The CheckMate 816 trial: a milestone in neoadjuvant chemoimmunotherapy of nonsmall cell lung cancer

Marie Mayenga [1], Ana Rita Pedroso [2], Marion Ferreira [3,4], Thomas Gille [5,6,7], Maria Joana Pereira Catarata [2,8] and Boris Duchemann [9,10]

[1]Department of Pulmonology, Foch Hospital, Suresnes, France. [2]Pulmonology Department, Local Health Unit of Braga, Braga, Portugal. [3]Department of Pneumology and Respiratory Functional Exploration, University Hospital of Tours, Tours, France. [4]INSERM, Centre d'Etude des Pathologies Respiratoires, Tours, France. [5]Inserm UMR 1272 "Hypoxia and the Lung", UFR Santé, Médecine, Biologie Humaine (SMBH), Université Sorbonne Paris Nord (USPN), Bobigny, France. [6]Department of Physiology and Functional Explorations, Avicenne University Hospital, Hôpitaux Universitaires de Paris Seine-Saint-Denis (HUPSSD), Assistance Publique - Hôpitaux de Paris (AP-HP), Bobigny, France. [7]Departement of Physiology and Functional Explorations, Jean Verdier University Hospital, Hôpitaux Universitaires de Paris Seine-Saint-Denis (HUPSSD), Assistance Publique - Hôpitaux de Paris (AP-HP), Bondy, France. [8]Tumour and Microenvironment Interactions Group, I3S-Institute for Health Research and Innovation, University of Porto, Porto, Portugal. [9]Department of Pulmonary Diseases, Avicenne Hospital, Bobigny, France. [10]Faculty of Medicine, University Paris-Saclay, Le Kremlin Bicêtre, France.

Corresponding author: Marie Mayenga (mmayenga@hotmail.fr)

Shareable abstract (@ERSpublications)
The CheckMate 816 trial marked a turning point, being the first phase III trial to demonstrate the benefit of neoadjuvant immunotherapy combined with chemotherapy in a population with resectable nonsmall cell lung cancer. https://bit.ly/3Tm5d6K

Cite this article as: Mayenga M, Pedroso AR, Ferreira M, *et al*. The CheckMate 816 trial: a milestone in neoadjuvant chemoimmunotherapy of nonsmall cell lung cancer. *Breathe* 2024; 20: 240044 [DOI: 10.1183/20734735.0044-2024].

Received: 2 March 2024
Accepted: 17 Aug 2024

Abstract

Advancements in immunotherapy in the perioperative setting have revolutionised the treatment of resectable nonsmall cell lung cancer (NSCLC). Here we present the methodology and results of the clinical trial CheckMate 816 demonstrating the benefit of neoadjuvant therapy with nivolumab plus chemotherapy compared with chemotherapy alone. Furthermore, this article discusses the implications for future practice in resectable NSCLC and the need for future research.

Introduction

Lung cancer is the leading cause of cancer mortality worldwide. The prognosis of nonsmall cell lung cancer (NSCLC) largely depends on the stage of the disease at the time of diagnosis. Despite advances in the early detection and treatment of lung cancer, early-stage lung cancer represents only a minority of cases. Patients with locally advanced NSCLC are a heterogenous group with various tumour sizes, lymph node involvement and contact with anatomical structures. Their management often requires multimodal approaches. Among patients with resectable NSCLC, 30–55% of those who undergo surgery will have a relapse of the disease or die due to lung cancer, with 5-year survival rates that can range from 68% for stage IB to 36% for stage IIIA [1, 2]. Thus, despite surgical management, the risk of post-operative recurrence remains high and represents a major challenge. Furthermore, current evidence demonstrates that clinical, surgical, pathological and genetic factors confer higher risk for disease recurrence in resectable NSCLC. Notably, age, smoking status, vessel and pleural visceral invasion, nodal involvement, histological differentiation, tumour spread through air spaces, epidermal growth factor receptor (EGFR) mutation and higher expression of CXC chemokine receptor 7 (CXCR7) are recognised risk factors associated with a higher post-operative risk of recurrence in NSCLC [2–4].

