Review Article

Updates in the Adjuvant Treatment of Non-Small Cell Lung Cancer

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Over the past decade there has been significant advancement in the systemic therapy of non-small cell lung cancer, especially in the metastatic setting. More recently, medications which have been proven in advanced disease have been shown to provide benefit in the adjuvant setting as well. We review two recent trials which have studied the use of EGFR-targeted therapies and checkpoint inhibitor therapies in patients who have undergone surgical therapy for resectable disease.

Take home message

- Over the past several years, significant advancements have been made in therapy and treatment of non-small cell lung cancer, specifically the metastatic setting.
- Decades of advancements have focused heavily on molecular-targeted therapy and checkpoint inhibitors, now providing benefits in not just metastatic setting but the adjuvant disease as well.
- This article examines two recent trials which have studied the use of EGFR-targeted therapies and checkpoint inhibitor therapies in patients who have undergone surgical therapy for resectable disease.

EGFR-TARGETED THERAPY

EGFR has been a target for therapy in advanced non-small cell lung cancer for over a decade. The incidence of EGFR mutation varies from a low of 14.1% in Europeans up to 38.4% in Chinese patients. Several medications have successfully targeted EGFR, and in 2018, the results of the FLAURA trial showed superior results with the use of osimertinib as compared to gefitinib or erlotinib in patients with advanced disease while maintaining similar toxicity profiles. Consequently, osimertinib has become the standard of care for first-line therapy in advanced EGFR mutation positive non-small cell lung cancer. Naturally, this has led to Osimertinib being studied in the adjuvant setting. Recent publication of data from the ADAURA trial showed significant improvement in disease-free survival with the use of Osimertinib compared to placebo.

The ADAURA study was a phase 3 double-blind trial that randomized patients with completely resected stage IB-IIIA lung cancer who were positive for the EGFR-mutation to receive either placebo or Osimertinib for 3 years, following completion of standard platinum-doublet adjuvant cytotoxic chemotherapy. The primary endpoint was disease-free survival in those with stage II-IIIA disease. A total of 682 patients were randomized - 339 received Osimertinib and 343 received placebo. After 24 months, 89% of those in the Osimertinib group were alive and disease-free as compared to 52% in the placebo group. Of those who had stage II – IIIA disease, 90% were disease-free in the Osimertinib group vs 44% in the placebo group, for an overall hazard ratio of 0.17 (99% CI 0.11- 0.26, P<0.001). The Osimertinib group also had less CNS disease vs placebo (2% vs 15%). Overall survival data were immature at the time of study publication. Based on these data, the data monitoring committee recommended that the study be stopped early.

Although the data are dramatic, the study itself has some significant flaws. In particular, the primary endpoint for ADAURA was disease-free survival rather than overall survival. That DFS is improved with long-term Osimertinib use is unsurprising, especially since two earlier EGFR-tar-
targeted therapies (gefitinib and erlotinib) had shown similar DFS improvements in previous trials. However those two previous medications have not become the standard because ultimately neither drug improved overall survival compared to placebo; the overall survival data for ADAURA has not yet matured, and it remains to be seen whether this will eventually reach that threshold. In addition, the potential societal costs are significant since osimertinib therapy currently costs approximately $200,000.00 per year in the United States; and the trial recommends 3 years of therapy.

Nevertheless, there is enough positive about the ADAURA study to consider its implementation in clinical practice. The magnitude of improvement of DFS is striking, and it is very likely that once the data mature, overall survival improvement will reach statistical significance. In addition, an argument can be made that prolonging disease-free survival has practical clinical benefits to the patient, since treating relapsed disease can result in significant morbidity and diminished quality of life. In particular, the improvement in CNS-recurrent disease could decrease the need for palliative radiation therapy or craniotomy. These are compelling reasons to discuss the option of Osimertinib as adjuvant therapy.

PD-L1 TARGETED THERAPY

Although the results from ADAURA are important and intriguing, they are limited to approximately 25% of patients with EGFR-mutation positive adenocarcinoma. A potentially more inclusive trial is IMpower010 which studied the use of the adjuvant checkpoint inhibitor atezolizumab.

Checkpoint inhibitors have been rapidly integrated into the treatment of advanced lung cancers in the last few years, following data that showed improved overall survival with nivolumab and pembrolizumab in the metastatic setting. The PACIFIC trial (initially published in 2017, updated in 2021) showed improvements in both DFS and OS in the adjuvant use of durvalumab after concurrent chemoradiation for unresectable lung cancer. Given these, the IMpower010 trial sought to evaluate adjuvant atezolizumab after surgery. Patients with resected non-small cell lung cancers stage IB-IIIA, who had already received standard four cycles of adjuvant platinum-based doublet chemotherapy if appropriate, were randomized to receive atezolizumab vs placebo for one year. The primary endpoint was disease-free survival (DFS), with overall survival (OS) as a secondary endpoint. After a total of 1005 evaluated patients, the use of adjuvant atezolizumab displayed improvement in DFS (HR 0.79, p=0.02) on the intent-to-treat analysis. Intriguingly, DFS correlated with degree of PD-L1 positivity. Analysis of all PD-L1 positive patients (PD-L1 > 1%) revealed a hazard ratio (HR) of 0.66 (CI 0.50 – 0.88, p=0.0039). Those patients who were considered “high-positive” (PD-L1>50%) had an even greater improvement in DFS (HR 0.43, CI 0.27 – 0.68) whereas the PD-L1 negative patients showed no improvement (HR 0.97, CI 0.72 – 1.31). Overall safety evaluation showed an increase in grade 3/4 adverse effects in the atezolizumab arm (21.8% vs 11.5%); there were 8 deaths (2%) in the atezolizumab arm vs 3 deaths (1%) in the control group.

The main criticisms of IMpower010 mirror those of ADAURA, in that the primary endpoint was disease-free rather than overall survival. Whether the overall data will show statistically significant OS improvements at maturity remains to be seen. In addition, it appears that the benefits of adjuvant atezolizumab are related to PD-L1 status, with higher PD-L1 positivity showing more DFS improvement, thus implying that stratification is an important strategy in choosing appropriate patients. The adverse effect profile will also need to be evaluated fuller since we are treating a population of patients who are otherwise healthy and may be cured following resection. In addition, the cost of one year of therapy with nivolumab approach $100,000.00 in the United States, which brings the societal burden of such therapies into the conversation as well.

FUTURE DIRECTIONS

After over a decade of having platinum doublet cytotoxic chemotherapy as the only proven adjuvant treatment in lung cancer, the last two years have seen both osimertinib and atezolizumab emerge as potentially practice-changing therapies. Despite the limitations inherent in these two trials, the data have been strong and certainly show significant clinical benefit in the appropriate populations. Similar trials are being conducted to further delineate the roles of other medications in the adjaunt setting. The ongoing ALINa trial is randomizing ALK-positive patients with stage IB-IIIA disease to receive either oral alectinib or platinum-doublet chemotherapy after resection. The ANVIL,10 PEARLS11 and BR5112 trials are studying the use of adjuvant nivolumab, pembrolizumab and durvalumab respectively in stage IB-IIIA patients, with results risk stratified based on the degree of PD-L1 positivity. These trials are expected to be completed between 2024 – 2027 and will give us more information on these drugs against lung cancer, but will likely also result in increased complexity with regards to their implementation. Though much remains to be determined over the next few years regarding the proper use of these medications, their availability implies overall improvement in outcomes for our patients.

CONFLICT OF INTEREST

None

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ETHICAL STATEMENTS

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ii. All authors: data collection and assembly
iii. All authors: data analysis, manuscript writing

All authors have approved the manuscript

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