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https://reachmd.com/programs/cme/the-precision-playbook-optimizing-treatment-selection-and-sequencing/36285/

Released: 07/31/2025
Valid until: 07/31/2026
Time needed to complete: 1h 06m

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

The Precision Playbook – Optimizing Treatment Selection and Sequencing

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Dr. Kerr:
Hello there. This is CME on ReachMD, and I'm Dr. Kerr. Here with me today are Dr. Leighl and Dr. Cho.

So now let's talk about how we can apply the data we've been discussing in our practice.

Dr. Leighl, can you talk about treatment selection and sequencing in our EGFR-mutated NSCLC patients?

Dr. Leighl:
Thanks, Dr. Kerr. So it's become amazing that we have so many options now in EGFR-mutant lung cancer. It used to be so great just to find a sensitizing mutation patient and put someone on an EGFR TKI. But now we really need to think, what is the best possible treatment for our patients?

Most of our patients, though, have higher-risk disease—brain metastases, co-alterations, greater disease burden—and would benefit from combination therapies, where we've seen longer survival, better progression-free survival, and better intracranial control. And so it's really important to, when we sit down with the patient, to look at these things, which mutation and the patient's disease characteristics and also the patient themselves. What are they interested in? How aggressive do they want to be? Do they want to add IV therapy? And are they able to withstand toxicity? And so a conversation that used to be very short, just a couple of minutes, can now be quite long or take multiple visits.

What is great, though, is that the drugs that we have now to treat both first-line patients with EGFR advanced lung cancer and also subsequent resistance have really improved. And it's so important to really understand what mechanisms of resistance can arise or develop after first-line therapy.

And of course, MET is one of the most important. It's been great to have new drugs that also target MET, whether they target them at the same time, such as amivantamab, where you get dual pathway inhibition of EGFR and MET. And what we've seen in the amivantamab plus lazertinib studies, which is a little different from osimertinib and chemotherapy or osimertinib alone, is that this combination really drives down the incidence of EGFR-driven and MET-driven resistance at the time of progression. So a very, very nice proof of concept. But of course, then the next question is, well, what is the next resistance mechanism and how do we overcome that?

I think it's also nice if somebody starts, for example, with a third-gen TKI—now that the new standard after, for example, osimertinib or lazertinib, is chemotherapy plus amivantamab—we know that many of our patients, whether it's true MET amplification or some form of resistance driven through MET signaling—you know, MET is an incredibly important pathway, and so to be able to add amivantamab or other EGFR-MET targeting really has been so important. We've seen improved survival with this, even without molecular testing. So even though it's not really a target-agnostic strategy, we can use it in a target-agnostic way. So this has been incredibly important.

More and more, though, we really need to think about the details of each patient's case. You really need a data-driven approach to personalizing treatment, from that initial diagnosis of EGFR-mutant lung cancer to changes over time, molecular resistance in the second- and then third-line settings.

Dr. Cho:
Regarding the patient selection and sequencing, I think it is important for me because I'm a big fan of more intensive therapy in EGFR-mutant lung cancer patients. So I believe that the most effective therapy should not be a last resort for our patients. Because if we look at all the global data, there are a lot of patient attrition rate.

With the emergence of all the combination approaches in first-line treatment, such as MARIPOSA and FLAURA2, I believe some patients—and probably many patients based on MARIPOSA high-risk analysis—many patients may need a more intensive therapy rather than single-agent third-generation EGFR TKI in the first-line setting.

Dr. Kerr:
So one of the issues that we've learned about in targeting genomic alterations such as EGFR is that patients develop resistance at some point in their treatment course. And in order to continue with our personalized approach to treating our patients, understanding the resistance mechanisms is quite important, which in turn raises questions about whether we should look for those resistance mechanisms.

So that concludes our discussion. We hope you found this review useful. Thank you for listening.

Announcer:
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