## Transcript Details

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**ReachMD**
www.reachmd.com
info@reachmd.com
(866) 423-7849

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Clinical evidence behind emerging targeted therapy strategies in patients with metastatic NSCLC

**Announcer:**
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**Dr. Gubens:**
This is CME on ReachMD, and I'm Dr. Matt Gubens. In this brief lecture, I'll take you through some clinical data evaluating emerging targeted therapy strategies in patients with advanced non-small cell lung cancer.

To start with, let's talk about c-MET. c-MET is overexpressed in about a quarter of patients with non-squamous EGFR wild-type non-small cell lung cancer. We've been hearing some data emerge about telisotuzumab vedotin, or Teliso-V, which is a first-in-class c-MET-directed antibody-drug conjugate. Here, the monoclonal antibody is linked to a microtubule inhibitor payload. And, at least in phase 1 studies, Teliso-V has shown promising activity and a good safety profile.

So at ASCO this year, Dr. Camidge presented the results of the LUMINOSITY trial. This enrolled patients with advanced metastatic non-small cell lung cancer who had prior systemic therapy and who had c-MET overexpression by IHC. The primary endpoint was overall response rate. The cohorts were non-squamous EGFR wild-type and EGFR-mutated patients, and there was also a squamous component.

So the squamous and EGFR-mutant cohorts met stopping criteria, but the wild-type cohort met criteria for expansion in stage 2. And the data showed us that the overall response rate was very impressive for a patient population already treated. A c-MET-high had a response rate of 35%, intermediate 23%. And the duration of response in the 7- to 9-month range. PFS was in the 5.5- to 6-month range, and overall survival in the 14.2- to 14.6-month range.

Safety in this drug, the things that we look out for include peripheral sensory neuropathy, which was seen in about 30% of patients, and some eye-associated symptoms, vision that's blurry, keratitis. Also, we're always on the lookout for the incidence of ILD in any of these antibody-drug conjugates, and this was seen in about 10% of patients. So this is important to follow in all of our ADCs, but including in Teliso-V.

Notably, this is before the FDA and a BLA, based on these data. And even further, there's a phase 3 study accruing that enrolls a similar patient population after first line where they'll be randomized 1:1 to either Teliso-V or standard of care docetaxel. So we'll look forward to those results where the coprimary endpoint will be PFS and OS and will hopefully help registration.

Turning tables, HER3 is a really important target. This is overexpressed in the large majority of non-small cell lung cancer in general, about 83%. But in patients with EGFR-mutated tumors, more like 85% to 100%. Keep in mind EGFR is HER1, so there's a natural kind of family connection here where HER3 is implicated in EGFR TKI resistance. Patritumab deruxtecan, or HER3-DXd, is a HER3 antibody linked to a topoisomerase inhibitor. And the phase 1 data were very impressive, 39% response rate in quite heavily pretreated EGFR

mutated non-small cell lung cancer with a variety of resistance mechanisms to the EGFR TKI.

So this led to HERTHENA-Lung01. In the study design here were patients with advanced progressive EGFR-mutant non-small cell lung cancer. Had already seen TKI, had already seen platinum-based chemo. They got patritumab deruxtecan, and the primary endpoint was overall response rate. And the overall response rate, again, third-line and beyond 30%, median PFS 5 and a half months, overall survival 11.9 months. Also importantly, as we investigate these ADCs, it's always important to see if there's CNS benefit. There was a confirmed CNS response rate of 33%, so very provocative in this patient population that does get brain metastatic disease.

The safety profile is, as we've seen before, there is some side effects like nausea, like fatigue. Really, the only lab-based abnormality we think about is thrombocytopenia. Again, always looking for ILD. Here, the ILD rates in an adjudicated fashion was about 5%, but most of this was grade 1 and 2.

Notably, this drug was before the FDA, and right now the data are actually thought to be sufficient for approval, but there were some issues about manufacturing that are being worked out. So we're hoping to see an FDA approval come through soon, especially since we also have seen some data from the randomized phase 3 HERTHENA-Lung02 trial.

These are patients who had had the EGFR TKI and were randomized to HER3-DXd against platinum-based chemo. Primary endpoint of PFS. We haven't seen the data yet, but according to a press release in September of 2024, this trial has met its primary endpoint of PFS. So potentially a second-line option in this really important area of need.

Well, my time is up. I hope I've given you something to think about. Thanks so much for listening.

**Announcer:**
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