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Unlocking Synergy: Exploring the Interaction Between LAG-3 and Other Immune Checkpoints

Announcer:
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Dr. Tawbi:
Hello. My name is Hussein Tawbi. I'm Professor and Deputy Chair of Melanoma Medical Oncology at MD Anderson Cancer Center, and today we'll be discussing Unlocking Synergy: Exploring the Interaction Between LAG-3 and Other Immune Checkpoints.

I think we've all been familiar with checkpoint inhibitors now, really transformed cancer care, and specifically in melanoma, we know of CTLA-4, which is a checkpoint that's very important at the time of T cell activation, and specifically works on naive T cells. We also know of PD-1, which is a marker that's expressed on activated T cells, and we know that blockade of CTLA-4 and PD-1 works really well independently and then potentially synergistically to improve the outcomes of patients with metastatic melanoma. We've been using these drugs as single agents or in combination for over a decade.

Of course, the search has been on for the next checkpoint inhibitor that would be of relevance. And I think LAG-3 has emerged as one of those checkpoints. Importantly, LAG-3 is a marker of exhaustion. It is co-expressed on activated T cells, again, antigen-specific T cells, co-expressed with PD-1. We know that as T cells become further and further exhausted, they become less capable of generating cytokines, of proliferating, of being able to do direct cytotoxicity. And we see LAG-3 as one of the additional markers of exhaustion that gets expressed on T cells after PD-1. And so this has been described, actually many years ago in the 90s as the checkpoint, but really has not been explored therapeutically until some data in 2012 emerged from Dr. Vignali's lab that showed that this the LAG-3 and PD-1 in combination, potentially maybe synergistic and can regulate T cell function. And shortly thereafter, this entered clinical trials. And now in 2022, we had FDA approval of the first combination of nivolumab and relatlimab.

So that study that I mentioned from 2012 from Dario Vignali's lab specifically showed that if you use LAG-3 on its own, you don't actually affect too much, either in terms of tumor control or in terms of CD8-positive T cell increase. But only if you use anti-LAG-3 and anti-PD-1 together do you see that synergistic effect. And this may be truly related to the way that LAG-3 works. The initial assumptions were that MHC class II is the only ligand for LAG-3, and that's the only way it can potentially work. But over time and actually again, from Dr. Vignali's lab, we've learned that LAG-3 could actually affect TCR signaling by affecting the ability of ZAP70 phosphorylation to occur by sequestering zinc and kind of preventing LCK from being able to phosphorylate ZAP70. So it's a really interesting mechanism that seems to be much more relevant for the way that LAG-3 is capable of modulating TCR signaling.

And since then, we've seen, you know, the antibody to LAG-3, relatlimab, which you know, we'll discuss in separate sessions, where it has a clinical activity. But this is a target that has multiple ways of being specifically modulated. There are a bunch of antibodies that are being developed, or even bispecifics that are being developed. There are some soluble antibodies that are also being developed as co-molecules. So there are multiple different ways that you could approach this particular pathway.

And I think really important to know that this is mostly related to the fact that MHC class II is not the only ligand for LAG-3; it turns out that there are multiple different ligands. They actually bind the different domains of LAG-3, and some of their function is not actually really clear at this point. So I think it's very important to know that while we have already explored LAG-3 as a therapeutic checkpoint whose blockade can lead to clinical responses, we really need a lot of better understanding of how the other ligands work and how they could potentially affect this function in the future.

So the take-home message is LAG-3 is a novel checkpoint with unique immune suppressive properties. There's synergy that's been observed preclinically and clinically between PD-1 and LAG-3 blockades. And we think that LAG-3 blockade is not only validated as a therapeutic target right now in combination with PD-1, but it really offers a whole array of potential combinations that could come through and different ways to modulate this target.

Thank you.

Announcer:
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