Context: state of the art before the CheckMate 816 study

Perioperative platinum-based chemotherapy in patients with operable stage II or IIIA NSCLC has been shown to improve survival. However, the benefit is modest, with a 5-year survival gain ∼5% in each setting, but with a higher level of evidence for adjuvant than for neoadjuvant treatment [2, 5, 6].

The 2017 European guidelines recommend platinum doublet chemotherapy whenever possible for stage IIB or IIIA tumours (tumour, node, metastasis (TNM), eighth edition) and to consider it for stage IIA tumours larger than 4 cm [7]. The 2021 guidelines from the American Society of Clinical Oncology (ASCO) recommend neoadjuvant chemotherapy for stage IIIA (N2) NSCLC, if complete resection is possible and perioperative mortality is estimated to be low (⩽5%); adjuvant platinum-based chemotherapy has to be proposed for patients with resected stage IIIA NSCLC who did not receive neoadjuvant systemic therapy [8].

The neoadjuvant approach seems to be interesting, enabling the tumour chemosensitivity to be assessed and disease stage reduced, while improving patient adherence to treatment. Table 1 provides a summary of the guidelines from European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN), alongside the drugs approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for resectable NSCLC [7, 9].

Immunotherapy has demonstrated its efficacy and has been approved alone or in combination with chemotherapy in the first-line treatment of metastatic NSCLC [10–12]. In the light of these results, several studies have focused on its neoadjuvant use in resectable NSCLC.

TABLE 1 Management of resectable of nonsmall cell lung cancer (NSCLC) according to NCCN and ESMO guidelines

Treatment modalities	NCCN guidelines/FDA approvals	ESMO guidelines/EMA approvals
Surgery	Stage IA: Lobectomy preferred, segmentectomy and wedge resection strongly advised for peripheral T1a, bN0 tumours	Stage IA: Lobectomy preferred; segmentectomy or wedge resection for specific patients
	Stage IB–IIA: Minimally invasive anatomical resections preferred; lobectomy preferred, segmentectomy or wedge in patients with poor respiratory reserve or comorbidities	Stage IB–IIA: Lobectomy preferred with systematic lymph node dissection
	Lung-sparing anatomic resection (sleeve lobectomy) is preferred over pneumonectomy	
	Mediastinal lymph node dissection or sampling recommended	
	Stage IIB–IIIA (N2): Multidisciplinary evaluation; consider neoadjuvant therapy	Stage IIB–IIIA (N2): Multidisciplinary team assessment; surgery typically after neoadjuvant therapy
Neoadjuvant therapy	Nivolumab or pembrolizumab+ ChT for those patients with tumours ⩾4 cm or node positive and no *EGFR* mutation or *ALK* rearrangement	Nivolumab in combination with platinum-based ChT in node positive or ⩾5 cm tumours with PD-L1 expression ⩾1% and no *EGFR* mutation or *ALK* rearrangement
		Pembrolizumab in combination with platinum-containing ChT in at high risk of recurrence adults with no *EGFR* mutation or *ALK* rearrangement
Adjuvant therapy	Stage IIA (T2b, N0): adjuvant ChT is recommended for high-risk features (*e.g.* poorly differentiated, visceral pleural and vascular invasion)	Stage IIA (T2b, N0): adjuvant ChT can be considered in resected primary tumour >4 cm
	Stage IIB–IIIA: adjuvant ChT is recommended	Stage IIB–IIIA: adjuvant ChT is recommended
Adjuvant therapy (immunotherapy and TKI)	Alectinib is indicated for completely resected stage II–IIIA or stage IIIB with *ALK* rearrangements	Alectinib is indicated as adjuvant treatment following complete tumour resection for *ALK*-positive NSCLC at high risk of recurrence
	Osimertinib is indicated for the adjuvant treatment in stages IB–IIIA and *EGFR* exon 19 deletions or exon 21 L858R mutations	Osimertinib is indicated for the adjuvant treatment in stages IB–IIIA and *EGFR* exon 19 deletions or exon 21 L858R mutations
	Atezolizumab is recommended in resected stage IIB–IIIA, stage IIIB (T3, N2), or high-risk stage IIA NSCLC with PD-L1 ⩾1% and negative for *EGFR* exon 19 deletion or exon 21 L858R mutations or *ALK* rearrangements	Atezolizumab is indicated as adjuvant treatment following complete resection and platinum-based ChT for NSCLC with a high risk of recurrence and ⩾50% PD-L1 expression without *EGFR* mutation or *ALK*-positive rearrangement
	Pembrolizumab is indicated in resected stage IIB–IIIA, stage IIIB (T3, N2), or high-risk stage IIA NSCLC and negative for *EGFR* exon 19 deletion or exon 21 L858R mutations or *ALK* rearrangements who received previous adjuvant ChT	Pembrolizumab is indicated for the adjuvant treatment of NSCLC at high risk of recurrence following complete resection and platinum-based ChT

