Neoadjuvant PD-1/PD-L1 inhibitors plus chemotherapy vs chemotherapy alone in resectable stage IB–IIIA NSCLC

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Introduction

Resectable stage IB–IIIA non-small cell lung cancer (NSCLC) remains a setting in which perioperative treatment decisions must balance the goals of improving pathological response, delaying recurrence, and ultimately prolonging survival. Platinum-based neoadjuvant chemotherapy has historically offered only modest benefit, which has driven interest in integrating immune checkpoint blockade earlier in the disease course. In particular, PD-1 and PD-L1 inhibitors combined with chemotherapy have emerged as a major therapeutic strategy in resectable NSCLC, supported by several contemporary randomized trials across neoadjuvant-only and perioperative treatment approaches [1–8].

The clinical question addressed in this meta-analysis is whether neoadjuvant or perioperative PD-1/PD-L1 inhibitor–based therapy plus chemotherapy improves outcomes compared with chemotherapy alone in patients with resectable stage IB–IIIA NSCLC. The outcomes of greatest interest in the available evidence include pathological complete response (pCR), major pathological response (MPR), event-free survival (EFS), and overall survival (OS), all of which are clinically relevant and commonly used in modern perioperative NSCLC trials.

The objective of this review was to synthesize randomized evidence comparing PD-1/PD-L1 inhibitor plus chemotherapy versus chemotherapy alone in resectable NSCLC, with emphasis on pooled effects for pathological and survival outcomes, consistency of treatment effects across studies, and the robustness of the evidence base.

Methods

Eligibility criteria and review question

This review focused on randomized interventional studies in humans evaluating PD-1 or PD-L1 inhibitor–based neoadjuvant or perioperative therapy combined with chemotherapy for resectable NSCLC. The target population was patients with resectable stage IB–IIIA NSCLC. Comparators were chemotherapy-only regimens, generally platinum-based. Small cell lung cancer and limited-stage small cell disease were excluded. The configured search framework targeted completed phase 2 or phase 3 trials published in English from 2010 onward.

Outcomes and effect measures

Outcomes specified in the configured review framework included survival and pathological endpoints. In the current validated dataset, the outcomes available for synthesis at the primary timepoint were:

- pathological complete response (pCR),
- major pathological response (MPR),
- event-free survival (or progression-free survival as captured in the dataset),
- overall survival (OS).

Other prespecified outcomes, such as R0 resection, disease-free survival, treatment-related adverse events, surgery delay, and surgery cancellation, were not present in the extracted dataset and therefore could not be meta-analyzed from the available evidence.

For binary pathological outcomes (pCR and MPR), pooled effects were reported as risk ratios (RRs). For time-to-event outcomes (EFS and OS), pooled effects were reported as hazard ratios (HRs). Random-effects models using restricted maximum likelihood (REML) were used for the primary syntheses. Fixed-effect versus random-effects comparisons were also available as sensitivity analyses for the main endpoints. Heterogeneity was summarized using tau-squared (τ^2), Cochran's Q where available, H-squared (H^2) where available, and I^2.

Study selection and flow

A PRISMA-style flow summary was available. A total of 68 records were identified and 68 were screened. Eighteen reports were sought for retrieval, all 18 were retrieved, and 18 were assessed for eligibility. No reports were excluded after full-text assessment. Fourteen studies were included in the dataset after screening, with the descriptive total after screening likewise reported as 14. Thirty-five records were excluded during screening. The flow is partly informative but not fully detailed regarding the exact relationship between all screened records and all included analytic datasets; this should be interpreted as the available study flow summary rather than a fully elaborated PRISMA diagram.

Data sources and provenance

Data were drawn from the analysis dataset underlying the included trial reports and related extracted records. The provenance summary indicates that extracted numerical items were traceable to source-linked records, with 115 items carrying provenance information across 26 total analysis items, and no provenance gaps flagged in the summary. Although the reported coverage percentage exceeds 100%, suggesting that multiple provenance links may exist for some analysis items, the key implication is that the numerical evidence used in this analysis had recorded provenance and no missing provenance was flagged in the summary. The available evidence also indicates that the included material comprised published trial reports and related extracted outcome data from validated records.

