Adjuvant immune checkpoint inhibition after complete resection of non-small cell lung cancer: A systematic review and meta-analysis of randomized trials

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Abstract. Use of adjuvant immune checkpoint inhibitors (ICIs) following non-small cell lung cancer (NSCLC) resection has been studied; however, assessing their benefit-risk profile requires considering recurrence control, survival evidence and toxicity together. The present study reviewed randomized trial evidence for postoperative adjuvant ICI therapy. In this PROSPERO-registered systematic review reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, five databases were searched. Eligible trials evaluated postoperative adjuvant ICI therapy compared against non-ICI management; studies of neoadjuvant-only or combined neoadjuvant-adjuvant perioperative regimens were excluded. Disease-free survival (DFS) was the primary endpoint. Primary DFS inference was based on Hartung-Knapp (HK)-adjusted confidence intervals and tests within a DerSimonian-Laird random-effects model; conventional intervals provided a comparison. Safety outcomes were assessed separately. Four randomized controlled trials (IMpower010, KEYNOTE-091/PEARLS, BR.31, EA5142/ANVIL; n=4,336) provided DFS data. The primary analysis with HK adjustment yielded a hazard ratio (HR) of 0.86 [95% confidence interval (CI), 0.74-1.01; P=0.0618; I^2=15.0%], with the interval encompassing no effect. Conventional Wald inference produced an identical HR but a narrower 95% CI (0.78-0.95; P=0.0035). Three compatible broad-population overall survival (OS) estimates were subjected to an exploratory synthesis, but no survival benefit was established (HR, 0.96; 95% CI, 0.84-1.10; P=0.5823; I^2=0.0%). The point estimates for trial-reported high-grade adverse events of any cause [risk ratio (RR), 1.45; conventional 95% CI, 1.18-1.78; HK 95% CI, 0.88-2.38] and serious adverse events (RR, 1.60; conventional 95% CI, 1.27-2.01; HK 95% CI, 0.94-2.73) were both >1, whereas the corresponding HK intervals encompassed 1. Deaths attributed to treatment occurred in 14 of 2,022 ICI-treated patients and 0 of 1,539 control patients across the three trials with comparative safety data. In conclusion, adjuvant ICI may improve DFS after complete resection of NSCLC, but the conservative model cannot rule out no benefit. An OS benefit has not been established. Following upfront surgery, the possibility of reducing recurrence with adjuvant ICI is weighed against treatment-related toxicity.

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Abbreviations: CI, confidence interval; DFS, disease-free survival; DL, DerSimonian-Laird; HK, Hartung-Knapp; HR, hazard ratio; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; OS, overall survival; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial; REML, restricted maximum likelihood; RR, risk ratio

Key words: NSCLC, resection, adjuvant immunotherapy, ICI, DFS, OS, toxicity, meta-analysis

Introduction

Non-small cell lung cancer (NSCLC) accounts for most lung cancer diagnoses worldwide (1). Lung cancer caused an estimated 1.9 million deaths worldwide in 2024 (2). Surgical resection is still the primary curative-intent strategy for resectable NSCLC (3). The recurrence risk after resection varies with stage and treatment context; a recent real-world study found lower relapse-free survival rates with more advanced disease stage (4). Platinum-based adjuvant chemotherapy confers a modest survival benefit; the Lung Adjuvant Cisplatin Evaluation meta-analysis estimated that the hazard ratio for mortality was 0.89 and the absolute 5-year survival gain was 5.4% (5). Preventing postoperative recurrence thus remains an important objective of systemic therapy after surgery.

Adjuvant immune checkpoint inhibitors (ICIs) have been investigated after NSCLC resection as a means of reducing postoperative recurrence. In IMpower010 (6,7), atezolizumab administered after adjuvant chemotherapy produced a hazard ratio (HR) for disease-free survival (DFS) of 0.85 [95% confidence interval (CI), 0.71-1.01] in the overall population, while KEYNOTE-091/PEARLS (8) reported a DFS benefit with pembrolizumab (HR, 0.76; 95% CI, 0.63-0.91). Subsequent trials in broad postoperative populations yielded estimates nearer the null: BR.31 (9) found an HR of 0.89 (95% CI, 0.75-1.07) with adjuvant durvalumab in *EGFR*/*ALK*-negative disease, and the HR for EA5142/ANVIL (10) was 0.97 (95% CI, 0.81-1.17) with nivolumab vs. observation. These inconsistent DFS results complicate the clinical interpretation of adjuvant ICI, particularly given the incomplete overall survival (OS) evidence and the clinical consequences of toxicity.

An earlier meta-analysis of IMpower010 (6,7), KEYNOTE-091/PEARLS (8) and BR.31 (9) included 3,401 patients and reported a favorable DFS estimate, no notable OS benefit and increased high-grade adverse events (11). Another review evaluated a broader evidence base that included randomized, single-arm and retrospective studies and encompassed treatment sequences involving preoperative immunotherapy (12). Neither review included EA5142/ANVIL (10). This additional phase III trial enrolled 935 patients and, at a median follow-up of 72.6 months, did not demonstrate improved DFS with nivolumab after planned standard adjuvant treatment. The availability of a further large randomized trial with long-term follow-up provides an important basis for reassessing the previously reported DFS benefit and its clinical implications. The present study provides an incremental update of the randomized evidence on the benefit-risk profile of ICI therapy after upfront surgery.

The current systematic review and meta-analysis was performed on randomized controlled trials (RCTs) of postoperative adjuvant ICI-containing therapy after NSCLC resection. The study sought to quantify the comparative effect on DFS, to pool OS where compatible estimates were available, to quantify key safety outcomes and to summarize prespecified exploratory subgroup analyses where trial-level estimates were compatible. The DFS estimate was interpreted alongside OS evidence, adverse-event burden and the limitations of aggregate subgroup data in the postoperative setting.

Patients and methods

Protocol and reporting. The current study examined postoperative adjuvant ICI-containing therapy after complete resection of NSCLC. This study was registered in PROSPERO (CRD420261417170; record created 6 June 2026) and was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 reporting statement (13), with searches reported according to PRISMA-S (14) and protocol clarifications outlined in Table SI. Since only published aggregate data from randomized trials were used, neither ethics approval nor informed consent was required.

Eligibility criteria. RCTs enrolling patients with resected NSCLC and assessing ICI-containing therapy given exclusively as postoperative adjuvant treatment were included. Comparator groups received placebo, observation, best supportive care or standard adjuvant treatment without ICI. Trials had to provide one or more efficacy or safety outcomes to be extracted. Quantitative synthesis was restricted to peer-reviewed full-text journal reports; conference abstracts, registry-only reports, preprints and other grey literature were ineligible. Studies evaluating neoadjuvant-only therapy, perioperative neoadjuvant plus adjuvant immunotherapy, advanced or metastatic NSCLC, non-randomized designs, protocol-only records, reviews, editorials, case reports and duplicate reports providing no new extractable data were excluded.

