Transcript Details

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Chairperson's Perspective: Precision in Practice: Advancing *EGFR*-Altered Metastatic NSCLC Through Guideline-Concordant, Case-Based Learning

Announcer:
Welcome to CME on ReachMD. This activity, titled "Chairperson's Perspective: Precision in Practice: Advancing EGFR -Altered Metastatic NSCLC Through Guideline-Concordant, Case-Based Learning" is provided by AXIS Medical Education. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Leighl:
Hello, and welcome to this educational activity. I'm Dr. Natasha Leighl, and today I will be discussing strategies for the management of patients with EGFR-mutated metastatic non-small cell lung cancer. So let's begin.

As you know, we've got an incredible wealth of genomic alterations which we can target for our patients with non-small cell lung cancer in advanced disease and even now in early stages. The most common, of course, are EGFR mutations in the tumor for which we have many different targeted therapies and new options. But also, of course, alterations in KRAS, ALK, ERBB2, ROS, BRAF, RET, MET, TRK, and a growing number every year.

It's so important that we get our molecular testing results before we start treatment for our patients, to make sure that they get the best possible precision therapy. Early studies have shown that doing molecular testing and having the results available before starting first-line therapy are clearly associated with improved outcomes. On this slide, you can see that patients where we even just do EGFR and ALK have better outcomes than those patients where we don't test, which I think really reflects the impact of receiving targeted therapy. But also, we've learned that having the test results before we start first line versus later on also is significantly associated with survival.

When we look at testing, it's so important that we look across exons 18 to 21 with the assays that we use routinely to really make sure that we identify all of the possible mutations. I'm really going to focus on the common, classic sensitizing mutations, representing about 85% of the cases that we see, deletions in exon 19, and point mutations in exon 21, the L858R mutation. But of course, it's so important to remember that with NGS testing, we're much more likely to find exon 20 insertions or alterations in exon 20, as well as alterations in exon 18 or uncommon mutations; all of them so important with new treatment options for our patients.

So we've seen incredible changes over the last 20 years. Even over the last 1 or 2 years, things have really changed. Today, the first-line standard, really around the world, has been at least osimertinib or third-generation TKI. This really focuses on intracellular inhibition or targeting that kinase domain which is constitutively activated. But now we, of course, have new combination therapies, adding chemotherapy to targeted therapy, for example, chemotherapy and osimertinib, and, very exciting, non-chemotherapy-containing combinations, such as amivantamab and lazertinib, where we combine extracellular strategies such as an EGFR and MET antibody with the third-generation TKI.

So this, really, for many of us, is where we start. For those with access to third-generation TKIs, the FLAURA study, I think, really did a great job of highlighting how third-generation kinase inhibitors can outperform first- and second-generation TKIs such as gefitinib or erlotinib and likely even drugs like afatinib. We saw that although response rates were the same, progression-free survival was significantly longer, a median PFS of 18.9 months, almost double what we saw with the first-gen TKIs. And I think a little bit to everyone's surprise, we saw improved survival, 38.6 months, compared to 31.8 months with many patients crossing over. In particular, the intracranial activity of third-gen TKIs like osimertinib has really been so important for our patients, that ability to treat brain metastases in our patients and to prevent or delay progression of disease.

Very, very manageable in terms of toxicity, rash, diarrhea, uncommonly low-grade paronychia. But also, we do need to remember that there can be some cardiac effects, such as QTc prolongation. Need to be thoughtful about concurrent medications and cardiac impact. So we do need to keep an eye on our patients' cardiac function. Interstitial lung disease and pneumonitis, thankfully, very, very uncommon. Again, something that we do need to educate our patients about and recognize early.

But what happens after those 19 months are up? And so we've had great data over the last 2 years with the FLAURA2 study and MARIPOSA study. In FLAURA2, chemotherapy, which is normally our subsequent or second-line treatment, was added to osimertinib and compared to osimertinib monotherapy alone in patients with common sensitizing mutations. Classic inclusion criteria, performance status 0 or 1, the classic sensitizing mutations, and patients with stable brain metastases were allowed. Now, they did do brain scans at baseline, but not necessarily regularly routinely after that, especially for patients without brain metastases.