Additional analyses

Publication bias and small-study effects were assessed using Egger's regression test and Begg's rank correlation test where feasible. Funnel plot summaries and trim-and-fill analyses were also available for pCR, MPR, EFS, and OS. These diagnostics were interpreted cautiously because the number of studies per endpoint was generally below 10. Leave-one-out sensitivity analyses were attempted for major endpoints but could not be completed because the analysis tool returned an internal error for pCR, MPR, EFS, and OS. Risk of bias information was available narratively for major included randomized trials, allowing qualitative interpretation, but not all subgroup restrictions were executable through the server-side tools.

Results

Study selection

The study flow identified 68 records, all of which were screened. Eighteen reports were sought for retrieval and all were retrieved. Eighteen full texts were assessed for eligibility, with no exclusions at the full-text stage. Fourteen studies were included after screening, while 35 records were excluded during screening. Because the available flow summary does not provide a more granular breakdown reconciling every record with every included analytic contribution, the PRISMA account should be considered complete only to the extent reported above.

Characteristics of included studies

The included evidence base consisted of randomized contemporary trials evaluating PD-1/PD-L1 inhibitor–chemotherapy combinations in resectable NSCLC, including KEYNOTE-671 [1], Neotorch [2], CheckMate 816 [3], RATIONALE-315 [4], a stage III perioperative nivolumab trial [5], TD-FOREKNOW [6], CheckMate 77T [7], and AEGEAN [8]. As shown in Table 1, the evidence base included both neoadjuvant-only and

perioperative strategies, with outcomes spanning pCR, MPR, EFS, and OS. Reported study sizes in Table 1 ranged from smaller trials with fewer than 100 total participants in some comparisons to large phase 3 trials enrolling approximately 400 patients per group. The trials were published between 2022 and 2025 and represent a mix of PD-1 inhibitors (including pembrolizumab, nivolumab, toripalimab, camrelizumab, and tislelizumab) and one PD-L1 inhibitor regimen (durvalumab) [1–8]. Outcome coverage was uneven across trials: pCR and MPR were not available for every study, and OS remained relatively immature in parts of the dataset.

The available extraction coverage also showed that only pCR, MPR, EFS/PFS, and OS had validated primary-timepoint data in the current dataset. No extracted rows were available for R0 resection, disease-free survival, treatment-related adverse events, surgery delay, or surgery cancellation.

Pathological complete response

The pooled pCR analysis included 6 studies. The pooled RR was 1.76 (95% CI: 1.42–2.10; k=6; I^2=0%). Heterogeneity was absent, with τ^2=0 and I^2=0% [34]. Fixed-effect and random-effects models were identical for this endpoint, indicating that the result was not sensitive to model choice [16].

The forest plot for pCR showed a consistent direction of effect favoring PD-1/PD-L1 inhibitor plus chemotherapy over chemotherapy alone, with no detectable between-study heterogeneity. The study-level data available for publication-bias diagnostics indicate that trials contributing to pCR generally showed positive effects on the log-RR scale, with one very imprecise Japanese subanalysis contributing substantial uncertainty but not materially altering the overall direction of effect [6].

Publication-bias diagnostics for pCR were not suggestive of important asymmetry. Egger's test was non-significant (p=0.4785; k=6), and Begg's test was likewise non-significant (Kendall's tau 0.1429, p=0.6971) [6,9]. Trim-and-fill imputed no missing studies and left the pooled estimate unchanged at RR 1.76 (95% CI: 1.42–2.09) [28]. These findings are reassuring, although all such diagnostics were underpowered because fewer than 10 studies were available.

Major pathological response

The pooled MPR analysis included 5 studies. The pooled RR was 1.12 (95% CI: 0.93–1.31; k=5; I^2=3.99%). Heterogeneity was very low, with τ^2=0.0021 and Q approximately 4.16 with 4 degrees of freedom [35]. Fixed-effect and random-effects estimates were essentially identical, again reflecting minimal between-study variation [17].

Overall, the MPR forest plot suggested little difference between treatment groups at the pooled level, and the confidence interval crossed the null. This contrasts with the clearer pCR signal and indicates that the pathological benefit may be more pronounced for complete rather than major response, or alternatively that the currently available MPR dataset is more limited.

Publication-bias assessments for MPR were also inconclusive but not strongly concerning. Egger's test showed no evidence of small-study effects (intercept 0.9219, p=0.4355; k=5) [4], and Begg's test was non-significant (Kendall's tau 0.556, p=0.193) [8]. Trim-and-fill imputed 1 study on the left side of the funnel and attenuated the pooled estimate modestly to RR 1.07 (95% CI: 0.89–1.25), without changing the overall interpretation that a clear MPR benefit was not demonstrated [29].

