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Perioperative immunotherapy for resectable non-small-cell lung cancer

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Abstract

Lung cancer, of which non-small-cell lung cancer (NSCLC) is the most common type, is the leading cause of cancer-related deaths. Anatomic pulmonary resection followed by adjuvant chemotherapy is considered the standard-of-care for patients with resectable NSCLC; however, postoperative relapses and metastases remain common. Immunotherapy, mainly with immune checkpoint inhibitors, has revolutionized the treatment of patients with metastatic NSCLC. In addition, it provides a new strategy for the perioperative treatment of resectable NSCLC. Initial encouraging results have been reported from clinical studies exploring different immunotherapeutic strategies for resectable NSCLC. This review summarizes the results of the latest clinical trials evaluating various perioperative immunotherapeutic approaches aimed at improving the outcomes of patients with resectable NSCLC.

Keywords Non-small-cell lung cancer, Immunotherapy, Neoadjuvant therapy, Adjuvant therapy

Lung cancer is the leading cause of cancer-related deaths in China and worldwide [1–3]. Non-small-cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for approximately 85% of all lung cancer cases. Approximately 40%–50% of NSCLC patients present with early-stage (stage I–III) resectable disease, [4, 5] for which surgery is the main treatment option. The combination of surgery and adjuvant platinum-based chemotherapy is the current standard-of-care for patients with resectable NSCLC, whereby chemotherapy improves the 5-year overall survival (OS) of patients undergoing resection by 5.4% [6]. However, for patients with advanced NSCLC, the rates of postoperative relapse and metastasis remain high, which presents a major challenges for effective NSCLC treatment [7].

Recently, modulating the immune system to attack malignant cells has proven successful in the treatment of various solid cancers. For instance, the use of immune checkpoint inhibitors (ICIs) has significantly improved the OS of patients with advanced NSCLC, considerably upgrading the traditional treatment approach [8]. The aim of perioperative neoadjuvant or adjuvant immunotherapy is to boost host immunity against tumor neoantigens and eliminate micrometastases in resectable malignancies. This approach has been investigated for the treatment of melanoma, esophageal cancer, and breast cancer [9–11]. Therefore, the potential of using ICIs perioperatively to decrease NSCLC recurrence and prolong the survival of patients with resectable disease is being investigated [12]. Initial encouraging reports have led to additional clinical research. This review focuses on the latest data from studies of perioperative immunotherapy aimed at improving the outcomes of patients with resectable NSCLC.

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Neoadjuvant immunotherapy

Neoadjuvant immunotherapy

CheckMate 159 was the first trial of a monoclonal antibody against programmed death-1 (PD-1) (nivolumab) as a neoadjuvant ICI regimen for resectable NSCLC (stage I–IIIA; 7th edition of the tumor, node, and metastasis [TNM] staging system) (Table 1) [13]. During this trial, Forde et al. administered two cycles of nivolumab to 21 patients. The regimen had an acceptable safety profile, meaning that patients could proceed to surgery without delay. Treatment-related adverse events (trAEs) of any grade occurred in five patients, and only one trAE was grade ≥ 3. The study reported a major pathological response (MPR) rate of 45% and a pathological complete response (pCR) rate of 10% in 20 patients who subsequently underwent surgery [13]. Responses were observed in patients with PD-1 ligand 1 (PD-L1)-positive and those with PD-L1-negative tumors. A significant association between the pathological response and the pretreatment tumor mutational burden (TMB) was observed. The latest report showed that the 5-year recurrence-free survival (RFS) and OS rates were 60% and 80%, respectively [14]. The presence of an MPR and pretreatment tumor PD-L1 positivity (tumor proportion score [TPS] ≥ 1%) were associated with favorable RFS rates. There were no cancer-related deaths among patients with an MPR.

In the ChiCTR-OIC-17013726 study, the safety and efficacy of a neoadjuvant immunotherapy comprising two cycles of the monoclonal anti-PD-1 antibody sintilimab were evaluated in 40 patients with resectable NSCLC (stage IA–IIIB; 8th TNM staging) (Table 1) [15]. Neoadjuvant trAEs occurred in 52.5% of the patients, and 10.0% of the trAEs were grade ≥ 3. The operation delay rate was 5.0%. Among the 37 patients who underwent surgery, the MPR rate was 40.5% and the pCR rate was 16.2% for the primary lesion [15]. Patients with squamous cell carcinoma (SQCC) exhibited a better response than those with adenocarcinoma. In the SQCC patients, a correlation was observed between the maximum standardized uptake values following neoadjuvant therapy and the achievement of pathologic remission [15]. Patients who underwent a R0 resection and were subsequently treated with adjuvant immunotherapy, alone or in combination with chemotherapy, had a 3-year OS rate of 88.5% and a 3-year disease-free survival (DFS) rate of 75.0% [16]. Among these patients, those with PD-L1 expression level ≥ 1% or high TMB had more favorable clinical outcomes. Furthermore, patients with high TMB had more favorable DFS and event-free survival (EFS) rates that those with low TMB. However, MPR and pCR were not significant predictors of DFS and EFS in this trial.

