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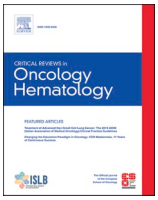

Surgical and survival outcomes with perioperative or neoadjuvant immune-checkpoint inhibitors combined with platinum-based chemotherapy in resectable NSCLC: A systematic review and meta-analysis of randomised clinical trials

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ABSTRACT

The use of neoadjuvant or perioperative anti-PD(L)1 was recently tested in multiple clinical trials. We performed a systematic review and meta-analysis of randomised trials comparing neoadjuvant or perioperative chemo-immunotherapy to neoadjuvant chemotherapy in resectable NSCLC. Nine reports from 6 studies were included. Receipt of surgery was more frequent in the experimental arm (odds ratio, OR 1.39) as was pCR (OR 7.60). EFS was improved in the experimental arm (hazard ratio, HR 0.55) regardless of stage, histology, PD-L1 expression (PD-L1 negative, HR 0.74) and smoking exposure (never smokers, HR 0.67), as was OS (HR 0.67). Grade $>=3$ treatment-related adverse events were more frequent in the experimental arm (OR 1.22). The experimental treatment improved surgical outcomes, pCR rates, EFS and OS in stage II-IIIB, EGFR/ALK negative resectable NSCLC; confirmatory evidence is warranted for stage IIIB tumours and with higher maturity of the OS endpoint.

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1. Introduction

Platinum-based neoadjuvant or adjuvant chemotherapy in resectable, early-stage non-small cell lung cancer (NSCLC) offers a modest but significant benefit in overall survival (OS) of approximately 5 % at 5 years (Pignon et al., 2008; NSCLC Meta-analysis Collaborative Group, 2014). While surgery and chemotherapy offer the opportunity for cure, recurrence is common.

The use of immune-checkpoint inhibitors (ICIs) either as a monotherapy or in combination with platinum-based chemotherapy in advanced NSCLC provided durable benefit to some patients, offering statistically and clinically significant improvements in progression-free survival (PFS), OS and quality-of-life (QoL) (Reck et al., 2022; Brahmer et al., 2017).

Recently, the phase III IMpower010 trial showed improved disease-free survival (DFS) in programmed death ligand 1 (PD-L1) positive and improved OS in PD-L1 50 % NSCLC after surgical resection and adjuvant platinum-based chemotherapy and the phase III KEYNOTE-091/PEARLS trial showed improved DFS with adjuvant pembrolizumab in PD-L1 unselected, resected NSCLC (Felip et al., 2021; Felip et al., 2023; O'Brien et al., 2022).

Neoadjuvant plus adjuvant administration of ICIs (i.e. perioperative) was shown to improve event-free survival (EFS) in resectable stage III-IV melanoma when compared to adjuvant only administration (Patel et al., 2023). Neoadjuvant ICIs were tested in multiple clinical trials in patients with resectable NSCLC leading to major pathological response (MPR) and pathological complete response (pCR) in 22–45 % and 9–16 % of patients, respectively (Forde et al., 2018; Cascone, 2021; Gao et al., 2020).

Building on previous knowledge acquired from chemo-immunotherapy combinations in the advanced setting, neoadjuvant or perioperative ICIs were then combined with platinum-based chemotherapy in resectable NSCLC (Forde et al., 2022; Forde et al., 2023; Provencio-Pulla et al., 2022; Provencio et al., 2022, 2023; Heymach et al., 2023; Lu et al., 2023; Wakelee et al., 2023; Lei et al., 2022, Rothschild, 2021). The biological rationale for preoperative chemo-immunotherapy combinations is to promote neoantigen recognition prior to primary tumour resection and to tackle mechanisms of intrinsic resistance to single-agent immunotherapy, ultimately leading to an improved eradication of micrometastatic disease (Mountzios et al., 2023). This strategy led to FDA and EMA approvals for neoadjuvant nivolumab in combination with platinum-based chemotherapy in node positive or $\geq$ 4 cm tumours and in node positive or $\geq$ 5 cm tumours with PD-L1 $\geq$ 1 %, respectively, based on the results of the CheckMate-816 clinical trial, showing statistically significant and clinically relevant improvements in EFS (Forde et al., 2022; Forde et al., 2023).

However, upon delay of surgery due to preoperative medical treatment, up to 20 % of patients with resectable disease at baseline do not receive surgical resection after neoadjuvant chemoimmunotherapy. Additionally, surgical resection of NSCLC after immunotherapy was shown to be technically challenging due to frequent hilar inflammation and fibrosis (Bott et al., 2019; Sepesi et al., 2022).

Aiming at assessing the efficacy and safety of this treatment strategy and focusing on specific subgroups that led to divergent regulatory approvals, we performed a systematic review and meta-analysis of randomised clinical trials comparing perioperative or neoadjuvant ICIs combined with platinum-based chemotherapy to neoadjuvant platinum-based chemotherapy in resectable NSCLC.

