Transcript Details

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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Keeping Pace in Lung Cancer - Breaking Barriers: Advances in Treating EGFR Exon 20 Insertions in NSCLC

Announcer:
Welcome to CME on ReachMD. This activity, titled **"Keeping Pace in Lung Cancer - Breaking Barriers: Advances in Treating EGFR Exon 20 Insertions in NSCLC"** is provided by **Prova Education**.

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Dr. Wakelee:
Hello, and welcome to this Keeping Pace in Lung Cancer Education Series.

EGFR [epidermal growth factor receptor] exon 20 insertion mutations represent 5 to 10% of EGFR mutations in non-small cell lung cancer. We now have one FDA-approved targeted therapy to treat this subset of patients. Today we're going to discuss the clinical data for this approved therapy and how to personalize treatment for our patients, as well as discuss drugs currently in development.

This is CME on ReachMD and I'm Dr. Heather Wakelee.

Dr. Bazhenova:
And I'm Dr. Lyuda Bazhenova.

Dr. Wakelee:
Lyuda, let's begin with a review of recent clinical trial data on treatment strategies for non-small cell lung cancer with EGFR exon 20 insertion mutations. What can you tell us?

Dr. Bazhenova:
So, for this indication we used to have two agents. Both of them were approved in second line. So, I'll start with the agent that is no longer available to our patients. Mobocertinib, an EGFR tyrosine kinase inhibitor. It was initially evaluated as a single-arm trial, in the patients with EGFR exon 20 insertions who had previously received platinum-doublet. It showed an overall response rate of 28%, and reasonable progression-free survival as well as overall survival. This drug recently was voluntarily withdrawn by the manufacturer due to the data from a phase 3 EXCLAIM-2 trial. This trial did not meet the primary endpoint, and the trial design was comparing first line mobocertinib versus platinum-doublet.

So, currently the only medication they have approved for that indication is amivantamab, which is an EGFR and MET [mesenchymal–epithelial transition factor] bispecific monoclonal antibody. It was evaluated as a monotherapy in the CHRYSALIS trial, which enrolled 81 patients. Overall response rate was 40%, duration of response was 11-month, median PFS [progression-free survival] of 8.3 months. Most common adverse events were rash, infusion-related reactions, and paronychia. Very recently, about a month ago in October, we had a presentation of PAPILLON trial at ESMO. PAPILLON trial, in my opinion, is actually very promising. It's a phase 3 study looking at the patients with EGFR exon 20 insertions newly diagnosed – so, treatment naïve. The trial randomized patients to amivantamab plus platinum-doublet versus platinum doublet alone.

The primary endpoint of the study was progression-free survival, and it showed the progression-free survival to be 11.4 months in

combination arm versus 6.7 months in the platinum-doublet. The difference was statistically significant with a hazard ratio of 0.39. If you look at the overall progression-free survival Kaplan-Meier curves, they separated very early and actually stay separate for the duration of the follow-up. And it's very encouraging that at 18 months, 31% of patients were without progression if they randomized to amivantamab chemo arm, versus only 3% of patients who were randomized to a platinum-doublet.

Responses were also higher in combination arm of 73% compared to 47% with the platinum-doublet. Overall survival was not mature at the time of the data presentation, but it's encouraging to see that the curves were slightly starting to separate. Toxicities – of course when you add drugs together, you are expected to see more side effects. And, in my opinion, toxicities were as expected in amivantamab arm, and we see common EGFR toxicities such as skin dryness, skin rash, paronychia, and diarrhea. MET-related toxicities were also seen, such as edema and hypoalbuminemia.

The one toxicity that was surprising to me, honestly, is higher incidence of neutropenia if you combined chemotherapy plus amivantamab compared to chemotherapy by itself.

