Immune Checkpoint Inhibitors and EGFR-TKIs as Adjuvant/Neoadjuvant Therapies for Resectable Non-small Cell Lung Cancer
A Systematic Review

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The findings and conclusions in this document are those of the author(s) who are responsible for its contents and do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (*eg*, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted health care topics of importance to clinicians, managers, and policymakers as they work to improve the health and health care of Veterans. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The program comprises 4 Centers around the US and a Coordinating Center, which are led by VA clinicians and scientists who are recognized leaders in the field of evidence synthesis. The Coordinating Center, located in Portland, Oregon, was created to manage program operations, ensure methodological consistency and quality of products, engage with stakeholders, and address urgent evidence synthesis needs. To ensure responsiveness to VA decision-makers, the ESP is governed by a Steering Committee of health system leadership and researchers. Nominations for ESP reviews are submitted via the program website.

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Operational Partners

Operational partners are system-level stakeholders who help ensure relevance of the review topic to the VA, contribute to the development of and approve final project scope and timeframe for completion, provide feedback on the draft report, and provide consultation on strategies for dissemination of the report to the field and relevant groups.

Michael Kelley, MD
Executive Director
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Peer Reviewers

The Coordinating Center sought input from external peer reviewers to review the draft report and provide feedback on the objectives, scope, methods used, perception of bias, and omitted evidence (see Appendix D for disposition of comments). Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Coordinating Center works to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

ABBREVIATIONS TABLE

AJCC/UICC	American Joint Committee on Cancer/Union for International Cancer Control
EGFR	Epidermal growth factor receptor
EGFRm+	Epidermal growth factor receptor mutation-positive
ESP	Evidence Synthesis Program
ICI	Immune checkpoint inhibitor
NSCLC	Non-small cell lung cancer
PD-L1	Programmed death ligand 1
TKI	Tyrosine kinase inhibitor

EXECUTIVE SUMMARY

Key Findings

Adjuvant Therapies

- In patients with non-small cell lung cancer (NSCLC) who have received 3–4 cycles of platinum-based chemotherapy after complete surgical resection, adjuvant therapy using the immune checkpoint inhibitors (ICIs) atezolizumab or pembrolizumab likely improves disease-free survival compared with best supportive care or placebo. For atezolizumab, results of prespecified exploratory analyses from the relevant trial suggest disease-free survival benefit of adjuvant therapy with atezolizumab may be limited to patients with programmed death ligand 1 (PD-L1) expression ≥ 50%, and that adjuvant atezolizumab may also improve overall survival in this population. Overall survival findings are interim and have not yet been formally tested for statistical significance. Overall survival data for pembrolizumab are less mature and have not been reported by PD-L1 expression level.
- In patients with resected, epidermal growth factor receptor (EGFR) mutation-positive stage II–IIIA NSCLC, adjuvant therapy with EGFR tyrosine kinase inhibitors (EGFR-TKIs) likely improves disease-free survival compared with adjuvant chemotherapy or placebo. The most recent and relevant available trial found that adjuvant therapy with osimertinib, a third-generation EGFR-TKI, led to substantially improved disease-free survival over placebo. Overall survival data from this trial are immature, limiting conclusions that can be made about overall survival benefits of adjuvant therapy using recent-generation EGFR-TKIs.
- ICIs and EGFR-TKIs currently approved for adjuvant use appear to be tolerable to most patients. Despite some remaining uncertainty about overall survival benefits, adjuvant therapy using these agents could be an option for selected patients with early NSCLC in addition to the current standard of care. For patients with stage II–IIIA NSCLC, this remains conventional adjuvant chemotherapy after surgical resection.

Neoadjuvant Therapies

- In patients with resectable NSCLC, neoadjuvant therapy with the ICI nivolumab plus platinum-based chemotherapy likely improves event-free survival, and may improve overall survival, compared with neoadjuvant chemotherapy alone. Results of prespecified subgroup analyses from the available clinical trial suggest patients with PD-L1 ≥ 50% may experience the largest disease-free survival benefit. Patients with tumors bearing EGFR mutations or anaplastic lymphoma kinase (ALK) rearrangements were excluded from the available trial, which may imply the need to test for these alterations prior to treatment.

NSCLC is the most common form of lung cancer and as many as 80% of patients present with locally advanced or metastatic disease. ICIs and EGFR-TKIs are important, and relatively recent, advancements in cancer treatment. In metastatic NSCLC, survival benefits of ICIs in combination with chemotherapy have been observed across PD-L1 expression levels for patients whose NSCLC is not driven by EGFR or other mutations, while EGFR-TKIs have shown more promise for patients with mutation-driven advanced NSCLC.

Clinical trials are investigating whether benefits of ICIs and EGFR-TKIs seen in metastatic NSCLC extend to early and locally advanced disease. To date, an EGFR-TKI (osimertinib) has

been approved for use as an adjuvant monotherapy in patients with certain EGFR mutations, while 2 ICIs (atezolizumab and pembrolizumab) have been approved for adjuvant use following adjuvant platinum-based chemotherapy. Approval of atezolizumab was limited to patients with PD-L1 expression on 1% or more of tumor cells. Another ICI, nivolumab, was recently approved as a neoadjuvant therapy in combination with platinum-doublet chemotherapy. FDA approval of adjuvant drugs was based on disease-free survival, while efficacy of neoadjuvant nivolumab was demonstrated using event-free survival and pathologic complete response. All 4 drugs were previously approved for treating more advanced NSCLC.