2. Methods

2.1. Included studies

We included randomised clinical trials (RCTs) reporting on effectiveness and/or safety of neoadjuvant or perioperative anti-PD(L)1 combined with platinum-based chemotherapy compared to neoadjuvant platinum-based chemotherapy for patients with resectable NSCLC. We applied no language or publication status restrictions. We considered RCTs studies for inclusion if one or more of the following comparisons were available:

- Perioperative anti-PD(L)1 combined with platinum-based chemotherapy compared to neoadjuvant platinum-based chemotherapy;
- neoadjuvant anti-PD(L)1 combined with platinum-based chemotherapy compared to neoadjuvant platinum-based chemotherapy.

A platinum-based chemotherapy regimen was defined as any platinum-based doublet given for at least one cycle. Reports regarding NSCLC not eligible for surgical resection at baseline were excluded.

2.2. Search strategy and selection processes

A literature search was conducted on the MEDLINE, EMBASE and CENTRAL databases on the 11th of June 2023 by the first authors (D.M. and F.T.G.). Medical Subject Headings (MeSH) for the MEDLINE and CENTRAL databases, Emtree for the EMBASE database and selected keywords were used to search for randomised clinical trials.

Abstracts from the American Society of Clinical Oncology (ASCO), ASCO Plenary Series, European Society of Medical Oncology (ESMO), European Lung Cancer Congress (ELCC), World Conference on Lung Cancer (WCLC) and American Association for Cancer Research (AACR) were additionally screened based on title and category (where available), regardless of their inclusion status in EMBASE; relevant reports not previously identified in the database search were selected for further investigation and eventual inclusion. Whenever judged appropriate by the first authors, we included results from unpublished online data matched to meeting abstracts. In case of multiple reports from the same trial, the most recent report for the investigated outcomes was selected.

The following baseline variables were extracted from all included studies: study name/reference, type of study (randomised phase II/phase III), primary endpoint, number of enrolled patients, randomisation rate, clinical stage at enrollment, stratification factors, histology, smoke, use of oncogene addicted-based exclusion criteria, treatment characteristics.

2.3. Endpoints

Primary endpoints:

- Receipt of surgery after preoperative treatment in all included studies;
- pCR, defined as no residual tumour cells in the primary tumour and resected lymph nodes in all included studies;
- EFS (defined as the time from randomization to any progression of disease precluding surgery, progression or recurrence of disease after surgery, progression of disease in the absence of surgery, or death from any cause) in studies comparing perioperative anti-PD(L)1 combined with platinum-based chemotherapy to neoadjuvant platinum-based chemotherapy.

Secondary endpoints:

- OS (defined as time from randomisation to death from any cause) in studies comparing perioperative anti-PD(L)1 combined with platinum-based chemotherapy to neoadjuvant platinum-based chemotherapy;
- Safety, defined as any grade treatment-related adverse events and grade > = 3 treatment-related adverse events in all included studies.

Exploratory endpoints:

- EFS in all included studies;

– OS in all included studies.

Subgroup analyses were pre-planned for stratification factors shared across multiple of the included trials. Exploratory subgroup analyses were performed on patients with clinical stage IIIB NSCLC and in never-smoker patients.

2.4. Statistical analysis

For each time-to-event endpoint, hazard ratios (HR) and their relative 95 % confidence intervals (95 % CI) were extracted; the overall effect was estimated with a random effects model based on inverse variance.

For categorical endpoints, the number of events for each group was collected; when the number of events was not available, the number of events was derived from the percentage of cases with an event. Odds ratios (OR) with the relative 95 % CI were estimated with a Mantel-Haenszel random effects model. Statistical heterogeneity between studies was quantified with Higgins' I^2. Comparisons between subgroups were carried out using a χ^2 test.

The risk of bias was assessed by the first authors (D.M. and F.T.G.) for each study and was reported graphically along with the primary endpoints.

This analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. All analyses were performed with RevMan Web version 5.3.1 by the first author (D.M.). The *alpha* for all analyses was set at 0.05.

2.5. Sensitivity analyses

We investigated the robustness of the results by performing and reporting the following sensitivity analyses, when appropriate:

– undertaking the analysis using a fixed-effect model in case of low statistical heterogeneity;
– excluding studies with high risk of bias;
– leave-one-out analysis to assess impact of single studies on the results.

2.6. Specific considerations

In the NADIM-II trial, the composite endpoint of PFS was judged as comparable to the composite endpoint of EFS available for all other eligible studies; those endpoints were analysed jointly. Accordingly, the term "EFS" was also used for the PFS results from the NADIM-II trial throughout the paper.

The included trials used both the 7th and 8th edition of AJCC TNM Cancer Staging Manual for clinical and pathological staging of NSCLC:

– As stage IB tumours $\geq$ 4 cm *per* AJCC TNM 7th edition are classified in the stage II category in the 8th edition of the Manual, those tumours were referred to as stage II tumours throughout the document, unless otherwise specified.
– Some of the patients enrolled in the included trials who presented with stage IIIA tumours per the 7th edition of the Manual may have stage IIIB tumours according to the 8th edition of the Manual; however, patient-level data were not available for this analysis. Therefore, to account for this potential source of bias, we planned an additional subgroup analysis on stage IIIB tumours *per* the 8th edition of the Manual.

Some of the included studies presented results for stage IIIA and stage IIIB tumours separately; when a pooled measure of outcome for all stage III tumours was not available at the study level, the separate estimates for stage IIIA and IIIB were included in the analyses.

