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.

ACKNOWLEDGMENTS

The present report was developed in response to a request from the VA National Oncology Program Office. The scope was further developed with input from Operational Partners (below) and the ESP Coordinating Center review team. The authors are grateful to Mark Deffebach, MD for providing content expertise during initial review scoping; Kathryn Vela, MLIS for literature searching; Payten Sonnen for data abstraction efforts and editorial and citation management support; David H. Hickam, MD, MPH for feedback on a draft version of this report; and the following individuals for their contributions to this project:

Operational Partners

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

Michael Kelley, MD
Executive Director
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Peer Reviewers

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

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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

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).

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 *Excluded:* 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 RCTs[37] 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:	*"Adjuvant ICIs **improve** overall survival"*	*"Adjuvant ICIs **likely improve** overall survival"*	*"Adjuvant ICIs **may improve** overall survival"*
Multiple RCTs with **low** risk of bias *- with or without -* **One or more NRCSs** with **low** or **moderate** risk of bias	Effect estimates **consistent** in direction **and** magnitude *- and -* CIs contain a **narrow** range of values **similar** in meaning to effect estimate(s)	Effect estimates **consistent** in direction **only** *- and/or -* 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 *- or -* **Multiple RCTs** with **some concerns,** or mixed ratings of **some concerns** and **low** risk *- with or without -* **One or more NRCSs not at critical** risk of bias	—	Effect estimates consistent in direction **and** magnitude *- and -* CIs contain a **narrow** range of values **similar** in meaning to effect estimate(s)	Effect estimates **differ** in direction and/or magnitude *- and/or -* 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** *- or -* **Multiple RCTs** with **high** risk of bias, or mixed ratings of **some concerns** and **high** risk *- with or without -* **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	**Insufficient Evidence** *("It is unclear whether neoadjuvant ICIs improve overall survival")*		
One or more NRCSs at **serious/critical** risk of bias, or with mixed ratings of **moderate and serious/critical** risk			
No available studies			

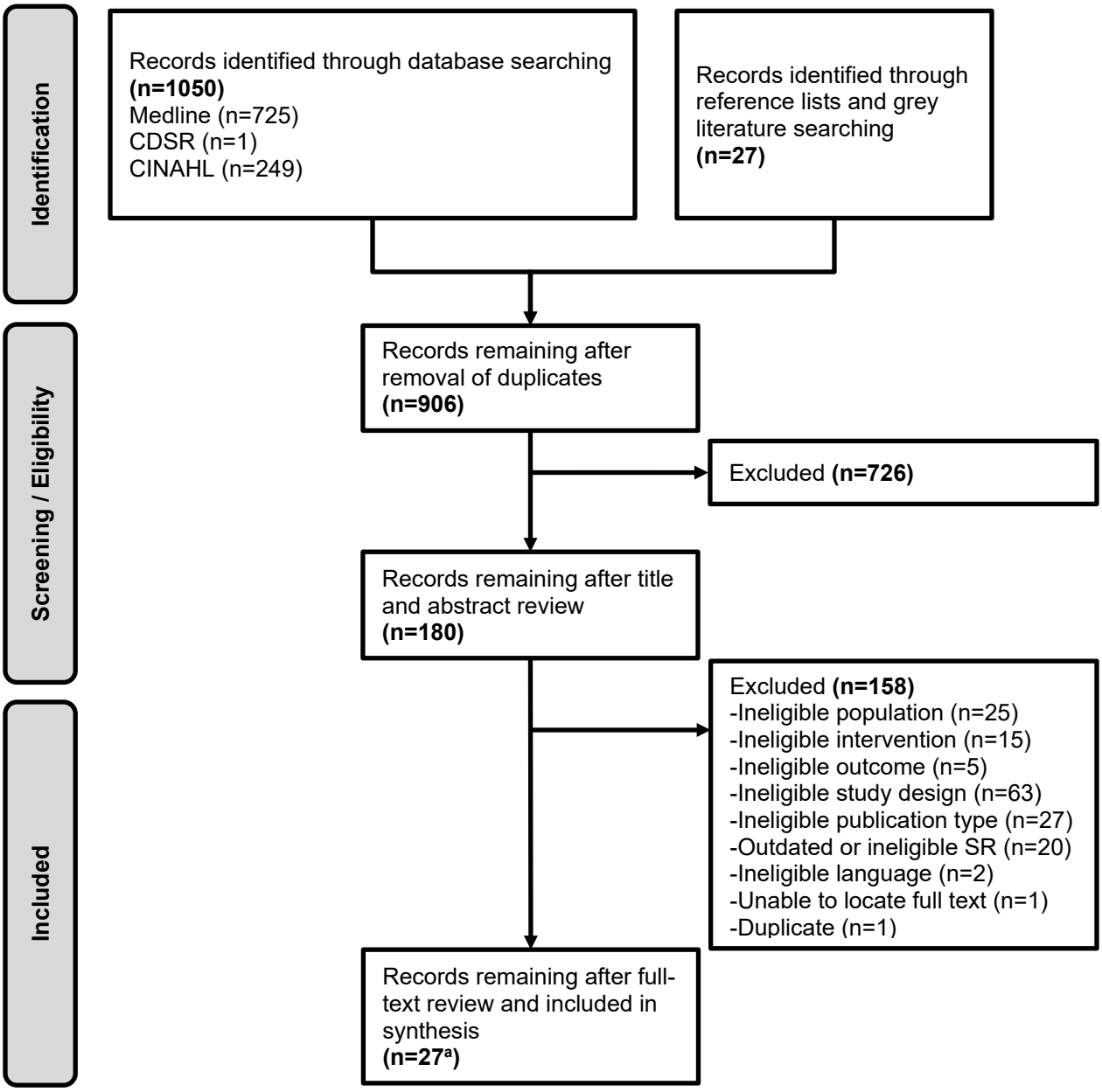
Abbreviations. NCRS=nonrandomized comparison study; RCT=randomized controlled trial.

