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Unlocking the Potential of HER3-Targeted Therapy: Breakthroughs in EGFR-Mutant NSCLC Therapeutic Approaches

Announcer:
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Chapter 1

Dr. Patel:
With the emergence of HER3 as a pivotal target heralding a new era in precision oncology, we find ourselves on the cusp of a rapidly evolving landscape in non-small cell lung cancer treatment. As HER3-directed ADCs become available, are you ready to usher in their transformative potential in overcoming treatment resistance within your patient population? This is CME on ReachMD, and I'm Dr. Jyoti Patel.

Dr. Jänne:
And I'm Dr. Pasi Jänne.

Dr. Patel:
Pasi, why don't we get started with a case. So, this patient is Lisa, a 43-year-old never-smoker who presented about 3 years ago with a diagnosis of EGFR-mutant lung adenocarcinoma. After evaluation, she unfortunately was found to have metastatic disease, or stage IV, with localized metastasis to regional lymph nodes, as well as bone. She underwent molecular sequencing, which showed EGFR exon 19 deletion. And she was initially treated with osimertinib. She had a pretty dramatic response, but unfortunately 1 year ago, Lisa’s disease progressed, and she was then treated with a combination of pemetrexed and carboplatin. After maintenance pemetrexed, she is now back because of disease progression with metastasis to her liver.

So, Pasi, unfortunately, this is not too uncommon to see in our practices. We know that patients with EGFR-mutant non-small cell lung cancer will eventually progress on a tyrosine kinase inhibitor, even osimertinib. What are some of the main factors that lead to TKI resistance?

Dr. Jänne:
Thanks, Jyoti. Certainly I agree with you that most patients who start on a frontline EGFR TKI inhibition, for example, osimertinib, will ultimately develop resistance. And I think that resistance can come in a couple of different flavors, it can be localized resistance, so there's one area of resistance, where our treatment may include local therapies or local modalities such as surgery or radiation. Or it can be more extensive resistance, as in Lisa's case. And in those situations resistance can be mediated by many different features. Resistance can be due to a new mutation in EGFR itself for example, a C797S mutation that causes osimertinib resistance. It can be due to other pathways that get turned on and can compensate for EGFR inhibition, so for example, MET amplification, HER2 amplification. It can be due to mutations in more downstream signaling pathways such as KRAS or BRAF that prevent the EGFR

inhibition from exerting its normal cellular effects because of those mutations. Or sometimes we see what's called state transformation where the adenocarcinoma that was initially diagnosed, transformed into either small-cell lung cancer or into squamous cell lung cancer.

So, certainly, resistance can come in multiple different varieties, and it's important to try to understand why and what is the mechanism of resistance through repeated sampling of the tumor or through a liquid biopsy if tumor biopsy is not feasible, as understanding the mechanism may help guide the subsequent treatment strategy.

Dr. Patel:
And so, I think you make a number of great points. One of them is understanding if there's histologic transformation. For those patients, we tend to treat them with small-cell regimen, if that's what they show. But what are the other typical outcomes for patients based on the standard of care options available currently?

Dr. Jänne:
Well, current standard of care options would really be chemotherapy. So, if we don't find any targetable resistance mechanisms, in general, we tend to treat patients with chemotherapy. And whether in that treatment process one continues osimertinib and adds chemotherapy to osimertinib, or switches osimertinib to chemotherapy, there is no trial evidence guidance to tell us which approach is better. In general, patients who had a central nervous system metastases and had a great response and subsequently progressed on osimertinib, we like to add chemotherapy to osimertinib to reduce the likelihood of recurrence of central nervous system metastases.

In other instances, for example, presence of a MET amplification, there are multiple studies looking at trying to add a MET inhibitor to osimertinib to see if that can reverse osimertinib resistance, and certainly some preclinical and clinical studies to suggest that that is a feasible approach.

Dr. Patel:
So, we know HER3 is expressed in the majority of lung adenocarcinomas. What do we know about HER3? And what role does it really play in oncogenesis, and potentially in EGFR TKI resistance?

