The Best Treatments to Use After Checkpoint Inhibition in Melanoma

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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 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 patients received a response. The responses appear to be durable, with patients continuing to respond for more than 2 years. There is some concern about the emergence of resistance, so we need to continue to develop new therapies that can overcome the resistance that occurs in these patients.
Table. Key Trials of Checkpoint Inhibition in Melanoma

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

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. 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 microenvironment 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. 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.

**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.

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. 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.

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References