Information sources and search strategy. Searches were performed on 13 June 2026 in PubMed/MEDLINE (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com/), Cochrane CENTRAL (https://www.cochranelibrary.com/central), Scopus (https://www.scopus.com/) and Web of Science Core Collection (https://www.webofscience.com/). Database-specific date fields and restrictions, including the 1 January 1975 start date for Web of Science, are detailed in Table SII. Supplementary searches using the trial names IMpower010, KEYNOTE-091/PEARLS, BR.31 and EA5142/ANVIL were conducted in these databases. ClinicalTrials.gov records were consulted for included trials to confirm registration and trial status, but ClinicalTrials.gov was not used as a standalone source for identifying records. The search strategies combined controlled vocabulary, where available, and free-text terms for 'NSCLC', 'resection', 'postoperative or adjuvant therapy', 'immune checkpoint inhibitors' and 'randomized trials'. No language restriction was applied, and neoadjuvant terms were not excluded at the search stage to avoid inadvertently excluding relevant postoperative records. Full search strategies are provided in Data S1; database platforms, search execution dates, date restrictions and record counts are summarized in Table SII.

Study screening and PRISMA flow process. Records were imported into Zotero (https://www.zotero.org/) and deduplicated through automated checks and manual verification. Two reviewers conducted independent title and abstract screening before assessing full texts; any dispute was settled via consensus or a third reviewer. During full-text assessment, the causes of exclusion were recorded, and multiple publications or companion reports were assigned to the same randomized trial if they described overlapping populations or reported updated outcomes. The PRISMA flow diagram reflects this record-level process; numerical counts are reported in the Results section and Fig. 1. Full-text exclusion categories and selected excluded reports are summarized in Tables SIII and SIV, respectively.

Data collection. Two reviewers collected data independently on a standardized extraction form. Collected items comprised trial name, registration number, design, disease stage, population, programmed death-ligand 1 (PD-L1) assay and expression thresholds, and trial eligibility criteria concerning EGFR and ALK alterations, where reported, intervention, comparator, adjuvant chemotherapy context, follow-up, reported HRs and CIs for time-to-event

outcomes, and available safety event counts for each arm. Disagreements were resolved through consensus, and the dataset was cross-checked against the cited trial reports before analysis. If a trial had multiple eligible reports, the latest eligible peer-reviewed full-text report for each outcome and analysis population was used; conference-only updates did not replace eligible full-text reports. Included-trial characteristics and associated publications are summarized in Tables SV and SVI, respectively. Trial-defined DFS was the primary efficacy outcome. Secondary outcomes comprised OS availability, trial-defined high-grade adverse events, serious adverse events, treatment-related death and prespecified subgroup estimates reported in a compatible form. Safety outcomes were extracted according to the definitions and safety analysis population of each trial; serious adverse events, high-grade adverse events and treatment-related deaths were assessed separately.

Risk of bias and certainty evaluations. The Cochrane RoB 2 tool was utilized by two reviewers to evaluate risk of bias independently at the outcome level (15), and any dispute was settled through consensus or a third reviewer. Evidence certainty was assessed with GRADE, considering risk of bias, inconsistency, indirectness, imprecision and publication bias (16).

Statistical analysis. The target estimand was the average comparative effect of postoperative adjuvant ICI-containing therapy vs. non-ICI postoperative management across eligible randomized trials; it was not intended to estimate an interchangeable drug-specific effect for all postoperative patients. Reported hazard ratios were analyzed on the log scale with standard errors derived from 95% CIs. The primary DFS meta-analysis used inverse-variance random-effects pooling with the DerSimonian-Laird (DL) estimator (17). Following peer review and given the availability of only 4 trials, Hartung-Knapp (HK) confidence intervals and tests (18), according to a t distribution with three degrees of freedom, became the primary basis for DFS inference alongside the DL variance estimator. This priority for inference was established during revision, rather than prespecified in the protocol; conventional Wald inference provided a comparison. The included trials and extracted effects were unchanged. HRs <1 favored adjuvant ICI. OS was pooled when at least two compatible broad-population HRs from peer-reviewed reports were available. For comparative binary safety outcomes, risk ratios (RRs) were calculated from extractable event counts in each arm, whereas treatment-related death was summarized mainly as absolute counts given the sparse events and absence of events in control arms. Exploratory analyses of treatment-related death compared a random-effects RR with a 0.5 continuity correction in trials with zero events in one arm and a fixed-effect Peto odds ratio (OR). Safety event counts and denominators came from the reported safety analysis population of each trial, which did not always match the DFS efficacy population in the primary pooled analysis. Heterogeneity was quantified using I^2 and τ^2 (19). Additional analyses compared common-effect and restricted maximum likelihood (REML) random-effects models and assessed leave-one-out estimates. Cumulative pooling and subgroup estimates served descriptive purposes; subgroup pooling required sufficiently comparable populations from at least 2 trials and did not override the primary analysis. Further exploratory analyses assessed placebo-controlled safety estimates and scenario-based absolute DFS translations under proportional-hazards assumptions, propagating the primary HK limits with comparator DFS held fixed; the open-label attenuation scenario remained a supplementary stress test without empirical calibration and did not serve as a robustness criterion. Begg's and Egger's tests were not performed because fewer than 10 trials were available for each meta-analysis. R version 4.5.3 was adopted for analysis with meta (version 8.5.0) and metafor (version 4.8-0) packages (20,21).

Results

Study selection. Database searches yielded 9,189 records. After removing 3,327 duplicates, the titles and abstracts of 5,862 records were screened, with 5,674 eliminated. Full texts were sought for 188 reports; 1 was unavailable and 187 reports were evaluated for eligibility. Of them, 170 were removed with documented reasons. The 17 eligible report records corresponded to 10 independent reports; linking companion and overlapping reports to their respective trials resulted in the inclusion of 4 distinct RCTs: IMpower010 (6,7), KEYNOTE-091/PEARLS (8), BR.31 (9) and EA5142/ANVIL (10). Each trial supplied data for the primary DFS meta-analysis (Fig. 1; Tables SIII-SVI).

Study characteristics. The 4 enrolled randomized trials comprised 4,336 participants in the populations contributing to the primary DFS analysis (Table I). Trial designs varied in comparator, adjuvant chemotherapy requirements, biomarker handling and driver-gene restrictions. Pembrolizumab and nivolumab target programmed cell death protein 1 (PD-1), whereas atezolizumab and durvalumab target PD-L1, and 1 trial evaluated each agent (Table I). IMpower010 and EA5142/ANVIL had open-label observation or standard-care controls, whereas KEYNOTE-091/PEARLS and BR.31 used placebo controls. Median follow-up time spanned 35.6 to 72.6 months. The primary reports for these 4 trials comprised 5 publications, including both the initial and long-term follow-up reports for IMpower010. Companion publications supplied additional follow-up, safety, regional cohort and PD-L1 assay data for IMpower010 (22-26).

Risk of bias. For DFS, KEYNOTE-091/PEARLS and BR.31 had a low risk of bias, whereas IMpower010 and EA5142/ANVIL raised some concerns, chiefly due to their open-label designs with observation or standard-care controls. Safety outcomes had a low risk of bias for KEYNOTE-091/PEARLS and some concerns for IMpower010 and BR.31. Outcome-level risk-of-bias assessments are shown in Figs. S1 and S2, and Tables SVII and SVIII.