And patients were stratified by whether they were Chinese, non-Chinese Asian, or non-Asian, the type of EGFR mutation, and performance status. Patients were randomized to osimertinib plus pemetrexed and carboplatin chemotherapy or cisplatin for up to 4 cycles with maintenance compared to standard-dose osimertinib alone.

The primary endpoint was progression-free survival, but secondary endpoints include the very important survival, which, of course, means so much to our patients and to us, as well as response rate, duration of response, and others.

As we heard reported last year, we saw a marked improvement which was clinically meaningful in terms of progression-free survival, a hazard ratio of 0.62 with the addition of chemotherapy, compared to osimertinib alone. Median PFS of 25.5 months, compared to 16.7, so of course, very similar to what we saw with osimertinib alone in the original FLAURA trial, in the control arm.

Patient subgroups really benefited across the board, in particular those patients with CNS metastases and EGFR L858R mutations. We've heard about median survival in terms of the second interim analysis. We're still awaiting final data. So far, a median survival not reached in the combination arm, 36.7 months in the osimertinib arm, and a hazard ratio of 0.75, which we hope in future will be significant. But of course, the final survival data are not yet mature.

In terms of toxicities, we know these well: myelosuppression, diarrhea, nausea, and, of course, osimertinib-related toxicities, including rash.

In the MARIPOSA study, this looked at a non-chemotherapy-based approach, so combining amivantamab plus lazertinib, which was compared to osimertinib. And in order to evaluate the contribution of lazertinib, or the contribution of the different components to the amivantamab and lazertinib combination, there's also a small number of patients randomized to the lazertinib arm 2:2:1. Again, same eligibility criteria for this trial, same stratification factors, although the history of brain metastases, yes or no, was also included in the stratification.

The primary endpoint was progression-free survival by blinded, independent radiology review and survival, response, and other endpoints also looked at as secondary endpoints. In particular, patients with and without brain metastases did have routine imaging of the brain.

We saw that for this study, also, with the combination of amivantamab and lazertinib, PFS was meaningfully improved. A hazard ratio of 0.70, median of 23.7 months with the combination amivantamab and lazertinib, and again osimertinib performing as expected, a median of 16.6 months for progression-free survival. We've also heard about the overall survival analysis. Although initially the interim did not meet the prespecified boundary, we have heard now that overall survival has reached statistical significance. The interim analysis showed an OS hazard ratio of 0.77, and we've seen further maturation of the data from there.

Toxicities, a little more intense than osimertinib alone. We do see paronychia in the first hour of the first dose of the first day with the intravenous formulation. We've seen infusion-related reactions in up to about two-thirds of patients. And we do see rash and also venous thromboembolic events. And so for that reason, we do offer these patients low-dose VTE prophylaxis.

These were the survival data that I was referring to. These are now mature, and this was presented at ELCC in 2025 with a significant hazard ratio of 0.75 favoring amivantamab and lazertinib. Median survival not yet reached, but in the osimertinib arm, 36.7 months. Again, performing as we would expect, and these survival curves continue to widen over time.

So this makes things a little complex. Now we talk about osimertinib, which is a preferred option, and also intensified therapy: amivantamab plus lazertinib or osimertinib plus pemetrexed-based platinum chemotherapy. And so, of course, there are a number of key questions. Who should get which? How do we decide? And I think we'll talk a little bit more about how do we choose intensified therapy for a select group of patients? How do we present this discussion? And then the much more difficult challenge of how do we choose between intensified regimens?

Those patients that probably benefit from combination to a greater extent include those with CNS metastases, those with high-volume disease, those with ctDNA in plasma at baseline, so those with a positive liquid biopsy, patients with co-alterations, such as TP53 or PIK3CA, and patients with liver metastases or other high-risk areas of disease. Patients where probably oncologists and patients are much more comfortable with monotherapy: patients with lung-only, low-volume disease, perhaps just a pleural effusion or small bilateral, minimally symptomatic lesions; patients who have a good prognosis and have negative liquid biopsies at baseline – we know that's associated with good outcome.