Dr. Jänne:
So, HER3 is expressed on the vast majority of EGFR-mutant cancers. And the mutant EGFR receptor transphosphorylates, or transactivates HER3, which activates downstream signaling pathways, namely the PI3 kinase-AKT pathway. HER3, although expressed in the vast majority of EGFR-mutant cancers, there are no genomic alterations in HER3 that drive resistance to EGFR TKIs, it's often co-expressed and can be transphosphorylated, as I mentioned, by EGFR, also by other mechanisms of resistance, for example, in the case of MET amplification, MET transphosphorylates HER3 and keeps that pathway active in those cancers. So, it's a good potential therapeutic target because it's present in the vast majority of EGFR-mutant cancers.

Dr. Patel:
And so, HER3 because it's overexpressed, is probably something we don't measure or report in our path reports. But certainly, I think because it's ubiquitous, has been a really exciting target in the development of this drug.

Dr. Jänne:
Absolutely. It is not typically measured but because of its ubiquitous nature it can be leveraged for antibody drug conjugates, or potentially other therapeutic approaches by targeting HER3 and using it as a way to anchor a new therapy that's more selective towards EGFR-mutant cancer cells than, for example, normal cells.

Dr. Patel:
I think that's great. In Chapter 2, we'll discuss potential options in third-line EGFR-mutant non-small cell lung cancer. Stay tuned.

Chapter 2

Dr. Patel:
Welcome back. In Chapter 1, we discussed the role of HER3 in EGFR-mutant lung adenocarcinoma, and its role in EGFR TKI resistance.

Let's go back to our patient, Lisa, who's progressed following second-line carboplatin and pemetrexed, now with metastasis in the liver. Pasi, Lisa represents the patients that we saw in the HERTHENA-Lung01 trial. Can you walk us through some of the most meaningful results as presented at World Lung in 2023?

Dr. Jänne:
Sure, so in the HERTHENA-Lung01 trial, patritumab DXd, or often referred to as HER3-DXd, was being evaluated as a single agent in

patients with EGFR-mutant lung cancer, who had previously received treatment with a platinum-based chemotherapy as well as osimertinib. So, similar to Lisa in our case. And what was found in the study was that about 30% of patients had a confirmed overall response with a median PFS of about 5.5 months and a median OS of about 1 year.

What was exciting in terms of looking at the patients who did have a response to HER3-DXd, was that the response was not limited to patients with any particular mechanism of resistance to EGFR inhibitors. So, patients could have had a secondary EGFR mutation, they could have had a non–EGFR-dependent resistance mechanism, for example MET amplification, HER2 amplification, KRAS mutation. Or in some instances, a resistance mechanism was not clearly identified and responses were seen independent of the resistance mechanism, which is, as we had anticipated based on the fact that HER3 is relatively ubiquitously expressed. But it was nice to see that in the clinical trial.

What was also observed in that trial was that about 30 patients of the 225 or so patients in the trial, had baseline brain metastases, who had not received prior radiation therapy. And in those individuals, a third of them, or 33%, had a confirmed central nervous system response with a duration of response lasting a median of 8.4 months. It was perhaps slightly unexpected an antibody drug conjugate, such as HER3-DXd, would have activity in the brain. I think we all think of these as pretty big molecules with potentially the inability to penetrate the blood-brain barrier, but it was certainly a nice thing to see and a nice thing to have additional options other than radiation treatment for patients with progressive CNS metastases.

Dr. Patel:
For those of you just tuning in, you're listening to CME on ReachMD. I'm Dr. Jyoti Patel, and here with me today is Dr. Pasi Jänne. We are here discussing the potential use of HER3-targeted ADCs as third-line therapy in EGFR-mutant non-small cell lung cancer.

So, Pasi, certainly, that was an exciting trial, particularly in this really heavily pretreated population, I think the survival benefits were certainly interesting, and compared quite favorably to our real-world estimates of how patients with EGFR mutations do on third and subsequent therapies. Clearly, the improvement in the outcomes for patients with CNS metastasis, I think, is also worthy of further study and we wait to see in subsequent trials what that looks like.

I guess just one kind of note. Remember, this trial was a dose-finding study and so getting the right dose was an important outcome of the trial. Patritumab deruxtecan is dosed at 5.6 mg/kg, unlike another antibody drug conjugate, trastuzumab-DXd, which is 5.4 mg/kg. But all in all, certainly an interesting and exciting trial.

As we really think about these results, so what are sort of key takeaways, Pasi, for particularly patients with CNS metastasis?

