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Review

Dancing with the Surgeon: Neoadjuvant and Adjuvant Immunotherapies from the Medical Oncologist's Perspective

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Perioperative treatment with conventional cytotoxic chemotherapy for resectable non-small cell lung cancer (NSCLC) has proven clinical benefits in terms of achieving a higher overall survival (OS) rate. With its success in the palliative treatment of NSCLC, immune checkpoint blockade (ICB) has now become an essential component of treatment, even as neoadjuvant or adjuvant therapy in patients with operable NSCLC. Both pre- and post-surgery ICB applications have proven clinical efficacy in preventing disease recurrence. In addition, neoadjuvant ICB combined with cytotoxic chemotherapy has shown a significantly higher rate of pathologic regression of viable tumors compared with cytotoxic chemotherapy alone. To confirm this, an early signal of OS benefit has been shown in a selected population, with programmed death ligand 1 expression ≥50%. Furthermore, applying ICB both pre- and post-surgery enhances its clinical benefits, as is currently under evaluation in ongoing phase III trials. Simultaneously, as the number of available perioperative treatment options increases, the variables to be considered for making treatment decisions become more complex. Thus, the role of a multidisciplinary team-based treatment approach has not been fully emphasized. This review presents up-to-date pivotal data that lead to practical changes in managing resectable NSCLC. From the medical oncologist's perspective, it is time to dance with surgeons to decide on the sequence of systemic treatment, particularly the ICB-based approach, accompanying surgery for operable NSCLC.

Keywords: Immune checkpoint inhibitors, Neoadjuvant therapy, Adjuvant therapy, Non-small-cell lung carcinoma

Introduction

In patients with non-small cell lung cancer (NSCLC), making treatment decisions begins with an appropriate clinical evaluation based on images and biopsies. Since patients with NSCLC are placed on a continuum of disease—other than patients whose disease is at the very early stage or the disseminated stage—a proportion of patients could benefit from both local and systemic therapies. Despite advances in treatment strategies for early-stage NSCLC, the 5-year overall survival (OS) for very early-stage IA3 is only 77%. This survival rate rapidly decreases to 36% and 26% in stage IIIA and IIIB, respectively, according to the American Joint Committee on Cancer (AJCC) eighth edition [1]. Failure to achieve long-term survival, even in patients with early-stage NSCLC, could be explained by the presence of minimal residual disease after local treatment, which cannot be identified either by radiologic evaluation or at the operation site. To increase the likelihood of cure, the necessity for systemic chemotherapy has been actively assessed. In addition to conventional cytotoxic chemotherapy, which eliminates residual disease by directly targeting cancer cells, immunotherapy, which was once used in the palliative setting, has now been introduced as an essential treatment option in the perioperative setting.

Conventional perioperative treatment

For patients who have undergone complete surgical resection of a primary tumor, the current guidelines recommend subsequent adjuvant chemotherapy based on surgical staging (stage IIA–IIIB). However, patients with stage

IB (T2aN0, T2a: tumor >3 cm but not ≥4 cm in the greater dimension) are under ongoing discussion regarding the benefits of adjuvant chemotherapy in some specific populations, such as in patients with poorly differentiated tumors, vascular invasion, wedge resection, visceral pleural involvement, and unknown lymph node status (Nx). The rationale for adjuvant chemotherapy can be observed from landmark meta-analysis data from the Lung Adjuvant Cisplatin Evaluation study [2], which included 4,584 patients with stages I–III, according to the AJCC sixth edition, from 5 different trials: JBR.10 (National Cancer Institute of Canada Clinical Trials Group study) [3], ALPI (Adjuvant Lung Project Italy) [4], ANITA (Adjuvant Navelbine International Trialist Association) [5], IALT (International Adjuvant Lung Cancer Trial) [6], and BLT (Big Lung Trial) [7]. In this study, chemotherapy significantly reduced the risk of death by 11% compared with no chemotherapy, corresponding to a 5-year absolute benefit of 5.4% from chemotherapy. Moreover, although the 5-year cancer-related death rate decreased by 6.9% in those who received adjuvant chemotherapy, the non-cancer-related death rate increased by 1.4%. However, in the subgroup analysis, a clinically significant benefit was observed only in patients with stage II and III disease, but not in those with stage IB disease. A further study, CALGB9633 (Cancer and Leukemia Group B 9633), included patients with stage IB (according to the AJCC sixth edition), segmented using a cut-off of 4 cm, and showed a potential benefit for OS only in patients with tumor size of 4 cm or higher, showing a hazard ratio (HR) of 0.69 (p=0.04) [8]. Despite the survival benefit of adjuvant therapy, the pitfall of this approach was a relatively low compliance rate, which remained between 64% and 76%. This might have been due to the chemotherapy regimen, which was applied as a doublet combined with cisplatin. Finally, since the previous landmark trials performed adjuvant cytotoxic chemotherapy based on staging according to either the AJCC sixth or seventh edition, caution needs to be taken in patient selection based on the TNM (tumor-node-metastasis) staging system because the AJCC eighth edition classified tumor size of 4 cm or higher as T2b, which corresponds to stage IIB (T2bN0M0).