Primary DFS analysis. Individual-trial estimates are provided in Table SIX. For the 4 RCTs comprising 4,336 participants, the primary DL random-effects analysis using HK inference estimated a DFS HR of 0.86 (95% CI, 0.74-1.01; P=0.0618;

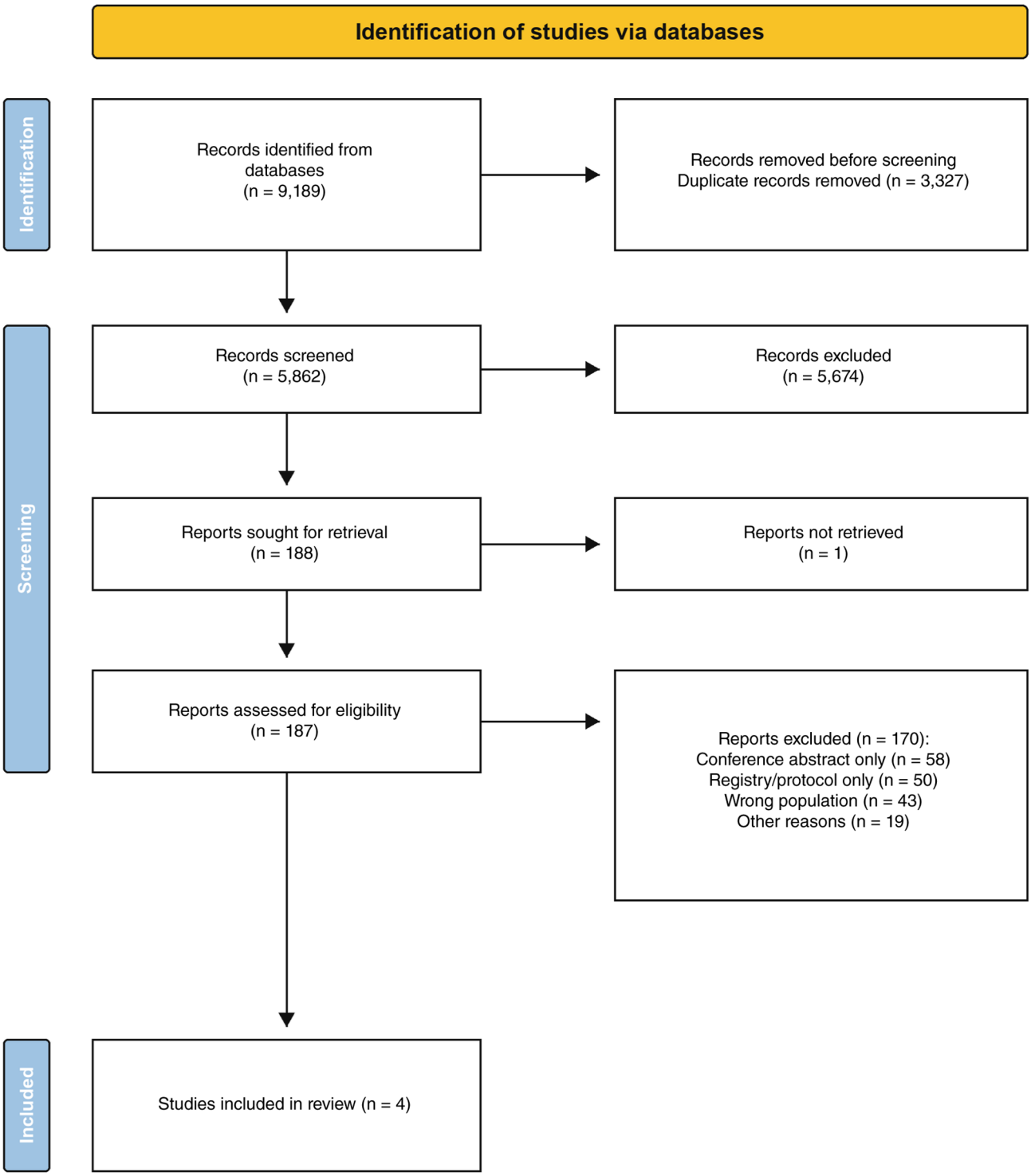


Figure 1. PRISMA 2020 flow diagram showing study selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

I^2=15.0%; τ^2=0.001) (Fig. 2A; Table II; Table SX). This interval encompassed a favorable effect as well as no effect. Conventional Wald inference produced an identical pooled HR with a narrower 95% CI of 0.78-0.95 (P=0.0035). Individual trial HRs were 0.85 for IMpower010, 0.76 for KEYNOTE-091/PEARLS, 0.89 for BR.31, and 0.97 for EA5142/ANVIL (Fig. 2A). In the cumulative analysis, pooling IMpower010 and KEYNOTE-091/PEARLS yielded an HR of 0.81; the estimate was 0.86 after all 4 trials were included (Fig. 2B).

OS. An exploratory synthesis of OS was conducted using the three compatible broad-population HRs available in peer-reviewed reports of eligible trials. IMpower010 (7) provided a broad-population OS HR of 0.97 (95% CI, 0.78-1.22), KEYNOTE-091/PEARLS (8) provided an OS HR of 0.87 (95% CI, 0.67-1.15; P=0.17) for its overall randomized population and EA5142/ANVIL (10) provided an exploratory intention-to-treat (ITT) OS HR of 1.02 (95% CI, 0.82-1.26). In BR.31 (9), OS data had not met the prespecified reporting threshold for maturity. Exploratory pooling of OS yielded an

Table I. Characteristics of the included randomized trials.

Trial	Patients, n	ICI	Control	Population	DFS HR (95% CI)
IMpower010	1,005	Atezolizumab	Best supportive care/observation	Stage IB-IIIA NSCLC after platinum chemotherapy	0.85 (0.71-1.01)
KEYNOTE-091/PEARLS	1,177	Pembrolizumab	Placebo	Stage IB-IIIA NSCLC	0.76 (0.63-0.91)
BR.31	1,219	Durvalumab	Placebo	Stage IB-IIIA NSCLC, *EGFR*/*ALK*-negative	0.89 (0.75-1.07)
EA5142/ ANVIL	935	Nivolumab	Observation	NSCLC ≥4 cm and/or N1/N2 after standard adjuvant therapy	0.97 (0.81-1.17)

Patient numbers correspond to the populations contributing the reported DFS estimates. *ALK*, anaplastic lymphoma kinase; CI, confidence interval; DFS, disease-free survival; *EGFR*, epidermal growth factor receptor; HR, hazard ratio; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer.

