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Future Directions: Targeting LAG-3 in Melanoma Treatment

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 I'm here to discuss with you Future Directions: Targeting LAG-3 in Melanoma Treatment.

So LAG-3 was first discovered in 1990 and has been considered a potential checkpoint for a very long time. But it was only until 2012 where some data from Dario Vignali's lab showed that the combination of the PD-1 and LAG-3 is potentially synergistic and can improve T cell function. And shortly thereafter, PD-1 and LAG-3 went into clinical trials. Then in 2002, we had the first combination nivolumab and relatlimab being FDA approved for the treatment of metastatic melanoma.

Here is the primary endpoint from RELATIVITY-047, which was a PFS endpoint by blinded independent review. And it showed unequivocally that the combination of nivolumab and relatlimab was better than single agent PD-1 in preventing progression or death, with a hazard ratio of 0.81, highly statistically significant, and a 1-year landmark of 48% PFS compared to 37%. We know that we've had an impact on overall survival, a 20% decrease but not statistically significant yet, and there is ongoing follow-up for this endpoint.

We also saw that there's a difference in response rate of around 10%. And if you look at these bar graphs, what you really see most evidently is that about 10% of patients that would have been otherwise been progressive disease are now responders. So it almost kind of reverses primary resistance in about 10% of patients.

And when we look at specific endpoints for subgroup analyses, I think PFS and OS are helpful, but really objective responses where you see the most kind of clear differences in these subgroups. And we really haven't seen with LAG-3 being positive or PD-L1 being positive or negative, we haven't seen any real significant differences. They're more prognostic at this point, but the benefit of the combination remains pretty consistent across all these subgroups.

And that is true as well with age, even with advancing age, with different melanoma subtypes, we even seen activity in acral and mucosal melanoma. BRAF mutations didn't matter at all.

So as we think about kind of how LAG-3 works, and what are the future ways to kind of think about modulating this pathway, it's really interesting to note that its mechanism remains not fully understood. And while we thought about MHC class II as the only interaction that matters, there are actually a bunch of different ligands that bind to LAG-3, like galectin-3 or FGL 1, that don't necessarily affect its interaction with MHC class II.

And the more we look at its molecular structure and how it functions, it seems that its most important impact is sequestering zinc and actually preventing this from allowing LCK to phosphorylate ZAP70 and entirely decreasing TCR signaling. So its ability to modulate TCR signaling is probably more relevant for its activity. And we see that as we actually see that with higher TCR signaling, with earlier

settings of the disease, like the neoadjuvant setting where there's probably more TCR activity, we see higher response rate. And we saw in the neoadjuvant setting, a pCR rate of 57% with NIVO and relatlimab.

We're really interested in seeing its potential activity in the brain. We're running this phase 2 trial. Again, we don't know the activity in the brain, and that's simply because this data has not been generated yet. And it'll be interesting to see where that goes. There are multiple ways you could potentially target LAG-3. So we know about the naked antibodies, but we have bispecifics that are being developed. There's even a LAG-3 immunoglobulin fusion protein that's being considered as a molecular modulator of the LAG-3 pathway. So there's a lot that we can potentially learn, but we also have single agent or naked antibodies that may actually have a different impact, like fianlimab being made by Regeneron in combination with cemiplimab, seems to have higher response rates, at least in the single arm trial; now almost 100 patients with 61% response rate. Of course, this needs to be confirmed in a randomized trial, but it is possible that different antibodies may actually have better activity.

So I do think that we have a lot of unanswered questions. We still don't know how the LAG-3 truly functions and its full structure. We don't have biomarkers or response in resistance. Trying to understand its role in brain metastases in the adjuvant setting in rare melanoma subtypes. And I'm excited about actually triplet combinations. This toxicity profile with only 22% grade 3/4 toxicity does allow us to potentially combine other drugs on top of it. So LAG-3 is a novel checkpoint that has unique immune suppressive properties. It's validated as a therapeutic target. It's now FDA approved, and really offers us many opportunities for additional research and potentially additional combinations.

Thank you.

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