Immunotherapy for non-small cell lung cancer

Immune checkpoint blockade (ICB) has opened a new era of NSCLC treatment. Programmed cell death-1 receptor (PD-1) and its ligand (PD-L1) are the most actively studied immune checkpoints. The scientific background of ICB as anti-cancer treatment starts with the concept that cancer arises from cells that escape tumor-immune interactions [9]. Considering successful cancer immunotherapy, 7 essential steps to reinvigorate the immune resistance caused by cancer immunoediting have been proposed [10]. Following the concept of cancer-immunity cycles, a cancer immunotherapy development program was conducted, focusing on the last step of the cycle: the interactions between cytotoxic T cells and tumor cells, which are mainly regulated by multiple immune checkpoints [11,12].

In patients with treatment-naïve advanced NSCLC, ICB is now considered the backbone of treatment of NSCLC without a driver mutation [13]. Treatment decisions are mainly guided by the PD-L1 protein expression profile in tumor cells. The Keynote-024 study evaluated patients with treatment-naïve NSCLC with PD-L1 expression ≥50%. In this phase III open-label, randomized controlled trial, patients were treated with either pembrolizumab monotherapy or cytotoxic chemotherapy for 2 years. After a median follow-up duration of 59.9 months, the median OS was 26.3 months for pembrolizumab and 13.4 months for the chemotherapy arm (HR, 0.62; 95% confidence interval [CI], 0.48–0.81). That study also provided an unprecedented outcome in patients with NSCLC, showing a 5-year OS rate of 31.9% for pembrolizumab and 16.3% for chemotherapy arm [14]. A similar study, the Keynote-042 study, which was conducted in patients with PD-L1 ≥1%, also demonstrated OS benefits in patients with PD-L1 expression ≥1%, showing an HR of 0.79 (95% CI, 0.70–0.89) [15]. However, the efficacy of ICB monotherapy remains debated, as an HR of 0.88 (95% CI, 0.75–1.04) was observed in an exploratory subgroup analysis of cases with PD-L1 expression between 1% and 49%.

Including patients without PD-L1 expression, pembrolizumab with cytotoxic chemotherapy showed a median OS of 22.0 and 17.2 months and 5-year OS rates of 19.4% and 18.4% in patients with adenocarcinoma and squamous cell carcinoma, respectively [16,17].

Perioperative immunotherapy

Based on the success of ICB treatment at an advanced stage, it has been hypothesized that ICB in the early stage of cancer may be effective when administered before or after surgery. Both adjuvant and neoadjuvant treatments have advantages and disadvantages (Table 1).

In regard to T-cell activation, it can also be hypothesized that ICB may be more effective when sufficient tumor volume is subjected to neoadjuvant therapy rather than after

Table 1. Advantages and disadvantages of neoadjuvant therapy

	Description
Advantages of neoadjuvant treatment	- Earlier attack of micro-metastases - Better compliance with the treatment - Increased operability and higher likelihood of achieving higher R0 resection - Ability to assess the response to the treatment (such as major pathologic response rate or complete pathologic response rate) - Ability to develop guidance for additional treatment (e.g., adjuvant therapy) - Likelihood of better priming an immune system that allows the construction of a larger T-cell receptor repertoire - Facilitation of further exploratory studies of tumor biology using resected specimens
Disadvantages of neoadjuvant treatment	- Risk of disease progression during the treatment - Increased surgical complexity - Increased perioperative morbidity, mortality, and adverse events - Same overall survival as without neoadjuvant treatment

tumor removal [17]; this has also been observed in preclinical mouse models and patients with melanoma showing greater T-cell expansion [18,19].