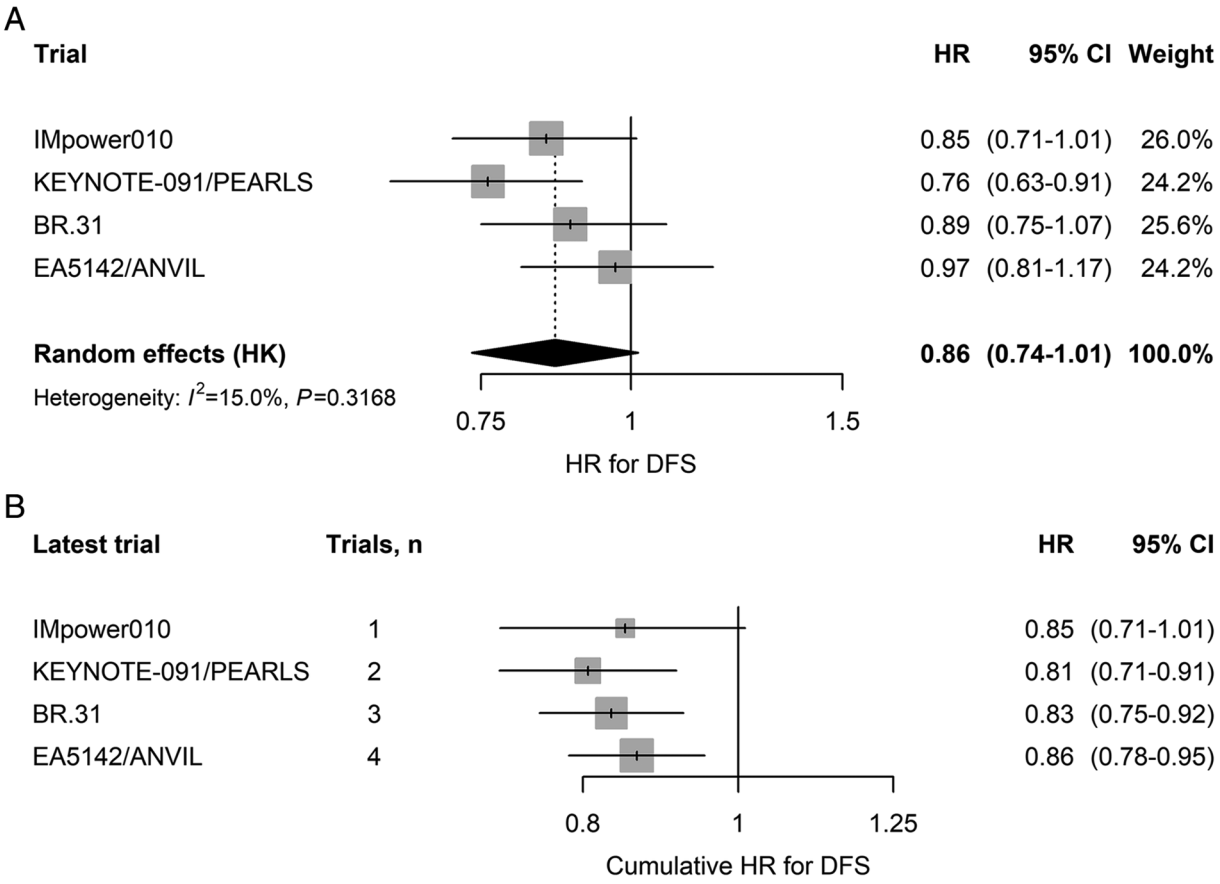


Figure 2. DFS with adjuvant immune checkpoint inhibitors. (A) Primary analysis showing the pooled estimate and its HK-adjusted 95% CI. The P-value accompanying I^2 is from Cochran's Q test for heterogeneity. (B) Cumulative estimates with Wald 95% CIs; each row includes all trials up to and including the trial named in that row. HRs below 1 favor ICI. CI, confidence interval; DFS, disease-free survival; HK, Hartung-Knapp; HR, hazard ratio; ICI, immune checkpoint inhibitor.

HR of 0.96 (95% CI, 0.84-1.10; P=0.5823; I^2=0.0%; τ^2=0.0000) (Table SXI).

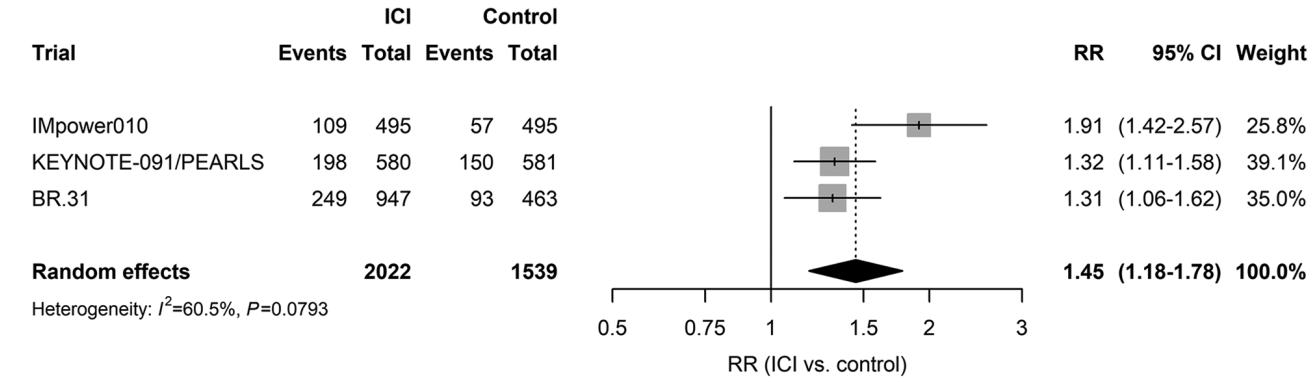
Safety. Comparative safety data were pooled from 3 RCTs based on the reported safety analysis population of each trial, which in some trials differed from the population included in the primary DFS synthesis. Safety data were available for IMpower010, KEYNOTE-091/PEARLS and BR.31 (Fig. 3; Tables II and SXII). Trials varied in safety definitions and ascertainment, including the thresholds for high-grade adverse events and the use of placebo or observation as the comparator. IMpower010 and BR.31 reported grade 3-4 adverse events, whereas KEYNOTE-091/PEARLS reported grade ≥3 adverse events; these reported categories were combined as high-grade

Table II. Summary of efficacy and safety outcomes.

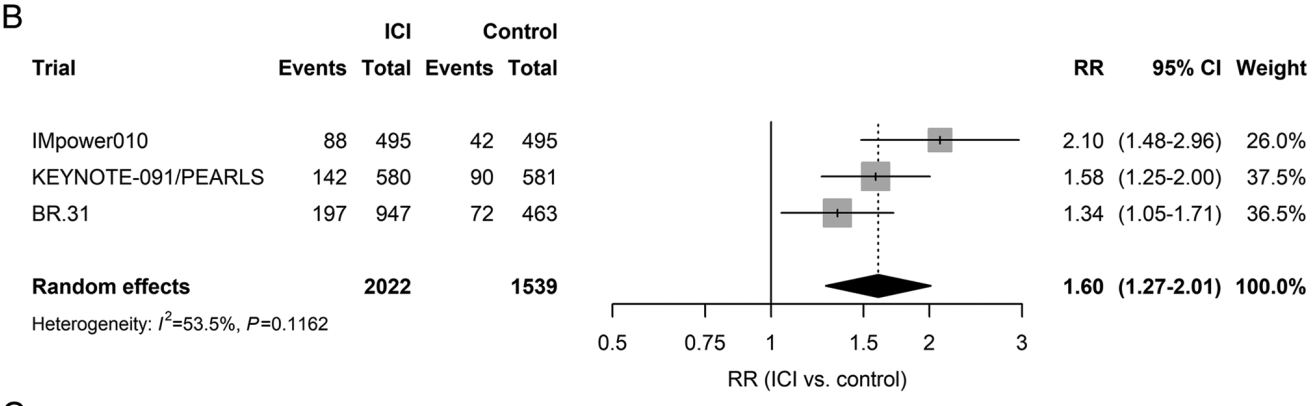
Outcome and analysis	Trials, n	Effect estimate (95% CI)	P-value	I^2 (%)	τ^2
Disease-free survival by HK analysis (primary)	4	HR, 0.86 (0.74-1.01)	0.0618	15.0	0.001
Disease-free survival by Wald analysis	4	HR, 0.86 (0.78-0.95)	0.0035	15.0	0.001
Overall survival by Wald analysis	3	HR, 0.96 (0.84-1.10)	0.5823	0.0	0.000
High-grade all-cause AEs by Wald analysis	3	RR, 1.45 (1.18-1.78)	-	60.5	0.020
High-grade all-cause AEs by HK analysis	3	RR, 1.45 (0.88-2.38)	-	60.5	0.020
Serious all-cause AEs by Wald analysis	3	RR, 1.60 (1.27-2.01)	-	53.5	0.022
Serious all-cause AEs by HK analysis	3	RR, 1.60 (0.94-2.73)	-	53.5	0.022

