Transcript Details

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The Potential Impact of RCC Molecular Subtypes on Treatment Outcomes

Dr. Takemoto:

You are listening to *Project Oncology* on ReachMD. On this episode, we'll hear from Dr. David Braun, who is an Assistant Professor of Medicine and a member of the Center of Molecular and Cellular Oncology at Yale Cancer Center. He'll be discussing his research that focused on how renal cell carcinoma molecular subtypes can impact treatment outcomes. Here is Dr. Braun now.

Dr. Braun:

A lot of work has been done really over the past few decades using a variety of modalities: from DNA sequencing, things like whole exome approaches to define the genetics of kidney cancer, to bulk RNA sequencing, conventional RNA sequencing, which has been used to try to identify different subtypes based on gene expression patterns, all the way to single-cell approaches that really try to take one cell at a time and figure what is the composition of the tumor microenvironment. And I think all of those have actually been incredibly valuable and have provided different insights, but I think the one that's sort of most evolved in terms of being closest to the clinic at this point really is using transcriptomic data, bulk RNA seq data, to try to classify tumors into different molecular subtypes.

And this really comes from foundational work led by Drs. Motzer, Rini, the team at Genentech, where they analyzed afterwards a post-hoc analysis of the IMmotion151 trial. This was a phase 3 trial of atezolizumab plus bevacizumab versus the TKI, sunitinib. While overall it was a negative trial—it did not lead to approval of those agents—they did a really remarkable job of identifying—again, using the gene expression patterns—different molecular subtypes. And why that was so important was that there was clear heterogeneity in how those patients did. And so this idea came up naturally: Can you actually use this molecular subtype information to help guide what kind of treatment patients should receive? If they have an angiogenic subtype, they might receive a certain type of treatment, an antiangiogenic; and if they have a more immune subtype, maybe they receive an immune-based therapy.

So that was sort of the hypothesis, and this had led to a lot of development in the field, including prospective clinical trials, but we don't really know how universal these subtypes are, and so this is where our work really came in, to use the knowledge that these subtypes are potentially really important, but let's take them and apply them to something that is an FDA-approved regimen. Specifically, here we applied it to data from the JAVELIN Renal 101 trial, which is axitinib plus avelumab versus sunitinib, so an FDA-approved regimen, and asked: Do these things still hold up? First of all, do these subtypes seem like they're real? Were they just sort of a one-off, a statistical fluke, or do they really seem real? And then the second question is, Okay, if they are real, do they actually subdivide patients in terms of how they do? Is it the same case where certain patients might not need immune therapy and certain patients might benefit, or do all patients sort of act in a similar fashion? And so that was really the background for the work that we did.

As we use our machine learning-based approach to classify these tumors, I think the first thing we recognized is these subtypes, I think, represent true biology. As we sort of looked at these different subtypes and as we classified them, they looked like there were transcriptomic patterns; there are genetic behaviors; we did some other forms of validation. They really looked like they are truly correct and distinct biological subtypes. But then the million-dollar question is, Does that actually help you to choose therapy? Is it that certain patients should get immune therapy and certain patients should not? And I think the answer is no to that question. I think what we had seen—and I think this is a really important finding—is that really, immunotherapy benefitted patients across the board. And it's not that every subtype did exactly the same. There are ones that clearly benefitted more, and there are ones that maybe didn't derive as much benefit. But overall, the group that got immune therapy across all the different molecular subtypes really did perform better and really did have a better clinical outcome.

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And so I think this sort of does a couple things. One is it really reaffirms that immunotherapy is a key component in the treatment of RCC and that it needs to be a component for the majority of patients unless there's a really good reason not to, so every front-line patient should receive an immunotherapy-based combination. And second, I think we still have a lot of work to do in terms of biomarker development, that even as we begin to untangle these different biological subtypes, actually having a tool or a biomarker that's going to help guide us to therapy 1 or therapy 2 is not something that we're there yet.

I think there's hope though. I think there's a number of groups who are starting to explore biomarkers like these in a prospective fashion. I think that's really exciting. But I think there's sort of progress made towards biomarker development, but nothing that's sort of actionable quite yet.

Dr. Takemoto:

That was Dr. David Braun talking about the potential impact of renal cell carcinoma molecular subtypes on treatment outcomes. To access this and other episodes in our series, visit *Project Oncology* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.

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