

## Research Article

# Neoadjuvant or Perioperative Immunotherapy in Resectable Non-Small Cell Lung Cancer: Pooled Analysis of Subgroups in Randomized Controlled Trial

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### Abstract

**Objectives:** This meta-analysis evaluates the efficacy of adding Anti-PD-1 or Anti-PD-L1 agents (ICI) to platinum-based chemotherapy in perioperative/neoadjuvant systemic therapy for resectable non-small cell lung cancer (NSCLC), focusing on specific subgroup outcomes.

**Methods:** Databases like PUBMED, Cochrane, and EMBASE, along with trials presented at major congresses until March 01, 2024, were screened for RCTs on perioperative or neoadjuvant ICI in resectable NSCLC.

**Results:** Eight RCTs involving 3387 patients were analyzed. The ICI arm showed significantly higher pCR rates (24.3% vs 4.0%; OR: 7.68, 95% CI 5.88-10.04, I<sup>2</sup>: 41%,  $p < 0.001$ ). Subgroup analyses based on age, smoking, gender, histology, stage, platinum agent, and PD-L1 levels consistently showed higher pCR rates in the ICI arm. Neoadjuvant ICI trials demonstrated significantly prolonged EFS in the ICI arm (HR: 0.66, 95% CI 0.48-0.89, I<sup>2</sup>: 0%,  $p < 0.01$ ). Perioperative ICI trials also showed significantly prolonged EFS (HR: 0.57, 95% CI 0.50-0.65, I<sup>2</sup>: 19%,  $p < 0.01$ ). Better EFS outcomes were observed across all subgroups except never-smokers. Additionally, perioperative ICI trials showed significantly prolonged OS in the ICI arm (HR: 0.66, 95% CI 0.53-0.81, I<sup>2</sup>: 0%,  $p < 0.01$ ).

**Conclusion:** Adding ICI to platinum-based systemic therapy in the perioperative or neoadjuvant treatment of resectable NSCLC significantly improves pCR, EFS, and OS.

**Keywords:** Resectable, non-small cell lung cancer, immune checkpoint inhibitor, perioperative, neoadjuvant, survival, pathological complete response

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Lung cancer stands as a predominant cause of cancer-related global mortality, affecting both males and females.<sup>[1]</sup> Non-small cell lung cancer (NSCLC) constitutes approximately 85% of all lung cancer cases, thus representing a substantial majority. Surgically resectable disease is present in about 25% to 30% of NSCLC patients at the time of diagnosis; however, surgical intervention in these cases often proves non-curative. A significant proportion, ranging from 25% to 70%, of patients post-resection experience recurrence.<sup>[2]</sup>

Over the past two decades, platinum-based adjuvant chemotherapy, widely accepted as the standard post-anatomical resection care, offers a marginal survival benefit. The Lung Adjuvant Cisplatin Evaluation (LACE) trial,<sup>[3]</sup> consolidating data from 4584 patients across five major clinical trials, has demonstrated a 5.4% absolute five-year survival advantage with adjuvant cisplatin-based chemotherapy compared to no chemotherapy. This benefit is particularly notable in patients with stage II and III tumors. Neoadjuvant chemotherapy has also been explored in this patient co-

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hort, revealing comparable survival outcomes to adjuvant chemotherapy.<sup>[4]</sup> It is clear that different treatment strategies are needed to improve the modest success achieved with adjuvant or neoadjuvant chemotherapy.

Advancements in our comprehension of cancer biology have spurred the development of numerous innovative treatments in cancer therapy. Immunotherapy agents targeting PD-1, PD-L1, and CTLA-4, collectively called immune checkpoint inhibitors (ICIs), have revolutionized thoracic oncology with remarkable efficacy. Within the realm of NSCLC, ICIs have significantly shifted the treatment paradigm, emerging as the first-line standard of care, either as monotherapy or in combination, for patients with metastatic NSCLC lacking targetable oncogenic mutations.

<sup>[5]</sup> Integrating a newly developed drug into cancer therapy typically evolves from palliative settings to curative environments following demonstrated efficacy, often enabling its utilization in earlier stages upon validation in a palliative context. In patients with unresectable NSCLC who do not exhibit disease progression following chemoradiotherapy, using durvalumab for consolidation purposes has demonstrated a survival benefit, underscoring the efficacy of ICIs in early-stage disease. The successes observed with ICIs in metastatic and unresectable non-metastatic settings have paved the way for their investigation into resectable NSCLC.

The IMpower010 trial<sup>[7]</sup> marks a significant milestone as the inaugural phase III clinical trial to establish the tangible advantages of adjuvant ICI post-surgical resection for NSCLC. Enrolling 1005 patients with completely resected stage IB-IIIa NSCLC (according to UICC/AJCC 7th edition criteria), participants were randomly assigned to either receive the PD-L1 inhibitor atezolizumab (at a dose of 1200 mg every 21 days for 16 cycles or up to 1 year) or best supportive care after adjuvant chemotherapy. Particularly noteworthy was the improvement in disease-free survival (DFS) demonstrated by atezolizumab compared to best supportive care in patients with stage II-IIIa NSCLC and PD-L1-positive tumors ( $\geq 1\%$  expression), with a Hazard Ratio [HR] of 0.66 and a 95% Confidence Interval [CI] of 0.50-0.88. Consequently, based on these findings, the U.S. Food and Drug Administration (FDA)

<sup>[8]</sup> approved the adjuvant use of atezolizumab in October 2021 for patients with stage II-IIIa NSCLC who have undergone surgical resection and adjuvant platinum-based chemotherapy and exhibit tumor PD-L1 expression  $\geq 1\%$ . Conversely, the PEARLS/KEYNOTE-091 trial<sup>[9]</sup> investigated the adjuvant use of checkpoint inhibitors in early-stage NSCLC with a distinctive approach, not mandating adjuvant chemotherapy. Among patients who did not receive adjuvant chemotherapy ( $n=167$ ), adjuvant pembrolizumab did not significantly benefit DFS (HR 1.25, 95% CI 0.76-2.05). However, in patients who did receive chemotherapy ( $n=1010$ ),

subgroup analysis revealed a significant improvement in DFS (HR 0.73, 95% CI 0.60-0.89). In January 2023, the FDA approved pembrolizumab for stage IB-IIIa NSCLC following resection and platinum-based chemotherapy.<sup>[10]</sup> Importantly, unlike the approvals for atezolizumab, the approval for pembrolizumab was not dependent on tumor PD-L1 expression, encompassing patients with PD-L1  $< 1\%$  tumors. This distinction highlights the separate regulatory pathways and considerations for these two checkpoint inhibitors in the adjuvant setting for early-stage NSCLC.