High-grade events comprised grade 3-4 events in IMpower010 and BR.31 and grade ≥3 events in KEYNOTE-091/PEARLS. Safety results are based on the safety populations of IMpower010, KEYNOTE-091/PEARLS and BR.31. EA5142/ANVIL was not included in comparative safety pooling as compatible observation-arm event counts were unavailable. Investigator-attributed treatment-related deaths occurred in 14 of 2,022 ICI-treated patients and 0 of 1,539 controls across these three trials. AE, adverse event; CI, confidence interval; HK, Hartung-Knapp; HR, hazard ratio; ICI, immune checkpoint inhibitor; RR, risk ratio; I^2, percentage of variability due to heterogeneity; τ^2, between-trial variance.

A



B



C

Trial	ICI events/total (%)	Control events/total (%)	Risk difference (percentage points)
IMpower010	4/495 (0.81)	0/495 (0.00)	+0.81
KEYNOTE-091/PEARLS	4/580 (0.69)	0/581 (0.00)	+0.69
BR.31	6/947 (0.63)	0/463 (0.00)	+0.63
Total (3 RCTs)	**14/2,022 (0.69)**	**0/1,539 (0.00)**	**+0.69**

Figure 3. Safety outcomes. (A) High-grade all-cause adverse events: Grade 3-4 for IMpower010 and BR.31 and grade ≥3 for KEYNOTE-091/PEARLS. (B) Serious all-cause adverse events. (C) Deaths attributed to treatment by investigators; risk differences are expressed in percentage points. Panels (A) and (B) present Wald 95% CIs; Table II provides HK intervals. CI, confidence interval; HK, Hartung-Knapp; ICI, immune checkpoint inhibitor; RCT, randomized controlled trial; RR, risk ratio.

Table III. Exploratory subgroup analyses of disease-free survival by PD-L1 expression.

Subgroup	Trials, n	HR (95% CI)	I^2 (%)	τ^2
PD-L1 ≥50%	4	0.77 (0.57-1.03)	59.1	0.053
PD-L1 ≥1%, trial-defined populations	2	0.84 (0.60-1.17)	74.9	0.045
PD-L1 ≥1%, stage II-IIIA	2	0.81 (0.61-1.07)	61.0	0.025

Estimates compare ICI with control within each subgroup; interaction testing was not performed. CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor; PD-L1, programmed death-ligand 1; I^2, percentage of variability due to heterogeneity; τ^2, between-trial variance.

adverse events of any cause, despite their differing grade thresholds. Across the three safety populations, trial-reported high-grade adverse events of any cause affected 27.5% (556 of 2,022) of ICI recipients and 19.5% (300 of 1,539) of controls; the point estimate was >1, but the HK interval encompassed 1 (conventional RR, 1.45; 95% CI, 1.18-1.78; I^2=60.5%; HK 95% CI, 0.88-2.38). Serious adverse events of any cause occurred in 427 out of 2,022 patients receiving ICI and 204 out of 1,539 controls (conventional random-effects RR, 1.60; 95% CI, 1.27-2.01; I^2=53.5%; HK 95% CI, 0.94-2.73). Treatment-related deaths occurred in 14 of 2,022 ICI-treated patients and 0 out of 1,539 controls; the relative estimate for these sparse events was imprecise (Table SXIII; Fig. S3). EA5142/ANVIL was described separately as it reported 25% grade 3 or higher treatment-related toxicity with nivolumab, including two treatment-related deaths, without providing compatible raw observation-arm counts for pooling.

Prespecified exploratory subgroup analyses. Prespecified exploratory PD-L1 subgroup estimates came from aggregate trial reports (Fig. 4; Tables III, SXIV and SXV). Pooling the PD-L1 ≥50% subgroup gave an HR of 0.77 (95% CI, 0.57-1.03; I^2=59.1%), trial-defined PD-L1 ≥1% populations in 2 trials gave an HR of 0.84 (95% CI, 0.60-1.17; I^2=74.9%) and stage II-IIIA disease with PD-L1 ≥1% gave an HR of 0.81 (95% CI, 0.61-1.07). These estimates describe effects within partly overlapping subgroups with differing population definitions, rather than comparisons between subgroups. Neither pooled interaction testing nor individual-patient analysis was available; these results cannot establish whether PD-L1 level, stage, prior chemotherapy or drug class modifies the treatment effect.

Sensitivity analyses and certainty of evidence. The primary HK-adjusted interval for DFS encompassed no effect (HR, 0.86; 95% CI, 0.74-1.01). Both REML random-effects and common-effect models produced pooled point estimates of ~0.86; the respective conventional 95% CIs were 0.78-0.95 and 0.79-0.95 (Fig. S4; Table SX). Leave-one-out analyses yielded point estimates from an HR of 0.83 to an HR of 0.90; the conventional intervals were exploratory and did not remove the uncertainty surrounding primary HK inference (Fig. S5; Table SXVI). Further exploratory analyses assessed placebo-controlled safety estimates for trial-reported high-grade adverse events of any cause (RR, 1.32) and serious adverse events (RR, 1.46) (Fig. S6; Table SXIII). To assist clinical interpretation, scenario-based absolute DFS translations with control DFS held fixed are presented (Table SXVII). An open-label attenuation scenario was included only in the supplementary materials as a stress test without empirical calibration, and was not used to draw conclusions (Fig. S7; Table SXVIII). Evidence certainty for DFS was moderate, with a one-level downgrade for serious imprecision as the primary HK interval encompassed benefit and no effect; risk-of-bias concerns related only to open-label outcome measurement in 2 of the 4 trials and were not judged to materially bias the pooled estimate. Certainty was low for high-grade and serious adverse events due to risk-of-bias and inconsistency concerns, and very low for treatment-related death due to risk-of-bias concerns, sparse events and imprecision. OS evidence was rated as low certainty since the exploratory synthesis of three compatible broad-population estimates was limited by imprecision and data maturity; certainty ratings and domain-level judgments are summarized in Tables SXIX and SXX.