3. Results

3.1. Included studies

The systematic literature search identified 149 records; after the exclusion of duplicated and not relevant reports, 9 reports from 6 studies were included (CheckMate-816 (Forde et al., 2022; Forde et al., 2023), NADIM-II (Provencio-Pulla et al., 2022; Provencio et al., 2022, 2023), AEGEAN (Heymach et al., 2023), NeoTORCH (Lu et al., 2023), KEYNOTE-671 (Wakelee et al., 2023), NCT04338620 (Lei et al., 2022); the PRISMA flow diagram of the study is shown in Fig. 1.

The total number of patients evaluated in this analysis is 2524. Four of the included studies were phase III clinical trials and 2 were randomised phase II clinical trials. Two studies (CheckMate-816 and NCT04338620) allowed administration of anti-PD(L)1 only in the neoadjuvant phase, while all other included studies administered perioperative anti-PD(L)1 in the experimental arm.

One study enrolled patients with stage IB-IIIA NSCLC (*per* AJCC 7th, CheckMate-816); three studies enrolled patients with stage II-IIIB NSCLC (*per* AJCC 8th, NeoTORCH, AEGEAN, KEYNOTE-671) and two study enrolled patients with stage IIIA-IIIB NSCLC (AJCC 8th, NCT04338620, NADIM-II). Results for the intention-to-treat (ITT) population of the NeoTORCH study were not available; thus, only patients in the stage III cohort were included.

Three studies (NCT04338620, KEYNOTE-671 and AEGEAN) allowed enrollment of patients with EGFR mutations or ALK fusions; in the AEGEAN study those patients were included in the ITT population and excluded in the modified ITT population). The characteristics of the included studies are summarised in Table 1. All of the included studies had unclear risks of bias in at least two categories (Fig. 2).

3.2. Receipt of surgery

A total of 2473 patients from 6 studies were included in the analysis on the receipt of surgery. Overall, 1992 (81 %) patients received surgery after neoadjuvant treatment, 1028 out of 1244 (83%) in the experimental arm and 964 out of 1229 (79 %) in the control arm. Receipt of surgery was more frequent in the experimental arm (OR 1.39, 95 % CI 1.02–1.91, Fig. 2); a sensitivity analysis performed with a fixed effects model confirmed the results from the primary analysis (Fig. S1).

The subgroup analysis on stage III was performed on 806 patients from 4 studies (not included: AEGEAN and KEYNOTE-671 due to missing data). Receipt of surgery was more frequent in the experimental arm (OR 1.94, 95 % CI 1.23–3.07, Fig. S2). Additional subgroup analyses were not performed due to missing data.

3.3. Pathologic complete response

A total of 2473 patients from 6 studies were included in the pCR analysis. Overall, 314 (13 %) patients achieved a pCR after neoadjuvant treatment, 270 out of 1244 (22 %) in the experimental arm and 44 out of 1229 (4 %) in the control arm. Pathologic complete response was more frequent in the experimental arm (OR 7.60, 95 % CI 4.34–13.32, Fig. 3 and Fig. S3); a sensitivity analysis performed with a fixed effects model confirmed the results of the primary analysis (Fig. S3).

The subgroup analysis for stage was performed on 1671 patients from 5 studies (not included: KEYNOTE-671 due to missing data) with available data for the pCR outcome. We did non find significant differences in treatment effect on the likelihood of pCR between patients with stage II and stage III NSCLC ($p = 0.45$, Fig. S4).

The subgroup analysis for histology was performed on 1179 patients from 3 studies (not included: KEYNOTE-671, NeoTORCH, NCT04338620 due to missing data). We did not find significant differences in treatment effect on the likelihood of pCR between patients with non-squamous and squamous NSCLC ($p = 0.42$, Fig. S5).

