

# Melanoma: ASCO20 Virtual Scientific Program Highlights for the Advanced Practitioner



With coverage by *The ASCO Post*, **Lisa Kottschade, APRN, MSN, CNP**, of Mayo Clinic, reviews clinical data on which patients with metastatic melanoma should receive combination therapy vs. single-agent PD-1 up front, and what to do at the time of progression on PD-1 monotherapy.

## Abstracts 10003, 10004, and 10005

### Melanoma: Clinical Trials Update on PD-1 and CTLA-4 Blockade

By *The ASCO Post Staff*

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**D**ouglas B. Johnson, MD, of Vanderbilt University Medical Center, discusses three important melanoma abstracts: the need for more than two doses of nivolumab plus ipilimumab in combination immunotherapy; antitumor activity for low-dose ipilimumab with pembrolizumab after disease progression on PD-1 antibodies;

and ipilimumab alone or in combination with anti-PD-1 therapy for metastatic disease resistant to PD-1 monotherapy (Abstracts 10003, 10004, and 10005). Below is a transcript of Dr. Johnson's commentary.

### A Phase II Study to Evaluate the Need For More Than Two Doses Of Nivolumab + Ipilimumab Combination Immunotherapy

This was a phase II clinical trial testing the need for whether more than two doses of ipilimumab and nivolumab are needed in patients with metastatic melanoma. In general, we give patients 4 doses of ipilimumab 3 mg/kg and nivolumab 1 mg/kg. We know that patients who develop toxicities and have to stop therapy early actually had just as good outcomes as patients who received 4 doses.

This study was aimed to see if a planned discontinuation of the therapy would be just as effective. Patients got 2 doses of therapy every 3 weeks and a scan at 6 weeks, and patients who had tumor shrinkage or stability had discontinuation of ipilimumab, and they continued nivolumab monotherapy. On the other hand, the patients who had tumor growth received 2 more doses of therapy. Two thirds of the patients in this trial stopped ipilimumab after 2 doses, whereas one third of patients needed more therapy. It turned out that in patients who received 2 doses, the overall response rate in this study was quite high, about 57%, and the progression-free survival and overall survival were excellent and very comparable to all 4 doses of therapy.

J Adv Pract Oncol 2020;11(6):609-611  
<https://doi.org/10.6004/jadpro.2020.11.6.8>

The good news is that it seems that only 2 doses is a reasonable strategy, certainly in patients not tolerating therapy very well. The downside is that the toxicity also didn't seem to be decreased. Even though only 2 doses of therapy were given (in the hopes to potentially mitigate the toxicities in the regimen), in the study, about 60% of patients had grade 3/4 toxicity, which is quite comparable with the all 4 dose therapy regimen. Now, it will be important with more long-term follow-up to see what the kinetics of these side effects were; perhaps some of the late side effects were mitigated. But still, 3 patients died from toxicity, which is a relatively high rate, and the grade 3/4 toxicity rate was in the 60% range. Therefore, this abstract tells us that perhaps patients having difficulty tolerating therapy can be discontinued early on their ipilimumab/nivolumab, but it does not necessarily dramatically reduce toxicities.

Another interesting thing to note is that this study told us that for patients who had tumor growth at 6 weeks (a small group of approximately 20 patients), none ultimately achieved a response with more ipilimumab and nivolumab. Therefore, this is more evidence that perhaps all 4 doses may not be necessary.

This is a small study. Practice may not be changed necessarily based on this study, but it is an interesting finding.

#### **Low-Dose Ipilimumab With Pembrolizumab, and Ipilimumab Alone or in Combination With Anti-PD-1 in Patients With Metastatic Melanoma Resistant To PD-1 Therapy**

Abstract 10004 was a small phase II study of low-dose ipilimumab 1 mg/kg, which is the same dose that was used in most of the lung and renal cancer studies, in combination with pembrolizumab. This was used in patients in whom single-agent anti-PD-1 therapy failed. This study had 70 patients, so was relatively small. It found a 27% response rate, with 5 patients of the 70 achieving a complete response. This reflects relatively good efficacy in this population.

Abstract 10005 was a retrospective study involving over 300 patients looking at patients in

a similar setting: Patients in whom anti-PD-1 monotherapy failed and were assigned ipilimumab/nivolumab combination or ipilimumab monotherapy. The idea was a continuation in adding ipilimumab or a switch to ipilimumab monotherapy. What was seen in this study was that the combination of ipilimumab/nivolumab (again, the continuation of anti-PD-1 and adding ipilimumab) was associated with a higher response rate, about 32% vs. 11% for ipilimumab monotherapy. In addition, overall survival and progression-free survival were higher in ipilimumab/nivolumab.

