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The Oncogenic Significance – and Promise – of HER3 in Pharmacotherapy

Announcer:
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Dr. Yu:
Hi everyone. Welcome our webcast, titled "The Oncogenic Significance and Promise of HER3 and Pharmacotherapy." My name is Dr. Helena Yu. I'm an associate attending and medical oncologist at Memorial Sloan Kettering Cancer Center in New York, and I'm joined today by my colleague, Dr. Makenzi Evangelist. Dr. Evangelist, do you want to introduce yourself?

Dr. Evangelist:
Sure, thanks for having me. My name's Dr. Makenzi Evangelist, and I am a medical oncologist with New York Oncology Hematology in Albany, New York, and I'm a professor at Albany Medical Center in Albany, New York.

Dr. Yu:
Great. It's a pleasure to have someone that we share patients with often to – you know, to work together on this. So in this webcast, we'll discuss the function and role of HER3 in emerging treatment options for patients with non-small cell lung cancer. Before we get started, let's quickly review our learning objectives. So, upon conclusion of this educational activity, participants should be able to: recognize the role of HER3 in oncogenesis and progression in non-small cell lung cancer, and understand the rationale for HER3-targeted therapeutics; identify HER3-targeted therapies currently in development for the treatment non-small cell lung cancer and their role in therapy; and recognize potential adverse effects associated with HER3-targeted therapies.

Now we'll start the discussion with a case of Dr. Evangelist.

Dr. Evangelist:
Great. So this is a 55-year-old Caucasian female patient of mine, who's a nonsmoker and she presented in December of 2017 with an enlarging right neck mass. Imaging revealed substantial right upper lobe mass, with extensive thoracic adenopathy, and pretty substantial superclavicular and cervical lymphadenopathy. Staging studies showed a solitary metastatic lesion to her right posterior fourth rib, and her brain MRI was negative for CNS metastases, so we biopsied her lymph node and that showed a poorly differentiated adenocarcinoma of lung origin. We received biomarker testing which showed a high PD-L1 of 100% but did identify an EGFR driver mutation – exon 21 L858R alteration. And so, she was started on first-line osimertinib.

Dr. Yu:
Great. So speaking of biomarkers and biomarker testing for patients with non-small cell lung cancer the NCCN guidelines do recommend complete biomarker testing. There are actually 9 actionable driver mutations that have FDA-approved targeted therapies. And so, you know, I think that it really is important, and the best way in my opinion to do it, is using a larger panel that has all of these mutations within the assay. And I really do think that molecular therapies have revolutionized how we treat non-small cell lung cancer,

with the majority of patients with these driver mutations getting targeted therapy in the first-line setting.

Dr. Evangelist:
Absolutely. And we've really learned over the last decade why this matters. It's really changed the landscape for lung cancer treatment, but unfortunately, we only see about half of patients with advanced non-small cell lung cancer and a driver mutation, actually receives biomarker-directed therapy, and despite having 9 FDA-approved lines of therapy for altered non-small cell lung cancer. And so, there's been studies that show that if patients get their biomarker-directed therapy up front, they do better. They have longer survival, and we know from many studies that even if patients have started a good first line treatment, they don't always go on to second line treatment.

And here you can see a breakdown of some of the biomarker testing that was done. NCCN recommends that targeted therapy in 48%, but over 50% of patients received other therapies. And you know, this case was important. We saw 100% PD-L1, but we knew it was the right thing to do, to get her on targeted therapy.

Dr. Yu:
Absolutely. I think PD-L1 isn't enough. We have to wait for those genomic biomarkers. So I guess that brings us to a good question. What do you – what is reflexive at your site, and how do you go about doing molecular testing on your, kind of new visits that you see?

