Editorial Commentary

Adjuvant osimertinib for resected EGFR-mutated non-small cell lung cancer: a game-changer?

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The treatment of early-stage non-small cell lung cancer (NSCLC) generally consists of anatomical pulmonary resection, with multi-modal treatment recommended for patients with Stage II and above. This usually involves surgical resection and chemotherapy, with the possibility of radiation therapy as well (1). Over the last two decades, significant strides have been made in the management of early-stage lung cancer, primarily due to the integration of adjuvant therapy following primary surgical treatment. Since 2004, significant advancements have emerged in the field of adjuvant therapy for lung cancer, including the utilization of platinum-based chemotherapy and immune checkpoint inhibitors targeting immune checkpoints T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein (PD-L1), and programmed cell death protein 1 (PD-1) (1). Cisplatin-based combination regimens are indicated in patients with stage II and IIIA disease after surgical resection, with multiple adjuvant studies demonstrating a 5.4% absolute survival benefit at 5 years (2,3). In 2021, atezolizumab was subsequently approved as adjuvant therapy in patients with early-stage resected NSCLC whose tumors express PD-L1, based on the results from IMpower010 (4). These breakthroughs have resulted in notable enhancements in both overall and disease-free survival rates, especially for patients with early-stage lung cancer without molecular driver alterations.

Over the same time period, the treatment of advanced lung cancer has been revolutionized by targeting molecular pathways involved in tumor proliferation. In patients with incurable metastatic lung cancer with specific driver mutations, these therapies have demonstrated significant improvements in progression-free survival (PFS) and overall survival (OS). Although there have been significant advances, a generalizable role for targeted therapies in the adjuvant setting remains uncertain due to the length of time for studies to mature and the evolving treatment field for each targetable alteration.

Epidermal growth factor receptor (EGFR) mutations, particularly EGFR-exon 19 deletions and EGFR-L858R, are the most frequent actionable genomic events in lung adenocarcinomas. These tumors arise due to constitutively activated EGFR signaling and are susceptible to EGFR tyrosine kinase inhibitors (TKIs) (5). EGFR mutations have been found to be prevalent in patients with NSCLC, specifically those with adenocarcinoma histology, of Asian ethnicity, female gender, and non-smokers or light smokers (6). While EGFR mutations can occur across all age groups, they are more commonly found in younger patients, typically under the age of 65 (7). Osimertinib has been proven to be efficacious in the treatment of advanced lung cancer with these specific EGFR mutations based on a phase III randomized clinical trial. The results showed

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that osimertinib significantly improved PFS compared to standard EGFR TKIs such as erlotinib or gefitinib, an effect that is due to overcoming the frequent EGFR T790M resistance mutation and improved central nervous system (CNS) penetration (8).

The ADAURA trial was conducted in lung cancer to evaluate the efficacy of adjuvant osimertinib in patients with early-stage NSCLC who had an EGFR exon 19 deletions and EGFR-L858R mutations. The trial aimed to determine whether adjuvant osimertinib could improve disease-free survival compared to placebo in this patient population. The ADAURA trial enrolled 682 patients with resected Stage IB–IIIA NSCLC with an EGFR exon 19 deletion or L858R mutation (9). After receiving adjuvant chemotherapy at investigator discretion, the patients were randomized in a 1:1 ratio to receive either osimertinib or placebo for up to three years. The primary endpoint of the study was disease-free survival (DFS), and the secondary endpoint was OS. In this updated analysis of the final, mature DFS data, all 682 patients had the opportunity of 3 years of treatment.

Recently, an updated analysis was published by Herbst *et al.* which included longer follow-up and exploratory analyses (10). In this analysis, 66% and 41% patients completed 3 years of planned adjuvant osimertinib and placebo treatment, respectively. Patients with stage II–IIIA disease, the median DFS was longer for the osimertinib group at 65.8 months than the placebo group at 21.9 months. At 48 months, the percentage of patients alive and disease-free was 73% for osimertinib and 38% for placebo. The OS data were immature at the time of this analysis. Benefit of osimertinib was correlated with stage of disease. Among patients with stage IB disease, the percentages alive and disease-free at 48 months were 80% for osimertinib and 59% for placebo the DFS HR was 0.41. Among those with stage II disease, these percentages were 74% and 42%, respectively; among those with stage IIIA disease, these percentages were 65% and 14% respectively (10).

