short review

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(Neo)adjuvant approaches in lung cancer—paving the road to a cure

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Summary Immune checkpoint inhibitors (ICI) have revolutionized the treatment landscape of metastatic non-small-cell lung cancer (NSCLC). During the past few years the focus of research has shifted toward examining these therapies in patients with early-stage NSCLC to improve long-term overall survival and cure rates. As recurrence rates are high and the relapse pattern in patients with completely resected early-stage NSCLC is predominantly systemic, high expectations rest on the integration of ICI therapy in their treatment approach. A large number of studies with adjuvant or neo-adjuvant ICI are ongoing. The first data from phase III studies have demonstrated improvements in disease-free survival and pathologic remissions, but overall survival data are mostly immature. Additionally, targeted therapies have also been explored in early-stage NSCLC. The first very promising results are available from EGFR-mutant and ALK-translocated NSCLC and have already changed our clinical practice for some patient subgroups. This review discusses the most recent results of phase III trials in the neoadjuvant, perioperative, and adjuvant setting for ICI and targeted therapies in early-stage resectable NSCLC.

Keywords Early stage · NSCLC · Immune checkpoint inhibitor · Targeted therapy · Surgery

Key messages

- Despite advances in therapeutic options, the prognosis of NSCLC remains poor.
- Recurrence rate is high after resection even in early tumor stages.
- Adjuvant chemotherapy provides only a moderate benefit for overall survival.
- Neoadjuvant and adjuvant use of checkpoint inhibitors improves disease-free survival (DFS) and increases the rate of pathological remissions.
- Adjuvant osimertinib is the first tyrosine kinase inhibitor to demonstrate a benefit in overall survival in patients with resected epidermal growth factor receptor-mutant (EGFRm) NSCLC; adjuvant alectinib is highly effective in anaplastic lymphoma kinase (ALK)-translocated resected NSCLC, significantly increasing the DFS compared to chemotherapy.

Lung cancer is the leading cause of cancer death worldwide and despite an intended curative treatment approach, the 5-year survival rate in stages I–III disease is less than 50%. The administration of adjuvant chemotherapy only leads to a small improvement in overall survival (OS) of approximately 5% [1]. Accordingly, new therapeutic approaches are needed for this patient population.

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Table 1 Phase III studies in the neoadjuvant and perioperative setting

	CheckMate 816	CheckMate 77T	Keynote-671	AEGEAN
Patients randomized	358 1:1	461 1:1	797 1:1	802 1:1
Treatment	Nivolumab + chemo-therapy	Nivolumab + chemo-therapy, Nivolumab adjuvant	Pembrolizumab + chemo-therapy, Pembrolizumab adjuvant	Durvalumab + chemo-therapy, Durvalumab adjuvant
Treatment setting	Neoadjuvant	Perioperative	Perioperative	Perioperative
Endpoint(s)	pCR, EFS	EFS	EFS, OS	pCR, EFS
Stages	II–IIIB	II–IIIB	II–IIIB	II–IIIB

EFS event-free survival, *OS* overall survival, *pCR* pathologic complete response

The current standard of treatment in stages IA/IB is surgical resection, provided the patient is fit for surgery. From stage IIA onward, additional application of up to four cycles of (neo)adjuvant chemotherapy is recommended [2]. Despite an intended curative therapeutic approach, 30–80% of patients experience recurrence [3]. In addition, (neo)adjuvant chemotherapy carries the risk of significant side effects, but adds only a slight advantage to OS, and leads to a complete pathologic response (pCR) only in a small proportion of patients. [4].

Data from studies of metastatic NSCLC suggest that some patients benefit from treatment with immune checkpoint inhibitors (ICI) in the long term [5]. By using ICI in early tumor stages, similar continuous immune responses could be achieved, thus reducing the risk of recurrence and improving OS. Theoretically, administering ICI in the neoadjuvant setting may be especially beneficial for antitumor immune response by increasing the shedding of neoantigens and the priming of T-cells in the setting of an intact rather than a resected primary tumor. This hypothesis was supported by several preclinical studies that showed improved OS among mice treated with neoadjuvant ICI as compared to adjuvant ICI treatment [6, 7].