Dr. Wakelee:
Yeah, I was really excited when I saw the data from the PAPILLON trial. We know that amivantamab is active in EGFR exon 20 as a single agent, but response rates were okay by itself but not fantastic. It didn't have that sense, like, when you have a classic EGFR mutation and you give a TKI [tyrosine kinase inhibitor] and it's, you know, amazing responses and well-tolerated; it was okay. And, you know, with the PAPILLON data – we've certainly seen other trials of combining chemo plus a targeted agent – but this hazard ratio of 0.4 was strikingly better than we've seen in most of those other trials where we've tried to take an active second-line agent and add it into first-line and hoped to see something. So, I actually was really impressed and felt that, even though we do add in the toxicity, to me, this really felt like it is the new standard for first-line in EGFR exon 20.

With that though, if we don't know the patient has EGFR exon 20, then it's really hard to know that that's the best choice for them. And I think as we talk about EGFR exon 20, it's always so important to emphasize the importance of testing. In this day and age where a lot of people are getting more extensive next-gen sequencing, we'll find it. But, for folks who are still depending on some of the rapid EGFR testing, you might miss the exon 20s if you aren't specifically looking for it. And so, I think that's always an important thing to emphasize. But I felt that with the PAPILLON and the combination of amivantamab and chemo, we've really made a big breakthrough and now have a clear standard first-line.

However, now that we no longer have mobocertinib, and if we bring amivantamab into first-line at the time of progression, then we sort of have a big void. And we know that there are a lot of exciting newer drugs being developed, specifically some of the tyrosine kinase inhibitors, and I was hoping you might be able to go through the data with those.

Dr. Bazhenova:
Absolutely. So, it's actually – I agree with you fully that eventually the patients will progress from the first-line therapy, whatever it may be, and we definitely need to, look for other alternatives. We have 3 tyrosine kinase inhibitors, with some data in that setting: sunvozertinib, zipalertinib, and furmonertinib.

So, sunvozertinib, also known as DZD9008, it's been evaluated in the WU-KONG trials. We had the recent update on WU-KONG6 trial at World Lung, which showed overall response rate of 60%, and most common adverse events, as expected with EGFR TKIs, were diarrhea at about 52% and rash at about 39.

Zipalertinib was another EGFR tyrosine kinase inhibitor, recently published in JCO [Journal of Clinical Oncology], looking at this drug as a single-arm monotherapy second-line trial. Overall response rate was about 39%, duration of response was 10 months, PFS about 10 months. And as expected, again, most common adverse events were rash at about 80%, paronychia at about 30%, and diarrhea at about 30%.

And the last drug that we are looking at is furmonertinib. It's also an EGFR tyrosine kinase inhibitor. Recently data was presented at [World Conference on Lung Cancer], and it's interesting – they presented both treatment naïve population as well as platinum pretreated population, and in the treatment naïve setting, the overall response rate's 70%, and in the platinum pretreated setting looking at two different doses, responses were ranging from 40 to 50%, responses were durable, progression-free survival was very respectable, and again, as with other drugs, most frequently observed adverse events were rash, dry skin, diarrhea, stomatitis, and nail changes.

Dr. Wakelee:
Yeah, it's so exciting to have these agents where we've been trying for so long to get good EGFR exon 20 agents. You know, there was some hope with mobocertinib, but never extreme enthusiasm, because of the response rates and tolerability challenges. Now, with these new agents, with these response rates now into the high 60s, approaching 70%, they start to feel more like the EGFR TKIs we

have for the classic mutations, which to me is really exciting. And I think there will certainly be room for studying them beyond second-line, back into first-line. You know, looking –we have lots of studies to do into the future, but just exciting to see these options.

Of course, we still have the toxicity and the toxicity challenges, especially with the diarrhea. And then with the amivantamab, the skin toxicities, the reactions. So, we have to be mindful that we still have some challenges for our patients. But just a lot of excitement and hope, especially because even though this is a pretty rare subset, there's such a focus on developing new agents.