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. [a]18 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 RCTs[43-47] 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 RCTs[48-61] 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 RCT[64] reporting survival outcomes and adverse events and 1 additional study[65] reporting adverse events.
- *Neoadjuvant EGFR-TKIs:* No RCTs; 3 additional studies[66-68] reporting survival outcomes and adverse events.
- *Combination Neoadjuvant-Adjuvant EGFR-TKIs:* One phase 2 RCT[69] 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 ≥ 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.

IMpower010[45-47] 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 ≥ 1%, and in the intention to treat (stage IB–IIIA) sample. Secondary endpoints included disease-free survival in patients with PD-L1 ≥ 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 ≥ 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 ≥ 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 ≥ 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	Stage III	ECOG Status 1	Disease-Free Survival						Overall Survival					
						Median	HR [95% CI] *Maturity*	2 Yrs	3 Yrs	4 Yrs	5 Yrs	Median	HR [95% CI] *Maturity*	2 Yrs	3 Yrs	4 Yrs	5 Yrs
			Months	*%*	*%*	*Months*		*%*	*%*	*%*	*%*	*Months*		*%*	*%*	*%*	*%*
IMpower010 (3)																	
IB–IIIA (ITT)[a]	Atezolizumab	507	32 (DFS) 46 (OS)	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		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 (OS)	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		47	43	35.3		62	49	38[†]	NA	NR		88[†]	79[†]	70[†]	**67**[†]
II–IIIA (PD-L1 <1%)	Atezolizumab	383	NA (DFS) 46 (OS)	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		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) 46 (OS)	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		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
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
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

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

[a]PD-L1 ≥ 1%: 56% in atezolizumab group; 51% in best supportive care group.

[b]PD-L1 ≥ 1%: 56% in atezolizumab group; 52% in best supportive care group.

[c]Excludes 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]).

[d]PD-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 ≥ 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 ≥ 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 ≥ 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 ≥ 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) 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 ≥ 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 osimertinib[15] 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 treatment[20] of metastatic EGFR mutation-positive NSCLC since 2018, and as a second-line therapy[19] 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 publication[56] 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 analysis[55] 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

