
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

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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.

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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 $\geq 50\%$, 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 $\geq 50\%$ 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 \geq 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 \geq 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.

EVIDENCE REPORT

INTRODUCTION

PURPOSE

The ESP Coordinating Center (ESP CC) is responding to a request from the VA National Oncology Program Office for a synthesis of evidence on the efficacy and safety of immune checkpoint inhibitors (ICIs) and epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) as adjuvant or neoadjuvant therapies for resectable non-small cell lung cancer (NSCLC), which is intended to inform the VHA's Oncology Clinical Pathways.

BACKGROUND

NSCLC is the most common form of lung cancer and as many as 80% of patients present with locally advanced or metastatic disease.¹⁻⁴ Patients diagnosed with earlier-stage disease typically undergo surgical resection of the tumor and may also be offered adjuvant therapies.^{1,3} Despite these interventions, NSCLC often recurs, and likelihood of survival falls precipitously with advancing stages of disease.^{1,5} Risk factors for lung cancer are prevalent among Veterans.⁶⁻⁸

ICIs and targeted therapies like EGFR-TKIs are important, and relatively recent, advancements in cancer treatment. ICIs block mechanisms that limit immune system activity, in turn increasing the production of tumor-specific immune cells that can attack cancer cells throughout the body.⁹ TKIs interrupt the activity of mutated genes involved in the unchecked cell growth that characterizes cancer.^{10,11} EGFR mutations are not present in all NSCLC.^{3,12,13} Similarly, the quantity of NSCLC cells expressing the regulatory pathways targeted by ICIs (including the programmed death 1 checkpoint and its ligand, PD-L1) varies among patients.³ In metastatic NSCLC, survival benefits of ICIs in combination with chemotherapy have been observed across PD-L1 expression levels for patients with NSCLC not driven by EGFR or other mutations, while EGFR-TKIs have shown more promise for patients with mutation-driven advanced NSCLC.^{1,3}

Clinical trials are investigating whether benefits of ICIs and EGFR-TKIs seen in metastatic NSCLC extend to early and locally advanced disease.^{5,14} 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.¹⁵⁻¹⁷ Approval of atezolizumab was limited to patients with PD-L1 expression on 1% or more of tumor cells.¹⁶ Another ICI, nivolumab, was recently approved as a neoadjuvant therapy (*ie*, prior to surgical resection) in combination with neoadjuvant platinum-doublet chemotherapy.¹⁸ 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 had been previously approved for treating advanced NSCLC.¹⁹⁻²⁴

Overall survival is generally considered the definitive efficacy outcome for curative-intent cancer therapies,²⁵⁻²⁷ but demonstrating overall survival benefit requires trials to enroll a large number of patients and to follow those patients for a long period.²⁸ In some cancers, such as early HER2-positive breast cancer, disease-free survival or other endpoints that are available sooner have been found to be surrogates of overall survival.²⁹ Improvement in an endpoint that is

a surrogate for overall survival corresponds to similar improvement in overall survival. Surrogacy varies across cancer types and subtypes and by treatment settings, 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.^{27,30-32}

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.^{33,34} 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.³³ 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.^{33,34}

These concerns are relevant to the VA setting, where lung cancers are the second-most frequently diagnosed cancers in Veteran women and men (behind breast and prostate cancers, respectively).^{35,36} 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 by clinicians, researchers, and policymakers about the use of approved agents. This review includes updated results from several key trials that were not available at the time of FDA approvals.

METHODS

PROTOCOL

A preregistered protocol for this review can be found on the PROSPERO international prospective register of systematic reviews ([CRD42022354489](https://www.crd42022354489)).

KEY QUESTIONS

The following key questions were the focus of this review:

Key Question 1	Among adults with resectable stage I-III NSCLC, what are the survival benefits and harms of adjuvant or neoadjuvant therapy using ICIs or EGFR-TKIs?
Key Question 1a	Do benefits or harms vary by patient characteristics (eg, age, comorbidities), molecular subgroups, or disease stage?

ELIGIBILITY CRITERIA

Study eligibility criteria are shown in the table below. For studies meeting these criteria, we employed a best-evidence approach to guide final decisions about study and outcome inclusion.

In the most well-developed research area, adjuvant therapy with EGFR-TKIs, we limited eligible studies to randomized controlled trials (RCTs). For adjuvant therapy with ICIs and neoadjuvant therapy with any eligible drug, we included RCTs and other comparative studies meeting eligibility criteria. Survival outcomes were the primary efficacy outcomes of interest in all areas. We prioritized overall and disease-free survival, and when these were not reported, we considered progression-free survival, event-free survival, and pathologic response measures. We did not include evidence from noncomparative studies (eg, single-group studies and case series). RCTs that were stopped early were eligible, but we examined outcome data only if the trial was terminated at a prespecified stopping boundary.

Population	Adults with stage I-III NSCLC who have undergone complete (R0) surgical resection (adjuvant) or with planned surgical resection (neoadjuvant)
Intervention	Adjuvant or neoadjuvant use of ICIs (anti-PD-1 or anti-PD-L1 antibodies including atezolizumab, durvalumab, nivolumab, pembrolizumab, and cemiplimab) or EGFR-TKIs (eg, gefitinib, erlotinib, afatinib, and osimertinib), with or without chemotherapy-based adjuvant therapy
Comparator	Surgical resection without adjuvant or neoadjuvant therapy using ICIs or EGFR-TKIs (eg, chemotherapy-based adjuvant therapy only, placebo intervention only)
Outcomes	Survival, pathologic response, adverse events
Study Design	RCTs, nonrandomized comparison studies <i>Excluded:</i> Retrospective observational studies, single-group studies, case series, and case studies

DATA SOURCES AND SEARCHES

To identify eligible studies, a research librarian searched Ovid MEDLINE, CINAHL, ClinicalTrials.gov, as other sources through August 2022 using terms for *non-small cell lung cancer, molecularly targeted agent, EGFR tyrosine kinase inhibitor, and immune checkpoint inhibitor* (see Appendix A for complete search strategies). Additional citations were identified through consultation with content experts and by hand-searching reference lists, the American Society of Clinical Oncology publications database (<https://ascopubs.org/>), and public search engines (eg, Google Scholar). Conference abstracts, professional group proceedings, and other non-peer-reviewed publications were included when they reported updated results of eligible studies not available elsewhere. English-language titles, abstracts, and full-text articles were independently reviewed by 2 investigators, and disagreements were resolved by consensus.

DATA ABSTRACTION AND RISK OF BIAS ASSESSMENT

Effect information and sample, intervention, and comparator characteristics of included studies were abstracted by 1 investigator, then checked by a second. For survival outcomes, we abstracted hazard ratios (HRs) and 95% confidence intervals (CIs), or *p*-values for log-rank tests when hazard ratios were unavailable. We also abstracted median survival, proportions of patients surviving up to 5 years, and maturity of survival outcome data (for RCTs only). When survival proportions were not reported but survival curves were available, we visually abstracted proportions using the WebPlotDigitizer platform (<https://apps.automeris.io/wpd/>). When RCTs did not report survival data maturity, we estimated maturity by dividing the total number of patients with an outcome event at the time of data cutoff by the number of patients randomized.

Study characteristics that could bias findings were assessed using Cochrane risk of bias tools for RCTs³⁷ and nonrandomized comparison studies.³⁸ Tools were completed independently by 2 investigators, and disagreements were resolved by consensus (see Appendix C). When assessing potential risks of bias, we considered several common sources of bias in clinical trials of cancer therapies and in studies with time-to-event outcomes.^{34,39} These included informative censoring, survival data immaturity, nonproportional hazards, and restriction of crossover in trials of non-novel drugs (drugs already approved for the treatment of more advanced NSCLC).

Informative censoring occurs when patients discontinue treatment and are censored for reasons related to the treatment itself, such as lack of benefit or intolerable side effects.^{34,40} Surrogate survival outcomes (eg, event-free or disease-free survival) may be at risk from informative censoring when there is disproportionate patient withdrawal or discontinuation of the trial drug because of adverse events. Survival data were considered immature when the proportion estimate of maturity was substantially lower than other available trials of the same therapy, when survival curves exhibited a long plateau (regardless of the proportion estimate of maturity), or when a trial explicitly reported that data were immature or made statements to that effect (eg, many or most patients had not yet experienced an outcome event).⁴¹ Survival curves were visually inspected for the following indicators of nonproportional hazards: curves that substantially diverged from one another, curves that crossed over with extensive follow-up remaining, and curves that separated late in follow-up.⁴² Differences in separation between curves over time was not considered a risk of bias when the largest and smallest separation would correspond to hazard ratios with similar meanings (eg, moderate to large survival benefits of the same therapy).

We considered survival findings from trials of adjuvant therapies using non-novel drugs to be at risk of bias when the trial restricted comparison-group patients from receiving the trial drug or similarly effective treatments for recurring disease. Comparing these patients can result in an apparent benefit of adjuvant therapy that is larger than what would be expected in clinical practice, where treatment of patients with disease recurrence would ordinarily not be delayed.

SYNTHESIS

Evidence was synthesized narratively by adjuvant and neoadjuvant applications and type of drug. We also investigated potential sources of variation in survival outcomes, including patient characteristics, disease severity, and prior treatment history. Whenever possible, we focused on estimates of survival that used information from the entire follow-up period (eg, hazard ratios from proportional hazards models) rather than survival estimates from single timepoints (eg, median survival or survival proportions). After synthesizing evidence for each outcome, we rated the strength of evidence for survival outcomes based on the methodology and risks of bias of available studies, the consistency and certainty of findings, and the directness of outcomes (whether reported outcomes are relevant to patients and providers).

Consistency in treatment effects occurs when studies conducted in independent settings and patient samples find similar effects. *Certainty* describes how similar the effects reported by a study, or set of studies, are to the true effect in the patient population of interest. Certainty is evident when the values in a confidence interval—the likeliest true values of an effect—are similar in meaning to the estimated effect. For example, if an estimate of overall survival is accompanied by a wide confidence interval with values that differ in direction and magnitude from the estimate, the true overall survival could be very different from the estimated overall survival. Often this occurs in small samples because it is unclear how representative a few patients are of a larger patient population, and therefore how near the effect in those few patients is to the effect in the population. In this way, certainty also reflects the amount of available evidence, given that larger studies and larger evidence bases tend to yield more precise findings.

Certainty and consistency describe different characteristics of an evidence base. In a group of studies, for instance, studies could be large and provide precise effect estimates. Despite certainty about effects in each study, studies may have been conducted in settings or patients that differed in obvious or unobserved ways, or delivered treatments at different dosages or frequencies. These differences may cause effects to vary in size and direction across studies. When estimates of these effects are synthesized, an overall conclusion about efficacy may not generalize to future studies or to real-world implementation of the treatment. In other words, the effect found by a future study could differ from the overall effect estimate, instead resembling the effect in an existing study that is most closely matched in design, setting, and patient characteristics. If available studies were small and provided imprecise effect estimates, future studies may also find a different effect. In this case, uncertainty about the treatment effect is because existing evidence provides an unclear picture of what the anticipated effect would be.

Strength of evidence was rated using the below criteria. Dashes (—) indicate strength of evidence levels that are unavailable because of the quantity, design, and risks of bias of relevant studies. For this review, directness was not assessed because eligibility criteria required studies to report clinically relevant outcomes.

	High Strength	Moderate Strength	Low Strength
Example Conclusion:	<i>“Adjuvant ICIs improve overall survival”</i>	<i>“Adjuvant ICIs likely improve overall survival”</i>	<i>“Adjuvant ICIs may improve overall survival”</i>
Multiple RCTs with low risk of bias - <i>with or without</i> - One or more NRCSs with low or moderate risk of bias	Effect estimates consistent in direction and magnitude - <i>and</i> - CIs contain a narrow range of values similar in meaning to effect estimate(s)	Effect estimates consistent in direction only - <i>and/or</i> - CIs contain a wider range of values that differ in meaning from effect estimate(s)	Effect estimates differ in direction
One RCT with low risk of bias - <i>or</i> - Multiple RCTs with some concerns , or mixed ratings of some concerns and low risk - <i>with or without</i> - One or more NRCSs not at critical risk of bias	—	Effect estimates consistent in direction and magnitude - <i>and</i> - CIs contain a narrow range of values similar in meaning to effect estimate(s)	Effect estimates differ in direction and/or magnitude - <i>and/or</i> - CIs contain a wider range of values that differ in meaning from effect estimate(s)
Multiple NRCSs with low risk of bias	—	—	—
One RCT with some concerns - <i>or</i> - Multiple RCTs with high risk of bias, or mixed ratings of some concerns and high risk - <i>with or without</i> - One or more NRCSs with any risk of bias rating	—	—	Low-strength evidence regardless of consistency or precision
Multiple NRCSs at moderate risk of bias, or with mixed ratings of low and moderate risk	—	—	—
One RCT with high risk of bias	—	—	—
One or more NRCSs at serious/critical risk of bias, or with mixed ratings of moderate and serious/critical risk	—	Insufficient Evidence (“It is unclear whether neoadjuvant ICIs improve overall survival”)	—
No available studies	—	—	—

Abbreviations. NCRS=nonrandomized comparison study; RCT=randomized controlled trial.

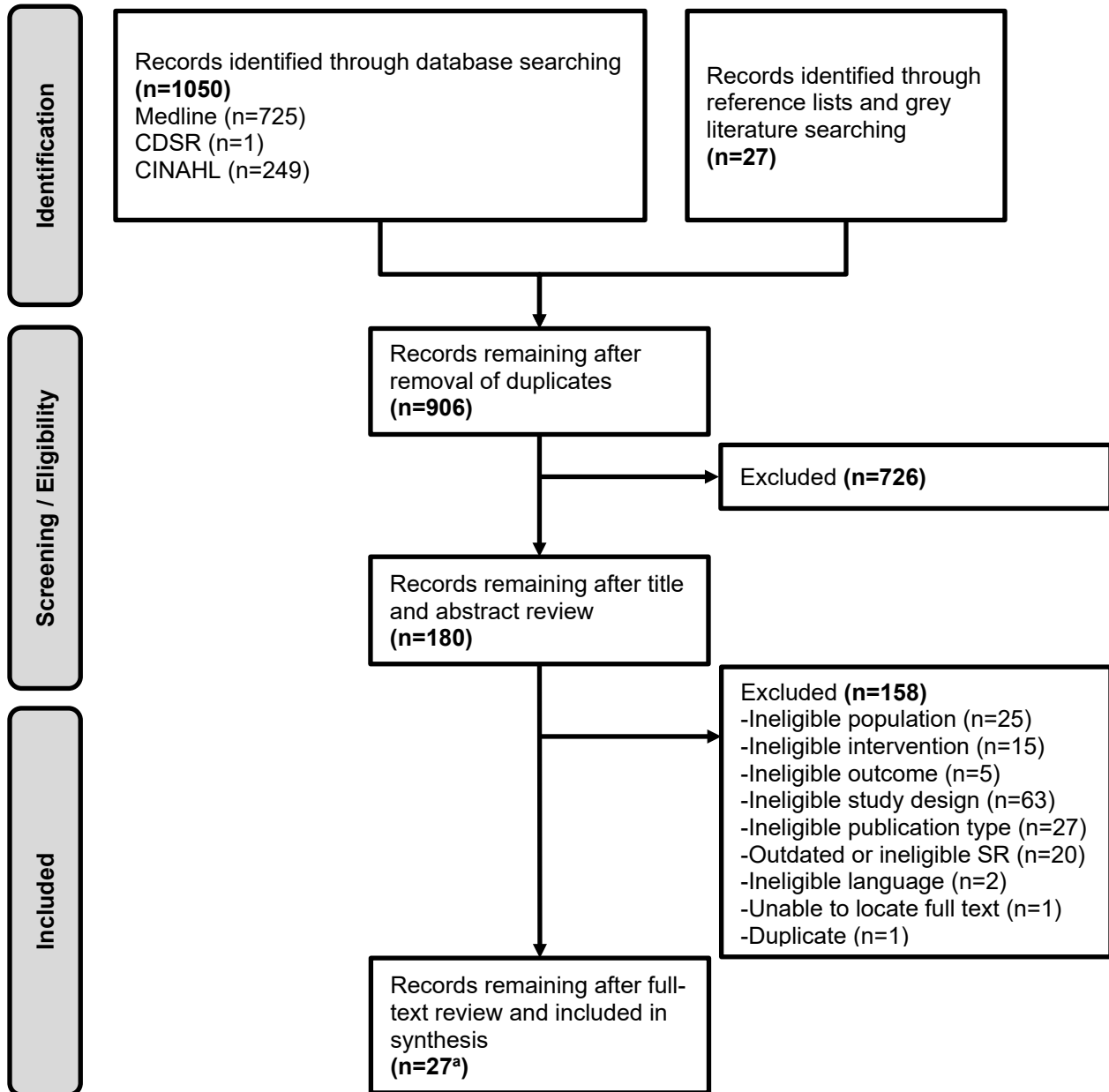


RESULTS

LITERATURE FLOW

The literature flow diagram (Figure 1) summarizes the results of the study selection process (see Appendix B for listing of excluded primary studies).

Figure 1. Literature Flowchart



Notes. ^a18 primary studies in 27 publications.

Abbreviations. CDSR=Cochrane Database of Systematic Reviews; CINAHL=Cumulative Index of Nursing and Allied Health; SR=systematic review.

LITERATURE OVERVIEW

Our search identified 906 potentially relevant articles. Of these, 18 primary studies (in 27 publications) met eligibility criteria:

- *Adjuvant ICIs*: Two phase 3 RCTs⁴³⁻⁴⁷ reporting survival outcomes and adverse events. We located updated results for 1 RCT (IMpower010) and subgroup analyses for the second RCT (PEARLS/KEYNOTE-091), both released in late 2022.
- *Adjuvant EGFR-TKIs*: Eight phase 2 or 3 RCTs⁴⁸⁻⁶¹ reporting survival outcomes and adverse events. We located updated results for 3 RCTs (ADAURA, EVAN, and RADIANT), including 2 updates released in late 2022 or early 2023. Two early RCTs^{62,63} that were terminated because of safety concerns were also identified.
- *Neoadjuvant ICIs*: One phase 3 RCT⁶⁴ reporting survival outcomes and adverse events and 1 additional study⁶⁵ reporting adverse events.
- *Neoadjuvant EGFR-TKIs*: No RCTs; 3 additional studies⁶⁶⁻⁶⁸ reporting survival outcomes and adverse events.
- *Combination Neoadjuvant-Adjuvant EGFR-TKIs*: One phase 2 RCT⁶⁹ reporting survival outcomes and adverse events.