Dr. Evangelist:
Yeah. Right now, we do have reflexive testing in that our surgeons will order it in operable settings, but in advanced settings it's still up to the medical oncologist. You know, tissue remains an issue. We need to have enough tissue acquired not only for treatment but also for enrollment on clinical trials, and so our pathologists don't do reflexive testing. It would be nice if we had that ability but we're still able to do comprehensive testing with NGS, and so that's standard of care for us.

Dr. Yu:
How long does it take for you to get those results back for most of your patients?

Dr. Evangelist:
So, the turnaround time is usually a few weeks. But you know, we really have been trying as a multidisciplinary group to communicate early so that we can get the testing ordered even before they see the medical oncologist.

Dr. Yu:
And then if possible, you try to wait for those results before you implement a treatment plan.

Dr. Evangelist:
Absolutely. I think with this case, she actually was admitted with worsening lymphadenopathy, and it was really difficult to wait, but we were able to get the results back. But had we not, then we will consider doing chemotherapy without immunotherapy until we get those results.

Dr. Yu:
Absolutely, that's my same practice, and I think similar to you, we do actually we do EGFR and ALK as reflexive testing – and KRS as well – but we do have to send off for you know, the full NGS panel. But I think liquid biopsies have helped there as well, right? Because I think the turnaround time there is more like 2 weeks.

Dr. Evangelist:
Yeah.

Dr. Yu:
So sometimes I send both, or if I want the results right away, I prioritize that liquid biopsy testing.

Dr. Evangelist:
I've started doing that, and I think payers are starting to appreciate how important this testing is, and oncologists are starting to realize that, you know, this is the right thing to do, so…

Dr. Yu:
Right. And reimbursement's not an issue.

Dr. Evangelist:
Yeah, yeah. I think the liquid is also a benefit for the patients who are really symptomatic or hospitalized, and their tissue is going to be delayed before it's sent out.

Dr. Yu:

Absolutely. So what happened with your patient?

Dr. Evangelist:
So, she was started on osimertinib and she had a really dramatic response. Because she had the lymph nodes, at 2 weeks, I was able to see a response, which was pretty remarkable. So she had an excellent partial response to therapy. She did have some toxicity which we don't see a lot with osimertinib – some dysgeusia and some loss of appetite – but that responded well to dose reduction, and she was able to stay on the drug. She did about 10 months on, have interval progression. Her primary tumor started to grow. We restaged her with a PET scan, and what was remarkable is that her lymphadenopathy had responded so beautifully to the osimertinib, but she did have some residual uptake in her primary. And so, we chose to keep her on osimertinib but to pursue local treatment with stereotactic body radiotherapy.

Dr. Yu:
That's great. And then it looks like you did biopsy her. And what did you guys find on genomic testing?

Dr. Evangelist:
Yeah, so we did a comprehensive NGS panel, and it did show that she had her original, EGFR mutations plus an acquired on-target EGFR mutation. We didn't see any transformation to small cell, so no histologic transformation. You can see a number of alterations they identified.

Dr. Yu:
Great. So in terms of EGFR acquired resistance, I think – it's interesting, as we get better and better EGFR inhibitors, the spectrum of resistance mechanisms have changed. You know, I would say that with first-line osimertinib, we are seeing less on-target resistance, and – as we've kind of gotten to a better on-target inhibitor, and more of that off-target resistance, and more of that histologic transformation that you mentioned. I think one thing that's important to highlight is that tumor tissue biopsies are the only way that we can identify histologic transformation, so if the suspicion is there it's something that you can see on a tumor tissue biopsy. And then I think the other thing to point out is, when we were dealing with earlier generation EGFR inhibitors, T790M as an acquired mutation really dominated, but here things are very diverse and a lot of the resistance mechanisms are really not seen on these NGS panels. And so, finding a therapy that transcends these different mechanisms of resistance will be important in the future.

