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Analyzing Key Data from LAG-3 Combinations in the Treatment of Metastatic Melanoma

Announcer:
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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 today we're going to be discussing key data from relatlimab and nivolumab in the treatment of metastatic melanoma.

So CheckMate 067, has really been the background for all of our treatments in the last decade or so for metastatic melanoma in the first line. And it had shown that single agent PD-1 is better than single agent CTLA-4, but the combination of ipilimumab and nivolumab potentially offers an advantage. And the 7.5-year survival now shows us that the median survival is about 50%, which is remarkable for our patients with melanoma. But we also know that CTLA-4 works in very specific situations. On one hand, we don't have a survival advantage, but on the other hand, we know that tough situations like brain metastases, the neoadjuvant space, you know, different melanoma subtypes, and even different malignancies can have an impact when you treat with CTLA-4 and PD-1. We also know that that comes at the risk of significant toxicity, almost 60% grade 3/4 adverse events.

So the other thing we know is we lose about half of our patients. So this is good, but it's not good enough. And the search has been on for all of the different potential ways to modulate this interaction with T cells and many, many checkpoints and potential agonists that have been considered, but really, LAG-3 has emerged as potentially one of the most impactful.

LAG-3 is a checkpoint that is co-expressed on activated T cells, co-expressed with PD-1, and leads to even deeper exhaustion than PD-1 alone. So the idea of potential synergy was brought through with some preclinical work that showed that when you do LAG-3 inhibition on its own, it doesn't really have much of an effect, but in combination with PD-1, it really impressively improves tumor control and increases CD8 positive T cells. And this bore out into the first phase 1 trial where the single agent did not really have much of an impact, and the combination showed all of what you would expect in terms of increasing activity. And in the first trial, where this was tried in the second-line setting in patients that were already PD-1 refractory, the response rates were somewhere around 13 and 18% in already refractory patients.

So this was enough of a background for us to take this combination to the first line with RELATIVITY-047, which was the first phase 3 trial, to look at the combination of nivolumab and relatlimab compared to nivolumab alone, with the primary endpoint being PFS by blinded, independent review. So last year at ASCO, I presented the updated data, and the PFS works remarkably better for the combination. The hazard ratio is 0.81, highly statistically significant. The 1-year PFS is 48% versus 37% for NIVO alone. We saw some impact on overall survival with an early separation of the curves and a hazard ratio of 0.80, but really not statistically significant at this point, and there's ongoing kind of analyses of this trial to see the impact.

What we were really pleased to see is the impact on melanoma-specific survival. So you know, melanoma-specific survival was

improved with the combination over single agent, and the confidence interval actually did not cross 1. So kind of indicating a true benefit in this situation.

We looked at all of the possible subgroups, LAG-3 positive, PD-L1 positive, BRAF mutated or not, and all of the subgroups essentially had about the same benefit across the board in terms of PFS, OS, and definitely in terms of objective response. But most importantly, this combination is really impactful in the fact that it is so much less toxic, the grade 3/4 adverse event rate is only 22%. And the profile of that is very similar to what we see with single agent PD-1 in terms of when it happens, the patterns of toxicity, the general distribution of toxicities, perhaps we're seeing a little bit more endocrine toxicities with it, but really not a significant extent.

And we're really excited to see that this is not the only LAG-3 antibody that's around. In fact, we already saw some data from fianlimab and cemiplimab, combination of PD-1 and LAG-3, that's being developed by Regeneron. And that combination also seems to have really interesting activity, again, mostly in the first line, 61% response rate is really impressive tumor control, as you see, and duration of response. But this remains to be confirmed in a randomized trial, and those trials are actually ongoing.

This is also one of many ways that we could potentially target a LAG-3, and again, there are bispecifics in development and different antibodies in development, and we're really looking forward to see some of these come through. LAG-3 is definitely an important checkpoint. It is a validated therapeutic target. It really provides the opportunity to improve upon existing therapies, and really, I like it as a potential backbone for future combinations as well. We still have a lot to learn in terms of response and resistance, and we currently don't have biomarkers in hand, but we're looking forward to be able to do that in the future.

Thank you.

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