Event-free survival

The pooled EFS analysis included 7 studies. The pooled HR was 0.57 (95% CI: 0.50–0.66; k=7; I^2=12.9%). On the log scale, the REML estimate was -0.5541 (95% CI: -0.6893 to -0.4190), with τ^2=0.0044 and low heterogeneity overall [18,36]. This corresponds to an approximately 42% to 43% relative reduction in the hazard of an event with immunochemotherapy versus chemotherapy alone.

The forest plot for EFS showed a consistently favorable direction of effect across studies, with modest spread around the pooled estimate and no major outlier pattern. Subgroup analysis by treatment strategy suggested similar effects for neoadjuvant-only and perioperative approaches. In the subgroup model, the neoadjuvant-only subgroup (k=2) had a log-HR estimate of -0.4929, while the perioperative subgroup (k=5) had a log-HR

estimate of -0.5738; the test for subgroup difference was not significant (p=0.6978). This suggests no evidence that the EFS benefit materially differed between neoadjuvant-only and perioperative strategies within the available data.

Table 2 presents a study-level classification and endpoint summary for the major trials contributing to subgroup interpretation.

TrialDrug (class)StrategyEFS HR (95% CI)OS HR (95% CI)pCR RR dataMPR RR dataKEYNOTE-671Pembrolizumab (PD-1 inhibitor)Perioperative0.58 (0.46–0.72)Not in validated set72/397 vs 16/400120/397 vs 44/400CheckMate 816Nivolumab (PD-1 inhibitor)Neoadjuvant only0.63 (0.44–0.89)0.72 (0.523–0.998)43/179 vs 4/17966/179 vs 16/179CheckMate 77TNivolumab (PD-1 inhibitor)Perioperative0.59 (0.44–0.79)0.43 (0.19–0.98)58/229 vs 11/232Not RR-ready (OR configured)AEGEANDurvalumab (PD-L1 inhibitor)Perioperative0.68 (0.53–0.88)Not availableNot in validated set122/366 vs 46/374NeotorchToripalimab (PD-1 inhibitor)Perioperative0.40 (0.28–0.57)0.62 (0.381–0.999)Not in validated setNot in validated setTD-FOREKNOWCamrelizumab (PD-1 inhibitor)Neoadjuvant only0.52 (0.21–1.29)Not availableNot available5/39 vs 2/43RATIONALE-315Tislelizumab (PD-1 inhibitor)PerioperativeNot available (empty)Not availableNot availableNot available

At the study level, KEYNOTE-671 [1] reported an EFS HR of 0.58 (95% CI: 0.46–0.72), CheckMate 816 [3] 0.63 (95% CI: 0.44–0.89), CheckMate 77T [7] 0.59 (95% CI: 0.44–0.79), AEGEAN [8] 0.68 (95% CI: 0.53–0.88), Neotorch [2] 0.40 (95% CI: 0.28–0.57), and TD-FOREKNOW [6] 0.52 (95% CI: 0.21–1.29). These values indicate broadly consistent EFS benefit across diverse PD-1/PD-L1 agents and treatment strategies.

Publication-bias diagnostics for EFS were not statistically significant. Egger's test yielded p=0.3691 (k=7) [5], and Begg's test gave Kendall's tau -0.3333 with p=0.3813 [10]. Trim-and-fill suggested possible missing less favorable studies on the right side of the funnel, imputing 3 studies and shifting the pooled HR from 0.57 (95% CI: 0.50–0.66) to 0.62 (95% CI: 0.52–0.73), but the adjusted estimate still favored the intervention [30]. Because only 7 observed studies were available, this analysis should be regarded as exploratory.

Overall survival

The pooled OS analysis included 3 studies. The pooled HR was 0.66 (95% CI: 0.51–0.85; k=3; I^2=0%). On the log scale, the pooled estimate was -0.4203 (95% CI: -0.6754 to -0.1651), with τ^2=0, Q=0.00, and I^2=0% [19,37]. This suggests a statistically significant OS benefit, although the evidence base was much smaller than for EFS.