Stage according to TNM (tumour, node, metastasis) classification eighth edition. NCCN: National Comprehensive Cancer Network; ESMO: European Society for Medical Oncology; FDA: US Food and Drug Administration; EMA: European Medicines Agency; ChT: chemotherapy: TKI: tyrosine kinase inhibitor; EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase; PD-L1: programmed death-ligand 1.

The biological rationale is that neoadjuvant immunotherapy could enable early limitation of micrometastatic invasion and has the advantage of using the tumour's existing antigenic repertoire to educate a still-intact immune system, including the lymphatic system [13]. The proof-of-concept work by Forde *et al.* [14] studied neoadjuvant nivolumab in 21 patients and observed a reduction in tumour residues on the surgical specimen. The phase II trial NADIM II, comparing neoadjuvant nivolumab plus chemotherapy in resectable stage IIIA NSCLC, showed promising results in terms of pathological complete response (pCR) rate and progression-free survival, with a satisfactory safety profile [15].

Methods

The CheckMate 816 study is a landmark trial as it was the first phase III trial to demonstrate the benefit of neoadjuvant immunotherapy combined with chemotherapy, in a resectable lung cancer population. It was an industrial trial, sponsored by Bristol Myers Squibb. The results of the first pre-specified interim analysis were published under the title "Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer" in April 2022 in the *New England Journal of Medicine* [16].

This international, randomised, open-label, phase III trial investigated the efficacy and safety of the neoadjuvant combination of chemotherapy and nivolumab (three cycles) *versus* chemotherapy alone in patients with resectable stage IB (⩾4 cm) to IIIA NSCLC (according to the staging criteria of the American Joint Committee on Cancer, seventh edition). Patients with *anaplastic lymphoma kinase* (*ALK*) translocation or *EGFR* mutations were excluded; however, their documentation was not mandatory, except *EGFR* in Asia for patients with non-squamous histology.

Patients were randomly assigned in a 1:1 ratio to receive either neoadjuvant nivolumab (360 mg) plus platinum-doublet chemotherapy, or neoadjuvant platinum-doublet chemotherapy alone, every 3 weeks for three cycles. Surgery had to be performed within 6 weeks of completion of neoadjuvant therapy. Adjuvant chemotherapy (up to four cycles) and/or radiotherapy could be given after surgery. It should be noted that a third treatment arm receiving nivolumab plus ipilimumab was closed to enrolment early, based on external trial data (the corresponding results were not presented within the publication).

The first primary endpoint was the blinded, independent central review assessment of event-free survival (EFS), defined as the time from randomisation to any disease progression precluding surgery, disease progression or recurrence after surgery, disease progression in the absence of surgery, or death from any cause. The second primary endpoint was pathological complete response, defined on the surgical specimen as viable tumour cell residue of 0% in the primary tumour and lymph nodes. The secondary endpoints were major pathological response (⩽10% residual viable tumour cells), time to death or distant metastases, and overall survival.