The IONESCO (IFCT-1601) trial assessed the feasibility of neoadjuvant immunotherapy comprising durvalumab, an anti-PD-L1 monoclonal antibody, in 46 patients with resectable NSCLC (stage IB ≥ 4 cm to IIIA, non-N2; 8th TNM staging) (Table 1) [17]. Among the 43 patients who underwent surgery, 41 (89%) achieved complete resection, and eight (19%) achieved an MPR. The 1-year median OS and DFS rates for the whole cohort were 89% and 78%, respectively. All patients with an MPR were disease-free at 12 months and none had grade ≥ 3 trAEs. However, the unexpected 90-day postoperative mortality of four patients led to the termination of the study; the deaths were associated with cardiovascular and respiratory comorbidities.

The phase 2 LCMC3 trial is the largest study to date of preoperative ICI monotherapy in early-stage NSCLC (Table 1) [18]. The study involved 181 patients with resectable NSCLC (stage IB–IIIB; 8th TNM staging) who

Table 1 Trials of neoadjuvant immunotherapy monotherapy for resectable NSCLC

Trial	Phase	Stage (Edition)	Neoadjuvant arm	Primary endpoints	Secondary endpoints
CheckMate159 (NCT02259621)	II	I–IIIA (7th)	Nivolumab * 2c	Safety	PR, RDR
ChiCTR-OIC-17013726	I	IA-IIIB (8th)	Sintilimab * 2c	Safety	ORR, MPR, DFS
IONESCO (IFCT-1601) (NCT03030131)	II	IB-IIIA (8th)	Durvalumab * 3c	R0 resection	RR, DFS, MPR, OS
LCMC3 (NCT02927301)	II	IB-IIIA (8th)	Atezolizumab * 2c	MPR	ORR
MK3475-223 (NCT02938624)	I	I-II (7th)	Pembrolizumab * 1/2c	Toxicity, MPR	mOS, mTR
PRICNEPS (NCT02994576)	II	I-IIIA (7th)	Atezolizumab * 1c	Toxicity	-
NEOMUN (NCT03197467)	II	II-IIIA (7th)	Pembrolizumab * 2c	AEs	DFS, OS

NSCLC Non-small cell lung cancer, *c* Cycle, *ORR* Objective response rate, *MPR* Major pathological response, *DFS* Disease-free survival, *mOS* Median overall survival, *mTR* Median time-to-recurrence, *PR* Pathological response, *RDR* Radiographic response, *RR* Response rate, *R0* Resection, *OS* Overall survival, *AEs* Adverse events

received a neoadjuvant immunotherapy consisting of up to two cycles of the anti-PD-L1 antibody atezolizumab. Of the 181 treated patients, 159 (88%) underwent curative surgery. In total, 175 of the 181 (97%) patients experienced ≥ 1 AE during the neoadjuvant period, of whom 20 (11%) had grade ≥ 3 trAEs. In the primary cohort without *EGFR* mutations or *ALK* rearrangements, the MPR and pCR rates were 20% and 6%, respectively. Notably, patients bearing tumors with *EGFR* or *ALK* alterations did not exhibit a radiographical response or MPR. In the subgroup analysis, the baseline PD-L1 TPS was correlated significantly with the pathological response, while *STK11* and *KEAP1* mutations were more frequent in patients with lower pathological regression rates. Chaft et al. found that the frequencies and expression profiles of certain innate immune cell subsets in the peripheral blood of patients before treatment could predict the pathological response [18]. The 3-year DFS and OS rates of patients receiving atezolizumab were approximately 72% and 80%, respectively. Patients with an MPR tended to have higher DFS and OS rates than those without an MPR. The latest results of the LCMC3 study were unveiled at the 2023 European Lung Cancer Congress. The exploratory analysis suggested that patients who received atezolizumab had better DFS and showed a trend toward improved OS than those who were not treated with the adjuvant immunotherapy [19].

Neoadjuvant immunotherapy and chemotherapy

In the majority of neoadjuvant immunotherapy clinical trials, the neoadjuvant immunotherapy is administered alongside the standard chemotherapy regimen, as generally, this dual therapy is associated with improved pathological responses and a more favorable prognosis than either monotherapy. The delineation of the mechanisms underlying the potential synergy between immunotherapy and chemotherapy [20] is an area of intensive research. For instance, chemotherapy can interfere with local tumor immunobiology to trigger a systemic immune response via the abscopal effect.

In the first published trial of neoadjuvant PD-L1 inhibitor therapy and chemotherapy for NSCLC (Table 2), Shu et al. administered atezolizumab in combination with the chemotherapeutic agents carboplatin and nab-paclitaxel to 30 NSCLC patients (stage IB–IIIA; 7th TNM staging) who subsequently underwent surgical resection [21]. All trAEs were manageable and did not compromise or delay surgery. Seventeen (57%) patients had an MPR and 10 (33%) had a pCR [21]. The MPR was significantly associated with the radiological response but not with the pretreatment PD-L1 expression level.