Dr. Yu:
And as we both mentioned, I think at progression, similar to at diagnosis cancer care guidelines do recommend a repeat biopsy. I often send off both plasma and tumor tissue biopsy. As you had mentioned, some of the clinical trials require the tumor tissue, but we want results more quickly sometimes, with the plasma testing. And that, you know, the majority of patients – about half – we don't find anything identified and – identifiable on the NGS testing. And that brings us to HER3 and the HER3 protein as a potential mechanism of resistance. So I guess in your practice, when do you re-biopsy and how do you act on those results and how do you treat your patients after osimertinib progression?

Dr. Evangelist:
Yeah, so I also will consider tissue biopsy if there's an accessible lesion or if a patient has a rapidly progressive lesion, then I'm starting to think about histologic transformation and I will also do a liquid biopsy, just because I have control over it and there's a good – a quick turnaround.

Dr. Yu:
Sure. Mm-hmm.

Dr. Evangelist:
And then I would say, in terms of treatment, you know, after that biopsy I'd like to do that with, sort of when patients are progressing but hopefully are not so symptomatic that I need to start treatment right away. I think, obviously, clinical trials are always great to consider if patients are eligible or you have access to them. There are certain mechanisms of resistance where we do see some case reports with potential combination therapies where we can add targeted therapies to osimertinib.

But really, as of now, no approved targeted therapies after progression on osimertinib. And so that really brings us to HER3, and its relevance in the acquired resistance setting, so there is the EGFR family of receptors. We know EGFR and we also know HER2 but there are 2 other HER receptors – HER3 and HER4. HER3 in and of itself, has actually pretty limited intrinsic kinase activity. It's not a driver mutation and really, it doesn't you know, HER3 signaling doesn't itself promote oncogenesis but it often heterodimerizes with other HER family members, particularly HER2 and EGFR, which should both sound familiar because those are driver mutation – genes that have driver alterations in non-small cell lung cancer. And so, in terms of HER3 and oncogenesis, we actually see HER3 overexpression in a number of cancers, including breast, lung and colon cancer. It is, as I mentioned, not oncogenic in and of itself, whether there's a

driver, a mutation or overexpression. But it does promote oncogenic activity. Through primarily PI3K and MAPK signaling. And then interestingly, HER3 overexpression is associated with poorer prognosis and so when it is seen in patients that have driver mutations there are shorter time to disease progression and shorter survival when we see HER3 expression. And then, you know, thinking about as new HER3 treatments are being developed, the real question is whether HER3 expression, or the degree of expression will be a biomarker for those treatments.

And then, specifically looking at HER3 in non-small cell lung cancer, actually the vast majority of tumors do express HER3 and interestingly there is enhanced expression in EGFR-mutant lung cancer and about a quarter of non-small cell lung cancers have very high HER3 expression, so I see scores of 3+. And then again, even in lung cancer, there is decreased time to metastatic progression or recurrence and shorter time of relapse-free survival when we see HER3 expression in lung cancer. And then, I think relevant to this talk, and this discussion, we do think that HER3 expression has a role in resistance to EGFR TKI therapy. We can see, in particular in the acquired resistance setting overexpression of HER3.

Dr. Yu:
And now, maybe to talk about antibody drug conjugates?

Dr. Evangelist:
Yeah, absolutely. We've seen, you know, over the last decade the development past chemotherapy to oral targeted therapies, and immunotherapy, and now we have another class of therapeutics – the antibody drug conjugates. And you know, we're starting to see more and more of these across a number of tumor types. Basically what they are is a way of distributing chemotherapy in a targeted fashion. So, we look at a monoclonal antibody that is linked to a chemotherapy through a linker, and there are a number of different cytotoxic agents that are used in these antibody drug conjugates.

But it allows us to more focus deliver the drug, and that allows us to limit toxicity and hopefully increase the therapeutic index at the drug, at the tumor type.

Dr. Yu:
I'm really excited about this class of drug. I think that sort of – all at once, there's a bunch of different, novel ADCs that we're looking at, and I do think it has promise because it is, as you said, Makenzi, I think a hybrid between chemotherapy and targeted therapy. And so has a lot of appeal for our patients. So, speaking of ADCs, do you have any experience using any of the different ADCs that we have available in non-small cell lung cancer?