Results

A total of 358 patients were included, 179 in the nivolumab plus chemotherapy arm and 179 in the chemotherapy alone arm. The median age was 64 years, there was a majority of stage IIIA (~63% in each group). The neoadjuvant treatment was fully completed in 93.8% and 84.7% of the patients in the nivolumab plus chemotherapy and in the chemotherapy alone arms, respectively; surgery was performed in 83.2% and 75.4% of the patients, respectively. The nivolumab plus chemotherapy arm led to shorter duration of surgery and to more minimally invasive approaches (and there was no difference between groups in the number of minimally invasive approaches or pneumonectomies).

Nivolumab plus chemotherapy showed an improvement in EFS, with a median EFS of 31.6 months (95% CI 30.2–not reached) *versus* 20.8 months with chemotherapy alone (95% CI 14.0–26.7). Hazard ratio for disease progression, disease recurrence or death was 0.63 (97.8% CI 0.43–0.91; p=0.005). At 2 years, the percentage of surviving patients without disease progression or recurrence was 63.8% with nivolumab plus chemotherapy, and 45.3% with chemotherapy alone. These results were confirmed in the different subgroups, with a greater benefit for stage IIIA than for IB or II, and in patients with a tumour programmed death-ligand 1 (PD-L1) expression level of ⩾1% than in those with a level of <1%.

Nivolumab plus chemotherapy also resulted in a significant increase in pathological complete responses: 24% (95% CI 18.0–31.0) *versus* 2.2% (95% CI 0.6–5.6) with chemotherapy alone. This benefit was observed in all subgroups, including PD-L1 negative patients.

Interestingly, the combination of nivolumab and chemotherapy was no more toxic than chemotherapy alone, with an incidence of grade 3 or 4 treatment-related side-effects of 33.5% and 36.9%, respectively. These were mainly represented by neutropenia, leading to discontinuation of treatment in 10.2% and 9.7%,

respectively, and delayed surgery in 3.4% and 5.1% of patients, respectively. The main results of CheckMate 816 study are depicted in table 2.

Discussion

Perioperative immunotherapy: a new era

These results mark a turning point in the management of locally advanced NSCLC, as this was the first phase III trial to demonstrate the benefit on EFS of pre-operative immunotherapy plus chemotherapy compared with chemotherapy alone [16]. This benefit seems to be observed in the whole study population, with a particular benefit for stage IIIA cancers, a population at high risk of recurrence, and for high PD-L1 levels. It is also important to underline that recent data have confirmed that perioperative treatment with nivolumab plus chemotherapy is associated with a higher percentage of patients with a pCR and longer survival, compared with chemotherapy alone [17]. Looking at an early stage of treatment, a neoadjuvant strategy with nivolumab plus chemotherapy resulted in a higher percentage of patients eligible for surgery, as compared with chemotherapy alone [18].

On the one hand, these results confirm the feasibility of the neoadjuvant association, with an acceptable toxicity profile (although more than a third of patients had a grade 3 or higher treatment-related adverse event and there were some permanent toxicities like endocrinopathies), and a relatively low number of non-operated patients. 28 patients did not benefit from surgery in the nivolumab group, due to tumour progression in 12, and 37 patients in the chemotherapy group, due to progression in 17 [16]. The results are reassuring and neoadjuvant chemoimmunotherapy did not appear to lengthen operative time or increase the risk of surgical complications. The neoadjuvant approach offers a number of advantages. Systemic treatment is more likely to be administered than in the adjuvant setting, since surgical complications, altered post-operative general condition or infection may be potential obstacles to treatment. The neoadjuvant setting also allows surgery to be planned and time to accompany the patient in pre-operative smoking cessation [17].

On the other hand, this trial demonstrated that neoadjuvant therapy with nivolumab plus chemotherapy significantly improved pCR rates compared with chemotherapy alone. This indicates a higher efficacy in eradicating cancer cells before surgery, which is crucial for achieving better long-term outcomes. Importantly, the study found that this combination therapy did not compromise the feasibility of surgery, with high rates of complete resection achieved.