Dr. Jänne:
Well, I think it's a therapy that has efficacy in the heavily pretreated population, where typically in this line of treatment, our comparison would be some other form of systemic chemotherapy, either docetaxel or some other form of treatment. And having the ability to also treat the brain I think, was a pleasant and surprising finding, but certainly something that's great for our patients to have additional pharmacologic agents to treat CNS metastases and not always have to resort to radiation which can have certainly both short-term and long-term side effects.

Jyoti, having seen these results as you consider potential of HER3-directed ADC, entering real-world practice, what did you find interesting about the safety data? And what would you tell your colleagues about how to address these?

Dr. Patel:
So, certainly, I think the toxicities were a little bit different than we had assumed. Primarily this drug is myelosuppressive, so primarily hematologic toxicities. Remember, this is potent chemotherapy that is directed at the cancer cell. But there is certainly some off-target activity. And so, I think we saw anemia neutropenia, and thrombocytopenia. And that was most in the early cycles.

One thing that we've always been worried with ADCs is the development of interstitial lung disease. And patients were excluded if they'd had prior pneumonitis, particularly from the TKI, we'll see it sometimes from osimertinib. But surprisingly, and thankfully in the trial, there really wasn't much ILD at all, and certainly less than other antibody drug conjugates in this space.

When we're talking about third-line options to our patients and how to manage some of these toxicities, you know, I think one piece of information is, yes, you'll still feel like, you know, you're getting systemic therapy that's potent, so definitely you'll have some hematologic toxicities. But generally these are less severe over time with subsequent cycles. We'd ask patients probably to do toxicity checks in the first cycle to make sure that they don't have excessive neutropenia, for example. But overall, I think the drug is pretty well tolerated again, in this heavily pretreated but clinical trial-eligible population.

Dr. Jänne:
Maybe I'll just add to the ILD seen in about 5.5% of patients in this trial, and most of them were grade 1 and grade 2 events, but it is

something to keep in mind and for your patients as we do for other antibody drug conjugates, that any respiratory symptoms, coughing, wheezing, shortness of breath, should be followed up with scans to make sure there's no evidence of ILD. Treatment often with corticosteroids should be promptly initiated if that is suspected in our patients. But a thorough workup needs to be done as well, as it's really a diagnosis of exclusion.

Dr. Patel:
I think that's great. In Chapter 3, we'll discuss future directions of HER3-directed ADCs in non-small cell lung cancer. Stay tuned.

Chapter 3

Dr. Patel:
Welcome back. In Chapter 2, we discussed the role of HER3-directed ADCs in EGFR-mutant lung adenocarcinoma, based on the data from the HERTHENA-Lung01 trial. Pasi, where do we go from here? There are trials looking at second-line patritumab and even combination therapies in the second line. What can you tell us about these?

Dr. Jänne:
Sure. So, the subsequent trials include HERTHENA-Lung02, which is for patients who have progressed solely on frontline osimertinib, so no prior chemotherapy, and are randomized to HER3-DXd at the 5.6-mg/kg dose, or platinum-based combination chemotherapy, cisplatin or carboplatin, depending on which part of the world you practice, and pemetrexed, with the primary endpoint being progression-free survival. And that will really hopefully help establish HER3-DXd as an effective treatment post EGFR TKI treatment.

There are also combination studies looking at HER3-DXd with osimertinib. The rationale for that comes from the fact that EGFR inhibition, if you look at in model systems, actually increases the total amount of HER3 that you find on the surface of EGFR-mutant lung cancer cells. And that increased presence of HER3 allows for greater internalization of HER3-DXd when it's bound to HER3. So it's sort of a dual effect of the two agents. Both have independent activity against the EGFR-mutant cancers. But there may be this interaction whereby osimertinib actually enhances the ability to take up HER3-DXd and through that additional mechanism leads to enhanced efficacy.

And there's a phase 1/phase 2 trial ongoing, evaluating first making sure that can we give full doses of both drugs together without running into major side effects. As you mentioned, osimertinib can lead to ILD, and so can HER3-DXd, so we want to make sure that giving the two agents together doesn't lead to a higher rate of ILD than would be expected by each individual agent. And then it will be evaluated as part of the same trial and in the second-line expansion cohorts, as well as first-line expansion cohorts, giving it together with osimertinib from the very beginning. And so, we look forward to both the HERTHENA-Lung02 and this combination trial to really help define the path of clinical development for HER3-DXd.

