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Novel Immune Checkpoint Strategies in Non-Small Cell Lung Cancer Care

Dr. Sands:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Jacob Sands, and joining me today to discuss his research on biomarker development for potential combinations of immune checkpoint strategies in non-small cell lung cancer is Dr. Aakash Desai, an Assistant Professor of Medicine at the O'Neal Cancer Center at the University of Alabama at Birmingham.

Dr. Desai, it's great to have you with us today.

Dr. Desai:
Thank you, Dr. Sands, and it's a pleasure to be here with you today.

Dr. Sands:
So let's dive right in. Can you provide us with a little background on your study and what prompted you to conduct this research?

Dr. Desai:
Absolutely. So as you know with non-small cell lung cancer, immunotherapy has really changed the landscape and our management algorithm for patients with advanced non-small cell lung cancer. Particularly, we are using anti-PD-1/PD-L1 axis inhibitors in clinic today, but there's obviously a lot of interest in other immune checkpoints, for example, LAG3, which have been tested in melanoma. There are a couple of trials ongoing and phase 2 studies that have been reported in lung as well as TIGIT, and what we were trying to look at through this study was to understand what other novel immune checkpoints may play a role specifically for non-small cell lung cancer and what would be the potential combination strategies that we could use based on the knowledge that we have.

Dr. Sands:
So there are a lot of potential markers out there. You've highlighted a couple. But what are the methods that you used in conducting this research?

Dr. Desai:
Yes. There are different ways we could look at the immune checkpoints. Obviously, there is the protein-level expression for which we would need a biobank of a lot of samples. The other things that we could have looked at was using some of the RNA expression or differential gene expression data, and some of that data is available publicly through the TCGA. And so we really wanted to see whether a different type of Omic strategy like transcriptomics using RNA sequencing could potentially inform us on these different novel immune checkpoints and how we can use this data to kind of identify potential combinations.

I think the other reason why it was interesting to me was also because I hope that we do get to a point where we're using proteomic data outside of just ISC-based protein expression, but I think we are already getting some data from RNA-based NGS on some of the RNA expression in some of our clinically approved NGS testing assays, and so, potentially, if we are able to identify subsets of different cancers on which immune checkpoints are overexpressed or underexpressed, we could utilize some of this knowledge to target IO combinations in a biomarker-based fashion.

Dr. Sands:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Jacob Sands, and I'm speaking with Dr. Aakash Desai about his research on the potential use of combination immune checkpoint strategies in the treatment of non-small cell lung cancer.

So, Dr. Desai, we talked a little bit about the methods. Let's dive into some of the results. What were some of the key findings in your study?

Dr. Desai:
So, as I mentioned, we analyzed the differential gene expression of some of the immune checkpoint targets using the TCGA data set, specifically the RNA sequencing data, and so we had about 537 primary lung adenocarcinoma samples as well as 59 normal lung tissue samples pre-immunotherapy receipt that we used to study these novel immune checkpoint strategies.

And so coming to the results, we looked at a different array of immune checkpoint targets. I'm going to mention just a few of those which maybe our listeners are more familiar with: CTLA4, TIGIT, LAG3, TIM-3, B7-H3, and IDO1. Some of these were the ones that we looked at the RNA expression, and what we found is that tumors showed significantly increased expression of GITR, CD73, 4-1BB, LAG3, TIGIT, CTLA4, B7-H3, and OX40. These are some of the other immune checkpoints outside of PD-1 and PD-L1 that we know today.

Furthermore, we wanted to see if by using hierarchical clustering, we could identify recurrent patterns of these immune checkpoint gene overexpressions such that we could sort of subset these different tumors into subtypes where one immune checkpoint is more overexpressed compared to another and where we could potentially harness that strategy for treatment. So we did find about six different clusters within this hierarchical clustering model. The first one being IDO1 high. We found a second cluster with CD276 and TNFRSF18, which were mediumly expressed; basically, the protein counterparts of the TNFRSF18 is the GITR, so G-I-T-R.

We also found another subset which had a high Vista, V-I-S-T-A, expression. We had another subset which is CD276 high which is the B7-H3, which is becoming increasingly relevant as we get some new molecules targeting this. And then the last couple of clusters we have were based on the NKG2A high as well as NKG2A and B7-H3 medium expressions, so six different clusters that we identified through these expression analyses.

