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Targeting Resistance in *EGFR*m NSCLC with HER3-Directed ADCs in the Community Setting

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Dr. Yu:
Hello and welcome to this educational activity. My name is Helena Yu. I am the research director of the Thoracic Oncology Service as well as an associate attending and medical oncologist at Memorial Sloan Kettering Cancer Center in New York.

Today we will be discussing HER3-directed antibody-drug conjugate therapies for the treatment of EGFR-mutant non-small cell lung cancer. So, let's get started. EGFR-mutant lung cancer represents 15 to 20% of all non-small cell lung cancer and the different driver mutations we see in non-small cell lung cancer you can see on the left.

A lot has happened in regards to drug development in the last 22 years. The EGFR mutation was discovered in 2004 and since that time various generations of EGFR inhibitors have been developed. We've begun to understand mechanisms of resistance to these EGFR inhibitors and more recently we've seen the advent of antibody-drug conjugate therapies for EGFR-mutant lung cancer.

In regards to first-line treatment for EGFR-mutant lung cancer, the standard of care would be osimertinib, which is a third-generation EGFR tyrosine kinase inhibitor. It was compared to earlier generation EGFR TKIs in the FLAURA study and was shown to have better progression-free survival as well as overall survival compared to earlier generation TKIs.

More recently, in the last year, there have been EGFR TKI-based combinations that have been assessed for first-line treatment. So one such regimen is the FLAURA2 regimen which is adding in platinum-based doublet chemotherapy to osimertinib as first-line treatment and that also demonstrated a progression-free survival benefit compared to osimertinib alone. And then there's the combination of amivantamab and lazertinib. Amivantamab is an EGFR-MET bispecific antibody, and lazertinib is a different third-generation EGFR TKI and that combination was also shown to be superior to osimertinib in regards to progression-free survival. We don't yet have the overall survival data for these combinations, but both are likely to be approved options that we could consider for our patients.

So although all patients respond to osimertinib, everyone subsequently develops resistance to therapy. We biopsy patients at the time of resistance to understand why the tumor has become resistant to targeted therapy. When we biopsy patients there can be different subsets of resistance. One such subset is on-target resistance, which means acquired alterations in EGFR like EGFR C797S. Resistance mutations can be off-target, which means acquired alterations or amplification in different bypass signaling pathways. And then, interestingly, we can see something called histologic transformation, which is when an adenocarcinoma becomes a squamous cell lung cancer or a small cell lung cancer and this change in histology drives resistance to targeted therapy.

About half the time we don't see a genomic alteration or histology change that drives resistance. And so, with such diverse resistance mechanisms, a targeted therapy that would be efficacious in all types of resistance is something that would be very valuable.

HER3 is part of the HER protein kinase family, which includes other driver mutations like HER2 as well as EGFR. The HER family

members heterodimerize with HER3 so there isn't signaling from the HER3 receptor alone, it needs to heterodimerize or pair with other receptors, and that heterodimerization leads to down-stream signaling that leads to self-proliferation, cancer cell survival.

HER3 expression also can mediate resistance to targeted therapy where we see up-regulation of HER3 in the acquired resistance setting. In terms of HER3 expression in non-small cell lung cancer, first we don't tend to see HER3 mutations or genomic alterations within non-small cell lung cancer, but we do tend to see HER3 protein expression and that's measured by immunohistochemistry. So, the way that we use IHC is we calculate an H-score which tells us the intensity of staining as well as the percent of cells that are positive and you can see some IHC staining for HER3 in the top right. When we look at HER3 expression within non-small cell lung cancer the degree of HER3 expression is related to both progression or recurrent disease as well as metastatic disease and so it is a negative prognostic biomarker within non-small cell lung cancer. However, because we aren't currently using HER3 expression in a clinical manner, HER3 testing by IHC is not currently recommended as standard of care.

So, when we think about the relevance of these novel HER3-directed therapies, I think that it is very exciting to think about how these different antibody-drug conjugates, including HER3-directed therapies, might be integrated into our clinical practice. Post osimertinib first-line treatment, we don't have any targeted therapies that are currently approved and so to have additional options besides standard cytotoxic chemotherapy would be really helpful.