The primary objective of this systematic review and meta-analysis is to investigate the combination of ICIs with neoadjuvant or perioperative chemotherapy. Trials concerning the use of ICIs as standalone agents or in combinations not involving chemotherapy are acknowledged but not elaborated upon, as they lie beyond the scope of this review. Despite recommendations advocating for neoadjuvant therapy as an alternative in thoracic oncology due to the low rates of pathological complete response (pCR) with conventional chemotherapies and the absence of a survival advantage compared to adjuvant approaches, it is seldom favored in routine clinical practice. However, the remarkable success rates of ICIs have rekindled interest in neoadjuvant use. The neoadjuvant treatment presents potential advantages such as tumor size reduction for more effective surgery, eradication of micrometastases, early activation of the immune response, monitoring of treatment response, and obtaining early insights into tumor biology.<sup>[10]</sup> It is also known to have better treatment adherence than adjuvant therapy. Despite these benefits, neoadjuvant therapy carries potential risks, with the most significant being the risk of losing the opportunity for resectability due to tumor progression. However, considering the aggressive nature of tumors that progress despite treatment, recurrence following resection is nearly inevitable, even without neoadjuvant therapy. In light of these hypotheses, some trials have been conducted investigating the combined use of neoadjuvant chemotherapy and ICI.

The CheckMate-816 trial<sup>[11]</sup> examined the efficacy of nivolumab for neoadjuvant use and notably became the first ICI to receive FDA approval for this indication. In this trial involving 358 patients with stage IB to IIIa NSCLC (according to the 7th edition of the AJCC staging system) and lacking known sensitizing EGFR mutations or ALK translocations, the addition of nivolumab to three cycles of neoadjuvant platinum-doublet chemotherapy substantially increased the rate of pCR by approximately 10-fold compared to chemotherapy alone (24.0% vs. 2.2%, respectively). Updated results<sup>[12]</sup> presented at the 2023 European Lung Cancer Congress revealed a clear 18% benefit in two-year event-free survival (EFS) (65% vs. 47%, respectively;

HR: 0.68, 95% CI: 0.49–0.93), and while overall survival (OS) data are still maturing, there is a trend favoring nivolumab (HR: 0.62, 95% CI: 0.36–1.05).

In addition to neoadjuvant or adjuvant approaches, there are increasing trials combining these two strategies, known as the perioperative approach. The first of these trials is the double-blind, randomized phase III Keynote-671 trial, which investigated the effectiveness of perioperative pembrolizumab in 797 treatment-naïve patients with resectable stage II-IIIB NSCLC, according to the AJCC 8th edition. Patients were randomly assigned to receive either neoadjuvant platinum-based doublet chemotherapy plus pembrolizumab or chemotherapy alone for four cycles, followed by 13 cycles of either pembrolizumab or placebo after surgery. The pCR rate in the pembrolizumab group was significantly higher compared to the control group (18.1% vs. 4.0%, respectively). Furthermore, both EFS and OS were significantly improved in the pembrolizumab group. Based on these findings, on October 16, 2023, the FDA approved<sup>[10]</sup> pembrolizumab for perioperative use in NSCLC.

Clinical trials often incorporate pre-planned and unplanned subgroup analysis to aid clinicians in selecting appropriate treatments. As the range of available treatment options expands, the challenge of determining which patients will derive the most benefit from these agents has intensified, leading to ongoing debates. This meta-analysis focuses on pooled analysis of subgroups from randomized controlled trials (RCTs) investigating the addition of ICI to platinum-based chemotherapy in the perioperative/neoadjuvant systemic treatment of resectable NSCLC. It specifically concentrates on neoadjuvant and perioperative use, excluding adjuvant trials from its scope.

## Methods

This systematic review and meta-analysis were conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.<sup>[13]</sup>

### Search Strategy

A literature search for published primary trials was carried out on PubMed (Medline), Cochrane Library, EMBASE, and ClinicalTrials databases, and trials presented at the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), and the World Lung Cancer Conference (WLCC) congresses were searched.

Trials published or presented until 01 March 2024 were searched using the following keywords: (lung cancer OR NSCLC) AND (immunotherapy OR immune checkpoint inhibitor OR nivolumab OR pembrolizumab OR atezolizumab OR ipilimumab OR durvalumab OR avelumab OR

tislelizumab OR cemiplimab OR camrelizumab OR dostarlimab OR toripalimab) AND (neoadjuvant OR perioperative OR preoperative). Reference lists of identified trials were checked to ensure that no trials were missed. Trials should preferably be full text, but only any research for which an abstract was available and results were adequately provided were included in our analysis.

RCTs were included comparing ICI plus chemotherapy versus chemotherapy +/- placebo in resectable NSCLC. Trials with relevant data shared in congress presentations were included even if the full text was not published. Unresectable and metastatic setting trials, retrospective trials, letters, reviews, and case reports were excluded.

Each trial's details, including authors' names, trial titles, publication year, journal or conference name, sample size, age, sex, histological subtype, smoking status, disease stage, type of chemotherapy, type of immunotherapy agent used, number of neoadjuvant and adjuvant cycles, PD-L1 level, grade 3-5 adverse events, and hazard ratio with 95% CI based on multivariate Cox regression analysis for survival, were recorded. Pooled analysis was conducted on parameters reported in at least two trials.