In addition, the trial showed that the safety profile during surgery was acceptable, with no increase in perioperative complications or mortality due to the addition of nivolumab. The intra-operative time were comparable between both arms, indicating that the complexity and difficulty of the surgical procedures were not adversely affected by the neoadjuvant treatment. Conversion rates to non-operable status were low, meaning that most patients initially deemed operable remained eligible for surgery after the neoadjuvant therapy. However, it has been observed that surgical resection of NSCLC after immunotherapy could be technically challenging due to frequent hilar inflammation and fibrosis [19]. These conditions can complicate the surgical procedure, making it more demanding for the operating

TABLE 2 Summary of the main results from CheckMate 816

	Nivolumab+chemotherapy	Chemotherapy alone
Patients, n	179	179
Histological type		
Squamous cell carcinoma	87 (48.6%)	95 (53.1%)
Non-squamous cell carcinoma	92 (51.4%)	84 (46.9%)
Surgery performed after neoadjuvant treatment	83.2%	75.4%
pCR	43 (24.0%)	4 (2.2%)
Median EFS	31.6 months	20.8 months
1-year EFS rate	76.1%	63.4%
2-year EFS rate	63.8%	45.3%
PD-L1 expression ⩾1%: pCR	32.6%	2.2%
PD-L1 expression <1%: pCR	16.7%	2.6%
Grade 3–4 adverse events	33.5%	36.9%

pCR: pathological complete response; EFS: event-free survival; PD-L1: programmed death-ligand 1.

surgeons. Despite these challenges, the overall intra-operative outcomes from the CheckMate 816 trial support the use of neoadjuvant nivolumab plus chemotherapy as a beneficial treatment strategy, improving resection rates and maintaining surgical safety in resectable NSCLC patients.

There are several significant limitations to the CheckMate 816 trial. First, the control group did not reflect the most common approach, which usually involves surgery followed by adjuvant chemotherapy. Nevertheless, there was no evidence of a difference in overall and disease-free survival with the timing of administration of chemotherapy before or after surgery [6]. At baseline patients' characteristics were well balanced between the two groups of treatment, including the disease stage. In each group, 176 patients (98%) received neoadjuvant treatment; and among these patients, 39 patients (22%) received adjuvant chemotherapy in the chemotherapy alone arm, and 21 patients (12%) in the nivolumab plus chemotherapy arm. Despite this difference the EFS benefit with nivolumab plus chemotherapy was maintained after adjustment for optional adjuvant therapy. Secondly, the changes to the trial protocol were not clearly justified, in the original protocol patients were randomised 1:1 to nivolumab plus ipilimumab *versus* chemotherapy alone. A third arm with nivolumab plus chemotherapy was added after enrolment began, and a further protocol amendment led to discontinuation of randomisation in the nivolumab plus ipilimumab arm on the basis of external data. A total of 113 patients were randomised to the neoadjuvant nivolumab plus ipilimumab arm, and 34 patients were randomised to the chemotherapy arm in the initial protocol. Those patients were not included in the primary analysis population. It must be noted, though, that the patients were selected, as 773 patients were screened and only 505 randomised. Finally, assessment of circulating tumour DNA (ctDNA) clearance was only performed on a subset of patients. Additional translational research is required to comprehend the predictive significance of ctDNA clearance.

The use of perioperative chemoimmunotherapy requires a change in practice, particularly in the diagnostic approach, since it implies a diagnosis and an accurate lymph node staging [18]. Accurate restaging of mediastinal lymph nodes is essential for an appropriate selection of stage IIIA–IIIB (N2) NSCLC patients for surgery after neoadjuvant therapy. Various methods are used for NSCLC staging, including imaging techniques like chest computed tomography and positron emission tomography-computed tomography, and invasive mediastinal staging with endoscopic procedures (endobronchial ultrasound/endoscopic ultrasound) [20]. In the CheckMate 816 trial, suspicious lymph nodes (pathologically enlarged or avid for fluorodeoxyglucose on positron emission tomography) at diagnosis required sampling for pathological confirmation, and restaging was radiological. The residual multilevel metastatic nodes are associated with lower survival rates and the decision to proceed for a surgery should be based in a reliable staging [20]. The most effective treatment for patient with multilevel N2 or borderline resectable disease remains to be defined and prospective trials are currently ongoing [21]. Therefore, a multidisciplinary team will have to define the best strategy to improve patients' healthcare pathway [22].

