Lung Cancer 209 (2025) 108760

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Research Paper

Attrition with adjuvant, neoadjuvant, and perioperative immunotherapy-based treatment protocols in patients with resectable non-small-cell lung cancer. A meta-analysis of prospective trials

Francesco Guerrera [a,b,1], Filippo Tommaso Gallina [c,1,*], Eleonora Balzani [d,1], Francesca Ambrosi [e,f], Alessandro Di Federico [g,h], Eleonora Faccioli [i], Giorgio Facheris [j], Roberto Ferrara [k,l], Alessandra Ferro [m], Federica Filipello [n], Raffaele Giusti [o], Carlo Greco [p,q], Marco Mammana [i], Daniele Marinelli [r], Antonio Nuccio [k,l], Alessandra Pittaro [s], Matteo Sepulcri [t], Giuseppe Viscardi [u], Pietro Bertoglio [v]

[a] Department of Cardio-Thoracic and Vascular Surgery, Azienda Ospedaliera-Universitaria Città della Salute e della Scienza di Torino, Turin, Italy
[b] Department of Surgical Sciences, University of Torino, Torino, Italy
[c] Thoracic Surgery Unit, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) "Regina Elena" National Cancer Institute, Rome, Italy
[d] Centro Interdipartimentale di Scienze Mediche - CISMED, Università di Trento, Trento, Italy
[e] Pathology Unit, Maggiore Hospital-AUSL Bologna, Bologna, Italy
[f] Department of Experimental, Diagnostic and Specialty Medicine (DIMES), University of Bologna, Bologna, Italy
[g] Medical Oncology, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy
[h] Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy
[i] Thoracic Surgery Unit, Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padova, Padua, Italy
[j] Radiation Oncology Department, ASST Spedali Civili and University of Brescia, Brescia, Italy
[k] Medical Oncology, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) San Raffaele Scientific Institute, Milan, Italy
[l] Università Vita-Salute San Raffaele, Milan, Italy
[m] Division of Medical Oncology 2, Veneto Institute of Oncology (IOV) - Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Padova, Italy
[n] Pathology Department, ASLCN2 Alba e Bra, Michele e Pietro Ferrero Hospital, Verduno, Cuneo, Italy
[o] Medical Oncology Unit, Sant'Andrea Hospital, Rome, Italy
[p] Department of Medicine and Surgery, Università Campus Bio-Medico di Roma, Rome, Italy
[q] Radiation Oncology, Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy
[r] Department of Experimental Medicine, Sapienza University, Rome, Italy
[s] Department of Medical Sciences, Pathology Unit, Città della Salute e della Scienza Hospital, Turin, Italy
[t] Radiation Oncology Unit, Veneto Institute of Oncology (IOV) - Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Padua, Italy
[u] Department of Pneumology and Oncology, Monaldi Hospital, AORN Ospedali dei Colli, Naples, Italy
[v] Division of Thoracic Surgery, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

ARTICLE INFO

Keywords:
Non-small cell lung cancer
Immunotherapy
Chemotherapy
Adjuvant
Neoadjuvant
Perioperative
Compliance
Adherence

ABSTRACT

Background: The use of immunotherapy (IOT) in treating non-small-cell lung cancer (NSCLC) has revolutionized care standards. However, full compliance with neoadjuvant, perioperative, and adjuvant treatment protocols remains a challenge. This study aims to evaluate compliance rates with IOT-based protocols in neoadjuvant, adjuvant, and perioperative settings.

Methods: A systematic review and *meta*-analysis were conducted on prospective clinical trials involving preoperative, perioperative, and postoperative IOT protocols in resectable NSCLC up to December 2024. Primary outcomes included compliance with medical treatment (e.g., omission of therapy rate, incomplete therapy rate, and omission of surgery rate), surgical outcomes (R0 resection rate), and post-treatment severe adverse events (AEs).

Results: A total of 30 studies, with 10,493 patients, were included. In the neoadjuvant settings, 26 studies (16 neoadjuvant; 10 perioperative) investigated IOT alone or in combination with chemotherapy. Almost all patients

* Corresponding author.
E-mail address: filippogallina92@gmail.com (F.T. Gallina).
[1] These authors contributed equally.

https://doi.org/10.1016/j.lungcan.2025.108760
Received 20 August 2025; Received in revised form 12 September 2025; Accepted 17 September 2025
Available online 22 September 2025

received at least one therapy administration, while 11.3 % experienced incomplete cycles. Surgery was not performed in 16.1 % of cases, and an R0 resection was achieved in 80.5 % of patients. Grade ≥ 3 AEs were observed in 67.7 % of patients. In the adjuvant setting, 14 studies evaluated IOT (4 adjuvant; 10 perioperative). Complete omission of adjuvant therapy occurred in 9,6 % of patients, while 34,6 % required a discontinuation or cycle reduction. Grade ≥ 3 were AEs observed in 19.0 % of patients. Overall protocol compliance was superior in neoadjuvant protocols (effect size: 0.78 [IC 95 %: 0.70–0.85]) compared to adjuvant protocols (effect size: 0.61 [IC 95 %: 0.53–0.69]) and perioperative protocols (effect size: 0.49 [IC 95 %: 0.43–0.55]). However, perioperative protocols showed similar compliance and Grade ≥ 3 AE rates compared to preoperative and postoperative protocols.

Conclusions: Compliance with treatment protocols in NSCLC remains a critical factor, particularly for radical surgery candidates. This study represents a landmark effort in synthesizing comprehensive data on compliance with immunotherapy protocols in resectable NSCLC. Improving protocol compliance through tailored strategies and multidisciplinary coordination is essential to maximize the therapeutic potential of immunotherapy in resectable NSCLC and enhance patient outcomes.

1. Introduction

Immunotherapy (IO) has revolutionized the treatment of resectable non-small cell lung cancer (NSCLC), whether used alone or in combination with traditional chemotherapy. The incorporation of IO into treatment plans has dramatically reshaped the therapeutic landscape, introducing new approaches aimed at enhancing patient outcomes. However, selecting the best setting of immunotherapy application—whether preoperative (neoadjuvant), postoperative (adjuvant), or a mix of both (perioperative)—is a crucial decision in modern clinical practice. Each strategy presents its own benefits and challenges [1,2].

Neoadjuvant IO is administered prior to surgical intervention to reduce tumor burdens and potentially enhance resectability, leading to better surgical outcomes and lower recurrence rates. Moreover, Neoadjuvant IO may also prime the immune system to better target possible residual disease [3]. Nevertheless, the main disadvantage is the risk of delayed surgery due to potential immune-related adverse events and the variability in patient response rates [4].

In contrast, adjuvant IO is administered after surgical intervention to eradicate residual disease and reduce the probability of recurrence. This approach benefits from the previously removed tumor, potentially allowing for a more focused and less aggressive treatment regime. On the downside, this strategy may miss the opportunity to exploit the potential for an enhanced immune response generated by the initial presence of the tumor. Moreover, a potential decrease in patients' performance status after surgery could delay systemic therapy initiation [4].

On the other hand, perioperative IO aims to leverage the advantages of both strategies by administering IO before and after surgery. This method potentially maximizes tumor burden reduction and residual disease eradication, offering a comprehensive strategy for disease management. Nonetheless, it also poses challenges, such as increased risk of cumulative adverse effects and complex treatment logistics, potentially impacting adherence to treatment protocols [5,6].

In this context, attrition with IO treatment protocols is a crucial factor influencing outcomes. This *meta*-analysis aims to evaluate and compare protocol compliance among trials utilizing different IO regimens in resectable NSCLC, offering insights into which strategy may provide the most reliable and effective management.

2. Materials and methods

This systematic review and *meta*-analysis followed the steps outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [7]. We followed the PRISMA extension statement for reporting systematic reviews incorporating network *meta*-analyses of health care interventions: checklist and explanations [8]. The Cochrane Handbook for Systematic Reviews of Intervention was chosen as the methodological guidance [9].

2.1. Included studies

Included studies were prospective clinical trials of neoadjuvant, adjuvant, or perioperative anti-PD-(L)1 in patients with resectable NSCLC. Both single-arm and randomized controlled trials (RCTs) were included. Case series and retrospective studies were excluded.

2.2. Data extraction

Two authors extracted data (including terminations and refusals) and separately evaluated the potential for bias (F.G. and P.B.).

2.3. Search strategy and selection processes

We performed an electronic search of PubMed (via the National Library of Medicine), EMBASE, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science from the database inception to January 2025.

Language restrictions were not imposed. Updated reports of eligible studies were added after manual screening, if available.

In this review, two reviewers (F.G. and P.B.) independently identified and assessed studies to determine their eligibility, and a third reviewer (E.B.) settled any disagreements that arose.

2.4. Outcomes

The primary outcomes were related to attrition with medical treatment and included omission of therapy rate, incomplete therapy rate, omission of surgery rate, and R0 resection rate. The pre-specified secondary outcomes were post-treatment severe adverse events (AEs).

2.5. Statistical analysis

Proportional *meta*-analysis was undertaken with the statistical software STATA 18.0 (Stata Corp, US). All *meta*-analyses used the Freeman–Tukey double-arcsine transformation model and presented a point estimate with 95 % confidence intervals. The Cochran Q test was performed to test for heterogeneity, and the I^2 test was carried out to test for inconsistency. Meta-analysis was carried out for both primary and secondary objectives, where sufficient data could be extracted from the primary studies.

3. Results

The PRISMA flow diagram presents the search results (Fig. 1). Initial screening identified 2908 studies. Of these, 238 search results were excluded during the preliminary screening because they were duplicates, and 2566 were excluded because they were unrelated to the topic. The full texts were retrieved from the remaining 67 articles, and 26 more reports were excluded according to our inclusion and exclusion criteria.

A total of 31 studies (41 reports) were included in the quantitative analysis [10–49] Table 1 summarises the pooled characteristics of the included studies.

In total, 17 of the included studies investigated IO alone or in combination with chemotherapy in a neoadjuvant setting, 4 in an adjuvant setting, and 10 in a perioperative setting. A total of 5425 patients were enrolled in the IO arms of the included trials: 958 (18 %) patients in the neoadjuvant group, 2734 (50 %) in the adjuvant group, and the remaining (1733–32 %) in the perioperative group.

