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How Does Symptom Severity Influence Choice of Frontline Therapy for a Patient with BRAF-Mutated Metastatic Melanoma?

Announcer:
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Dr. Buchbinder:
Hello and welcome. Today we're going to talk a bit about how symptom severity influences the choice of frontline therapy for a patient with BRAF-mutated metastatic melanoma. My name is Elizabeth Buchbinder, and I'm a Melanoma Medical Oncologist from Dana Farber Cancer Institute in Boston.

Dr. Luke:
I'm Jason Luke from the UPMC Hillman Cancer in Pittsburgh. I'm very excited to participate today.

Dr. Buchbinder:
Well, it's great to have you here today and I'm glad to be able to have this conversation. So first, I'm going to present a little about the patient. So this is a patient with BRAF-mutated metastatic melanoma. It's a 58-year-old man who was admitted with confusion and observed on MRI to have a parietal mass. Resection showed melanoma with a BRAFV600E mutation. Systemic imaging showed metastasis in multiple nodes, liver, bone. The LDH was elevated at 2 times the upper limit of normal. And the patient has follow-up as an outpatient after discharge from this admission, and is observed to have lost 20 pounds in the last 2 months, but still plans to return to work full time.

Now one of the biggest questions in our patients with BRAF-mutated melanoma is where to start. So we've got some amazing options in terms of immunotherapy, targeted therapy. But where do we begin? And this trial, the DREAMseq trial really helped to answer this. And what it did is it randomized patients to immunotherapy with combination ipi/nivo versus targeted therapy with combination dabrafenib and trametinib, targeting BRAF-MEK. And what it showed is that long term, when you look at 2 years out, there was a 20% improvement in overall survival in the group that got immunotherapy over those that got targeted therapy, Really demonstrating that patients did better long term with immunotherapy. What's really interesting about this trial, though, is this beginning group where you do see that patients started on immunotherapy initially did a little bit worse, while patients who were started on targeted therapy did well initially and then subsequently did worse with worse long-term overall survival.

There has also been another study, the SECOMBIT trial, which actually looked at a similar question but added a third arm. So in this study, the two treatments that were tested were encorafenib and binimetinib, or ipilimumab and nivolumab with arm A starting on targeted therapy with enco/bini, arm B starting an immunotherapy with ipilimumab and nivolumab. But a third arm added that gave 8 weeks of the encorafenib and binimetinib as targeted therapy, switched to ipi/nivo, and then only it progression, then switch back to targeted therapy. And what was seen is that when you look at the different arms, and you look at how patients did long term, there was a similar long-term benefit for patients who started on immunotherapy, and patients who had this short run-in of targeted therapy and then switched to immunotherapy.

Now why this is important in our cases, in someone with a lot of symptoms, sometimes you don't have time to start them on immunotherapy initially. So it's something to think about.

So one of the things that's been thought about a lot in these patients who have BRAF mutations is can we actually consider adding both immunotherapy and targeted therapy upfront and giving them together? And there have been several trials of triplet therapy testing BRAF-MEK plus PD-1 in combination. And what has been seen as it some of the trials have been positive with a benefit to the triplet. However, the control arm in these trials is targeted therapy alone. And we know from DREAMseq, that long-term patients do better starting an immunotherapy. And in addition, in all of these cases, we're looking at just PD-1 alone, where based on

DREAMseq, you would probably be considering combination immunotherapy as opposed to single agent PD-1 inhibition alone in a patient like this, if you're going to go with the immunotherapy approach, suggesting that although these triplet regimens may have shown some benefit in these trials, how we use them in clinical practice is still kind of yet to be determined with most of us not using a ton of these in the front line.

So the question is, do you start directly with immunotherapy? And I think a lot of this has to do with patients. But actually, maybe I'll pause here, and we can have a bit of a discussion about this patient and where we might start. So Jason, I don't know if you want to discuss this patient a bit?

Dr. Luke:
Yeah, absolutely. Thanks. And it is a complicated situation right now. You know, to rehash, we recognize the patient was diagnosed with brain metastasis de novo and had substantial clinical decline in the context of the management of those brain metastases. So this patient certainly has very high-risk disease; we generally think of brain metastases as the highest risk disease. They also had elevation of the LDH. And so both of those are poor risk factors. And I think we have to take that into account. You know, in that scenario, then based on the DREAMseq data, we would think that trying to get the patient to immunotherapy as quickly as possible would really be our priority. That being said, if the patient is declining too rapidly, we know we'll get a rapid response from BRAF-targeted therapy, and then perhaps could have the opportunity to salvage the patient with immunotherapy thereafter.

So I think we would need to talk through these issues and really try to tease out what this would mean for an individual patient, how would it impact on their lifestyle? We noted from the case the patient still plans to go to work. And so, what would that mean, in terms of which treatments? What I would say is that I would try to get this patient to immunotherapy as quickly as might be possible. But I wouldn't necessarily be dogmatic about it here. It could be the case that running in targeted therapy for some number of a month or two or something like that, in order to allow the patient to optimize their performance status, and then going back to combination immunotherapy really could be a reasonable way to go. I would be unlikely to use the triple regimen here, because of really the modest benefit that was only seen in some studies, as well as relative substantive toxicity that was seen. Rather, I would probably either just jump into combination immunotherapy or perhaps run-in targeted therapy for a little while, and then switch to immunotherapy thereafter.

Dr. Buchbinder:
So I completely agree. This is a patient that I am absolutely at some point going to be giving full dose ipilimumab with standard nivo, at some point because of the brain metastases. And because of the fact that with, one, you're very concerned that there could be additional brain metastasis that arise. Whether that is after a brief run-in of targeted therapy in order to control symptoms and control disease, this is someone I'm very concerned about with the high LDH, the brain metastasis, and the amount of disease. Timing for that depends a lot on the conversation with the patient, and whether – so for us also, a big part of this is whether they're still in the hospital, still on steroids after surgery for their brain met, because those are patients that you're really going to be thinking about targeted therapy upfront in order to get them off the steroids from postop for the brain met. And then also in order to get them out of the hospital where unfortunately, we cannot really give immunotherapy in the hospital because of factors associated with that. So I agree.

Dr. Luke:
Yeah, and I think one point to emphasize that we didn't show data for but the long-term outcomes for patients with brain metastases who get ipi/nivo and go into response is truly excellent. And so, for that reason, we try to get all patients who have brain metastases to ipi/nivo combination at some point. And so whether that's right away, or after the BRAF inhibitor, I really can't emphasize enough that PD-1 monotherapy is not really the appropriate choice for such a patient. You need to get them to ipi/nivo at some point. it's really the only regimen that we have that really can show long-term durable response in those brain metastases.

Dr. Buchbinder:
Alright, thank you. This was an excellent discussion of a difficult patient that we often face, a patient with BRAF-mutated metastatic melanoma with brain mets and aggressive disease. I hope this was helpful.

Announcer:

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