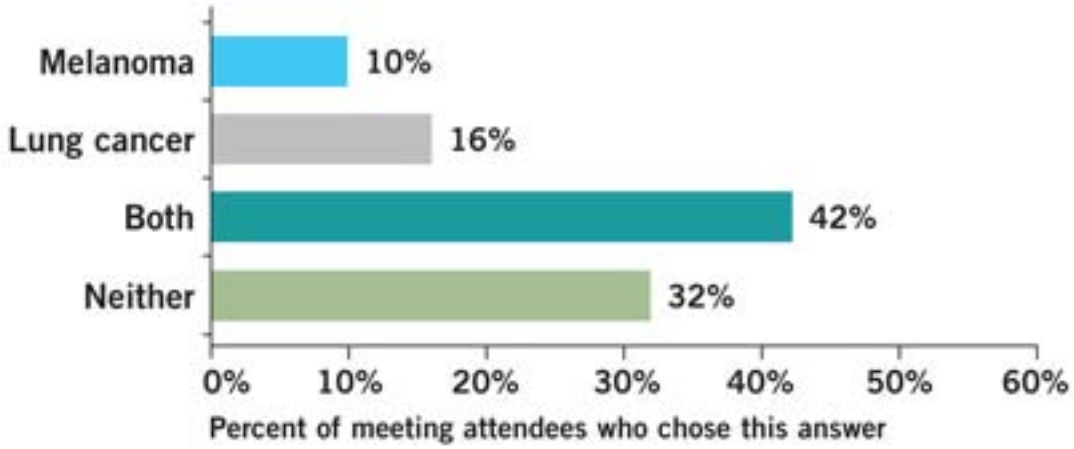
Year in Review

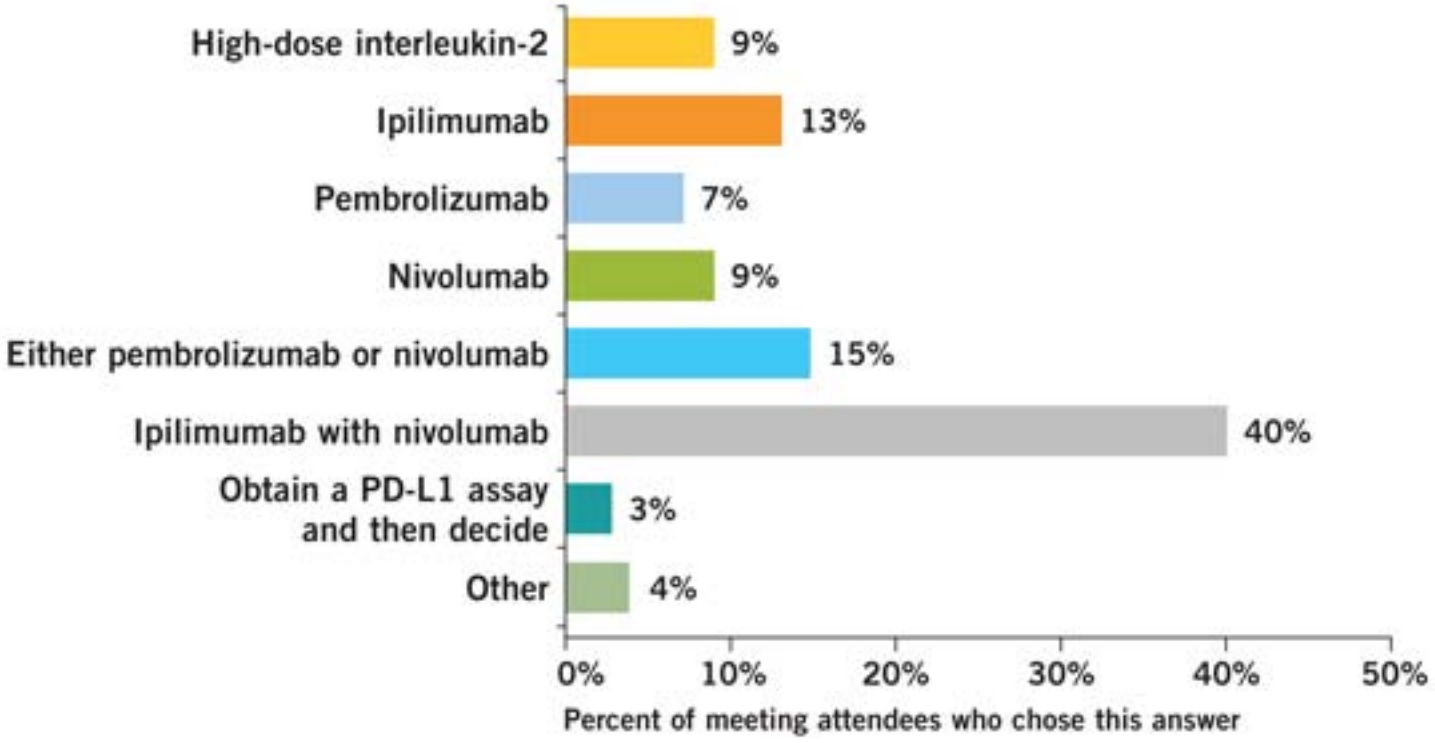
Proceedings from a Multitumor CME Symposium Focused on the Application of Emerging Research Information to the Care of Patients with Common Cancers