Overall survival is usually considered the definitive efficacy outcome for curative-intent cancer therapies, and concerns have been raised about whether endpoints used for FDA approvals are adequate surrogates of overall survival in the context of adjuvant and neoadjuvant therapies for early NSCLC. A related concern is that if long-term adjuvant therapy forestalls recurrence of NSCLC—but ultimately does not confer a survival benefit—the therapy may place undue treatment burden and complication risk on patients, particularly when the same drugs are established therapies for advanced NSCLC. From this view, it has been argued that clinical trials of adjuvant therapies must demonstrate overall survival improvement against a control group that had a substantial number of patients cross over to receive the trial drug for disease recurrence. Otherwise, any apparent overall survival benefit could be the result of comparing patients who received an active treatment to patients for whom standard-of-care treatment (an EGFR-TKI or ICI approved to treat advanced NSCLC) has been delayed.

These concerns are relevant to the VA setting, where lung cancers are the second-most frequently diagnosed cancers in Veteran women and men. To inform decision-making about the treatment of VA patients with resectable NSCLC, we reviewed and critically appraised evidence from clinical trials and other comparative studies on survival benefits and potential harms of neoadjuvant and adjuvant therapy using ICIs and EGFR-TKIs. We also describe considerations and concerns raised about the use of approved therapies.

We searched Ovid MEDLINE, CINAHL, ClinicalTrials.gov, and other sources for relevant studies published through August 2022 (see Appendix A). Additional citations were identified through consultation with content experts and by hand-searching reference lists, the American Society of Clinical Oncology publications database, and public search engines. Conference abstracts, professional group proceedings, and other non-peer-reviewed publications were included when they reported updated results of eligible studies not available elsewhere.

Our search identified 906 potentially relevant articles. Of these, 18 primary studies (in 27 publications) met eligibility criteria. We identified updated results from several key trials that were not available at the time of FDA approvals. Evidence from these studies was synthesized narratively by adjuvant and neoadjuvant applications and type of drug, and we also investigated potential sources of variation in survival outcomes. Statements of findings use terms that reflect strength of evidence ratings. For example, if a therapy was associated with improved overall survival in high-strength evidence, the finding would be that the therapy "improves overall survival." If the evidence was moderate strength, the corresponding statement would be "*likely* improves overall survival;" and for low-strength evidence, "*may* improve overall survival."

Adjuvant therapy with ICIs (2 phase 3 RCTs)

In patients with NSCLC who have received 3–4 cycles of platinum-based chemotherapy after complete surgical resection, adjuvant therapy using the ICIs atezolizumab or pembrolizumab likely improves disease-free survival compared with best supportive care or placebo. Results of prespecified exploratory analyses from the pivotal trial of atezolizumab (IMpower010) suggest disease-free survival benefit may be limited to patients with PD-L1 ≥ 50%, and that adjuvant atezolizumab may also improve overall survival in this population. Overall survival findings are interim and have not yet been formally tested for statistical significance. The available trial of adjuvant pembrolizumab, PEARLS/KEYNOTE-091, has not reported overall survival results by PD-L1 expression level.

Adjuvant therapy with EGFR-TKIs (6 phase 2 or 3 RCTs)

In patients with resected, EGFR mutation-positive stage II–IIIA NSCLC, adjuvant therapy with EGFR-TKIs likely improves disease-free survival compared with adjuvant chemotherapy or placebo. The most recent and relevant available trial, ADAURA, found that adjuvant therapy with osimertinib, a third-generation EGFR-TKI, led to substantially improved disease-free survival over placebo. Overall survival data from this trial are immature, limiting conclusions that can be made about overall survival benefits of adjuvant therapy using recent-generation EGFR-TKIs.

Neoadjuvant therapy with ICIs (1 phase 3 RCT)

In patients with resectable NSCLC, neoadjuvant therapy with the ICI nivolumab plus platinum-based chemotherapy likely improves event-free survival, and may improve overall survival, compared with neoadjuvant chemotherapy alone. Results of prespecified subgroup analyses from the available clinical trial, CheckMate 816, suggest patients with PD-L1 ≥ 50% may experience the largest disease-free survival benefit. Overall survival data from this trial have not yet matured, and the reported hazard ratio for overall survival, though fairly large in magnitude, has not crossed the trial's adjusted significant threshold. Rates of pathologic complete response were similar regardless of disease stage and were significantly greater than neoadjuvant chemotherapy alone. Treatment benefits were apparent even with limited use of adjuvant chemotherapy. Patients with tumors bearing EGFR mutations or ALK rearrangements were excluded from the available trial, which may imply the need to test for these alterations prior to treatment.

CONCLUSIONS

ICIs and EGFR-TKIs currently approved for adjuvant use appear to be tolerable to most patients with early NSCLC. Despite some remaining uncertainty about overall survival benefits, adjuvant therapy using these agents could be an option for selected patients with resectable NSCLC in addition to the current standard of care. For patients with stage II–IIIA NSCLC, this remains conventional adjuvant chemotherapy after surgical resection. In the neoadjuvant setting, neoadjuvant therapy with the ICI nivolumab plus platinum-based chemotherapy likely improves event-free survival, and may improve overall survival, for patients with resectable NSCLC compared with neoadjuvant chemotherapy alone. Planned analyses of more mature survival data, particularly in important patient subgroups, may help to clarify remaining questions about the use of ICIs and EGFR-TKIs as adjuvant and neoadjuvant therapies for resectable NSCLC.