The first-in-class medication is one called patritumab deruxtecan. The other name for it is HER3-DXd, which is an antibody-drug conjugate that is composed of three parts. HER3-DXd has a fully human anti-HER3 monoclonal antibody, patritumab, and then ADCs always have a chemotherapy payload and in this case it's a topoisomerase I inhibitor payload, so an exatecan derivative. The payload and the antibody are combined, bound together by a cleavable linker. And so when we talk about ADCs, one terminology that we might hear of is something called the drug-to-antibody ratio and that really describes how many molecules of a chemotherapy payload are attached to a single antibody. And so, the higher the drug-to-antibody ratio, theoretically the more potent the ADC might be.

The first study to look at HER3-DXd was a first-in-human phase 1 study that helped assess the ideal dose for the phase 2 study. And here you can see the schema for the HERTHENA-Lung01 study, which is the registrational phase 2 study. The phase 1 study really demonstrated that HER3-DXd can be given safely, and it was focused on patients with EGFR-mutant lung cancer. Similarly, HERTHENA-Lung01 assessed patients with EGFR-mutant lung cancer that had progressed on the most recent systemic therapy. They needed to have been previously treated with both an EGFR targeted therapy as well as prior platinum-based chemotherapy. Patients with asymptomatic treated or untreated brain metastases were allowed to enroll and, while HER3 wasn't assessed prospectively, pretreatment tumor tissue was required for retrospective assessment of HER3 expression.

So the study initially consisted of 2 cohorts: one with a fixed dose of HER3-DXd of 5.6 mg/kg given intravenously every 3 weeks, as well as an up-titration cohort where increasing doses of HER3-DXd were assessed.

After enrollment of a small number of patients based on benefit-risk assessment of the phase 1 data of these different dosing schedules, the fixed dose of 5.6 mg/kg was chosen to complete accrual. So, a total of 225 patients were enrolled at the fixed dose of 5.6 mg/kg and the primary endpoint of the study was confirmed overall response rate by independent central radiology review. You can see the table on the bottom right shows the baseline characteristics of patients on study and they really were consistent with what we see for EGFR-mutant lung cancer with an enrichment in female patients as well as Asian race. Notably, more than half of patients had a history of CNS metastases, which is quite common in EGFR-mutant lung cancer and the study focused on the 2 common sensitizing mutations, exon 19 deletions as well as L858R, and all patients had received prior EGFR TKI as well as platinum-based chemotherapy.

And here you can see the waterfall plot that shows the percentage of disease shrinkage of target lesions on her HER3-DXd. And you can see that the majority of patients did have tumor shrinkage on therapy. The confirmed overall response rate with maximal follow-up was 29.8%. And then on the waterfall plot you can see that patients had different mechanisms of resistance to previous EGFR TKI including EGFR independent, dependent, and unidentified resistance mechanisms and you can see that HER3-DXd was effective in all of those different scenarios.

Importantly, the study authors wanted to assess intercranial efficacy. As I mentioned, this patient population has more than a 50% cumulative incidence of brain metastases. And so, they identified 30 patients that were treated on study that had brain metastases at baseline but had not received prior radiotherapy and so these were measurable CNS lesions. And when looking at intercranial response rate, that was 33.3%, so very similar to the systemic or overall response rate, really demonstrating that this drug has CNS activity. And you can see from the CT images on the right, where you can see complete resolution of a lesion while on therapy.

So, one important thing to understand is to see whether response to HER3-DXd is associated with degree of HER3 expression. So one thing that's important to note is that this study focused on EGFR-mutant lung cancer and the majority of EGFR mutant lung cancers do express some degree of HER3. So there were very few HER3-negative patients that were enrolled. But when you separated out

patients that had a response to therapy, stable disease, or progressive disease, you can see there is complete overlap of HER3 expression between those three groups and so the degree of HER3 expression really does not predict response to HER3-DXd.

When we think about toxicity the important thing to think about with antibody-drug conjugates is that they are a hybrid between targeted therapy and chemotherapy. So they can have chemotherapy-like side effects and that would include cytopenias including thrombocytopenia and neutropenia and anemia, as well as sometimes nausea, vomiting, and alopecia. And then sometimes there can be toxicities that are associated with the antibody, which might be side effects similar to what we see with targeted therapy.