Characteristics of primary studies are presented in Tables 1–4 and discussed in the following sections. Key characteristics and findings of RCTs are also highlighted in callout boxes in the results sections below. Unless otherwise noted, information presented in callout boxes pertains to the sample used in each trial’s prespecified main analysis (usually an intention-to-treat or “full-analysis” sample).

ADJUVANT THERAPY USING ICIs

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. For atezolizumab, results of prespecified exploratory analyses from the relevant trial (IMpower010) suggest disease-free survival benefit of adjuvant atezolizumab may be limited to patients with PD-L1 \geq 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. Evidence on survival benefits of adjuvant therapy with ICIs was considered moderate strength.

IMpower010⁴⁵⁻⁴⁷ is an open-label, multicenter RCT that randomized adults with resected stage IB–IIIA NSCLC (AJCC/UICC 7th edition) to receive atezolizumab (for up to 16 cycles or 1 year) or best supportive care after complete surgical resection and 1–4 cycles of adjuvant platinum-based chemotherapy. Best supportive care patients received regular scans for recurrence. Primary endpoints were investigator-assessed disease-free survival in patients with stage II–IIIA disease, patients with stage II–IIIA disease and PD-L1 \geq 1%, and in the intention to treat (stage IB–IIIA) sample. Secondary endpoints included disease-free survival in patients with PD-L1 \geq 50%, and overall survival in the intention to treat sample. At least 80% of patients received 4 cycles of adjuvant chemotherapy prior to randomization and just under half had an ECOG performance status of 1. Disease severity, PD-L1 status, and adjuvant chemotherapy exposure were well balanced across arms. Patients in the atezolizumab group were treated for a median of 10.4 months (interquartile range = 4.8–10.6). 65% of patients received the full 16 cycles of atezolizumab.

IMpower010

Atezolizumab / Best Supportive Care

N = 442 / 440
PD-L1 \geq 1%: 56% / 51%

Disease-free Survival

32% mature (2021)
Median (mo.): 42.3 / 35.3
4 yrs.: 48% / 38%
HR: 0.79 [0.64, 0.96]

Overall Survival

26% mature (2022)
Median (mo.): NR / NR
5 yrs.: 71% / 67%
HR: 0.95 [0.74, 1.24]

Follow-up (med.): 32 mo.
(DFS), 46 mo. (OS)

At an interim analysis of disease-free survival in the full stage II–IIIA (any PD-L1 status; 32% data maturity in early 2021), adjuvant therapy with atezolizumab resulted in modestly improved disease-free survival compared with best supportive care (Table 1). When examined by PD-L1 status, however, disease-free survival benefit was not apparent for patients with PD-L1 < 1% (HR = 0.97, 95% CI [0.72, 1.31]). In prespecified exploratory analyses in the PD-L1-positive group, patients with PD-L1 between 1–49% did not appear to experience improved disease-free survival over best supportive care (HR = 0.87, 95% CI [0.60, 1.26]). In contrast, patients with PD-L1 \geq 50% appeared to experience the greatest benefit (HR = 0.43, 95% CI [0.27, 0.68]).

Updated overall survival results for the stage II–IIIA sample were released in late 2022 at 26% data maturity. Results should be interpreted with caution because they were prespecified as exploratory and because the hierarchical analysis approach used in the trial means they have not been formally tested for statistical significance. Overall survival findings were consistent with disease-free survival. Compared with best supportive care, adjuvant atezolizumab appeared to improve overall survival in patients with PD-L1 \geq 50% (HR = 0.43, 95% CI [0.24, 0.78]), but not for patients with PD-L1 between 1–49% (HR = 0.95, 95% CI [0.59, 1.54]). For patients with PD-L1 < 1%, overall survival favored best supportive care (HR = 1.36, 95% CI [0.93, 1.99]).

Table 1. Characteristics and Survival Outcomes of Trials Comparing Adjuvant ICIs after Chemotherapy to Best Supportive Care or Placebo

Study (Phase) Stages (Sample)	Groups	N	Median Follow-up Months	Stage III %	ECOG Status 1 %	Disease-Free Survival					Overall Survival						
						HR [95% CI]					HR [95% CI]						
						Median Maturity	2 Yrs	3 Yrs	4 Yrs	5 Yrs	Median Maturity	2 Yrs	3 Yrs	4 Yrs	5 Yrs		
IMpower010 (3)																	
IB-IIIa (ITT) ^a	Atezolizumab	507	32 (DFS)	40	46	NR	0.81 [0.67, 0.99]	71	58	51 [†]	NA	NR	0.995 [0.78, 1.28]	88 [†]	79 [†]	77 [†]	72[†]
	BSC	498	46 (OS)	42	43	37.2	32% (2021)	64	53	43 [†]	NA	NR	26% (2022)	89 [†]	81 [†]	73 [†]	69[†]
II-IIIa (ITT) ^b	Atezolizumab	442	32 (DFS)	46	45	42.3	0.79 [0.64, 0.96]	70	56	48 [†]	NA	NR	0.95 [0.74, 1.24]	88 [†]	78 [†]	76 [†]	71[†]
	BSC	440	46 (OS)	47	43	35.3		62	49	38 [†]	NA	NR		88 [†]	79 [†]	70 [†]	67[†]
II-IIIa (PD-L1 <1%)	Atezolizumab	383	NA (DFS)	NA	NA	36.1	0.97 [0.72, 1.31]	NA	NA	NA	NA	NR	1.36 [0.93, 1.99]	NA	NA	NA	NA
	BSC	383	46 (OS)	NA	NA	37.0		NA	NA	NA	NA	NR		NA	NA	NA	NA
II-IIIa (PD-L1 ≥1%)	Atezolizumab	248	33	47	43	NR	0.66 [0.50, 0.88]	75	60	51 [†]	NA	NR	0.71 [0.49, 1.03]	91 [†]	82	79 [†]	77
	BSC	228		50	45	35.3		61	48	43 [†]	NA	NR		87 [†]	79	72 [†]	68
II-IIIa (PD-L1 1-49%)	Atezolizumab	247	NA	NA	NA	32.8	0.87 [0.60, 1.26]	NA	NA	NA	NA	NA	0.95 [0.59, 1.54]	NA	NA	NA	NA
	BSC	247		NA	NA	31.4		NA	NA	NA	NA	NA		NA	NA	NA	NA
II-IIIa (PD-L1 ≥50%)	Atezolizumab	229	NA (DFS)	NA	NA	NR	0.43 [0.27, 0.68]	NA	NA	NA	NA	NA	0.43 [0.24, 0.78]	98^{†c}	89^c	85^{†c}	85^c
	BSC	229	46 (OS)	NA	NA	35.7		NA	NA	NA	NA	NA		87^{†c}	78^c	70^{†c}	68^c
PEARLS/KEYNOTE-091 (3)																	
IB-IIIa (ITT) ^c	Pembrolizumab	590	36	30	36	53.6	0.76 [0.63, 0.91]	67	58	51 [†]	44 [†]	NR	0.87 [0.67, 1.15]	89	82	76 [†]	75 [†]
	Placebo	587		28	42	42.0	40% (2021)	59	50	45 [†]	45 [†]	NR	18% (2021)	88	80	74 [†]	70 [†]
IB-IIIa (PD-L1 <1%)	Pembrolizumab	233	NA	NA	NA	47.4	0.78 [0.58, 1.03]	69 [†]	56 [†]	47 [†]	38 [†]	NA	NA	NA	NA	NA	NA
	Placebo	232		NA	NA	34.9		59 [†]	53 [†]	47 [†]	44 [†]	NA	NA	NA	NA	NA	NA
IB-IIIa (PD-L1 1-49%)	Pembrolizumab	189	NA	NA	NA	44.2	0.67 [0.48, 0.92]	65 [†]	55 [†]	49 [†]	41 [†]	NA	NA	NA	NA	NA	NA
	Placebo	190		NA	NA	31.3		54 [†]	45 [†]	45 [†]	45 [†]	NA	NA	NA	NA	NA	NA
IB-IIIa (PD-L1 ≥50%)	Pembrolizumab	168	NA	31	31	NR	0.82 [0.57, 1.18]	68	66	60 [†]	60 [†]	NA	NA	NA	NA	NA	NA
	Placebo	165		30	39	NR		67	58	51 [†]	51 [†]	NA	NA	NA	NA	NA	NA

Notes. Boldface indicates updated findings or newly reported data. Survival proportions denoted with a dagger (†) were abstracted from survival curves using the WebPlotDigitizer platform.

^aPD-L1 ≥ 1%: 56% in atezolizumab group; 51% in best supportive care group.

^bPD-L1 ≥ 1%: 56% in atezolizumab group; 52% in best supportive care group.

^cExcludes 20 patients with EGFR mutation-positive or anaplastic lymphoma kinase (ALK)-positive NSCLC. Patients are included in overall survival HR (without 20 patients = 0.42 [0.23, 0.78]).

^dPD-L1 ≥ 1%: 61% in pembrolizumab group; 60% in placebo group.

Abbreviations. BSC=best supportive care; DFS=disease-free survival; ECOG=Eastern Cooperative Oncology Group performance-status; HR=hazard ratio; ITT=intention-to-treat sample; NA=not available; NR=not reached; OS=overall survival; PD-L1=programmed death ligand 1 expression; Yrs=years.



Thirteen additional months of follow-up data on adverse events were available with the updated interim results. Adverse events of any grade were more frequent in patients receiving atezolizumab (93%; 68% treatment related) than patients receiving best supportive care (71%). Twice as many grade 3 or 4 adverse events occurred in the atezolizumab group (22.0% vs 11.5%; 7.5% treatment related). Grade 5 events were rare in both groups (1.8% and 0.6%, respectively). At the earlier data cutoff, the most common treatment-related grade 3 or 4 events were hypothyroidism, pruritis, and rash. Immune-mediated adverse events of any grade occurred in 52% of patients receiving atezolizumab and 9% of patients receiving best supportive care. No adverse events in the best supportive care group were attributed to treatment. 54% of patients who discontinued atezolizumab did so because of adverse events, compared with 4% of patients who discontinued best supportive care.

Finally, although the study protocol did not allow patients in the best supportive care group to receive atezolizumab at the time of recurrence, 12 (6%) of 212 patients with recurrence were treated with atezolizumab with or without another anticancer therapy. In all, 131 best supportive care patients with recurrence received 1 or more non-protocol systemic therapies (including other ICIs, EGFR-TKIs, and chemotherapy), 82 received radiotherapy, and 37 had 1 or more additional surgeries. Similar proportions of patients in the atezolizumab group received these treatments after recurrence. The extent of non-protocol treatment in the PD-L1 \geq 50% subgroup, and the proportion of DFS events that were recurrence or new malignancy, are unclear.

PEARLS/KEYNOTE-091,^{43,44} a second phase 3 multicenter RCT, used a triple-blind design and randomized patients with completely resected stage IB–IIIA NSCLC (AJCC/UICC 7th edition) to receive pembrolizumab (for 18 cycles or 1 year) or placebo. Prior adjuvant chemotherapy was not required, but like IMpower010, at least 80% of patients in both groups previously received 3–4 doses of platinum-based adjuvant chemotherapy. Patients with any PD-L1 status were enrolled. Disease-free survival in the full sample of stage IB–IIIA patients and the subgroup of patients with PD-L1 \geq 50% were primary endpoints; to date, only overall survival in the full IB–IIIA sample has been reported. Most patients had stage II–IIIA disease and about 40% had an ECOG performance status of 1. Patient characteristics, disease severity, and exposure to prior adjuvant chemotherapy were balanced across groups. 52% of treatment-group patients received the planned 18 cycles of pembrolizumab. Median duration and number of treatments were similar in both groups.

PEARLS/KEYNOTE-091
Pembrolizumab / Placebo

N = 590 / 587
PD-L1 \geq 1%: 61% / 60%

Disease-free Survival
40% mature (2021)
Median (mo.): 53.6 / 42.0
5 yrs.: 44% / 45%
HR: 0.76 [0.63, 0.91]

Overall Survival
18% mature (2021)
Median (mo.): NR / NR
5 yrs.: 75% / 70%
HR: 0.87 [0.67, 1.15]

Follow-up (med.): 36 mo.

At an interim analysis with data at 40% maturity (Table 1), disease-free survival was moderately improved for patients receiving pembrolizumab compared with placebo (HR = 0.76, 95% CI [0.63, 0.91]). Overall survival did not significantly differ between groups in the full sample of patients with stage IB–IIIA disease. Subgroup analyses of overall survival by PD-L1 expression level have not yet been reported. In subgroup analyses by disease stage, only patients with stage II disease experienced significant disease-free survival benefit. Disease-free survival was improved by a similar magnitude for stage IB patients receiving pembrolizumab, but the hazard ratio was nonsignificant. In contrast to IMpower010, minimal benefit was observed for patients with stage IIIA disease (HR = 0.92, 95% CI [0.69, 1.24]), although it is important to note that this estimate incorporates patients with PD-L1 < 1%. The largest disease-survival benefit of

pembrolizumab was found in stage IB–IIIA patients with PD-L1 between 1% and 49% (HR = 0.67, 95% CI [0.48, 0.92]). Nonsignificant improvements in disease-free survival were observed in patients with PD-L1 \geq 50% and PD-L1 < 1 %.

Disease-free survival in patients with stage IB–IIIA disease did not differ by patient age, sex, or ECOG status. Adjuvant pembrolizumab did not appear to improve disease-free survival without prior adjuvant chemotherapy (HR = 1.25, 95% CI [0.76, 2.05]). Contrary to IMpower010, current smokers appeared to benefit from receiving pembrolizumab (HR = 0.42, 95% CI [0.23, 0.77]) more than former or never smokers. Patients with squamous tumors also did not appear to benefit (HR = 1.04, 95% CI [0.75, 1.45]) compared with patients with non-squamous tumors (HR = 0.67, 95% CI [0.54, 0.83]). Only subgroup estimates by PD-L1 expression level were adjusted for smoking status and tumor histology, so differences in disease-free survival by prior adjuvant chemotherapy use may be confounded by smoking status and tumor histology. Findings on prior adjuvant chemotherapy use are at risk of confounding by disease stage because disease stage influences the likelihood that adjuvant chemotherapy is offered to patients with NSCLC.

Adverse events of any grade occurred in 96% of patients receiving pembrolizumab and 91% of patients receiving placebo. Grade 3 or 4 adverse events occurred in 32% of pembrolizumab group patients and 25% of placebo patients. As in IMpower010, grade 5 adverse events were rare in both groups (2% and 1%, respectively). Treatment-related adverse events of any grade occurred in 75% of pembrolizumab patients and 52% of placebo patients. The most common treatment-related adverse events of any grade were hypothyroidism, pruritis, diarrhea, and fatigue. 15% of treatment group patients experienced a grade 3 or worse treatment-related adverse event, compared with 4% of placebo patients. The most frequent of these in the pembrolizumab group were pneumonitis and diarrhea. Immune-mediated adverse events and infusion reactions occurred in 39% of patients receiving pembrolizumab and 13% of patients in the placebo group. 47% of patients who discontinued pembrolizumab did so because of adverse events, compared with 14% of those who discontinued placebo.

Finally, 90% or more of disease-free survival events in both groups were recurrence or new malignancy. Patients with recurrence in the placebo group were not permitted to receive pembrolizumab, and it is not clear from the trial protocol or available publications whether patients with recurrence were treated off-protocol with pembrolizumab, other ICIs or systematic anticancer therapies, or radiotherapy.

Combination Neoadjuvant-Adjuvant Therapy

No studies with published findings were found comparing combination neoadjuvant-adjuvant therapy with the same ICI to placebo or neoadjuvant-adjuvant chemotherapy alone. NADIM-II ([NCT03838159](https://clinicaltrials.gov/ct2/show/study/NCT03838159)) is an open-label phase 2 RCT that randomized 90 patients with resectable stage III NSCLC (AJCC/UICC 7th edition) to receive 3 cycles of nivolumab plus platinum-based chemotherapy preoperatively followed by 6 months of adjuvant nivolumab, or 3 cycles of platinum-based chemotherapy preoperatively followed by an additional 3 cycles of adjuvant chemotherapy.

Preliminary findings on progression-free and overall survival were made available in a late 2022 conference presentation.⁷⁰ At 24 months of follow-up, overall survival was significantly improved in the nivolumab plus chemotherapy group compared with the chemotherapy-alone group (HR = 0.37, 95% CI [0.14, 0.93]; 85.3% versus 64.8%, respectively). Progression-free

survival also appeared to favor nivolumab plus chemotherapy, but this result was nonsignificant (HR = 0.56, 95% CI [0.28, 1.15]; 67.3% versus 52.6%, respectively). In the nivolumab plus chemotherapy group, patients with PD-L1 \geq 1% were significantly more likely to experience improved progression-free survival compared with patients with PD-L1 < 1% (HR = 0.26, 95% CI [0.08, 0.77]). A comparable analysis for overall survival has not been reported. Because findings from NADIM-II have not yet been reported in a peer-reviewed publication, we did not include the trial in strength of evidence ratings.

Strength of Evidence

Evidence on disease-free survival benefits of adjuvant therapy using ICIs was considered moderate strength. Evidence on overall survival benefits was considered low strength. Immaturity of survival data and differences in reporting of trial findings are the main limitations of available evidence and create uncertainty about the magnitude of survival benefits, especially by PD-L1 expression level. Another concern in both trials is that patients receiving ICIs discontinued adjuvant therapy because of adverse events at a much higher rate than patients receiving placebo or best supportive care. Because neither trial counted treatment discontinuation due to adverse events toward disease-free survival outcomes, survival estimates may be at risk of bias from informative censoring.

Underway Studies

A phase 3, placebo-controlled trial of adjuvant durvalumab ([NCT02273375](#)) in approximately 1400 patients with resected stage IB–IIIA NSCLC is expected to conclude in early 2024. According to its registration information, the trial will report disease-free by several PD-L1 expression levels and by EGFR mutation status. Overall survival will be assessed as a secondary endpoint in the same subgroups. ANVIL ([NCT02595944](#)) is a phase 3 trial comparing adjuvant nivolumab to observation alone in about 900 patients with resected stage IB–IIIA disease and previous adjuvant chemotherapy, and is expected to conclude in late 2025. Disease-free and overall survival are both planned primary endpoints. NADIM-ADJUVANT ([NCT04564157](#)), another phase 3 trial in patients with stage IB–IIIA disease, is currently recruiting and will compare initial adjuvant therapy with nivolumab plus chemotherapy followed by adjuvant nivolumab, to adjuvant chemotherapy alone. Disease-free and overall survival will be assessed as primary and secondary endpoints, respectively.

