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Data-Driven Decisions – The Changing Landscape of *EGFR*-Mutated NSCLC

Announcer:
Welcome to CE on ReachMD. This activity is provided by Medcon International. This episode is part of our MinuteCE curriculum.

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

Dr. Cho, can you review recent efficacy data on EGFR-mutated non-small cell lung cancer that is changing the treatment landscape?

Dr. Cho:
Sure. In the FLAURA study, osimertinib, third-generation EGFR TKI, significantly improved the PFS and OS compared to first-generation EGFR TKI in the first-line treatment of EGFR-mutant advanced NSCLC.

In the subsequent FLAURA2 study, osimertinib chemotherapy plus chemotherapy significantly prolonged PFS and duration of response than osimertinib monotherapy in EGFR-mutant NSCLC. More patients experienced grade 3 or worse severe toxicity in the combination arm. There was a favorable trend in OS with osimertinib plus chemotherapy combination.

In the MARIPOSA study, amivantamab plus lazertinib was compared with osimertinib in treatment-naïve EGFR-mutant NSCLC. Amivantamab plus lazertinib significantly improved PFS over osimertinib in first-line EGFR-mutant advanced NSCLC with a hazard ratio of 0.7. In addition, amivantamab plus lazertinib compared to osimertinib showed benefit in patients regardless of brain metastases. Responses were more durable with the combination. Based on MARIPOSA study, US FDA, EMA, and other regulatory agencies approved the first-line amivantamab plus lazertinib.

More recently, in a final OS analysis, amivantamab plus lazertinib significantly reduced mortality by 25% compared to single-agent osimertinib. More than 1-year median overall survival benefit is anticipated for this combination compared to osimertinib. About 60% of patients were alive at 3 years in the combination arm. Twice as many patients receiving amivantamab plus lazertinib were intracranially progression-free at 3 years and had a longer intracranial duration of response compared to osimertinib.

High-risk features occur commonly in first-line EGFR-mutant NSCLC because it carries a poor prognosis. Combination of amivantamab plus lazertinib significantly improved the PFS compared to osimertinib in these high-risk subgroups with brain metastasis, liver metastasis, p53 co-mutation, detectable baseline ctDNA, and no ctDNA clearance at week 9. Importantly, almost 90% of patients in the first-line EGFR-mutant NSCLC have at least 1 high-risk feature, and their PFS was only roughly 1 year on osimertinib.

After progression on first-line osimertinib, amivantamab plus chemo improved the PFS compared to chemo alone and now approved in this indication.

Dr. Leighl:
As we've seen these new data emerge and be published, it's been great to see these taken up into guidelines around the world—NCCN,

ASCO, also ESMO in the Living Guidelines. And the challenge, I think, for us as clinicians has been, now that we have intensified therapy, understanding who should have intensified therapy, who can still have TKI alone, whether it's osimertinib or another third-generation TKI. And then within the intensified therapy, who should have osimertinib plus chemotherapy, who should have this chemo-free combination, amivantamab–lazertinib. And so of course some of that's funding, some of that's what people are comfortable with, and also a really fulsome discussion with patients.

Dr. Kerr:
Yeah, and I think that one of the interesting things around these data is the emergence of the significance of particular prognostic factors and how they might inform a treatment decision about escalation of therapy. And in this particular context that we're discussing today, the presence of the p53 co-mutation appears to be a poor prognostic factor.

And of course, again, a general phenomenon is the failure to clear ctDNA or the presence of ctDNA at baseline. So these, in turn, will of course pose particular challenges for the laboratory as another factor that has to be delivered during the context of biomarker testing to inform treatment decisions.

Well, that's all we have time for today. We hope this review has been useful to your practice.

Announcer:
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