### Outcome Measures

The primary objective of this meta-analysis was to investigate the contribution of adding an ICI to preoperative chemotherapy on the pCR rate and EFS in resectable NSCLC. pCR was defined as the absence of invasive cancer cells in the lung and lymph nodes (ypT0/Tis and N0). EFS was defined as the time from randomization to disease progression preventing surgery, local or distant recurrence, or death from any cause. Additionally, separate analysis were conducted for clinicopathological subgroups. The clinicopathological subgroups included age (<65 vs. >65 years), gender (male vs. female), smoking status (never vs. current/former), histological subtype (squamous vs. non-squamous), stage (II vs. III), chemotherapy agent used (cisplatin vs. carboplatin), PD-L1 level (<1% vs. 1%-49% vs. >50%), and number of neoadjuvant cycles (three vs. four). Analysis were conducted for both pCR and EFS for selected subgroups. While all trials were included in the subgroup analysis for pCR, only trials involving perioperative treatment were included in the EFS subgroup analysis. Since there were few trials investigating only neoadjuvant immunotherapy and inadequate subgroup analysis, they were not included in the EFS subgroup analysis.

The secondary objective was to compare the rates of grade 3-5 adverse events and OS. Trials providing results for at least two of the investigated parameters were included in the pooled analysis.

## Statistical Methods

This meta-analysis was performed using Review Manager, version 5.4 (RevMan), a proprietary software provided by the Cochrane Collaboration. For Pcr and adverse events, the odds ratio (OR) and 95% CI were calculated based on the number of events obtained from the trials using the Mantel-Haenszel method. The hazard ratio (HR) and 95% CI were converted to log equivalents to compare survivals and analyzed using the inverse variance method. The  $I^2$  test was used to assess statistical heterogeneity between trials. The fixed-effects model was used if heterogeneity was low ( $I^2 \leq 50\%$ ); otherwise ( $I^2 > 50\%$ ) random-effects model was used. If heterogeneity was detected, a sensitivity analysis was performed by excluding each run individually, then recalculating the pooled outcome estimates. For the overall effect Z test, p-value  $< 0.05$  was considered statistically significant.

## Trial Quality and Bias Assessment

The trial examined the RCTs' methodological quality using the Cochrane Collaboration Risk of Bias Tool under the following headings: selection bias, performance bias, detection bias, attrition bias, and reporting bias. Publication bias was assessed visually using the funnel plot chart.

## Results

### Characteristics of Included Studies

A comprehensive review of databases and conference abstracts identified 693 studies. Following evaluations, eight RCTs were deemed suitable for analysis.<sup>[12, 13, 15-20]</sup> Figure 1 presents a flowchart illustrating the literature search and selection/exclusion process.

Of these trials, with a total patient count of 3387, two were randomized phase II trials<sup>[18, 20]</sup> (NADIM II and TD-FOREKNOW), while the remaining six were phase III trials<sup>[12-13, 15-17, 19]</sup> (AEGEAN, Neotorch, Keynote-671, CheckMate-77T, CheckMate-816, and RATIONALE-315). CheckMate-816 and TD-FOREKNOW trials utilized ICIs solely in the neoadjuvant phase, whereas in other trials, ICIs were used in the perioperative setting (combining neoadjuvant and adjuvant phases). The adjuvant treatment duration in the NADIM II trial was six months, while in other perioperative trials, it was completed for one year. Only the CheckMate-816 trial included stage IB patients (including stage IB-III), while AEGEAN, Keynote-671, and CheckMate-77T trials included patients with stages II-IIIb. Neotorch, NADIM II, RATIONALE-315, and TD-FOREKNOW trials included only stage III patients. Table 1 presents the patient characteristics of the included trials.

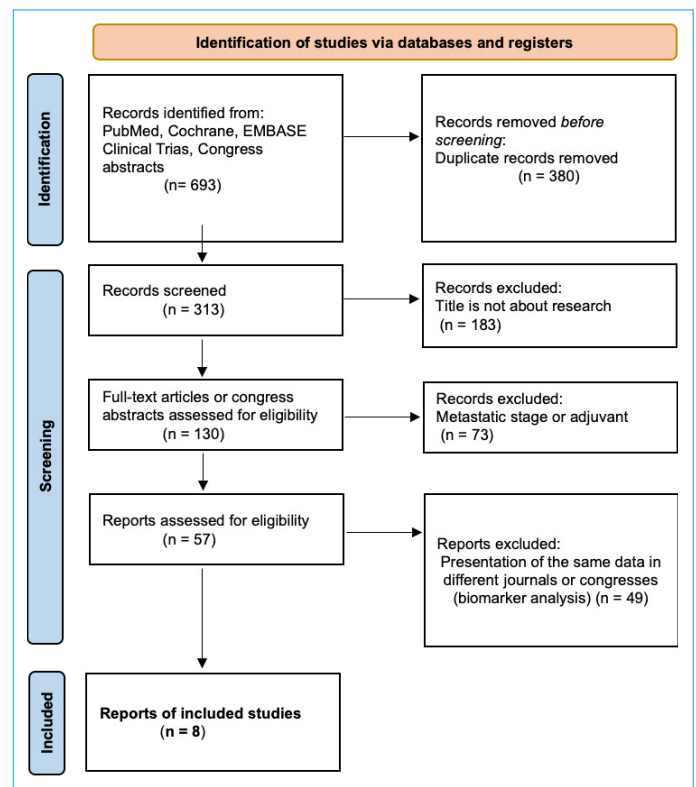


Figure 1. Flowchart for study selection process.

## Efficacy

### Pathological Complete Response

In a pooled analysis of eight trials (n: 3,387), the pCR rate was significantly higher in the ICI arm compared to the control arm (24.3% vs 4.0%, respectively; OR: 7.68, 95% CI 5.88-10.04,  $I^2$ :41%, Z test  $p < 0.001$ ) (Fig. 2).

### Subgroup Analysis According to Clinicopathological Features for pCR

Four trials<sup>[12, 15, 17, 20]</sup> reporting subgroup results for participants below and above 65 years were available. In the pooled analysis of these trials, the ICI arm demonstrated significantly higher pCR rates in both the under 65 and over 65 age groups (for those under 65 years, 23.3% vs 3.7%, respectively; OR: 7.65, 95% CI 4.35-13.44; for those over 65 years, 20.0% vs 4.2%, respectively; OR: 5.12, 95% CI 3.10-8.48) (Fig. S1).