3.1. Omission or treatment discontinuation/reduction and adverse events (AEs)

3.1.1. Preoperative setting

In the preoperative settings, which included 27 studies (17 neoadjuvant; 10 perioperative), only a small proportion of patients did not receive any drug administration (0.6 %) (Overall Event Proportion −EP-0.00 [IC 95 %: 0.00–0.00]), while 11.3 % experienced incomplete cycles (Overall EP 0.06 [IC 95 %: 0.03–0.09]) (EP neoadjuvant 0.05 [IC 95 %: 0.02–0.10]; EP perioperative 0.07 [IC 95 %: 0.03–0.13], P = 0.72) (Fig. 2a). Grade 3–4 AEs were observed in 23.5 % of patients (Overall EP 0.17 [IC 95 %: 0.11–0.24]) (EP neoadjuvant 0.14 [IC 95 %: 0.07–0.22]; EP perioperative 0.23 [IC 95 %: 0.12–0.24], P = 0.20) (Fig. 2b), while toxicity-related mortality during the neoadjuvant period was 0.6 %. Incomplete treatment was related to treatment toxicity in 6.3 % of the cases.

3.1.2. Adjuvant setting

In the adjuvant setting, which included 14 studies (4 adjuvant; 10 perioperative), complete omission of adjuvant therapy occurred in 9.6 % of patients (0.1 % adjuvant; 29.9 % perioperative) (Overall EP 0.12 [IC 95 %: 0.04–0.02]) (EP adjuvant 0.01 [IC 95 %: 0.00–0.02]; EP perioperative 0.22 [IC 95 %: 0.10–0.36]; P < 0.01) (Fig. 3a), while 34.6 % required a discontinuation or cycle reduction (38.6 % adjuvant; 25.2 %

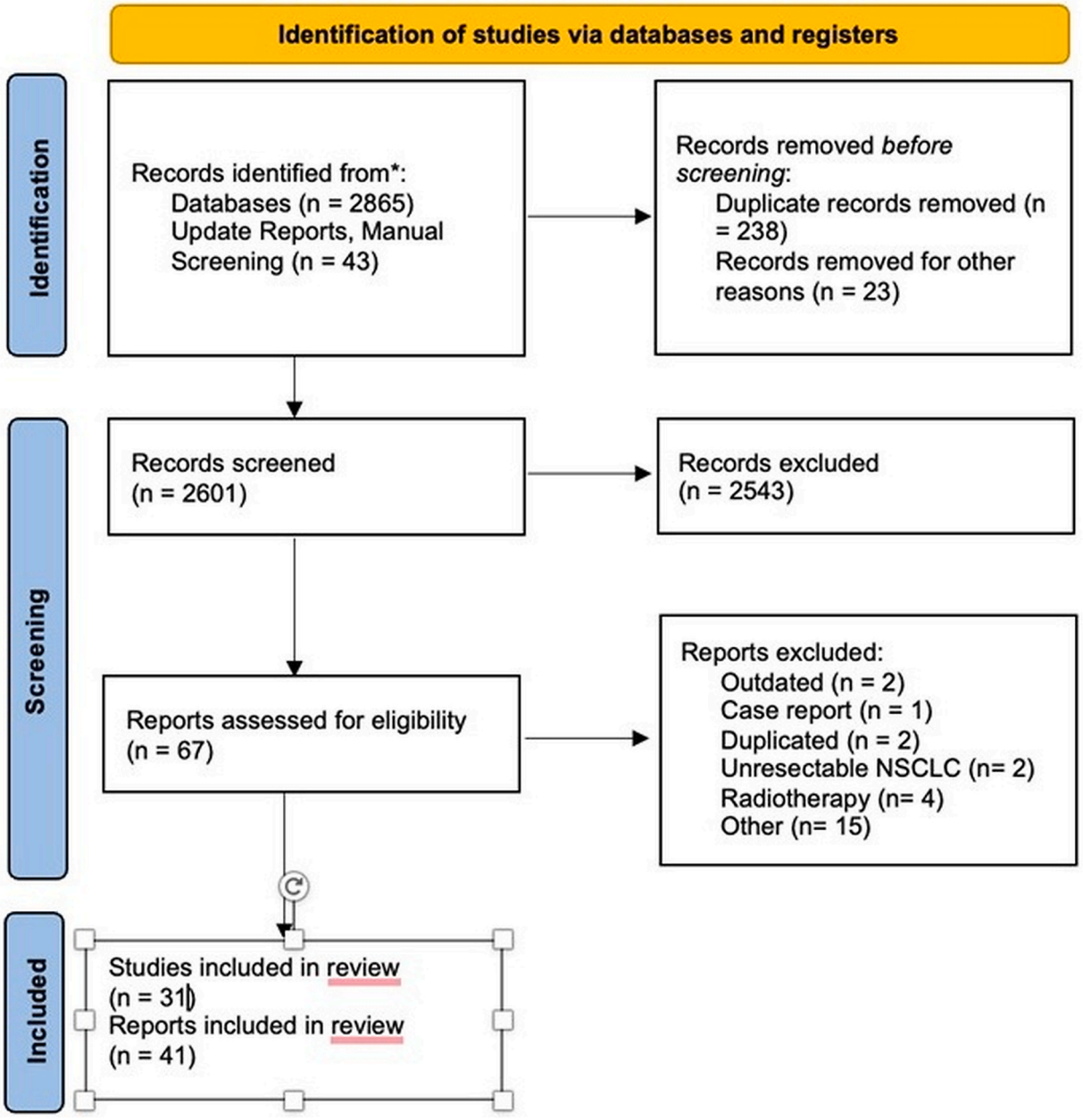

Fig. 1. PRISMA flow diagram. The diagram illustrates the study selection process and provides reasons for excluding records during the screening. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1
Characteristics of the included studies.

Protocol Name	Trial Number	Year Start Recruitment	Phase	Enrollement Completion	Setting (Single – Multicenter)	Single Nation – Multination	Design	Stage (to double check edition)	TNM edition	EGFR/ ALK included	Experimental Drug	REF
IMpower010	NCT02486718	2015	3	Completed	Multicenter	Multination	Adjuvant only	IB (>4 cm)-IIIA	7th edition	Yes	Atezolizumab	https://doi.org/10.1016/S0140-6736(21)02098-5
PEARLS/KEYNOTE-091	NCT02504372	2016	3	Completed	Multicenter	Multination	Adjuvant only	IB (>4 cm)-IIIA	7th edition	Yes	Pembrolizumab	https://doi.org/10.1016/S1470-2045(22)00518-6
CANOPY A	NCT03447769	2018	3	Completed	Multicenter	Multination	Adjuvant only	II-IIIB (T > 5c m N2)	8th edition	Yes	Canakinumab	https://doi.org/10.1200/JCO.23.00910
BR.31	NCT02273375	2015	3	Completed	Multicenter	Multination	Adjuvant only	IB (>4 cm)-IIIA	7th edition	Yes	Durvalumab	-
Checkmate 159	NCT02259621	2015	2	Completed	Multicenter	Single Nation (US)	Neoadjuvant only	I-IIIA	7th edition	No	Nivolumab	10.1056/NEJMoa1716078
LCMC3	NCT02927301	2017	2	Completed	Multicenter	Single Nation (US)	Neoadjuvant only	IB-IIIB (no T4, no N3)	8th edition	No	Atezolizumab	10.1016/j.jtcvs.2022.10.007
neoSCORE	NCT04459611	2020	2	Completed	Single-center	Single Nation	Neoadjuvant only	IB-IIIA	8th edition	No	Sintilimab	10.1038/s41392-023-01355-1
ChiCTR-OIC-17013726	ChiCTR-OIC-17013726	2018	1b	Completed	Single-center	Single Nation	Neoadjuvant only	IA–IIIB (>2 cm)	8th edition	EGFR excluded	Sintilimab	10.1016/j.jtho.2020.01.017
NEOSTAR (Arm A –B)	NCT03158129	2017	2	Completed	Single-center	Single Nation	Neoadjuvant only	IA-IIIA (N2 single station)	7th edition	Yes	Nivolumab	10.1016/j.jtcvs.2022.01.019 - 10.1038/s41591-020-01224-2
NEOSTAR (Arm C –D)	NCT03158129	2018	2	Completed	Single-center	Single Nation	Neoadjuvant only	IB (> 4 cm)-IIIA (N2 single station)	7th edition	Yes	Nivolumab	10.1016/j.jtcvs.2023.09.073 - 10.1038/s41591-022-02189-0
NCT02716038	NCT02716038	2016	2	Completed	Multicenter	Single Nation (US)	Neoadjuvant only	IB–IIIA	7th edition	Yes	Atezolizumab	10.1016/S1470-2045(20)30140-6
NEOMUN-trial	NCT03197467	2018	2	Completed	Single-center	Single Nation (XX)	Neoadjuvant only	II-IIIA (N+)	7th edition	Yes	Pembrolizumab	10.1016/j.lungcan.2021.01.018
IoNESCO	IFCT-1601 -NCT03030131	2017	2	Completed	Multicenter	Single Nation (France)	Neoadjuvant only	IB(> 4 cm)-IIIA(not N2)	8th edition	Yes	Durvalumab	10.1136/jitc-2022-005636
Checkmate 816	NCT02998528	2017	3	Completed	Multicenter	Multination	Neoadjuvant only	IB (4 cm)-IIIA	7th edition	No	Nivolumab	10.1056/NEJMoa2202170
NeoCOAST	NCT03794544	2019	2	Completed	Multicenter	Multination	Neoadjuvant only	IA3–IIIA	8th edition	Yes	Durvalumab	10.1158/2159-8290.CD-23-0436
TD-FOREKNOW	NCT04338620	2020	2	Completed	Multicenter	Single Nation (CHN)	Neoadjuvant only	IIIA-IIIB (T3N2 only)	8th edition	No	Camrelizumab	10.1001/jamaoncol.2023.2751
NCT04304248	NCT04304248	2019	2	Completed	Single-center	Single Nation (XX)	Neoadjuvant only	IIIA-IIIB (T3-T4N2 only)	8th edition	No	Toripalimab	10.1080/2162402X.2021.1996000
TOP1201	NCT01820754	2013	2	Completed	Single-center	Single Nation (XX)	Neoadjuvant only	IB-IIIA	7th edition	Yes	Ipilimumab	10.1016/j.athoracsur.2017.09.030
Lung-Mate001	ChiCTR1900023758	2019	2	Completed	Single-center	Single Nation (XX)	Neoadjuvant only	IB to IIIA	8th edition	No	Sintilimab	10.1016/j.athoracsur.2022.01.039
Neo-Pre-IC	NCT04326153	2020	2	Completed	Single-center	Single Nation (XX)	Neoadjuvant only	IIIA-IIIB	8th edition	No	Sintilimab	10.1016/j.eclinm.2024.102422
PRINCEPS	NCT0299457	2016	2	Completed	Single-center	Single Nation (XX)	Neoadjuvant only	IA(>2 cm)-IIIA	7th edition	Yes	Atezolizumab	https://www.esmo.org/oncology-news/neoadjuvant-atezolizumab-is-safe-in-resectable-nsclc