The OS forest plot showed all three studies favoring immunochemotherapy, with no detectable heterogeneity. Study-level coordinates from the bias diagnostics showed log-HR values of -0.8440 for the stage III perioperative nivolumab study [5], -0.3285 for the nivolumab plus chemotherapy OS report linked to CheckMate 816 [3], and -0.4780 for Neotorch [2], corresponding to consistent survival benefit across the available trials [7]. In the study classification table, CheckMate 816 [3] had an OS HR of 0.72 (95% CI: 0.523–0.998), CheckMate 77T [7] 0.43 (95% CI: 0.19–0.98), and Neotorch [2] 0.62 (95% CI: 0.381–0.999), although the validated pooled primary OS set comprised only 3 studies.

Publication-bias assessment for OS was highly uncertain because of the very small number of studies. Egger's test was formally significant (p=0.0272), but this was based on only 3 studies and was explicitly described as unstable and not suitable for firm inference [7]. Begg's test could not be performed because k<4 [11]. Trim-and-fill imputed 2 studies on the right side of the funnel and attenuated the pooled HR from 0.66 (95% CI: 0.51–0.85) to 0.72 (95% CI: 0.58–0.90), but again this should be interpreted very cautiously given the sparse dataset [31].

Risk of bias and certainty considerations

A qualitative RoB 2 assessment was available for seven major trials. KEYNOTE-671 [1], CheckMate 77T [7], and AEGEAN [8] were judged low risk overall, while CheckMate 816 [3], Neotorch [2], TD-FOREKNOW [6], and RATIONALE-315 [4] were judged as having some concerns, mainly related to open-label design and, for some studies, less clearly independent blinded outcome assessment. No trial in the provided RoB summary was labeled high risk overall. This pattern supports reasonable internal validity of the evidence base, while acknowledging some limitations in open-label studies.

GRADE-style summaries in the evidence base judged certainty as high for pCR, high for EFS, high for OS, and moderate for MPR, with MPR downgraded primarily for imprecision because the confidence interval crossed the null [38–41]. These certainty assessments should be interpreted alongside the limited number of studies for some outcomes and the incompleteness of formal RoB data in the extracted quantitative tool outputs.

Discussion

This meta-analysis of randomized trials in resectable stage IB–IIIA NSCLC found that adding a PD-1/PD-L1 inhibitor to chemotherapy was associated with improved pCR, EFS, and OS compared with chemotherapy alone, while the evidence for MPR was less definitive. The clearest pathological signal was observed for pCR, with a pooled RR of 1.76 and no observed heterogeneity. The survival findings were also clinically important: the pooled HR was 0.57 for EFS and 0.66 for OS, both favoring immunochemotherapy. Across these endpoints, between-study heterogeneity was low or absent, which strengthens confidence in the consistency of the observed effects.

The pCR result appears especially robust. Both fixed-effect and random-effects models gave identical results, heterogeneity was absent, and publication-bias diagnostics did not suggest major distortion. This pattern is consistent with convergent evidence from multiple contemporary randomized trials, including pembrolizumab-, nivolumab-, and other PD-1 pathway–based regimens [1–3,5,7]. In contrast, the pooled MPR estimate was closer to the null and not statistically conclusive. Several explanations are possible within the boundaries of the available evidence: MPR may be more variably defined or measured across studies, the effect may genuinely be smaller than for pCR, or the smaller number of analyzable MPR datasets may simply limit precision.

The EFS findings are particularly important from a clinical perspective because they extend beyond pathological response and suggest that the benefit of perioperative immunochemotherapy translates into improved time-to-event outcomes. The low heterogeneity and the non-significant subgroup interaction between neoadjuvant-only and perioperative strategies suggest that the EFS benefit is not obviously confined to one treatment strategy. At the same time, the subgroup analysis was based on only 2 neoadjuvant-only and 5 perioperative studies, so the absence of an interaction should not be interpreted as definitive equivalence between strategies.

The OS analysis is encouraging but remains less mature. Only 3 studies contributed to the primary pooled OS estimate, and although the pooled HR of 0.66 favored treatment with no detectable heterogeneity, OS remains the sparsest major endpoint in the current evidence base. This limited evidence base also undermines the interpretability of publication-bias testing for OS: a formally significant Egger result with only 3 studies is not reliable, and Begg's test could not even be performed. Accordingly, the OS benefit should be viewed as promising but still less secure than the EFS and pCR findings.