Adjuvant immunotherapy

The first study to report the clinical outcomes of adjuvant treatment was the IMpower010 study [20], which was a phase 3 open-label study conducted in patients with completely resected stage IB (tumor ≥4 cm) to IIIA NSCLC based on the AJCC seventh edition. In that study, patients were randomized 1:1 to receive either adjuvant atezolizumab (1,200 mg) or best supportive care after adjuvant platinum-based chemotherapy. In total, 1,280 patients were enrolled after undergoing resection and 1,005 patients were eligible for randomization after treatment. After a median follow-up duration of 32.2 months, a primary analysis was performed in the subgroup with stage II–IIIA disease with PD-L1 expression ≥1% (n=476) showing an HR of 0.55 (95% CI, 0.55–0.83; p=0.0039) for disease-free survival (DFS). Extending the patient group to stage II–IIIA regardless of PD-L1 expression (n=882), using the SP263 antibody, showed a slightly lower DFS (HR, 0.79; 95% CI, 0.64–0.96; p=0.020). However, in the intention to treat (ITT) population (n=1,005), including stage IB-IIIA, the HR for DFS was 0.81 (95% CI, 0.67–0.99; p=0.040), which failed to meet the pre-defined statistical cut-off (Fig. 1). The magnitude of clinical benefit in patients with PD-L1 expression ≥50% was shown by an HR for DFS of 0.43 (95% CI, 0.27–0.68). That study included patients with *EGFR* (n=117, 11.6%) and *ALK* mutations (n=33, 3.3%). The updated OS, with a median follow-up duration of 45 months, was reported in the International Association for the Study of Lung Cancer World Conference on Lung Cancer 2022, showing an HR for OS of 0.71 (95% CI, 0.49–1.03) in stage II–IIIA cases with PD-L1 expression ≥1%. The OS benefit was prominent in stage II–IIIA cases with PD-L1 expression ≥50%, showing an HR of 0.45 (95% CI, 0.24–0.78) [21]. Based on this result, the U.S. Food and Drug Administration (FDA) approved 1-year therapy with atezolizumab in patients with stage II–IIIA tumors with PD-L1 expression 1% in October 2021 [22]. The European Medicines Agency approved atezolizumab in patients with PD-L1 expression ≥50% that do not harbor *EGFR* or *ALK* mutations [23]. However, there are foreseen challenges in this approach. Among the patients who underwent surgery, 21.5% could not be randomized. The major reason was the withdrawal of informed consent by the participants (31.3%), followed by disease relapse (19.6%), other reasons (14.9%), and adverse events (12.4%). In addition, adverse events (AEs) leading to discontinuation of treatment occurred in 18.2% of those who received atezolizumab, and grade 3 or 4 immune-related AEs were observed in 7.9% of patients, underscoring the need for caution while applying adjuvant immunotherapy.

Another landmark adjuvant trial conducted in the same population was the KEYNOTE-091/PEARLS study [24]. In the interim analysis of this study, the median DFS was 53.6 versus 42.0 months (HR, 0.76; 95% CI, 0.63–0.91; p=0.0014) in the ITT population (n=1,177) regardless of PD-L1 expression. However, in the subgroup with a PD-L1 tumor proportion score by 22C3, a median DFS of 50% or higher was not reached in both groups (HR, 0.82; 95% CI, 0.57–1.18; p=0.14). The discrepancy in DFS outcomes in the PD-L1 50% subgroup between the KEYNOTE-091 and IMpower010 studies remains to be carefully observed through long-term follow-up results.