Now, of course, there are many important patient factors. In order to get intensified therapy, your patient needs to have a good functional status, and they need to want to have this intensified therapy, the potential for better outcomes with the risk of more toxicity and more intense treatment burden. Our patients that have lower functional status, patients that are much more interested in quality and minimal visits to the hospital and minimal treatment burden, those with comorbidities so potential contraindications to chemotherapy, and those where coming to the cancer center frequently and being able to have that circle of care to help manage toxicity is a challenge, those with social barriers, these might be patients that we really do recommend monotherapy for.

And once patients progress on these great new treatments, what's next? It really has become incredibly challenging. And we've moved from that old paradigm of third-generation TKI or osimertinib to platinum-based chemotherapy to a number of different options. There's a lot of interest in development still looking at fourth-generation kinase inhibitors and really looking at accelerating on-target inhibition. So perhaps adding a MET TKI, if there's a new and emergent alteration, such as MET amplification or a new fusion. And also off-target strategies. So adding VEGF and PD-1 to chemotherapy, adding chemotherapy. There's some clinical trials in both of these spaces. And we've heard about some data now with ADCs, HER3 ADCs, MET ADCs and potentially continuing the targeted therapy, and TROP2. And while these consistently improve progression-free survival, we are looking to hear more about the overall survival data and looking at potential approvals in this untargeted approach and space. So lots to watch out for here. Definitely, I think the essential factors are that it's really important to do molecular testing and it's really important to participate in trials.

But there is a treatment that's been clearly shown to do better than platinum-based chemotherapy alone after osimertinib failure, and this is now approved around the world, and this comes from the MARIPOSA-2 study, adding amivantamab to chemotherapy.

So the original study looked at a 4-drug combination, amivantamab, lazertinib, pemetrexed, and platinum, compared to chemotherapy alone, and then a 3-drug arm—this was a much smaller arm—again, to look at the contribution of amivantamab to chemotherapy without lazertinib. So again, it was a 2:2:1 randomization. And the, again, eligibility criteria, patients were to have progressed after osimertinib, have good performance status, stable brain metastases, and again, common sensitizing mutations.

Stratification included how recently patients received osimertinib as first- or second-line therapy, whether patients were of Asian ethnicity, and whether or not patients had a history of brain metastases.

And the main endpoint was progression-free survival by blinded, independent radiology review. But many other secondary outcomes, including ORR, overall survival, and intracranial PFS.

So as you can see, progression-free survival was significantly improved when we added amivantamab or amivantamab and lazertinib to chemotherapy. But the differences between the 2 arms where we added treatment really weren't very different. Now, these aren't direct comparisons, but the hazard ratio for adding amivantamab 0.48 compared to chemotherapy alone and for adding amivantamab, Lazertinib, and chemotherapy, 0.44. And of course, at the risk of increased toxicity, which has led to the drug approval around the world of amivantamab plus chemotherapy as the new standard after patients progress on osimertinib.

What was very interesting was that when we looked at intracranial progression-free survival, amivantamab, of course, a large molecule, we didn't think that it would really improve intracranial progression-free survival compared to chemotherapy. But what was interesting was that both the 4-drug arm, including lazertinib, and the 3-drug arm, not including a TKI, so just amivantamab and chemotherapy, had better intracranial PFS. A hazard ratio of 0.55 for amivantamab plus chemotherapy, and 0.58 for the combination of 4 drugs, including the TKI.

So this is really quite interesting and, I think, speaks to the importance of really understanding that perhaps the blood-brain barrier is not as intact as we think in these patients with brain metastases and prior radiation and other treatments. And also that controlling extracranial disease probably is very important to improving progression throughout the body, including intracranially. And so based on these data, this is a new and very important standard for our patients.