The subgroup analysis for PD-L1 was performed on 1073 patients

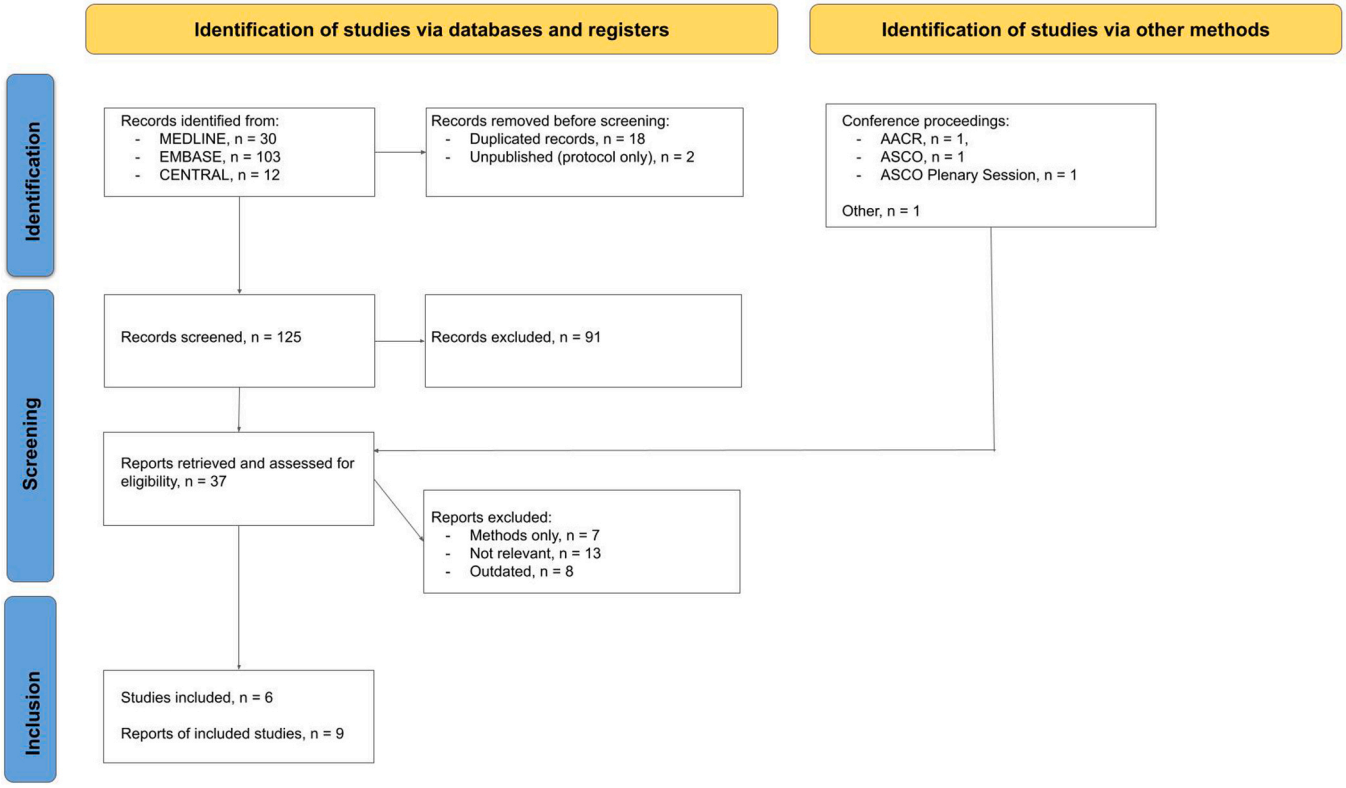

Fig. 1. PRISMA flow diagram of the study.

from 2 studies (not included: NADIM-II, KEYNOTE-671, NeoTORCH, NCT04338620 due to missing data). We did not find significant differences in treatment effect on the likelihood of pCR between patients with PD-L1 positive and PD-L1 negative NSCLC (p = 0.36, Fig. S6).

3.4. Event-free survival

A total of 2025 patients from 4 studies were included in the primary EFS analysis; CheckMate-816 and NCT04338620 were excluded from the analysis due to study design (i.e.. neoadjuvant-only administration of anti-PD(L)1). EFS was improved in the experimental arm (HR 0.55, 95 % CI 0.44–0.69, Fig. 4); a sensitivity analysis performed with a fixed effects model confirmed the results of the primary analysis (Fig. S7).

The subgroup analysis for stage was performed on 2023 patients from 4 studies. We did not find significant differences in treatment effect on EFS between patients with stage II and stage III NSCLC (p = 0.24, Fig. S8).

The subgroup analysis for histology was performed on 2020 patients from 4 studies. We did not find significant differences in treatment effect on EFS between patients with non-squamous and squamous NSCLC (p = 0.61, Fig. S9).

The subgroup analysis for PD-L1 was performed on 2014 patients from 4 studies. We found a significant difference in treatment effect on EFS between patients with PD-L1 positive and PD-L1 negative NSCLC (p = 0.02, Fig. S10). However, a significant improvement in EFS with the experimental treatment was shown in both PD-L1 positive and PD-L1 negative tumours.

3.5. Overall survival

A total of 1287 patients from 3 studies were included in the OS analysis (not included: AEGEAN due to missing data); CheckMate-816 and NCT04338620 were excluded from the primary OS analysis due to study design. OS was improved in the experimental arm (HR 0.67, 95 % CI 0.52–0.85, Fig. 5); a sensitivity analysis performed with a fixed effects model confirmed the results of the analysis (Fig. S11). Subgroup analyses for the OS endpoint were not performed due to missing data.

3.6. Safety

A total of 2524 patients from 6 studies were included in the safety analysis. We did not find significant differences in any grade treatment-related adverse events (OR 1.26, 95 % CI 0.80–1.97, Fig. S12) or grade >= 3 treatment-related adverse events (OR 1.22, 95 % CI 0.97–1.54, Fig. 6); however, a sensitivity analysis performed with a fixed effects model showed a higher rate of grade >= 3 adverse events in the experimental arm (Fig. S13).

3.7. Exploratory analyses

A total of 2473 patients from 6 studies were included in the exploratory EFS analysis. EFS was improved in the experimental arm regardless of experimental treatment modality (p = 0.33, Fig. S14).

A total of 1643 patients from 4 studies (not included: AEGEAN and NCT04338620 due to missing data) were included in the exploratory OS analysis. OS was improved in the experimental arm regardless of experimental treatment modality (p = 0.78, Fig. S15).