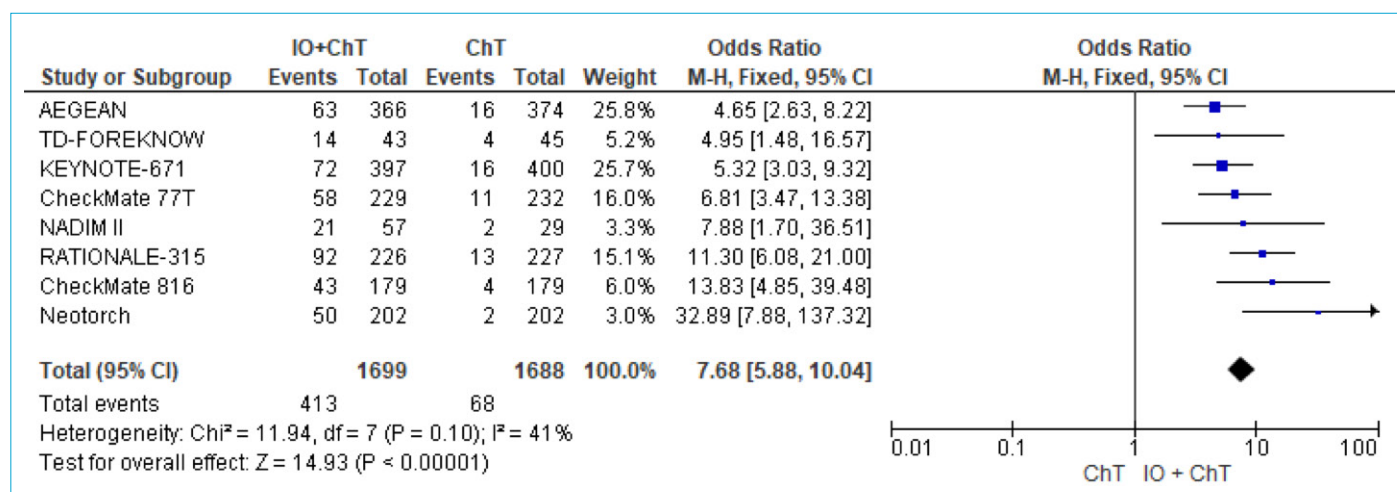
Five trials<sup>[12, 15, 17-18, 20]</sup> reporting subgroup results based on sex were available. In the pooled analysis of these trials, both male and female genders showed significantly higher pCR rates in the ICI arm (for males, 23.6% vs 4.5%, respectively; for females, 20.6% vs 3.7%, respectively) (Fig. S2).

Five trials<sup>[12, 15, 17-18, 20]</sup> reported results based on smoking status. In the pooled analysis of these trials, regardless of smoking exposure, the ICI arm exhibited significantly high-



**Table 1.** Characteristics of included studies

Trial	Design	Total number of patients	Drug and Cycles	Age (median)	Stage	PD-L1 positivity rate	Squamous histology rate	Median follow-up (months)
AEGEAN	Double blind, randomized phase III, Perioperative	740	Durvalumab 4 x Q3W (N) AND 12 x Q3W (A)	65	Stage 2 (30%) Stage 3A (45%) Stage 3B (25%)	67%	49%	11,7
Neotorch	Double blind, randomized phase III, Perioperative	404	Toripalimab 3 x Q3W (N) AND 14 x Q3W (A)	63	Stage 3A (67%) Stage 3B (32%)	66%	78%	18,3
Keynote-671	Double blind, randomized phase III, Perioperative	797	Pembrolizumab 4 x Q3W (N) AND 13 x Q3W (A)	64	Stage 2 (30%) Stage 3A (55%) Stage 3B (15%)	64%	43%	25,2
CheckMate-77T	Double blind, randomized phase III, Perioperative	454	Nivolumab 4 x Q3W (N) AND 12 x Q4W (A)	66	Stage 2 (35%) Stage 3 (64%)	56%	51%	25,4
NADIM-II	Open-label, randomized phase II, Perioperative	86	Nivolumab 4 x Q3W (N) AND 6 x Q4W (A)	64	Stage 3 (100%)	52%	41%	26,1
RATIONALE-315	Double blind, randomized phase III, Perioperative	453	Tislelizumab 4 x Q3W (N) AND 8 x Q6W (A)	62	Stage 2 (40%) Stage 3A (60%)	58%	78%	22
CheckMate-816	Open-label, randomized phase III, Neoadjuvant	358	Nivolumab 3 x Q3W (N)	65	Stage 1B/2 (35%) Stage 3A (64%)	50%	51%	41,4
TD-FOREKNOW	Open-label, randomized phase II, Neoadjuvant	88	Camrelizumab 3 x Q3W (N)	61	Stage 3A (75%) Stage 3B (25%)	missing data	59%	14,1

**Figure 2.** Forest plot for pathological complete response.

er pCR rates (For current/former smokers, 24.2% vs. 4.8%, respectively; for never smokers, 11.0% vs 1.0%, respectively). In the chemoimmunotherapy combination arm, the pCR rate in participants with smoking exposure was more than twice that of those who had never smoked (24.2% vs

11.0%, respectively) (Fig. S3).

Five trials<sup>[12, 15, 17-18, 20]</sup> reported results based on histological subtypes. In the pooled analysis of these trials, the pCR rates were significantly higher in the ICI arm for both squamous and non-squamous subtypes (for squamous, 25.7% vs. 6.0%,

respectively; for non-squamous, %19.6 vs %2.4, respectively) (Fig. S4).

Differences were observed in the number of trials reporting subgroup analysis results based on stage. While two trials<sup>[15, 17]</sup> reported results for stage II, five trials<sup>[12, 15, 17, 18, 20]</sup> provided data for stage III. In the pooled analysis of these trials, regardless of stage, the pCR rates were significantly higher in the ICI arm (for stage II, 21.4% vs 4.1%, respectively; for stage III, 21.9% vs 4.2%, respectively) (Fig. S5). When subdividing stage III into IIIA and IIIB subgroups, the difference in pCR rates favoring the ICI arm was more pronounced in stage IIIA (for stage IIIA, 21.2% vs 3.7%, respectively; for stage IIIB, 13.8% vs 3.7%, respectively) (Fig. S6).