The LungMate 001 trial investigated the safety and effectiveness of neoadjuvant sintilimab immunotherapy in combination with chemotherapy (carboplatin with gemcitabine or pemetrexed) in 50 patients with resectable NSCLC (stage IIIA, 8th TNM staging) (Table 2) [22]. Of the enrolled patients, four (8%) experienced grade ≥ 3 adverse events (AEs). The authors reported an MPR rate of 43.3% and a pCR rate of 20%. Additionally, 76.7% of the patients who underwent surgery experienced pathological downstaging. There was a significant correlation between the pathological and radiological responses. Notably, a large proportion of patients had improved pulmonary function after neoadjuvant chemoimmunotherapy The 12-month DFS and OS rates were 85.3% and 93.7%, respectively; moreover, these values did not have

Table 2 Trials of neoadjuvant immunotherapy combination regimens for resectable NSCLC

Trial	Phase	Stage (Edition)	Neoadjuvant arm	Primary endpoints	Secondary endpoints
NCT02716038	II	IB-IIIA (7th)	Atezolizumab * 4c + chemo	MPR	/
LungMate 001	II	IIIA (8th)	Sintilimab * 2-4c + chemo	AEs, MPR	DFS, OS, R0 resection
CheckMate 816 (NCT02998528)	III	IB–IIIA (7th)	Nivolumab + chemo / nivolumab + ipilimumab + chemo	EFS, pCR	MPR, OS
NEOSTAR (NCT03158129)	II	I-IIIA (7th)	Nivolumab ± ipilimumab / chemo	MPR	RFS
NeoCOAST (NCT03794544)	II	I-IIIA (8th)	Durvalumab ± oleclumab or monalizumab or danvatirsen	MPR	pCR
CANOPY-N (NCT03968419)	II	IB-IIIA (8th)	Canakinumab + pembrolizumab/ canakinumab / pembrolizumab	MPR	ORR
TOP1201 (NCT01820754)	II	IB-IIIA (7th)	Chemo + (ipilimumab + chemo) * 2c	CTCs	Toxicity, mDFS
EAST ENERGY (NCT04040361)	II	IB-IIIA (8th)	Pembrolizumab + ramucirumab	MPR	Safety, pCR, OS, ORR
ChiCTR-2000033588	II	IIA-IIIB (8th)	Camrelizumab + apatinib	MPR	Safety, EFS, DFS, ORR, pCR

NSCLC Non-small cell lung cancer, *c* Cycle, *ORR* Objective response rate, *MPR* Major pathological response, *DFS* Disease-free survival, *mDFS* Median disease-free survival, *OS* Overall survival, *AEs* Adverse events, *CTCs* Circulating T cells, *pCR* Pathological complete response, *RFS* Recurrence-free survival, *EFS* Event-free survival

significant difference when stratified by the radiological response, pathological response, or PD-L1 expression.

The CheckMate 816 study by Forde et al. was the first phase 3 study to explore the clinical value of neoadjuvant chemoimmunotherapy for resectable NSCLC (Table 2) [23]. A total of 258 patients with resectable NSCLC (stage IB–IIIA; 7th TNM staging) were randomly assigned to receive nivolumab plus platinum-based chemotherapy or chemotherapy alone. Patients with *EGFR* mutations or *ALK* translocations were excluded. The inclusion of nivolumab in the combination therapy regimen did not increase the incidence of trAEs. Surgery was cancelled for 15.6% of the patients in the chemoimmunotherapy group and 20.7% of the patients in the chemotherapy group. The surgery duration was shorter, a thoracoscopic approach was more common, and pneumonectomies were less frequent in the chemoimmunotherapy group versus the chemotherapy group. The pCR rates of the chemoimmunotherapy and chemotherapy groups were 24.0% and 2.2%, respectively. pCR and MPR rates were associated with stage, PD-L1 expression, and histologic type. In the initial report, the median EFS was 31.6 months for the immunochemotherapy group and 20.8 months for the chemotherapy group. Neoadjuvant nivolumab plus chemotherapy improved the EFS of most subgroups, especially patients with stage IIIA disease, PD-L1 expression $\geq$ 1%, or a non-squamous histologic type. The percentage of patients with circulating tumor DNA (ctDNA) clearance was higher with nivolumab plus chemotherapy group. ctDNA clearance appeared to be associated with longer EFS and pathological response. On the basis of these results, the regimen used in CheckMate 816 was approved by the US Food and Drug Administration (FDA) for the neoadjuvant treatment of patients with resectable NSCLC [24]. In the updated report, the 3-year EFS for the neoadjuvant immunochemotherapy and chemotherapy arms was 57% and 43%, respectively [25]. A lower recurrence rate was also reported for the immunochemotherapy group than the chemotherapy group (28% versus 42%, respectively).