A recent meta-analysis from eight randomised clinical trials in neoadjuvant immunochemotherapy showed patients with stage III disease had better 2-year EFS than those with stage IB–II disease [23]. Although immunotherapy plays crucial roles in the earlier stages with improved pathological responses and enhanced surgical outcomes, the choice between neoadjuvant and adjuvant approaches depends on the individual patient and tumour factors such as tumour size, lymphovascular invasion and other biomarkers such as ctDNA. Stage IB NSCLC encompasses a heterogeneous group of patients with varying risks of recurrence. Identifying which patients will benefit most from neoadjuvant therapy remains a challenge, and ongoing trials continue to refine these strategies. In this trial, stage IB NSCLC patients, specifically those with tumours of $\geqslant$4 cm, benefited from the addition of nivolumab to the treatment regimen. However, there is a lack of data regarding patient selection and the absolute benefit of adjuvant immunotherapy after neoadjuvant immunochemotherapy.

The fields of perioperative treatments have been constantly evolving in recent months. The IMPOWER-010 and PEARLS trials evaluated the adjuvant use of atezolizumab and pembrolizumab and observed a benefit in overall survival with atezolizumab in patients with a PD-L1 level of $\geqslant$50% [24–26]. Moreover, several trials are evaluating the perioperative (pre- and post-operative) use of immunotherapy [27–30]. These trials show significant improvements in pCR rates with the addition of immunotherapy to chemotherapy compared with chemotherapy alone. The range of pCR improvements is generally between 20 and 30%, with some studies like NADIM II reporting even higher rates [27, 29, 30]. Regarding survival, early results are promising across the trials with significant improvements in EFS. Nevertheless, only the KEYNOTE-671 trial included overall survival as one of the primary endpoints and demonstrated a significantly improved overall survival in the pembrolizumab arm (HR 0.72 (5% CI 0.56–0.93); p=0.00517) [31].

Notably, patients with higher PD-L1 expression levels generally had greater benefit from neoadjuvant immunotherapy combined with chemotherapy. However, significant improvements in clinical outcomes

were observed even in patients with low or negative PD-L1 expression, underscoring the broad applicability of these treatment regimens [15, 27–29]. These results suggest that while PD-L1 expression is a useful biomarker for predicting response to neoadjuvant immunotherapy, it should not be the sole criterion for patient selection. The consistent benefits across all PD-L1 subgroups highlight the potential for widespread use of neoadjuvant immunotherapy in resectable NSCLC. Furthermore, the combination of immunotherapy and chemotherapy resulted in manageable safety profiles across all trials. Immune-related adverse events are more common in the combination groups, but these are generally manageable with standard care [15, 27–29]. Nevertheless, the burden of immune-related adverse events in the context of neoadjuvant immunotherapy necessitates careful monitoring and management strategies to mitigate their impact on treatment adherence and patient outcomes. The occurrence of immune-related adverse events can complicate surgical procedures due to hilar inflammation and fibrosis that often makes surgical resection of NSCLC technically challenging [32].

In addition, many questions remain unanswered, such as the specific populations of *EGFR*- and *ALK*-mutated patients, the assessment of resectability and the definitive place of circulating biomarkers. For this reason, the appropriate therapeutic sequence remains to be defined in the heterogeneous population of locally advanced NSCLC.