(*continued on next page*)

Table 1 (*continued*)

Protocol Name	Trial Number	Year Start Recruitment	Phase	Enrollement Completion	Setting (Single — Multicenter)	Single Nation — Multination	Design	Stage (to double check edition)	TNM edition	EGFR/ ALK included	Experimental Drug	REF
NADIM	NCT03081689	2017	2	Completed	Multicenter	Single Nation (ES)	Perioperative	IIIA	7th edition	No	Nivolumab	10.1016/S1470-2045(20) 30453-8 -10.1093/ejcts/ ezab007
NADIM II	NCT03838159	2019	2	Completed	Multicenter	Single Nation (ES)	Perioperative	IIIA–IIIB (N3 excluded)	8th edition	No	Nivolumab	10.1056/NEJMoa2215530
SAKK 16/14	NCT02572843	2016	2	Completed	Multicenter	Single Nation (CHE)	Perioperative	IIIA (N2)	7th edition	Yes	Durvalumab	10.1200/JCO.21.00276
AEGEAN	NCT03800134	2019	3	Completed	Multicenter	Multination	Perioperative	IIA–IIIB (N2)	8th edition	No	Durvalumab	10.1056/NEJMoa2304875
KEYNOTE 671	NCT03425643	2018	3	Completed	Multicenter	Multination	Perioperative	IIA–IIIB (N2)	8th edition	Yes	Pembrolizumab	10.1056/NEJMoa2302983
ChiCTR2000033588	ChiCTR2000033588	2020	2	Completed	Single-center	Single Nation (XX)	Perioperative	IIA-IIIB (T3N2 only)	8th edition	No	Camrelizumab	10.1016/j.jtho.2023.02.019
Neotorch	NCT04158440	2020	3	Completed	Multicenter	Single Nation (CHN)	Perioperative	II-IIIB (N2 only) (interim analysis of stage III only)	8th edition	Yes	Toripalimab	10.1001/jama.2023.24735
TOP1501	NCT02818920	2017	2	Completed	Multicenter	Single Nation (US)	Perioperative	IB-IIIA	7th edition	Yes	Pembrolizumab	10.1016/j. jtcvs.2021.02.099
Checkmate 77T	NCT04025879	2019	3	Completed	Multicenter	Multination	Perioperative	IIA(>4 cm)-IIIB (N2 only)	8th edition	No	Nivolumab	10.1056/NEJMoa2311926
Rationale-315	NCT04379635	2020	3	Completed	Multicenter	Single Nation (CHN)	Perioperative	II-IIIA	8th edition	No	Tislelizumab	10.1016/j. annonc.2023.10.054

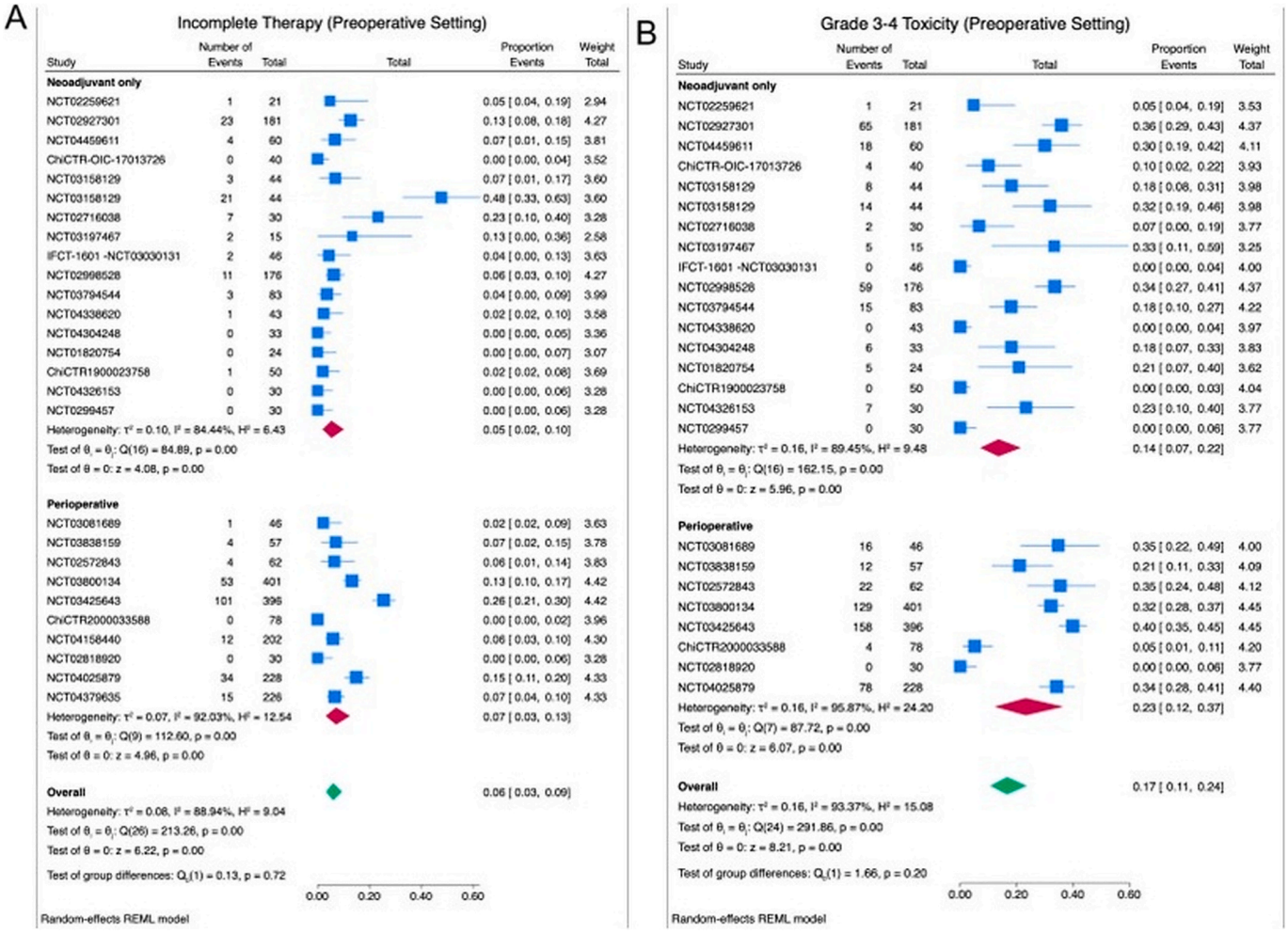

Fig. 2. (a) Omission or treatment discontinuation in preoperative setting; (b) grade 3–4 treatment toxicity in preoperative setting.

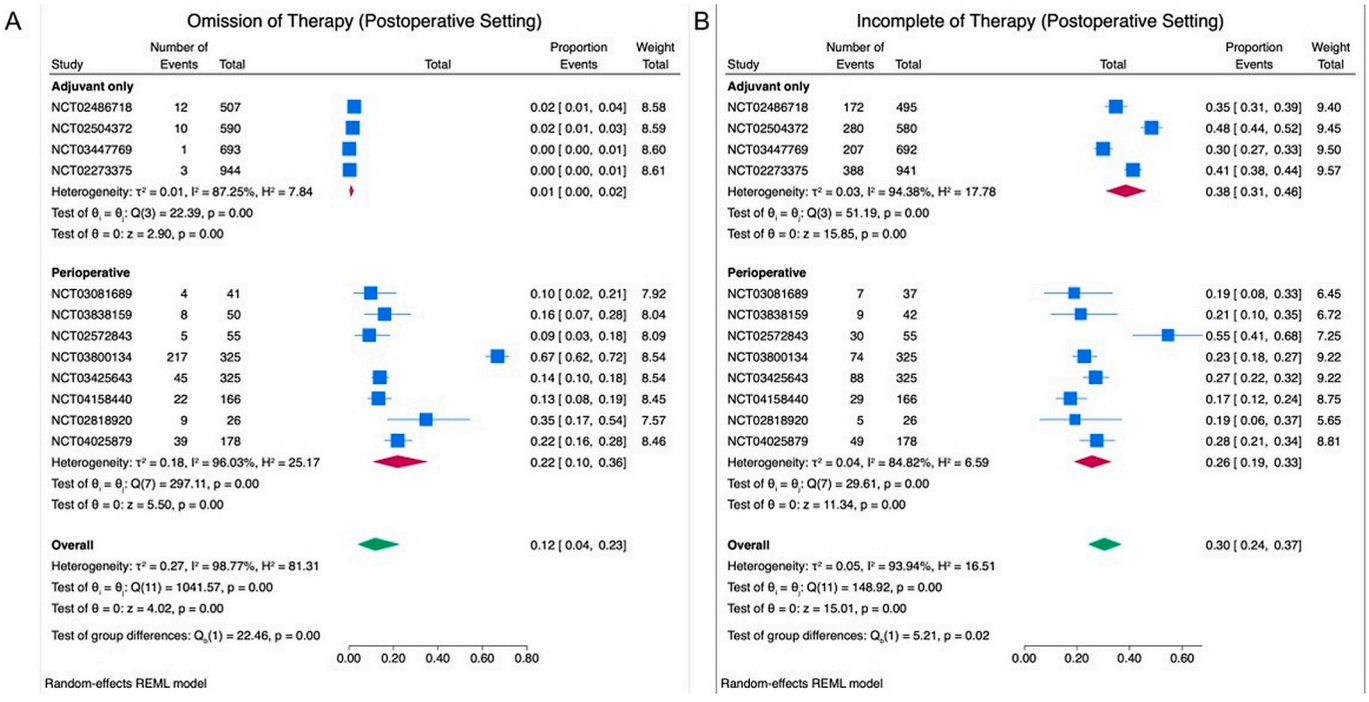

Fig. 3. (a) Treatment omission in the adjuvant setting; (b) Treatment discontinuation in the adjuvant setting;

perioperative) (Overall EP 0.30 [IC 95 %: 0.24–0.37]) (EP adjuvant 0.38 [IC 95 %: 0.31–0.46]; EP perioperative 0.26 [IC 95 %: 0.19–0.33]; P = 0.02) (Fig. 3b). Grade 3–4 AEs were observed in 21.5 % of patients (25.3 % adjuvant; 12.7 % perioperative) (Overall EP 0.17 [IC 95 %: 0.10—0.25]) (EP adjuvant 0.24 [IC 95 %: 0.19–0.30]; EP perioperative 0.13 [IC 95 %: 0.05–0.24]; P = 0.08) (Fig. S1) while toxicity-related mortality during the adjuvant period was 0.8 % (1.1 % adjuvant; 0 % perioperative) (EP adjuvant 0.01 [IC 95 %: 0.01–0.02]; EP perioperative 0.00 [IC 95 %: 0.00–0.00]). In the perioperative setting, the omission of adjuvant therapy was related to postoperative complications in 6,4% of the cases, preoperative treatment toxicity in 1.7 %, progression in 1.6 %, and patient decision in 2.6 %. Incomplete treatment was related to treatment toxicity in 13.1 % of the cases (14.2 % adjuvant; 9.6 % perioperative), progression in 13.9 % (15.3 % adjuvant; 10.1 % perioperative), and patient decision in 5.3 % (6.1 % adjuvant; 2.5 % perioperative).