Three trials<sup>[12, 15, 17]</sup> reported results based on the type of platinum used. In the pooled analysis of these trials, regardless of the type of platinum drug used, the pCR rates were significantly higher in the ICI arm (for cisplatin, 19.7% vs 2.6%, respectively; for carboplatin, 22.0% vs 4.7%, respectively) (Fig. S7).

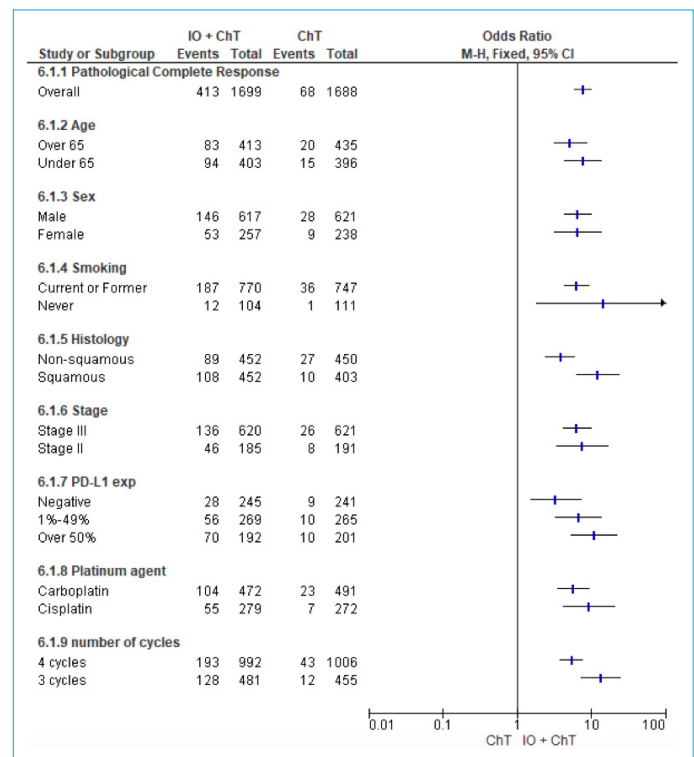
Five trials<sup>[12, 15, 17, 18, 20]</sup> reported results based on PD-L1 expression levels. Although the difference was more pronounced in the PD-L1 positive group (PD-L1 > 1%), both PD-L1 positive and negative subgroups showed significantly higher pCR rates in the ICI arm (for PD-L1 positive, 29.7 % vs 4.6%, respectively; for PD-L1 negative, %12.7 vs %4.0, respectively) (Fig. S8). We further subdivided the PD-L1 positive group into two subgroups (PD-L1: 1-49% vs >50%) and conducted a separate analysis. As the rate of PD-L1 positivity increased, the pCR rate also increased; however, in all groups, the pCR rate was significantly higher in the ICI arm (for PD-L1: 1-49%, 20.8% vs 3.8%, respectively; for PD-L1 >50%, %36.5 vs %4.5, respectively) (Fig. S9).

In four trials<sup>[12, 16, 18, 20]</sup>, a neoadjuvant treatment of three cycles was administered, while in three trials<sup>[13, 15, 17]</sup>, four cycles were used. The RATIONALE-315 trial included three or four cycles of treatment, but subgroup analysis results based on the cycle count were not provided, so it was not included in this analysis. Regardless of the number of cycles administered, the pCR rates were significantly higher in the ICI arm (for three cycles, 26.6% vs 2.9%, respectively; for four cycles, 19.4% vs 4.2%, respectively) (Fig. S10).

Across all comparisons, heterogeneity was relatively low, and a fixed-effect model was utilized. A comparison of PCR analysis results according to subgroups is given in Figure 3.

## Event-Free Survival

In a pooled analysis of all eight trials, the ICI arm demonstrated significantly better EFS (HR: 0.58, 95% CI 0.52-0.65,  $I^2$ : 3%, Z test  $p < 0.01$ ) (Figure S11). While the CheckMate-816 and TD-FOREKNOW trials solely utilized ICI in