A phase 2 trial of adjuvant pembrolizumab or observation in patients with completely resected stage I NSCLC ([NCT04317534](#)) is currently recruiting and will also assess disease-free (primary endpoint) and overall survival (secondary endpoint). Two trials investigating combination neoadjuvant-adjuvant therapy with ICIs in patients with resected stage II–IIIB disease are described in more detail below. KEYNOTE-671, a double-blind phase 3 trial ([NCT03425643](#)), is underway and compares neoadjuvant pembrolizumab plus platinum-doublet chemotherapy to a placebo ICI plus neoadjuvant platinum-doublet chemotherapy, followed by adjuvant pembrolizumab or a placebo ICI. Approximately 800 patients with resectable stage II–IIIB NSCLC have been recruited. Planned outcomes include event-free survival, overall survival, and pathologic complete response, and primary data collection is expected to conclude in 2026. A similarly designed trial using nivolumab ([NCT04025879](#)) is also expected to conclude in 2024.

ADJUVANT THERAPY USING EGFR-TKIs

In patients with resected, 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, ADAURA, found that adjuvant therapy with osimertinib, a third-generation EGFR-TKI, led to substantially improved disease-free survival over placebo. Evidence on disease-free survival benefits of adjuvant therapy with EGFR-TKIs was considered moderate strength, largely based on findings from ADAURA. 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. Evidence on overall survival benefits of adjuvant EGFR-TKIs was considered low strength.

We identified 8 trials investigating adjuvant therapy with EGFR-TKIs in patients with resected NSCLC. Two were early placebo-controlled trials^{62,63} of first-generation EGFR-TKIs that did not enroll patients based on EGFR mutation status and that were terminated early due to concerns about treatment harms. We did not consider evidence from these trials. Characteristics and findings of the 6 remaining trials are shown in Table 2. Perhaps the most widely discussed recent trial of adjuvant EGFR-TKIs is ADAURA.⁵⁴⁻⁵⁶ Findings on disease-free survival from an unplanned interim analysis led to FDA approval of the third generation EGFR-TKI osimertinib¹⁵ for adjuvant use in patients with resected stage IB–IIIA NSCLC bearing the most common EGFR mutations (exon 19 deletion or exon 21 L858R mutations). Osimertinib has been FDA approved as a first-line treatment²⁰ of metastatic EGFR mutation-positive NSCLC since 2018, and as a second-line therapy¹⁹ for a subgroup of EGFR mutation-positive patients with metastatic disease since 2015.

ADAURA is a double-blind, phase 3 RCT that randomized patients with resected, EGFR mutation-positive stage IB–IIIA NSCLC (AJCC/UICC 7th edition) to 3 years of adjuvant therapy with osimertinib or placebo. 60% of patients in both arms had previously received adjuvant chemotherapy. Two-thirds or more of patients had an ECOG performance score of 0, lymph node status of N0 or N1, and had never smoked (1% were current smokers). In both groups, one-third of patients had stage IB, II, or IIIA disease. Median age was comparable to other trials in this group but was slightly higher for in the osimertinib group (64 versus 62 years). 68–72% of patients were female and two-thirds were Asian. Overall, disease severity and patient characteristics were well balanced. Investigator-assessed disease-free survival in the subsample of patients with stage II–IIIA disease was the trial’s primary endpoint. Overall survival was a secondary endpoint, likely because the trial was not powered to demonstrate differences in overall survival.⁵⁴

ADAURA

Stage II-IIIa Subsample
Osimertinib / Placebo

N = 233 / 237
EGFRm+: 100% / 100%

Disease-free Survival

51% mature (2022)
Median (mo.): 65.8 / 21.9
3 yrs.: 84% / 34%
HR: 0.23 [0.18, 0.30]

Overall Survival

5% mature (2020)
Median (mo.): NR / NR
3 yrs.: 92% / 89%
HR: 0.40 [0.09, 1.83]

Follow-up (med.):
44 mo. / 20 mo.

Results of the unplanned interim analysis that led to FDA approval of adjuvant osimertinib were published in 2020. A prespecified interim analysis of disease-free survival was planned when data reached 50% maturity. Results of the planned analysis as well as updated adherence and adverse event data were reported in a late-2022 conference presentation^{71,72} and subsequent peer-reviewed publication⁵⁶ that was located before finalization of this report. To date, the only overall survival findings available are from the earlier unplanned interim analysis when data

were at only 5% mature. At the 2022 cutoff, 66% of patients in the osimertinib arm had completed the planned 3 years of adjuvant therapy, compared with 41% in the placebo arm. Median treatment duration was 36 months and 25 months, respectively.

With disease-free survival data at 51% maturity, adjuvant therapy with osimertinib resulted in significantly longer disease-free survival than placebo in patients with stage II–IIIA disease. In prespecified subgroup analyses in the overall stage IB–IIIA sample, benefits were similar for male and female patients, patients younger than 65 and 65 or older, and Asian patients and patients of other races/ethnicities. Benefits were somewhat smaller, but did not significantly differ, for patients with history of smoking (versus never smokers), patients with exon L858R mutations (versus exon 19 deletion), patients with stage IB or II disease (versus stage IIIA), and patients who had received previous adjuvant chemotherapy (versus those who had not). In a post hoc analysis in the overall sample restaged using the AJCC/UICC 8th edition manual, the proportion of patients in each stage was not substantially altered and main disease-free survival findings were consistent with those reported under 7th edition staging. After restaging, 22 patients were staged as IA, IIIB, or IV.

For overall survival, the reported hazard ratio corresponds to a large survival difference in favor of osimertinib, but the estimate is based on immature survival data and its wide confidence interval means that it is very uncertain whether the true survival benefit is larger, smaller, or in a different direction than the effect suggested by the hazard ratio. No subgroup analyses of overall survival have been reported, and a final overall survival analysis is planned when data have reached 20% maturity (corresponding to approximately 94 deaths in the stage II–IIIA sample).

The finding that disease-free survival benefits among IB–IIIA patients were similar regardless of prior adjuvant chemotherapy is at risk of confounding by disease stage, as discussed for PEARLS/KEYNOTE-091. We located a secondary analysis⁵⁵ of data from the unplanned cutoff that reported within-stage estimates of disease-free survival by adjuvant chemotherapy use, which addresses this confounding risk. In patients with stage II and IIIA disease, disease-free survival improvements with osimertinib were comparable regardless of prior adjuvant chemotherapy use. Improvement was not as substantial, but still significantly favored osimertinib, in stage IB patients who had not received adjuvant chemotherapy (HR = 0.38, 95% CI [0.15, 0.88]). Disease-free survival in patients with stage IB disease who received prior adjuvant chemotherapy was not reported (too few outcome events occurred in this subgroup).

Prior adjuvant chemotherapy was much less common in stage IB patients (26%) than in patients with stage II and IIIA disease (71–80%). This difference likely explains the low number of outcome events among stage IB patients who received adjuvant chemotherapy, and is consistent with an interaction between disease stage and likelihood of adjuvant chemotherapy exposure. Moreover, except in the stage IB subgroup, all disease-free survival curves comparing study arms in the stage II–IIIA sample and by prior adjuvant chemotherapy and disease stage exhibit clear divergence (likely violating the proportional hazards assumption). Accounting for this would probably not change the overall interpretation of hazard ratios, but it does suggest that the magnitude of disease-free survival benefit of adjuvant osimertinib varies over time.

Table 2. Characteristics and Survival Outcomes of Trials Comparing Adjuvant EGFR-TKIs to Placebo or Chemotherapy in EGFRm+ Patients

Study (Phase) Stages (Sample)	Groups	N	Disease-Free Survival				Overall Survival											
			Median Follow-up	Stage III	Med. Tx. Duration ^c	ECOG Status 1	HR [95% CI]				HR [95% CI]							
			Months	%	Months	%	Median Months	Maturity	2 Yrs	3 Yrs	4 Yrs	5 Yrs	Median Months	Maturity	2 Yrs	3 Yrs	4 Yrs	5 Yrs
ADAURA (3) <i>II-IIIa (FAS)</i>	Osimertinib	233	44	50	36	36 ^a	65.8	0.23 [0.18, 0.30]	90	84	70	53[†]	NR	0.40 [0.09, 1.83] ^b	100	92 [†]	NA	NA
	Placebo	237	20	50	25	36 ^a	21.9	51% (2022)	46	34	29	25[†]	NR	5% (2020)	93	89 [†]	89 [†]	NA
RADIANT (3) <i>IB-IIIa (EGFRm+)</i>	Erlotinib	102	60 ^d	18	21	39	47.8	0.75 [0.48, 1.16]	75	64	44	NA	NR	1.19 [0.61, 2.31]	90	83	75	70
	Placebo	59		31	22	36	28.5	52% (2014)	54	42	42	NA	NR	24% (2014)	91	85	80	66
EVAN (2) <i>IIIa-N2 (ITT)</i>	Erlotinib	51	55	100	24	57	42.4	0.38 [0.20, 0.70]	81	54	48[†]	48	84.2	0.37 [0.19, 0.73]	97 [†]	95 [†]	86 [†]	85
	Cis+Vin	51	64	100	74%	55	21.0	82% (2022)	45	20	13[†]	NA	61.1	53% (2022)	86 [†]	67 [†]	53 [†]	51
ADJUVANT (3) <i>II-IIIa (FAS)</i>	Gefitinib	111	80	65	22	65	30.8	0.56 [0.40, 0.79]	65 [†]	40	28 [†]	23	75.5	0.92 [0.62, 1.36]	86 [†]	73 [†]	58 [†]	53
	Cis+Vin	111		64	84%	77	19.8	65% (2020)	39 [†]	33	27 [†]	23	62.8	45% (2020)	78 [†]	68 [†]	58 [†]	51
EVIDENCE (2) <i>II-IIIa (FAS)</i>	Icotinib	151	25	66	22	68	47.0	0.36 [0.24, 0.55]	82 [†]	64	43 [†]	NA	NR	0.91 [0.42, 1.94]	94 [†]	86 [†]	83 [†]	NA
	Cis+Vin/Pem	132		61	68%	70	22.1	35% (2020)	46 [†]	33	32 [†]	NA	NR	10% (2020)	93 [†]	90 [†]	79 [†]	NA
IMPACT (3) <i>II-III (ITT)</i>	Gefitinib	116	70	64	NA ^e	19	35.9	0.92 [0.67, 1.28]	64	48	45 [†]	32	NR	1.03 [0.65, 1.65]	94	92	86 [†]	78
	Cis+Vin	116		65	78%	22	25.1	65% (2020)	52	45	38 [†]	34	NR	31% (2020)	94	88	82 [†]	75

Notes. Boldface indicates updated findings or newly reported data. Survival proportions and related values denoted with a dagger (†) were abstracted from survival curves using the WebPlotDigitizer platform.

^aCalculated in overall (IB-IIIa) sample.

^bHR reported with 99.98% confidence interval.

^cFor adjuvant chemotherapy arms, value is proportion (%) completing 4 treatment cycles.

^dCalculated in overall (EGFRm+ and EGFRm-) sample.

^e61% treated for the planned 2 years.

Abbreviations. CT=chemotherapy; EGFRm+=epidermal growth factor receptor mutation positive; ECOG=Eastern Cooperative Oncology Group performance-status; FAS=full analytic sample; HR=hazard ratio; ITT=intention-to-treat sample; med=median; NA=not available; NR=not reached; tx=treatment; Yrs=years.



Any-grade adverse events were common in both arms. Grade 3 or worse events were less frequent but occurred more often in the osimertinib group (23% versus 14%). Treatment-related grade 3 or worse adverse events were also more common with osimertinib (11% versus 2%). The most reported any-grade adverse events attributed to osimertinib were diarrhea, paronychia, and skin dryness and itchiness. At the late-2022 update, 13% of patients receiving osimertinib and 3% of placebo patients had discontinued treatment because of an adverse event. Treatment discontinuation for any reason was more frequent in the placebo group (60%) than in the osimertinib group (34%). 84% of patients who discontinued placebo did so because of disease recurrence, and overall, disease recurrence and metastases were more common in the placebo group than in the osimertinib group (recurrence: 60% versus 27%; distant metastases: 31% versus 13%). Patients in the placebo group were permitted to receive osimertinib on recurrence, but the proportion of these patients actually receiving osimertinib is not clear.

ADAURA shares several features with RADIANT,^{51,52} an earlier phase 3 trial of a first-generation EGFR-TKI. Both trials used blinded placebo-controlled designs, planned to deliver 2 or more years of adjuvant therapy, and were eligible to patients with resected stage I–III NSCLC. Overall, both trials enrolled fewer patients with stage IIIA disease and ECOG performance status of 1 (compared with stage IA or II disease and ECOG status of 0). ADAURA enrolled only EGFR mutation-positive patients, while RADIANT reported findings in a well-balanced subsample of 161 EGFR mutation-positive patients (17% of the main sample). Both trials included patients regardless of prior adjuvant chemotherapy use. In addition, the trial enrolled more patients with stage I disease (51%, compared with 32% in ADAURA), randomized on a 2:1 basis, and planned to deliver adjuvant therapy for 2 years rather than 3 years as in ADAURA. About 60% of patients were male and two-thirds were former smokers (11% were current smokers). In ADAURA, most patients had never smoked and two-thirds were female. Median age was comparable between trials.

RADIANT

EGFRm+ Subsample
Erlotinib / Placebo

N = 102 / 59
EGFRm+: 100% / 100%

Disease-free Survival

52% mature (2014)
Median (mo.): 46.4 / 28.5
4 yrs.: 44% / 42%
HR: 0.75 [0.48, 1.16]

Overall Survival

24% mature (2014)
Median (mo.): NR / NR
5 yrs.: 70% / 66%
HR: 1.19 [0.61, 2.31]

Follow-up (med.): NA
(60 mo. in main sample)

Erlotinib and placebo groups in the EGFR mutation-positive subsample of RADIANT were well balanced on most patient and disease characteristics, and the distribution of these characteristics was comparable to the main sample of patients with EGFR-mutated or wild-type NSCLC. Groups were imbalanced by disease stage and prior adjuvant chemotherapy use, however. More patients in the erlotinib group had stage I disease (52% versus 41%) and more patients in the placebo group had stage IIB or IIIA disease (59% versus 38%). In both the main sample and the EGFR mutation-positive subgroup, more patients in the placebo group received adjuvant chemotherapy before the trial (56% versus 45% in the EGFR mutation-positive subgroup). Just over half of patients in the EGFR mutation-positive subgroup completed adjuvant therapy or placebo as planned, and the median treatment duration was also similar in both groups (21 and 22 months, respectively). Median treatment duration in the main sample was 12 and 22 months, respectively. Dose reductions were much more common in erlotinib-group patients in both samples (44–46% versus 3–4%), and discontinuation because of adverse events was similarly imbalanced.

RADIANT reported final follow-up results with disease free-survival data at 52% maturity, overall survival data at 24% maturity, and a median follow-up of 60 months in the main sample.

In EGFR mutation-positive patients, adjuvant erlotinib resulted in a small and nonsignificant disease-free survival improvement compared with placebo (Table 2). Overall survival appeared to be somewhat worse with adjuvant erlotinib than with placebo. Subgroup analyses were reported only at an earlier interim analysis and only for the disease-free survival in the full patient sample.

34% of EGFR mutation-positive patients in the erlotinib group experienced disease recurrence, compared with 53% of patients receiving placebo. Patients were not permitted to receive treatment with the trial drug on recurrence. No other details were provided about the types and extent of subsequent treatments for recurrence. In the EGFR mutation-positive subgroup, 93% of patients in the erlotinib group experienced an any-grade event compared with 41% of placebo-group patients. No grade 3 or worse adverse events occurred in the placebo group, compared with 19% in the erlotinib group. The most common of these were rash and diarrhea. 30% of patients discontinued erlotinib because of adverse events (versus 5% in the placebo group).

Earlier Investigational Trials

A second group of investigational RCTs compared early-generation EGFR-TKIs to standard care (adjuvant platinum-doublet chemotherapy) in patients whose NSCLC was generally more advanced (Table 2). Across trials, two-thirds or more of patients had stage IIIA disease with N2 lymph node status, and in 3 of the 4 trials, the majority of patients had an ECOG performance status of 1. These trials also differed from the placebo-controlled trials by limiting enrollment to patients who had not previously treated with systematic anti-cancer therapies or radiotherapy.

Survival findings reported by 3 of 4 available trials are based on relatively mature survival data. The most mature data is from the EVAN trial,^{57,58} an open-label phase 2 RCT that was also the only trial to enroll only patients with stage III disease (AJCC/UICC 7th edition). Patients were randomized to 2 years of erlotinib or 4 cycles of platinum doublet chemotherapy. At baseline, just over half of patients had an ECOG status of 1 and 97% of patients had an N2 lymph node status. Most patients were nonsmokers and female, and median patient age was 58. Disease severity and patient characteristics were well balanced.

Adherence to adjuvant therapies was high in both groups. 78% of patients in the erlotinib group were treated for longer than 18 months, while 74% of patients in the chemotherapy group completed the planned 4 treatment cycles. Final disease-free and overall survival findings were reported in late 2022. Both disease-free survival and overall survival were significantly longer for patients who received adjuvant erlotinib compared with those who received adjuvant chemotherapy. Nonsignificant differences favored male patients, smokers, and patients with an EGFR mutation involving an exon 19 deletions (versus exon 21 L858R mutations). In the erlotinib group, patients with a mutation to the UBXN11 gene cooccurring with the EGFR mutation experienced significantly poorer disease-free survival (HR = 3.76, $p = .011$) compared to those without the co-mutation. Overall survival benefit also appeared to favor patients with exon 19 deletions and ECOG statuses of 0, and smokers, but these differences were nonsignificant.

EVAN

Erlotinib / CT

N = 51 / 51

EGFRm+: 100% / 100%

Disease-free Survival

82% mature (2022)

Median (mo.): 42.4 / 21.0

4 yrs.: 48% / 13%

HR: 0.38 [0.20, 0.70]

Overall Survival

53% mature (2022)

Median (mo.): 84.2 / 64.1

5 yrs.: 85% / 51%

HR: 0.37 [0.19, 0.73]

Follow-up (med.): 55 / 64 mo.

43.1% of patients in the erlotinib group experienced disease recurrence, compared with 54.9% of patients treated with chemotherapy. Two-thirds (68%) of patients with recurrence in the chemotherapy group were subsequently treated with an EGFR-TKI, most with a first-generation TKI like erlotinib. Any-grade adverse events occurred in 58% of patients treated with erlotinib and 65% of patients receiving chemotherapy. Most any-grade events were attributed to treatment in both groups. Treatment-related grade 3 or higher adverse events were more frequent in the chemotherapy group (26% versus 8%). No deaths were attributed to treatment and discontinuing treatment due to adverse events was rare in both groups.