3.2. Omission of surgery and R0 resection

Considering neoadjuvant and perioperative trials, surgery was not performed in 16.3 % (Overall EP 0.13 [IC 95 %: 0.10–0.17]) of cases (EP neoadjuvant 0.11 [IC 95 %: 0.07–0.17]; EP perioperative 0.18 [IC 95 %: 0.16–0.19], P = 0.07), while 12.3 % of the patients experienced delays in programmed surgery (Fig. 4a). When specified, the reasons for planned surgery omission were patients' decisions in 3.5 % of the cases, surgeon decisions in 2.4 %, treatment toxicity in 2.6 %, and disease progression in 4.7 %.

An R0 resection was achieved in 91.3 % of operated patients (Overall EP 0.96 [IC 95 %: 0.93–0.98]) (Fig. 4b) (EP neoadjuvant 0.97 [IC 95 %: 0.94–0.99]; EP perioperative 0.94 [IC 95 %: 0.89–0.97], P = 0.37), while a macroscopic incomplete resection was documented in 2.6 % of the cases (Overall EP 0.01 [IC 95 %: 0.01–0.02]) (EP neoadjuvant 0.01 [IC 95 %: 0.00–0.03]; EP perioperative 0.01 [IC 95 %: 0.89–0.97], P = 0.56). (Fig. S2) An intraoperative death was observed in 0.1 % of the operated patients.

3.3. Protocol compliance

Scheduled treatment compliance (Overall EP 0.79 [95 % CI: 0.70–0.87]) was superior in neoadjuvant protocols (EP 0.93 [95 % CI: 0.88–0.97]) compared to perioperative protocols (EP 0.49 [95 % CI: 0.43–0.55], P < 0.01) (Fig. 5a).

Similarly, when considering overall protocol compliance (i.e., scheduled treatment accomplishment and R0 resection), neoadjuvant protocols outperformed perioperative ones (EP 0.78 [95 % CI: 0.70–0.85] vs. EP 0.49 [95 % CI: 0.43–0.55], P < 0.01) (Fig. 5b).

Within perioperative protocols, compliance in the preoperative phase was similar to neoadjuvant strategies (EP 0.77 [95 % CI: 0.72–0.82], P = 0.94), while compliance in the postoperative phase mirrored that of adjuvant-only strategies (EP 0.60 [95 % CI: 0.53–0.66], P = 0.78).

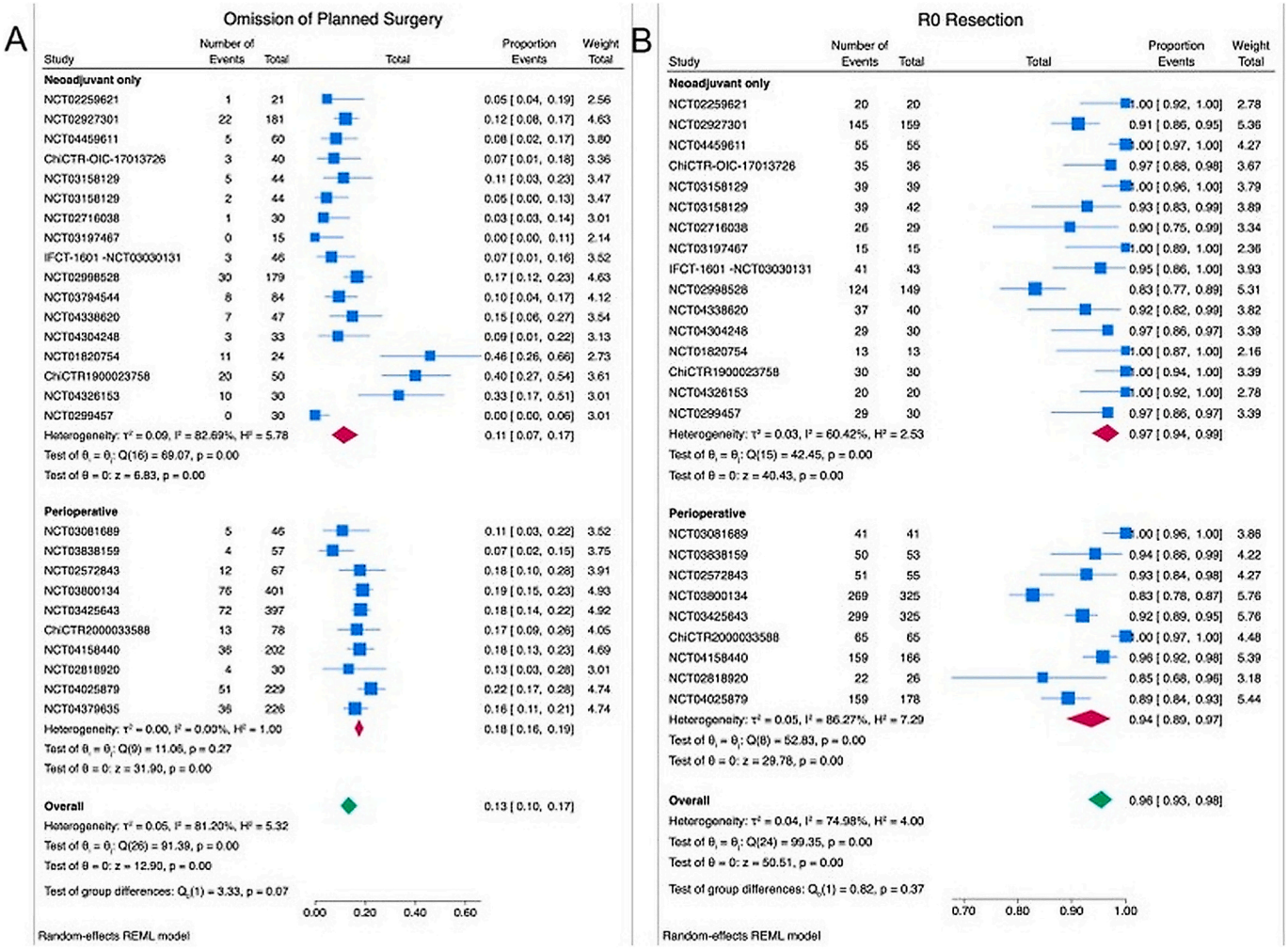

Fig. 4. (a) Omission of surgery in neoadjuvant and perioperative setting; (b) R0 resection in neoadjuvant and perioperative setting;

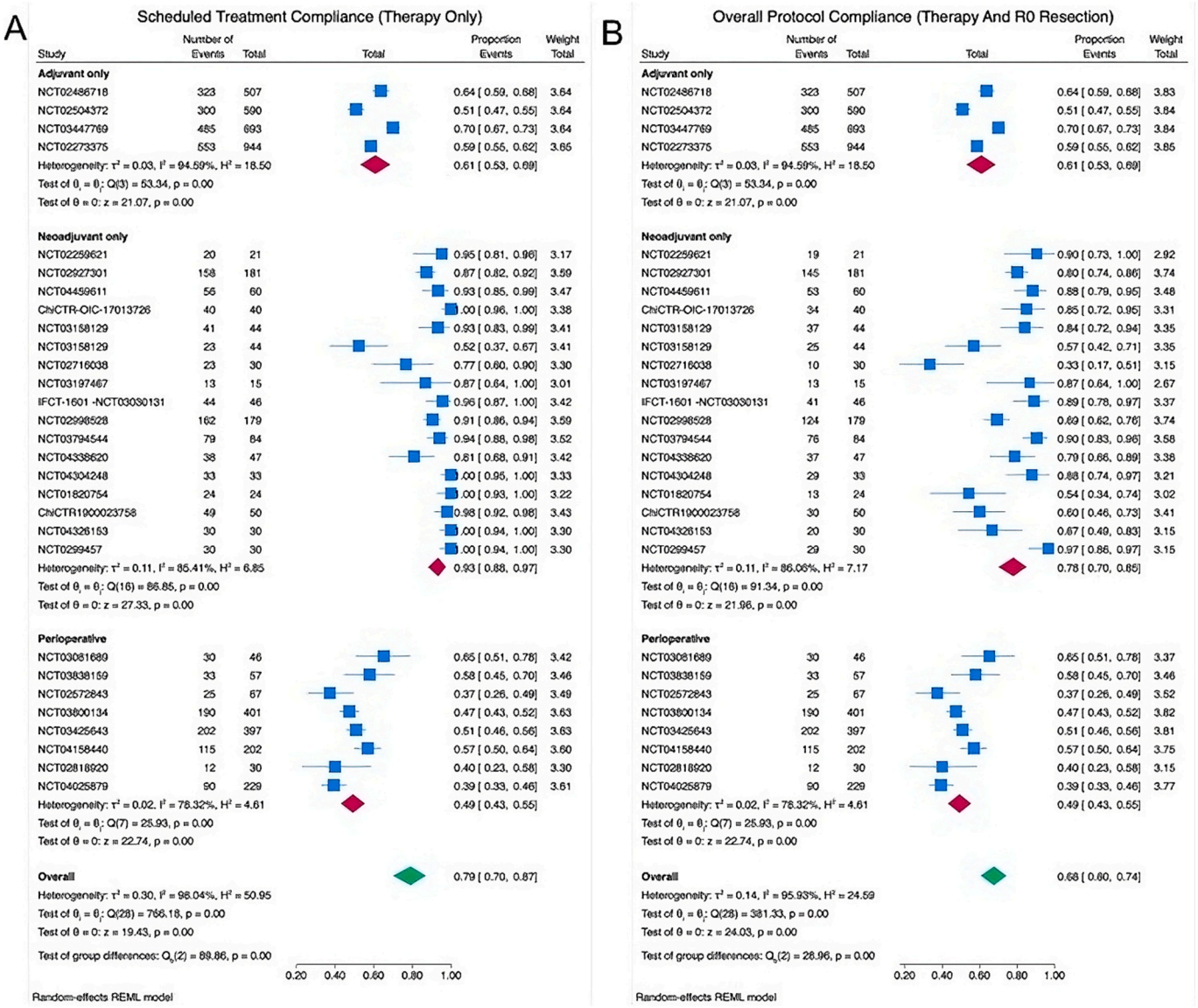

Fig. 5. (a) Scheduled treatment compliance in all study; (b) Overall protocol compliance including treatment and R0 resection in all study;