Several limitations should be acknowledged. First, the dataset did not include several clinically relevant outcomes mentioned in the broader review framework, including R0 resection, disease-free survival, adverse events, surgery delay, and surgery cancellation. As a result, this report cannot provide a balanced pooled assessment of efficacy and perioperative safety trade-offs. Second, outcome availability was uneven across trials, with not all studies contributing to each endpoint. Third, publication-bias diagnostics were underpowered for all major outcomes because k was always below 10 and was particularly sparse for OS. Fourth, leave-one-out analyses could not be completed because of technical errors in the sensitivity-analysis tool, so influence diagnostics remain incomplete. Fifth, although a qualitative RoB table was available, risk-of-bias metadata were not fully integrated into all quantitative tools, limiting some planned sensitivity analyses.

There are also interpretive issues related to clinical heterogeneity. The included trials used different checkpoint inhibitors, varied in whether treatment was neoadjuvant-only or perioperative, and may have differed in stage mix and follow-up maturity. Although the statistical heterogeneity was low, this does not eliminate the possibility of meaningful clinical differences across regimens or populations. Moreover, some studies in the broader extraction matrix extended beyond the core eight trials in Table 1, reflecting subanalyses or additional outcome reports; this underscores the need to distinguish unique trials from outcome-specific reports when interpreting pooled evidence.

Overall, the available evidence supports the use of PD-1/PD-L1 inhibitor plus chemotherapy in resectable NSCLC, particularly for improving pCR and EFS. The OS signal is favorable but currently based on fewer studies. Future updates with more mature survival follow-up, more complete OS reporting, and fuller extraction of safety and surgical outcomes will be important to refine benefit-risk assessment.

Conclusions

In randomized evidence for resectable stage IB–IIIA NSCLC, neoadjuvant or perioperative PD-1/PD-L1 inhibitor plus chemotherapy improved pathological complete response and event-free survival compared with chemotherapy alone, and available overall survival data also favored the immunochemotherapy strategy. The pooled pCR was 1.76 (95% CI: 1.42–2.10; k=6; I^2=0%), the pooled EFS HR was 0.57 (95% CI: 0.50–0.66; k=7; I^2=12.9%), and the pooled OS HR was 0.66 (95% CI: 0.51–0.85; k=3; I^2=0%). By contrast, the pooled MPR result was not clearly significant at RR 1.12 (95% CI: 0.93–1.31; k=5; I^2=3.99%).

Taken together, the evidence supports a clinically meaningful benefit of adding PD-1/PD-L1 blockade to chemotherapy in the neoadjuvant or perioperative management of resectable NSCLC. However, the evidence base remains more mature for pCR and EFS than for OS, and important safety and surgical outcomes were not available in the current dataset.

References

References

- [1] Spicer et al. (2024). Neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab compared with neoadjuvant chemotherapy alone in patients with early-stage non-small-cell lung cancer (KEYNOTE-671): a randomised, double-blind, placebo-controlled, phase 3 trial.. Lancet (London, England) (2024). doi:10.1016/S0140-6736(24)01756-2 · PMID:39288781
- [2] Lu et al. (2024). Perioperative Toripalimab Plus Chemotherapy for Patients With Resectable Non-Small Cell Lung Cancer: The Neotorch Randomized Clinical Trial.. JAMA (2024). doi:10.1001/jama.2023.24735 · PMID:38227033
- [3] Forde et al. (2022). Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer.. The New England journal of medicine (2022). doi:10.1056/NEJMoa2202170 · PMID:35403841
- [4] Yue et al. (2025). Perioperative tislelizumab plus neoadjuvant chemotherapy for patients with resectable non-small-cell lung cancer (RATIONALE-315): an interim analysis of a randomised clinical trial.. The Lancet. Respiratory medicine (2025). doi:10.1016/S2213-2600(24)00269-8 · PMID:39581197
- [5] Provencio et al. (2023). Perioperative Nivolumab and Chemotherapy in Stage III Non-Small-Cell Lung Cancer.. The New England journal of medicine (2023). doi:10.1056/NEJMoa2215530 · PMID:37379158
- [6] Lei et al. (2023). Neoadjuvant Camrelizumab Plus Platinum-Based Chemotherapy vs Chemotherapy Alone for Chinese Patients With Resectable Stage IIIA or IIIB (T3N2) Non-Small Cell Lung Cancer: The TD-FOREKNOW Randomized Clinical Trial.. JAMA oncology (2023). doi:10.1001/jamaoncol.2023.2751 · PMID:37535377
- [7] Cascone et al. (2024). Perioperative Nivolumab in Resectable Lung Cancer.. The New England journal of medicine (2024). doi:10.1056/NEJMoa2311926 · PMID:38749033
- [8] Heymach et al. (2023). Perioperative Durvalumab for Resectable Non-Small-Cell Lung Cancer.. The New England journal of medicine (2023). doi:10.1056/NEJMoa2304875 · PMID:37870974