Phase II studies have already shown that the neoadjuvant use of checkpoint inhibitors significantly increases the proportion of major pathologic response (MPR), defined as less than 10% of viable tumor cells detectable upon resection after neoadjuvant ICI therapy, as compared to neoadjuvant chemotherapy alone. In small patient populations, MPR rates of 15–45% were achieved. The rates of pathologic complete response (pCR) were also increased to up to 15% [8, 9]. The combination of immunotherapy and chemotherapy enabled further improvement in pathological response, so that this therapeutic approach was pursued in numerous phase III studies [10, 11]. Table 1 provides an overview of phase III studies in the neoadjuvant setting.

In the randomized controlled phase III Checkmate 816 trial, patients with resectable stage IB-IIIA NSCLC received three cycles of platinum-based chemotherapy and the checkpoint inhibitor nivolumab versus platinum-based chemotherapy alone. Surgery was performed within 6 weeks of the last cycle of neoadjuvant therapy. Adjuvant chemotherapy and radiotherapy could then be given depending on the postoperative tumor stage. Endpoints of this study were pCR and event-free survival (EFS). The combination therapy achieved a pCR in 24% of the patients, but only in 2.2% in the control group. The EFS was also significantly increased from 20.8 months to 31.6 months (hazard ratio [HR]: 0.63). Additionally, pCR and MPR rates correlated with EFS—independent of the tumor stage and PD-L1 expression.

The safety profile of the combination therapy was also consistent with previous publications and had no negative impact on the feasibility of surgery as compared to chemotherapy alone.

Analyses of surgical outcomes also showed that patients in the combination group were more likely to undergo minimally invasive resection using video-assisted thoracoscopic surgery (VATS) lobectomy. The rate of pneumonectomies was also lower [12]. Both are relevant in terms of peri- and postoperative morbidity and mortality as well as for the patient's postoperative course. It is clear from the VIOLET study that a minimally invasive surgical procedure using VATS is preferable to an open lobectomy if technically feasible [13].

The study results support the neoadjuvant use of nivolumab in combination with chemotherapy as a new treatment option for patients with resectable NSCLC. However, the number of neoadjuvant therapy cycles administered must be critically questioned—it is known from data on adjuvant chemotherapy that a cumulative dose of 300 mg/m^2 cisplatin must be administered in order to generate the benefit in OS [1]. Continuation of chemotherapy in the adjuvant setting was permitted in this study (26/179 patients in the study arm, 44/179 patients in the control arm). A recently presented data update showed that patients with a pCR had improved EFS and OS compared with those without, in both treatment arms. Furthermore, PD-L1 status also positively influenced OS, with 3-year OS rates of 85% versus 66% in patients with PD-L1 ≥1% compared to 71% versus 60% in patients with PD-L1 <1% [14].

Positive EFS data from several phase III trials in the perioperative setting—where ICI therapy is given as both neoadjuvant and adjuvant treatment—add further evidence to the benefit of perioperative ICI therapy in early-stage NCLC. The most recently published data are from the AGEAN, KEYNOTE 671, and CheckMate 77T studies.

Table 2 Phase III studies in the adjuvant setting

	Immune checkpoint inhibitor		Targeted therapy	
	IMpower-010	Keynote-091/PEARLS	ADAURA	ALINA
Patients randomized	1005 1:1	1177 1:1	682 1:1	257 1:1
Treatment	Atezolizumab, 1 year	Pembrolizumab, 1 year	Osimertinib, 3 years	Alectinib, 2 years
Endpoint(s)	DFS	DFS	DFS	DFS
Stages	IB–IIIA	IB–IIIA	IB–IIIA	IB–IIIA

DFS disease-free survival

The phase III AEGEAN trial evaluated treatment-naive patients with resectable stage IIA–IIIB NSCLC. Patients were assigned to durvalumab plus platinum-based chemotherapy or to matched placebo every 3 weeks for four cycles, followed by surgery, and an additional 12 cycles of durvalumab or placebo, respectively. The 12- and 24-months EFS rates with durvalumab were 73.5 and 63.3% versus 64.5 and 52.4% with placebo. There benefit from durvalumab was regardless of age, sex, performance status, race, smoking history, disease stage, PD-L1 expression, and neoadjuvant platinum therapy. The combination therapy led to an improvement in pCR (17.2% vs. 4.3%, $p=0.000036$) and MPR rates (33.3% vs. 12.3%, $p=0.000002$; [15]).