Importantly, CNS DFS data from the updated ADAURA analysis demonstrate clear prevention of recurrent disease in the brain with osimertinib. CNS DFS was improved with osimertinib in the stage II-IIIA (HR, 0.24; 95% CI: 0.14 to 0.42) and overall population (HR, 0.36; 95% CI: 0.23 to 0.57) (10). The majority of CNS recurrences in the osimertinib group occurred after treatment was completed.

These updated ADAURA trial results confirm that adjuvant osimertinib for a duration of 3 years is the standard of care for patients with resected EGFR-mutant NSCLC, in line with the Food and Drug Administration (FDA) approval for this indication. However, several questions remain unanswered. First, it is unclear which patient populations benefit the most from adjuvant osimertinib. Additionally, we are still awaiting OS data and whether the benefit will be maintained with longer follow-up, as there is evidence that adjuvant therapy may delay but not prevent recurrence. Third, the optimal duration of osimertinib treatment is uncertain, and three years of treatment may not be feasible for all patients due to toxicity and cost. Furthermore, adjuvant osimertinib may impact long-term quality of life of patients, so selection and personalization of therapy depending on risk of recurrence and other comorbid conditions will be increasingly important in the context of a shared decision-making discussion to start this treatment.

Stage selection for adjuvant osimertinib

The current FDA accelerated approval label for adjuvant osimertinib allows use as an adjuvant therapy in all patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, with no specific recommendations regarding disease stage (11). Therefore, understanding its clinical utility in different stages is critical for clinicians to make informed treatment decisions. Based on the ADAURA trial, there is increasing benefit by stage, higher in stage II–IIIA disease, as demonstrated by the significantly improved DFS observed in the osimertinib group compared to the placebo group.

It is noteworthy that patients with stage IB lung cancer with tumors between 3.1–4 cm were also included in the ADAURA trial, despite not generally having an indication for adjuvant chemotherapy. Although the study did report DFS for this subgroup, it will be important to evaluate the durability of benefit in this subgroup, as overall survival is a critical endpoint in the treatment of early-stage lung cancer. It is worth noting that the NCCN guidelines currently recommend observation for patients with stage IB NSCLC after surgical resection, and further studies are needed to determine the optimal adjuvant strategies for stage I NSCLC.

Overall survival

Recently, AstraZeneca released a press statement stating Osimertinib demonstrated a statistically significant and clinically meaningful improvement in OS, a key secondary endpoint of the study (12). At this time, the data has not

been released for further evaluation, but it will be important to assess the access to Osimertinib in the placebo population after recurrence. Additionally, these data from ADAURA generally indicates that osimertinib postpones relapse while patients remain on it, but it unclear if it fully eradicates disease in patients with minimal residual disease (MRD) after surgery. Longer-term evaluation of overall survival benefit, with 5- and 10-year follow-up, may be important to assess the permanence of the benefit in preventing recurrence rather than just delaying it.

Geographic representation

While a large majority of trials are conducted in the United States, the ADAURA trial was an international multicenter trial, with a total of 212 sites in 25 countries participating. The trial enrolled patients from various regions, including Asia, Europe, North America, and South America. The largest number of patients in the trial were enrolled from Asia, with 422 patients (62%) from this region.

Despite that, it is important to note that the trial was a global study that included patients from various regions, including North America, Europe, and South America. While the results of the ADAURA trial should be generalizable to patients with EGFR-mutated NSCLC in the United States and other regions of the world, there may be potential differences in patient populations and treatment patterns between countries. Clinicians should take into account the patient's individual characteristics, medical history, and treatment preferences, but regional differences in drug approval and reimbursement policies may affect access to this therapy as well.