Comparable findings on disease-free survival were reported by the ADJUVANT⁵⁹⁻⁶¹ trial, which has also been reported as ADJUVANT-CTONG1104. ADJUVANT was an open-label phase 3 trial that was somewhat larger than EVAN and enrolled patients with stage II and IIIA disease (64% were stage IIIA; AJCC/UICC 7th edition). Like EVAN, patients were randomized to 2 years of adjuvant therapy (gefitinib) or 4 cycles of platinum-doublet chemotherapy. Disease stage and lymph node status were balanced across group, but the proportion of patients with an ECOG status of 1 was somewhat higher in the chemotherapy group (77% versus 65%). In both groups, 59% of patients were female and two-thirds had never smoked. Median patient age was 58 in the gefitinib group and 60 in the chemotherapy group.

Virtually all patients randomized to receive gefitinib began therapy, and 68% were treated for longer than 18 months. Based on data that had reached 65% maturity at the time of final cutoff in early 2020, disease-free survival was significantly improved for patients treated with adjuvant gefitinib compared with adjuvant chemotherapy. Overall survival appeared to favor adjuvant gefitinib for patients with exon 19 deletion (HR = 0.76, 95% CI [0.44, 1.32]) but not for patients with exon 21 L858R mutations (HR = 1.13, 95% CI [0.64, 1.98]), though treatment effects in both groups and the interaction effect were nonsignificant.

Disease recurrence occurred in two-thirds of patients in both treatment groups, and most patients in both groups discontinued adjuvant therapy because of recurrence. Subsequent treatment was delivered to 68% of patients in the gefitinib group and 74% of patients in the chemotherapy group; 37% and 52%, respectively, were treated with targeted therapy alone or in combination with another treatment. Regardless of the type of adjuvant therapy received, treating recurrent NSCLC with an EGFR-TKI resulted in significantly improved overall survival compared with receiving no subsequent treatment. With a median follow-up of 80 months, median overall survival of patients who had received adjuvant gefitinib and were treated with an EGFR-TKI at recurrence was not reached. Patients in the adjuvant chemotherapy group who were treated with an EGFR-TKI at recurrence survived for a median of 62.8 months. For patients treated with other therapies at recurrence, median overall survival was 35.3 months and 49.5 months, respectively. Patients with recurrence who did not receive subsequent treatment had the poorest overall survival: 28.7 months for patients who had received adjuvant gefitinib and 15.6 months for those who had received adjuvant chemotherapy. Importantly, treating recurrence with non-targeted treatments resulted in markedly smaller overall survival benefit (versus not treating recurrence) for patients who had received adjuvant EGFR-TKIs (HR = 0.70, 95% CI [0.37, 1.32]) compared with those who had received adjuvant chemotherapy (HR = 0.17, 95% CI [0.07,

ADJUVANT

Gefitinib / CT

N = 111 / 111

EGFRm+: 100% / 100%

Disease-free Survival

65% mature (2020)

Median (mo.): 30.8 / 19.8

5 yrs.: 23% / 23%

HR: 0.56 [0.40, 0.79]

Overall Survival

45% mature (2020)

Median (mo.): 75.5 / 62.8

5 yrs.: 53% / 51%

HR: 0.92 [0.62, 1.36]

Follow-up (med.): 80 mo.

0.41]). Results of these analyses should be interpreted with caution because all subgroups had small sample sizes and ADJUVANT was the only trial to report this type of analysis.

Any-grade adverse events, grade 3 or worse events, and serious events were all more frequent with adjuvant chemotherapy. Grade 3 events occurred in 12% of patients in the gefitinib group and 48% of patients in the chemotherapy group (rates of serious events were 7% and 23%, respectively). The most common grade 3 or worse adverse events for patients receiving gefitinib were elevated liver enzymes; in the chemotherapy group, the most frequent higher-grade events were neutropenia, leucopenia, and vomiting.

EVIDENCE⁵⁰ is a phase 3, open-label RCT that reports less mature survival data than EVAN and ADJUVANT but is otherwise similarly designed. Patients with resected stage II–IIIA NSCLC (AJCC/UICC 7th edition) received 2 years of adjuvant icotinib or 4 cycles of platinum-doublet chemotherapy. Like ADJUVANT, about two-thirds of patients had stage III disease, N2 lymph node status, and an ECOG performance status of 1. Median patient age was 59, and an even number of female and male patients were enrolled. About a third of patients were current smokers. Patient characteristics and disease severity were well balanced across groups. At an early 2020 data cutoff, 43% of patients had received the planned 2 years of adjuvant icotinib (34% were still receiving the drug). No patients were still receiving chemotherapy and 68% had completed 4 treatment cycles. With data at 35% maturity, disease-free survival was significantly better for patients receiving adjuvant icotinib. Overall survival data were only 10% mature, but as in ADJUVANT, overall survival was similar with adjuvant icotinib and chemotherapy. 27% of patients in the icotinib group and 49% of patients in the chemotherapy group experienced disease recurrence. Details on subsequent treatment of patients with recurrence were not available. Frequencies and types of adverse events were comparable to EVAN and ADJUVANT, and like those trials, discontinuing adjuvant therapy because of adverse events was rare.

The final trial in this group is IMPACT,⁵³ a recently reported, open-label phase 3 RCT. Like other trials in this group, patients with resected stage II–IIIA NSCLC (AJCC/UICC 7th edition) were randomized to 2 years of adjuvant gefitinib or 4 cycles of platinum-based chemotherapy, and the majority of patients had stage IIIA disease with N2 lymph node status and were female. At the same time, the trial enrolled considerably fewer patients with a baseline ECOG performance status of 1 (20% versus 56–71%) and also enrolled no current smokers (one-quarter to one-third of patients in the other 3 trials were current smokers). The median patient age of 64 was also 5 to 6 years higher than other trials.

61% of patients received the planned 2 years of adjuvant gefitinib and 78% completed 4 cycles of adjuvant chemotherapy. At a late 2020 cutoff, disease-free survival and overall survival data had reached 65% and 31% maturity, respectively. Neither disease-free survival nor overall survival significantly

EVIDENCE

Icotinib / CT

N = 151 / 132

EGFRm+: 100% / 100%

Disease-free Survival

35% mature (2020)

Median (mo.): 47.0 / 22.1

4 yrs.: 43% / 32%

HR: 0.36 [0.24, 0.55]

Overall Survival

10% mature (2020)

Median (mo.): NR / NR

4 yrs.: 83% / 79%

HR: 0.91 [0.42, 1.94]

Follow-up (med.): 25 mo.

IMPACT

Gefitinib / CT

N = 116 / 116

EGFRm+: 100% / 100%

Disease-free Survival

65% mature (2020)

Median (mo.): 35.9 / 25.1

5 yrs.: 32% / 34%

HR: 0.92 [0.67, 1.28]

Overall Survival

31% mature (2020)

Median (mo.): NR / NR

5 yrs.: 78% / 75%

HR: 1.03 [0.65, 1.65]

Follow-up (med.): 70 mo.

differed between groups. Disease-free survival was similar for patients receiving adjuvant gefitinib or adjuvant chemotherapy regardless of disease stage and former or never smoker status. Adjuvant therapy with gefitinib may have resulted in some disease-free survival benefit for patients 70 years or older, female patients, and patients with exon 19 deletions, while adjuvant chemotherapy may have been more beneficial for male patients and those with exon 21 L858R mutations. All subgroup interactions and within-subgroup treatment effects were nonsignificant.

A similar proportion of patients experienced recurrence in each group, and most patients with recurrence received subsequent treatment. Discontinuation because of adverse events was comparable in both groups. Like other trials in this group, nearly all patients experienced any-grade adverse events. The most common grade 3 or worse adverse events were the same as those reported in other trials, including elevated liver enzymes in the gefitinib group and neutropenia and leukopenia in the chemotherapy group.

Combination Neoadjuvant and Adjuvant Therapy

Using the same EGFR-TKI for both neoadjuvant and adjuvant treatment has an unclear effect on the survival of patients with resectable NSCLC. EMERGING-CTONG 1103,⁶⁹ a phase 2 multicenter RCT, randomized 72 treatment-naïve patients with potentially resectable, EGFR mutation-positive stage IIIA NSCLC (AJCC/UICC 7th edition) to receive erlotinib for 42 days prior to resection and up to 1 year postoperatively, or 2 cycles of chemotherapy (gemcitabine plus cisplatin) preoperatively and postoperatively. Progression-free survival was significantly longer for patients treated with erlotinib, but overall survival did not significantly differ between groups (53% maturity). Postoperative lymph node downstaging occurred in 11% of patients treated with erlotinib and 3% of patients treated with chemotherapy. 60% of chemotherapy-group patients experienced relapse or metastasis after resection, and it is unclear whether patients received erlotinib on recurrence.

EMERGING-CTONG 1103

Erlotinib / CT

N = 37 / 35

EGFRm+: 100% / 100%

Progression-free Survival

85% mature (2018)

Median (mo.): 21.5 / 11.4

1 yr.: 33% / 13%

HR: 0.39 [0.23, 0.67]

Overall Survival

53% mature (2018)

Median (mo.): 45.8 / 39.2

5 yrs.: 40% / 18%

HR: 0.77 [0.41, 1.45]

Follow-up (med.): 33 mo.

Strength of Evidence

Evidence on disease-free survival benefits of adjuvant therapy with EGFR-TKIs was considered moderate strength, largely based on findings from ADAURA, which provides the most recent and clinically relevant evidence on adjuvant EGFR-TKIs. 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. Evidence on overall survival benefits of adjuvant EGFR-TKIs was considered low strength.

The most pressing concerns about available trials of adjuvant EGFR-TKIs are related to outcome data maturity and quality, attrition, and subsequent treatment of comparison-group patients experiencing disease recurrence. In addition, disease-free and overall survival curves in ADAURA and EVIDENCE, disease-free survival curves in RADIANT and ADJUVANT, and overall survival curves in EVAN all exhibit nonproportional hazards (meaning that reported hazard ratios may not accurately represent differences in survival between trial arms over time).

In RADIANT, many more patients discontinued adjuvant erlotinib because of adverse events, raising concerns about informative censoring. In ADAURA, patients also discontinued osimertinib because of adverse events at a higher rate than placebo, but the difference was not as pronounced as in RADIANT. RADIANT did not permit treatment of patients with recurrence with the trial drug, and while ADAURA and the available comparative effectiveness trials generally allowed crossover, the extent and characteristics of subsequent treatment were not always clear.

For combination neoadjuvant and adjuvant therapies, EMERGING-CTONG 1103 was a small trial with an open-label design, and as the only trial found that investigated a combination neoadjuvant-adjuvant therapy using an EGFR-TKI, provides insufficient evidence on the efficacy of this approach.

Underway Studies

ADAURA2, a placebo-controlled trial of osimertinib limited to patients with stage IA disease ([NCT05120349](#)), began recruitment in mid-2022 and is expected to conclude in 2032. Disease-free and overall survival will be assessed as primary and secondary endpoints, respectively. An open-label phase 3 trial comparing adjuvant erlotinib to observation in patients with stage IB–IIIA NSCLC (ALCHEMIST; [NCT02193282](#)) is expected to conclude in 2026 and will report overall survival as its primary endpoint). A placebo-controlled trial ([NCT02125240](#)) of adjuvant icotinib in patients with stage II–IIIA disease was expected to conclude in late 2021, but we could not locate any published findings.

NEOADJUVANT THERAPY USING ICIs

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 \geq 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, and treatment benefits were apparent even with limited use of adjuvant chemotherapy. We considered evidence on survival benefits of neoadjuvant nivolumab plus platinum-based chemotherapy to be moderate strength. 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.

CheckMate 816⁶⁴ randomized patients with resectable stage IB–IIIA NSCLC (AJCC/UICC 7th edition) to receive 3 cycles of preoperative nivolumab plus platinum-based chemotherapy or platinum-based chemotherapy alone. Standard-of-care adjuvant chemotherapy was optional for patients in both groups. Efficacy endpoints included event-free survival, pathological complete response, and overall survival assessed by blinded independent review. Approximately two-thirds of patients were male, had an ECOG performance status of 0, and stage IIIA NSCLC. Nearly 90% of patients were current or former smokers. Patients with any PD-L1 status were eligible; 50% of patients had PD-L1 \geq 1% and 22% had PD-L1 \geq 50%. Patients with previous anti-cancer treatment or tumors bearing EGFR mutations or anaplastic lymphoma kinase (ALK) rearrangements were excluded. Disease severity, PD-L1 status, and patient characteristics were well balanced.

CheckMate 816

Nivolumab+CT / CT

N = 179 / 179

PD-L1 \geq 1%: 50% / 50%

Event-free Survival

56% mature (2020)

Median (mo.): 31.6 / 20.8

4 yrs.: 64% / 45%

HR: 0.65 [0.47, 0.90]

Overall Survival

31% mature (2020)

Median (mo.): NR / NR

3 yrs.: 80% / 63%

HR: 0.57 [0.38, 0.87]

Follow-up (med.): 30 mo.

Treatment completion rates were high in both arms: 94% of patients in the nivolumab plus chemotherapy group and 85% of patients in the chemotherapy-only group completed the prespecified 3 treatment cycles, and over 75% of patients in both groups underwent definitive surgery. Complete resection (R0) was achieved in 83% of patients who underwent surgery in the nivolumab plus chemotherapy group and 78% of patients in the chemotherapy-only group. Adjuvant chemotherapy use was limited in both groups (12% of the nivolumab plus chemotherapy group and 22% of the chemotherapy-only group).

At the most recent data cutoff in late 2021 (56% data maturity), event-free survival in the sample of patients with stage IB–IIIA NSCLC was significantly improved after nivolumab plus chemotherapy compared with chemotherapy alone, adjusting for optional adjuvant therapy (Table 3). In unadjusted subgroup analyses by disease stage, however, event-free survival benefit was apparent only among patients with stage IIIA disease (HR = 0.54, 95% CI [0.37, 0.80]; stage IB–II HR = 0.87, 95% [0.48, 1.56]). In the stage IB–IIIA sample, overall survival appeared to be longer for patients receiving nivolumab plus chemotherapy (HR = 0.57, 95% CI [0.38, 0.87]; 31% maturity). Although the confidence interval accompanying this estimate excludes 1, it was

not considered statistically significant based on the trial's adjusted significance level of 0.0033. Subgroup analyses have not yet been reported for overall survival.

In prespecified subgroup analyses of event-free survival by PD-L1 status (among stage IB–IIIA patients), only patients with PD-L1 \geq 1% experienced event-free survival benefits from nivolumab. The largest improvement was in patients with PD-L1 \geq 50%. Event-free survival benefits for patients receiving nivolumab plus chemotherapy were similar for patients older and younger than 65, male and female patients, and for those with ECOG status of 0 or 1, but may have differed by smoking status (never smoked HR = 0.33, 95% CI [0.13, 0.87]; current/former smoker HR = 0.68, 95% CI [0.48, 0.96]) and by type of neoadjuvant chemotherapy (carboplatin HR = 0.31, 95% CI [0.14, 0.67]; cisplatin HR = 0.71, 95% CI [0.49, 1.03]). Subgroup analyses by PD-L1 status and patient and treatment characteristics were not reported by disease stage.

Pathologic complete response followed a similar pattern to event-free survival, with the exception that pathologic complete response did not appear to be influenced by disease stage (the proportion of patients with pathologic complete response was 21–22% after nivolumab plus chemotherapy in both stage IB–II and stage IIIA subgroups). Within the nivolumab plus chemotherapy group, patients with pathologic complete response experienced a much larger event-free survival benefit than patients without a complete response (HR = 0.13, 95% CI [0.05, 0.37]). This comparison could not be made in the chemotherapy-only group because only 2% of patients in that group achieved pathologic complete response (compared with 24% of patients in the nivolumab plus chemotherapy group). 31% of patients in the nivolumab plus chemotherapy group were radiographically downstaged after treatment, compared with 24% of patients treated with chemotherapy alone.

Any-grade adverse events occurred in 90% or more of patients in both groups. Grade 3 or 4 treatment-related adverse events occurred in approximately one-third of patients in each group. The most common of these were neutropenia and decreased neutrophil count and both occurred at about the same frequency in each group. Serious events and discontinuation of treatment due to adverse events were rare and balanced across groups. 21% of patients treated with nivolumab plus chemotherapy received subsequent treatment for recurrence, compared with 44% of patients treated with chemotherapy alone (24% of these patients were subsequently treated with an ICI, most frequently pembrolizumab, nivolumab, or atezolizumab).

We identified 2 additional studies of neoadjuvant ICIs that were not included in strength of evidence ratings. One study, a small phase 2 RCT⁷³ comparing neoadjuvant camrelizumab plus chemotherapy to neoadjuvant chemotherapy alone, was still recruiting and preliminary findings were only available in a conference abstract. A second small study⁶⁵ was not included because the ICI (nivolumab) was delivered without concurrent chemotherapy.

Strength of Evidence

We considered evidence on disease-free survival benefits of neoadjuvant nivolumab plus platinum-based chemotherapy to be moderate strength. Evidence on overall survival was judged to be low strength. CheckMate 816 is moderately sized and was at low risk of bias. Findings demonstrating survival benefits of neoadjuvant nivolumab plus platinum-based chemotherapy are precisely estimated, consistent across surrogate measures and definitive measures, and were based on outcomes assessed by blinded independent reviewers.

Table 3. Characteristics and Survival Outcomes of Studies Comparing Neoadjuvant ICIs Plus Chemotherapy to Chemotherapy Alone

Study (Phase) Stages (Sample)	Groups	N	Median Follow-up Months	Stage III %	ECOG Status 1 %	Event-Free Survival ^a					Overall Survival						
						Median Months	HR [95% CI]				Median Months	HR [95% CI]					
							Maturity	2 Yrs %	3 Yrs %	4 Yrs %		5 Yrs %	Maturity	2 Yrs %	3 Yrs %	4 Yrs %	5 Yrs %
CheckMate 816 (3)																	
IB-III A (ITT) ^b	Nivo+Plat-doublet CT	179	30	63	31	31.6	0.65 [0.47, 0.90] ^c	64	50 [†]	NA	NA	NR	0.57 [0.38, 0.87]	83	80 [†]	NA	NA
	Plat-doublet CT	179		64	35	20.8	56% (2020)	45	39 [†]	NA	NA	NR	31% (2020)	71	63 [†]	NA	NA
IB-III A (PD-L1 <1%)	Nivo+Plat-doublet CT	78	NA	NA	NA	25.1	0.85 [0.54, 1.32]	52	35 [†]	NA	NA	NA	NA	NA	NA	NA	NA
	Plat-doublet CT	77		NA	NA	18.4		40	36 [†]	NA	NA	NA	NA	NA	NA	NA	NA
IB-III A (PD-L1 ≥1%)	Nivo+Plat-doublet CT	89	NA	NA	NA	NR	0.41 [0.24, 0.70]	76	70 [†]	NA	NA	NA	NA	NA	NA	NA	NA
	Plat-doublet CT	89		NA	NA	21.1		50	39 [†]	NA	NA	NA	NA	NA	NA	NA	NA
IB-III A (PD-L1 ≥50%)	Nivo+Plat-doublet CT	38	NA	NA	NA	NR	0.24 [0.10, 0.61]	85	78 [†]	NA	NA	NA	NA	NA	NA	NA	NA
	Plat-doublet CT	42		NA	NA	19.1		49	43 [†]	NA	NA	NA	NA	NA	NA	NA	NA

Notes. Survival proportions and related values denoted with a dagger (†) were abstracted from survival curves using the WebPlotDigitizer platform.