These two studies together suggest that when anti-PD-1 monotherapy fails, we probably should be adding ipilimumab, instead of just switching patients to ipilimumab monotherapy. There is a prospective study that has nearly completed accrual that may give us more information on this, but in the absence of that data, that may be what I will be leaning towards.

These two studies also bring up one key question, which is whether a sequential approach is also reasonable rather than starting patients on ipilimumab/nivolumab. So there are two possible approaches: start with ipilimumab/nivolumab as a combination or start with anti-PD-1 and then add ipilimumab if the disease progresses. I think these studies do suggest that that kind of sequential approach is reasonable. Doing a bit of math, if a third of patients respond to anti-PD-1 monotherapy and never require any additional therapy, plus roughly a quarter of patients respond to the addition of ipilimumab at progression, that brings us to about half of patients, which is quite comparable to ipilimumab/nivolumab combination therapy.

Ultimately, what can be taken from these two abstracts, is that perhaps for patients who have a rapidly progressing disease, symptomatic disease, bulky disease, I'm going to start with ipilimumab/nivolumab upfront. But, for patients who may have low volume, asymptomatic disease, this sort of sequential strategy is reasonable. Start with anti-PD-1, then add ipilimumab at progression.

These three studies provide some important information about dose, schedule, and duration of anti-PD-1 therapy and ipilimumab. ●

### The Advanced Practitioner Perspective

Lisa Kottschade, APRN, MSN, CNP  
Mayo Clinic

While ipilimumab and nivolumab remain the staple of treatment for metastatic melanoma, there is still a lot we don't know about who should receive combination therapy vs. single-agent PD-1 up front, and what to do at the time of progression on PD-1 monotherapy. Additionally, for those who receive combination therapy up front, we ultimately don't know the exact number of induction doses patients need to receive to achieve the best response and help minimize toxicity. The three abstracts described previously attempt to shed some light on these questions and can help provide guidance to advanced practitioners who treat metastatic melanoma.

#### Evaluating the Need for More Than Two Doses Of Nivolumab + Ipilimumab Combination Immunotherapy

In this phase II study, the researchers tried to see if patients with metastatic melanoma can have as good responses with fewer doses of combination checkpoint inhibitor therapy. This would have potential benefits on a number of fronts, most importantly in reduced toxicity as well as potential cost savings. While this is a smaller open-label trial, it has produced some thought-provoking results.

Early discontinuation (after 2 cycles) after initial response was possible in about 68% of patients. While this is intriguing, it did not appear to affect the amount of toxicity that was experienced. There was still a significantly high number of grade 3 and 4 events, including 3 deaths across all study participants. Given the small study size, these results should not be generalized for all patients, and further investigation will be needed. However in patients who may be experiencing early toxicity after a couple of doses of induction therapy, but are having a response, there are some data to show that early discontinuation may be an option.

#### Low-Dose Ipilimumab With Pembrolizumab, and Ipilimumab Alone or in Combination With Anti-PD-1 in Patients With Metastatic Melanoma Resistant To PD-1 Therapy

In these two abstracts, the investigators tried to tackle the issue of what the next line of treat-

ment should be for patients who progress on PD-1 monotherapy. As described in Abstract 10004, the authors prospectively investigated the regimen of low-dose ipilimumab (1 mg/kg) in combination with standard dosing pembrolizumab after PD-1 failure. In Abstract 10005, the investigators looked retrospectively at 330 patients after PD-1 failure. Patients received either ipilimumab alone or ipilimumab in combination with PD-1.

In the prospective study, the addition of low-dose ipilimumab to pembrolizumab showed a response rate of approximately 30%. But more notable was a lower toxicity rate than one would expect with combination checkpoint inhibitor therapy. This is an especially interesting finding and may be important for the patient population that may be at high risk for serious morbidity and would thus be poor candidates for traditional dual checkpoint inhibitor therapy as frontline therapy.

While not a randomized prospective study, the second study helps to tease out the addition of ipilimumab to PD-1 after progression on PD-1 vs. single-agent ipilimumab. In patients who were not *BRAF*-mutated (*BRAF*<sub>m</sub>) those who received dual checkpoint did significantly better than those who received ipilimumab alone. This difference was not as robust in the *BRAF*<sub>m</sub> population. Interestingly, in the *BRAF*<sub>m</sub> population, those who had received prior BRAF therapy had lower response rates than those who were BRAF-therapy naïve.

All three of these abstracts, while not definitively practice changing, have helped to provide some guidance in terms of the dose, duration, and toxicity of checkpoint inhibitor therapy in metastatic melanoma. They also provide additional talking points for advanced practitioners when discussing treatment options to patients both at the time of diagnosis and at the time of progression. However, advanced practitioners need to interpret this data with caution, given the small sample size in two of the studies and the retrospective nature of the third study.

**Disclosure:** Ms. Kottschade has served as a consultant for Array BioPharma.