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NSCLC Care: Predicting Response to Dato-DXd with a TROP2 Biomarker

Announcer:
You're listening to *On the Frontlines of Non-Small Cell Lung Cancer* on ReachMD. And now, here's your host, Dr. Jacob Sands.

Dr. Sands:
This is *On the Frontlines of Non-Small Cell Lung Cancer* on ReachMD. I'm Dr. Jacob Sands, and today, I'm joined by Dr. Marina Garassino to discuss new research of a biomarker of TROP2 expression that may be an effective predictor of outcomes in patients with advanced or metastatic non-small cell lung cancer treated with datopotamab deruxtecan, or Dato-DXd. Dr. Garassino is a Professor of Medicine and Director of the Thoracic Oncology Program at the University of Chicago. And I'm especially excited about this one, as I had the pleasure of working with her on this research. Dr. Garassino, welcome to the program.

Dr. Garassino:
Hello, everyone. And thank you for having me to share the exciting data.

Dr. Sands:
So let's dive right in, Dr. Garassino. What does the current therapeutic landscape for patients with advanced or metastatic non-small cell lung cancer look like, particularly after having gotten initial platinum-based chemotherapy?

Dr. Garassino:
This is a very difficult scenario because in the first line, for those patients without actionable alterations, we treat them with immunotherapy-containing regimens, and clearly, we treat the patients with actionable alterations with the corresponding tyrosine kinase inhibitors. The big problem, I would say, of the last maybe 20 years is how to continue after the progression with tyrosine kinase inhibitors or with immunotherapy-containing regimen. There is an incredible amount of antibody drug conjugates that are coming in this space with results that, in my opinion, should be interpreted and should be optimized for the patients. I would say the most three important antibody drug conjugates are the TROP2 antibody drug conjugates. The first one is Dato-DXd, which is a TROP2 antibody drug conjugate that must be internalized to be active. The second is a sacituzumab govitecan that does not need to be internalized to be active. And then there is also patritumab deruxtecan, which is an HER2 antibody drug conjugate that recently received FDA approval, not just in the space of patients with actionable alterations, but also for all patients who are expressing HER2 at the immunochemistry.

Dr. Sands:
So what do you make of the Dato-DXd data in that second line?

Dr. Garassino:
The data of Dato-DXd that were presented more than a year ago at ESMO showed that there was a benefit in terms of progression-free survival. It seems that there is a lot of benefit in patients with non-squamous histology and with actionable alterations. So it's important not to think that this drug is only for patients with actionable alterations, but there is some benefit in the overall population of patients with a non-squamous histology, and we have to understand who they are and how we can select them.

The other part that I think is very important is that although we talk about antibody drug conjugates as though they are all the same, the mechanisms of actions of all of these drugs is different. So I think that we are starting an era where we should talk about TROP2 as the target, but we have to dig very well on the mechanism of action, and we know also that they have a different safety profile. And the different safety profile is, again, related to the fact that if they share the same antibody, they are not the same. So I think we should start to think by drug and not by the big category of antibody drug conjugate.

Dr. Sands:
Now you've highlighted TROP2 as really being a target, so let's look specifically at the new biomarker research that you presented. This was related to TROPION-Lung01; can you start with just explaining the objectives and methodology of that study?

Dr. Garassino:
So the novelty of this new biomarker that is called the QCS-NMR is that, first of all, as I said multiple times before, it starts from the mechanism of action of the drug. And I just want us to remember that Dato-DXd must be internalized, and it's not enough that the Dato-DXd binds to the surface of the cells. So the Dato-DXd must be internalized, and when it is internalized, we can find the TROP2 also in the cytoplasm. And so binding the TROP2 also in the cytoplasm can increase the activity. So the first thing is that the biomarker is taking into account not just the TROP2 on the surface of the cells, but also the TROP2 in the cytoplasm.