4. Discussion

The introduction of immune checkpoint inhibitors (ICIs) has reshaped the resectable non-small cell lung cancer (NSCLC) treatment landscape. Landmark trials (e.g., CheckMate 816, KEYNOTE-671, AEGEAN, IMpower010) have demonstrated the efficacy of neoadjuvant, adjuvant, and perioperative immunotherapy, leading to its integration into clinical practice. However, adherence to immunotherapy (IO) protocols remains a key challenge, influenced by toxicity, logistical factors, and patient selection. [50–52].

Attrition to immunotherapy (IO) protocols in patients with resectable NSCLC is globally good, but there remains significant room for improvement. This *meta*-analysis—the first to comprehensively assess compliance across neoadjuvant, adjuvant, and perioperative IO-based strategies—sheds light on the real-world applicability of these treatments and offers valuable insights into their critical points of failure and success. [53].

Our analysis highlights several significant insights and contrasts:

1. Neoadjuvant protocols have the highest adherence, with fewer treatment omissions and better completion rates than other strategies. However, this advantage fades when overall protocol compliance (including surgery and resection completeness) is considered.
2. Postoperative therapies face significant attrition, with a substantial proportion of patients failing to initiate IO after surgery, particularly when preceded by chemotherapy. The reasons for treatment omission or discontinuation are primarily attributable to postoperative complications and toxicity but also to patient-related factors, highlighting areas for clinical and organizational improvement.
3. Even if perioperative protocols exhibit the lowest compliance, they do not intrinsically result in lower adherence when their preoperative and postoperative phases are analyzed separately. Similarly, toxicity incidence results are reasonably similar. This indicates that their logistical demands, more than their tolerability, account for the observed lower global compliance.

The preoperative setting demonstrates excellent tolerability. Nearly all patients initiated treatment, and incomplete cycles occurred in a minority of cases. Interestingly, toxicity was responsible for only approximately half of the incomplete treatments (6 %), with the remaining cases linked to less well-defined factors—potentially

organizational, clinical, or motivational—that are rarely addressed in published studies. This points to an important area for intervention: optimizing pathway organization and patient engagement before surgery. In this regard, emerging data support the integration of neoadjuvant prehabilitation as a means to enhance patient readiness and maintain adherence throughout the treatment continuum. As shown by Schmid et al., structured prehabilitation during neoadjuvant therapy can mitigate functional decline, foster patient empowerment, and ultimately contribute to improved completion rates and surgical readiness in patients with locally advanced NSCLC [54].

Despite the high treatment completion rates, 16.3 % of patients did not undergo surgery. In nearly half of these cases, the omission was due to patient (3.5 %) or surgeon (2.4 %) decisions more than progression or toxicity. This suggests that the actual bottleneck in the neoadjuvant setting may be in the transition to surgery, not in the therapy itself. These data emphasize the need for better pre-treatment selection, shared decision-making, and possibly more flexible protocols that accommodate re-evaluation after induction [55].

On a positive note, the oncological outcomes are excellent when surgery is performed. The weighted *meta*-analysis showed an R0 proportion rate 0.96, and intraoperative mortality was negligible. These results confirm that surgery after IO is not only feasible but offers a high likelihood of radical resection, supporting the integration of neoadjuvant IO into standard pathways—provided the patient is appropriately selected.

Compliance is significantly more challenging in the postoperative setting. Almost 10 % of patients failed to initiate postoperative IO, and over a third discontinued or reduced treatment. The primary causes were toxicity and postoperative complications, but patient decisions also accounted for a non-negligible proportion of omissions. In perioperative protocols specifically, patient refusal was responsible for 2.6 % of omissions and 2.5 % of incomplete treatments, while in the adjuvant-only setting, these figures were 6.1 % and 5.3 %, respectively. These results suggest that postoperative vulnerability—whether clinical, psychological, or logistical—is a central factor limiting compliance [56,57]. They also underscore the fact that perioperative regimens may benefit from more rigorous patient selection, especially as these patients appear more likely to maintain postoperative adherence compared to those receiving adjuvant IO alone. This is supported by our finding of a statistically significant lower rate of incomplete therapies in perioperative vs. adjuvant protocols, possibly reflecting more selective inclusion criteria and better preparation in the perioperative cohort.

Besides, when analyzing adherence to medical therapy alone, as expected, neoadjuvant protocols showed the highest compliance, followed by adjuvant and perioperative regimens. However, this apparent hierarchy disappears when perioperative regimens are dissected into their pre- and postoperative phases. We observed that, consequently, the preoperative adherence of perioperative protocols aligns closely with neoadjuvant trials, and the postoperative adherence mirrors that of adjuvant-only strategies. This finding highlights a critical point: the lower global compliance observed in perioperative regimens is more likely a result of protocol complexity than inherent intolerance. It also suggests that perioperative IO could be delivered as reliably as the other strategies with adequate clinical and logistical support [58,59].

Finally, when adopting a broader definition of adherence—including completion of systemic therapy and achievement of R0 resection—the advantage of neoadjuvant protocols becomes less evident. While adherence to IO is excellent, the fact that a subset of patients fails to proceed to surgery inevitably lowers the overall compliance to the whole therapeutic pathway. This phenomenon underscores an important message: complete therapy administration is not enough if it is not followed by surgical resection, which remains the cornerstone of curative treatment in resectable NSCLC. Thus, optimizing pre-treatment staging, minimizing the delay between restaging and surgery, and improving patient commitment are crucial elements for real-world success. In this context, recent evidence highlights the growing role of multimodal prehabilitation in enhancing patients' functional status and resilience ahead of surgery. These structured interventions have been shown to improve postoperative outcomes and may contribute to reducing therapy attrition by increasing the likelihood of patients reaching surgery in optimal condition [60,61].

In light of these findings, several practical strategies can be implemented to optimize outcomes and minimize treatment attrition. First, rigorous pre-treatment selection that accounts for objective measures of fitness, tumor biology, and patient preferences is essential to reduce the risk of therapy dropout or surgical omission. Moreover, the adoption of structured perioperative care pathways, including enhanced recovery after surgery (ERAS) protocols, may improve postoperative recovery, thereby increasing eligibility for adjuvant immunotherapy and reducing discontinuation due to complications. An integrated multidisciplinary approach should consistently guide therapeutic decisions, allowing teams to anticipate compliance challenges and adapt treatment protocols proactively. Finally, improved communication and patient education—especially when managing complex perioperative regimens—can foster greater patient engagement and reduce voluntary discontinuation of therapy.

5. Conclusions

Compliance with treatment protocols in NSCLC remains a critical factor, particularly for radical surgery candidates. This study represents a landmark effort in synthesizing comprehensive data on compliance with immunotherapy protocols in resectable NSCLC. This *meta*-analysis confirms that IO-based protocols in resectable NSCLC are generally well tolerated and feasible. Still, their real-world application is affected by a combination of clinical, surgical, and patient-related factors. Neoadjuvant strategies are associated with high treatment adherence and excellent surgical outcomes, yet may be limited by non-negligible dropout before surgery. Adjuvant and perioperative protocols face more significant challenges in completion, particularly postoperatively, due to toxicity and postoperative vulnerability. However, the low mortality and high R0 rates across settings are reassuring and provide a strong rationale to continue pursuing IO in multimodal strategies. Ultimately, refining patient selection and streamlining treatment pathways will be key to translating the promise of perioperative immunotherapy into a widespread and consistent benefit.

Funding

The work reported in this publication was funded by the Italian Ministry of Health, RC-n. project -2025-2797270.

CRediT authorship contribution statement

Francesco Guerrera: Writing – original draft, Methodology, Conceptualization. **Filippo Tommaso Gallina:** Writing – original draft, Methodology, Conceptualization. **Eleonora Balzani:** Methodology, Formal analysis, Data curation. **Francesca Ambrosi:** Visualization, Validation, Supervision. **Alessandro Di Federico:** Validation, Investigation, Conceptualization. **Eleonora Faccioli:** Visualization, Supervision, Methodology. **Giorgio Facheris:** Visualization, Validation, Investigation. **Roberto Ferrara:** Visualization, Validation, Supervision. **Alessandra Ferro:** Validation, Resources, Project administration. **Federica Filipello:** Visualization, Validation, Supervision. **Raffaele Giusti:** Visualization, Validation, Supervision. **Carlo Greco:** Resources, Methodology, Investigation. **Marco Mammana:** Validation, Supervision, Conceptualization. **Daniele Marinelli:** Supervision, Software, Conceptualization. **Antonio Nuccio:** Resources, Methodology, Investigation. **Alessandra Pittaro:** Visualization, Validation, Supervision. **Matteo Sepulcri:** Visualization, Resources, Investigation. **Giuseppe Viscardi:** Visualization, Validation, Supervision. **Pietro Bertoglio:** Writing – original draft, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2025.108760.

References

[1] M. Sorin, C. Prosty, L. Ghaleb, K. Nie, K. Katergi, M.H. Shahzad, L.R. Dubé, A. Atallah, A. Swaby, M. Dankner, T. Crump, L.A. Walsh, P.O. Fiset, B. Sepesi, P. M. Forde, T. Cascone, M. Provencio, J.D. Spicer, Neoadjuvant chemoimmunotherapy for NSCLC: a systematic review and meta-analysis, JAMA Oncol. 10 (5) (2024 May 1) 621–633.