Importantly, when assessing the safety of a clinical trial and a novel therapy I look at the rate of treatment-emergent adverse events that were associated with treatment discontinuation and that was relatively low on this study at 7.1%. You can see that there was cytopenias that were seen. Those were mostly front-loaded in the early part of the study and very few were related or associated with clinical sequelae like clinical bleeding or febrile neutropenia. One important class effect of these antibody-drug conjugates is something called interstitial lung disease or pneumonitis which we know can occur with chemotherapy, can occur with targeted therapy, but does also occur with these deruxtecan backbone antibody-drug conjugates. This was looked at by an independent adjudication committee and the rate of ILD or pneumonitis on study was 5.3%.

So, the registrational phase 2 study is complete with results that had been already presented. What is ongoing is this confirmatory phase 3 study that is focusing on the same patient population, so patients with metastatic EGFR-mutant lung cancer that have received prior EGFR TKI. The notable difference is that this is prior to patients receiving platinum-based chemotherapy. So they were allowed to received TKI and then they were randomized 1:1 to receiving HER3-DXd versus platinum-based chemotherapy, which would be the standard of care off-study. And the primary endpoint of this study is progression-free survival by independent central radiology review, and we haven't yet seen results for the study. It's ongoing.

So, when we think about or when we note the status of patritumab deruxtecan it did have a breakthrough designation and was seeking accelerated approval and the approval of this drug was expected but we note that in June of 2024 this year, the FDA issued something called a complete response letter. And this is important to note that this CRL, this complete response letter, did not identify any issues with the efficacy or safety data submitted, but the drug approval was delayed due to an inspection of the third-party manufacturing facility. And so, we know that remedy of this situation is currently ongoing, and we do expect approval of HER3-DXd in the future.

So, HER3-DXd is not the only HER3-directed antibody-drug conjugate that is currently in development. There is another agent called BL-B01D1 which is a bispecific EGFR-HER3 antibody-drug conjugate. And the initial data was from the phase 1 study that was done in China and that looked at various different solid tumors including lung cancer that was both EGFR-mutant as well as EGFR wild-type. But when focusing on the EGFR-mutant non-small cell lung cancer they treated 40 patients and the response rate was 67.5%. So really a meaningful clinical efficacy in this patient population. And based on this phase 1 completed in China, there is an ongoing global study assessing BL-B01D1 in different solid tumors including EGFR-mutant lung cancer.

In regards to safety with BL-B01D1, similar to HER3-DXd different chemotherapy-related side effects were seen including cytopenia, nausea, vomiting, stomatitis, and alopecia. In regards to treatment-emergent adverse events that led to treatment discontinuation, that was quite low at 3%. And although pneumonitis or interstitial lung disease was rare, it was identified in one case and it was grade 2.

A different agent is SHR-A2009, which is a different HER3-directed antibody-drug conjugate and this also was looked at in patients with non-small cell lung cancer and the vast majority had EGFR-mutations and were previously treated with a third-generation EGFR TKI. Response rate to this drug was 25% in 36 patients treated. And so also looked quite promising and this drug is development is currently ongoing.

In regards to adverse events, in this initial phase 1 there weren't any dose-limiting toxicities that were seen up to the highest dose assessed. In regards to treatment-related adverse events very similar profile with some cytopenia seen as well as nausea, vomiting, alopecia, and fatigue. And the rate of treatment-related adverse events leading to treatment discontinuation was 7.1%.

So, a lot of us have a lot of excitement of how these HER3-directed antibody-drug conjugates will improve clinical outcomes for our patients with EGFR-mutant lung cancer. So, our standard of care treatment algorithm presently is to proceed with a third-generation EGFR TKI that could be with cytotoxic chemotherapy or without. After progression on osimertinib, if chemotherapy wasn't used in the first-line setting, you can use chemotherapy in the second-line setting, but after that there aren't any targeted therapies that are approved in that later-line setting. And so our options really are just cytotoxic chemotherapy to have different antibody-drug conjugates including HER3-DXd. And some of these other agents for use in this space is really an exciting prospect and we look forward to the results of the study that's assessing HER3-DXd compared to platinum-based chemotherapy. Because there is that question about whether we can utilize these therapies prior to standard cytotoxic chemotherapies. And so, when we think about treatment-emergent adverse events I think something that's critical, is to understand what the different class adverse events are and to be able to detect

them properly and be able to manage those adverse events well.