And so there is a system that apparently is very complicated, but in reality is very simple. That is, you have to stain your samples with a TROP2 antibody. And then when you test for TROP2, our human eye is not able to appreciate very well the TROP2 in the cytoplasm. And for this reason, we can take advantage of the digital pathology and artificial intelligence, and there is a system that is able to magnify the TROP2 in the cytoplasm and create a ratio between the concentration of the TROP2 in the cytoplasm and the TROP2 in the surface of the cells. The system is very simple because the pathologists in the future will have only to stain for the TROP2. Then there is an automated system that is able to divide the tumor and the non-tumor. And the system is able to magnify the TROP2 and create this ratio that is called NMR. That is a ratio between the TROP2 in the surface of the cell over the TROP2 expressed in the surface of the cell plus the cytoplasm. And the ratio is counterintuitive because with the ratio, you see that less is more; so if the ratio is very low—in at least 70 percent of the tumor cells—we call the test positive. And we call the test negative when it's not expressed in 70 percent of the tumor cells or it is less than a concentration that was found in a training set. And so basically, we will have to stain a slide, put this slide in the scanner, scan the slide, put it in the computer, and the computer will say positive or negative.

So the results that we have are only for the population of patients with non-squamous and not for the population with squamous and with actionable alterations. And these tests are ongoing, but the test is really able to split the population of patients who respond to Dato-DXd with the population who do not respond to Dato-DXd. And what I believe is very important is that there is no prognostic effect or predictive effect on docetaxel. So it seems that at least for the preliminary data, this is really a pure predictive biomarker.

Dr. Sands:
For those just tuning in, you're listening to *On the Frontlines of Non-Small Cell Lung Cancer* on ReachMD. I'm Dr. Jacob Sands, and I'm speaking with Dr. Marina Garassino about her research on a new biomarker for TROP2 that may predict therapeutic response to datopotamab deruxtecan in patients with metastatic non-small cell lung cancer.

Now, Dr. Garassino, you've highlighted a lot of data with that last answer, and so essentially to just summarize that for our audience, it's in the non-squamous, non-small cell lung cancer population where we really saw the benefits within TROPION-Lung01 and that this test that you're speaking about was more specifically looked at tumors without actionable genomic alterations with non-squamous, non-small cell lung cancer. So in that population, what did you see and what was presented as far as those outcomes? How much of a difference did that make with a positive test and being higher intracellular expression?

Dr. Garassino:
Just to give you an idea in terms of progression-free survival, the response rate in the population with TROP2-positive was doubled, was 32.7 percent compared to 16.9 percent. And also, the progression-free survival was more than double, corresponding to about 7 months in the population of NMR-positive, compared to less than 3 months in the population of NMR-negative. So I think that the benefit is really visible and huge because you can double all the outcomes. And the hazard ratio for the progression-free survival was 0.57 and was exactly the opposite for the population NMR-negative. And we are excluding the squamous population. So the training set was done in the population that was just with non-squamous and without actionable alteration.

Clearly, we all want to know what is happening in the patients with actionable alterations and the patients in the squamous population. The results are ongoing, and the analyses are ongoing, so stay tuned because maybe they will be presented in the next congresses.

Dr. Sands:
Now as we approach the end of our program, Dr. Garassino, any final takeaway points that you'd like to share with the audience?

Dr. Garassino:
I think that docetaxel after 30 years is still the standard of care, which is terrible for our patients because there is not so much activity and the toxicity is important. So I think that we are seeing an incredible amount of new drugs that are coming. I think we should work to redefine the targets and the biomarkers to personalize as much as we can the treatment for our patients. I think that this was the story of non-small cell lung cancer, and working on personalizing the treatment was crucial to improve the treatments. And so I really hope that

we will have a spectrum of fantastic drugs that will be able to improve the outcomes of our patients.

Dr. Sands:
With those key takeaways in mind, I want to thank my guest, Dr. Marina Garassino, for joining me to discuss a normalized membrane ratio biomarker of TROP2 that may predict clinical outcomes involving datopotamab deruxtecan, like what we saw from this data looking at TROPION-Lung01. Dr. Garassino, it was wonderful having you on the program.

Dr. Garassino:
Thank you so much for having me.

Announcer:
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