Discussion

In the present systematic review and meta-analysis, the primary HK-adjusted DFS estimate suggested a possible postoperative benefit while remaining compatible with no effect. Conventional inference appeared more favorable using the same trials and pooled point estimate. Exploratory OS pooling did not demonstrate a survival benefit. Safety point estimates were >1, but HK intervals for high-grade and serious adverse events lacked precision. Clinical interpretation must therefore account for recurrence risk, trial-specific eligibility and treatment-related toxicity.

EA5142/ANVIL expands the evidence from the earlier 3-trial summary by 935 patients, bringing the total to 4,336. It contributes an additional randomized DFS comparison and an exploratory OS estimate; comparative safety pooling remains based on the 3 trials with compatible event counts. The trial evaluates the addition of nivolumab after completion of surgery and planned standard adjuvant treatment, directly informing a decision faced by patients treated with upfront surgery. Although EA5142/ANVIL did not meet its co-primary DFS endpoints, its inclusion only modestly attenuated the pooled estimate within the eligible full-text dataset, from an HR of 0.83 without ANVIL to 0.86 with all 4 trials. The updated estimate also remained close to the HR of 0.85 reported by Mamede *et al* (11), although report selection differed between the 2 reviews. Leave-one-out estimates ranged from 0.83 to 0.90, indicating that the favorable direction of the pooled estimate did not depend on any single trial. These findings support the stability of the estimated direction of effect as

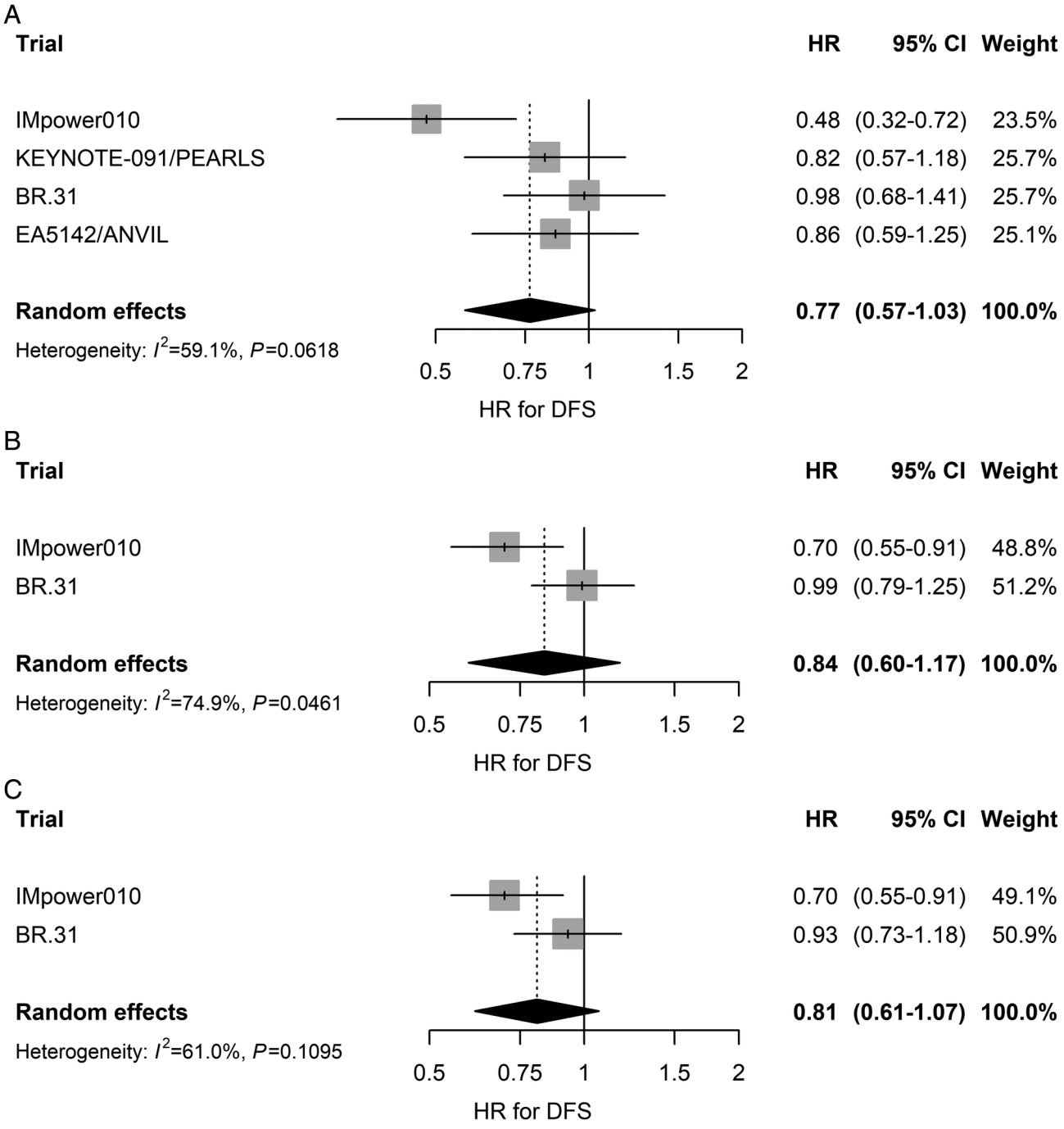


Figure 4. Exploratory analyses of disease-free survival according to PD-L1 expression. (A) PD-L1 ≥50%. (B) PD-L1 ≥1%, populations defined by each trial. (C) PD-L1 ≥1%, stage II-IIIA. Estimates represent ICI vs. control comparisons within subgroups; interaction testing was not performed. CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor; PD-L1, programmed death-ligand 1.

the randomized evidence expands. Compared with the 3-trial synthesis by Mamede *et al* (11), the present update incorporates ANVIL and explicitly examines how HK-adjusted inference affects the interpretation of DFS. For the same 4 trials, the HK-adjusted confidence interval included no effect (0.74-1.01), whereas the conventional Wald interval excluded it (0.78-0.95). This update informs the interpretation of postoperative ICI therapy by bringing the additional randomized efficacy evidence together with available OS and comparative safety findings to assess the balance between recurrence prevention and treatment-related toxicity.

The risk of postoperative recurrence supports consideration of systemic treatment after resection, although adjuvant chemotherapy has historically conferred only a modest survival gain. The absolute implications of a relative DFS effect depend on baseline risk. The present study reports conditional, fixed-time scenarios assuming proportional hazards, rather than pooled absolute risk estimates. With comparator DFS values of 50 and 80%, the point estimates correspond to absolute DFS differences of 4.9 and 2.5 percentage points, respectively; intervals derived from the primary HK limits encompass zero in both scenarios. These calculations treat the comparator

DFS probability at the specified time point as a fixed input; the intervals reflect uncertainty in the pooled HR only. They do not account for uncertainty in baseline risk, postoperative recovery, comorbidity or competing mortality. They cannot identify patients with a proven favorable benefit-risk balance and require interpretation alongside the observed safety outcomes.

Distinguishing DFS from OS matters clinically in the adjuvant setting. The primary DFS estimate (HR, 0.86; HK 95% CI, 0.74-1.01) is compatible with both a reduction in recurrence or death and no effect; exploratory pooling of OS from 3 trials did not demonstrate a benefit (HR, 0.96; 95% CI, 0.84-1.10). Delaying recurrence may be meaningful to patients with higher baseline risk, but the available aggregate evidence does not show whether an average DFS effect leads to a longer survival time. Follow-up maturity, subsequent treatment, competing mortality and differences in trial populations may influence that relationship.