Immunotherapy for Melanoma — Adil Daud, MD

Have you administered an anti-PD-1 antibody outside of a clinical trial setting to a patient with...



A 54-year-old asymptomatic patient with a surgically excised primary melanoma is found 1 year later to have several small bilateral metastases in the lung on routine follow-up, confirmed to be BRAF wild-type. PS = 0. In general, what would you recommend as first-line systemic treatment?



DR LOVE: Getting into melanoma, we had a case situation, and, Adil, maybe you can talk about how you would think this one through: 54-year-old patient, has a primary melanoma removed, now has several small, bilateral mets in the lung. The patient is asymptomatic, BRAF wild type, performance status 0. In general, what would you be thinking about?

The most common answer here is the combination of ipi and nivo. There's a smattering that says ipi. Adil, how would you think this one through? Do you think there are any answers here that you just don't think are the best approach to this patient?

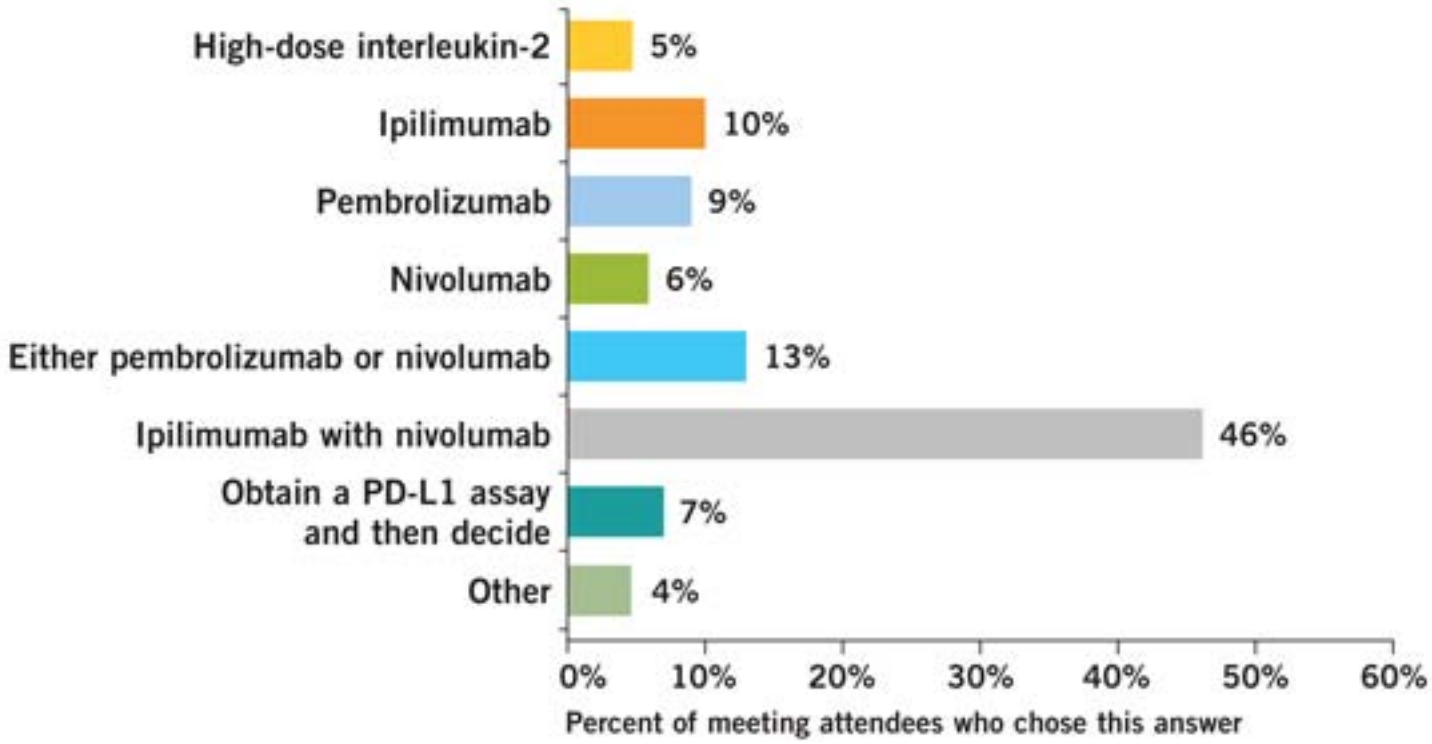
DR DAUD: These are patients who are highly responsive to PD-1. So I would prefer the pembro or nivo coin flip answer. Ipi, I think, as a first-line treatment, basically does not have a lot of data behind that. And ipi with nivo might be overkill for this particular patient.