[2] A. Vaccaro, Z. Rahal, H. Kadara, T. Cascone, A roadmap to precision immunotherapy for early-stage non-small cell lung cancer, Cancer Discov. 15 (5) (2025 May 2) 884–889.

[3] E.A. Mittendorf, F. Burgers, J. Haanen, T. Cascone, neoadjuvant immunotherapy: leveraging the immune system to treat early-stage disease, Am. Soc. Clin. Oncol. Educ. Book 42 (2022 Apr) 1–15.

[4] E.G. Dunne, C.N. Fick, J.M. Isbell, J.E. Chaft, N. Altorki, B.J. Park, J. Spicer, P. M. Forde, D. Gomez, P. Iyengar, D.H. Harpole Jr, T.E. Stinchcombe, M. Liberman, M.J. Bott, P.S. Adusumilli, J. Huang, G. Rocco, D.R. Jones, The emerging role of immunotherapy in resectable non-small cell lung cancer, Ann. Thorac. Surg. 118 (1) (2024 Jul) 119–129.

[5] P.M. Forde, J. Spicer, S. Lu, M. Provencio, T. Mitsudomi, M.M. Awad, E. Felip, S. R. Broderick, J.R. Brahmer, S.J. Swanson, T. Kato, J. Lee, H. Borghaei, N.K. Altorki, M. Gettman, A. Nicholas, R.S. Heist, M. Yilmaz, J.C. Yang, J. Vansteenkiste, F. De Marinis, N. Girard, H.J. Mann, C.T. Harbison, V. Velcheti, S.J. Antonia, Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer, N. Engl. J. Med. 386 (21) (2022 May 26) 1973–1985.

[6] M. Provencio, E. Nadal, A. Insa, R. García-Campelo, J. Casal Rubio, M. Dómine, M. Majem, D. Rodríguez-Abreu, A. Martínez-Martí, V. Calvo, J.A. Rodríguez-Portal, M. Cobo, G. López-Vivanco, Y. Garcia, A. Artal, E. Carcereny, J. De Castro, E. Castañón, P. Lianes, M. Lázaro, D. Isla, L. Paz-Ares, Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM II): an open-label, multicentre, randomised, phase 2 trial, Lancet Respir. Med. 12 (3) (2024 Mar) 251–264.

[7] M.J. Page, J.E. McKenzie, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, C.D. Mulrow, L. Shamseer, J.M. Tetzlaff, E.A. Akl, S.E. Brennan, R. Chou, J. Glanville, J. M. Grimshaw, A. Hróbjartsson, M.M. Lalu, T. Li, E.W. Loder, E. Mayo-Wilson, S. McDonald, L.A. McGuinness, L.A. Stewart, J. Thomas, A.C. Tricco, V.A. Welch, P. Whiting, D. Moher, The PRISMA 2020 statement: an updated guideline for reporting systematic reviews, BMJ 29 (372) (2021 Mar) n71.

[8] B. Hutton, G. Salanti, D.M. Caldwell, A. Chaimani, C.H. Schmid, C. Cameron, J. P. Ioannidis, S. Straus, K. Thorlund, J.P. Jansen, C. Mulrow, F. Catala-Lopez, P. C. Gotzsche, K. Dickersin, I. Boutron, D.G. Altman, D. Moher, The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations, Ann. Intern. Med. 162 (11) (2015 Jun 2) 777–784.

[9] J.P.T. Higgins, J. Thomas, J. Chandler, M. Cumpston, T. Li, M.J. Page, V.A. Welch (Eds). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.3 (updated February 2022). Cochrane, 2022. Available from: https://training.cochrane.org/handbook.

[10] J.V. Heymach, T. Mitsudomi, D. Harpole, M. Aperghis, S. Jones, H. Mann, T. M. Fouad, M. Reck, Design and rationale for a phase III, double–blind, placebo–controlled study of neoadjuvant durvalumab + chemotherapy followed by adjuvant durvalumab in patients with resectable stage II–III NSCLC: the AEGEAN trial, Clin. Lung Cancer 23 (3) (2022 May) e247–e251, https://doi.org/10.1016/j.cllc.2021.09.010.

[11] J.V. Heymach, D. Harpole, T. Mitsudomi, J.M. Taube, G. Galffy, M. Hochmair, T. Winder, R. Zukov, G. Garbaos, S. Gao, H. Kuroda, G. Ostoros, T.V. Tran, J. You, K.Y. Lee, L. Antonuzzo, Z. Papai-Szekely, H. Akamatsu, B. Biswas, A. Spira, J. Crawford, H.T. Le, M. Aperghis, G.J. Doherty, H. Mann, T.M. Fouad, M. Reck, Perioperative durvalumab for resectable non–small–cell lung cancer, N. Engl. J. Med. 389 (18) (2023 Nov 2) 1672–1684, https://doi.org/10.1056/NEJMoa2304875.

[12] J. Zhao, L. Zhao, W. Guo, S. Wang, X. Tao, L. Li, Y. Mao, F. Tan, Y. Gao, N. Wu, J. Ying, Q. Xue, N. Li, S. Gao, J. He, Efficacy, safety, and biomarker analysis of neoadjuvant camrelizumab and apatinib in patients with resectable NSCLC: a phase 2 clinical trial, J. Thorac. Oncol. 18 (6) (2023 Jun) 780–791, https://doi.org/10.1016/j.jtho.2023.02.019.

[13] T. Cascone, A.M. Varghese, P.M. Forde, M. Mino-Kenudson, J. Spicer, D. P. Carbone, Z.R. Chalmers, M. Reck, J.R. Brahmer, D.J. Kwiatkowski, T. De Pas, T. Mok, M. Provencio, H. Loong, M.G. Krebs, National surgical trial group. abstract: CheckMate 77T: Phase III trial of perioperative nivolumab in resectable NSCLC, J. Clin. Oncol. 42 (17_suppl) (2024) LBA8007. Presented at ASCO Annual Meeting 2024.

[14] M.J. Bott, S.C. Yang, B.J. Park, P.S. Adusumilli, V.W. Rusch, J.M. Isbell, R. J. Downey, J.R. Brahmer, R.J. Battafarano, E. Bush, J. Chaft, P.M. Forde, D. R. Jones, S.R. Broderick, Initial results of pulmonary resection after neoadjuvant nivolumab in patients with resectable Non–small cell lung cancer, J. Thorac. Cardiovasc. Surg. 158 (1) (2019 Jul) 269–276, https://doi.org/10.1016/j.jtcvs.2018.11.124.

[15] T.R. Cottrell, E.D. Thompson, P.M. Forde, J.E. Stein, A.S. Duffield, V. Anagnostou, N. Rekhtman, R.A. Anders, J.D. Cuda, P.B. Illei, E. Gabrielson, F.B. Askin, N. Niknafs, K.N. Smith, M.J. Velez, J.L. Sauter, J.M. Isbell, D.R. Jones, R. J. Battafarano, S.C. Yang, L. Danilova, J.D. Wolchok, S.L. Topalian, V. E. Velculescu, D.M. Pardoll, J.R. Brahmer, M.D. Hellmann, J.E. Chaft, A. Cimino-Mathews, J.M. Taube, Pathologic features of response to neoadjuvant anti–PD–1 in resected NSCLC: proposal for quantitative irPRC, Ann. Oncol. 29 (8) (2018 Aug) 1853–1860, https://doi.org/10.1093/annonc/mdy218.

[16] P.M. Forde, J.E. Chaft, K.N. Smith, et al., Neoadjuvant PD–1 blockade in resectable lung cancer, N. Engl. J. Med. 378 (21) (2018 Apr 12) 1976–1986, https://doi.org/10.1056/NEJMoa1716078.

[17] P.M. Forde, J. Spicer, S. Lu, M. Provencio, T. Mitsudomi, M.M. Awad, E. Felip, S. R. Broderick, J.R. Brahmer, S.J. Swanson, et al., Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer, N. Engl. J. Med. 386 (21) (2022 May 26) 1973–1985, https://doi.org/10.1056/NEJMoa2202170.

[18] S. Gao, N. Li, S. Gao, Q. Xue, J. Ying, S. Wang, X. Tao, J. Zhao, Y. Mao, B. Wang, K. Shao, W. Lei, D. Wang, F. Lv, L. Zhao, F. Zhang, Z. Zhao, K. Su, F. Tan, Y. Gao, N. Sun, D. Wu, Y. Yu, Y. Ling, Z. Wang, C. Duan, W. Tang, L. Zhang, S. He, N. Wu, J. Wang, J. He, Neoadjuvant PD-1 inhibitor (Sintilimab) in NSCLC, J. Thorac. Oncol. 15 (5) (2020 May) 816–826, https://doi.org/10.1016/j.jtho.2020.01.017.

[19] F. Zhang, W. Guo, B. Zhou, S. Wang, N. Li, B. Qiu, F. Lv, L. Zhao, J. Li, K. Shao, Q. Xue, S. Gao, J. He, Three-year follow-up of neoadjuvant programmed cell death protein-1 inhibitor (sintilimab) in NSCLC, J. Thorac. Oncol. 17 (7) (2022 Jul) 909–920.

[20] S. Peters, A.W. Kim, B. Solomon, D. Gandara, R. Dziadziuszko, A. Brunelli, et al., IMpower030: phase III study evaluating neoadjuvant atezolizumab plus chemotherapy in resectable stage II–IIIB NSCLC, Ann. Oncol. 30 Suppl 2 (2019) ii30, https://doi.org/10.1093/annonc/mdz064.014.

[21] M. Wislez, J. Mazières, A. Lavolé, G. Zalcman, O. Carré, T. Egenod, et al., Neoadjuvant durvalumab for resectable non–small–cell lung cancer (IFCT–1601 IONESCO): results from a multicenter study, J. Immunother. Cancer 10 (10) (2022 Oct) e005636, https://doi.org/10.1136/jitc-2022-005636.

[22] H. Wakelee, M. Liberman, T. Kato, et al., Perioperative pembrolizumab for early-stage non–small-cell lung cancer, N. Engl. J. Med. 389 (6) (2023 Aug 10) 491–503, https://doi.org/10.1056/NEJMoa2302983.

[23] V.W. Rusch, A. Nicholas, G.A. Patterson, et al., Surgical results of the Lung Cancer Mutation Consortium 3 trial: a phase II study investigating atezolizumab as neoadjuvant therapy in resectable NSCLC, J. Thorac. Cardiovasc. Surg. 165 (3) (2023 Mar) 828–839.e5, https://doi.org/10.1016/j.jtcvs.2022.10.007.