Table 1: Characteristics of Included Studies

Citation	Study Title	Year	Journal
Spicer et al. (2024)	Neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab compared with neoadjuvant chemotherapy alone in	2024	Lancet (London, England)

Citation	Study Title	Year	Journal
	patients with early-stage non-small-cell lung cancer (KEYNOTE-671): a randomised, double-blind, placebo-controlled, phase 3 trial.		
Lu et al. (2024)	Perioperative Toripalimab Plus Chemotherapy for Patients With Resectable Non-Small Cell Lung Cancer: The Neotorch Randomized Clinical Trial.	2024	JAMA
Forde et al. (2022)	Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer.	2022	The New England journal of medicine
Yue et al. (2025)	Perioperative tislelizumab plus neoadjuvant chemotherapy for patients with resectable non-small-cell lung cancer (RATIONALE-315): an interim analysis of a randomised clinical trial.	2025	The Lancet. Respiratory medicine
Provencio et al. (2023)	Perioperative Nivolumab and Chemotherapy in Stage III Non-Small-Cell Lung Cancer.	2023	The New England journal of medicine
Lei et al. (2023)	Neoadjuvant Camrelizumab Plus Platinum-Based Chemotherapy vs Chemotherapy Alone for Chinese Patients With Resectable Stage IIIA or IIIB (T3N2) Non-Small Cell Lung Cancer: The TD-FOREKNOW Randomized Clinical Trial.	2023	JAMA oncology
Cascone et al. (2024)	Perioperative Nivolumab in Resectable Lung Cancer.	2024	The New England journal of medicine
Heymach et al. (2023)	Perioperative Durvalumab for Resectable Non-Small-Cell Lung Cancer.	2023	The New England journal of medicine

Figures

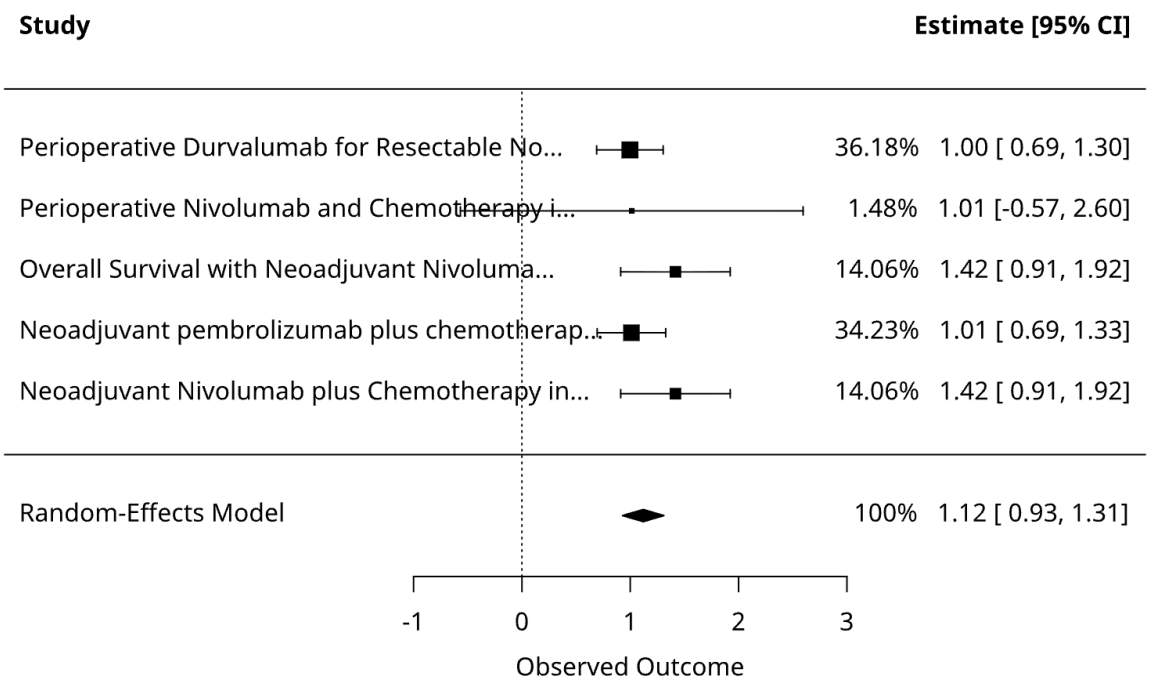

Figure 1: Forest Plot — Major pathological response (MPR) (primary) [RR]