The exploratory subgroup results do not establish a validated threshold for selecting patients for adjuvant ICI. Although the pooled PD-L1 ≥50% HR was 0.77 (95% CI, 0.57-1.03), heterogeneity was substantial and the 4 trials differed in assay, stage, driver-gene eligibility, comparator and chemotherapy context. A favorable estimate within one trial or stratum does not demonstrate a between-stratum interaction, and the aggregate data could not support formal treatment by PD-L1, stage or chemotherapy interaction testing (27,28). The interventions involved four distinct drugs: Atezolizumab and durvalumab, which target PD-L1, and pembrolizumab and nivolumab, which target PD-1. Given one trial for each drug and two for each class, apparent differences between classes would be confounded by trial design and population; no inference of PD-1 vs. PD-L1 superiority was therefore made. For *EGFR*-mutated and *ALK*-positive disease, genotype-directed adjuvant treatments offer separate options supported by trial evidence (29,30). Neoadjuvant and perioperative ICI regimens involve a different treatment sequence and fell outside this summary (31-34). The International Association for the Study of Lung Cancer (IASLC) consensus emphasizes multidisciplinary assessment and biomarker testing when selecting treatment pathways for resectable NSCLC (35). A US Veterans Health Administration cohort reported increasing uptake of adjuvant immunotherapy following upfront resection during 2017-2023 (36).

Several limitations constrain interpretation of these findings. The DFS analysis comprised only 4 RCTs, reducing the precision of HK inference and preventing reliable assessment of small-study effects; the decision during revision to prioritize HK is recorded. The exploratory OS synthesis drew on 3 compatible broad-population peer-reviewed trials without establishing a survival advantage; mature OS follow-up is therefore needed to determine whether the observed DFS signal leads to a longer survival time. Safety pooling included 3 trials with extractable comparative event counts, while EA5142/ANVIL provided descriptive toxicity evidence; the rarity of treatment-related deaths resulted in imprecise estimates. Subgroup interpretation was constrained by aggregate-data reporting, differing PD-L1 assays and cutoffs, variation in stage definitions, chemotherapy and comparator contexts, and driver-gene handling, without individual-patient data or formal interaction tests to establish treatment-effect modification. Each drug was evaluated in a single trial, precluding an unconfounded comparison of PD-1 and PD-L1 agents. Prospective postoperative ctDNA monitoring has shown prognostic value for recurrence after resection, but none of the 4 included RCTs validated ctDNA-guided selection for adjuvant ICI (37). A real-world registry of adjuvant atezolizumab documented treatment-related adverse events and discontinuation; data from this single-arm study cannot be combined with the comparative all-cause safety outcomes assessed within the present study (38). Future updates with mature OS, harmonized toxicity reporting and patient-level or reconstructable time-to-event data may clarify which postoperative patients have a favorable benefit-risk balance with adjuvant ICI.

In conclusion, adjuvant ICI may improve DFS following complete NSCLC resection, but the conservative model cannot rule out no benefit. An OS improvement has not been demonstrated across the trial populations as a whole. After upfront surgery, adjuvant ICI remains a postoperative option for delaying recurrence, and its potential benefit must be weighed against treatment-related toxicity.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

CM, YY and CL were responsible for study conceptualization. CM, YY and RC were responsible for the methodology. CM, YY, RC and CL performed data validation. The formal analysis was performed by RC, CM and YY. CM and YY conducted the literature searches, screened records, assessed full-text eligibility and extracted study data. CL was responsible for resources. CM and YY performed data curation. CM and YY prepared the original draft. CM, YY, RC and CL reviewed and edited the manuscript. CM, YY and RC performed study visualization. CL supervised the project and CL was responsible for project administration. Funding was acquired by CL. CM and RC confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