EFS was evaluated among 296 never-smoker patients from 4 studies (not included: NADIM-II and NCT04338620 due to missing data) and was improved in the experimental arm (HR 0.59, 95 % CI 0.40–0.88, Fig. S16); however, after the exclusion of CheckMate-816, EFS was only numerically improved in the experimental arm (HR 0.67, 95 % CI 0.43–1.04, Fig. S17).

EFS was evaluated among 315 stage IIIB patients from 2 studies (not included: NADIM-II, KEYNOTE-671, CheckMate-816 and NCT04338620 due to missing data) and was numerically improved in the experimental arm (HR 0.51, 95 % CI 0.19–1.39, Fig. S18).

Table 1
Characteristics of included studies.

	CheckMate-816 (Forde et al., 2022, 2023)	NADIM-II (Provencio et al., 2022; Provencio-Pulla et al., 2022; Provencio et al., 2023)	AEGEAN (Heymach et al., 2023)	NeoTORCH (Lu et al., 2023)	KEYNOTE-671 (Wakelee et al., 2023)	NCT04338620 (Lei et al., 2022)
Study design	PhIII, open-label	PhII, open-label	PhIII, double-blind, P-controlled	PhIII, double-blind, P-controlled	PhIII, double-blind, P-controlled	PhII, open-label
Enrolled pts (ITT)	358	90	740	Missing data (stIII: 404)	797	94
Randomisation	1:1	2:1	1:1	1:1	1:1	1:1
Primary endpoint	pCR, EFS	pCR	pCR, EFS	EFS, MPR in stIII and ITT	EFS, OS	pCR
cTNM	IB-IIIA (AJCC 7th)	IIIA-IIIB (AJCC 8th)	II-IIIBN2 (AJCC 8th)	II-IIIBN2 (AJCC 8th)	II-IIIBN2 (AJCC 8th)	IIIA-IIIB (AJCC 8th)
Stratification	Stage, PD-L1, sex	None	Stage, PD-L1	Stage, PD-L1, type of surgery, histology	Stage, PD-L1, histology, region	None
Histology	sq: 51%, nonsq: 49%	sq: 41 %, nonsq: 59 %	sq: 49 %, nonsq: 51 %	sq: 77 %, nonsq: 23 %	sq: 43 %, nonsq: 57 %	sq: 67 %, nonsq: 33 %
Smoke	NS: 11%	NS: 6 %	NS: 14 %	NS: 12 %	NS: 13 %	NS: 23 %
Stage	StIII: 64%, stIB-II: 36%	StIII: 100 %	StIII: 71 %, stII: 29 %	StIII: 100 % (missing data for stII)	StIII: 70 %	StIII: 100 %
Oncogene addicted exclusion	ALK, EGFR	ALK, EGFR	ALK, EGFR	ALK, EGFR excluded from mITT	None	None
Exp	N + Pl-d q3wks x3 cycles	N + Cb/pac q3wks x3	D + Pl-d q3wks x4	T + Pl-d q3wks x3	P + Pl-d q3wks x4	C + Pl-d q3wks x3
SoC	Pl-d q3wks x3	Cb/pac q3wks x3	Plac + Pl-d q3wks x4	Plac + Pl-d q3wks x3	Plac + Pl-d q3wks x4	Pl-d q3wks x3
Adj, exp	Optional adj CHT + /- RT	Adj N q4wks x6	Adj D q4wks x12	Adj T + Pl-d q3wks x1 → T q3wks x13	Adj P q3wks x13 + optional RT	Obs
Adj, SoC	Optional adj CHT + /- RT	Obs	Adj Plac q4wks x12	Adj P + Pl-d q3wks x1 → P q3wks x13	Adj Plac q3wks x13 + optional RT	Obs
MPR rates	exp: 36.9%, SoC: 8.9%	exp: 52.6 %, SoC: 13.8 %	exp: 33.3 %, SoC: 12.3 %	exp: 48.5 %, SoC: 8.4 %	exp: 30.2 %, SoC: 11 %	exp: 65.12 %, SoC: 15.56 %
pCR rates	exp: 24%, SoC: 2.2%	exp: 36.8 %, SoC: 6.9 %	Exp: 17.2 %, SoC: 4.3 %	exp: 28.2 %, SoC: 1 %	exp: 18.1 %, SoC: 4 %	exp: 32.56 %, SoC: 8.89 %

N: nivolumab; D: durvalumab; T: toripalimab; P: pembrolizumab; C: camrelizumab; Pl-d: platinum-doublet; Cb: carboplatin; Pac: paclitaxel; Plac: placebo; obs: observation; neo: neoadjuvant; adj: adjuvant; CHT: chemotherapy; RT: radiotherapy; st: stage; q3wks: every 3 weeks; q4wks: every 4 weeks; SoC: standard-of-care arm; exp: experimental arm; Ph: phase; pts: patients; ITT: intention-to-treat; EFS: event-free survival, pCR: pathological complete response; MPR: major pathological response; inv: investigator-assessed; centr: central evaluation; BICR: blinded independent central review; NE: not evaluable; I: indeterminate; pneumo: pneumonectomy; lob: lobectomy; hist: histology; nonsq: non-squamous; sq: squamous;