Future perspectives for clinical practice and research

It is important to emphasise that this study focused on the pivotal concept of pathological response, making it one of its primary outcomes. This known prognostic parameter, highlighted in the study by Forde *et al.* [14], is one of the most important benefits of the addition of immunotherapy in the neoadjuvant setting, when pCR is exceptional after chemotherapy alone. This trial is pioneering in prospectively demonstrating the predictive effect of the pCR on patients' prognosis. Pathologists will need to learn how to determine this new tool, to follow the guidelines of its analysis, and clinicians will need to better understand its interpretation in order to define the best subsequent management of the disease [33]. The choice of therapeutic approach must take into account precise staging, patient and tumour characteristics; further studies are now needed to personalise perioperative therapy, in particular regarding tumour characteristics and response to neoadjuvant chemoimmunotherapy.

Conflict of interest: M. Mayenga reports personal fees from AstraZeneca and LEO pharma. B. Duchemann reports payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Roche, Pfizer, AstraZeneca, Chiesi, Amgen, Lilly, Medscape, MSD and Sanofi. T. Gille reports personal fees from Boehringer Ingelheim and Roche, and non-financial support from Oyxvie, LVL Medical, Vitalaire and Asten (oxygen providers), not related to the topic of this article. The remaining authors have no conflicts to declare.

References

1 Rosner S, Reuss JE, Zahurak M, *et al.* Five-year clinical outcomes after neoadjuvant nivolumab in resectable non-small cell lung cancer. *Clin Cancer Res* 2023; 29: 705–710.
2 Uramoto H, Tanaka F. Recurrence after surgery in patients with NSCLC. *Transl Lung Cancer Res* 2014; 3: 242–249.
3 Park HK, Choi YD, Yun J-S, *et al.* Genetic alterations and risk factors for recurrence in patients with non-small cell lung cancer who underwent complete surgical resection. *Cancers (Basel)* 2023; 15: 5679.
4 Chen H-Z, Bertino EM, He K. Tumor spread through air space (STAS) is an important predictor of clinical outcome in stage IA lung adenocarcinoma. *J Thorac Dis* 2017; 9: 2283–2285.
5 Pignon J-P, Tribodet H, Scagliotti GV, *et al.* Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol* 2008; 26: 3552–3559.
6 Lim E, Harris G, Patel A, *et al.* Preoperative versus postoperative chemotherapy in patients with resectable non-small cell lung cancer: systematic review and indirect comparison meta-analysis of randomized trials. Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews. York, Centre for Reviews and Dissemination, 2009. www.ncbi.nlm.nih.gov/books/NBK77366/
7 Postmus PE, Kerr KM, Oudkerk M, *et al.* Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017; 28: iv1–i21.
8 Daly ME, Singh N, Ismaila N, *et al.* Management of stage III non–small-cell lung cancer: ASCO Guideline. *J Clin Oncol*; 2022; 40: 1356–1384.
9 Ettinger DS, Wood DE, Aisner DL, *et al.* NCCN guidelines insights: non-small cell lung cancer, version 2.2023. *J Natl Compr Canc Netw* 2023; 21: 340–350.
10 Gandhi L, Rodríguez-Abreu D, Gadgeel S, *et al.* Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med* 2018; 378: 2078–2092.

