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Finding the Optimal Treatment for *EGFR*-mutated Metastatic NSCLC

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Dr. Liu:
Welcome to CME on ReachMD. I'm Dr. Stephen Liu, and today I'm joined by my colleagues, Dr. Joshua Sabari and Dr. Susan Scott, and we'll review emerging strategies in EGFR-mutated metastatic non-small cell lung cancer.

Let's begin by diving into the rapidly evolving landscape of frontline EGFR-mutated metastatic lung cancer. Susan, can you briefly review the FLAURA studies which previously established osimertinib as first-line standard of care in this population?

Dr. Scott:
Absolutely. So FLAURA study introduced the third-generation TKI, osimertinib, which was compared to first- and second-generation EGFR TKIs. This demonstrated a significant improvement in median progression-free survival to about 19 months with osimertinib used in the frontline. The overall response rate was higher, 80%, and it also had more response in the brain with a CNS progression hazard ratio of 0.47.

FLAURA2 took this a step further, and is a study adding chemotherapy to that osimertinib backbone. So FLAURA2 was looking at, again, frontline metastatic EGFR lung cancer, untreated patients. The median progression-free survival with the addition of chemotherapy was 25.5 months. Overall response rate was about the same but really improving the duration of that frontline therapy with the addition of chemotherapy.

Dr. Liu:
It's not the only combination strategy that's improved outcomes over TKI alone. Josh, we saw the MARIPOSA trial that evaluated the combination of the EGFR-MET bispecific antibody amivantamab and lazertinib, another third-generation EGFR kinase inhibitor. Could you review these data and perhaps comment on how you view them relative to the FLAURA regimens?

Dr. Sabari:
Sure, it's a great question, and really exciting to see three FDA-approved regimens now in the frontline setting. So amivantamab, as you mentioned, is an EGFR and MET bispecific antibody. We combined it with lazertinib, a third-generation EGFR tyrosine kinase inhibitor, very similar in my clinical experience to osimertinib. And this is really dual inhibition of EGFR, and it's chemotherapy-free in that setting.

So we did a randomized phase 3 study on the MARIPOSA trial. Three arms, amivantamab and lazertinib versus the control arm of osimertinib alone. There was a third arm of lazertinib for contribution of components. It was not powered to show superiority of lazertinib to any of the other arms. And primary endpoint here being progression-free survival as well as overall survival. And we did see a dramatic improvement in progression-free survival, 23.7 months for amivantamab and lazertinib versus about 16–16.5 months for osimertinib. So clearly, progression-free survival better for the combination of amivantamab and lazertinib versus osimertinib alone.

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If you compare the PFS head-to-head with the FLAURA2 trial of osimertinib plus chemotherapy, it looks like osi plus chemo, 25.5 months, might have been somewhat better. But it's important to note that on the ami/laz trial, on the MARIPOSA trial, we did monitor the CNS routinely, so we captured true intracranial progression-free survival. Whereas on the FLAURA2 trial, we didn't really have that CNS monitoring, only in patients with active, treated CNS metastases up front.

Now, what about the overall survival? And this is the largest EGFR-directed frontline study to date. Over 1,000 patients enrolled. And we did see a dramatic improvement in overall survival for amivantamab plus lazertinib versus osimertinib alone, not reached. Median overall survival not reached for amivantamab and lazertinib versus about 36.8 months for osimertinib alone. And if you look statistically and you map out how the patients would have done, it seems to be about a 12-month benefit for amivantamab and lazertinib over osimertinib alone. So clearly a significant improvement.

Now, there are clearly toxicities. We know that amivantamab and lazertinib have a different tox profile than osimertinib alone.

Dr. Liu:
And we could talk for hours on this subject, but briefly, Susan, how have the results of these trials impacted your decision-making in this frontline EGFR setting?

Dr. Scott:
Yeah, I use all three regimens, and I really appreciate the ability to tailor the first-line approach to each patient, including their disease, their tumor characteristics, their overall health, and then of course, their goals and priorities.

Dr. Liu:
Yeah. Joshua, anything else to add?

Dr. Sabari:
Yeah. I mean, I think we're looking forward to seeing the data for FLAURA2 overall survival. I think that will really help us make a clinical decision with patients. And we have to weigh the toxicities and the quality-of-life benefit for our patients. We all want patients to live longer, but we want them to live longer with good quality of life. So this really becomes an individualized discussion with your patient in your clinic.

Dr. Liu:
Yeah, I think the exciting thing here is that we have better options. Now, while in 2018 a median PFS of 18.9 months with osimertinib was impressive, but it's not going to cut it anymore. We need better. These are better. They're offering better options for our patients. And in some high-risk subgroups, like L858R, we're not even getting to a median PFS of 18.9, it's closer to a year, which is not a very long time. I welcome these combination strategies, and hope to continue building on them.

On that note, actually, Susan, any thoughts on the potential role of ADCs, antibody drug conjugates, in this setting?

Dr. Scott:
Yeah, so there are several ADCs under investigation for EGFR-mutated lung cancer. They're targeting EGFR itself, HER3, MET, Trop2 and others. So datopotamab deruxtecan is under review based on some phase 2 data in later lines of therapy, but it is also being investigated with or without osimertinib in the phase 3 trial up front. And it's also being investigated against platinum chemotherapy in pretreated EGFR disease. And we are awaiting the outcomes of these studies.