And so, when we think about antibody-drug conjugates and mechanisms of toxicity, the primary toxicity is largely from the cytotoxic chemotherapy payload. That affects both the cell of interest, which is of course the tumor cell, but also can lead to bystander effect and release of that chemotherapy payload to other neighboring cells. And then sometimes there can also be toxicities that are related to the antibody and so, for example, for HER2-directed antibodies you can see cardiotoxicity because of HER2 expression on cardiomyocytes.

Here is an illustration of the bystander effect where typically we see an ADC get internalized after binding to the target antigen and then should be entering the tumor cell and then cleaved with the payload being released while inside the tumor cell, but then they're can be payload released from either the dying tumor cells or prematurely released that does kill adjacent cells and that's where we see some of the toxicity with these ADCs.

In regards to a very important toxicity that is, as I mentioned before, pneumonitis or interstitial lung disease, again this is relatively rare but also a class effect of these deruxtecan backbone ADCs and it's just really critical to have a high suspicion for this, and to diagnose it early because patient outcomes are best when treatment is immediately implemented.

And so, in terms of workup for suspected ADC-related interstitial lung disease, I think the first thing is that, especially in lung cancer, it can be a very challenging diagnosis because the majority of our patients do have shortness of breath and cough and respiratory symptoms. But really, I counsel my patients if there is a change from baseline in terms of your respiratory symptoms, I would just, be very quick to hold the antibody-drug conjugate while we're trying to gather more information. So, if your ever have a suspicion for ILD, you hold the antibody-drug conjugate. You look out for other causes of potential infectious or inflammatory changes and that typically means potentially starting steroids or treating infection if appropriate. And then always referral to some of my colleagues like pulmonary to get a diagnostic biopsy or bronchoscopy can be really critical and, of course, further imaging to assess any radiographic findings.

And so, again, when we think about managing interstitial lung disease or pneumonitis it's screening, having an actual suspicion for ILD, scanning at first sign of change in symptoms, synergy with care teams, so reaching out to pulmonary or other colleagues, stopping treatment, and then steroids as our main stay of treatment for pneumonitis. And, typical and similar to grading of other adverse events, we can grade interstitial lung disease or pneumonitis by the CTCAE criteria. And so, if patients have asymptomatic pneumonitis where we see something on imaging when patients feel completely fine, we still hold pertuzumab deruxtecan, but once those radiographic findings resolve, it can be appropriate to resume pertuzumab deruxtecan or HER3-DXd. But importantly, if somebody has symptomatic interstitial lung disease or pneumonitis, we still have to do the same things; stop drug, initiate corticosteroids, think about treating other causes like infection but we don't tend to restart. And so the guidelines currently are if patients have grade 2 or greater pneumonitis, we permanently discontinue HER3-DXd.

In terms of nausea and vomiting with HER3-DXd all of us are very familiar with this toxicity. We give platinum-based chemotherapy and other regimens that induce nausea and so it's really just using the appropriate medications that we use with our other emetogenic cancer therapies. So, dexamethasone, a 5-HT3 receptor antagonist, and an NK-1 receptor antagonist. So and often times with these different ADCs I also do a prolonged steroid taper, which I think can be helpful, but definitely giving antiemetics with therapy is key to managing nausea.

In regards to neutropenia, again we're comfortable with this because we do give cytotoxic chemotherapy. Always worth it to hold or delay dosing if neutropenia is seen. If there's concern for infection, you can give growth factor support as intervention. And then if neutropenia is severe you can always think about giving prophylactic dose growth factor support like Neulasta with therapy.

Febrile neutropenia of course a more serious sequelae where we do have to give G-CSF and of course if there's any febrile neutropenia recommendation would be to administer G-CSF with further doses of HER3-DXd. And thrombocytopenia, again it typically is not associated with clinical sequelae, and you would just need to hold and restart when platelets are at a normal level.

So when I think about the toxicity or the safety profile of HER3-DXd it really is just being aware of symptoms and having a very low threshold for imaging because of that concern for pneumonitis or interstitial lung disease and then just managing the nausea, the fatigue, like we do with chemotherapy supportive measures to help insure that our patients have the best experience on these novel therapies.

