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Commentary: A new hope: Do ADAURA trial results change the paradigm for treatment of resectable lung adenocarcinoma?

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CENTRAL MESSAGE

Longer follow-up data from the ADAURA trial are required to determine whether osimertinib is associated with improved overall survival before adopting targeted therapy in adjuvant settings.

The advent of targeted therapy for oncologic drivers in the treatment of lung adenocarcinoma (LUAD) has the potential to propel the field into hyperspace. Jones and colleagues¹ have presented a well-crafted and optimistic review of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors—their past, present, and future. As the third iteration of EGFR-tyrosine kinase inhibitors, osimertinib has demonstrated superior efficacy and safety compared with gefitinib or erlotinib.² ADAURA randomized patients with completely resected IB to IIIA EGFR-variant positive (EGFRm+) LUAD to 3 years of adjuvant osimertinib versus placebo.³ Osimertinib was found to have dramatic benefits in disease-free survival (DFS); however, these benefits are more ambiguous than they appear at first glance.

The authors contrast the modest benefits of adjuvant chemotherapy with the striking potential benefits of adjuvant osimertinib. The Lung Adjuvant Cisplatin Evaluation trial demonstrated improved overall survival with adjuvant chemotherapy, where the overall hazard ratio (HR) of death was 0.89 (95% CI, 0.82-0.96; $P = .005$). This correlates with a 5-year benefit of 5.4%.⁴ In contrast, in ADAURA, overall DSF at 24 months was 90% with osimertinib versus 44% with placebo (overall HR, 0.17; 99% CI, 0.11-0.26) for patients with stage II to IIIA LUAD. ADAURA presents an 83% reduction in disease recurrence and death, a

benefit that far outstrips the current standard of care and inspires hope for a new era in the treatment of resectable LUAD.

Nonetheless, we temper our optimism at the promise of osimertinib with caution. ADAURA raises many clinical and economical questions. Although half of study participants were randomized to receive daily osimertinib for 3 years, applying this regimen in practice carries a prohibitive cost of more than \$200,000 per patient per year in the United States.⁵ The authors acknowledge the chief limitation of ADAURA—we do not know if adjuvant osimertinib improves overall survival. Other randomized trials, including Gefitinib Versus Vinorelbine Plus Cisplatin as Adjuvant Treatment For Stage II–IIIA (N1–N2) EGFR-Mutant Non–Small Cell Lung Cancer (ADJUVANT/CTONG1104)⁶ and Erlotinib Versus Chemotherapy as First Line Treatment of EGFR Mutation–Positive Advanced Non–Small Cell Lung Cancer (OPTIMAL)⁷ have failed to show improvements in DFS correlating with overall survival. Is the great financial burden of osimertinib worth an unclear survival advantage?

What are the implications of ADAURA on patients with lower-risk, stage IB LUAD? Because thoracic surgeons are primarily responsible for the treatment of early-stage LUAD, we will be faced with the decision to refer patients for standard adjuvant chemotherapy or to targeted adjuvant therapy based on tumor genetic profiling. The ADAURA subset of stage IB patients demonstrated a much less remarkable HR of 0.5 compared with 0.17 in stage II or

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IIIA LUAD. We find it disconcerting that only 60% of patients in ADAURA received adjuvant chemotherapy and note an unusually high rate of recurrence in the placebo arm. There are too many unknowns to disregard the proven survival advantage of adjuvant chemotherapy for the unproven benefit of osimertinib.

Longer follow-up is required to see if ADAURA endures the test of time and adjuvant osimertinib confers a survival advantage. Regardless, we are certain that there is an imminent and inevitable paradigm shift toward targeted therapy in the treatment of resectable LUAD on the horizon.

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Commentary: Targeting our attention

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The expert opinion article by Jones and colleagues¹ is an extremely well-written essay that describes and provides context to the recently published ADAURA trial, which demonstrated dramatic improvements in survival for patients with stage IB-IIIa epidermal growth factor receptor mutation-positive non-small cell lung cancer who received adjuvant osimertinib.² Because of its clarity and efficiency presenting key results and background, we have little to add and recommend it highly as a review article.

Instead, we wish to emphasize how this article portends a front of rapidly changing paradigms for our specialty for

Recruiting multidisciplinary surgical trials (gray slices, traditional; color slices, nontraditional).

CENTRAL MESSAGE

Successful thoracic surgeons will need to adapt by studying targeted signaling pathways with immunotherapies and integrate them into their practices.

which we need to prepare. A review of current protocols open for enrollment reveals an explosion of new studies using novel treatment combinations with different sequencing in resectable non-small cell lung cancer. Figure 1 summarizes this review, with the gray slices representing studies that push eligibility to stages beyond that traditionally covered under clinical treatment guidelines. Some trials use a neoadjuvant approach (N), whereas others use an

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