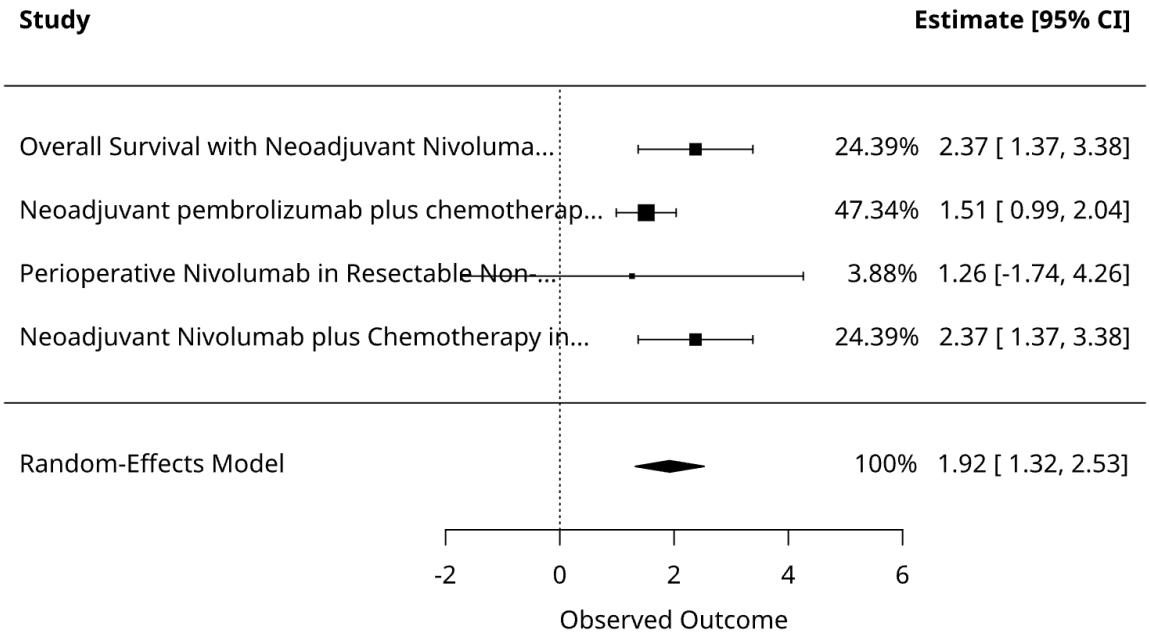

Figure 2: Forest Plot — Pathological complete response (pCR) (primary) [RR]