^aEligible events were disease progression, disease recurrence, or death. Corresponding hazard ratio adjusted for optional adjuvant therapy.

^bPD-L1 ≥ 1%: 50% in nivolumab group; 50% in chemotherapy group.

^cHR adjusted for optional adjuvant therapy.

Abbreviations. CT=chemotherapy; ECOG=Eastern Cooperative Oncology Group performance-status; HR=hazard ratio; ICI=immune checkpoint inhibitor; ITT=intention-to-treat sample; NA=not available; NR=not reached; PD-L1=programmed death ligand 1 expression; Plat=platinum; Yrs=years.



NEOADJUVANT THERAPY USING EGFR-TKIs

Neoadjuvant therapy using EGFR-TKIs has an unclear impact on progression-free, disease-free, and overall survival. Conclusions are based on evidence from 3 very small nonrandomized comparison studies⁶⁶⁻⁶⁸ in patients with resectable stage IIIA NSCLC (Table 4). In all studies, patients received preoperative erlotinib or standard-of-care chemotherapy based on their EGFR mutation status. The duration of neoadjuvant erlotinib varied from 4 to 7 weeks across studies. Chemotherapy or chemoradiotherapy was offered after resection. Studies reported progression-free survival,⁶⁸ disease-free survival,^{66,67} and overall survival.⁶⁶⁻⁶⁸

In all studies, survival was comparable in neoadjuvant erlotinib and chemotherapy groups or favored neoadjuvant chemotherapy at the end of follow-up. One study⁶⁸ ($N = 24$) reported hazard ratios indicating a potentially large survival benefit of neoadjuvant chemotherapy, but the small size of the study means that this ratio corresponds to a difference of only 1 or 2 outcome events. Median survival suggests a possible, but more modest, benefit of chemotherapy over erlotinib for progression-free survival (9 months versus 6.9 months, $p = .07$) and overall survival (28.1 months versus 14.5 months, $p = .20$). In the subset of patients who underwent resection, however, differences were more pronounced. Median progression-free survival significantly differed between subgroups and was nearly 4 times longer in resected chemotherapy patients (28.9 months versus 8.6 months, $p = .02$). Median overall survival increased in both subgroups but still favored neoadjuvant chemotherapy (57.3 months versus 25.5 months, $p = .16$). Importantly, each subgroup had only 6 to 7 patients and complete resection was achieved in more patients in the neoadjuvant chemotherapy group (71%, versus 50%).

Strength of Evidence

The small size of available trials, paired with their nonrandomized design and lack of statistical adjustment for potential confounders, means that evidence is currently insufficient to draw conclusions about the efficacy of neoadjuvant EGFR-TKIs compared with neoadjuvant chemotherapy. A 3-arm placebo-controlled trial (NeoADAURA; [NCT04351555](https://clinicaltrials.gov/ct2/show/study/NCT04351555)) comparing neoadjuvant osimertinib and neoadjuvant osimertinib plus platinum-based chemotherapy in about 300 patients with resected stage II–IIIB NSCLC is expected to conclude in 2029. The trial's primary endpoint is pathologic complete response, and disease-free and overall survival will be assessed as secondary endpoints.

Table 4. Characteristics and Survival Outcomes of Studies Comparing Neoadjuvant EGFR-TKIs to Chemotherapy Alone

Study (Phase) Stages (Sample)	Groups	N	Disease-Free Survival				Overall Survival											
			Median	ECOG			HR [95% CI] or		HR [95% CI] or									
			Follow-up	Stage III	EGFRm+	Status 1	Median	p-value	2 Yrs	3 Yrs	4 Yrs	5 Yrs	Median	p-value	2 Yrs	3 Yrs	4 Yrs	5 Yrs
Months	%	%	%	Months	%	%	%	%	Months	%	%	%	%					
Zhao 2021 (2) <i>IIIA-N2 (NA)</i>	Erlotinib	14	29	100	100	NA	14.1 [†]	p = 0.41	43 [†]	29	29 [†]	NA	NR	p = 0.84	85 [†]	64	64 [†]	NA
	Plat-based CT	15	30	100	0	NA	NR		57 [†]	57	57 [†]	NA	NR		64 [†]	64	64 [†]	NA
Xiong 2020 (NA) <i>IIIA-N2 (NA)</i>	Erlotinib	8	NA	100	100	NA	10.2	p = 0.25	25 [†]	17 [†]	NA	NA	51.0	p = 0.12	75 [†]	59 [†]	59 [†]	30 [†]
	Cis	12	NA	100	0	NA	8.0		12 [†]	NA	NA	NA	20.9		38 [†]	26 [†]	26 [†]	NA
								Progression-Free Survival				Overall Survival						
Zhong 2015 (2) <i>IIIA-N2 (NA)</i>	Erlotinib	12	24	100	100	NA	6.9	2.26 [0.91, 5.61]	NA	NA	NA	NA	14.5	1.79 [0.73, 4.40]	42 [†]	17 [†]	17 [†]	9 [†]
	Gem+Cis	12		100	0	NA	9.0		33 [†]	11 [†]	NA	NA	28.1		58 [†]	50 [†]	50 [†]	20 [†]

Notes. Survival proportions and related values denoted with a dagger (†) were abstracted from survival curves using the WebPlotDigitizer platform. Only treatment-group patients in Zhao 2021 were enrolled in phase 2 trial. Sample sizes and survival outcomes for Xiong 2020 are for patients who underwent surgical resection.

Abbreviations. CT=chemotherapy; EGFRm+=epidermal growth factor receptor mutation positive; ECOG=Eastern Cooperative Oncology Group performance-status; EGFR-TKI=epidermal growth factor receptor-tyrosine kinase inhibitor; HR=hazard ratio; ITT=intention-to-treat sample; NA=not available; NR=not reached; Plat=platinum; Yrs=years.



DISCUSSION

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 suggest disease-free survival benefit may be limited to patients with PD-L1 $\geq 50\%$, 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.

Trials of adjuvant ICIs report contradictory findings about the role of PD-L1 expression levels in disease-free survival outcomes. IMpower010 observed no disease-free survival benefit in patients with PD-L1 $< 1\%$, a small and nonsignificant improvement in patients with PD-L1 between 1–49%, and substantial benefit in patients with PD-L1 $\geq 50\%$. This pattern is consistent with the understanding that increased PD-L1 expression should correspond to greater efficacy of ICIs. In contrast, PEARLS/KEYNOTE-091 reported a modest (but nonsignificant) improvement in disease-free survival for patients with PD-L1 $< 1\%$, and a larger benefit in patients with PD-L1 between 1–49% than in patients with PD-L1 $\geq 50\%$. Trial investigators attributed this inconsistency to overperformance of placebo group patients. The trial employed stratified randomization on known prognostic factors (including PD-L1 expression level) and there appeared to be no critical baseline differences between groups, which suggests that better-than-expected outcomes in the placebo group could be due to chance or imbalance in unknown prognostic factors such as molecular biomarkers. Estimates from PEARLS/KEYNOTE-091 also include patients with stage IB disease, which differs from IMpower010 (stage II–IIIA only), and the trials employed different (validated) methods for measuring PD-L1 expression.

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.

A recently published meta-analysis⁵ on the efficacy of adjuvant EGFR-TKIs pooled all included trials and reached similar conclusions with respect to disease-free and overall survival outcomes, and also found that osimertinib was more effective than first-generation EGFR-TKIs at preventing brain metastasis. We did not take the approach of pooling all trials on adjuvant EGFR-TKIs because we concluded that trials were too varied in methodological, treatment, and patient characteristics. Even when synthesizing evidence among relatively similar trials, survival outcomes were notably varied. Inconsistency in results could also be due to differences in EGFR-TKI generation or outcome maturity and reporting, among other factors. An example of the importance of data maturity can be seen in RADIANT, which initially reported a statistically significant and moderate-size disease-free survival benefit of adjuvant erlotinib in the EGFR mutation-positive subsample. With just over a year of additional follow-up, however, the disease-free survival difference between arms was noticeably smaller and no longer significant.

Group differences in disease recurrence, discontinuation because of adverse events, and subsequent therapy observed in several trials of adjuvant EGFR-TKIs could also have contributed to effect variability. When discontinuation because of adverse events mainly occurs in the treatment group, disease-free survival outcomes can be exaggerated in favor of the treatment through informative censoring: patients are censored (because of the toxicity of the trial drug) before experiencing recurrence, while many similar patients in the comparison group remain in the trial (having never been exposed to the trial drug) and ultimately experience recurrence or other eligible outcome events.

A related concern is imbalanced disease recurrence. In ADAURA, for instance, twice as many placebo-group patients experienced recurrence (compared with patients in the osimertinib group), and 85% of these patients discontinued treatment. It has been suggested that differences in recurrence and treatment discontinuation, especially in trials that largely enrolled patients with earlier-stage disease (stage IB or II), may mean that included patients were understaged.⁷⁴ This may be due, in part, to differences in the use of imaging to determine eligibility. For example, ADAURA did not require confirmation of disease stage with imaging studies, meaning that some included patients may have been at a more advanced disease stage that, if known, would have made them ineligible for the trial. Including a substantial number of understaged patients could have exaggerated observed disease-free survival benefits of adjuvant osimertinib.

In ADJUVANT, a mutation was identified that cooccurred with the EGFR mutation and predicted poorer disease-free survival for patients receiving adjuvant targeted therapy (but not chemotherapy). IMPACT and RADIANT did not test for this co-mutation, but it is possible that it was more prevalent among patients in those trials and resulted in poorer disease-free survival in adjuvant EGFR-TKI groups. It has been suggested that the limited disease-free survival benefit seen in IMPACT may be because the trial enrolled fewer patients with an ECOG status of 1 than other comparative-effectiveness trials.⁵³ This observation is not supported by subgroup analyses from 2 included trials that found disease-free survival benefits were similar for patients with ECOG status of 0 or 1 (EVIDENCE), or favored patients with a status of 0 (EVAN).

Adverse events associated with ICIs or EGFR-TKIs in the adjuvant setting do not appear to be more severe than adjuvant chemotherapy, though the long treatment period of adjuvant therapy with ICIs or EGFR-TKIs may have implications for tolerability, the practicality of long-term treatment adherence, the risk that patients develop resistance to drugs that are important in the treatment of advanced NSCLC, and healthcare costs.^{10,74,75} Moreover, overall survival benefit of adjuvant EGFR-TKIs in mature outcome data has only been shown in EVAN, a comparatively small trial limited to patients with stage III-N2 disease, and overall survival data from recent trials of adjuvant ICIs and EGFR-TKIs have not yet matured. Nonetheless, ICIs and EGFR-TKIs currently approved for adjuvant use likely confer a disease-free survival benefit and appear to be tolerable to most patients. Despite 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 disease, this remains conventional adjuvant chemotherapy after surgical resection.⁷⁶

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. 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, and treatment benefits were apparent even with limited use of adjuvant chemotherapy.

Adherence to neoadjuvant nivolumab plus chemotherapy was high, and the therapy had a comparable safety profile to neoadjuvant chemotherapy alone. With both therapies, stage 3 or worse adverse events were infrequent and serious adverse events were rare. This is consistent with results of a recent meta-analysis¹⁴ that synthesized adverse event data mainly from single-group studies of neoadjuvant ICIs, the average rate of grade 3 or worse adverse events was similarly low (15%), and surgical complications and delays after neoadjuvant therapy with ICIs were also rare (10% and 3%, respectively). 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.

Finally, we found insufficient evidence to draw conclusions about the efficacy of neoadjuvant ICIs without concurrent neoadjuvant chemotherapy, neoadjuvant therapy using EGFR-TKIs, or combination neoadjuvant-adjuvant therapy with the same ICI or EGFR-TKI.

REVIEW LIMITATIONS

We did not include evidence from single-group studies in this review. Well-conducted single-group studies can be informative in research areas where few or no RCTs are available, and we recognize that excluding evidence from this type of study may be a limitation of this review.

Visual abstraction of survival proportions was necessary for several included trials. We used tools that improve the accuracy of visually abstracted data, but these survival proportions are likely less accurate than those reported directly in publications. We also visually assessed survival curves for nonproportional hazards, and survival data maturity estimates we calculated are approximate. Judgments made about data immaturity and violations of the proportional hazards assumption involved some degree of subjectivity.

FUTURE RESEARCH

As noted, inconsistency in trial design, methodology, and patient and treatment characteristics limits the informativeness of available evidence and may contribute to variation in trial findings. The main barrier to synthesis, however, is variability in data analysis and reporting. Included trials of adjuvant therapies used different sample compositions for main analyses (*eg*, stage IB–IIIA or stage II–IIIA), were missing subgroup analyses (*eg*, by ECOG status), compared different subgroups (*eg*, PD-L1 < 1% versus ≥ 1%, or PD-L1 < 1% versus 1–49% versus ≥ 50%), and finally, differed in whether main or subgroup analyses accounted for important interaction effects (*eg*, comparing survival in stages IB, II, and IIIA *within* groups defined by PD-L1 expression or EGFR mutation status). Trials may not have conducted all relevant analyses because of concerns about statistical power, because the importance of certain analyses or moderating factors had not yet become clear, or because key subgroup analyses are being reserved for secondary publications.

Many of these gaps could be addressed by pooling and analyzing patient-level data using an integrative data analysis (IDA) or individual participant data (IPD) meta-analysis approach. Either technique would increase the number of patients in important subgroups and allow for the definitions of key groups (eg, by disease stage and PD-L1 expression level) to be harmonized across studies. Subgroup analyses would gain statistical power, and by combining data from small and large trials, all analyses would be at lower risk of bias from prognostic imbalance (even after randomization, small RCTs can remain imbalanced in the likelihood that patients will respond to treatment or worsen despite treatment). The role of subsequent treatment after recurrence and potential effect modifiers could also be more fully investigated, or adjusted for in key analyses. Often, a barrier to using IDA or IPD methods is unwillingness of trial investigators to share anonymized patient-level data. Advocacy from health system leadership may help to overcome this obstacle.

Clinical data available in an integrated health system like the VA can be useful for assessing the applicability of clinical trial findings to real-world clinical practice. A recent example⁷⁷ of a study with this aim used the VA Informatics and Computing Infrastructure (VINCI) to identify health records of Veterans with unresected stage III NSCLC treated with definitive concurrent chemoradiotherapy followed by adjuvant therapy with an ICI (durvalumab). Progression-free survival and overall survival among these patients was compared to a historical cohort of patients treated with concurrent chemoradiotherapy alone, identified using the VA Cancer Registry System (VACRS). Survival differences were then compared with those observed in the pivotal clinical trial on adjuvant durvalumab in locally advanced, unresectable NSCLC (PACIFIC⁷⁸). The study found that overall survival was improved with the addition of adjuvant durvalumab but not to the extent seen in the PACIFIC trial—findings that, at once, confirm the applicability of trial findings to the VA patient population and identify an efficacy-to-effectiveness gap.

VA health system data also has the potential to inform therapy delivery. In the advanced NSCLC setting, a recent retrospective analysis⁷⁹ of data from the VA Corporate Data Warehouse (CDW) and other VA databases found that only half of patients with evidence of highly targetable mutations had clinical documentation showing their provider was aware of gene sequencing results (available through the VA's National Precision Oncology Program). This finding does not directly apply to the treatment of resectable NSCLC, but it does underline the importance of ensuring provider awareness of existing resources and how they can be employed in the delivery of emerging therapies. Another recent study⁸⁰ used VA data to examine racial differences in the delivery of first-line treatments for stage I NSCLC. Similar analyses may be useful in the adjuvant setting, where barriers to healthcare access and utilization experienced by minority Veterans^{80,81} could conceivably impact long-term treatment adherence.

Lastly, to maintain a feasible scope, we did not include evidence on the treatment of resectable NSCLC with other targetable features, such as ALK rearrangements. This could be a topic for future evidence reviews, given that at least 1 key trial comparing adjuvant therapy with an ALK-TKI (alectinib) or platinum-based chemotherapy is underway (ALINA; [NCT03456076](#)). In the adjuvant setting, another potential review topic is patient-reported outcomes. Patient-reported outcomes of clinical trials are often published well after survival findings.^{34,82} For example, a recently published analysis⁸³ of health-related quality of life data from the ADAURA trial found that quality of life was similar for patients treated with osimertinib or placebo and did not diminish during the treatment period in either group. Quality of life and other patient-reported outcomes from clinical trials can be more severely impacted by assessment and missing data

biases than survival outcomes, but generally speaking, trial characteristics and limitations that influence the validity of survival outcomes can also affect patient-reported outcomes.^{34,82,84}

Despite these concerns, synthesizing and critically assessing the evidence that is available on patient-reported outcomes of long-term adjuvant therapy with EGFR-TKIs or ICIs may help to inform clinical decision-making. Evidence on the cost-effectiveness of adjuvant therapies^{85,86} is also developing and may benefit from a future review.

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.