							Disease-Free Survival						Overall Survival					
Study (Phase) *Stages (Sample)*	Groups	N	Median Follow-up	Stage III	Med. Tx. Duration[c]	ECOG Status 1	Median	HR [95% CI] *Maturity*	2 Yrs	3 Yrs	4 Yrs	5 Yrs	Median	HR [95% CI] *Maturity*	2 Yrs	3 Yrs	4 Yrs	5 Yrs
			Months	*%*	*Months*	*%*	*Months*		*%*	*%*	*%*	*%*	*Months*		*%*	*%*	*%*	*%*
ADAURA (3)	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
II–IIIA (FAS)	Placebo	237	20	50	25	36[a]	**21.9**	*51% (2022)*	**46**	**34**	**29**	**25**†	NR	*5% (2020)*	93	89†	89†	NA
RADIANT (3)	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
IB–IIIA (EGFRm+)	Placebo	59		31	22	36	28.5	*52% (2014)*	54	42	42	NA	NR	*24% (2014)*	91	85	80	66
EVAN (2)	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**
IIIA-N2 (ITT)	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)	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
II–IIIA (FAS)	Cis+Vin	111		64	84%	77	19.8	*65% (2020)*	39†	33	27†	23	62.8	*45% (2020)*	78†	68†	58†	51
EVIDENCE (2)	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
II–IIIA (FAS)	Cis+Vin/Pem	132		61	68%	70	22.1	*35% (2020)*	46†	33	32†	NA	NR	*10% (2020)*	93†	90†	79†	NA
IMPACT (3)	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
II–III (ITT)	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.

[a]Calculated in overall (IB-IIIA) sample.

[b]HR reported with 99.98% confidence interval.

[c]For adjuvant chemotherapy arms, value is proportion (%) completing 4 treatment cycles.

[d]Calculated in overall (EGFRm+ and EGFRm-) sample.

[e]61% 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.

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.

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.

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 ADJUVANT[59-61] 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.

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.

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,

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.

EVIDENCE[50] 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.

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.

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.

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.

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

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 ≥ 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 816[64] 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 ≥ 1% and 22% had PD-L1 ≥ 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 ≥ 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 ≥ 1% experienced event-free survival benefits from nivolumab. The largest improvement was in patients with PD-L1 ≥ 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 RCT[73] 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 study[65] 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	Stage III	ECOG Status 1	Event-Free Survival[a]						Overall Survival					
						Median	HR [95% CI] *Maturity*	2 Yrs	3 Yrs	4 Yrs	5 Yrs	Median	HR [95% CI] *Maturity*	2 Yrs	3 Yrs	4 Yrs	5 Yrs
			Months	*%*	*%*	*Months*		*%*	*%*	*%*	*%*	*Months*		*%*	*%*	*%*	*%*
CheckMate 816 (3)																	
IB–IIIA (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–IIIA (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
IB–IIIA (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
IB–IIIA (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

Notes. Survival proportions and related values denoted with a dagger (†) were abstracted from survival curves using the WebPlotDigitizer platform.
[a]Eligible events were disease progression, disease recurrence, or death. Corresponding hazard ratio adjusted for optional adjuvant therapy.
[b]PD-L1 ≥ 1%: 50% in nivolumab group; 50% in chemotherapy group.
[c]HR 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 studies[66-68] 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 study[68] ($N = 24$) 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) 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	Median Follow-up	Stage III	EGFRm+	ECOG Status 1	Disease-Free Survival						Overall Survival					
							Median	HR [95% CI] or *p*-value	2 Yrs	3 Yrs	4 Yrs	5 Yrs	Median	HR [95% CI] or *p*-value	2 Yrs	3 Yrs	4 Yrs	5 Yrs
			Months	*%*	*%*	*%*	*Months*		*%*	*%*	*%*	*%*	*Months*		*%*	*%*	*%*	*%*
Zhao 2021 (2)	Erlotinib	14	29	100	100	NA	14.1†	*p* = 0.41	43†	29	29†	NA	NR	*p* = 0.84	85†	64	64†	NA
IIIA-N2 (NA)	Plat-based CT	15	30	100	0	NA	NR		57†	57	57†	NA	NR		64†	64	64†	NA
Xiong 2020 (NA)	Erlotinib	8	NA	100	100	NA	10.2	*p* = 0.25	25†	17†	NA	NA	51.0	*p* = 0.12	75†	59†	59†	30†
IIIA-N2 (NA)	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)	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†
IIIA-N2 (NA)	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 ≥ 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 ≥ 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 ≥ 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-analysis[5] 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 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-analysis[14] 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 example[77] 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 (PACIFIC[78]). 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 analysis[79] 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 study[80] 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 analysis[83] 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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