So how do we make it easier? And so in the PALOMA program, we looked at how do we make the journey better for patients? And can subcutaneous delivery improve things? So I had the honor of presenting the PALOMA-3 study at ASCO in 2024 and we published this in the *Journal of Clinical Oncology*, and we showed that subcutaneous amivantamab and lazertinib after osimertinib and chemotherapy in patients with advanced EGFR-mutated lung cancer has the same outcomes clinically, is really noninferior to intravenous amivantamab and lazertinib. We showed the same response rate. We showed actually slightly better PFS with subq amivantamab compared to IV. And in particular, we showed better tolerability. And I'll talk a little bit more about that.

One of the things that we didn't expect to see was a difference in overall survival, but we actually did see a significant difference in overall survival. This was one of our secondary endpoints with a hazard ratio of 0.62.

Very exciting, because this is a potentially better way, of course, to deliver the treatment, and may lead to downstream benefits for patients for reasons that we are still exploring.

Also, very importantly, it improves the patient journey. So we showed that the incidence of infusion-related reactions really decreases, 13% compared to the usual 66%. But again, you know even if you're using IV amivantamab, it's really in that first hour of the first dose on the first day, and often we're able to just interrupt the treatment, let things settle down, and then resume with more premedication.

The other interesting thing we found was that venous thrombotic events, of course a concern with amivantamab and lazertinib, was actually lower when we used subcutaneous treatments. So is it that there's some intravenous or direct irritation when we give the antibody? That might be part of it. But clearly this is an exciting way to move forward, although I think in the meantime, we do recommend that we give prophylactic anticoagulation, both for our patients receiving IV and subcutaneous amivantamab, although you know, clearly subcutaneous is associated with a better safety profile.

We've heard a lot about the TROP2 ADCs in this space, all oncogene-addicted lung cancers. And there was a nice pooled analysis of datopotamab deruxtecan, which is a TROP2 ADC from the TROPION-Lung01 and Lung05 studies. And these pooled patients had actual genomic alterations, including EGFR, ALK, and others, and had received prior treatments, including prior targeted therapies. And this was looking at the dose of 6 mg/kg every 3 weeks. And they showed that in patients with EGFR-mutant lung cancer, the overall response rate was 42.7%, some patients achieving a complete response and a median duration of response of 7 months, a median PFS of 5.8 months. So, very interesting in the pretreated or third-line population.

Very important to remember, with all new drugs, new toxicities, stomatitis, in particular, ocular events, and we do need to be very mindful of interstitial lung disease.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Natasha Leighl, and I'm discussing strategies for managing EGFR-mutant non-small cell lung cancer.

So it's been a very exciting time for our patients with common alterations, but also for our patients with less common and more challenging alterations, including our patients with exon 20 insertions. We've seen now that there have been 2 drug approvals, one dating back to 2021 with second-line amivantamab, based on the outcomes of the CHRYSALIS study. We were really honored to be part of that program. And more recently, in the first-line setting, moving amivantamab up to first line and adding it to platinum chemotherapy, which up until now was the standard of care for these patients.

And these are some of the data in pretreated patients from the CHRYSALIS study. We showed that amivantamab monotherapy in our patients that were pretreated with exon 20 insertion mutations, the overall response rate was 40%, the median duration of response now closing in on 12-plus months, and the median PFS across all patients 8.3 months. In the first-line setting in the PAPILLON study, again, we heard about this at ESMO in 2023. Very exciting. When we add amivantamab to chemotherapy and compare it to chemotherapy in the first-line in these patients, higher response rates, 73%, greater progression-free survival, 11 months compared to 6.7 months, and also better overall survival.

And I'll go into some of the details with the PAPILLON study that's really helped us establish the first line of treatment. These patients, of course, are treatment naïve. They have documented exon 20 insertions, good performance status, 0 or 1, and they were stratified by performance status, the presence of brain metastases, which was allowed, and prior TKI use. Amivantamab was given weekly. The dose a little different, a little higher than what we use in sensitizing mutations. Chemotherapy given in standard doses for the first 4 cycles with pemetrexed and carboplatin. And the primary endpoint, progression-free survival. Again, important secondary endpoints, including response, PFS2, and overall survival. These patients were allowed to cross over to second-line amivantamab, which had reflected the standard of care until this time.