DR LOVE: What's your take on that, Evan. Nowadays, is ipi firs line really passé?

DR LIPSON: Yes, I think it is. There was a study recently comparing pembrolizumab and ipilimumab in patients just like this. Clearly, pembrolizumab was the winner there. I think ipilimumab is no longer the first treatment of choice for a patient like this one.

With regard to ipi plus nivo versus using a PD-1 inhibitor alone, I think the jury is still out on that a little bit. I side with Adil, who would use a PD-1 inhibitor in some cases. In others, where this patient could potentially tolerate some increased side effects, you might choose to go with the combination of ipi plus nivo.

A 54-year-old symptomatic patient with a surgically excised primary melanoma is found 1 year later to have metastatic disease in the lung and liver, confirmed to be BRAF wild-type melanoma. In general, what would you recommend as first-line systemic treatment?



DR LOVE: We always try to tease out, by changing these cases, how you're really thinking it through, Adil. So we pretty much presented the same case, but now we're saying the patient is symptomatic. We see even more people going towards ipi and nivo. Now how do you think it through, Adil?

DR DAUD: Lung and liver met, definitely that lowers your chance of response to PD-1. We looked at 225 patients, and we presented that data at ASCO a few months ago. Basically, once you have liver mets in that picture PD-1 is less likely to respond. I think the number is 20% or something like that. I think ipi/nivo, you might have a higher response rate. So I would agree with using ipi/nivo in this patient population.

DR LOVE: As you can imagine, we've been talking about checkpoint inhibitors all day long, but nobody has the experience that you all do, particularly in melanoma. Evan, first, if you could reflect a little bit on the types of tolerability and side effect issues you see with the combination. I've heard people say it's kind of the same thing you see with ipi, just a lot more of it. Is that the way you look at it?

DR LIPSON: There's certainly an element of that. If you look at the studies recently published with ipilimumab and nivolumab in combination, you're probably looking at about a half of those patients, 50% approximately, who are going to get some Grade 3/4 side effect that needs intervention in some way.

With regard to the types and severity, we certainly see autoimmune toxicities that span all organ systems. When I tell patients that they need to keep in touch with us no matter what happens, I make sure that they understand it could be any part of their body. We've seen odd neurologic toxicities and skin toxicities and lung, et cetera. I encourage patients to really have their game turned up and keep a really sharp eye out for anything that changes.

I would say that, in general, most of the toxicities we see with the combination are treatable, manageable, when they're caught early. We have all had cases where somebody has waited too long to call, for example, and things haven't gone very well. But…

DR LOVE: Let's talk about some of them specifically. I like your idea, the idea that anything could be affected. Your colleague, Julie Brahmer, says she tells her patients anything that ends with an "itis" could happen. But, for practical purposes, Adil, there are several syndromes. The one we were worried about and we still worry about with ipi is colitis. What about the combination? More of it?

DR DAUD: More of it, more frequent. With ipi, it's infrequent for somebody to develop colitis before the second or third dose of ipi. With ipi/nivo, especially if you're treating somebody who has had previous immunotherapy treatment, it can happen with the very first dose. That's uncommon to happen with ipi.

You can see things like eye inflammation, lung — pneumonitis, uveitis. You can see hepatitis, liver function test abnormalities, pancreatitis, which isn't really common to see with ipi alone. Some neurologic syndromes and myopathy, neuropathies, and then fevers and chills. Again, not common to see fevers and chills with ipi alone. Actually, not common to see fevers and chills with PD-1 alone either. But the combination, you can see pyrexia. And a lot of times it'll happen after the second/third treatment. You might use Tylenol or you might use low-dose prednisone for it possibly. I think it's changing the spectrum of toxicities, maybe making it earlier on and more severe. I've seen some pneumonitis that has been pretty serious.

