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Frontline Treatment: A Patient With BRAF WT Metastatic Melanoma - What Is the Optimal ICI Regimen?

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Dr. Luke:
Hello, I'm Jason Luke from the UPMC Hillman Cancer Center in Pittsburgh, Pennsylvania. I'd like to welcome you to our discussion today, surrounding frontline treatment of a patient with BRAF wild-type metastatic melanoma. What is the optimal immune checkpoint inhibitor regimen?

Dr. Buchbinder:
Hi, I'm Elizabeth Buchbinder. I'm a Melanoma Medical Oncologist at Dana Farber Cancer Institute in Boston.

Dr. Luke:
Thanks so much for joining me today, Dr. Buchbinder. So we'll go over our case. This patient with BRAF wild-type metastatic melanoma is a 64-year-old woman who was diagnosed with a T4a melanoma on the posterior left calf. Patient underwent a wide local excision and sentinel lymph node evaluation, and this was negative. At the time, there was no adjuvant therapy that would be offered to such a patient. The patient went on to have recurrence of disease with multiple pulmonary nodal and L-spine lesions. Patient was asymptomatic, but the lactate dehydrogenase was elevated. Biopsy of a nodal metastasis showed BRAF wild-type status with a mutation in NRAS at Q61R and staining as PD-L1 positive in the tumor.

So we'll come back to directly how we'll manage this patient in just a second. But to level set, we're going to go through a few data points to outline how we think about managing patients with melanoma.

And we now have long-term survival data for multiple immune checkpoint inhibitors in the management of metastatic melanoma with the seminal CheckMate-067

clinical trial demonstrating a 5-year overall survival for anti-PD-1 with nivolumab at 44%. And this was very similar to what was seen in the KEYNOTE-006 study of pembrolizumab at 38.7%. With combination immunotherapy, again from CheckMate-067, we know again, that 5-year overall survival was 52%. And even with longer follow-up beyond that, we know that patients can have durable survival over a long period of time.

Now one question that arises when we think about the use of combination PD-1 plus CTLA4 immunotherapy is the side effect profile which is substantially more toxic than a PD-1 monotherapy approach. And a number of clinical trials now have looked at what we call flipped dosing of ipi/nivo to use a lower dose of ipilimumab and a higher dose of anti-PD-1. And we published a series comparing these various regimens a few years ago.

And to summarize that briefly, it's essentially the case that the overall clinical benefit appears to be maintained using the flipped dose of ipi/nivo, and when compared with the sort of standard dose that we usually use. In a randomized phase 3 clinical trial called the

CheckMate-511 study showed this kind of a result, and several single-arm cohorts from a clinical trial called KEYNOTE-029 also supported that. So in my clinical practice, I commonly use that flipped dose of ipi/nivo in the attempt to reduce the toxicity associated with the combination immunotherapy.

And of course, in melanoma, we have a new combination regimen as well, with the approval of relatlimab, in combination with nivolumab. And those data that supported that approval came from the RELATIVITY-047 clinical trial, which randomized patients to receive nivolumab and relatlimab, versus nivolumab and a placebo. And those data hit the primary endpoint for progression-free survival, showing more than a doubling of PFS, as well as an absolute increase of approximately 10% in the response rate. In that clinical trial, we've now learned that it did not meet the prespecified statistical threshold for overall survival. However, there was what appeared to be a clinically meaningful difference in that regard. And of course, patients could, after progression on the trial, go on to get other treatments that would not have been available, say at the time of CheckMate-067.

So we now have three different immune checkpoint inhibitor options with PD-1, PD-1 plus CTLA4, and PD-1 plus LAG-3. Long-term data suggest that these regimens are all quite active in the BRAF wild-type population, with subgroup analysis from CheckMate-067 again really emphasizing that overall survival advantage that's maintained out over a long period of time.

So as we go back to our case then, and think about how we manage this patient, just to rehash, this is a mid 60s-year-old lady who developed multifocal metastatic disease in lung, lymph nodes, and bone with elevated LDH and BRAF wild-type. So having reviewed all that, Dr. Buchbinder, how would you think about your initial management? And what factors would allow you to choose which of those regimens you think would be the best for this patient?

Dr. Buchbinder:
So in terms of thinking about starting out a patient, we think about how quickly we can get a response if they have a lot of symptoms associated with their disease. And in general, we do see the fastest response was standard dose ipi/nivo. And so as a result, if someone has a lot of symptoms, I'll think about that.

The other factors that we look at in a patient like this are the LDH, whether that's elevated. And then in BRAF wild-type patients, one of the things that's important from that ipi/nivo versus nivo alone data, the last slide that we saw, is the fact that the benefit for combination ipi/nivo was not as substantial in patients who had BRAF wild-type melanoma. And actually, those patients often do very well on single agent PD-1 alone.