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APPENDIX A: SEARCH STRATEGY

SYSTEMATIC REVIEWS

Search for current systematic reviews (limited to last 7 years)			
Date Searched: 08-22-22			
A. Bibliographic Databases:	#	Search Statement	Results
MEDLINE: Systematic Reviews Ovid MEDLINE(R) ALL 1946 to August 19, 2022	1	Carcinoma, Non-Small-Cell Lung/ or Lung Neoplasms/	250378
	2	(lung cancer or lung neoplasm* or lung carcinoma* or nslc or lung tumor* or lung tumour*).ti,ab,kw.	218639
	3	(non small cell* or nonsmall cell*).ti,ab,kw.	82273
	4	2 and 3	79798
	5	1 or 4	270498
	6	Neoadjuvant Therapy/ or Chemotherapy, Adjuvant/	63639
	7	(neoadjuvant or adjuvant).ti,ab,kw.	189953
	8	6 or 7	211194
	9	Gefitinib/ or Afatinib/ or Nivolumab/ or Immune Checkpoint Inhibitors/ or Protein Kinase Inhibitors/	69196
	10	(gefitinib or erlotinib or afatinib or osimertinib or atezolizumab or durvalumab or nivolumab or pembrolizumab or cemiplimab or EGFR tyrosine kinase inhibitors or anti-PD-1 or anti-PD-L1 or checkpoint inhibitor* or check-point inhibitor*).ti,ab,kw.	45217
	11	9 or 10	98653
	12	5 and 8 and 11	781
	13	(<u>systematic review.ti. or meta-analysis.pt. or meta-analysis.ti. or systematic literature review.ti. or this systematic review.tw. or pooling project.tw. or (systematic review.ti,ab. and review.pt.) or meta synthesis.ti. or meta-analy*.ti. or integrative review.tw. or integrative research review.tw. or rapid review.tw. or umbrella review.tw. or consensus development conference.pt. or practice guideline.pt. or drug class reviews.ti. or cochrane database syst rev.jn. or acp journal club.jn. or health technol assess.jn. or evid rep technol assess summ.jn. or jbi database system rev implement rep.jn. or (clinical guideline and management).tw. or ((evidence based.ti. or evidence-based medicine/ or best</u>	535251

		<u>practice*.ti. or evidence synthesis.ti,ab.) and (((review.pt. or diseases category/ or behavior.mp.) and behavior mechanisms/ or therapeutics/ or evaluation studies.pt. or validation studies.pt. or guideline.pt. or pmcbook.mp.)) or (((systematic or systematically).tw. or critical.ti,ab. or study selection.tw. or ((predetermined or inclusion) and criteri*).tw. or exclusion criteri*.tw. or main outcome measures.tw. or standard of care.tw. or standards of care.tw.) and ((survey or surveys).ti,ab. or overview*.tw. or review.ti,ab. or reviews.ti,ab. or search*.tw. or handsearch.tw. or analysis.ti. or critique.ti,ab. or appraisal.tw. or (reduction.tw. and (risk/ or risk.tw.) and (death or recurrence).mp.)) and ((literature or articles or publications or publication or bibliography or bibliographies or published).ti,ab. or pooled data.tw. or unpublished.tw. or citation.tw. or citations.tw. or database.ti,ab. or internet.ti,ab. or textbooks.ti,ab. or references.tw. or scales.tw. or papers.tw. or datasets.tw. or trials.ti,ab. or meta-analy*.tw. or (clinical and studies).ti,ab. or treatment outcome/ or treatment outcome.tw. or pmcbook.mp.))) not (letter or newspaper article).pt.</u>	
	14	<u>12 and 13</u>	51
	15	<u>limit 14 to english language</u>	50
CDSR: Protocols and Reviews	1	(Non-Small-Cell Lung Carcinoma or Lung Neoplasms).kw.	45
EBM Reviews - Cochrane Database of Systematic Reviews 2005 to August 17, 2022	2	(lung cancer or lung neoplasm* or lung carcinoma* or nslc or lung tumor* or lung tumour*).ti,ab,kw.	97
	3	(non small cell* or nonsmall cell*).ti,ab,kw.	53
	4	2 and 3	53
	5	1 or 4	72
	6	(Neoadjuvant Therapy or Chemotherapy, Adjuvant).kw.	91
	7	(neoadjuvant or adjuvant).ti,ab,kw.	296
	8	6 or 7	296
	9	(Gefitinib or Afatinib or Nivolumab or Immune Checkpoint Inhibitors or Protein Kinase Inhibitors).kw.	13
	10	(gefitinib or erlotinib or afatinib or osimertinib or atezolizumab or durvalumab or nivolumab or pembrolizumab or cemiplimab or EGFR tyrosine kinase inhibitors or anti-PD-1 or anti-PD-L1 or checkpoint inhibitor* or check-point inhibitor*).ti,ab,kw.	22
	11	9 or 10	29

	12	5 and 8 and 11	1
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Search for current systematic reviews (limited to last 7 years)		
Date Searched: 08-22-22		
B. Non-bibliographic databases	Evidence	Results
AHRQ: evidence reports, technology assessments, U.S Preventative Services Task Force Evidence Synthesis	http://www.ahrq.gov/research/findings/evidence-based-reports/search.html Search: non-small-cell lung cancer AND (neoadjuvant OR adjuvant)	0
CADTH	https://www.cadth.ca Search: non-small-cell lung cancer AND (neoadjuvant OR adjuvant) Nivolumab-Ipilimumab for Non-Small Cell Lung Cancer – Details. 2021. https://www.cadth.ca/nivolumab-ipilimumab-non-small-cell-lung-cancer-details Keytruda for Non-Squamous NSCLC – Details. 2019. https://www.cadth.ca/keytruda-non-squamous-nsclc-details Keytruda for Squamous NSCLC – Details. 2020. https://www.cadth.ca/keytruda-squamous-nsclc-details	3
EPPI-Centre	http://eppi.ioe.ac.uk/cms/Default.aspx?tabid=62 Search: lung cancer	0
NLM	http://www.ncbi.nlm.nih.gov/books Search: non-small-cell lung cancer AND (adjuvant OR neoadjuvant)	0
VA Products - VATAP, PBM and HSR&D publications	A. http://www.hsr.d.research.va.gov/research/default.cfm B. http://www.research.va.gov/research_topics/ Search: lung cancer	0

Search for systematic reviews currently under development (includes forthcoming reviews & protocols)		
Date Searched: 08-22-22		
D. Under development :	Evidence:	Results :
AHRQ topics in development (EPC Status Report)	KV emailed 08-22-22; CA responded 08-22-22, no duplication	0
PROSPERO (SR registry)	<p>http://www.crd.york.ac.uk/PROSPERO/</p> <p>Search: non-small-cell lung cancer AND (neoadjuvant OR adjuvant)</p> <p>Chunhua Xu, wei liu, Qian Zhang, Tiantian Zhang, Li Li, Chunhua Xu. A systematic review and meta-analysis of neoadjuvant chemoimmunotherapy in stage III non-small cell lung cancer.. PROSPERO 2022 CRD42022325531 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022325531</p> <p>Xuhao Wang, Fanqi Meng. A systematic review and network meta-analysis protocol of neoadjuvant chemoimmunotherapy for patients with resectable non-small-cell lung cancer. PROSPERO 2022 CRD42022328166 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022328166</p> <p>Xuhao Wang, Fanqi Meng. A systematic review and network meta-analysis protocol of neoadjuvant Immune Checkpoint Inhibitor therapy for patients with resectable non-small-cell lung cancer. PROSPERO 2021 CRD42021258132 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021258132</p> <p>Guishi Wang, Tiantian Wang. A systematic review and network meta-analysis protocol of various neoadjuvant therapies Immune for patients with resectable non-small-cell lung cancer. PROSPERO 2021 CRD42021269087 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021269087</p> <p>Rui-Lian Chen, Ling-Ling Sun, Yang Cao, Jie-Tao Lin, Ying Zhang, Jing-Xu Zhou, Si-Yu Wang, Wei Hou, Li-Zhu Lin. Adjuvant EGFR-TKI for EGFR-mutant patients with resected non-small cell lung cancer: a meta-analysis from randomized controlled trials. PROSPERO 2020 CRD42020181942 Available from:</p>	22

	<p>https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020181942</p> <p>Rui-Lian Chen, Han-Rui Chen, Ling-Ling Sun, Yang Cao, Jie-Tao Lin, Ying Zhang, Jing-Xu Zhou, Si-Yu Wang, Wei Hou, Li-Zhu Lin. Adjuvant EGFR-TKI for EGFR-mutant patients with resected non-small cell lung cancer: a meta-analysis from randomized controlled trials. PROSPERO 2020 CRD42020190776 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020190776</p> <p>Ran Zhong, Wenhua Liang, Caichen Li, Jianxing He. Adjuvant EGFR-TKIs versus standard chemotherapy for patients with resected NSCLC: a meta-analysis. PROSPERO 2021 CRD42021240657 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021240657</p> <p>Ye Zhao, Hai-ming Feng, Jin-hui Tian, Qin Yu, Long Ge, Bin Li, Cheng Wang, Ke-hu Yang, Jian-kai Wang. Adjuvant treatments after chemoradiotherapy in patients with locally advanced inoperable non-small cell lung cancer (NSCLC): a systematic review and network meta-analysis.. PROSPERO 2021 CRD42021239433 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021239433</p> <p>Jessa Gilda Pandya,, Joanmarie Balolong, Marcelo Imasa. Adjuvant Tyrosinase Kinase Inhibitors in Nonsquamous non-small cell lung cancer with EGFR driver mutations: A Meta-analysis of randomized trials. PROSPERO 2020 CRD42020197421 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020197421</p> <p>Yongxing Bao, Shuang Sun, Xu Yang, Yunsong Liu, Yang Wang, Zhouguang Hui. Comparison of Different adjuvant EGFR-TKIs for Resected Non small cell lung cancer – a Systematic Review and Network Meta-Analysis. PROSPERO 2022 CRD42022300589 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022300589</p> <p>Yi Yang, Yingyao Chen, Dai Lian, Ying Tao. Comparative safety and efficacy of PD-1/PD-L1 inhibitors in the first-line treatment for locally advanced or metastatic non-squamous non-small cell lung cancer: A systematic review and network meta-analysis. PROSPERO 2021 CRD42021275631 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021275631</p> <p>Manting Wang, Liang Hengrui, Liang Wenhua, He Jianxing. Comparison of immune-related adverse events (irAEs) of combination of PD-(L)1 inhibitors and chemotherapy versus PD-(L)1 inhibitors for non-small cell lung cancer: a meta-analysis of randomised controlled trials. PROSPERO 2020 CRD42020139923 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020139923</p>	
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	<p>Michela Febbraro, Arani Sathiyapalan, Rosalyn Juergens. Effects of anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKIs) in the first-line treatment of metastatic ALK positive non-small cell lung cancer (NSCLC): A systematic review and meta-analysis. PROSPERO 2021 CRD42021247914 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021247914</p> <p>Pengfei ZHAO, Hongchao ZHEN, Hong ZHAO, Lei ZHAO, Bangwei CAO. Efficacy and safety of adjuvant EGFR-TKIs for resected non-small cell lung cancer: A systematic review and meta-analysis based on randomized control trials. PROSPERO 2022 CRD42022309877 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022309877</p> <p>Dongyu Li, Nan Sun, Jie He. Efficacy and safety of adjuvant therapy for epidermal growth factor receptor mutated, non-small cell lung cancer: systematic review and network meta-analysis.. PROSPERO 2022 CRD42022334185 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022334185</p> <p>Chris Dickhoff, Idris Bahce, Suresh Senan, Ezgi Ulas. Efficacy and safety of neoadjuvant immune checkpoint inhibitors in operable non-small cell lung cancer: a systematic review. PROSPERO 2021 CRD42021235759 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021235759</p> <p>Peng Xie, Xiaolin Li, Wenjie Tang, Jinming Yu, Xindong Sun, Xueqi Xie, Haiyan Zeng, Jie Liu, Yinjun Dong, Guanglei Zhao, Chungang Wang, Dongdong Du. EGFR inhibitors as adjuvant therapy for resected non-small cell lung cancer harboring EGFR mutations: a meta-analysis. PROSPERO 2018 CRD42018093144 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42018093144</p> <p>Boxue He, Qidong Cai, Pengfei Zhang. EGFR-TKIs as neoadjuvant therapy for non-small cell lung cancer: a meta-analysis. PROSPERO 2020 CRD42020197989 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020197989</p> <p>Jun Dang, He Wang, Jun Chen, Tingting Liu, Guang Li. Neoadjuvant immunotherapy and neoadjuvant chemotherapy in resectable non-small cell lung cancer: A systematic review and hypothesis-generating meta-analysis. PROSPERO 2021 CRD42021278661 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021278661</p> <p>Dong Chen, Jianfei Shen. Neoadjuvant treatments of EGFR-Mutated IIIa NSCLC : A meta-analysis. PROSPERO 2021 CRD42021221136 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021221136</p>	
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	<p>Xiaohui Jia, Hong Xu. Safety and efficacy of neoadjuvant immune checkpoint inhibitors in resectable non-small cell lung cancer : a Meta analysis. PROSPERO 2020 CRD42020173557 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020173557</p> <p>Xiaoshun Shi, Xiaoying Dong, Jianxue Zhai, Zhen Ni. The efficacy and safety of neoadjuvant EGFR-TKIs for patients with non-small cell lung cancer (NSCLC) : a meta analysis. PROSPERO 2020 CRD42020187031 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020187031</p>	
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PRIMARY STUDIES

Search for primary literature		
Date searched: 08-22-22		
MEDLINE		
#	Search Statement	Results
1	Carcinoma, Non-Small-Cell Lung/ or Lung Neoplasms/	250378
2	(lung cancer or lung neoplasm* or lung carcinoma* or nslc or lung tumor* or lung tumour*).ti,ab,kw.	218639
3	(non small cell* or nonsmall cell*).ti,ab,kw.	82273
4	2 and 3	79798
5	1 or 4	270498
6	Neoadjuvant Therapy/ or Chemotherapy, Adjuvant/	63639
7	(neoadjuvant or adjuvant).ti,ab,kw.	189953
8	6 or 7	211194
9	Gefitinib/ or Afatinib/ or Nivolumab/ or Immune Checkpoint Inhibitors/ or Protein Kinase Inhibitors/	69196
10	(gefitinib or erlotinib or afatinib or osimertinib or atezolizumab or durvalumab or nivolumab or pembrolizumab or cemiplimab or EGFR tyrosine kinase inhibitors or anti-PD-1 or anti-PD-L1 or checkpoint inhibitor* or check-point inhibitor*).ti,ab,kw.	45217
11	9 or 10	98653
12	5 and 8 and 11	781
	limit 12 to English language	725
CINAHL		
#	Search Statement	Results
1	(MH "Carcinoma, Non-Small-Cell Lung") OR (MH "Lung Neoplasms")	49649
2	lung cancer or lung neoplasm* or lung carcinoma* or nslc or lung tumor* or lung tumour*	68650
3	non small cell* or nonsmall cell*	26497
4	S2 and S3	25890
5	S1 or S4	55949
6	(MH "Neoadjuvant Therapy") OR (MH "Chemotherapy, Adjuvant")	17798
7	neoadjuvant or adjuvant	46413

8	S6 or S7	46413
9	(MH "Gefitinib") OR (MH "Afatinib") OR (MH "Nivolumab") OR (MH "Immune Checkpoint Inhibitors") OR (MH "Protein Kinase Inhibitors")	8518
10	gefitinib or erlotinib or afatinib or osimertinib or atezolizumab or durvalumab or nivolumab or pembrolizumab or cemiplimab or EGFR tyrosine kinase inhibitors or anti-PD-1 or anti-PD-L1 or checkpoint inhibitor* or check-point inhibitor*	14085
11	S9 or S10	19046
12	S5 and S8 and S11	265
13	limit S12 to English language	249

APPENDIX B: EXCLUDED PRIMARY STUDIES

Exclude reasons: 1=Ineligible population, 2=Ineligible intervention, 3=Ineligible comparator, 4=Ineligible outcome, 5=Ineligible timing, 6=Ineligible study design, 7=Ineligible publication type, 8=Outdated or ineligible systematic review (*not shown*), 9=Non-English language, 10=Unable to locate full text.

Citation	Exclude Reason
Pembrolizumab plus Chemotherapy Doubled Response Rate Over Chemotherapy Alone in NSCLC. <i>Personalized Medicine in Oncology</i> . 2016;5(9):384-384.	E1
Ahn HK, Choi YL, Han JH, et al. Epidermal growth factor receptor mutation and treatment outcome of mediastinoscopic N2 positive non-small cell lung cancer patients treated with neoadjuvant chemoradiotherapy followed by surgery. <i>Lung Cancer</i> . 2013;79(3):300-306.	E2
Andreano A, Bergamaschi W, Russo AG. Immune checkpoint inhibitors at any treatment line in advanced NSCLC: Real-world overall survival in a large Italian cohort. <i>Lung Cancer</i> . 2021;159:145-152.	E2
Anonymous. Atezolizumab Extends DFS after NSCLC Relapse. <i>Cancer Discovery</i> . 2021;11(11):OF3.	E7
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Aokage K, Miyoshi T, Wakabayashi M, et al. Prognostic influence of epidermal growth factor receptor mutation and radiological ground glass appearance in patients with early-stage lung adenocarcinoma. <i>Lung Cancer</i> . 2021;160:8-16.	E2
Bai H, Wang Z, Chen K, et al. Influence of chemotherapy on EGFR mutation status among patients with non-small-cell lung cancer. <i>Journal of Clinical Oncology</i> . 2012;30(25):3077-3083.	E2
Bar J, Urban D, Redinsky I, et al. OA11.01 Neoadjuvant Pembrolizumab for Early Stage Non-Small Cell Lung Cancer. <i>Journal of Thoracic Oncology</i> . 2021;16(10):S865-S866.	E6
Beattie R, Furrer K, Dolan DP, et al. Two centres experience of lung cancer resection in patients with advanced non-small cell lung cancer upon treatment with immune checkpoint inhibitors: safety and clinical outcomes. <i>European Journal of Cardio-Thoracic Surgery</i> . 2021;60(6):1297-1305.	E6
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Bryant AK, Sankar K, Strohhahn GW, et al. Prognostic and Predictive Role of PD-L1 Expression in Stage III Non-small Cell Lung Cancer Treated With Definitive Chemoradiation and Adjuvant Durvalumab. <i>International Journal of Radiation Oncology, Biology, Physics</i> . 2022;113(4):752-758.	E1