DR LOVE: Just to get more pragmatic, Evan, in terms of diarrhea, for example, what would it take you to hold treatment? When do you bring in corticosteroids? Practically speaking, how do you manage it?

DR LIPSON: It's an excellent question. I think the sorts of conversations that I have with community oncologists who call with these sorts of issues are exactly what you're asking now, which is: Practically, how do I approach somebody who's having a toxicity that I believe is autoimmune and I'm trying to sort out how severe things are? And what should I do?

We categorize things in essentially three categories. Those are the mild toxicity, so an episode or two of diarrhea per day, no blood in the stool, no abdominal cramping, essentially, no other symptoms. In that Grade 1 sort of a toxicity, in general, we don't withhold therapy or, if we do, it's for a brief time. We give some supportive care, maybe a dose of an antidiarrheal a time or two per day. In the cases where that is enough to calm the flames and it doesn't get beyond that, then a Grade 1 toxicity can often resolve in time with some supportive care.

The second would be a Grade 2 toxicity, where you're straddling the fence between a mild and a somewhat more severe toxicity. In a Grade 2, in general, we do withhold the dose. At least with PD-1, you have the luxury of having that antibody present for probably 3 months at a time with a single dose of drug. I tell my patients, "There's no rush to get the drug back on board. Let's get your colon back where it needs to be before we think about redosing the drug." We often hold drugs for a Grade 2.

If the symptoms have not resolved within a couple of days and we've nailed down that this is an autoimmune toxicity, we're generally then talking about low-dose corticosteroids, so half a milligram or a milligram per kilogram of body weight per day of prednisone or equivalent. That's a moderate toxicity and a moderate dose of steroids that usually gets things under control. However, if things get more serious — and this is the third category, a Grade 3/4 toxicity — almost inevitably, without exception, we hold drug and oftentimes discontinue it permanently.

Those patients sometimes get admitted to the hospital for close observation. Oral corticosteroids are often effective, but if it's, in particular, diarrhea, oftentimes you'll give an oral corticosteroid and it goes right through them. They're not really absorbing the steroid as they should. It oftentimes needs intravenous corticosteroids, a milligram or two per kilogram of prednisone or equivalent.

There are severe cases where that level of support and that level of corticosteroid administration does not do the trick. Those are steroid-refractory cases. In those cases, we use infliximab for ongoing side effects.

DR LOVE: Another issue, Adil, are autoimmune contraindications, the patient with a history of Crohn's disease, multiple sclerosis, all different kinds of potential autoimmune problems. On the other hand, you're facing a patient who has a very serious and usually fatal possibility or situation. How do you decide about whether to use these kinds of agents in people with autoimmune problems?

DR DAUD: Evan has done a lot of work on these patients. My guide is usually, if it's something like rheumatoid arthritis, if it's something that is potentially manageable, I would say it's not a contraindication and go ahead and do your PD-1 or do ipi/nivo if you need to.

I think in cases where it's multiple sclerosis or if it's transplant, what has been very interesting to me, just reading the literature, is that it isn't necessarily a contraindication. Evan was just telling me about a couple of patients they've reported on at Hopkins, where patients had transplant, treated with ipi and, surprisingly, didn't cause allograft rejection or allograft loss. I think we are learning more, that autoimmune diseases can sometimes even respond better, and I've heard this about Crohn's disease, too, that it can actually not necessarily be aggravated just because you're using PD-1, or ipi. Evan, do you want to comment on that?

DR LIPSON: I think the best way to sum it up is that it's highly variable and unpredictable. We've certainly had cases where, for example, the patient has a remote history of asthma, comes in and gets anti-PD-1 and, lo and behold, there's the first asthma flare in 25 years. Conversely, we've had patients who have had psoriasis, visible, active psoriasis on the skin. We give anti-PD-1. Psoriasis does nothing. Its often hard to predict what's going to happen. I agree with Adil that the more potentially serious an exacerbation of an underlying autoimmune toxicity would be, the more seriously you have to be cautious about the use of the drugs.

DR LOVE: I think this also introduces, again, the support staff and the whole concept of toxicity in systemic therapy nowadays. This is not about myelosuppression or the typical side effects we've associated with chemotherapy. It's a complete paradigm shift that everybody in the office has to be aware of.

The combination of ipilimumab and nivolumab resulted in improved progression-free survival compared to nivolumab in...