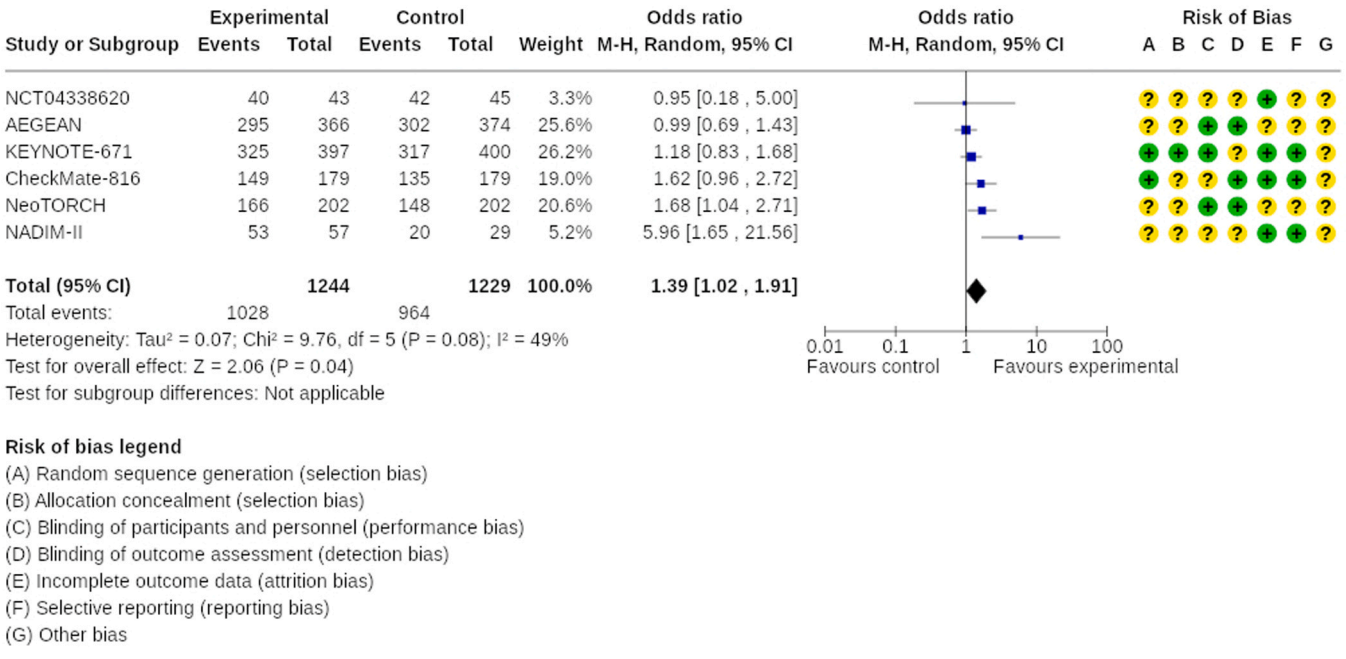

Fig. 2. Receipt of surgery.

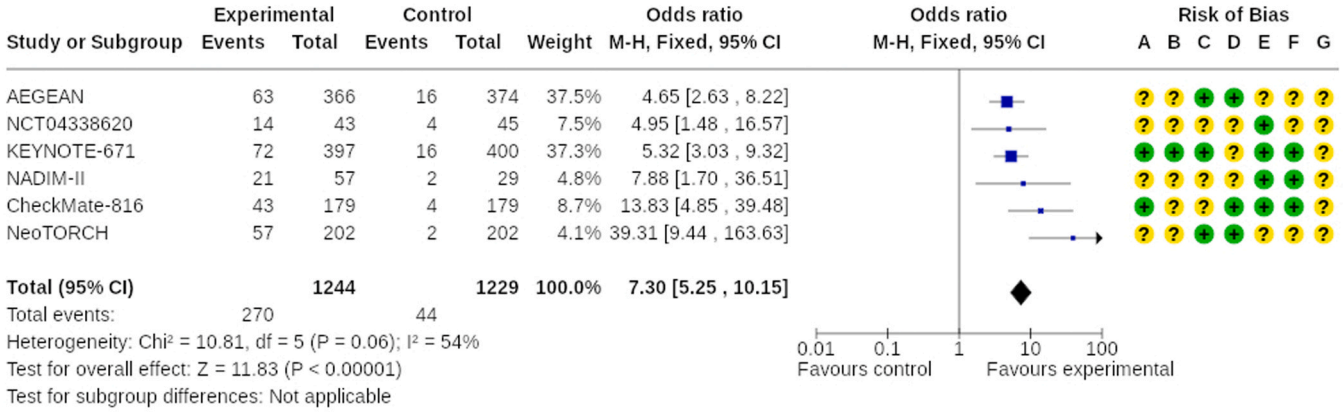

Fig. 3. Pathologic complete response.