We also, of course, have data with osimertinib, where at standard dosing, not so great, at double-dosing, we can get some activity, but it tends to be very short lived. So, it's great that we're seeing agents that are really more focused on the exon 20.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Heather Wakelee, and here with me today is Dr. Lyuda Bazhenova. We're discussing advances in treatment strategies for our patients with non-small cell lung cancer with EGFR exon 20 insertions.

Dr. Bazhenova:
So Heather, this is very exciting, and we have a lot of new data. But the question to you is: How do you incorporate clinical trial data in patient care when you see, let's say come this Monday, you see an EGFR, newly diagnosed EGFR exon 20 insertion patient in the clinic, what do you discuss with the patient?

Dr. Wakelee:
It's such an important part of the care that we provide, because you and I, we have multiple jobs. Primary job, of course, is caring for patients and doing the best possible thing we can with them and for them. But we also are engaged in the trials, at the conferences, being on the cutting edge, and so where you bring those two together can be challenging. And certainly, I've had a lot of longer conversations with patients in the last few weeks trying to help them understand this new data that's coming out so quickly.

Where we have opportunities in the US people don't always have in other parts of the world, is because amivantamab is already approved, and of course, chemotherapy is already approved, we do have the option – I haven't tried it yet – but I think we would be able to combine the amivantamab and chemo for our patients, even though that's not a fully approved combination yet, but something we can talk about with them.

So, clearly, we don't have opportunities yet with these newer agents, but we try to keep tabs on where there might still be trials that are open, and opportunities for them. I've definitely had patients come from Northern California down to Southern California where there was a great trial. I know we've had patients go back and forth, and so trying to keep aware of what's available.

There are a lot of challenges around single patient INDs but those are options as well. Usually, though, try to encourage the patients that if they're doing okay in what they're on now, even though something that sounds even better is coming, we don't have to jump to that yet. It's more important that we keep them doing okay, feeling well on what they're on, but with that promise of the future as these new agents get approved, and then hoping that they come through quickly.

So, try to keep patients informed but also keep them balanced in the reality of what we're able to do now. And then if they really are in a situation where we don't have any other alternatives, to then look at what we can do to get access to agents that we don't have easy access to at this particular time.

But it's about that education and the back-and-forth discussions. I don't know if you have different strategies than that?

Dr. Bazhenova:
Yeah. The same, I think. My number one choice is always a clinical trial, if I have an access to that. And I do the same thing – we have patients go to different institutions for clinical trials. But I completely share your impression about PAPILLON trial. I think the response rate is really striking, and the 18 months PFS is certainly what grabbed my attention. And many of those patients with EGFR exon 20 insertions, they're younger patients, so I think for a younger person, that progression-free survival, even if it doesn't result in improvement in overall survival, that also means that I don't have to deliver bad news to the patient and the patient does not have to deliver bad news to their family or their children. So, I think, it's really hard to put the price on that. But I do believe that prolonging progression-free survival is important for our patients.

Dr. Wakelee:
Yeah. Completely agree.

So, it is absolutely striking how quickly the field is moving in opportunities for patients with EGFR exon 20. We just had this exciting data at ESMO 2023 with the chemo plus amivantamab. For patients who are started on chemo already, we've got amivantamab second-line approved. And now we have this pipeline of 3 really promising targeted agents for EGFR exon 20. We've got other opportunities with

antibody–drug conjugates that are looking promising, and a lot of work still being done. So, it's a much more promising time, I think, for this patient population where we've had a lot of challenges with opportunities to what to treat them with in the past.

Dr. Wakelee:
Thank you, Lyuda, for that fantastic discussion of all that's exciting and new going on in the world of EGFR exon 20. And thanks to our audience for participating.

Dr. Bazhenova:
Thank you, Heather. It was a pleasure to be here and discuss that space with you.

Dr. Wakelee:
Great. And as a reminder, be sure to tune into our other episodes in the Keeping Pace series for additional discussions on non-small cell lung cancer.

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