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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Can You Use a Dual Checkpoint Inhibitor Regimen in an Unfit Patient With BRAF WT Metastatic Melanoma?

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Dr. Buchbinder:
Hello and welcome. Today we are going to talk about the topic, can you use a dual checkpoint inhibitor regimen in an unfit patient with BRAF wild-type metastatic melanoma. My name is Elizabeth Buchbinder. I'm an Assistant Professor at Dana Farber Cancer Institute and Harvard Medical School in Boston, and I'm here today with Jason Luke.

Dr. Luke:
Hello, I'm Jason Luke. I'm an Associate Professor at the University of Pittsburgh and at UPMC Hillman Cancer Center.

Dr. Buchbinder:
Great. So I'm going to start us off by talking about a case. Today, we're going to talk about an unfit patient with BRAF wild-type metastatic melanoma. So this is a 72-year-old man with a previous medical history of deformative arthritis who lives alone and presents with back pain. On exam, he is found to have a T4b primary on the upper back, so a thick primary, and imaging is done which shows metastatic disease in multiple vertebrae as well as nodal change. The biopsy of the node identifies a BRAF wild-type, NRAS Q61K, PD-L1 negative melanoma. The patient is able to complete activities of daily living but not able to work in his tool garage as he used to. And now, Dr. Luke is going to discuss some of the background that we think about when considering treatment for a patient like this.

Dr. Luke:
Thanks. So, I mean, as the audience knows we've had a major change in the landscape of melanoma therapeutics over the last 10 years or so. On our screen, we are showing now the seminal data that underpins the activity of anti-PD-1 antibodies as well as combinations with anti-PD-1 plus anti-CTLA-4 as well as anti-PD-1 with anti-LAG-3. And, as all the audience will be aware, these studies started with the KEYNOTE-006 Study, which was the phase 3 study, comparing pembrolizumab to ipilimumab in treatment naïve patients showing a major advantage for pembrolizumab versus ipilimumab in 5-year overall survival rates nearly 40%. And these are followed up by 2 anti-PD-1 clinical trials with nivolumab, the CheckMate 066 Study, mostly done in Europe, which randomized patients who received nivolumab versus chemotherapy, again, showing a major advantage as had been expected. And then the seminal study CheckMate 067, which randomized patients into 3 arms; 1 to ipilimumab plus nivolumab; 1 to nivolumab, and 1 to ipilimumab with both of the PD-1-containing regimens actually compared to the IPI monotherapy regimen. And as is now well understood, more than 50% of patients were still alive at the 5-year landmark and, in fact, the median was only reached at about 7.5 years on this study. And of course, more recently, we've got a new entry into our combination immunotherapy regimens in melanoma; that being PD-1 plus LAG-3 with relatlimab and so the RELATIVITY-047 study randomized patients that received RELA-NIVO, as we call it, versus nivolumab alone, where we saw, in fact, a similar magnitude of benefit in terms of absolute improvement both for progression-free and overall survival for NIVO-RELA as compared to what we had seen in CheckMate 067 to IPI plus NIVO.

So, all of these are regimens that are potentially of some value and how we think about using them really has to do with the upside of benefit and potentially the downside of toxicity.

And in that regard, it's important to note there actually has been a randomized phase 3 clinical trial of looking at different doses of nivolumab and ipilimumab with an attempt to, hopefully, decrease the toxicity. On the CheckMate 511 study looked at nivolumab plus ipilimumab at 1 mg/kg versus the standard of nivolumab plus ipilimumab at 3 mg/kg. And what was seen in this clinical trial was essentially an overlap in the Kaplan-Meier Survival Plots for both progression-free and overall survival. So, in clinical practice, it's a debate but many think it's reasonable to use the low-dose or flipped-dose regimen as many people have described it. Because, of course, using the lower dose of ipilimumab is associated with a reduced amount of immune-related adverse events or high-grade toxicities that patients experience. So, whereas we see that approximately 50% of patients who receive the standard dosing of nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, with the flipped dose, NIVO3 IPI1, we see that that rate of treatment-related adverse events that are severe drops to about a 30% rate. So that's an improvement that we think is meaningful and, of course, it's a debate which patients you might use which regimen in, but it's important to note we do have this flexibility in case you're worried about toxicity for your patient.