And we can see that in PAPILLON, we saw a dramatic benefit in terms of progression-free survival benefit, a hazard of 0.395, associated with the addition of amivantamab first line. And again, as I mentioned, a median PFS of 11.4 compared to 6.7 months, and also improved overall survival, this sort of with longer follow-up, but a hazard of 0.675, a *P* value of 0.10. So a very clear trend. And this has really led to the regulatory approval around the world.

On the horizon, though, we have a number of exciting new agents with ongoing frontline trials comparing to chemotherapy. These include drugs like zipalertinib, which is being added to chemotherapy versus chemotherapy alone, and a number of exciting new kinase inhibitors, such as sunvozertinib, furmonertinib, and others, where they're being compared in the first-line setting to chemotherapy. One of these, the furmonertinib, FURVENT study, has completed approval, and we hope the others will complete soon. Of course, this is on the background of the recent publication of mobocertinib versus chemotherapy first line in these patients where we did not improve outcome and this had toxicity. But I think we're all very, very hopeful that these new agents, which have superior efficacy and less toxicity, may present new hope and competition on the horizon.

We did hear some updated data from the zipalertinib program at ASCO this past year, presented by Dr. Helena Yu and colleagues, where they demonstrated a confirmed response rate of 35% in their primary efficacy population. In patients that had not had prior exon 20 insertion-directed targeted therapy, it was higher at 40%. But in patients who had had prior amivantamab or other exon 20-targeting therapy, it was 24%. So I think this is promising. The median duration of response, about 8.8 months. So very, very durable. Very well tolerated. The most common adverse events, 7% of patients with anemia, low rate of pneumonitis 2.5%, low rate of severe rash 2.5%, and transaminase, and diarrhea. So really looking forward to these new TKIs entering the therapeutic arena.

So across all of these agents, be they TKIs, monoclonal antibodies, all of these are associated with some clinically relevant EGFR inhibition-associated AEs, whether it's skin, which is of course the most common, lung, GI disorders, ocular. With the addition of chemotherapy, of course, we need to be mindful of blood counts, cardiac events, also, with targeted therapy like osimertinib. And we also need to be mindful of things like stomatitis, edema with MET-targeted therapies, infusion-related reactions, and VTEs. And so it's really important that all of our patients have very specialized care to support toxicity management.

So prophylaxis has really emerged as something that we should all be doing. Not only do we want to make sure that patients have great skin care and great teaching in your clinic as they start these new agents, we also really want to decrease the risk of inflammation, decrease the risk of infection, and really try and keep skin intact to prevent dose reduction, to prevent holding the dose or stopping treatment, and, of course, to improve the journey for our patients. So of course, avoiding hot water and irritants, not scratching, making sure that cleansing products and moisturizers are nontoxic or nonirritating, avoiding the sun, treating underlying skin conditions, and being mindful of things like Staph aureus colonization and treating for that if we need to. Steroids, as we need to. Usually, for most

patients, we don't need topical antibiotics, but we'll talk a little bit more about some of the prophylactic strategies that we've taken, for example, with amivantamab and lazertinib. And of course, for patients with severe toxicity, we do want to make sure that they have either prophylactic treatment with doxycycline. We do want to make sure that they have dermatologic follow-up, and that we do follow these patients very closely.

I think for grade 2 and grade 3 toxicity, it's really important that we're always thinking a little bit ahead. When your patient has a grade 1, colleagues like Nicolas Girard, he really says treat it like a grade 2 rash. If your patient has a grade 2 rash, already start treating it like a grade 3 rash so that we can get ahead of this. Really important to remember that the grade of rash is related to the surface area that it covers, not necessarily the severity. And so of course, if your patient has a more severe grade 1 rash, you're going to want to be escalating the treatment.

So, again, really be very careful. Make sure your patients have moisturizers. Stay away from the sun, high-potency steroids, make sure you look for a Staph aureus superinfection. And for patients that have challenges with this, do involve expert dermatology help. Treat them, for example, with doxycycline or minocycline or other antibiotics as important, as relevant. And then some dermatologists will even be recommending things such as isotretinoin or other things. And so, again, we do try and maintain drug doses through grade 1 and grade 2. But of course, for grade 3, you're going to need to give your patient a treatment break while we get things under control.