Neoadjuvant dual immunotherapy

Cascone et al. reported the results of the phase 2 NEOSTAR trial of nivolumab or nivolumab plus ipilimumab in 44 patients with resectable NSCLC (stage I–IIIA; 7th TNM staging) (Table 2) [26]. After surgical resection, adjuvant standard-of-care therapy was provided. Grade 3–5 trAEs were reported in 3 (13%) patients treated with nivolumab and 2 (10%) patients treated with nivolumab plus ipilimumab. Among the 37 patients who underwent surgery in the trial, an MPR was achieved in 5 (24%) patients who received nivolumab monotherapy and in 8 (50%) patients who were treated with nivolumab plus ipilimumab. Moreover, the pCR rate was 10% after nivolumab monotherapy and 38% after dual immunotherapy.

NeoCOAST was a randomized phase 2 study of durvalumab alone or combination with oleclumab (an anti-CD73 antibody), monalizumab (an anti-NKG2A antibody), or danvatirsen (an anti-STAT3 antisense oligonucleotide) as a neoadjuvant treatment strategy (Table 2) [26]. Eighty-four patients with resectable NSCLC (stage IA > 2 cm –IIIA; 8th TNM staging) were randomized into four neoadjuvant immunotherapy groups. The MPR and pCR rates were 11.1% and 3.7% in the durvalumab monotherapy group, 19.0% and 9.5% in the durvalumab plus oleclumab group, 30.0% and 10.0% in the durvalumab plus monalizumab group, and 31.3% and 12.5% in the durvalumab plus danvatirsen group. The MPR and pCR rates were higher in the combination immunotherapy groups compared with durvalumab monotherapy group [27]. The trAEs occurred in 9 (34.6%), 12 (57.1%), 10 (50.0%), and 7 (43.8%) patients, respectively. Safety profiles and the proportion of patients for whom surgery was feasible were similar across the four groups. The NeoCOAST-2 trial is now underway to evaluate the potential role of various immunotherapy combinations as neoadjuvant and adjuvant therapies for resectable NSCLC [28].

Neoadjuvant immunotherapy plus antiangiogenic therapy

Several recent trials assessed the efficacy and safety of neoadjuvant immunotherapy plus antiangiogenic therapy in resectable NSCLC. In the phase 2 ChiCTR-2000033588 trial (Table 2), Zhao et al. enrolled 78 patients with stage IIA-IIIB (8th TNM staging) to receive neoadjuvant camrelizumab (an anti-PD-1 antibody) and apatinib (an antiangiogenic agent). Among the 65 patients who had surgery, 37 (57%) had an MPR and 15 (23%) achieved a pCR. A total of 4 (5%) patients experienced grade $\geq$ 3 trAEs. There was no grade 4 or 5 trAEs. Collectively, neoadjuvant camrelizumab plus apatinib was found to have promising response rates and manageable toxicity [29]. Additional trials, such as NCT04040361 and NCT04762030, may evaluate other ICIs along with different antiangiogenic drugs.

Neoadjuvant immunotherapy plus radiotherapy

Radiotherapy is an important treatment option for solid tumors. Radiotherapy can kill the inhibitory stromal cells and induce immunogenic cell death. The expression of various proinflammatory cytokines induced by radiotherapy may also change the inflammatory tumor microenvironment [30, 31]. Neoadjuvant immunotherapy plus radiotherapy achieved promising results in recent clinical trials. In the NCT02904954 trial, a total of 60 patients (stage I-IIIA, 7th TNM staging) were enrolled

and assigned to either the durvalumab monotherapy group or the durvalumab plus stereotactic body radiotherapy group. MPR was observed in 2 (6.7%) patients in the durvalumab group and 16 (53.3%) patients in the durvalumab plus radiotherapy group. Grade ≥ 3 AEs occurred in 5 (17%) patients in the monotherapy group and 6 (20%) patients in the durvalumab plus radiotherapy group [32]. More evidence is required to evaluate the combination of immunotherapy and radiotherapy.

Adjuvant immunotherapy

The IMpower010 trial was the first phase 3 study to evaluate the efficacy and safety of adjuvant atezolizumab immunotherapy after cisplatin-based chemotherapy in patients with completely resected NSCLC (selected stage IB–IIIA, 7th TNM staging) (Table 3) [33]. After chemotherapy (1–4 cycles), 1,005 patients were assigned to receive atezolizumab for up to 1 year (16 cycles) or best supportive care. AEs of any grade occurred in 459 of 495 (93%) patients who received atezolizumab and in 350 of 495 (71%) patients who received best supportive care. Grade ≥ 3 AEs occurred in 116 (24%) patients who received atezolizumab and 60 (13%) patients who received best supportive care. After a median follow-up of 32.2 months, patients with stage II–IIIA disease who were treated with atezolizumab exhibited longer DFS than those receiving best supportive care. This difference was especially clear for the subgroup of patients with a PD-L1 expression ≥ 1%. The subgroup analyses did not show a difference between the DFS of atezolizumab-treated and untreated patients with different *EGFR/ALK* mutation status. However, this result should be interpreted with caution owing to the large proportion of patients with unknown mutation status. After a median follow-up of 45.3 months, the results indicate a positive trend favouring atezolizumab in PD-L1 subgroup analyses, especially in the PD-L1 expression ≥ 50% stage II-IIIA subgroup [34]. On the basis of these results, the FDA approved atezolizumab as a adjuvant treatment for stage II–IIIA NSCLC patients with PD-L1 expression ≥ 1% [35].

