population	Treatments	ORR	Median PFS	Median OS	2-y OS	3-y OS
Anti-CTLA-4 trials								
MDX010-20 (Hodi, 2010) ⁸	676	Previously treated	Ipilimumab + gp100 vs ipilimumab alone vs gp100 alone	5.7% vs 11.0% vs 1.5%	2.76 mo vs 2.86 mo vs 2.76 mo	10.0 mo vs 10.1 mo vs 6.4 mo	22% vs 24% vs 14%	NA
CA184-024 (Robert, 2011) ⁹	502	Treatment-naive	Ipilimumab 10 mg/kg + dacarbazine vs placebo + dacarbazine	38% vs 26%		11.2 mo vs 9.1 mo	28.5% vs 17.9%	20.8% vs 12.2%
Pooled Analysis, OS (Schadendorf, 2015) ¹⁰	1861	68% previously treated 32% treatment-naive	-	-	-	11.4 mo	-	22%
Anti-PD-1 Trials								
KEYNOTE-001 (Ribas, 2016) ¹¹	655	77% previously treated 23% treatment-naive	Pembrolizumab 10 mg/kg every 2 wk vs pembrolizumab 10 mg/kg every 3 wk vs pembrolizumab 2 mg/kg every 3 wk	38.0% vs 31.6% vs 31.5%	4 mo (overall) 14 mo (treatment-naive)	23 mo (overall) 31 mo (treatment-naive)	49%	40%
KEYNOTE-002 (Ribas, 2015) ¹²	540	Previously treated	Pembrolizumab 2 mg/kg vs pembrolizumab 10 mg/kg vs chemotherapy	21% vs 25% vs 4%	2.9 mo vs 2.9 mo vs 2.7 mo	13.4 mo vs 14.7 mo vs 11.0 mo	50%	40%
KEYNOTE-006 (Robert, 2015) ¹³	834	66% treatment-naive	Pembrolizumab 10 mg/kg every 2 wk vs pembrolizumab 10 mg/kg every 3 wk vs ipilimumab 3 mg/kg every 3 wk	33.7% vs 32.9% vs 11.9%	5.5 mo vs 4.1 mo vs 2.8 mo	NR vs NR vs 16.0 mo	55.1% vs 55.3% vs 43%	NA
CheckMate 066 (Robert, 2015) ¹⁴	418	<i>BRAF</i> -wild-type only Treatment-naive	Nivolumab vs dacarbazine	40% vs 13.9%	5.1 mo vs 2.2 mo	NR vs 10.8 mo	57.7% vs 26.7%	NA
CheckMate 037 (Weber, 2015) ¹⁵	405	Previously treated	Nivolumab vs chemotherapy	31.7% vs 10.6%	4.7 mo vs 4.2 mo	NA	NA	NA
Combination Trials								
CheckMate 067 (Larkin, 2015) ¹	945	Treatment-naive	Ipilimumab + nivolumab vs nivolumab alone vs ipilimumab alone	57.6% vs 43.7% vs 19.0%	11.5 mo vs 6.9 mo vs 2.9 mo	NA	NA	NA

CTLA-4, cytotoxic T-lymphocyte-associated protein 4; gp100, glycoprotein 100 peptide vaccine; mo, months; N, number of patients; NA, not available; NR, not reached; ORR, overall response rate; OS, overall survival; PD-1, programmed death 1; PFS, progression-free survival; wk, weeks; y, year(s).

patients were still alive after 5 years of follow-up.² We may be able to improve on this with a combination of CTLA-4 and PD-1 inhibitors.

H&O Do we know why certain patients experience these durable responses?

GM That is a very important area of research. We can enrich somewhat in predicting response if the tumor is positive for programmed death ligand 1 (PD-L1), but this positivity is not a powerful predictor on its own. The classic factors that we examine when predicting response are burden of disease, visceral site involvement, and lactate dehydrogenase level. We also look at tumor biological factors, including PD-L1 expression, but we need additional predictive markers.

One area of interest is to examine the tumor micro-environment at the time of commencing therapy to determine the presence and type of tumor-infiltrating leukocytes. This information in combination with PD-L1 expression is a promising approach to predicting benefit, but much more clinical validation is needed.

Biomarkers are valuable because they identify which treatments will work and spare patients the toxicity of treatments that will not work. Anti-PD-1 monotherapy is very well tolerated, whereas the combination of CTLA-4 and PD-1 inhibitors is quite toxic, so it would be a significant step forward to be able to predict who will derive adequate, durable clinical benefit from anti-PD-1 therapy alone.

H&O For how long should PD-1 inhibitors be administered?

GM This is currently one of the biggest medical practice questions in our field. Essentially, we do not know. Do patients need to remain on treatment for life to receive continued benefit? We certainly hope not, and to address this question, trials have been planned that randomly assign patients to discontinuation or continuation of therapy. The most relevant data we have were presented by Dr Caroline Robert at the 2016 annual meeting of the American Society of Clinical Oncology.³ In a study of 655 patients, 95 patients had a complete response to pembrolizumab (Keytruda, Merck), and these 95 patients ceased therapy after a median of 23 months. The response persisted after cessation of pembrolizumab in 97% of cases.

We also need to learn how long therapy must continue in patients who experience a durable partial response. Certainly, we start to think about ceasing therapy at 2 years, but this practice is based less on data and more on the fact that patients get tired of coming to the oncology unit for an intravenous infusion every 2 or 3 weeks, which

interferes with quality of life and lifestyle. Of course, one of the benefits of ipilimumab is that patients receive 4 induction doses, and then therapy ceases. This is excellent from a quality-of-life point of view.

