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Patient Case: Tailoring First-Line Treatment for a Patient With Metastatic Melanoma and Impaired Performance Status

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCE curriculum.

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Dr. Tawbi:
Hello. My name is Hussein Tawbi. I'm Professor and Deputy Chair of the Department of Melanoma Medical Oncology at MD Anderson Cancer Center, and I'm here today to discuss with you a specific case on how we tailor first line treatment for patients with metastatic melanoma and potentially impaired performance status.

So here's a 65-year-old lady who developed metastatic disease after having stage IIIB and being treated with adjuvant nivolumab. About a couple of years later, she presented with lung and lymph node metastases. She was checked for brain MRI and was negative. We note that her performance status is somewhat limited. Does have a BRAF mutation and your typical comorbidities for this age.

What would you choose for this patient? NIVO+RELA, NIVO+IPI, PD-1 monotherapy, or BRAF and MEK inhibitors? We now know that combination immunotherapy is advantageous over both PD-1 and BRAF/MEK, and in this case, we could choose nivolumab and relatlimab for this patient because she does not have brain metastases or other comorbidities, and at this point, has only M1b disease. So we'll kind of walk through how we arrive to that conclusion.

This is CheckMate-067 data that's really governed how we treat patients with melanoma for a decade, IPI+NIVO has an advantage over both single agent PD-1 and CTLA-4, although we know that that's not a statistically significant survival advantage, but the median survival is about 72 months, as you can see from this data.

We know that we do this, but we also induce about 60% grade 3/4 toxicities, which is a lot to handle by most patients. We have learned how to manage them, but they are still not easy to manage.

So nivolumab and relatlimab really emerged based on this phase 3 trial, RELATIVITY-047, where it compared this combination to single agent PD-1, and the primary endpoint was PFS by blinded, independent review. And there was an absolute benefit in terms of PFS, a significant decrease in the risk of progression or death, hazard ratio of 0.81, so clearly better than single agent PD-1. There was an impact on overall survival that did not reach statistical significance yet, but certainly about a 20% difference. And we know that that happens with only 22% grade 3/4 adverse events, which is, again, very much advantageous in this population. We also know that the pattern of toxicity is very similar to what we see with single agent PD-1, again, a higher incidence, but relatively similar pattern.

Now when you're choosing first-line therapy, one of the things we immediately think about is, what do you do in the second line? So it's really important to review the data that we have in hand from treatment with these agents in the second line. So we know that PD-1, LAG-3 in the second line has only about a 13% response rate. And this was published by Paolo Ascierto in JCO and RELATIVITY-020. And so in RELATIVITY-047, we wanted to look at what happens with NIVO+IPI after treatment with NIVO and RELA. So we had data

from some patients that were treated in the second line, and you see that NIVO and IPI had a 25% response rate, very much similar to what we see with the combination after single agent PD-1. So you still have a potential to benefit from IPI+NIVO in the second line.

And I think you know, it immediately makes us think, why is NIVO+RELA so much more effective in the first line than the second line? And I think it is related to the mechanism of action. And we discussed how it actually impacts TCR signaling and modulates it. So the higher TCR signaling you have, like you have on the left side, the more likely you are to impact the outcome with the LAG-3 blockade. And that's what we see in the neoadjuvant setting. And so we know that with nivolumab and relatlimab in the neoadjuvant setting, the pCR rate was 57%. And we actually didn't have a lot of toxicity in the neoadjuvant phase; it was only grade 3/4 toxicity of basically 0%. So we know that the pCR rate was improved over a single agent, PD-1 in the neoadjuvant setting, and that's a lot better than even what we see in the metastatic setting.

Now we still have a lot to learn about this combination. We say that brain metastases are currently standard to be treated with IPI and NIVO, but that's simply because we haven't generated the data yet, and we're running this phase 2 trial at MD Anderson looking at nivolumab and relatlimab for brain metastases. Once that data is available, we'll know if this is a combination that has an impact in that space.

So in summary, I think nivolumab and relatlimab really provides an objective response and PFS benefit over PD-1 without a question, and that is with a modest increase in grade 3/4 toxicity, and it's still a lot less than what we see with PD-1, CTLA-4. But we really think that this is going to be a definite first-line option for you to think about. And we're really trying to understand its role in multiple other situations, including adjuvant, neoadjuvant, and potentially in patients with brain metastases.

So with that, I'll thank you for your attention. I look forward to discussing other topics with you.

Announcer:
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