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Overcoming EGFR Resistance With HER3-Directed ADCs

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCE curriculum.

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Dr. Yu:
This is CME on ReachMD, and I'm Dr. Helena Yu. In this brief lecture, I'll take you through some clinical data evaluating the use of HER3-directed antibody-drug conjugates to overcome EGFR resistance in advanced non-small cell lung cancer.

So as you all know, ADCs are a recently discovered class of drugs that include antibody to a tumor target, a linker, and then a chemotherapy cytotoxic payload. And many of these have been developed with the first ones being approved, including trastuzumab deruxtecan, in breast and lung cancer. So in terms of HER3 antibody-drug conjugates, patritumab deruxtecan is the first in class.

And the registrational phase 2 study is the HERTHENA-Lung01 study. And this took patients with EGFR-mutant lung cancer with prior treatment on EGFR TKI and platinum-based chemotherapy and proceeded to enroll them on 5.6 mg/kg intravenous of every 3 weeks of HER3-DXd. And the primary endpoint here on this study was overall response rate.

So in that study, 225 patients were treated at 5.6 mg/kg, and the overall response rate was 29.8% with a median progression-free survival of 5.5 months. The waterfall plot from the study really shows that the majority of patients had tumor shrinkage with treatment, and I think importantly when patients had different mechanisms of resistance to prior EGFR TKI, EGFR dependent, on target, off target, or unknown, they all seemed to have benefit with HER3-DXd. So it did transcend the different mechanisms of resistance.

In regards to safety, we know that these ADCs are a hybrid between targeted therapy and chemotherapy. So we do see some chemotherapy-related toxicities including cytopenias, fatigue, nausea, alopecia. So those are seen with HER3-DXd. A class effect of these different ADCs is interstitial lung disease or pneumonitis. That was seen on the phase 2 study at a frequency of 5%. So present but not as high as what is seen with some of the other ADCs.

Because patients with EGFR-mutant lung cancer often have brain metastases there's great interest in understanding how these novel targeted therapies may affect disease in the brain. And so on the HERTHENA-Lung01 study, about 40% of patients did have known brain metastases, but a subset, 30 of them, had a brain metastases that was measurable that did not receive prior radiation. And this was to look at intracranial response rate. So in those 30 patients that had measurable CNS disease, the overall response rate intracranially was 33.3%. And the disease control rate was 76.7%, really showing that there is efficacy in the CNS for HER3-DXd.

So there are some ongoing studies with HER3-DXd. One is the ongoing phase 3 study, which is looking at patritumab deruxtecan versus platinum-based chemotherapy after progression on EGFR TKI. So this is seeing whether HER3-DXd might be given in the place of chemotherapy prior to chemotherapy. Another interesting study is the study looking at HER3-DXd in combination with osimertinib. There is some rationale for these oncogene-addicted tumors to continue the targeted therapy while adding on additional therapies. And so this study is also ongoing. And there is also a first-line cohort to see if osimertinib plus HER3-DXd in the first-line setting is an option as well.

There are other drugs in this space. One such drug is BL-B01D1 which is an EGFR-HER3 bispecific antibody-drug conjugate. The primary data from the initial phase 1 was done in China, but it did show that in patients with non-small cell lung cancer, and in particular patients with EGFR-mutant lung cancer, there does appear to be efficacy. So this is definitely an evolving field where we certainly will see more ADCs in this space.

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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