Financial toxicity

There is an additional concern for long-term financial toxicity that may result from the clinical implications of the ADAURA trial data. Osimertinib is an expensive drug, and the three-year duration of treatment may not be feasible for all patients due to the cost. Even patients within the United States have widely varying drug coverage, and it is common for our patients to have initial co-pays of many thousands of dollars per year which are only somewhat mitigated by patient assistance programs. It is critical for healthcare providers and policymakers to carefully consider the financial impact of Osimertinib treatment and to develop strategies to ensure that patients have access to this therapy, while also ensuring that the cost of treatment does not lead to undue financial hardship for patients and their families. Cost-effectiveness analyses are needed to evaluate the cost-effectiveness of Osimertinib compared to other adjuvant treatments and to determine the optimal duration of treatment for different patient populations.

Quality of life

While the updated results of the ADAURA trial confirm the benefit of adjuvant osimertinib in reducing the risk of disease recurrence or death among patients with resected EGFR-mutated NSCLC, it is important to consider the potential impact of treatment on the quality of life of patients. Specifically, the prolonged duration of osimertinib treatment (up to three years) may cause significant side effects, such as fatigue, skin rash, and gastrointestinal symptoms, which could impair patients' physical and emotional well-being. In addition to short-term reversible effects, 5–10% of patients may have more serious issues such as drug-induced pneumonitis, reduction of ejection fraction leading to congestive heart failure, and QT prolongation. Therefore, it is important to balance the potential benefits and risks of osimertinib treatment, taking into account patients' individual preferences, comorbidities, and quality of life.

Patient selection

Identifying patients who are most likely to benefit from osimertinib treatment is an area of active research. Circulating tumor DNA (ctDNA) analysis could be used to identify patients with minimally residual disease who are at high risk of recurrence and may benefit from adjuvant therapy, which has been demonstrated in the TRACERx lung study (13). Other studies have shown that ctDNA analysis can be used to monitor treatment response and detect disease recurrence earlier than traditional imaging methods, which may allow for more timely and targeted intervention (14).

Given the presence of targetable mutations in patients with EGFR mutations, if ctDNA analysis detects the presence of EGFR mutations after surgery, this may suggest that there is residual disease that is at risk of recurrence and may benefit from adjuvant osimertinib therapy. With emerging ultrasensitive ctDNA detection technologies, we would consider in the future analyzing for ctDNA presence before stopping adjuvant osimertinib, and perhaps continuing with periodic surveillance monitoring afterward

to detect recurrence. If either of these tests are positive, we would consider increasing the duration of adjuvant osimertinib beyond the current 3 years. Because ctDNA is specific but not perfectly sensitive to detect residual disease, we do not currently adjuvant using ctDNA to select patients to start adjuvant osimertinib, nor follow during the 3-year course.

Conclusions

Further studies are needed to validate the use of MRD or ctDNA analysis to guide adjuvant osimertinib therapy in early-stage lung cancer. Ongoing studies are evaluating the use of ctDNA analysis to guide adjuvant therapy with osimertinib and other targeted therapies in patients with early-stage lung cancer. These studies will help to determine the clinical utility and effectiveness of using MRD or ctDNA analysis to guide adjuvant therapy in this setting.

The updated results of the ADAURA trial provide evidence that adjuvant Osimertinib significantly improves DFS in specific patients with resected EGFR-mutated NSCLC, and prevents recurrence including CNS disease. The ADAURA trial also highlights the importance of molecular testing in early stage NSCLC patients, as it allows for the identification of those who may benefit from targeted therapy. As more targeted therapies are developed, it is important to continue to improve our understanding of the genetic landscape of NSCLC and to identify new therapeutic targets. Despite this, several questions remain unanswered, and further studies are needed to determine the optimal duration of treatment and patient selection criteria. In addition, the long-term impact of osimertinib treatment on the development of resistance and the emergence of new mutations in EGFR remains unclear, and future research should address these questions to optimize treatment strategies for EGFR-mutated NSCLC. Despite these limitations, adjuvant Osimertinib has become a new standard in preventing recurrence of early-stage NSCLC, and we look forward to emerging data on other adjuvant molecular targeted therapies across oncogene driven NSCLC.

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