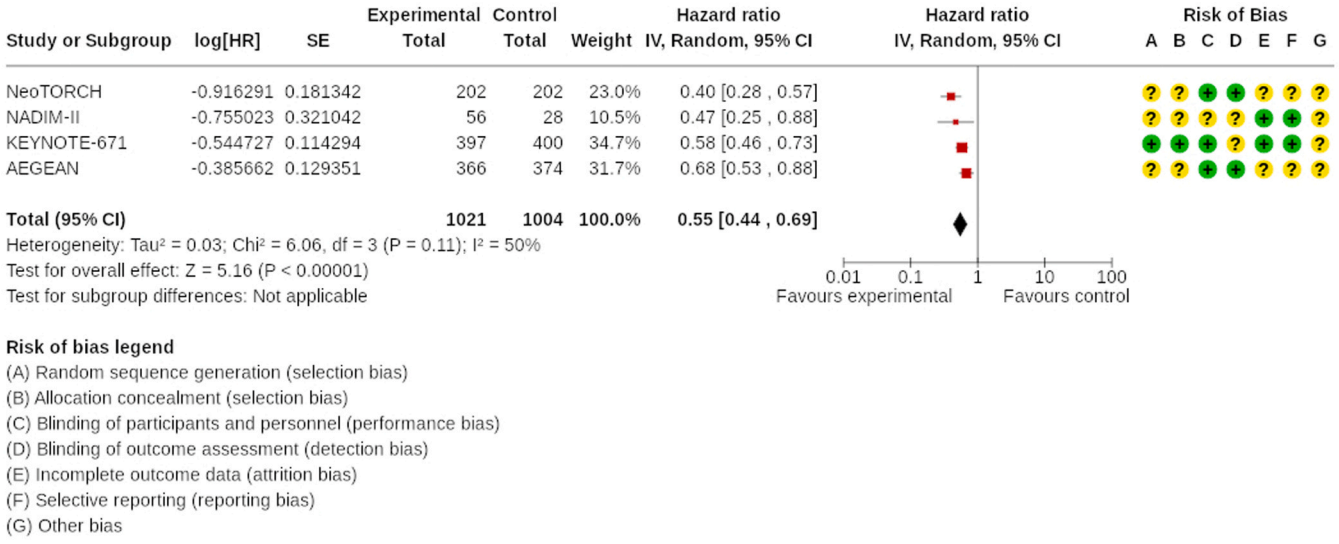

Fig. 4. Event-free survival in studies with administration of perioperative anti-PD(L)1 combined with platinum-based chemotherapy.

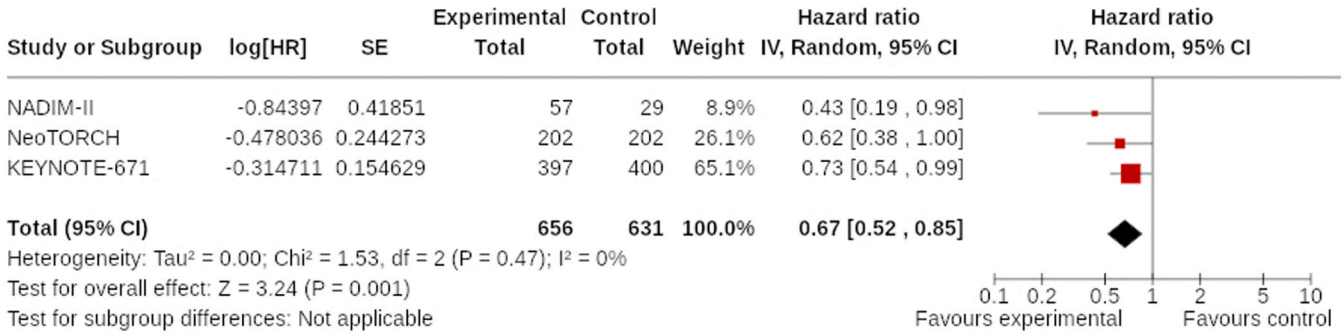

Fig. 5. Overall survival in studies with administration of perioperative anti-PD(L)1 combined with platinum-based chemotherapy.