The phase 3 PEARLS/ KEYNOTE-091 study enrolled 1,177 patients with stage IB–IIIA NSCLC who had undergone surgical resection (Table 3) [36]. Eligible participants were assigned to the pembrolizumab (a humanized, monoclonal PD-1inhibitor) or placebo groups for up to 18 cycles. Over 85% of the participants had received previous adjuvant chemotherapy. AEs of any grade occurred in 556 (96%) of participants who received pembrolizumab and in 529 (91%) of participants who received placebo. Grade ≥ 3 AEs occurred in 198 (34%) of patients in the pembrolizumab group and in 150 (26%) of patients in the placebo group. After a median follow-up of 35.6 months, median DFS was 53.6 months in the pembrolizumab group versus 42.0 months in the placebo group of the overall population. Subgroup analyses suggested that pembrolizumab treatment was more beneficial for current smokers, patients with non-squamous histology, patients with *EGFR* mutations, and patients who received adjuvant chemotherapy than for patients who did not belong to these groups. At the 2023 American Society of Clinical Oncology (ASCO) annual meeting, outcomes for the patients who received prior adjuvant chemotherapy were presented. Median (DFS was 58.7 months in the pembrolizumab arm versus 34.9 months in the placebo arm. Estimated 18-month DFS rates were 73.8% and 63.1%, respectively [37]. On the basis of these results, the FDA approved pembrolizumab for adjuvant treatment following resection and platinum-based chemotherapy for stage IB (T2a ≥ 4 cm), II, or IIIA NSCLC [38].

Combining perioperative therapy with neoadjuvant and adjuvant immunotherapy

The Swiss Group for Clinical Cancer Research (SAKK) reported the benefit of two sequential doses of durvalumab after neoadjuvant chemotherapy (cisplatin and docetaxel) in patients with resectable stage IIIA (N2 node-positive; 7th TNM staging) NSCLC, followed by

Table 3 Trials of adjuvant immunotherapy for resectable NSCLC

Trial	Phase	Stage (Edition)	Adjuvant arm	Primary endpoints
IMpower010 (NCT02486718)	III	IB-IIIA (7th)	Atezolizumab + chemo/ chemo	DFS
PEARLS/ KEYNOTE-091 (NCT02504372)	III	IB-IIIA (7th)	Pembrolizumab 1y / placebo	DFS
ANVIL (NCT02595944)	III	IB-IIIA (7th)	Nivolumab 1y / placebo	DFS, OS
IFCT-1401 (NCT02273375)	III	IB-IIIA (7th)	MEDI4736 1y / placebo	DFS
MERMAID 1 (NCT04385368)	III	II-III (8th)	Durvalumab + SoC chemo / placebo	DFS
MERMAID 2 (NCT04642469)	III	II-III (8th)	Durvalumab 1y / placebo	DFS

NSCLC Non-small cell lung cancer, *chemo* Chemotherapy, *y* Year, *DFS* Disease-free survival, *OS* Overall survival, *SoC* Standard of care

adjuvant durvalumab for 1 year (Table 4) [39]. Of the 55 patients who underwent surgery, 34 (62%) had an MPR and 10 (18%) achieved a pCR, with postoperative lymph node downstaging occurring in 37 (67%) patients. A correlation between the radiographical and pathological responses was observed. Patients with a PD-L1 expression ≥ 25% had a higher chance of achieving pCR than those who had lower PD-L1 values. The 1-year EFS rate for patients treated with the chemoimmunotherapy regimen was 73%, which according to the SAKK previous analysis results, exceeded the historical 1-year EFS rate reported for patients receiving chemotherapy alone [40]. Furthermore, achieving an MPR was significantly associated with both OS and EFS, while achieving a pCR predicted EFS.

The TOP 1501 trial administered two cycles of neoadjuvant pembrolizumab immunotherapy to 30 NSCLC patients (stage IB–IIIA; 7th TNM staging) (Table 4) [41]. After surgery, adjuvant chemotherapy or radiation therapy were considered, followed by four cycles of adjuvant pembrolizumab immunotherapy. Five patients were not considered candidates for surgery owing to disease progression. In the remaining cohort, seven of 25 (28%) patients achieved an MPR, and three (12%) patients attained a pCR [41].