References

1. Luo G, Zhang Y, Rumgay H, Morgan E, Langselius O, Vignat J, Colombet M and Bray F: Estimated worldwide variation and trends in incidence of lung cancer by histological subtype in 2022 and over time: A population-based study. Lancet Respir Med 13: 348-363, 2025.
2. Sung H, Filho AM, Laversanne M, Ferlay J, Siegel RL, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2024: GLOBOCAN estimates of incidence and mortality worldwide for 34 cancers in 186 countries. CA Cancer J Clin 76: e70090, 2026.
3. Zer A, Ahn MJ, Barlesi F, Bubendorf L, De Ruysscher D, Garrido P, Gautschi O, Hendriks LE, Jänne PA, Kerr KM, *et al*: Early and locally advanced non-small-cell lung cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol 36: 1245-1262, 2025.
4. Gray JE, Salomonsen RJ, Diaz Perez I, Wang A, Cai L, Wetherill G, Xiao Y, Fielden C and Georgoulia N: Real-world clinical characteristics, treatment patterns, and clinical outcomes in US patients with stage I-III resected NSCLC without known EGFR mutations: The RESECT study. Drugs Real World Outcomes 12: 175-188, 2025.
5. Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, Dunant A, Torri V, Rosell R, Seymour L, *et al*: Lung adjuvant cisplatin evaluation: A pooled analysis by the LACE Collaborative Group. J Clin Oncol 26: 3552-3559, 2008.
6. Felip E, Altorki N, Zhou C, Csoszi T, Vynnychenko I, Goloborodko O, Luft A, Akopov A, Martinez-Marti A, Kenmotsu H, *et al*: Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): A randomised, multicentre, open-label, phase 3 trial. Lancet 398: 1344-1357, 2021.
7. Felip E, Altorki N, Zhou C, Rittmeyer A, Vallieres E, Sugawara S, Kang JH, Chiappori A, Luft A, Akopov A, *et al*: Five-Year survival outcomes with atezolizumab after chemotherapy in resected stage IB-IIIA Non-Small cell lung cancer (IMpower010): An Open-Label, randomized, phase III trial. J Clin Oncol 43: 2343-2349, 2025.
8. O'Brien M, Paz-Ares L, Marreaud S, Dafni U, Oselin K, Havel L, Esteban E, Isla D, Martinez-Marti A, Faehling M, *et al*: Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): An interim analysis of a randomised, triple-blind, phase 3 trial. Lancet Oncol 23: 1274-1286, 2022.
9. Goss GD, Darling GE, Westeel V, Nakagawa K, Massuti B, Perrone F, McLachlan SA, Kang JH, Wu YL, Dingemans AC, *et al*: Adjuvant durvalumab in completely resected Early-stage Non-Small cell lung cancer J Clin Oncol 44: 553-564, 2026.
10. Chaft JE, Sun Z, Rudin CM, Khullar OV, Simone CB, Oettel K, Kozono D, Sunkara R, Faller B, Isbell JM, *et al*: Adjuvant nivolumab vs observation in resected Non-Small cell lung cancer: A randomized clinical trial. JAMA 336: 464-472, 2026.
11. Mamede I, Stecca C, Gazzoni G, Alves ACF, Ronchi F and Ernani V: Adjuvant immune checkpoint inhibitors in early-stage non-small cell lung cancer: Insights from a systematic review and meta-analysis. Clin Transl Oncol 28: 1257-1266, 2026.
12. Huang H, Bao P, Jin H, Li W, Shen H, Qin Z, Pan Y, Su X and Kong D: Adjuvant immunotherapy improves survival in completely resected stage IB-III NSCLC: A systematic review and meta-analysis. Front Oncol 15: 1493221, 2025.
13. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, *et al*: The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 372: n71, 2021.
14. Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ and Koffel JB: PRISMA-S: An extension to the PRISMA Statement for reporting literature searches in systematic reviews. Syst Rev 10: 39, 2021.
15. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, *et al*: RoB 2: A revised tool for assessing risk of bias in randomized trials. BMJ 366: l4898, 2019.
16. Schunemann H, Brozek J, Guyatt G and Oxman A: GRADE handbook for grading quality of evidence and strength of recommendations. GRADE Working Group: 2013. Available online: https://gdt.gradepro.org/app/handbook/handbook.html.
17. DerSimonian R and Laird N: Meta-analysis in clinical trials. Control Clin Trials 7: 177-188, 1986.
18. IntHout J, Ioannidis JPA and Borm GF: The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. BMC Med Res Methodol 14: 25, 2014.
19. Higgins JP, Thompson SG, Deeks JJ and Altman DG: Measuring inconsistency in meta-analyses. BMJ 327: 557-560, 2003.
20. Balduzzi S, Rucker G and Schwarzer G: How to perform a meta-analysis with R: A practical tutorial. Evid Based Ment Health 22: 153-160, 2019.
21. Viechtbauer W: Conducting meta-analyses in R with the metafor package. J Stat Softw 36: 1-48, 2010.
22. Felip E, Altorki N, Zhou C, Vallieres E, Martinez-Marti A, Rittmeyer A, Luft A, Akopov A, Kenmotsu H, Sugawara S, *et al*: Overall survival with adjuvant atezolizumab after chemotherapy in resected stage II-IIIA non-small-cell lung cancer (IMpower010): A randomised, multicentre, open-label, phase III trial. Ann Oncol 34: 907-919, 2023.
23. Lee JM, Vallières E, Ding B, Johnson A, Bhagwakar J, Rashidi S, Zhu QC, Gitlitz BJ, Weksler B, Costas K and Altorki N: Safety of adjuvant atezolizumab after pneumonectomy/bilobectomy in stage II-IIIA non-small cell lung cancer in the randomized phase III IMpower010 trial. J Thorac Cardiovasc Surg 166: 655-666. e7, 2023.
24. Kenmotsu H, Sugawara S, Watanabe Y, Saito H, Okada M, Chen-Yoshikawa TF, Ohe Y, Nishio W, Nakagawa S and Nagao H: Adjuvant atezolizumab in Japanese patients with resected stage IB-IIIA non-small cell lung cancer (IMpower010). Cancer Sci 113: 4327-4338, 2022.
25. Okada M, Sugawara S, Watanabe Y, Saito H, Chen-Yoshikawa TF, Goto Y, Nishio W, Nakagawa S, Hayashi M and Kenmotsu H: IMpower010: 5-year outcomes of atezolizumab in japanese patients with resected stage IB-IIIA Non-small cell lung cancer. Cancer Sci 117: 749-758, 2026.
26. Zhou C, Srivastava MK, Xu H, Felip E, Wakelee H, Altorki N, Reck M, Liersch R, Kryzhanivska A, Oizumi S, *et al*: Comparison of SP263 and 22C3 immunohistochemistry PD-L1 assays for clinical efficacy of adjuvant atezolizumab in non-small cell lung cancer: Results from the randomized phase III IMpower010 trial. J Immunother Cancer 11: e007047, 2023.
27. Kent DM, Rothwell PM, Ioannidis JPA, Altman DG and Hayward RA: Assessing and reporting heterogeneity in treatment effects in clinical trials: A proposal. Trials 11: 85, 2010.
28. Sun X, Briel M, Walter SD and Guyatt GH: Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ 340: c117, 2010.
29. Tsuboi M, Herbst RS, John T, Kato T, Majem M, Grohe C, Wang J, Goldman JW, Lu S, Su WC, *et al*: Overall survival with osimertinib in resected EGFR-mutated NSCLC. N Engl J Med 389: 137-147, 2023.
30. Wu YL, Dziadziuszko R, Ahn JS, Barlesi F, Nishio M, Lee DH, Lee JS, Zhong WZ, Horinouchi H, Mao WM, *et al*: Alectinib in resected ALK-positive non-small-cell lung cancer. N Engl J Med 390: 1265-1276, 2024.

31. Wakelee H, Spicer JD, Gao S, Liberman M, Tsuboi M, Kato T, Chen KN, Dooms C, Majem M, Martinengo GL, *et al*: Five-year outcomes of perioperative pembrolizumab for early-stage non-small-cell lung cancer from the randomized KEYNOTE-671 study. Ann Oncol: Aug 21, 2026 (Epub ahead of print). doi: 10.1016/j.annonc.2026.08.005.
32. Heymach JV, He J, Harpole D, Mitsudomi T, Taube JM, Gao S, Urban L, Kang JH, Orlandi FJ, Rodriguez-Cid J, *et al*: Perioperative durvalumab for resectable non-small cell lung cancer: Updated outcomes from the phase III AEGEAN trial. J Clin Oncol: Aug 28, 2026 (Epub ahead of print). doi: 10.1200/JCO-25-02659.
33. Cascone T, Awad MM, Spicer JD, He J, Lu S, Sepesi B, Tanaka F, Taube JM, Cornelissen R, Havel L, *et al*: Perioperative nivolumab in resectable lung cancer. N Engl J Med 390: 1756-1769, 2024.
34. CheckMate 816 Investigators. Overall survival with neoadjuvant nivolumab plus chemotherapy in lung cancer. N Engl J Med 393: 741-752, 2025.
35. Spicer JD, Cascone T, Wynes MW, Ahn MJ, Dacic S, Felip E, Forde PM, Higgins KA, Kris MG, Mitsudomi T, *et al*: Neoadjuvant and adjuvant treatments for early stage resectable NSCLC: Consensus recommendations from the International Association for the Study of Lung Cancer. J Thorac Oncol 19: 1373-1414, 2024.
36. Kumar A, Tohmasi S, Eaton DB Jr, Seyoum N, Brandt WS, Thomas TS, Chang SH, Tokaz M, Yan Y, Patel MR, *et al*: Real-world adoption of adjuvant therapies for resected stage IB-III non-small-cell lung cancer. Cancers (Basel) 17: 2961, 2025.
37. Xia L, Pu Q, Kang R, Mei J, Li L, Yang Y, Deng S, Feng G, Deng Y, Gan F, *et al*: Dynamic ctDNA informs whole-course postoperative precise management of NSCLC (LUNGCA study). J Natl Cancer Inst 117: 1474-1484, 2025.
38. Passiglia F, Reale ML, Pasello G, Viscardi G, Attili I, Mazzoni F, Galetta D, Catania C, Andrikou K, Russo A, *et al*: Adjuvant atezolizumab in surgically resected NSCLC patients with PD-L1 expression ≥50%: Real-world data from the Italian ATLAS registry. Oncologist 31: oyaf428, 2026.



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