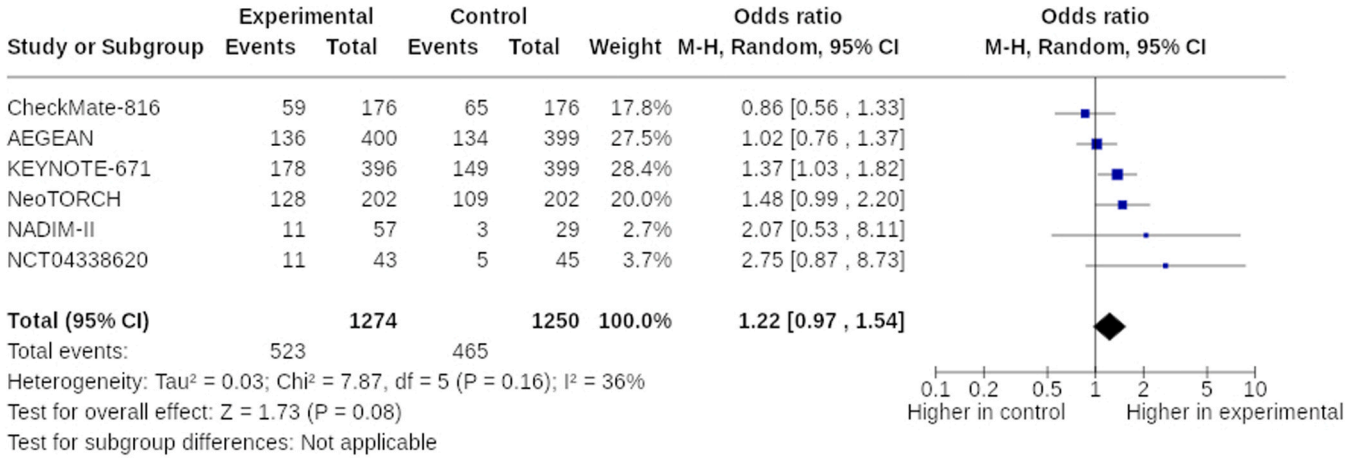

Fig. 6. Safety in all included studies: grade > = 3 treatment-related adverse events.

4. Discussion

Single-agent ICIs or a combination of chemotherapy and ICIs currently serve as the standard-of-care first-line treatments for patients with advanced NSCLC without actionable driver alterations (Gandhi et al., 2018; Paz-Ares et al., 2018). These approaches are also under investigation in resectable NSCLC.

Here, we present the results of a systematic review and meta-analysis of randomised clinical trials in resectable NSCLC. Our study compares perioperative or neoadjuvant anti-PD(L)1 therapy combined with platinum-based chemotherapy against neoadjuvant platinum-based chemotherapy alone. We found substantial evidence to support the use of perioperative or neoadjuvant anti-PD(L)1 combined with platinum-based chemotherapy in most patients. This is due to statistically significant and clinically relevant improvements in both surgical and survival outcomes. However, our analysis also raises numerous points for discussion.

The vast majority of patients evaluated in our analysis had clinical stage IIIA disease. Therefore, while it seems likely that chemo-immunotherapy improves outcomes also in resectable stage IIIB NSCLC, more evidence is needed in this highly heterogeneous subset of tumours. We found that patients who underwent neoadjuvant chemo-immunotherapy were more likely to proceed with surgical treatment compared to those who received neoadjuvant chemotherapy alone. Although we were unable to conduct a subgroup analysis focused on the receipt of surgery in patients with stage IIIB tumours due to missing data, we believe that, especially in tumours with more advanced stages and nodal involvement, it is critical to assess the impact of adding ICIs to neoadjuvant chemotherapy on the completion of planned surgery (Deng et al., 2022). While all the trials included in our analysis enrolled patients with resectable NSCLC at baseline, we currently lack clear evidence regarding the role of chemoimmunotherapy for borderline resectable disease—particularly in patients that are potentially eligible for concurrent chemoradiotherapy followed by consolidation immunotherapy (Bott et al., 2018; Spigel et al., 2022).

While patients with PD-L1 positive NSCLC were shown to have a larger EFS improvement, both patients with PD-L1 positive and PD-L1 negative tumours had improved outcomes with chemoimmunotherapy in our analysis (Mok et al., 2019; Reck et al., 2016). However, the conclusions stemming from the PD-L1 subgroup analyses are hampered by the heterogeneity in PD-L1 assessment among trials and by the missing PD-L1 status in a relatively small fraction of patients.

The histology-based subgroup analyses showed similar results among squamous and non-squamous NSCLC. However, 77 % of the patients enrolled in the NeoTORCH trial had squamous histology while all other included trials had lower rates. Therefore, it is likely that the results in squamous NSCLC are significantly affected by the NeoTORCH trial, which also had the largest overall improvement in EFS and whose results were only available for patients with stage III tumours. At last, EGFR and ALK-positive NSCLC were excluded by most of the trials included in our analyses, as ICIs are known to have low efficacy in patients with those actionable alterations in advanced NSCLC (Lee et al., 2017). Accordingly, we believe that perioperative chemo-immunotherapy is not a preferred choice for resectable, EGFR-mutated or ALK-positive NSCLC.

Multiple ongoing clinical trials are testing additional agents, different treatment schedules, and ICI-ICI combinations with chemotherapy. In our analysis, clinical outcomes were improved regardless of whether the anti-PD(L)1 treatment was administered in a perioperative or solely neoadjuvant fashion. Therefore, exploratory evidence suggests that adjuvant anti-PD(L)1 treatment could be omitted in selected patients who have experienced previous high-grade adverse events and show evidence of a pCR after surgery (Forde et al., 2022; Provencio et al., 2023; Wakelee et al., 2023). However, since the aim of our meta-analysis was not to compare these two treatment modalities, it remains unclear whether perioperative immunotherapy yields better clinical outcomes than neoadjuvant-only treatment.

In conclusion, adding anti-PD(L)1 agents to neoadjuvant platinum-based chemotherapy led to improved surgical outcomes, pCR rates, EFS, and OS in patients with resectable NSCLC. These findings support the routine use of this treatment approach in patients with resectable, stage II-IIIB NSCLC, excluding those with ALK and EGFR aberrations. Further confirmatory evidence is warranted for stage IIIB tumours and with higher maturity of the OS endpoint.

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Declaration of Competing Interest

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.critrevonc.2023.104190.

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