The LungMate 002 trial analyzed the safety and efficacy of neoadjuvant humanized PD-1 inhibitor toripalimab immunotherapy plus carboplatin-based chemotherapy in patients with *EGFR*/*ALK*-wildtype NSCLC (stage II–III; 8th TNM staging) (Table 4) [42]. Adjuvant chemotherapy was administered to all eligible patients after surgery. In addition, some patients opted to receive maintenance immunotherapy for 1 year after surgery. Of the 50 patients enrolled in the trial, 36 (72.0%) underwent surgery with R0 resection. Eventually, 20 (55.6%) patients achieved an MPR and 10 (27.8%) a pCR. The radiological response was significantly correlated with the pathological response. The 12-month progression-free survival (PFS) rate was 88.9% and the OS rate was 100.0% in patients who underwent surgery. pCR was associated with better survival outcomes than MPR. Patients who received maintenance immunotherapy showed a trend toward longer PFS than those who did not; however, the difference was not statistically significant.

The phase 2 NADIM trial enrolled 46 patients with stage IIIA (7th TNM staging) NSCLC to receive three cycles of neoadjuvant nivolumab in combination with chemotherapy (paclitaxel and carboplatin) prior to surgery, followed by adjuvant nivolumab monotherapy for 1 year (Table 4) [43]. The presence of known *EGFR* mutations or *ALK* translocations was an exclusion criterion. In the study, 34 of 41 patients who underwent surgery had an MPR (83%) and 26 (63%) achieved a pCR. The PD-L1 TPS was significantly higher in patients who had

Table 4 Trials of neoadjuvant and adjuvant immunotherapy for resectable NSCLC

Trial	Phase	Stage (Edition)	Neoadjuvant arm	Adjuvant arm	Primary endpoints
SAKK 16/14 (NCT02572843)	II	IIIA (7th)	Chemo * 3c + durvalumab * 2c	Durvalumab 1y	EFS
TOP1501 (NCT02818920)	II	IB-IIIA (7th)	Pembrolizumab * 2c	Pembrolizumab * 4c	Surgical feasibility rate
LungMate 002	II	II-III (8th)	Toripalimab + chemo * 2–4 c	Chemo ± toripalimab	Safety, MPR
NADIM (NCT03081689)	II	IIIA (7th)	Nivolumab ± chemo * 3c	Nivolumab * 1y	PFS
NADIM II (NCT03838159)	II	IIIA-IIIB (8th)	Nivolumab ± chemo * 3c	Nivolumab * 6 m	pCR
AEGEAN (NCT03800134)	III	IIA-IIIB (8th)	Durvalumab + chemo * 4c / placebo + chemo	Durvalumab * 12c + chemo / placebo + chemo	pCR, EFS
KEYNOTE-671 (NCT03425643)	III	II-IIIB (8th)	Pembrolizumab + chemo * 4c / placebo + chemo	Pembrolizumab * 13c + chemo / placebo + chemo	EFS, OS
CheckMate 77 T (NCT04025879)	III	II-IIIB (8th)	Nivolumab + chemo / placebo + chemo	Nivolumab + chemo / placebo + chemo	EFS
IMpower 030 (NCT03456063)	III	II-IIIB (8th)	Atezolizumab + chemo * 4c / placebo + chemo	Atezolizumab * 4c + chemo/ placebo + chemo	MPR, EFS
RATIONALE 315 (NCT04379635)	III	II-IIIA (8th)	Tislelizumab + chemo / placebo + chemo	Tislelizumab + chemo / placebo + chemo	MPR, EFS
Neotorch (NCT04158440)	III	II-IIIB (8th)	Toripalimab + chemo / placebo + chemo	Toripalimab + chemo / placebo + chemo	MPR, EFS
NCT05116462	III	IIB-IIIB (8th)	Sintilimab + chemo / placebo + chemo	Sintilimab / placebo	EFS, pCR

NSCLC Non-small cell lung cancer, *c* Cycle, *y* Year, *MPR* Major pathological response, *DFS* Disease-free survival, *OS* Overall survival, *EFS* Event-free survival, *PFS* Progression-free survival, *pCR* Pathological complete response

achieved a pCR than in those without a pCR. However, no significant differences of the PD-L1 TPS were identified stratified by MPR status. Of the 46 patients receiving neoadjuvant therapy, 43 (93%) had trAEs of any grade and 14 (30%) had grade ≥ 3 AEs. The 24-month PFS and OS of the intention-to-treat population were 77.1% and 89.9%, respectively. Neither PD-L1 expression nor TMB predicted survival. In the updated report, the PFS and OS at 36 months were 69.6% and 81.9%, respectively [44]. The ctDNA levels after neoadjuvant treatment were significantly associated with PFS and OS, which outperformed clinical responses in the prediction of survival. The NADIM II trial was subsequently initiated on the basis of these promising results. This second trial, researchers randomly assigned 86 patients with resectable NSCLC (stage IIIA–IIIB; 8th TNM staging) to receive three cycles of neoadjuvant nivolumab plus platinum-based chemotherapy or chemotherapy alone (Table 4) [45]. After pulmonary resection, patients in the experimental group with R0 resection received adjuvant nivolumab for 6 months. In the intention-to-treat population, the pCR rate was 37% in the experimental group and 7% in the control group. A higher pCR rate was also observed across all chemoimmunotherapy- versus chemotherapy-treated subgroups; the difference was especially significant for patients with a PD-L1 TPS ≥ 1%. Likewise, the MPR rate was higher in the experimental group than in the control group (53% versus 14%). The 24-month PFS rates of the experimental and control groups were 67.2% and 40.9%, respectively, while the corresponding 24-month OS rates were 85.0% and 63.6%, respectively. Baseline circulating tumor DNA level was associated with differences in PFS and OS, while the TMB did not hold any prognostic value.