**Figure 3.** Forest plot for pathological complete response by clinico-pathologic subgroups.

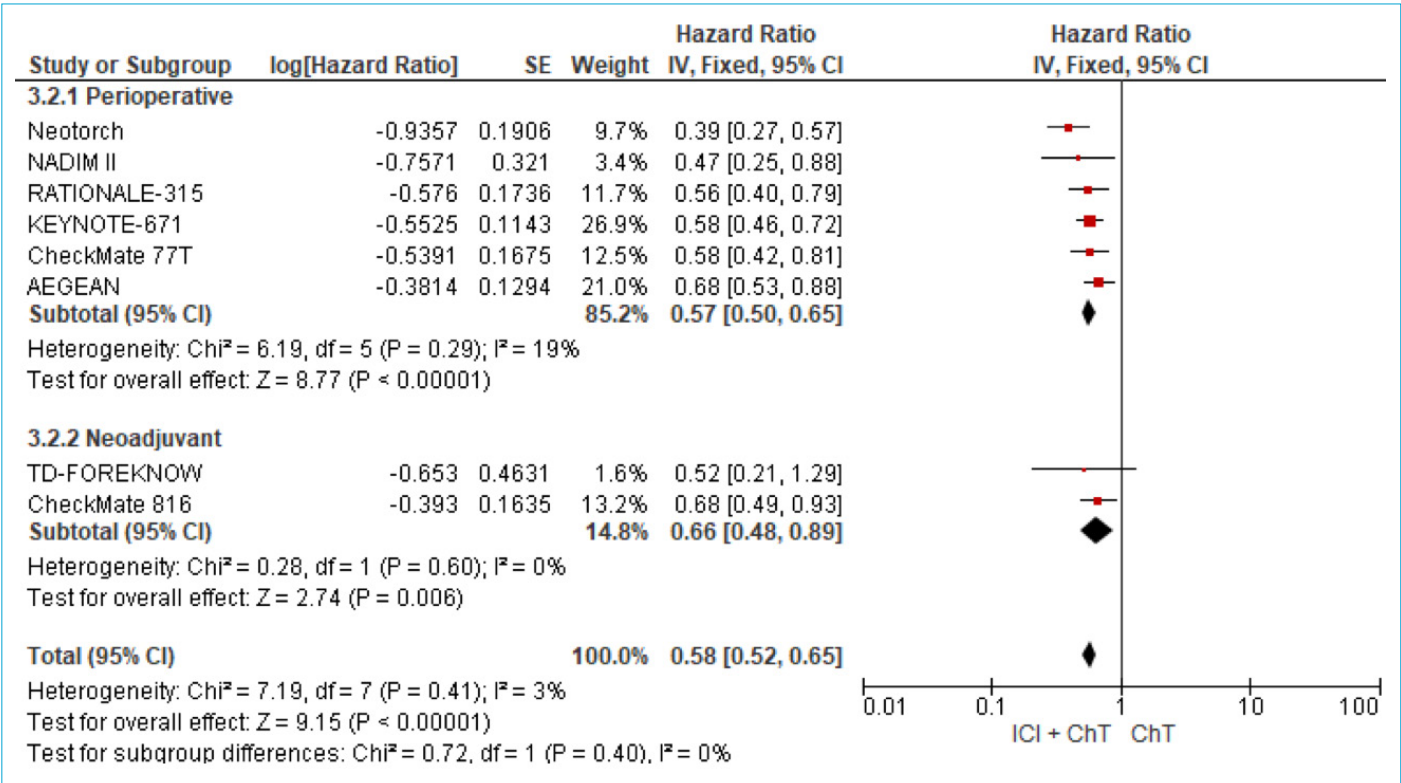
the neoadjuvant setting, the other six trials employed it neoadjuvant and perioperative in the adjuvant phase. To minimize the potential impact of usage patterns on EFS, separate analysis were conducted for neoadjuvant and perioperative use.

In the combined analysis of two trials<sup>[12, 20]</sup> evaluating the neoadjuvant phase, there was a significant EFS benefit favoring the ICI arm with a 34% relative advantage (HR: 0.66, 95% CI 0.48-0.89,  $I^2$ : 0%, Z test  $p < 0.01$ ). The two-year EFS rates were 67.1% vs 50.9%, respectively. For the six trials<sup>[13, 15-19]</sup> evaluating ICI in the perioperative setting, a significant relative benefit of 43% favored the ICI arm in EFS (HR: 0.57, 95% CI 0.50-0.65,  $I^2$ : 19%, Z test  $p < 0.01$ ) (Fig. 4). Five reported two-year EFS rates among these trials, and the pooled analysis showed 64.6% vs 47.1%, respectively.

## Subgroup Analysis According to Clinicopathological Features for EFS (Perioperative)

Due to the limited number of trials using only neoadjuvant ICI and insufficient subgroup analysis results in these trials, they were excluded. Subgroup analysis for EFS were performed using trials where ICI was used perioperatively.

Subgroup analysis for EFS were conducted based on age in five trials.<sup>[13, 15, 17-19]</sup> The pooled analysis revealed significantly better EFS in the ICI arm for both the under 65 and over 65 age groups (HR: 0.58, 95% CI 0.48-0.70,  $I^2$ : 0%, Z test



**Figure 4.** Forest plot for event-free survival.

$p < 0.01$  for under 65; HR: 0.61, 95% CI 0.51-0.74,  $I^2$ : 0%, Z test  $p < 0.01$  for over 65) (Fig. S12).

Four trials<sup>[13, 15, 17, 19]</sup> provided subgroup results based on sex. In the pooled analysis, male and female genders showed significantly better EFS in the ICI arm (HR: 0.58, 95% CI 0.50-0.68 for males; HR: 0.64, 95% CI 0.48-0.85 for females) (Fig. S13).

Four trials<sup>[13, 15, 17, 19]</sup> provided EFS results based on smoking status. In the pooled analysis, individuals who were active or former smokers showed significantly better EFS in the ICI arm (HR: 0.58, 95% CI 0.50-0.68). However, among those who had never smoked, although there was a tendency favoring ICI, the difference was not statistically significant (HR: 0.77, 95% CI 0.52-1.14) (Fig. S14).

All six trials<sup>[13, 15-19]</sup> reported EFS outcomes according to histological subtype. In the pooled analysis of these trials, both squamous and non-squamous histological subtypes showed significantly better EFS in the ICI arm (HR: 0.53, 95% CI 0.45-0.63 for squamous; HR: 0.62, 95% CI 0.51-0.75 for non-squamous) (Fig. S15).

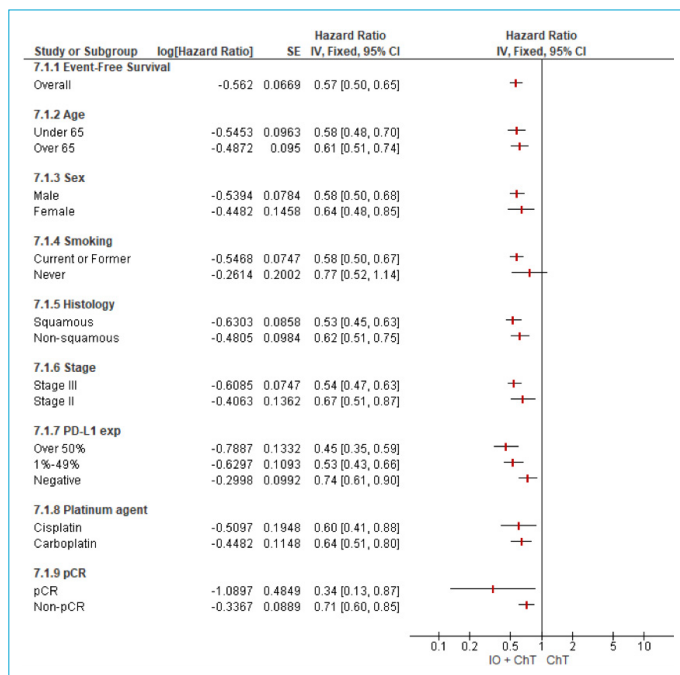
Four trials<sup>[13, 15, 17, 19]</sup> reported EFS outcomes for stage II, while all perioperative trials<sup>[13, 15-19]</sup> reported outcomes for stage III. Although the benefit was more pronounced for stage III, the ICI arm showed significantly better EFS (HR: 0.67, 95% CI 0.51-0.87 for stage II; HR: 0.54, 95% CI 0.47-0.63 for stage III) (Fig. S16).