Dr. Evangelist:
Yeah, over the last year I've had some experience with trastuzumab deruxtecan after it became approved for patients with advanced, HER2-mutated, non-small cell lung cancer in the second line setting. And so, I've had a little bit of experience with that. And back in the day, I treated patients with trastuzumab who had breast cancer, so I had some familiarity with some of the toxicities that go along with targeting HER2. So as you mentioned, trastuzumab deruxtecan is the only approved ADC that it – you know, for use in non-small cell lung cancer, but one that I'm really excited about is patritumab deruxtecan, which is a HER3 ADC. It's a first-in-class antibody drug conjugate that targets HER3. Actually it's quite similar to trastuzumab deruxtecan. It actually has the same linker, and the same exatecan topoisomerase I inhibitor payload. But of course, the targeted part of it is not a HER2 antibody, but it is a HER3 antibody. So, it has been looked at in several studies, and the first study where this drug was evaluated was a dose escalation study that focused on patients with EGFR-mutant lung cancer after progression on EGFR TKI, and after platinum-based chemotherapy.

So you can see here on this slide, the schema. Patients were given escalating doses of HER3 DXD. And a number of patients – 57 – were, were treated in the dose escalation portion. This is a – something that's familiar to most, the waterfall plot looking at disease shrinkage with patritumab deruxtecan. You can see here that in this EGFR-mutant lung cancer population after chemotherapy, after EGFR TKI, the overall response rate was 39%, the median PFS was 8.2 months. And so these are, you know, quite reasonable efficacy, especially in the heavily pretreated setting. And then, what I think is especially interesting – it might be hard to see, but on the bottom of the slide, you can see that patients had different mechanisms of resistance to EGFR TKIs, including BRAF alterations, C797, MET amplification. And this did seem to transcend those mechanisms of resistance, and really was active in a variety of different cancers, which I think holds a lot of promise when resistance mechanisms are so heterogenous.

Dr. Yu:
So what happens with that case of yours?

Dr. Evangelist:
Yeah, so our patient continued the osimertinib. We tried to reattempt some dose escalation, but we were unable to. She held on and had stable disease, but then was really found to have systemic progression including disease in the abdomen. And so, we transitioned

her to chemotherapy with carboplatin and pemetrexed. She had a short response to treatment, and then had further disease progression, and that's when we sent her down for clinical trial enrollment.

Dr. Yu:
Great.

Dr. Evangelist:
And so she actually did enroll in that study that we just mentioned – the phase 1 study of patritumab deruxtecan. She enrolled late in 2020. She actually did really well. One of the common side effects – remember, this is chemotherapy, so we do see some cytopenias – she did briefly have some grade 3 cytopenia early on in her treatment course. We had a brief interruption and then resumed with a dose reduction with good tolerability.

Speaking of the toxicity profile, you can see here on this slide, that really the safety profile was – indicated that this drug was tolerable and manageable. As I mentioned, we do see some of those cytopenias, so thrombocytopenia, neutropenia – they actually are, kind of enhanced, maybe early on in the treatment, and then actually kind of resolve as treatment goes on. There is some fatigue and nausea which you know, again, this is sort of chemotherapy-related. And then, I think what is always of interest for these ADCs and targeted therapies in general is thinking about pneumonitis. And so, the adjudicated ILD frequency on the phase 1 study was 6%. How does this compare to some of the other ADCs that you've worked with. Have you ever seen pneumonitis?

Dr. Yu:
I have not seen it, but there's a lot of talk about pneumonitis with trastuzumab deruxtecan with breast cancer and lung cancer usage, and it seems to be dose-related. But certainly we have become more familiar with some of these pneumonitises, and interstitial lung disease with some of our targeted agents.