Dr. Patel:
And the landscape is certainly changing. What do you think about other second-line options, such as amivantamab plus chemotherapy? Or now we have data about amivantamab plus lazer. Would that be a second-line option? Or ami alone? And certainly, you mentioned before that sometimes people who develop mutations or resistance to osimertinib, develop mutations on EGFR. So, what about the next generation TKIs?

Dr. Jänne:
All of these different approaches are being evaluated. And I think, a couple of things. One is, for example, take MET amplification, where combinations of MET inhibitors are being evaluated with EGFR inhibitors. What we don't know, clinically, is that a better approach than, let's say, using a HER3 ADC? Or using some other combination? What is the best therapeutic approach based on the specific resistance mechanism? And I don't think we completely know that, and hopefully, that'll get defined a little bit more through subsequent clinical trials.

I think the other piece that needs some clarification moving forward is that: are there biomarkers for efficacy for HER3-DXd? And as mentioned before, vast majority of EGFR-mutant cancers express HER3, but at least in the trials to date, the phase 1 trial as well as in the HERTHENA-Lung01 trial, the degree of HER3 expression doesn't completely correlate with efficacy of HER3-DXd. And maybe we need better ways of measuring HER3 expression or whether there are other biomarkers that will ultimately correlate with efficacy of HER3-DXd, or other ADCs, I think remains to be determined. But certainly, I think is a need as we'd like to use or tailor the most effective third-line therapy post osimertinib and chemotherapy to the patients most likely to benefit from them. And that could be some characteristic of their tumor that we, as a community, have not yet defined.

Dr. Patel:
I think that's great. And the other piece of that certainly is that all these decisions need to be made in the context of good communication between the physician and patient. So, certainly, as we now think about sequencing, there may be different tolerances for toxicity in

different settings. There may be wishes for intensification early on vs later. And, you know, it's certainly become much more complicated than it was 10 years ago when there was only one answer. Now, thankfully, we have multiple different promising drugs to think about and how to sequence and personalize them based on not only the tumor, but also on the patient.

Dr. Jänne:
Yes. Certainly having options is great. And I agree with you 100%, that discussing with the patient the different options, not only the efficacy, but also what are the different side effects and is key into making a joint decision about the best path forward.

So, Jyoti, with all the excitement around HER3-directed ADCs in lung cancer, are we on the cusp of seeing similar results in other solid tumors?

Dr. Patel:
So, it seems that HER3 is going to be important across a number of tumors. And certainly, now we're seeing a phase 1/2 trial in breast cancer. Again, this is a population that we have targeted HER2 for a very long time, and so, now we're seeing some early results with HER3 targeting. My assumption is that we'll continue to see this in patients with gastric cancer in the future, but certainly I think this is the beginning of a long string of research into this particular biomarker.

So, Pasi, I've really enjoyed this conversation. Can you offer our learners some practical take-home messages to remember regarding the potential of HER3-directed ADCs for the treatment of EGFR-mutant non-small cell lung cancer?

Dr. Jänne:
Sure. So, I think it's important to recognize that this is a potential treatment option for patients who have been treated with prior EGFR TKIs, and/or platinum-based chemotherapy. We hope the medicine becomes available at some point. It is not yet approved by the regulatory agencies, but there are trials where you can potentially enter your patient if he or she is interested either in one of the trials that I mentioned earlier or other HER3 ADCs or combination ADCs that are being evaluated. So, it is an exciting time to have this potential treatment avenue available through trials but hopefully, at some point soon, available as a regular treatment option for our patients.

Dr. Patel:
So, I'd echo that. The dataset that is most mature, certainly in patients who have received osimertinib and platinum-based chemotherapy. And in that population, this is certainly promising, and certainly compares quite favorably to other standard options, such as docetaxel and ramucirumab. This is a rapidly changing landscape, and so, you know, we may be able to select patients that benefit from HER3-directed therapy earlier, so maybe in the second-line setting or even combination in the first. But we hope this is available for our patients and certainly carries with it promise for improvements in outcome.

And that's all the time we have today. So, I want to thank our audience for listening in and thank Dr. Jänne for sharing his valuable insights It was really great speaking with you today, Pasi.

Dr. Jänne:
Thank you very much. Yeah, I enjoyed it as well.

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