We also have some interesting data on combination treatment with CTLA-4 and PD-1 inhibitors showing that discontinuing treatment early because of toxicity does not obviously reduce the duration of response.⁴

H&O Could you talk more about the reasons for discontinuing treatment?

GM As I mentioned earlier, sometimes people who have responded to therapy stop taking it because they are tired of getting regular infusions. Regarding toxicity, immune-related adverse events are the most common reason for stopping treatment. The rate of clinically significant immune-related adverse events ranges from approximately 10% with anti-PD-1 monotherapy to more than 50% with a combination of anti-CTLA-4 and anti-PD-1 agents. So, these adverse events are quite common. The median number of cycles delivered in the pivotal trial of anti-CTLA-4 and anti-PD-1 agents was 4.¹

Cost is another reason why some patients might stop taking a drug. This is especially the case for patients who do not have insurance coverage or who live in an area, such as much of Asia, where reimbursement for these expensive drugs is limited.

H&O What treatment options are available for patients after checkpoint inhibition?

GM Few options are available, so this is an area in major need of innovation. One study is currently evaluating the combined use of anti-CTLA-4 and anti-PD-1 agents in patients with disease that has not responded to or has progressed during anti-PD-1 monotherapy, and we await these data eagerly.⁵ Many other approaches are being developed. Multiple clinical trials are looking at treatments for patients with primary or secondary resistance to checkpoint inhibitors. These treatments include combined targeted therapies, immunotherapies, novel checkpoint inhibitors, and injectable agents to alter the tumor microenvironment and elicit an immune response. Cytotoxic drugs also are being used in combination with immunotherapies, although more so in other types of cancer than in melanoma.

It is difficult to say at this point which of these approaches is the most promising. Some studies are looking at immune checkpoint molecules, such as anti-CD137, that act on more than just T cells. There are also very interesting data on combining MEK inhibitors with anti-PD-1 therapy because MEK inhibitors can favorably affect T-cell

biology in a tumor. Another very interesting approach is to inject stimulator of interferon genes (STING) agonists into tumors to change the tumor microenvironment.

In our practice, we strongly encourage eligible patients to enroll in clinical trials. For a patient who has already received PD-1 inhibitor monotherapy, the combination of an anti-CTLA-4 agent and an anti-PD-1 agent is worthy of consideration. For a patient who already has received anti-CTLA-4 and anti-PD-1 agents in combination, a clinical trial of an investigational approach is best.

Speaking anecdotally, I have on occasion seen that adding radiotherapy of progressive lesions to treatment with an anti-PD-1 agent can produce good responses. And of course, patients who have a *BRAF* mutation have treatment options in the form of BRAF and MEK inhibitors. Another investigational approach in patients with a *BRAF* mutation is to add inhibitors of the BRAF pathway to anti-PD-1 therapies.^{6,7}

H&O Is there anything that you would like to add?

GM We have made some wonderful advances that clearly provide major benefits to patients. It is important that we not stop innovating, however, because we still have patients whose disease does not respond to or progresses on immune checkpoint therapies. We need to keep the foot on the accelerator in terms of innovation, and we need to continue to study tumor biology and conduct innovative clinical trials.

Disclosure

Dr McArthur has received research funding from Celgene, Genentech-Roche, Bristol-Myers Squibb, Amgen, Merck, Novartis, and Array.

References

- Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med*. 2015;373(1):23-34.
- Hodi FS, et al. Durable, long-term survival in previously treated patients with advanced melanoma who received nivolumab monotherapy in a phase I trial. Paper presented at: American Association for Cancer Research Annual Meeting; April 16-20, 2016; New Orleans, Louisiana. Abstract CT001.
- Robert C, Ribas A, Hamid O, et al. Three-year overall survival for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001 [ASCO abstract 9503]. *J Clin Oncol*. 2016;128(22)(suppl).
- Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Efficacy and safety in key patient subgroups of nivolumab (NIVO) alone or combined with ipilimumab (IPI) versus IPI alone in treatment-naïve patients with advanced melanoma (MEL) (CheckMate 067). Paper presented at: European Cancer Congress 2015; September 25-September 29; Vienna, Austria. Abstract 3303.
- ClinicalTrials.gov. Ipilimumab vs ipilimumab plus nivolumab in patients with stage III-IV melanoma who have progressed or relapsed on PD-1 inhibitor therapy. <https://clinicaltrials.gov/ct2/show/NCT02731729>. Identifier: 02731729. Accessed March 15, 2017.
- ClinicalTrials.gov. A phase 1b study of atezolizumab in combination with vemurafenib or vemurafenib plus cobimetinib in participants with BRAFV600-mutation positive metastatic melanoma. <https://clinicaltrials.gov/ct2/show/NCT01656642>. Identifier: 01656642. Accessed March 15, 2017.
- ClinicalTrials.gov. A study of the safety and efficacy of pembrolizumab (MK-3475) in combination with trametinib and dabrafenib in participants with advanced melanoma (MK-3475-022/KEYNOTE-022). <https://clinicaltrials.gov/ct2/show/NCT02130466?term=02130466&rank=1>. Accessed March 15, 2017.
- Hodi FS, O'Day SJ, McDermott DE, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363(8):711-723.
- Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med*. 2011;364(26):2517-2526.
- Schadendorf D, Hodi FS, Robert C, et al. Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in unresectable or metastatic melanoma. *J Clin Oncol*. 2015;33(17):1889-1894.
- Ribas A, Hamid O, Daud A, et al. Association of pembrolizumab with tumor response and survival among patients with advanced melanoma. *JAMA*. 2016;315(15):1600-1609.
- Ribas A, Puzanov I, Dummer R, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. *Lancet Oncol*. 2015;16(8):908-918.
- Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med*. 2015;372(26):2521-2532.
- Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med*. 2015;372(4):320-330.
- Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. 2015;16(4):375-384.