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Biologic Rationale for Targeting HER3 and Role in EGFR Resistance

Announcer:
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Dr. Jänne:
This is CME on ReachMD, and I'm Dr. Pasi A. Jänne, a thoracic medical oncologist from the Dana-Farber Cancer Institute in Boston. Today, I'll provide a brief overview of the biologic rationale for targeting HER3 in advanced non-small cell lung cancer and its role in EGFR resistance.

Now, there are 4 ERBB family members: EGFR, which is the focus of our discussions today, especially EGFR-mutant lung cancer, but the other family members, including HER2, HER3, and HER4, are also often co-expressed on EGFR-mutant cancers. HER3 is expressed in the vast majority of EGFR-mutant lung cancers. It's biologically used to activate PI3-kinase signaling, but genetic alterations in HER3 are not a known resistance mechanism to EGFR inhibitors unlike, for example, HER2.

Prior studies done several years ago looked at the prognostic role of HER3 in lung cancers and found that high HER3 expression was associated with a higher fraction of patients having metastatic cancer, whereas lower expression was correlated with a lower incidence of metastatic cancer. And if you look at patients with stage I and II lung cancer who had only had surgery, those patients in whose cancers expressed high degree of HER3 had a worse overall survival compared to those that expressed a low level of HER3. Now, these studies were done at a time where we didn't do routine genomic testing because those things hadn't been discovered yet. So you have to sort of analyze this data in that light and context.

Now, we can think about resistance mechanism to EGFR TKIs, summarized in the slide, in 4 different categories: mutations in the target of EGFR, so EGFR T790M or C797S for osimertinib; bypass signaling pathways like MET amplification, HER2 amplification, acquired oncogenic rearrangements, sometimes we see ALK or RET rearrangements in resistant cancers; mutations in downstream signaling pathways like in the PI3-kinase or MAP kinase signaling pathway or in the cell cycle, genes; or cell state transformation where adenocarcinomas, where EGFR mutations are found transforming into small cell or squamous cell cancers.

And this study from Memorial Sloan Kettering shows the distribution of these resistance mechanisms following first-line osimertinib or later-line osimertinib and shows that although we find these different categories, there is a significant percentage of patients, especially those treated after first-line therapy, where we do not have a known targetable resistance mechanism. On the right hand, you see an example of squamous cell transformation.

If we look at preclinical models of patient-derived tumor models from those treated with either erlotinib or osimertinib, you can see in red that the vast majority of those cancers express HER3. In the context of this, we've also looked at HER2 expression, and you see some HER2 expression, but it's not as abundant or frequent as HER3 expression is.

HER3 doesn't have an active kinase domain by itself, and upon ligand binding, which is neuregulin, HER3 heterodimers with EGFR or

HER2, and in that way, leads to activation of downstream signaling pathways. And because of its role in other cancers, there's been active area of developing therapies against HER3. Many antibody-based therapies have been tested as single antibodies, including patritumab, which is the antibody component of HER3-DXd, as well as some bispecific antibodies. Here, what we're talking about today are shown on the right side of the slide, antibody-drug conjugate U3-1402, which is the other name for patritumab deruxtecan, or HER3-DXd, where the antibodies conjugated to a cytotoxic chemotherapy payload and in this way specifically delivered to cells that express HER3, and in our case, EGFR-mutant tumors that co-express HER3.

Well, my time is up. I hope you found this overview useful, and thanks again for listening.

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