Citation	Exclude Reason
Bryant AK, Sankar K, Strohbehn GW, et al. Timing of Adjuvant Durvalumab Initiation Is Not Associated With Outcomes in Stage III Non-small Cell Lung Cancer. <i>International Journal of Radiation Oncology, Biology, Physics</i> . 2022;113(1):60-65.	E1
Bryant AK, Sankar K, Zhao L, et al. De-escalating adjuvant durvalumab treatment duration in stage III non-small cell lung cancer. <i>European Journal of Cancer</i> . 2022;171:55-63.	E1
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Chang AY. The role of gefitinib in the management of Asian patients with non-small cell lung cancer. <i>Expert Opinion on Investigational Drugs</i> . 2008;17(3):401-411.	E2
Chen T, Ning J, Campisi A, et al. Neoadjuvant PD-1 Inhibitors and Chemotherapy for Locally Advanced NSCLC: A Retrospective Study. <i>Annals of Thoracic Surgery</i> . 2022;113(3):993-999.	E6
Chen Y, Yan B, Xu F, et al. Neoadjuvant chemoimmunotherapy in resectable stage IIIA/IIIB non-small cell lung cancer. <i>Transl Lung Cancer Res</i> . 2021;10(5):2193-2204.	E6
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Chung KP, Shih JY, Yu CJ. Favorable response to gefitinib treatment of lung adenocarcinoma with coexisting germline and somatic epidermal growth factor receptor mutations. <i>Journal of Clinical Oncology</i> . 2010;28(34):e701-703.	E6
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Citation	Exclude Reason
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Nishida T, Saito Y, Fukai R. Neoadjuvant gefitinib therapy: a potential standard therapy for non-small cell lung cancer. <i>Journal of Thoracic Disease</i> . 2022;14(4):799-801.	E7
Ohri N, Halmos B, Bodner WR, et al. Who Benefits the Most From Adjuvant Durvalumab After Chemoradiotherapy for Non-small Cell Lung Cancer? An Exploratory Analysis. <i>Practical Radiation Oncology</i> . 2021;11(2):e172-e179.	E1
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Citation	Exclude Reason
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APPENDIX C: QUALITY ASSESSMENT OF INCLUDED STUDIES

RANDOMIZED CONTROLLED TRIALS (ROB-2)

Trial Name or Author, Year	Risk of Bias from Randomization Process	Risk of Bias from Deviation from Intended Interventions (Assignment)	Risk of Bias from Deviation from Intended Interventions (Adherence)	Risk of Bias from Missing Outcome Data	Risk of Bias in Measurement of Outcome	Risk of Bias in Selection of Reported Result	Overall Bias (Low, Some Concerns, High)
IMpower010 ⁴⁵⁻⁴⁷	Low Patients were randomly assigned (1:1) by a permuted-block method with a block size of four to either the atezolizumab arm or best supportive care arm with an interactive voice-web response system. Randomisation was stratified by sex (female vs male), tumour histology (squamous vs non-squamous), extent of disease (stage IB vs stage II vs stage IIIA), and PD-L1 expression status. Baseline balance.	Low Used open-label (unblinded) design. Only patients without disease recurrence after CT were enrolled.	Some concerns (DFS); Low (OS) Substantial differential discontinuation due to adverse events. Similar proportions of patients received non-protocol treatment at recurrence.	Low Explicit criteria for censoring.	Some concerns (DFS); Low (OS) Investigators assessing differential outcomes were aware of treatment assignment. Subgroup analysis of PD-L1 > 1%.	Low Protocol available. No changes to primary endpoints reported.	Some concerns (DFS); Low (OS)
Feng 2015 ⁴⁸	Some concerns Does not appear to use stratified randomization. Baseline balance.	Some concerns Blinding not described.	Some concerns Blinding not described. Limited deviations.	Low	Some concerns Investigators assessing outcomes may have been aware of treatment assignment.	Some concerns Protocol not registered until after enrollment began. Funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.	Some concerns
CheckMate 816 ⁶⁴	Low Stratified randomization by gender at birth and disease stage. Baseline balance.	Low Used open-label (unblinded) design but probably limited deviations due to context.	Low Used open-label (unblinded) design but limited deviations. Most patients in both groups completed treatment, but	Low Explicit criteria for censoring.	Low Assessment of primary endpoint was blinded. Subgroup analysis by PD-L1 expression level.	Low Protocol-specified primary outcome (MPR) changed to secondary outcome due to health authority feedback. Rationale provided in	Low

Trial Name or Author, Year	Risk of Bias from Randomization Process	Risk of Bias from Deviation from Intended Interventions (Assignment)	Risk of Bias from Deviation from Intended Interventions (Adherence)	Risk of Bias from Missing Outcome Data	Risk of Bias in Measurement of Outcome	Risk of Bias in Selection of Reported Result	Overall Bias (Low, Some Concerns, High)
			subsequent treatments were more frequent in CT only group (not considered a risk of bias because progression event counted toward EFS then was subsequently censored).			supplement, and MPR reported in supplement.	
EVIDENCE ⁵⁰	Low Randomization stratified by EGFR mutation subtype, clinical stage, and resection method. Baseline balance.	Some concerns Used open-label (unblinded) design. Substantially greater number of pts. in control group did not receive assigned treatment.	Some concerns Used open-label (unblinded) design	Some concerns Substantially greater number of pts. in control group missing crucial assessments.	Some concerns Investigators assessing outcomes were aware of treatment assignment. DFS and OS curves exhibit nonproportionality.	Some concerns Protocol not available.	Some concerns
Huang 2021 ⁶⁵	Some concerns Randomization method not described, and randomization does not appear to be stratified. Groups did not differ significantly in baseline characteristics but were substantially imbalanced in size.	Some concerns Blinding not described.	Some concerns Blinding not described. Deviations not permitted by design.	Low	High Outcomes were retrospectively collected, suggesting that patients with missingness were not included in the study; investigators assessing outcomes may have been aware of treatment assignment. Did not examine subgroups by PD-L1 expression.	Some concerns No protocol/registration available.	High
RADIANT ^{51,52}	Some concerns Baseline balance in main groups; in EGFRm+ subgroup more patients in the erlotinib arm having stage IB	Low	Some concerns (DFS); Low (OS) Many more patients discontinued treatment because of adverse events	Low	Some concerns Investigators assessing outcomes may have been aware of treatment assignment.	Low	Some concerns



Trial Name or Author, Year	Risk of Bias from Randomization Process	Risk of Bias from Deviation from Intended Interventions (Assignment)	Risk of Bias from Deviation from Intended Interventions (Adherence)	Risk of Bias from Missing Outcome Data	Risk of Bias in Measurement of Outcome	Risk of Bias in Selection of Reported Result	Overall Bias (Low, Some Concerns, High)
	and more patients in the placebo arm having stage IIIA disease. A smaller proportion of patients receiving erlotinib had lobectomies and received adjuvant chemotherapy. Randomization stratified according to stage, histology, previous adjuvant chemotherapy, smoking status, EGFR status, and country.		in treatment arm (not considered an eligible outcome event.)		Violation of proportional hazards for EGFRm+ subgroup.		
Li 2014 ⁴⁹	Some concerns Randomization method not described. Randomization was stratified according to gender (male vs female) and smoking history (current or former vs never) only. Baseline balance.	Some concerns Used open-label (unblinded) design.	Some concerns Used open-label (unblinded) design.	Low	Some concerns Investigators assessing outcomes may have been aware of treatment assignment.	Some concerns No protocol/registration available.	Some concerns
PEARLS/ KEYNOTE-091 ^{43,44}	Low Triple-blinded design. Randomization was stratified by disease stage (IB vs II vs IIIA), receipt of adjuvant chemotherapy (yes vs no), PD-L1 tumor proportion score (TPS; percentage of tumor cells with membranous PD-L1 staining; <1% vs 1–49% vs ≥50%), and geographical region (Asia vs eastern Europe vs western Europe vs the rest of the world). Baseline balance.	Low Triple-blinded design.	Some concerns Triple-blinded design. Median duration and number of treatments were similar in both groups. Substantial differential discontinuation due to adverse events. Unclear whether there was balance in nonprotocol treatment of recurrences.	Low	Low Subgroup analyses by EGFR mutation status and PD-L1 expression.	Some concerns. No changes to primary endpoints apparent. Reporting of subgroup analysis by prior adjuvant therapy at risk of confounding by disease stage.	Some concerns



Trial Name or Author, Year	Risk of Bias from Randomization Process	Risk of Bias from Deviation from Intended Interventions (Assignment)	Risk of Bias from Deviation from Intended Interventions (Adherence)	Risk of Bias from Missing Outcome Data	Risk of Bias in Measurement of Outcome	Risk of Bias in Selection of Reported Result	Overall Bias (Low, Some Concerns, High)
IMPACT ⁵³	Low Randomization stratified/balanced by institution, stage (II vs III), sex (male vs female), and age. Baseline balance.	Low.	Some concerns Used open-label (unblinded) design.	Some concerns	Low Assessment of primary endpoint was blinded.	Low	Some concerns
ADAURA ^{54,55,71,72}	Low Randomization was according to disease stage (IB, II, or IIIA), EGFR mutational status (Ex19del or L858R), and race (Asian or non-Asian). Baseline balance.	Low	Low Double-blinded.	Low	Low Some concerns for DFS curves for with adjuvant chemotherapy (all stages) and without CT (stage IIIA) due to nonproportionality.	Low	Low
EVAN ^{57,58}	Low Randomization was stratified by EGFR mutation type (exon 19 vs 21), histology, and smoking status (smoker vs non-smoker). Baseline balance.	Some concerns Used open-label (unblinded) design.	Some concerns Used open-label (unblinded) design.	Low	Some concerns Investigators assessing outcomes may have been aware of treatment assignment. OS curve exhibits nonproportionality.	Low	Some concerns
ADJUVANT ⁵⁹⁻⁶¹	Low Randomization stratified by lymph node status (N stage [N1 vs N2]) and EGFR mutation subtype (exon 19 deletion vs exon 21 Leu858Arg). Baseline balance.	Low Used open-label (unblinded) design but probably limited deviations due to context.	Some concerns Used open-label (unblinded) design. Substantially more control group participants did not receive treatment as allocated.	Low	Some concerns Individuals with a direct role in the conduct and analysis of the trial did not have access to the randomisation schedule and were masked to treatment assignment until the database was locked. DFS curve exhibits nonproportionality and converge at 48 months.	Low	Some concerns

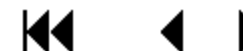
Trial Name or Author, Year	Risk of Bias from Randomization Process	Risk of Bias from Deviation from Intended Interventions (Assignment)	Risk of Bias from Deviation from Intended Interventions (Adherence)	Risk of Bias from Missing Outcome Data	Risk of Bias in Measurement of Outcome	Risk of Bias in Selection of Reported Result	Overall Bias (Low, Some Concerns, High)
EMERGING-CTONG 1103 ⁶⁹	Low Randomization was stratified according to lymph node status (single-station N2 vs multiple station N2), histology, smoking status (never vs former vs current), and sex (male vs female). Baseline balance.	Some concerns Used open-label (unblinded) design.	Some concerns Used open-label (unblinded) design.	Low	Some concerns Investigators assessing outcomes may have been aware of treatment assignment.	Low	Some concerns

Abbreviations. CT=chemotherapy; EGFR=epidermal growth factor receptor; EGFRm+=EGFR mutation positive; PDL=programmed cell death ligand; TKI=tyrosine kinase inhibitor.

NONRANDOMIZED COMPARISON STUDIES (ROBINS-I)

Author Year	Bias Due to confounding	Selection Bias	Bias in Classification of Interventions	Bias Due to Departures from Intended Interventions	Bias Due to Measurement of Outcomes	Bias Due to Missing Data	Bias in the Selection of Reported Results	Overall Bias (Low, Moderate, Serious, Critical, No Information)
Xiong 2020 ⁶⁶	Moderate Study is unrandomized and provides unadjusted comparisons, but most relevant baseline characteristics appear to be balanced.	No information Unclear how patients were selected (by investigators, consecutively, etc).	Moderate Specific edibility criteria provided, but method for determining EGFRm status not described.	Moderate Appears that all patients completed neoadjuvant treatment as allocated. Groups differed in proportion receiving resection as planned. CT offered to both groups after surgery.	Moderate Assessors likely unblinded to group status.	Serious Survival reporting only for those receiving resection (12/15 in treatment, 8/16 in control).	Moderate No protocol available, but no indication of selective reporting.	Serious
Zhao 2021 ⁶⁷	Serious Study is unrandomized and provides unadjusted comparisons between 2 groups of patients from different sources (a single group trial for tx group and a database for ctrl group). Groups significantly differ in CEA at baseline.	Serious Selection of patients from database is not described (ie, presumably more than 15 database pts met eligibility criteria, so how was the subset of 15 selected?).	Low Specific edibility criteria and method for determining EGFRm status described.	Low Appears that all patients completed neoadjuvant treatment as allocated. CT offered to both groups after surgery. All pts underwent resection.	Serious Assessors likely unblinded to group status. Unclear if outcome assessment differed for trial (tx) and database (ctrl) pts.	Low Appears that most or all data were available.	Moderate Protocol available only for tx group pts, but no indication of selective reporting.	Serious
Zhong 2015 ⁶⁸	Moderate Study is unrandomized and provides unadjusted comparisons, but most relevant baseline characteristics appear to be balanced (with the exception of nonsignificant differences in smoking duration and daily cigarette consumption).	No information Unclear how patients were selected (by investigators, consecutively, etc).	Moderate Specific edibility criteria provided, but method for determining EGFRm status not described.	Moderate Appears that all patients completed neoadjuvant treatment as allocated. Groups differed in proportion receiving resection as planned.	Moderate Assessors likely unblinded to group status.	Low Appears that most or all data were available.	Low Protocol available and no indication of selective reporting.	Moderate

Abbreviations. CEA=carcinoembryonic antigen; CT=chemotherapy; ctrl=control; EGFRm=epidermal growth factor receptor mutation; tx=treatment.



APPENDIX D: PEER REVIEW DISPOSITION

Comment #	Reviewer #	Comment	Author Response
<i>Are the objectives, scope, and methods for this review clearly described?</i>			
1	1	Yes	—
2	2	Yes	—
3	3	Yes	—
4	4	No - The authors should start with the relevant clinical questions and then develop the evidence. It reads like the process was inverted	It is unclear what it is meant by this feedback.
5	5	Yes	—
6	6	Yes	—
<i>Is there any indication of bias in our synthesis of the evidence?</i>			
7	1	No	—
8	2	No	—
9	3	No	—
10	4	No	—
11	5	Yes - Significant tendency to ascribe lack of evidence for adjuvant therapy but in same paragraph say confidently that administering therapy at relapse may be just as good as in adjuvant setting (without evidence to support this statement).	Thank you, we have addressed this comment as discussed in further detail below.
12	6	No	—
<i>Are there any published or unpublished studies that we may have overlooked?</i>			
13	1	No	—
14	2	No	—
15	3	No	—
16	4	No	—
17	5	Yes - Mentioned several in the attachment.	We added a discussion of NADIM II findings, however we did not formally include the trial in strength of evidence ratings because findings

Comment #	Reviewer #	Comment	Author Response
			have not yet been released in a peer-reviewed publication. We have added ALCHEMIST to the listing of underway studies.
18	6	Yes - ALCHEMIST (EGFR cohort closed to accrual, awaiting future analysis)	We have added ALCHEMIST to the listing of underway studies.
<i>Additional suggestions or comments can be provided below.</i>			
19	1	Excellent review.	—
20	2	<p>This is a well-conducted, evidence synthesis and summary of results of clinical trials testing anti-PD1 immune checkpoint blockade, and EGFR tyrosine kinase inhibition, as peri-operative treatment for specific subgroups of patients with stage I-III non-small cell lung cancer treated with surgery. One of the goals of this evidence synthesis and data summary is to develop clinical policies for the VA system which are independent of F.D.A. drug labels. As such, the words/language used in the Key Findings of the executive summary, and elsewhere in the text of the document (especially Discussion and Conclusions), are important, and worth careful consideration so as to avoid inaccurate value assignments based on words/language.</p> <p>Just looking at the words used in the Executive Summary and Conclusions of the document, one could conclude that the magnitude of disease free survival benefit afforded by either immunotherapy, or anti-PD1 checkpoint blockade, is similar. This is not accurate. The magnitude of disease free survival benefit afforded by osimertinib is much higher than atezolizumab or pembrolizumab.</p> <p>The biggest judgment in the language summary (one with which I happen to agree) is to limit consideration of adjuvant anti-PD1 to patients with PDL1 \geq 1% (which is a reasonable departure from the F.D.A. label for pembrolizumab). This deserves, perhaps, a sentence in the text of the document to summarize the justification for this departure.</p> <p>Just looking at the words of the Discussion, one could conclude that the benefit of neoadjuvant nivolumab (added to chemotherapy) is clearer than the benefit of adjuvant atezolizumab or pembrolizumab. This is not accurate. The magnitude of disease free survival benefit is similar with</p>	<p>Thank you, we have addressed these points throughout. With respect to diagnostic testing, based on the inconsistent nature of reporting and pre-specification of subgroup analyses by potential diagnostic criteria (as discussed by several other reviewers), as well as other methodological limitations we note, we felt we could not conclude that testing for the features you described is essential (though we agree that there is the strong suggestion of this). We have added some content on diagnostic implications in the discussion.</p>

Comment #	Reviewer #	Comment	Author Response
		<p>either approach. I agree that the availability of pathologic response for risk assessment is unique, and the shorter treatment duration may reduce cost which is worth mentioning, but those distinctions should not result in language that might suggest superior efficacy, or clearer evidentiary support.</p> <p>The main impact of the clinical studies considered in this review, in terms of patient care and management, is a fundamental change in diagnostic testing for early stage lung cancers. Based on ADAURA, it is now essential to test resected lung adenocarcinomas for EGFR exon 19 deletion and L858R to allow for consideration of adjuvant EGFR TKI. Based on CHECKMATE 816, it is now essential to test patients being considered for neoadjuvant chemotherapy plus nivolumab for activating/sensitizing EGFR mutations and ALK fusions. Based on the results of IMPOWER-010 and PEARLS it is now essential to test resected lung cancers being considered for adjuvant ICI to be tested for PDL1 expression by IHC (note different, but equally valid methods for measuring PDL1 in the 2 studies). These new diagnostic standards of care should be highlighted as Key Findings.</p>	
21	2	Suggest adding language about new diagnostic (molecular pathology) standards as a Key Finding	See response to previous comment.
22	2	Suggest not using identical language to summarize/describe the disease free survival benefit of adjuvant ICPI vs EGFR TKI. Perhaps summarize a range of hazard ratios to reflect these, or drop the use of "likely" when describing the effect of EGFR TKIs to distinguish this difference in magnitude.	We have added information on magnitude where possible.
23	2	Add a sentence at the end of the ICI evidence brief summarizing why it is reasonable to limit consideration of adjuvant ICI to PDL1 >= 1%, which is a "rule out" determination of a PEARLS subgroup based on consideration of both IMPOWER-010 and PEARLS.	See response to first comment.
24	2	Page 5, Line 32: I disagree that lung cancers with EGFR activating/sensitizing mutation have a worse prognosis. In fact, they may be more likely to be found in stage IA tumors, and may have a better prognosis (D'Angelo, J Thorac Oncol. 2012 Dec;7(12):1815-1822; among others)	This language has been removed.
25	2	Page 37, Line 46: I disagree that there is clearer support for neoadjuvant therapy with ICIs. There are some clear advantages including lower cost, and availability of pathologic response for risk assessment, but adding risk	We have revised our conclusion with these points in mind.