The second global phase III trial that provided data recently at the June 2023 ASCO convention in Chicago is the KEYNOTE-671 trial. Treatment-naive patients with resectable stage II–IIIB NSCLC were included and assigned to pembrolizumab every 3 weeks plus cisplatin and gemcitabine or pemetrexed for up to four cycles, or matched placebo plus the respective chemotherapy, followed by surgery, and an additional 13 cycles of pembrolizumab or placebo. Investigator-assessed EFS and OS served as the primary endpoints. Median EFS was not reached with pembrolizumab, versus 17.0 months with placebo (HR: 0.58, $p<0.00001$). Additionally, mPR (30.2% vs. 11.0%) and pCR rates (18.1% vs. 4.0%) were significantly improved. All subgroups benefited from the addition of pembrolizumab and, interestingly, in an exploratory analysis performed by MPR status, pathologic response was associated with improved EFS regardless of treatment arm [16]. In KEYNOTE-671, for the first time a perioperative phase III study in resectable early-stage NSCLC was able to demonstrate as OS benefit. At a median follow-up of 36.6 months, median OS was not reached in the pembrolizumab arm and it was 52.4 months in the placebo arm (HR: 0.72, $p=0.00517$; [17]).

The most recent data in the perioperative setting are from the CheckMate 77T study, presented in September 2023 at the ESMO conference. The trial involved 461 patients with untreated resectable stage IIA–IIIB NSCLC, of whom 77% underwent definitive surgery. Neoadjuvant nivolumab plus chemotherapy followed by adjuvant nivolumab significantly improved median EFS compared with chemotherapy plus adjuvant placebo (not reached vs. 18.4 months, HR: 0.58, $p=0.00025$). The benefits of neoadjuvant nivolumab plus chemotherapy/nivolumab were also seen in pCR rates (25.3% vs. 4.7%) and MPR rates (35.4% vs. 12.1%; [18]).

In summary, neoadjuvant and perioperative treatment strategies appear to be very promising in terms of improved pathologic response and disease-free survival (DFS). These results have led to the approval of CM816 by the European Medicines Agency (EMA), while the KN671, CM77T, and AEGEAN regimens have not yet been approved in Europe. The different chemotherapy backbones that have been used in the trials usher in several therapeutic opportunities. Early data on OS are also very encouraging, although not mature yet.

Table 2 lists the phase III studies in the adjuvant setting.

The first results concerning immune checkpoint inhibitor therapy in the adjuvant setting were reported by the IMpower010 study, which showed that adjuvant administration of atezolizumab after up to four cycles of adjuvant chemotherapy in patients with resectable NSCLC in stages IB–IIIA can significantly improve DFS as compared to best supportive care. This advantage was particularly pronounced in patients with high PD-L1 expression ≥ 50% (HR: 0.43). Likewise, the benefit of adjuvant immunotherapy appeared to be more pronounced in patients with higher tumor stages and positive nodal status. The tolerability of atezolizumab was good [19]. In the KEYNOTE091 study, adjuvant pembrolizumab demonstrated a significant DFS benefit compared to placebo (HR: 0.76) in patients with resected NSCLC in stages IB–IIIA. In contrast to atezolizumab, patients with high PD-L1 expression ≥ 50% did not appear to draw more benefit from the addition of immunotherapy (HR 0.82) [20].

These results led to the approval of atezolizumab in the adjuvant setting only in patients with high PD-L1 expression ≥ 50%, whereas pembrolizumab is approved irrespective of PDL-1 status by the EMA. Therefore, it appears essential to identify better biomarkers beyond PD-L1 to aid in the selection of patients who benefit particularly from adjuvant ICI.

The right patient selection for the optimal treatment approach seems to be one of the biggest challenges we face in early-stage lung cancer. What we have learned so far is that there are certain patient populations most likely not benefitting from the ad-

dition of ICI, such as patients with oncogenic-driven lung cancer [21]. Omitting ICI therapy in this patient cohort and sparing possible therapy-related side effects should be mandated. We know from the metastatic setting that patients with *EGFR*-mutant (EGFRm) NSCLC do not benefit from ICI alone and combinations with chemotherapy only result in modest PFS improvement. Therefore, molecular testing before surgery is highly recommended.

