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Strategies in *EGFR*-mutated Unresectable Stage III 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, to review emerging strategies in EGFR-mutant unresectable stage III non-small cell lung cancer.

Josh, we now have updated data from the landmark phase 3 LAURA trial. Could you start us off with a brief overview of those data?

Dr. Sabari:
Yeah. So remember, in driver mutation-negative patients, we use the PACIFIC regimen where we use consolidation durvalumab. Particularly in the EGFR-mutant population, which is what the LAURA trial studied, these are patients we know do not benefit from consolidation or adjuvant durvalumab. So this is a randomized trial, phase 3, that looked at patients post concurrent chemo RT, randomizing them to get osimertinib, a third-generation EGFR TKI, versus placebo. And primary endpoints here being progression-free survival and overall survival. And I remember seeing this data about last year, now, quite an impressive improvement in median progression-free survival for patients receiving osimertinib in the consolidation setting, 39.1-month median PFS versus only about 5.6 months for placebo, showing us that essentially all these patients with unresectable disease will essentially recur.

When you then look at overall survival, that's a lot more controversial, right? Because at progression, most patients would have gone on to receive osimertinib, but still, at the 3-year landmark, we do see an 84% median overall survival for osimertinib versus 74% for placebo.

One really important takeaway from this trial is that these patients are getting indefinite osimertinib, and I think that's the right thing to do in this patient population.

Dr. Liu:
Striking how few patients we cure with chemoradiation alone in this setting, and 5.6 in a setting where we're reaching for cure really was eye-opening. So clear benefit here. Standard of care, but we always have to look at the flip side of that coin. Susan, what are the safety outcomes from this study?

Dr. Scott:
Yeah. So there is, of course, a higher grade of toxicity in the osimertinib arm compared to the placebo arm. One important thing that we looked at was pneumonitis. So there was about a 10% higher rate of radiation pneumonitis in the osimertinib arm compared to placebo, though only 2% were grade 3 or higher. There was a higher rate of discontinuation than placebo, about 13% in Osimertinib arm versus 5%. But again, as Josh mentioned, this is an indefinite kind of treatment with osimertinib, so a long time to continue therapy, a long time to experience side effects.

So what does this mean for patients? It's a really great option for the patients with EGFR-mutated tumors following chemoradiation.

Exactly as you guys said. The recurrence in stage III unresectable disease is close to 90%, so the vast majority of patients really do benefit from the early addition of EGFR-directed therapy.

Dr. Liu:
Yeah, I think this will translate to an OS benefit. But at the same time, there's also I think some value in just delaying progression, especially when that progression is often in the brain. So I think a new standard of care in this setting. Given these advances for patients with historically limited treatment options, what challenges remain for this patient population and where do we go from here, Josh?

Dr. Sabari:
I think biomarker testing is critical. I mean, here we assume we knew the EGFR mutation, so all patients with lung cancer, not only stage IV but now we know in early stage, as well as stage III B and C unresectable, need testing. I think the tox profile, we all feel very confident and comfortable with the side effect profile for osimertinib. But some of these are low-level toxicities that sort of occur over a long time. And I bring up paronychia, GI tox, for example, these are grade 1 and 2 but could sort of affect patients' quality of life. But for me, as you mentioned, these patients have very high rates of recurrence. We saw only 5.6 median PFS on the control arm. This is a no-brainer, I think we should utilize this in all patients in clinical practice.

Dr. Liu:
Susan, what other challenges are out there for this and for other driver subtypes?

Dr. Scott:
Yes, I think for the EGFR-mutated tumors, I think identifying patients that might be able to discontinue therapy or avoid it altogether would be ideal, because continuing treatment indefinitely is daunting, but it is going to be our standard of care for the time being.

Great discussion. Unfortunately, though, our time is up. So thanks everyone for listening.

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