Comment #	Reviewer #	Comment	Author Response
		prior to surgery (the neoadjuvant approach in general) is particularly risky because it may interfere with surgery. We need longer follow-up to demonstrate the clear advantage to this approach, which is theoretically due to generating a more powerful immune response with cancer antigens still present.	
26	2	Page 40, Line 30-35: I disagree with this statement, and you need to be careful with this sort of language. This statement reads as if the currently available evidence suggests the superiority of conventional adjuvant chemotherapy for most patients, and to not give ICI or EGFR TKI. This is not accurate, so the language must be chosen more carefully. As ICI and EGFR TKI are clearly additional therapies, i.e. given in addition to traditional chemotherapy, perhaps the best rhetorical approach is to state that the standard of care remains to offer conventional adjuvant chemotherapy to stage II-III patients. Then, additional therapy may be considered for selected patients. This, at least, allows the reader a better appreciation for these major advances, even though these advances have not yet demonstrated overall survival benefit	Thank you, this statement has been removed.
27	3	It is unclear to me why treatments that have been shown in trials to have a statistically significant probability of being true based on randomized phase III evidence is only designated as "likely" true. If you characterize the benefit in DFS from adjuvant osimertinib as merely "likely", with a hazard ratio for DFS of 0.20, it suggests a bias such as characterizing gravity or evolution as a mere theory. I would say that there is no reasonable question that adjuvant osimertinib dramatically improves DFS, even if it does not improve OS.	"Likely" corresponds to strength of evidence ratings, as described in the Methods section. However, we have added additional information about effect magnitude and refined the wording of conclusions so as not to minimize substantial disease-free survival benefit where it is apparent.
28	3	One way it seems that uncertainty is introduced is by including a great deal of discussion of older data with inferior agents and smaller trials. I would argue in favor of temporal discounting, so that the most recent data from larger trials are far more heavily weighted in conclusions than negative results with inferior agents. There is no question that gefitinib and erlotinib are inferior to osimertinib, so pooling a lot of older results with far more recent results just dilutes the more appropriate conclusions to draw from more recent work. At the very least, it should be well noted that more recent data with osimertinib are more definitive than older and more equivocal work with unquestionably inferior EGFR TKIs.	Thank you, we have more explicitly accounted for drug generation in our synthesis and conclusions.
29	3	At the bottom of page 1 (line 57), note is made comparing the toxicity of immunotherapy compared to adjuvant chemotherapy. In fact, this is a false dichotomy that presumes an "either/or" approach when a "both/and"	We have revised the introduction to avoid this suggestion.

Comment #	Reviewer #	Comment	Author Response
		strategy that incorporates both chemotherapy and immunotherapy is very likely the most appropriate. I don't think the question should be framed as if immunotherapy should be considered as a replacement of standard chemotherapy.	
30	3	The opening sentence of the conclusions on page 4 of the report suggests that reactive treatment initiated as needed at the time of relapse, may result in a survival benefit compared to adjuvant EGFR TKI use "for most patients". While it is possible that treatment only as needed at the time of relapse could produce comparable, statistically non-inferior results as adjuvant EGFR TKI therapy for all, the premise that treating patients only at relapse, with some relapsing with brain metastases and rapidly declining performance status, would be superior in overall survival to proactive adjuvant therapy is barely theoretically feasible, and no experienced clinician in the field considers it remotely plausible that reactive treatment will be superior. To me, this conveys either inappropriate judgment or bias against the data presented in the ADAURA trial.	We have removed statements that could be taken to imply that reactive treatment is superior, and refined conclusions in general.
31	3	The last sentence in the second paragraph of page 6, starting at line 25, states that lack of an OS benefit in a trial in which there has been extensive crossover "is a more conclusive indicator that the therapy is ineffective". That is an incorrect conclusion. Seeing an absence of improvement in OS when there has been crossover demonstrates that the TIMING of a treatment is not critical, but there can still be a remarkably effective therapy given early or late that leads to comparable survival in the face of crossover.	Thank you, this paragraph has been revised.
32	3	As I noted in point 2 above, the data collection portrayed in the flowchart on page 11 does not factor in the exceptionally high probability that research with newer agents could be different from research with older agents. In my mind, this is a fundamental question. Reviews of the newest iPhone don't include an extensive discussion of the features and challenges of iPhones from the earliest years. We are far more interested in the latest, best iteration, not the cumulative record that includes inferior ones, especially not having them weighed equally.	We have more explicitly accounted for drug generation in our synthesis and conclusions.
33	3	The opening paragraph of page 13 of the report appropriately characterizes the lack of certainty whether identified improvements in DFS with adjuvant ICIs will translate into improvements in OS. That said, many clinicians, and I would even say most, feel it is appropriate to give patients	See response to first comment.

Comment #	Reviewer #	Comment	Author Response
		"the benefit of the doubt" while we await this information, particularly when the surrogate endpoints point in a favorable direction.	
34	3	The same issue of wanting to give patients "the benefit of the doubt" applies to adjuvant TKI (specifically osimertinib) in EGFR mutation-positive resected NSCLC; the concluding sentence at the bottom of page 18 of the report is true, but it is a particularly uncharitable and strict way of viewing the state of the field today that is out of step with how nearly all thoracic oncologists view the prospect of benefit vs. risk of overtreatment vs. undertreatment based on the results of ADAURA as we know them today.	Thank you, we have refined this section along the same lines as discussion of DFS benefits for TKIs.
35	3	The sentence starting at line 13 of page 24 of the report notes how certain trials address the question of whether EGFR TKI therapy can/should replace chemotherapy in the adjuvant setting, most US-based thoracic oncologists feel that this is not the optimal question to be asking, because the benefits may well be additive.	We have refined this section with this feedback in mind.
36	4	In regard to adjuvant ICI there are 2 trials which led to the approval and clinical availability of atezolizumab and pembrolizumab. The atezolizumab trial used a hierarchical design and the DFS benefit has been established for patients with stage II and III with a PD-L1 $\geq 1\%$, and for pembrolizumab the benefit was observed in stage IB-III, regardless of PD-L1 status. The results demonstrate benefit in different patient populations according to stage and PD-L1 expression. In the summary statement there is a general statement of DFS for PD-L1 $\geq 1\%$ and stage II and III patients for ICI. In order, to clarify I think there needs to be separate statements about each agent	We have incorporated this feedback.
37	4	In the summary statement I recommend clarify the overall survival benefit observed to date rather than "may improve overall survival." For instance, "data on overall survival with adjuvant ICI is immature at this time" This clarifies for a clinician	We have incorporated this feedback.
38	4	The cut-off of PD-L1 $\geq 1\%$ for pre-operative chemotherapy and ICI is unclear since the ITT analysis included all patients. Only 43% of patients had PD-L1 $< 1\%$ (n=145) which is inadequately powered for a definitive analysis	We have revised discussion of the role of PD-L1 status.
39	4	A common clinical question is adjuvant EGFR TKI or ICI for patients with an EGFR mutation and who are eligible for ICI. The data that are available are small subset analyses, but given the clinical question a brief paragraph discussing the issue may be valuable.	Thank you for this suggestion, we have added this information for IMpower010 (PEARLS does not

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			report this analysis within the PD-L1-positive sample).
40	4	A lot of subset and exploratory analyses are included in the document. Many times these are insufficiently powered and susceptible to an imbalance of prognostic factors. I realize these are included to be “comprehensive” but the results can be misleading. I would restrict the reporting to primary and secondary analyses, unless there is a well-defined clinical question (please see above).	We have pared down discussion of post hoc/exploratory subgroup analyses and/or added cautionary notes about their interpretation.
41	4	I do not see the value of discussing trials of adjuvant EGFR TKI's that were performed in unselected patients (e.g. BR.19, RADIANT) since the use is restricted to patients with a confirmed EGFR mutation. The EGFR mutation positive patient population is the relevant patient population for clinicians	We have reduced discussion of the 2 trials that were terminated early and that used unselected patients (BR19, Tsuboi 2005). As already noted in the Results section, our discussion of RADIANT focused on the EGFRm+ subsample.
42	4	The manuscript would benefit a narrower focus on the clinically relevant studies and their merits and weaknesses to assist the clinician. The most relevant studies for clinical care and health system decision making are: adjuvant osimertinib (Wu et al NEJM 2020), the IMpower010 (Felip et al Lancet 2021), PEARLS/Keynote-091 (O'Brien et al Lancet Oncology 2022), Checkmate 0816 (Forde et al NEJM 2022)	We have pared down discussion of studies using older-generation EGFR-TKIs.
43	4	On page 5, the prognostic implications of EGFR mutant and EGFR wild-type NSCLC are debated, especially in the surgically resectable patient population. I recommend removing the statement “in NSCLC, mutations to the EGFR are associated with poor prognosis” The cited references do not address this issue.	This statement has been removed.
44	4	The underway studies sections are hard to cover since there are numerous studies which have different treatment plans, stages and maturity. These paragraphs are not helpful	Thank you for this feedback; however, we feel it is important to highlight when additional evidence may become available.
45	4	When discussing the adjuvant EGFR TKI's trials I would include the differences in design in that ADUARA was an active therapy vs placebo, and the other trials were an investigational therapy (EGFR TKI) vs a standard therapy (platinum-based doublet). This context is important for interpreting the HR	Thank you for this feedback; this information is already discussed in the initial paragraphs of the adjuvant EGFR-TKI section and reflected in the structure of the section.

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46	4	I would include a statement that the OS data is immature for the EGFR TKI trials in the table as a footnote	We have incorporated maturity into the tables.
47	4	In the interval between developing the evidence synthesis and currently the ADURA update has been published in JCO	Thank you for bringing this to our attention; we have updated references accordingly.
48	4	I would include the duration of EGFR TKI therapy in table 2 since this may influence the report of the DFS at specific time points	Thanks, however we feel there is already a great deal of information presented in these tables. And, while planned treatment duration did differ somewhat across trials, overall there was similarity.
49	4	On page 28, I do not understand the discussion about patients discontinuing the placebo at a higher rate than the active therapy for disease progression as a concern. Patients on the control arms are expected to come off study therapy at the time of disease progression and this would suggest the active arm has greater efficacy	We have clarified this section.
50	4	On page 30, when discussing the role of neoadjuvant chemotherapy an important detail is the rate patients in each arm went to surgical resection and the rate of R0 surgical resection in each arm. Please include this in the text	This information has been added.
51	4	On page 31, I am uncertain why the single arm trial nivolumab or chemotherapy is included. This trial does not investigate chemotherapy with immunotherapy which is the goal of this section. I also do not understand why other trials that have not been analyzed or completed accrual are included in this section.	The trial mentioned was not single arm, though we have substantially reduced discussion of the trials referenced.
52	4	On page 40, please include the comparison for the ALINA trial	This information has been added.
53	5	Would strongly suggest having lung cancer content experts as co-authors, there are many within the VA system. While the authors have done a good job collating the evidence there are clear deficiencies in the interpretation of the nuances of the data and statements made that no practicing oncologist would consider accurate. For example the arbitrary selection of PD-L1 1%+ disease for neoadjuvant or adjuvant therapy without a nuanced discussion of the study results is not good. The biggest debate in this area of oncology is whether adjuvant atezolizumab should be offered to just 50%+ or 1%+ per the label but this is not explored. Similarly the nuances of the PEARLS trial (unusual results	We have refined discussion of the role of PD-L1 status throughout the report, particularly in the discussion.

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		for the co-primary endpoint in PD-L1 50%+) are not discussed in any detail.	
54	5	Key findings – adjuvant therapy with ICIs: the comparison is not with "no additional chemotherapy". Additional chemotherapy is not a standard here, the comparison is best supportive care (impower010) or placebo (PEARLS trial). Not sure about the use of "likely" here, what does it mean? Two phase 3 trials have shown improved DFS.	"Likely" corresponds to strength of evidence ratings, as described in the Methods section. However, we have added additional information about effect magnitude and refined the wording of conclusions so as not to minimize substantial disease-free survival benefit where it is apparent.
55	5	Key findings – adjuvant therapy with TKIs: Again, likely is an unusual term, particularly when the HR for DFS is so strong in this setting. The comparison in Adaura was not adjuvant chemotherapy alone. Patients were not required to receive adjuvant chemo in either arm, Please review the study design again. Again, this is being stated in a very unusual way, I would just state the actual study design rather than selecting out study subgroups like this.	See previous response.
56	5	Key findings – adjuvant therapies with ICIs or EGFR-TKIs: This is uncertain, at least as uncertain as the previous statements. DFS is an accepted surrogate in the adjuvant setting for lung cancer by FDA and most regulatory authorities worldwide. At the very least adjuvant atezolizumab is very likely to result in an OS benefit for pts with PD-L1 50% or greater lung cancer, see the presentation from ESMO 2022.	We have refined this statement.
57	5	Key findings – neoadjuvant therapy with ICIs: Would add in parenthesis that patients with non squamous tumors should be tested for EGFR and ALK alterations prior to treatment as such patients were excluded from CheckMate 816. I would not suggest selecting out the PD-L1 positive group, CheckMate 816 was a small trial (358 pts compared to 2-3 times that many in the adjuvant trials) in the context of phase 3 randomized studies for early stage cancer and the subgroups are very underpowered. For comparison the DFS benefit HR from adjuvant chemotherapy vs. no adjuvant chemotherapy (Pignon et al, LACE meta analyses 2008) has essentially the same HR as the HR for chemo nivo vs. chemo alone in CheckMate 816. And you have a strong recommendation for adjuvant chemo, this seems contradictory. The recent NICE assessment and approval of neoadjuvant chemo-nivolumab in the UK showed cost effectiveness for all comers irrespective of PD-L1.	Thank you, we have refined this statement.

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58	5	Page 1, line 54: Reword sentence, the benefit of ICIs alone has not been shown in PD-L1 negative advanced lung cancer.	This sentence has been reworded.
59	5	Page 2, line 7: Pembro is only approved after adjuvant chemo.	This sentence has been corrected.
60	5	Page 2, line 19: This concern has been almost exclusively applied to TKIs not ICIs	This sentence has been reworded.
61	5	Page 2, line 52: Need to reword, this is a misconception, the comparator is not additional or no additional chemo as nobody would give more chemo here.	This sentence has been reworded.
62	5	Page 2, line 55: A more nuanced discussion would be helpful here. If you want to take a very pragmatic approach then just offering adjuvant atezolizumab to PD-L1 50%+ would not be unreasonable, that is the approach many health systems outside US are taking. But the way this is worded currently really does not make sense when you look at the two trials.	We have refined this section.
63	5	Page 3, line 11: As mentioned this is an unusual way to look at the data. The applicable study for a US population is Adaura, trials such as CTONG really are not applicable to a US population both in terms of demographics and also treatment approach which is non standard.	We have refined this section.
64	5	Page 3, line 32: As mentioned above would not use underpowered subgroup here, even if you do the DFS benefit is the same as adjuvant chemo	We have refined this section.
65	5	Page 4, line 5: No data to support this statement	This statement has been removed.
66	6	Stage definitions changed between design and reporting of most clinical studies (AJCC edition 7) and current practice (AJCC edition 8). In particular, tumors 3-4 cm and tumors 4-5 cm without node involvement moved from stage group IA to IB and IB to IIA, respectively. Thus, in the current staging system, no RTCs include stage I (i.e., IB) by AJCC edition 8. The language throughout the manuscript should include a designation of the staging system used to describe the study.	We have added staging information for trials, when available.
67	6	Page 29, paragraph starting on line 20. ALCHEMIST study of adjuvant erlotinib was partially accrued prior to being closed. When ADAURA led to FDA approval of osimertinib. The primary endpoint is overall survival. https://clinicaltrials.gov/ct2/show/NCT02194738 .	This information has been added.

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68	6	Page 19, paragraph starting on line 35-36. The radiographic imaging studies performed to determine the stage of patients is not consistent between clinical trials and standard clinical practice in the US. That variation affects the true stage of the study population. For example, if PET scans are not performed, then some patients who are thought to have stage I-III may actually have stage IV. The ADAURA study did not require imaging studies that met US standards: neither PET scan nor brain MRI with contrast were required. This is a significant limitation in understanding how to apply the results of ADAURA since some patients may have actually had stage IV disease and contributed to the improvement in observed DFS.	We have noted this point alongside concerns already raised about understaging.
69	6	PD-L1 subgroup analyses should be discussed as PD-L1-high (50%-100%), PD-L1-low (1%-49%) and PD-L1-zero (0%). Studies that combine results from 2 groups obscure the clinically meaningful impact of the PD-L1 result. This is most frequently done by combining PD-L1-high and PD-L1-low. The result is that the combined group may have a significant outcome but that significance is driven by the PD-L1-high group while the PD-L1-low group is not significant. Clinicians may then apply the results of the study to those with PD-L1 \geq 1% rather than PD-L1 \geq 50%. Studies that do not separately report these 3 PD-L1 groups are obscuring the results. An example is IMPower010 survival results, page 10, paragraph starting on line 3.	We have expanded our discussion of the role of PD-L1 status and result reporting throughout the report.
70	6	IMPower010 statistical plan is one of hierarchical design with OS being the 4th of 4 analyses. Because the 3rd analysis (PFS in stage IB-III A) is not statistically significant (and is unlikely to be significant in the future), OS cannot be formally assessed for survival. Thus, the results discussed on page 10 have not been formally tested and must be indicated as “hypothesis generating” and for “descriptive purposes only”.	This information has been added.
71	6	Page 18, paragraph starting on line 22 (Underway Studies) should include a description of the primary endpoint (and whether there is hierarchical design) and whether overall survival is any endpoint. That is, whether overall survival be formally analyzed.	This information has been added.
72	6	Page 21, paragraph starting on line 11-12. What was the overall rate of drug discontinuation for toxicity in the two arms? This is the most important comparison. What fraction of patients in the osimertinib arm did not complete 3 years of drug for reasons other than disease progression?	This comparison is included in the current text: At the late-2022 update, 13% of patients receiving osimertinib and 3% of placebo patients had

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73	6	Page 21, line 25 and following paragraphs. Would describe only the EGFR-mutant subsample of RADIANT. Otherwise, the comparisons to ADAURA are meaningless. The main cohort is not relevant and including it makes it difficult to focus on the EGFR-mutant subsample. If it must be included, describe it separately from the EGFR-mutant subsample.	discontinued treatment because of an adverse event. As currently written, the discussion of RADIANT focuses on the EGFRm+ subsample.
74	6	Page 22, paragraph beginning on line 41. BR21 and the Tsubi (reference 68) trial participants were not selected by EGFR mutation and analyses were not done or were no informative by EGFR status. Thus, this paragraph is not helpful and should be reduced to a sentence, a footnote, or removed entirely.	Discussion of these trials has been substantially reduced.