The compelling OS data from the phase III ADAURA trial showed the importance of targeted therapies even in the early-stage setting. Across all patients enrolled in the study, the 5-year OS rate was 88% versus 78% (HR: 0.49, $p<0.001$) and the benefit remained consistent in patients regardless of prior chemotherapy. Hence, the third-generation EGFR-TKI osimertinib has been established as the adjuvant standard of care for patients with resected EGFRm NSCLC.

According to an interim analysis of the phase III ALINA trial presented at a Presidential Symposium of the ESMO Congress 2023, adjuvant targeted treatment with alectinib was associated with significant DFS benefit as compared to platinum-based chemotherapy, with favorable results for alectinib seen in both the stage II–IIIA population ($n=231$, HR: 0.24, $p<0.0001$) and the intention-to-treat (ITT; stage IB–IIIA) populations ($n=257$, HR 0.24, $p<0.0001$). The 2-year DFS rates with alectinib and chemotherapy were 93.8% versus 63.0%, respectively, in the stage II–IIIA population and 93.6% versus 63.7%, respectively, in the ITT population [22]. Alectinib also led to a clinically meaningful CNS-DFS benefit compared with chemotherapy in the ITT population (HR: 0.22), which is clinically highly relevant as brain metastases are common in patients with ALK-positive NSCLC. Despite these positive results that were presented, OS data are still immature and long-term data are required to assess the impact of alectinib on prognosis.

Conclusions

Based on these recently emerged promising data, immune checkpoint inhibitors (ICI) will most likely become standard of care at least in defined subgroups of patients with resectable non-small-cell lung cancer (NSCLC), either in the neoadjuvant, perioperative, or adjuvant setting. To assess which patients benefit from which treatment approach, trials comparing adjuvant versus non-adjuvant treatment in patients who previously received neoadjuvant treatment are needed. We know from everyday clinical practice that it is often difficult to motivate patients to undergo adjuvant systemic treatment after potentially curative surgery. A retrospective analysis of over 800 patients with resected stage IB–IIIA NSCLC from France, Germany, and the United Kingdom found that 52% eligible patients did not receive adjuvant therapy. Reasons for this included comorbidities, complications due to surgery, and poor patient performance status [23, 24]. Thus, neoadjuvant and perioperative approaches currently appear to be the most promising approaches, allowing for the application of ICI treatment to a higher proportion of patients and for discussing the continuation of adjuvant ICI on an individual patient-by-patient basis. For patients with oncogenic-driven lung cancer, targeted therapies are able improve disease-free survival and the first positive data on overall survival have been presented in the EGFRm cohort. This again highlights the importance of comprehensive molecular testing already at the time of diagnosis.

The use of ICI and targeted therapies in early tumor stages is an important step to improve the prognosis of patients with lung cancer, especially with the advent of lung cancer screening, which is likely to cause an increase in the diagnosis of earlier tumor stages However, many open questions still remain: It is still unclear whether ICI should be given to all patients or given according to biomarker selection such as PD-L1 status. There is also debate about the number of therapy cycles that should be administered in the neoadjuvant setting, and for how long treatment should be continued in the adjuvant setting. Hopefully analysis of circulating tumor DNA will provide guidance in making these postoperative treatment decisions. The question of whether the clinical endpoints of pathologic complete response, major pathologic response, disease-free survival, and event-free survival are suitable surrogate endpoints for overall survival still needs further investigation, despite growing evidence of their prognostic value [25]. The scientific value for translational research and early assessment of treatment response are undoubtedly the strengths of the pathologic endpoints. But when talking about cure, overall survival is what counts most for patients and these data are still immature.

Currently, there is legitimate hope that these emerging novel (neo-)adjuvant treatment approaches can improve prognosis in early-stage NSCLC patients. Given the increasing treatment options for early-stage lung cancer, we should aim for detecting lung cancer as early as possible. Lung cancer screening is still not implemented in Europe but most likely become increasingly important. For now, it is probably the best way for reaching the goal of an actual cure from lung cancer in an increasing proportion of patients.

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