11 Paz-Ares L, Luft A, Vicente D, *et al.* Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med* 2018; 379: 2040–2051.
12 Reck M, Rodríguez-Abreu D, Robinson AG, *et al.* Pembrolizumab *versus* chemotherapy for PD-L1–positive non–small-cell lung cancer. *N Engl J Med* 2016; 375: 1823–1833.
13 Wu X, Chau YF, Bai H, *et al.* Progress on neoadjuvant immunotherapy in resectable non-small cell lung cancer and potential biomarkers. *Front Oncol* 2022; 12: 1099304.
14 Forde PM, Chaft JE, Smith KN, *et al.* Neoadjuvant PD-1 blockade in resectable lung cancer. *N Engl J Med* 2018; 378: 1976–1986.
15 Provencio M, Nadal E, Insa A, *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* 2020; 21: 1413–1422.
16 Forde PM, Spicer J, Lu S, *et al.* Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N Engl J Med* 2022; 386: 1973–1985.
17 Jiang J, Wang Y, Gao Y, *et al.* Neoadjuvant immunotherapy or chemoimmunotherapy in non-small cell lung cancer: a systematic review and meta-analysis. *Transl Lung Cancer Res* 2022; 11: 277–294.
18 Liu Z, Gao Z, Zhang M, *et al.* Real-world effectiveness and prognostic factors analysis of stages I–III non-small cell lung cancer following neoadjuvant chemo-immunotherapy or neoadjuvant chemotherapy. *Ann Thorac Cardiovasc Surg* 2022; 28: 111–120.
19 Marinelli D, Gallina FT, Pannunzio S, *et al.* Surgical and survival outcomes with perioperative or neoadjuvant immune-checkpoint inhibitors combined with platinum-based chemotherapy in resectable NSCLC: a systematic review and meta-analysis of randomised clinical trials. *Crit Rev Oncol Hematol* 2023; 192: 104190.
20 Kwiatkowski R, Zieliński M, Paluch J, *et al.* Enhancing patient selection in stage IIIA–IIIB NSCLC: invasive lymph node restaging after neoadjuvant therapy. *J Clin Med* 2024; 13: 422.
21 Reck M, Nadal E, Girard N, *et al.* MDT-BRIDGE: neoadjuvant durvalumab plus chemotherapy followed by either surgery and adjuvant durvalumab or chemoradiotherapy and consolidation durvalumab in resectable or borderline-resectable stage IIB–IIIB NSCLC. *Clin Lung Cancer* 2024; 25: 587–593.
22 Hong T, Sun T, Zhang M, *et al.* Surgical perspective in neoadjuvant chemoimmunotherapy for stage II–III non-small cell lung cancer. *Thorac Cancer* 2021; 12: 2796–2802.
23 Banna GL, Hassan MA, Signori A, *et al.* Neoadjuvant chemo-immunotherapy for early-stage non–small cell lung cancer: a systematic review and meta-analysis. *JAMA Netw Open* 2024; 7: e246837.
24 Felip E, Altorki N, Zhou C, *et al.* 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* 2021; 398: 1344–1357.
25 Felip E, Altorki N, Zhou C, *et al.* 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* 2023; 34: 907–919.
26 O'Brien M, Paz-Ares L, Marreaud S, *et al.* 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* 2022; 23: 1274–1286.
27 Wakelee H, Liberman M, Kato T, *et al.* Perioperative pembrolizumab for early-stage non-small-cell lung cancer. *N Engl J Med* 2023; 389: 491–503.
28 Chaft JE, Dziadziuszko R, Haddock Lobo Goulart B. Moving immunotherapy into the treatment of resectable non-small cell lung cancer. *Am Soc Clin Oncol Educ Book* 2024; 44: e432500.
29 Heymach JV, Mitsudomi T, Harpole D, *et al.* Design and rationale for a phase III, double-blind, placebo-controlled study of neoadjuvant durvalumab+chemotherapy followed by adjuvant durvalumab for the treatment of patients with resectable stages II and III non-small-cell lung cancer: The AEGEAN Trial. *Clin Lung Cancer* 2022; 23: e247–e251.
30 Provencio M, Nadal E, González-Larriba JL, *et al.* Perioperative nivolumab and chemotherapy in stage III non-small-cell lung cancer. *N Engl J Med* 2023; 389: 504–513.
31 Spicer JD, Gao S, Liberman M, *et al.* LBA56 Overall survival in the KEYNOTE-671 study of perioperative pembrolizumab for early-stage non-small-cell lung cancer (NSCLC). *Ann Oncol* 2023; Suppl. 2, 34: S1297–S1298.
32 Feng Y, Guo K, Jin H, *et al.* Adverse events of neoadjuvant combination immunotherapy for resectable cancer patients: a systematic review and meta-analysis. *Front Immunol* 2023; 14: 1269067.
33 Travis WD, Dacic S, Wistuba I, *et al.* IASLC multidisciplinary recommendations for pathologic assessment of lung cancer resection specimens after neoadjuvant therapy. *J Thorac Oncol* 2020; 15: 709–740.