Dr. Liu:
Yeah, we need more regimens, more active agents.

Continuing that discussion of EGFR-mutant metastatic lung cancer in the second-line and beyond, Josh, how are emerging therapies reshaping this paradigm? Can you talk a little bit about the role of amivantamab here in the second-line setting?

Dr. Sabari:
Well, again, it's important, Stephen, what did someone get in the frontline setting? That's going to guide what we think about in the second-line. But in the historical paradigm, in the older paradigm, where all patients received third-generation EGFR TKI, in the second-line setting, things were pretty dismal. It was really chemotherapy alone. A lot of people used off-label osimertinib in combination with chemotherapy. We look forward to seeing some of that data from a prospective trial, the COMPEL trial.

But currently we have the data for MARIPOSA-2. MARIPOSA-2 takes amivantamab and combines it with chemotherapy. We looked at that versus chemotherapy alone. There was a third arm of the trial of amivantamab, lazertinib, and chemotherapy, but due to toxicity, that arm was discontinued or held. So when we look at amivantamab plus chemo versus chemotherapy alone, a significant improvement here in progression-free survival, 6.3 months for ami plus chemo versus about 4 months for chemotherapy alone.

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Dramatic improvement in objective response rate. We're looking at 64% for ami/chemo versus about 36% for chemotherapy.

What really was exciting to me though is the intracranial progression-free survival improvement with amivantamab and chemo, 12.5 months median versus 8.3 months with chemotherapy alone. So again, you do still have the same tox profile with amivantamab in the second-line setting—the cutaneous tox, the infusion-related reaction, slight increased risk of venous thromboembolism—but I think this is an additional benefit to patients to continue EGFR-directed therapy, and it has become my standard of care in the second-line setting.

Dr. Liu:
Yeah, I completely agree. For me, patients progressing on osimertinib alone, MARIPOSA 2 is our standard of care, really robust activity.

Susan, do you think ADCs have the opportunity to maybe replace them in a second-line setting?

Dr. Scott:
That's a great question, Stephen. I'm excited about some of the ADCs coming in the pipeline, but I'm not sure if they're going to replace second-line MARIPOSA-2 regimen, or if it will be in sequence.

Yes. So recently, we saw that HER3-DXd was withdrawn from its BLA application, and we don't have that as a kind of forthcoming option. Datopotamab deruxtecan is also being reviewed in this indication for pretreated EGFR-mutated lung cancer. So these are patients that have previously received tyrosine kinase inhibitor and chemotherapy, based on the TROPION-Lung01 study — just a subgroup of that study actually, and the TROPION-Lung05 study, again a subgroup of those studies with EGFR-mutated lung cancer.

I'd like to see some more data with longer follow-up. Certainly, the overall response rate in TROPION-Lung05 does appear improved compared to docetaxel, which is less than 10% in some of these AGA, or actual genomic alteration–driven lung cancers. But these are small numbers, and among this group, that 4.4-month median progression-free survival versus 3.7 months with docetaxel isn't quite what I'd like to see for an immense shake-up. But I'm hopeful that with longer-term data and kind of refining this approach, we're going to have more and more options.

Dr. Liu:
Yeah, I think options are great to have. But one thing about all of these options, right, as opposed to two of the ADCs, they're sort of empiric in nature. Josh, what about a personalized or biomarker-driven strategy in the resistance setting?

Dr. Sabari:
Yeah, that's a great point. And if you had asked me this question 3 or 4 years ago, I'd have said, this is where I put my money. Right? Looking at patients, what resistance mechanisms do they have? Can we target them? C797S being one of the more common ones, 10 to 12% of my patients. MET amplification, another common one, about 10% of my patients. And remember, you have to re-sequence your patients at progression in an effort to identify resistance mechanisms.

And unlike the first- and second-generation EGFR inhibitors, where most patients developed one resistance mechanism like T790M, a point mutation in exon 20, status post a third-generation EGFR TKI, the resistance mechanisms are sort of all over the place.

But focusing specifically on MET overexpression and MET amplification, we actually saw exciting data presented at ASCO 2025. The SAVANNAH data of savolitinib, a MET tyrosine kinase inhibitor, plus osimertinib. And we saw impressive 58% response rate in this population. They did have a control arm of savolitinib plus placebo. Again, I would never do that in my clinical practice. Response rates as low as 16%. You want to keep EGFR inhibition on board. And when you look at progression-free survival for savolitinib plus osimertinib, 8.3 months. So this is an important finding. It should be, sort of confirmed on a phase 3. There is a phase 3 study ongoing, the SAFFRON trial.

I'll tell you, it's very hard, though, in my clinical practice to get those resistance biopsies. And I'm in an academic setting, we probably do it in 30-40% of patients. We do heavily rely on liquid biopsy, ctDNA, circulating tumor DNA. But again, I think having an agnostic approach, a biomarker-agnostic approach, may be easier in the clinic.

Dr. Liu:
I think there's value in biopsy, and we always want to do it when possible, not just for looking at MET and other acquired alterations but certainly histologic transformation. But your point, I think, is spot on, that even though it can often be our intention, it's not always feasible. And that's just sort of the reality of things. But whenever present, I think this is a good option. I look forward to more data.

It's been another great discussion, but unfortunately, our time is up. So thanks everyone for listening.

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