In the subgroup analysis based on PD-L1 expression<sup>[13, 15-19]</sup>, the benefit increased as PD-L1 expression levels rose, with significant EFS advantages favoring ICI observed across all expression levels (HR: 0.74, 95% CI 0.61-0.90 for PD-L1 <1%; HR: 0.53, 95% CI 0.43-0.66 for PD-L1 1-49%; HR: 0.45, 95% CI 0.35-0.59 for PD-L1 >50%) (Fig. S17).

Only two trials<sup>[15, 17]</sup> reported EFS results based on the type of platinum agent used. In the pooled analysis of these two trials, irrespective of the type of platinum used, significantly better EFS was observed in the ICI arm (HR: 0.60, 95% CI 0.41-0.88 for cisplatin; HR: 0.64, 95% CI 0.51-0.80 for carboplatin) (Fig. S18).

Three trials<sup>[13, 17, 18]</sup> reported EFS results based on the pCR status. Regardless of the pCR status, significantly better EFS was observed in the ICI arm (HR: 0.34, 95% CI 0.13-0.87 for the pCR group; HR: 0.71, 95% CI 0.60-0.85 for the non-pCR group) (Fig. S19).

In the comparison based on PD-L1 expression,  $I^2$ :54% heterogeneity was observed in the PD-L1 1%-49% group. Therefore, a random effects model was utilized for this comparison. A fixed effects model was used for all other comparisons, where heterogeneity was low (most of them  $I^2$ : 0%). A comparison of EFS analysis results according to subgroups is given in Figure 5.



**Figure 5.** Forest plot for event-free survival by clinicopathologic subgroups.

## Overall Survival

Five trials<sup>[12, 13, 16, 18, 19]</sup> reported the OS outcome. In the pooled analysis of these trials, there was a significant improvement in OS in the ICI arm with a 35% reduction in risk (HR: 0.65, 95% CI 0.53-0.79,  $I^2$ : 0%, Z test  $p < 0.01$ ) (Fig. S20). In additional analysis after excluding the CheckMate-816 trial, which included only neoadjuvant ICI, OS was still significantly better in the ICI arm (HR: 0.66, 95% CI 0.53-0.81,  $I^2$ : 0%, Z test  $p < 0.01$ ). In the pooled analysis of three perioperative trials reporting two-year OS rates, the two-year OS rate was 83.7% in the ICI arm compared to 77.4% in the control arm.

## Toxicity

Seven trials<sup>[12, 13, 15, 16, 18-20]</sup> reporting grade 3-5 adverse events data were included in the analysis. In the pooled analysis, grade 3-5 adverse events were higher in the ICI arm (49.4% vs. 45.5%, OR: 1.21, 95% CI 1.04-1.41,  $I^2$ : 32%, Z test  $p$ : 0.01). There was no significant difference between the arms in terms of treatment-related deaths (1.0% vs 0.7%, OR: 1.35, 95% CI 0.64-2.86,  $I^2$ : 0%, Z test  $p$ : 0.43).

## Quality of Studies and Publication Bias

The quality assessment of the selected RCTs is presented in Figure S21. Since all trials were randomized controlled trials, it can be said that the trials were of high quality. Additionally, the funnel plot appears to be relatively symmetric, indicating a low risk of bias (Fig. S22-S23).

## Discussion

Our meta-analysis, encompassing the largest number of RCTs conducted to date on the perioperative treatment of resectable NSCLC with chemotherapy and ICI combination, demonstrates a significant improvement in pCR, EFS, and OS with the addition of ICI to chemotherapy. This beneficial impact was consistently observed across all subgroups for pCR, while for EFS, it was noted in all subgroups except for never-smokers. Although there was a notable trend towards improvement in never-smokers, the difference did not reach statistical significance. Due to the lack of reported data for subgroups, a pooled analysis of subgroups could not be conducted for OS.

According to the pooled analysis of all included trials, adding immunotherapy to chemotherapy significantly increases the pCR rate (24.3% vs 4.0%, respectively). Subgroup analysis conducted regardless of age, gender, smoking status, histological subtype, stage, PD-L1 level, platinum agent used, and number of neoadjuvant treatment cycles consistently showed higher pCR rates favoring ICI in all subgroups. Although the difference in pCR rates between the ICI and control arms was significant in all subgroups, notable variations were observed in terms of smoking status and PD-L1 level. The pCR rate with ICI was approximately twice as high in smokers compared to non-smokers. These results are consistent with the known correlation between smoking and increased mutational neoantigen burden, which in turn correlates with response to ICI therapy.<sup>[21]</sup> Furthermore, our findings suggest that PD-L1 expression, commonly used as a biomarker in advanced-stage NSCLC,<sup>[22]</sup> may also have predictive value in early-stage disease. The pCR rate was 12.7% in PD-L1 negative patients, while it increased to 35.5% in the group with PD-L1 expression >50%. As demonstrated in metastatic disease, the effectiveness of single-agent ICI therapy in the group with PD-L1 expression >50% suggests its potential use in early-stage disease, particularly in the subset of frail patients. The gold standard endpoint in cancer research is OS.<sup>[23]</sup> However, due to the longer lifespan of patients with early-stage cancer, surrogate endpoints are often used to accelerate the approval of innovative treatments. pCR is one of the most commonly used endpoints in neoadjuvant or perioperative treatments for early-stage cancers. Although pCR has been accepted by the FDA as a surrogate for survival outcomes in neoadjuvant therapy for breast cancer,<sup>[24,25]</sup> its applicability in other cancer types, including resectable NSCLC, is still evolving. A meta-analysis<sup>[26]</sup> of neoadjuvant trials in resectable NSCLC showed that while pCR strongly correlates with two-year EFS, it does not correlate with OS. Although there is not a consensus on surrogate endpoints



in resectable NSCLC, all included trials in our analysis consider pCR as a primary or secondary endpoint. The long-term outcomes of these trials will contribute to further understanding of surrogate endpoints.