[24] J.E. Chaft, F. Oezkan, M.G. Kris, et al., LCMC Study investigators. Neoadjuvant atezolizumab for resectable non–small cell lung cancer: an open–label, single–arm phase II trial, Nat. Med. 28 (10) (2022 Oct) 2155–2161, https://doi.org/10.1038/s41591-022-01962-5.

[25] P. Zhang, J. Dai, F. Sun, et al., Neoadjuvant sintilimab and chemotherapy for resectable stage IIIA NSCLC: a phase II study, Ann. Thorac. Surg. 113 (2) (2022 Feb) 389–398, https://doi.org/10.1016/j.athoracsur.2022.01.039.

[26] M. Provencio, E. Nadal, A. Insa, et al., Perioperative chemotherapy and nivolumab in non–small–cell lung cancer (NADIM): five–year clinical outcomes from a multicentre, single–arm, phase 2 trial, Lancet Oncol. 25 (11) (2024 Nov) 1453–1464, https://doi.org/10.1016/S1470-2045(24)00498-4.

[27] M. Provencio, E. Nadal, A. Insa, et al., Neoadjuvant chemotherapy and nivolumab in resectable non–small–cell lung cancer (NADIM): an open–label, multicentre, single–arm, phase 2 trial, Lancet Oncol. 21 (11) (2020 Nov) 1413–1422, https://doi.org/10.1016/S1470-2045(20)30453-8.

[28] A. Romero Román, J.L. Campo-Cañaveral de la Cruz, I. Macía, I. Escobar Campuzano, S. Figueroa Almánzar, M. Delgado Roel, C. Gálvez Muñoz, E.M. García Fontán, I. Muguruza Trueba, L. Romero Vielva, J.R. Cano Garcia, E. Martínez Téllez, C. Partida González, M.F. Jiménez López, U. Jiménez Maestre, R. Mongil Poce, D. Sánchez Lorente, A. Álvarez Kindelán, M. Pulla Provencio, Outcomes of surgical resection after neoadjuvant chemoimmunotherapy in locally advanced stage IIIA non-small-cell lung cancer, Eur. J. Cardiothorac. Surg. 60 (1) (2021) 81–88.

[29] M. Provencio, E. Nadal, J.L. González-Larriba, A. Martínez-Martí, R. Bernabé, J. Bosch-Barrera, J. Casal-Rubio, V. Calvo, A. Insa, S. Ponce, N. Reguart, J. de Castro, J. Mosquera, M. Cobo, A. Aguilar, G. López Vivanco, C. Camps, R. López-Castro, T. Morán, I. Barneto, D. Rodríguez-Abreu, R. Serna-Blasco, R. Benítez, C. Aguado de la Rosa, R. Palmero, F. Hernando-Trancho, J. Martín-López, A. Cruz-Bermúdez, B. Massuti, A. Romero, Perioperative nivolumab and chemotherapy in stage III non-small-cell lung cancer, N. Engl. J. Med. 389 (6) (2023 Aug 10) 504–513.

[30] C. Sun, X. Wang, Y. Xu, G. Shao, X. Chen, Y. Liu, P. Zhang, X. Lin, X. Ma, S. Qiu, H. He, Z. Yang, K. Ma, Efficiency and safety of neoadjuvant PD-1 inhibitor (sintilimab) combined with chemotherapy in potentially resectable stage IIIA/IIIB non-small cell lung cancer: Neo-Pre-IC, a single-arm phase 2 trial, E Clin. Med. 19 (68) (2024 Jan) 102422.

[31] C.A. Shu, J.F. Gainor, M.M. Awad, C. Chiuzan, C.M. Grigg, A. Pabani, R. F. Garofano, M.B. Stoopler, S.K. Cheng, A. White, M. Lanuti, F. D'Ovidio, M. Bacchetta, J.R. Sonett, A. Saqi, N.A. Rizvi, Neoadjuvant atezolizumab and chemotherapy in patients with resectable non-small-cell lung cancer: an open-

