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Emerging Therapeutic Developments in Non-Targetable Metastatic NSCLC

Announcer:
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Dr. Liu:
Welcome to CME on ReachMD. I'm Dr. Stephen Liu, and I'm joined by my colleagues, Dr. Joshua Sabari and Dr. Susan Scott. Today, we'll discuss emerging treatment options in non-targetable, metastatic non-small cell lung cancer—those without an actionable genomic alteration.

Josh, let's start with you. What's your impression of where, if at all, Trop2-directed ADCs are going to fit in the management of non-small cell lung cancer?

Dr. Sabari:
Yeah, Stephen, thanks. So it's been quite a wild ride for Trop2. We know this is a biomarker ADC that is non-responsive to high levels of Trop2 expression. We see responses in low, intermediate, and high. So really, we don't have an effective biomarker to date.

TROPION-Lung01 looked at this drug, Dato-DXd versus docetaxel in the second-line setting. Positive for PFS but unfortunately negative for overall survival. It was interesting, if you look at the squam population, hazard ratio of 1.2, it's really harming that patient population. We'll have to see where these drugs move into the frontline setting.

Dr. Liu:
I think it's an interesting biomarker, really looking at the uptake of the drug, not just expression of the target, because we know Trop2 IHC, not really predictive of benefit. But because this ADC requires internalization to really break that linker and deliver the payload, this new biomarker using digital pathology and AI really allows us to see how much of that receptor is being trafficked into the cell. And that's probably a better predictor. And so far what we've seen is that it does seem to predict response. I think we need prospective data, I think we need more data, but I'm optimistic that the biomarker will help us deliver these drugs where they're going to be most effective.

Dr. Scott, are there any other therapies emerging in this space that appear promising? What about sac-TMT, maybe just the future of Trop2 in non-small cell lung cancer?

Dr. Scott:
Absolutely. I think we've got several Trop2 ADCs in the pipeline. Sacituzumab tirumotecan is another topoisomeraseI payload Trop2 ADC. So this one is also being looked at in the frontline. So we're seeing some promising activity. Increasing overall response rate with higher PD-L1 level, so something that we're excited to look at as time goes on. It's being combined with immune checkpoint inhibitors in the OptiTROP study, and something that we're looking forward to seeing. Hopefully it's safe to give these drugs with immunotherapy in the frontline, and we need to see if they can replace chemotherapy for patients that need that.

Another option is datopotamab deruxtecan, as we've talked a lot about. The TROPION-Lung02 study looked at datopotamab plus

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pembrolizumab with or without chemotherapy at a couple of different doses in several different cohorts. This did demonstrate pretty good safety and tolerability as well as activity, both with and without the combination of the two cytotoxics, so datopotamab plus chemotherapy.

TROPION-Lung08 is a chemo-free regimen being looked at in PD-L1 high tumors, so this is PD-L1greater than50%, combining datopotamab plus pembrolizumab, looking at progression-free and overall survival. And that study is ongoing but something to look forward to, to see if we can have different cytotoxics or move these ADCs, particularly the Trop2 ADCs, into the frontline. Definitely to be seen.

Dr. Liu:
Josh, do you think this is a winning strategy? What are the future implications of emerging therapies like this in patients with non-targetable non-small cell lung cancer?

Dr. Sabari:
Yeah, I think platinum doublet, carboplatin and pemetrexed, have been a mainstay since the early2000s. Relatively well tolerated as we know how to use them. And I think the ADCs can improve upon that by replacing carboplatin and pemetrexed, but we have to do it with better toxicity. So for me, it's got to be biomarker, biomarker, biomarker. And we have to better understand the tox profile, particularly ILD for some of these deruxtecan-based payloads, the topo I payloads.

Dr. Liu:
I think there's rationale that ADCs may be better partners for checkpoint inhibitors. And if, by using the bystander effect, by disrupting the architecture, can that facilitate more immune-mediated antitumor effects? And could this lead to better long-term survival, to a higher tail? I think that's possible. If it's just an additive benefit that's modest and transient, I don't think that's enough to move the needle. But I'm optimistic, and I do hope that it will lead to survival benefits. But we'll need randomized data to really show that, demonstrate that clearly.

A great discussion, both of you. Unfortunately, our time is up, so I want to thank everyone for listening.

Announcer:
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