In our pooled analysis, the addition of ICI to chemotherapy significantly increased EFS both in the neoadjuvant and perioperative settings. None of the included trials directly compared neoadjuvant and adjuvant chemoimmunotherapy. Therefore, no conclusion can be drawn regarding the need for adjuvant ICI in the perioperative setting. The two-year EFS rates were similar for neoadjuvant (67.1%) and perioperative (64.6%) use, leaving the question of whether adjuvant use is necessary unanswered. As the phase II TDFOREKNOW trial did not report subgroup analysis data for EFS, subgroup analysis for neoadjuvant ICI use could not be performed. Subgroup analysis for EFS only included trials using perioperative ICI. Except for the subgroup of never-smokers, EFS was significantly better in the ICI arms for all other subgroups. As previously mentioned, it is known that the efficacy of ICIs increases due to neoantigens caused by smoking. In our analysis, the EFS benefit was more pronounced in smokers, but there was still a relative risk reduction of 23% (HR: 0.77) for non-smokers. The lack of significance in this difference may be due to the small number of patients in this group. Similar to the pCR analysis, EFS was correlated with PD-L1 levels. As PD-L1 levels increased, the EFS benefit also increased. EFS analysis according to PCR status is a topic that requires special attention. We could only include three trials in the analysis for the pCR subgroup, making interpretation of the results difficult. However, it was observed that perioperative ICI was beneficial in both patients who achieved pCR and those who did not. Because the number of patients in whom PCR was obtained was small and their prognosis was excellent, it is difficult to draw a conclusion about the necessity of adjuvant treatment with the data obtained from these trials with a relatively short follow-up period. In patients who did not achieve pCR, we found a hazard ratio of 0.72 for perioperative ICI use in terms of EFS. Only the CheckMate 816 trial reported this data for neoadjuvant use, with an HR of 0.86 in patients who did not achieve pCR. Although indirect comparisons are not ideal, the impression is that adjuvant ICIs may benefit patients who do not achieve pCR. Additional prospective trials are needed to clarify the benefit of adjuvant ICIs. Four of the perioperative ICI trials completed the treatment in one year, including the adjuvant phase in addition to the neoadjuvant phase, while the CheckMate-77T trial applied nivolumab for one year independent of the neoadjuvant phase, and the NADIM II trial used adjuvant nivolumab for six months. In the pooled analysis of the four trials that completed the total treatment in one

year, the HR for EFS was 0.57, while 0.58 in the CheckMate-77T trial. Although the NADIM II trial is a phase II trial, the HR for EFS was the lowest at 0.47. Although it is not appropriate to compare these values indirectly with each other, it is clear that there are points to be clarified regarding the duration of adjuvant consolidation ICI in perioperative ICI use. Future trials are needed better to define the safest and most effective treatment durations to minimize unnecessary costs and toxicities.

The only trial included in our analysis that used OS as the primary endpoint was the KEYNOTE-671 trial. According to the median follow-up of 25.2 months in this trial, the benefit of ICIs on OS was demonstrated. In other trials, OS was selected as a secondary endpoint. In the pooled analysis of the five trials reporting OS results, ICIs significantly improved OS (HR: 0.65). Excluding the CheckMate-816 trial, which investigated only neoadjuvant ICI use, and focusing on the four trials investigating perioperative ICI use, the HR for OS was 0.66. In the CheckMate-816 trial, the HR was 0.61, and during the median follow-up of 41.4 months, this benefit had yet to reach statistical significance. Although the CheckMate-816 trial included stage IB patients, a similar risk reduction for OS is observed compared to perioperative use. As mentioned earlier, this raises questions about the use of adjuvant ICI in patients receiving neoadjuvant ICI.

Finally, adverse events in grades 3-5 were more prevalent in the ICI arms, with a net difference of 4%. However, there was a similar incidence of grade 5 adverse events. Although the difference between grade 3-4 adverse events was statistically significant, the lack of a significant numerical difference suggests that the combination of these agents is safe. While not the focus of our study, rates of surgical interventions and increased surgical complications have been previously investigated, and no significant risk is identified in these aspects.<sup>[10-27,28]</sup>

This meta-analysis has some limitations. Including stage Ib patients in the CheckMate-816 trial, who generally have a better prognosis, may have contributed to the more favorable outcomes of neoadjuvant ICI use. While three trials included only stage III patients, four included stage II and III patients. Although there is a risk of heterogeneity based on disease stage in the overall analysis, we believe that conducting subgroup analysis based on disease stage has minimized this risk. Another difference in baseline patient characteristics is the inclusion of approximately 7% of patients with EGFR mutations or ALK translocations in the KEYNOTE-671 trial. Even though it represents a small portion of patients, it is a point that should be considered. Finally, the median follow-up period of the included trials varies between 11.7 and 41.4 months. Although relative-

ly short follow-up periods do not significantly affect pCR analysis, it is clear that more extended follow-up periods are needed for survival results.

## Conclusion

This meta-analysis demonstrates a significant improvement in the rate of pCR with the addition of ICI to chemotherapy in the neoadjuvant treatment of resectable NSCLC. Additionally, perioperative chemoimmunotherapy shows significant improvements in EFS and OS compared to chemotherapy alone. However, due to the scope of the included trials, we were unable to analyze the net contribution of ICI in the neoadjuvant and adjuvant stages of perioperative treatment separately. Prospective trials are needed to determine which patients receiving neoadjuvant chemoimmunotherapy should continue with adjuvant ICI maintenance and the optimal duration of this therapy.

## Disclosures

\*Part of this meta-analysis was presented as a poster at the European Lung Cancer Congress 2024.

**Ethics Committee Approval:** Since this study is a meta-analysis of previously published data, ethical approval is not required.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** The author declare that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of the manuscript.

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