label, multicentre, single-arm, phase 2 trial, Lancet Oncol. 21 (6) (2020 Jun) 786–795.
[32] T. Cascone, G. Kar, J.D. Spicer, R. García-Campelo, W. Weder, D.B. Daniel, D. R. Spigel, M. Hussein, J. Mazieres, J. Oliveira, E.H. Yau, A.I. Spira, V. Anagnostou, R. Mager, O. Hamid, L.Y. Cheng, Y. Zheng, J. Blando, T.H. Tan, M. Surace, J. Rodriguez-Canales, V. Gopalakrishnan, B.R. Sellman, I. Grenga, Y. Soo-Hoo, R. Kumar, L. McGrath, P.M. Forde, Neoadjuvant durvalumab alone or combined with novel immuno-oncology agents in resectable lung cancer: the phase II NeoCOAST platform trial, Cancer Discov. 13 (11) (2023 Nov 1) 2394–2411.
[33] F. Eichhorn, L.V. Klotz, M. Kriegsmann, H. Bischoff, M.A. Schneider, T. Muley, K. Kriegsmann, U. Haberkorn, C.P. Heussel, R. Savai, I. Zoernig, D. Jaeger, M. Thomas, H. Hoffmann, H. Winter, M.E. Eichhorn, Neoadjuvant anti-programmed death-1 immunotherapy by pembrolizumab in resectable non-small cell lung cancer: first clinical experience, Lung Cancer 153 (2021 Mar) 150–157.
[34] M. Shao, J. Yao, Y. Wang, et al., Two vs three cycles of neoadjuvant sintilimab plus chemotherapy for resectable non-small-cell lung cancer: neoSCORE trial, Sig Transduct Target Ther 8 (2023) 146, https://doi.org/10.1038/s41392-023-01355-1.
[35] T. Cascone, W.N. William Jr, A. Weissferdt, C.H. Leung, H.Y. Lin, A. Pataer, M.C. B. Godoy, B.W. Carter, L. Federico, A. Reuben, M.A.W. Khan, H. Dejima, A. Francisco-Cruz, E.R. Parra, L.M. Solis, J. Fujimoto, H.T. Tran, N. Kalhor, F. V. Fossella, F.E. Mott, A.S. Tsao, G. Blumenschein Jr, X. Le, J. Zhang, F. Skoulidis, J.M. Kurie, M. Altan, C. Lu, B.S. Glisson, L.A. Byers, Y.Y. Elamin, R.J. Mehran, D. C. Rice, G.L. Walsh, W.L. Hofstetter, J.A. Roth, M.B. Antonoff, H. Kadara, C. Haymaker, C. Bernatchez, N.J. Ajami, R.R. Jenq, P. Sharma, J.P. Allison, A. Futreal, J.A. Wargo, I.I. Wistuba, S.G. Swisher, J.J. Lee, D.L. Gibbons, A. A. Vaporciyan, J.V. Heymach, B. Sepesi, Neoadjuvant nivolumab or nivolumab plus ipilimumab in operable non-small cell lung cancer: the phase 2 randomized NEOSTAR trial, Nat. Med. 27 (3) (2021 Mar) 504–514.
[36] B. Sepesi, N. Zhou, W.N. William Jr, H.Y. Lin, C.H. Leung, A. Weissferdt, K. G. Mitchell, A. Pataer, G.L. Walsh, D.C. Rice, J.A. Roth, R.J. Mehran, W. L. Hofstetter, M.B. Antonoff, R. Rajaram, M.V. Negrao, A.S. Tsao, D.L. Gibbons, J. J. Lee, J.V. Heymach, A.A. Vaporciyan, S.G. Swisher, T. Cascone, Surgical outcomes after neoadjuvant nivolumab or nivolumab with ipilimumab in patients with non-small cell lung cancer, J. Thorac. Cardiovasc. Surg. 164 (5) (2022 Nov) 1327–1337.
[37] H. Feldman, B. Sepesi, C.H. Leung, H. Lin, A. Weissferdt, A. Pataer, W. N. William Jr, G.L. Walsh, D.C. Rice, J.A. Roth, R.J. Mehran, W.L. Hofstetter, M. B. Antonoff, R. Rajaram, D.L. Gibbons, J.J. Lee, J.V. Heymach, A.A. Vaporciyan, S. G. Swisher, T. Cascone, Surgical outcomes after chemotherapy plus nivolumab and chemotherapy plus nivolumab and ipilimumab in patients with non-small cell lung cancer, J. Thorac. Cardiovasc. Surg. 167 (4) (2024 Apr) 1444–1453.e4.
[38] T. Cascone, C.H. Leung, A. Weissferdt, A. Pataer, B.W. Carter, M.C.B. Godoy, H. Feldman, W.N. William Jr, Y. Xi, S. Basu, J.J. Sun, S.S. Yadav, F.R. Rojas Alvarez, Y. Lee, A.K. Mishra, L. Chen, M. Pradhan, H. Guo, A. Sinjab, N. Zhou, M. V. Negrao, X. Le, C.M. Gay, A.S. Tsao, L.A. Byers, M. Altan, B.S. Glisson, F. V. Fossella, Y.Y. Elamin, G. Blumenschein Jr, J. Zhang, F. Skoulidis, J. Wu, R. J. Mehran, D.C. Rice, G.L. Walsh, W.L. Hofstetter, R. Rajaram, M.B. Antonoff, J. Fujimoto, L.M. Solis, E.R. Parra, C. Haymaker, I.I. Wistuba, S.G. Swisher, A. A. Vaporciyan, H.Y. Lin, J. Wang, D.L. Gibbons, J. Jack Lee, N.J. Ajami, J. A. Wargo, J.P. Allison, P. Sharma, H. Kadara, J.V. Heymach, B. Sepesi, Neoadjuvant chemotherapy plus nivolumab with or without ipilimumab in operable non-small cell lung cancer: the phase 2 platform NEOSTAR trial, Nat. Med. 29 (3) (2023 Mar) 593–604.
[39] S. Lu, W. Zhang, L. Wu, W. Wang, P. Zhang, Neotorch Investigators, W. Fang, W. Xing, Q. Chen, L. Yang, J. Mei, L. Tan, X. Sun, S. Xu, X. Hu, G. Yu, D. Yu, N. Yang, Y. Chen, J. Shan, L. Xing, H. Tian, X. Zhang, M. Zhou, H. Fang, G. Wu, Y. Liu, M. Ye, L. Cao, J. Jiang, X. Li, L. Zhu, S. Li, M. Kang, A. Zhong, K. Chen, N. Wu, Q. Sun, H. Ma, K. Cai, C. Wang, G. Lin, K. Zhu, Y. Zhang, X. Zhang, H. Hu, W. Zhang, J. Chen, Z. Yang, X. Hang, J. Hu, Y. Huang, Z. Zhang, L. Zhang, L. Liu, D. Lin, J. Zhang, G. Chen, Y. Li, L. Zhu, W. Wang, W. Yu, D. Cao, P. Keegan, S. Yao, Perioperative toripalimab plus chemotherapy for patients with resectable non-small cell lung cancer: the neotorch randomized clinical trial, JAMA 331 (3) (2024) 201–211.
[40] S.I. Rothschild, A. Zippelius, E.I. Eboulet, S. Savic Prince, D. Betticher, A. Bettini, M. Früh, M. Joerger, D. Lardinois, H. Gelpke, L.A. Mauti, C. Britschgi, W. Weder, S. Peters, M. Mark, R. Cathomas, A.F. Ochsenbein, W.D. Janthur, C. Waibel, N. Mach, P. Froesch, M. Buess, P. Bohanes, G. Godar, C. Rusterholz, M. Gonzalez, M. Pless, Swiss Group for Clinical Cancer Research (SAKK). SAKK 16/14: durvalumab in addition to neoadjuvant chemotherapy in patients with stage IIIA (N2) non-small-cell lung cancer-a multicenter single-arm phase II trial, J. Clin. Oncol. 39 (26) (2021 Sep 10) 2872–2880.
[41] P.M. Polanco, A.A. Mokdad, H. Zhu, M.A. Choti, S. Huerta, Association of adjuvant chemotherapy with overall survival in patients with rectal cancer and pathologic complete response following neoadjuvant chemotherapy and resection, JAMA Oncol. 4 (7) (2018 Jul 1) 938–943.
[42] C.J. Yang, F. McSherry, N.R. Mayne, X. Wang, M.F. Berry, B. Tong, D.H. Harpole Jr, T.A. D'Amico, J.D. Christensen, N.E. Ready, J.A. Klapper, Surgical outcomes after neoadjuvant chemotherapy and ipilimumab for non-small cell lung cancer, Ann. Thorac. Surg. 105 (3) (2018 Mar) 924–929.
[43] B.C. Tong, L. Gu, X. Wang, D.A. Wigle, J.D. Phillips, D.H. Harpole Jr, J.A. Klapper, T. Sporn, N.E. Ready, T.A. D'Amico, Perioperative outcomes of pulmonary resection after neoadjuvant pembrolizumab in patients with non-small cell lung cancer, J. Thorac. Cardiovasc. Surg. 163 (2) (2022 Feb) 427–436.
[44] Z.R. Zhao, C.P. Yang, S. Chen, H. Yu, Y.B. Lin, Y.B. Lin, H. Qi, J.T. Jin, S.S. Lian, Y. Z. Wang, J.Q. You, W.Y. Zhai, H. Long, Phase 2 trial of neoadjuvant toripalimab with chemotherapy for resectable stage III non-small-cell lung cancer, Oncoimmunology 10 (1) (2021 Oct 25) 1996000.
[45] E.B. Garon, S. Lu, Y. Goto, P. De Marchi, L. Paz-Ares, D.R. Spigel, M. Thomas, J. C. Yang, A. Ardizzoni, F. Barlesi, S. Orlov, H. Yoshioka, G. Mountzios, S. Khanna, C. Bossen, M. Carbini, S. Turri, A. Myers, B.C. Cho, Canakinumab as adjuvant therapy in patients with completely resected non-small-cell lung cancer: results from the CANOPY-A double-blind, Randomized Clinical Trial. J Clin Oncol. 42 (2) (2024 Jan 10) 180–191.
[46] G. Goss, et al. LBA48 CCTG BR.31: A global, double-blind placebo-controlled, randomized phase III study of adjuvant durvalumab in completely resected non-small cell lung cancer (NSCLC). Ann. Oncol. 35, S1238.
[47] E. Felip, N. Altorki, C. Zhou, E. Vallières, A. Martínez-Martí, A. Rittmeyer, A. Chella, M. Reck, O. Goloborodko, M. Huang, R. Belleli, V. McNally, M. K. Srivastava, E. Bennett, B.J. Gitlitz, H.A. Wakelee, Overall survival with adjuvant atezolizumab after chemotherapy in resected stage II-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase III trial, Ann. Oncol. 34 (10) (2023 Oct) 907–919.
[48] E. Felip, N. Altorki, C. Zhou, T. Csőszi, I. Vynnychenko, O. Goloborodko, A. Luft, A. Akopov, A. Martinez-Marti, H. Kenmotsu, Y.M. Chen, A. Chella, S. Sugawara, D. Voong, F. Wu, J. Yi, Y. Deng, M. McCleland, E. Bennett, B. Gitlitz, H. Wakelee, IMpower010 Investigators. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial, Lancet 398 (10308) (2021) 1344–1357, https://doi.org/10.1016/S0140-6736(21)02098-5, 2021 Sep 20. Erratum in: Lancet. 2021 Nov 6;398(10312):1686.
[49] M. O'Brien, L. Paz-Ares, S. Marreaud, U. Dafni, K. Oselin, L. Havel, E. Esteban, D. Isla, A. Martinez-Marti, M. Faehling, M. Tsuboi, J.S. Lee, K. Nakagawa, J. Yang, A. Samkari, S.M. Keller, M. Mauer, N. Jha, R. Stahel, B. Besse, S. Peters, EORTC-1416-LCG/ETOP 8-15 – PEARLS/KEYNOTE-091 Investigators. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial, Lancet Oncol. 23 (10) (2022) 1274–1286.
[50] B.J. Schneider, et al., Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update, J. Clin. Oncol. 39 (36) (2021 Dec 20) 4073–4126, https://doi.org/10.1200/JCO.21.01440. Epub 2021 Nov 1. Erratum in: J Clin Oncol. 2022 Jan 20;40(3):315. doi: 10.1200/JCO.21.02786. PMID: 34724392.
[51] L. Fehrenbacher, et al., Updated efficacy analysis including secondary population results for OAK: A randomized phase III study of atezolizumab versus docetaxel in patients with previously treated advanced non-small cell lung cancer, J Thorac Oncol. 13 (8) (2018 Aug) 1156–1170, https://doi.org/10.1016/j.jtho.2018.04.039. Epub 2018 May 17. Erratum in: J Thorac Oncol. 2018 Nov;13 (11):1800. doi: 10.1016/j.jtho.2018.08.003. PMID: 29777823.
[52] S. Khozin, et al., Real-world outcomes of patients with metastatic non-small cell lung cancer treated with programmed cell death protein 1 inhibitors in the year following U.S. regulatory approval, Oncologist. 24 (5) (2019 May) 648–656, https://doi.org/10.1634/theoncologist.2018-0307. Epub 2018 Dec 27. PMID: 30591549; PMCID: PMC6516117.
[53] F.T. Gallina, et al., Establishing survival benchmarks in the era of peri-operative immunotherapy, Lung Cancer. 8 (202) (2025 Mar), https://doi.org/10.1016/j.lungcan.2025.108491. Epub ahead of print. PMID: 40081109.
[54] S. Schmid, E.M. Minnella, Y. Pilon, M. Rokah, R. Rayes, S. Najmeh, J. Cools-Lartigue, L. Ferri, D. Mulder, C. Sirois, S. Owen, B. Shieh, L. Ofiara, A. Wong, S. Sud, G. Baldini, F. Carli, J. Spicer, Neoadjuvant prehabilitation therapy for locally advanced non-small-cell lung cancer: optimizing outcomes throughout the trajectory of care, Clin. Lung Cancer 23 (7) (2022 Nov) 593–599.
[55] F. Guerrera, et al., The outcomes of salvage surgery for non-small cell lung cancer after immune checkpoint inhibitor or targeted therapy treatment. a multi-center international real-life study, Eur. J. Surg. Oncol. 51 (6) (2025) 109592, https://doi.org/10.1016/j.ejso.2025.109592.
[56] D. Marinelli, et al., Improved event-free survival after complete or major pathologic response in patients with resectable NSCLC Treated with neoadjuvant chemoimmunotherapy regardless of adjuvant treatment: a systematic review and individual patient data meta-analysis, J. Thorac. Oncol. 20 (3) (2025 Mar) 285–295, https://doi.org/10.1016/j.jtho.2024.09.1443.
[57] D. Marinelli, F.T. Gallina, A response to the letter to the editor "Patients with resectable NSCLC undergoing neoadjuvant chemoimmunotherapy: to adjuvant or not to adjuvant?", J. Thorac. Oncol. 20 (3) (2025 Mar) e43–e44, https://doi.org/10.1016/j.jtho.2024.12.015. PMID: 40049768.
[58] A.J. Patel, H. Hemead, J. Law, A. Wali, P. De Sousa, E. Lim, Impact of the timing of immunotherapy administration on overall survival for resectable non-small cell lung cancer (iACORN study): a systematic review and meta-analysis of randomised trials, Eur. J. Cancer 214 (2025 Jan) 115118.
[59] A. Nuccio, F. Salomone, A. Servetto, B. Ricciuti, D. Marinelli, A. Bulotta, G. Veronesi, M.C. Garassino, V. Torri, B. Besse, G. Viscardi, R. Ferrara, Neoadjuvant versus perioperative chemo-immunotherapy according to pathological response in resectable NSCLC: a reconstructed individual patient data meta-analysis, J. Natl Cancer Inst. 11 (2025 Apr) djaf090.
[60] A.R. Cho, T. Najafi, A.V. Ramanakumar, L. Ferri, J. Spicer, S. Najmeh, J. Cools-Lartigue, C. Sirois, S. Soh, D.J. Kim, F. Carli, The effect of multimodal prehabilitation on postoperative outcomes in lung cancer surgery, J. Thorac. Cardiovasc. Surg. 169 (6) (2025 Jun) 1631–1644.e2.
[61] A. Moyen, C. Fleurent-Grégoire, C. Gillis, R. Zaks, F. Carli, C. Scheede-Bergdahl, J. Spicer, J. Cools-Lartigue, S. Najmeh, J.A. Morais, V. Mazurak, S. Chevalier, Novel multimodal intervention for surgical prehabilitation on functional recovery and muscle characteristics in patients with non-small cell lung cancer: study

protocol for a randomised controlled trial (MMP-LUNG), BMJ Open Respir. Res. 12 (1) (2025 May 22) e002884.