Dr. Sands:
So you've named a handful of targets there that have been an area of drug development and certainly increasingly important as drugs do come forward. More recently, B7-H3, of course, one that you mentioned there at the end. What do you see as the steps toward this work leading to clinically meaningful landscape changes? I think you've laid a foundation upon which a lot of this drug development can happen. What are the steps in the process of that?

Dr. Desai:
Yeah, absolutely. So as you mentioned very correctly, this is some data that's hypothesis-generating and potentially foundational as it was obtained from publicly available data sets like TCGA, but I think we need to validate this in a larger external data set. If we are trying to introduce these molecules in the post-immunotherapy setting, we potentially need those samples which are post-immunotherapy. As you know, sometimes it's difficult to obtain second biopsies after first-line treatment, but I think those would be really the areas where we need to focus and validate some of this data.

Some of the second-line strategies that are being developed are sort of agnostic to what's going on in the tumor microenvironment or on the tumor itself in terms of expression of these different molecules, but I'm hopeful that in the future, once we see that a patient experiences disease progression after their standard first-line chemoimmunotherapy, either through biopsies or sort of NGS data, that we can then tailor their second-line treatment based on what we find is the resistance mechanism. Is that B7-H3 overexpression where we are identifying there where we could use some of these B7 and H3 targeted agents, or is it more sort of the NKG2A pathway? So trying to really understand the mechanism of resistance and the pathways of resistance, including these immune checkpoints and then treating them with those agents, so sort of thinking about precision oncology within immune oncology as we treat patients, especially those who have progressed or experienced disease progression through chemoimmunotherapy first line.

Dr. Sands:
And could you speak a little bit about how this was RNA sequencing data—and that's a little bit different than I think the genomics people are used to with the initial standard of DNA sequencing. Of course, RNA sequencing is also done in some cases, but can you speak a bit to RNA sequencing in general and the potential scalability of that?

Dr. Desai:
We have a lot of commercial assays out there which use DNA NGS but also RNA NGS. There are actually assays, some of which actually report RNA NGS but reported as research use only, so I think there is the ability to do this RNA NGS and get more RNA sequencing data from our daily practice, and as and when this becomes validated, this could essentially inform us like how we use right now in our patients with targeted therapies, right? Like, we have a patient with EGFR. As we found out, initially, when we started them on crizotinib and then they developed the T790M, which we then have been able to detect, and then came osimertinib. So I'm hoping

that with advancements in RNA-based NGS testing, we could potentially use some of this data on amplification of the gene or overexpression of the gene to then correlate it with potential overexpression of the protein or the immune checkpoint marker and then use that data to tailor our treatments as we already do in oncogene-driven subset of non-small cell lung cancer but potentially bring some of that into the non-oncogene-driven non-small cell lung cancer paradigm.

Dr. Sands:
Now we've had some real advances in the therapeutic landscape, and I think we're at a really critical juncture where we need now a big jump in our biomarker and diagnostics technology, so I think this is such an important step. And I really encourage our listeners to read the full abstract and the data as presented. But we've covered a lot kind of skimming the surface. Before we close, Dr. Desai, do you have any final takeaways that you'd like to leave our audience with?

Dr. Desai:
Well, I think just kind of agreeing with what you just said. We have a lot of different molecules in the pipeline. We have a lot of different targets. I think we now need to think about how do we use the data that we have and the samples that we have to really understand the biology and then tailor our approaches and our clinical trials based on those kind of biomarker-based approaches rather than for all-comers. We found that with the immunotherapy that PD-L1, although not a perfect biomarker, has helped us hone in on the subset of patients that would really benefit from immunotherapy, and so I think we take that as a paradigm of biomarker-based immuno-oncology and then take it to the next level with some of these molecules and checkpoints that we have.

Dr. Sands:
Well, this has been an interesting discussion on an emerging area in non-small cell lung cancer research. I want to thank my guest, Dr. Aakash Desai, for joining me to share his findings. Dr. Desai, it was a pleasure having you on the program.

Dr. Desai:
Thank you so much. It was a pleasure talking to you, and I appreciate the opportunity to share our research.

Dr. Sands:
For ReachMD, I'm Dr. Jacob Sands. 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.