Dr. Evangelist:
And I think what's particularly challenging in lung cancer is that patients always or often have shortness of breath or cough, and so trying to tease out what exactly is disease, what may be infection, what might be inflammation or pneumonitis becomes more challenging, but I do think that in this lung cancer population, although of course ILD exists, it does seem to be at a lower frequency than they have been seeing in breast cancer or sometimes with other ADCs.

Dr. Yu:
So speaking of breast cancer, this drug – patritumab deruxtecan – has been studied in breast cancer. So here you – on this slide, you can see that patritumab deruxtecan, in patients with advanced breast cancer – and they did look at HER3 expression, but as you can see here, that the response rates were fairly substantial despite HER2 expression, I think. And we similarly that the side effects seem to be in line with chemotherapy-induced myelosuppression. But really fairly low rates of ILD.

Dr. Evangelist:
I think that that's an important point to bring up. I think I failed to mention, but in the non-small cell lung cancer study, we did look at HER3 expression to see if that was a biomarker that tracked with disease. And actually, all patients on this study, or all cancers did express HER3 and we didn't really see a clear correlation between HER3 expression and response to treatment. So I think in this instance, the biomarker really is an enriched population, which is EGFR-mutant lung cancer and it does seem to be active in a significant number of patients with that type of cancer.

In terms of future directions there are a lot of ongoing studies with patritumab deruxtecan and other ADCs as well. The ones that are most interesting or intriguing I think are the large, phase 2 study that potentially might lead to approval of patritumab deruxtecan, which actually is – has completed accrual and we're waiting for results there. There is a study in the second-line setting that's randomizing patritumab deruxtecan to chemotherapy, and this after first-line EGFR TKI. And then, I'm very interested about the results from the osimertinib plus HER3 DXD study, where patients are on osimertinib, progress, and then they get the HER3 DXD added in. I think this brings, sort of, us to an interesting, kind of endpoint, where we talk about, you know, where do you see this drug fitting in into our treatment sequencing for EGFR-mutant lung cancer, should it get approved?

Dr. Yu:
Well, I think that the longer we can stay on a more targeted approach – it may not be targeted therapy, but an antibody drug conjugate makes a lot of sense to me – that we would use that.

It is chemotherapy as the cytotoxic agent, and I think it makes sense that it would be in the second-line setting, or after progression of patients who've received up-front chemotherapy with carboplatin pemetrexed.

Dr. Evangelist:

I totally agree. I think that there are a lot of studies that we're awaiting results for, and so I think there's going to be a lot of moving parts. I'm interested to see if the 402 study, combining chemotherapy and osimertinib is positive, because if we use both of those in the first-line setting, I can certainly see something like HER3 DXD fitting quite nicely in the second-line setting. And then, I'd like to see those results with combination with osimertinib, because I think there could be value with continuing the targeted therapy that blocks the driver mutation, but adding in an ADC in that setting.

Great. So I think in terms of practice pearls, that we went over hopefully today HER3 is overexpressed across a range of different cancer types, and boosts the oncogenic activity of other HER receptors. HER3 overexpression is linked to poor prognosis, and linked to treatment resistance in numerous types of anticancer therapy. One HER3-targeted ADC, patritumab deruxtecan, has really demonstrated promising efficacy and safety in patients with EGFR-mutant lung cancer after progression on EGFR inhibitors, and there's some early data showing promise in metastatic breast cancer as well. Overall, patritumab deruxtecan has a tolerable and manageable side effect profile and we're really excited to see these current and future trials read out, that will help us elucidate the precise role in therapy or in sequencing this drug may have a place in – for non-small cell lung cancer and breast cancer patients.

Dr. Yu:
Well, thank you Makenzi, and it was a pleasure to talk to you about this really interesting topic.

Dr. Evangelist:
Absolutely.

Dr. Yu:
And I want to thank the viewers for joining us today as well. I hope that the things that we talked about prove useful in your clinical practice.

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