There are many other things, of course, that our patients get. They can get diarrhea. Hydrate, give anti-diarrheals. Be very mindful of diet. Sometimes patients, by watching fruit or watching fiber or coffee, for example, they may be able to control their own diarrhea. But do be mindful of this. Make sure that your patients get hydrated as needed. Make sure that you monitor their electrolytes. Octreotide can be helpful, and even things like antibiotics. And of course, always remember your patients are at risk of other things, so always check for C. difficile and other stool pathogens.

And of course, there are many other things: stomatitis, neutropenia, ocular events, cardiac events, lung toxicity, and peripheral edema, most commonly with amivantamab, for example. We'll manage that with compression stockings. But it's really important that you and your team and your patient be very aware of what can happen, to recognize toxicity, and to act early and to really have a network that you can work with to make sure that your patient gets the best possible care. In particular, I really believe, here in Toronto, that our nursing colleagues are among the best people to really help us keep an eye on this and help us manage. In other jurisdictions, it'll also be led by pharmacists as well. But I think there's really a role for a much bigger team than just you and the oncology team to help with this.

We've learned in the COCOON study earlier this year that prophylaxis can go a long way to really helping prevent toxicity for our patients. The COCOON regimen, which involved prophylactic antibiotics for 12 weeks, steroid cream, also vinegar and water soaks or chlorhexidine soaks for patients' nails that were receiving amivantamab and lazertinib really can decrease the risk of skin adverse events and really decrease the severity by more than 50%.

We found that using dexamethasone prophylaxis 8 mg twice a day, starting 2 days before and then ending with 1 dose prior to the usual dexamethasone given with IV amivantamab, really decreased the rate of infusion-related reactions. So if you are using IV amivantamab, until we get access to subq, the SKIPPirr regimen really helps. Published by Dr. Spira and colleagues earlier this year in the *Journal of Thoracic Oncology*.

Also, we've shown that prophylactic anticoagulation really can substantially decrease the risk of VTEs by almost 50% with very minimal increased risk to patients.

So very important to prevent all these with simple and accessible preventative approaches. And I really think that prevention of AEs and patient education and really making sure the whole team is on board to help prevent AEs is the key to better patient outcomes. The SKIPPirr regimen, as I talked about, dexamethasone 8 mg BID, 2 days and 1 day, and then 1 hour before the first infusion. VTE prophylaxis, according to your local guidelines. Dermatologic prophylaxis, 12 weeks of antibiotics, then topical clindamycin lotion, chlorhexidine or vinegar soaks for the nails, and, of course, moisturizer. And so I think this is really important as we move into some of these novel regimens such as amivantamab and lazertinib, which have great anti-cancer benefit but also can cause some more toxicity. And so preventing these is so important.

So my key takeaways. It's really critical to conduct comprehensive molecular testing before your patients start first-line treatment. And

you really need to work with your colleagues, whether it's the people who get the tissue sample, your pathologists, or your molecular team, to really make sure that you get that for every patient, every time. First-line treatment landscape for our patients with advanced EGFR-mutant lung cancer has really evolved. So many great options and a number of guideline-recommended combination therapies that show improved outcomes compared to monotherapy. Of course, adding chemotherapy improves progression-free survival and CNS progression-free survival. Amivantamab and lazertinib improve PFS, overall survival, and CNS progression-free survival. And in our patients with sensitizing mutations that progress on osimertinib, we of course have amivantamab plus chemotherapy as a new second-line approach. For our patients with exon 20 insertions, amivantamab plus chemotherapy as the new current standard of care first line. Multidisciplinary management, close follow-up, and education for everyone, the provider teams and the patient, really can help us improve the journey for our patients and help us manage adverse events as well as prevent them. Shared decision-making, more important than ever as we weigh what's important to our patients with the treatment that they pursue.

So with that, I want to thank you so much for tuning in to today's activity. We'll conclude. Thank you for participating.

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