In addition, there's the option of nivo and relatlimab, which we don't have as much long-term data on, but which shows benefit over single agent PD-1 inhibition alone.

So in a patient like this, we'll have a real discussion about side effects associated with each of these different regimens, deciding between single agent PD-1 inhibition PD-1 with relatlimab, or combination ipilimumab and nivolumab. And often in a patient like this, I'll favor either nivolumab and relatlimab, or ipilimumab and nivolumab at the flip dosing in order to avoid toxicity.

Dr. Luke:
Yeah, I think those are really good points, and you highlighted a couple of different patients-specific factors that can really help to guide this. So I'd really emphasize those again, just bring them to the forefront for those that are listening. You know, I think the really high-risk features that we think about in metastatic melanoma are the lactate dehydrogenase in the presence of brain mets being two really overriding factors. In addition to that, though, we do also take into account issues surrounding other sites of anatomy for metastases. So, in my practice, my experience with bone metastases is they can be particularly difficult to manage, as well as the number of organ sites that are involved. And when we get to three or more organ sites, that also can be a predictor of high-risk disease.

So in a patient like this, I would absolutely be leaning towards using combination immunotherapy. And as was alluded to, I think the question then becomes, you know, which of these regimens full-dose ipi/nivo as we talked about, flipped dose ipi/nivo, or nivolumab and relatlimab would be the best for the patient. And again, as was alluded to, I think it is a nuanced conversation here. And this is really where a conversation with a patient and what their goals are, is really going to matter the most.

Despite the randomized evidence, I think a lot of people still think that the full-dose ipi/nivo packs a little bit bigger punch than the lower dose ipi/nivo. I'll say that in my practice, I almost exclusively use the low dose ipi/nivo. But some patients would say, ‘Well give me the most powerful thing that you got,’ and of course, that comes with the toxicity profile of more than a 50% risk of immune-related adverse events, if you use the full dose of ipi/nivo.

And of course, then we have the newer data for nivo and relatlimab. And I really use that regimen where I would have otherwise used anti-PD-1 monotherapy. And so here again, in a patient with elevated LDH and bone metastases, I probably would not use PD-1 monotherapy in such a patient, but you know, using nivo plus relatlimab wouldn't be wrong there. But in my practice, I would probably

bias towards using combination PD-1 and CTLA4, whether it be at the full dose or at the flip dose kind of an approach.

You know, one thing I think that's probably worth thinking about, Dr. Buchbinder, also, of course, is the sequencing of our therapies. Do you have any comments or want to make any, you know, considerations around, well, if you start with one, do you go to the other one if you need to? Or what do we know about that space right now?

Dr. Buchbinder:
Yeah, so that space is still an area that's really being figured out in terms of we know that in patients who have previously had PD-1 inhibition, the response to nivo and relatlimab in the second-line setting is only about 12%. So it's pretty low. Now, whether patients who received an nivo and relatlimab in the frontline and then receive ipi/nivo in the second line will do – how those patients will do, we don't know. We know post PDL-1 response rate is quite a bit higher in the 27-30% range. But post nivo and relatlimab, that data, there are only some case reports out there, which suggests that perhaps it may be lower. I think we tend to think it might be higher, and so as a result, there's a little more comfort right now starting with nivo and relatlimab, and going to ipi/nivo second line, but in truth, we really don't have that data yet.

Dr. Luke:
Yeah, I think those are really important points. And I think it emphasizes that while there's been transformative impact on the management of melanoma with immune checkpoint blockade, once we get into the second line, if our initial treatment doesn't work, it actually isn't the case that we're having curative intent for all of these patients. And it can become very difficult to figure out which treatment would be the best. And again, coming back to our case then, that's why we really use some of these initial factors that are patient-level factors. like bone mets, like LDH, etcetera, to really drive at how are we going to manage that toxicity versus efficacy consideration. And sometimes it's worth risking more side effects just because we're concerned that if we don't get the kind of benefit we need in that frontline setting, we may or may not really have a good option, you know, as we go on from there.

So that's great. Any further comments about this case, Dr. Buchbinder?

Dr. Buchbinder:
No, I think we've covered most of the dilemmas we have in terms of thinking about a frontline wild-type BRAF patient with metastatic melanoma.

Dr. Luke:
Yeah, absolutely. And I think the good news coming out of this is that our expectation here is for long-term survival in 50% or more of such patients. And certainly, that's a major change in our field over the last 10 to 15 years, which of course is good, but not quite good enough as we move forward with even more agents coming in the pipeline.

So with that, I'd like to say thanks for participating and listening in on our conversation. We hope it's valuable in the management of your patients in your practice.

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