And when comparing that with the nivolumab and relatlimab regimen, we see even further improvement. And so, again, whereas about 50% of patients will get high-grade immune-related adverse events from CheckMate 067, with a high incidence of colitis with RELATIVELY-047 with nivolumab and relatlimab, instead, what we see is a rate of high-grade immune-related adverse events in the area of 22% with only single digits in low numbers of colitis events. And so that looks very attractive, of course, noting that the follow-up period for NIVO plus RELATIVITY-047 is only about 2 years at this point and that's just not as long as we've known about NIVO plus IPI.

But all of these, of course, are good regimens to choose from and really something that I think practitioners should start to get an experience base using so that they can try to choose the optimal therapy for an individual patient.

And that then, of course, brings us back to our case. And just to rehash it quickly, we have a 72-year-old man with a deep primary melanoma who didn't present and, unfortunately, has metastatic disease in the bones of the spine at the time of presentation. No BRAF mutation, and so the question is what should we do for this patient? And so, Dr. Buchbinder, I'll throw it back to you. Lots of options here. What do you think the best treatment would be in your practice for such a patient?

Dr. Buchbinder:
Yeah, so definitely lots of options here and lots of things to consider. I think one of the biggest factors that I consider in a case like this actually is the history of arthritis and the question of, you know, he obviously is able to do most of his activities but not able to do everything that he wants to do, so does have symptomatic arthritis. And the risk with any sort of immunotherapy is that you can worsen arthritis and that this can impact on quality of life and impact on how a patient is able to function, and so when considering that, it often factors into a decision for a patient like this. With a lot of the trials, patients who had active autoimmune disease and, in his case, it's not totally clear how much of this is inflammatory arthritis versus osteoarthritis given the description we have here, but when patients with true autoimmune disease were not included in many of those trials. With those patients though, I've had a lot of success and many of my colleagues have as well treating them with single agent PD-1 inhibition and not having severe worsening of arthritis or having worsening that then could be controlled with kind of minimal intervention; low-dose steroids or lower dose interventions. So this is the patient that I would be very quick to give single agent PD-1 inhibition to. In terms of combinations, it would be a real discussion with the patient. And I think if I was going to choose a combination, it would be nivolumab and relatlimab given the lower risk of toxicity, but it would be a discussion around the pros and cons of that approach. Obviously, the improvement seen in overall survival, although not reaching statistical significance is obviously very provocative, and so it makes you think it would be better and that's in a modern era when patients could have gone onto other therapies after so it makes it even more provocative as opposed to the IPI NIVO data where, at that point, most of those patients did not go on to get subsequent IPI NIVO if they were on the NIVO-alone arm.

So, in general, I would say definitely could get single agent PD-1 inhibition, would consider nivolumab and relatlimab, but it would be a clear discussion with the patient in terms of deciding what to do here.

Dr. Luke:
And I think that that's probably the key is sort of that discussion with the patient. You know, we've got multiple options as physicians here but a lot of it is going to be goals of care, what does the patient want to do, and what is their perspective. Because I would add a wrinkle here that, in my practice, I might actually choose the NIVO plus low-dose IPI regimen for this patient. And the reason I would say that is not to dispute anything that was said, because I actually agree with all of it, except to say that with bone metastases, we see that long-term outcomes are actually really problematic in melanoma and that's really where IPI might be able to add something that would be distinguished from other therapies that would at least, you know, tacitly, we understand right now. That isn't to say it's the best idea

though because, to Dr. Buchbinder's point, it might cause a lot of toxicity. And so, the question then becomes with this patient, what is the benefit here? Is he going for maximum success? Is he going for limited toxicity? Where is the goal here? And I think that's at the crux of the issue. We have so many options now in melanoma that it really is a personalized adaptive sort of goals of care-based approach that we need to have with patients. And I think probably importantly their caregivers as well. So, with that, Dr. Buchbinder, any further thoughts about this case?

Dr. Buchbinder:
No, I agree. And I agree with you in terms of the IPI, it's what we go to when we're thinking about those more difficult locations in terms of bone, liver, places like that, brain, but obviously a tough case and definitely a discussion with the patient.

Dr. Luke:
Absolutely. So, we'd like to thank all of you for joining us today. We think it was a great discussion. We hope it's insightful and we can add to your practice.

Dr. Buchbinder:
Thank you.

Announcer:
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