And so finally, thinking about shared decision-making and individualized treatment planning, as we all know this is really critical for a lung cancer and for a, when patients have a terminal diagnosis, understanding what their goals are with treatment is really critical. And so, there are, as we know, a wide range of treatment modalities and options and so it really is key to have both buy-in from the patient as well as multiple specialists in order to provide individualized treatment plans for our patients. And that might be considering involvement of a thoracic surgeon, say if we need a PleurX placed or pleurodesis, radiation oncologist if there is a painful bone metastases, and so all of these different specialists can be really critical as part of our treatment plan for our patients. And we know, that

given this multi-disciplinary treatment, is associated with longer overall survival as well as better quality of life outcomes for our patients and so, really critical.

And I think this is a particularly relevant in EGFR-mutant lung cancer where there are oral therapies as well as intravenous therapies, understanding what people's goals are, how able they are to come to the clinic for intravenous treatments. Whether they are concerned about alopecia because of ongoing work commitments really becomes critical. And as the complexity of cancer care increases it's going to be even more important when our patients have more options to really understand what they value and to shape our treatment plans based on their values. And so again, shared decision-making is a fundamental method of care that's central to our individualization of treatment. It ensures optimal care and communication with our patients' and is really, just something that we practice and do on a day-to-day basis. That really is important in our relationships with our patients.

And so again, why do I think that this is important? I think it's important because it allows us to tailor our treatment to the goals and needs of individual patients because an 88-year-old patient that lives in a nursing home is very different than a 36-year-old with young children, who's married that, we're managing with the same disease, say EGFR-mutant lung cancer, and so it's pretty intuitive to state that we won't treat those patients the same and so we do the shared decision-making oftentimes even without acknowledging it overtly.

So to end with a few case studies. case study 1 is a 46-year-old woman with EGFR Exon 19 deletion-positive lung cancer who initially was started on osimertinib with chemotherapy, based on the FLAURA2 regimen, had an initial good response, but subsequently had progression. And this was multisite progression in the liver, bone, and lung and a repeat biopsy showed no additional acquired mutations. So, what is the next best treatment option for this patient?

I think this question has several options that could be potentially correct. Single agent docetaxel certainly is a second-line chemotherapy. I probably wouldn't choose carboplatin-pemetrexed or amivantamab because of the recent use of carboplatin and pemetrexed in the first-line setting. The question notes that there was no acquired mutation, so no acquired MET amplification, so I would not use capmatinib. But in the setting of prior osimertinib and prior platinum-based chemotherapy, if approved, my preferred choice would likely be patritumab deruxtecan and the idea is that the approval will be in this setting.

The second case study was a 63-year-old woman with L858R-positive EGFR-mutant lung cancer with metastases to bone, brain, and lung. She was treated with osimertinib, but then developed clinical progression and then was treated with carboplatin and pemetrexed. She then developed a new pleural effusion as well as dyspnea upon exertion and then a dry cough. She was started in the third-line setting on patritumab deruxtecan and after 3 cycles had a marked improvement in her symptoms with improvement of dyspnea, her cough resolved, imaging showed resolution of her pleural effusion, as well as shrinkage of her pulmonary metastases. And then when she presented for cycle 6 of HER3-DXd she had new onset dyspnea over the last week, and when you checked oxygen saturation it was 87% on room air. She also had a productive cough with some yellow sputum. What is the appropriate next step for this patient? In this case the correct answer is all of the above. Any time there is a concern for ILD or pneumonitis I would immediately hold the potential offending agent, patritumab deruxtecan. You want to treat for other potential causes like infection, so starting antibiotics. Low threshold to start steroids in the setting of these symptoms. And then I would want to refer to pulmonary for further workup and consideration for bronchoscopy or further intervention.

The key takeaways are that HER3-directed antibody-drug conjugate therapies may be a new treatment option for EGFR-mutant lung cancer with prior EGFR TKI exposure and importantly the response, or efficacy, was similar with different mechanisms or resistance to targeted therapy. Management of treatment-emergent adverse events really requires a multi-disciplinary approach with proactive monitoring for pneumonitis and early management of other symptoms like nausea and vomiting. And then finally, shared decision-making is, of course, crucial to ensure that our patient's goals of therapy are included when selecting treatment.

Thanks very much. With that, we will conclude today's activity and thank you so much for your participation.

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