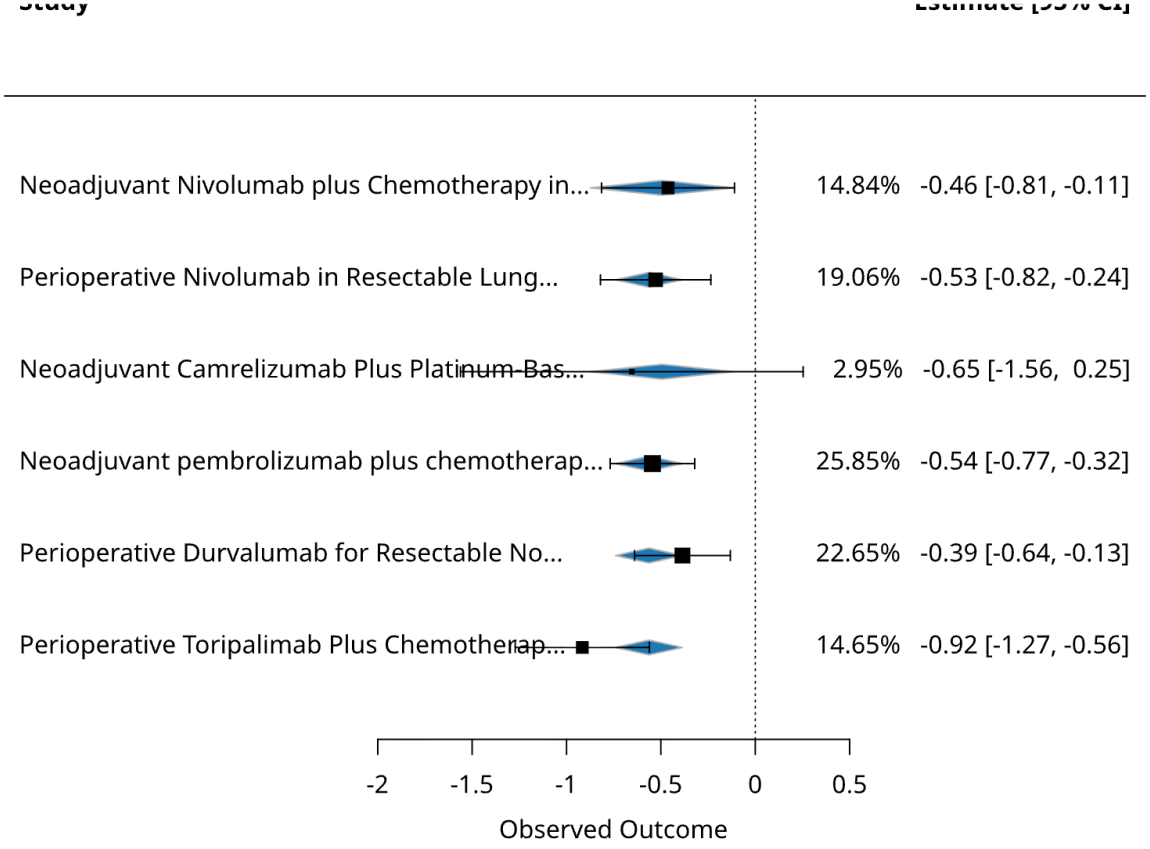

Figure 3: Forest Plot — Event-free survival (or progression-free survival) (primary) [HR]

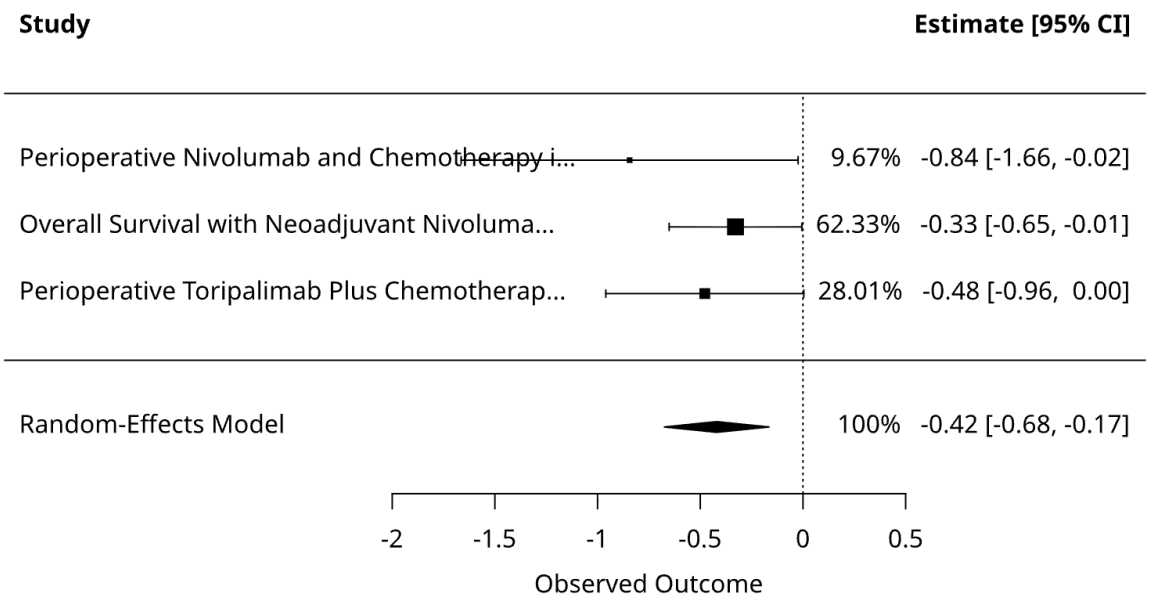

Figure 4: Forest Plot — Overall survival (OS) (primary) [HR]