The phase 3 AEGEAN study was designed to compare the clinical value of using platinum-based chemotherapy plus durvalumab or placebo prior to surgery, followed by adjuvant durvalumab monotherapy or placebo, in resectable NSCLC (stage IIA–IIIB with N2; 8th TNM staging) (Table 4) [46]. Patients with *EGFR* or *ALK* alterations were excluded. a total of 1480 patients were enrolled and 802 patients were randomly assigned [47]. 77.6% of the patients in the durvalumab group and 76.7% of those in the placebo group received curative thoracic surgery. At 24 months, EFS was 63.3% in the durvalumab group and 52.4% in the placebo group. The pCR rate was 17.2% in the durvalumab group, higher than that of 4.3% in the placebo group. The corresponding MPR rates were 33.3% and 12.3%, respectively [48]. The benefits of EFS and pCR with durvalumab were observed regardless of stage and PD-L1 expression. AEs ≥ grade 3 occurred in 42.4% of patients with durvalumab and in 43.2% with placebo, which indicated a comparable safety profile.

The interim analysis results of the randomized phase 3 KEYNOTE-671 trial were presented at the 2023 ASCO annual meeting. The trial, designed to explore the role of perioperative pembrolizumab immunotherapy in patients with resectable NSCLC (stage II, IIIA, or IIIB with N2 status; 8th TNM staging), enrolled 797 participants, who were assigned to receive four cycles of neoadjuvant pembrolizumab plus cisplatin-based chemotherapy or chemotherapy alone (Table 4) [49]. After surgery, the adjuvant phase of the trial was initiated, whereby the patients received up to 13 cycles of pembrolizumab or placebo [49]. Notably, patients with *EGFR* or *ALK* alterations were not excluded. An MPR occurred in 30.2% of the participants in the pembrolizumab group and in 11.0% of the participants in the placebo group, while a pCR was achieved in 18.1% and 4.0% of the participants, respectively; the differences in both MPR and pCR were statistically significant. The 2-year EFS was 62.4% in the pembrolizumab group and 40.6% in the placebo group (HR, 0.58; 95% CI, 0.46–0.72). The EFS advantage associated with pembrolizumab treatment was generally consistent across most subgroups, including stage, histological type, and PD-L1 expression. The exploratory analyses found that MPR and pCR were correlated with better EFS. The results of the second interim analysis were presented at the European Society of Medical Oncology (ESMO) Congress in 2023 [50]. With 254 (31.9%) deaths, OS was significantly improved in the pembrolizumab group. The 36-month OS was 71.3% in the pembrolizumab group and 64.0% in the placebo group. Additionally, EFS continued to be improved in the pembrolizumab group.

Clinical considerations and controversies

Neoadjuvant versus adjuvant immunotherapy

Whether neoadjuvant therapy is superior to adjuvant therapy is one of many open questions with respect to perioperative management for resectable NSCLC. However, there is no ongoing trial directly comparing the two methods. The adoption of neoadjuvant immunotherapy brings unique advantages, such as better patient compliance for planned systemic therapy, early eradication of potential micrometastases, and immune response mobilization. The risk of surgical delays or cancellations persists owing to rapid disease progression or treatment-related toxicities. A crucial timeframe was required to assess the efficacy of ICIs and identify potential biomarkers capable of improving patient selection. Few biomarkers of immunotherapeutic efficacy and patient survival are sufficiently reliable. Whether neoadjuvant immunotherapy can reduce the extent of resection remains unclear, as evidenced by comparable percentages of patients undergoing pneumonectomy in the NADIM II

and KEYNOTE-671 trials, regardless of ICI adoption. Moreover, a more difficult dissection regarding pulmonary artery and vein may occur in patients receiving neoadjuvant chemoimmunotherapy owing to local inflammatory reaction [51].

Advantages of adjuvant therapy include a potentially shorter interval between diagnosis and surgery and higher surgical compliance owing to the absence of neoadjuvant-therapy-associated AEs, which may render a patient unfit for surgery. However, adjuvant therapy compliance remains suboptimal. For instance, in the Impower 010 and PEARLS studies, only 65% and 52% patients, respectively, completed their full treatment course as set out in the trial protocol. Another potential advantage of adjuvant therapy is that it could limit any risks and complications associated with systemic therapy before surgery. Moreover, adjuvant therapy offers more flexibility to patients in terms of their duration of postoperative recovery; this allows more time for older patients with cardiovascular and respiratory comorbidities or patients undergoing extensive resection to recover from surgery. Moreover, oncologists and pathologists could conduct comprehensive pathological and molecular testing during this extended phase of recovery to guide future treatment decisions.

Biomarkers for tumor response to neoadjuvant therapy

In the above-mentioned trials, the tumor response rate and patient prognosis vary considerably owing to factors such as preoperative assessment methods, clinical stage, and patient population characteristics. Thus, significant interest lies in standardizing clinical trial findings by identifying optimal and reliable biomarkers of immunotherapeutic efficacy. Potential candidates may include tissue-based biomarkers, blood-based biomarkers, or biomarkers of the pathological response.

Tissue-based biomarkers

The PD-L1 expression level on the primary tumor is widely used to guide treatment decisions in metastatic disease; [52] There is no consensus on its predictive value, but most studies showed the PD-L1 expression was closely related to the efficacy in patients with resectable NSCLC undergoing neoadjuvant immunotherapy. The CheckMate 159 trial firstly reported that PD-L1 expression was associated with pathological response [13]. The updated result indicated that pretreatment tumor PD-L1 positivity correlated with favorable RFS [14]. LCMC3 trial also showed that the baseline PD-L1 TPS was correlated significantly with the pathological remission [18]. Similar results were found regarding the pCR rate in both NADIM and NADIM II studies [43].

TMB is the total number of genetic mutations within the tumor specimen; thus, it reflects the extent of neoantigen formation, which is considered to have predictive value in advanced NSCLCl; [53] however, the predictive value of this biomarker is not well shown in early-stage NSCLC with perioperative immunotherapy. In the CheckMate 159 trial, for example, Forde et al. found that MPR was significantly associated with pretreatment TMB [13]. Although TMB was also positively associated with pathological response in the LCMC3 study, this relationship did not reach statistical difference [18]. By contrast, TMB predicted neither pathological response nor survival in the NADIM and NADIM II trials [43, 45].

Blood-based biomarkers

The identification of blood-based biomarkers is a research hotspot in the diagnosis and treatment of cancer. Using blood-based biomarkers avoids the need for repeated biopsies, which is of great importance to patients with locally advanced disease and a relatively long treatment course. In the NADIM trial, peripheral blood samples were taken from 29 patients before and after neoadjuvant chemoimmunotherapy [54]. Patients who achieved a pCR had a distinctive peripheral blood immune profile, including higher frequencies of PD-1^+ $CD4^+$ T cells and lower numbers of CTLA-4^+ natural killer cells. Interest has also grown in monitoring changes in ctDNA levels in response to ICI treatment. In the NADIM trial, ctDNA clearance after neoadjuvant treatment predicted better PFS and OS [44]. In the CheckMate 816 study, the proportion of patients with ctDNA clearance was higher with chemoimmunotherapy group. ctDNA clearance appeared to be associated with pathological response and favorable EFS [23]. Therefore, ctDNA dynamics during neoadjuvant treatment may be an early predictor of favorable outcomes.

Optimal cycles of neoadjuvant immunotherapy before surgery

Two to four cycles of neoadjuvant chemoimmunotherapy or immunotherapy are generally adopted in most clinical trials. The neoSCORE trial was the first randomized trial to evaluate the potential clinical value of different numbers of neoadjuvant immunochemotherapy (sintilimab plus platinum-based chemotherapy) cycles for resectable NSCLC [55]. The study demonstrated that increasing the number of neoadjuvant treatment cycles from two to three improved both the MPR and pCR rates, although statistical significance was not reached [55]. The long-term oncological benefits of two versus three cycles of neoadjuvant therapy will be investigated at follow-up. Additionally, the potential difference between three and four cycles of neoadjuvant immunochemotherapy in

resectable lung SQCC will be explored in the phase 3 neoSCORE II trial (NCT05429463).

Conclusion

In conclusion, recent studies and clinical trials have confirmed the safety and clinical value of perioperative immunotherapy for resectable NSCLC. It is possible that immunotherapy may change the default treatment strategy for patients with resectable NSCLC. However, the benefits and risks (e.g., AEs) associated with immunotherapy must be weighed up. Moreover, additional clinical evidence is needed to further optimize the protocol (e.g., composition, dosage, and timing) of immunotherapy regimens. Furthermore, more reliable tumor and serum biomarkers are needed to predict immunotherapeutic efficacy.

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Authors' contributions
Conceptualization: Xiaodong Yang, Dongliang Bian, Deping Zhao, Gening Jiang, Yuming Zhu, Peng Zhang; Writing—Original draft preparation: Xiaodong Yang, Dongliang Bian; Supervision: Jie Yang, Liang Duan, Haifeng Wang; Writing—Reviewing and Editing: Xiaodong Yang, Dongliang Bian, Deping Zhao, Gening Jiang, Yuming Zhu, Peng Zhang;

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Declarations

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