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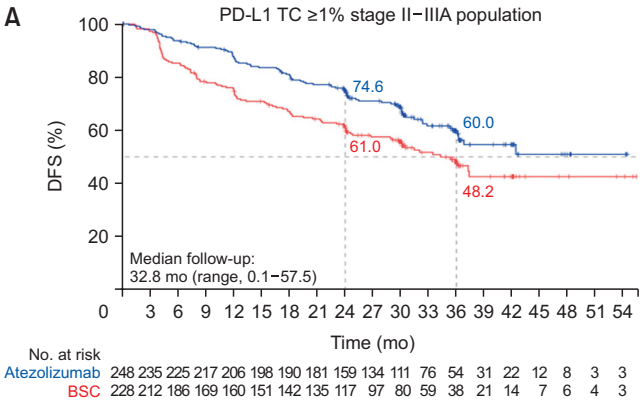
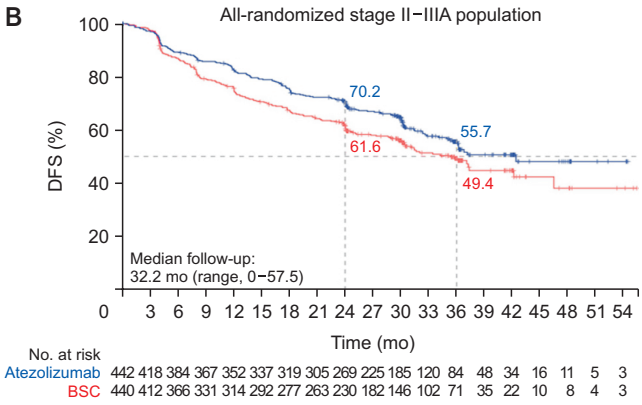
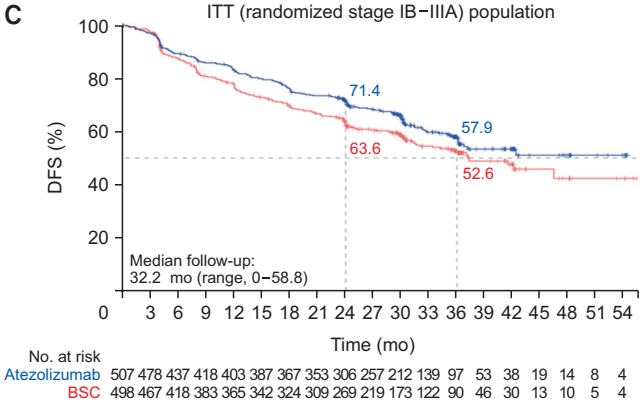


	Atezolizumab (n=248)	BSC (n=228)
Median DFS (95% CI), mo	NE (36.1–NE)	35.3 (29.0–NE)
Stratified HR (95% CI)	0.66 (0.50–0.88)	
p-value	0.004	



	Atezolizumab (n=442)	BSC (n=440)
Median DFS (95% CI), mo	42.3 (36.0–NE)	35.3 (30.4–46.4)
Stratified HR (95% CI)	0.79 (0.64–0.96)	
p-value	0.02	



	Atezolizumab (n=507)	BSC (n=498)
Median DFS (95% CI), mo	NE (36.1–NE)	37.2 (31.6–NE)
Stratified HR (95% CI)	0.81 (0.67–0.99)	
p-value	0.04	

Fig. 1. (A–C) Disease-free survival (DFS) benefit observed in the IMPower-010 study. PD-L1, programmed cell death ligand-1; TC, tumor cell; ITT, intention to treat; BSC, best supportive care; CI, confidence interval; HR, hazard ratio; NE, not evaluable.

Neoadjuvant immunotherapy

The underlying strategy for neoadjuvant immunotherapy is based on T-cell expansion, following the hypothesis that more T-cell expansion might be induced in earlier stages of cancer, when the T-cell function is less impaired, before surgery compared with adjuvant therapy [25]. The clinical efficacy of neoadjuvant ICB has been primarily evaluated in patients with surgically resectable NSCLC using 2 preoperative doses of nivolumab, a PD-1 inhibitor, in patients with surgically resectable stage I–IIIA NSCLC [26]. In that study, a major pathological response (MPR) was observed in 45% of the resected tumors, along with an increase in the number of T-cell clones, without delaying surgery. As a follow-up study, the landmark phase 3 clinical trial, CheckMate-816, included patients with newly diagnosed, resectable stage IB (≥4 cm) to IIIA NSCLC, according to the AJCC seventh edition, without driver mutation [27]. In that study, patients were 1-to-1 randomized and treated with nivolumab and chemotherapy or nivolumab alone. Surgery was performed within 6 weeks after the last dose of treatment. The primary endpoints of

that study were pathologic complete response (pCR) and event-free survival (EFS). Of note, the study arm demonstrated a significantly higher pCR rate (24.0% versus 2.2%; odds ratio [OR], 13.94; 95% CI, 3.49–55.75; p<0.0001) and MPR rate (36.9% versus 8.9%; OR, 5.70; 95% CI, 3.16–10.26) (Fig. 2A). The depth of response was also of substantial magnitude in the study arm, showing a median percentage of viable tumors of 10%, which was much lower than the 74% observed in the control arm. The significant benefit in pathologic response also led to an EFS difference, with a median EFS of 31.6 months versus 20.8 months (HR, 0.63; 95% CI, 0.43–0.91; p=0.0052) (Fig. 2B). Most importantly, despite the fact that that study was conducted in a very-early-stage population, the OS curve showed an early separation even after a median follow-up duration of 29.5 months (Fig. 2C). In that study, multiple surgical parameters were reported. In the study arm, surgical delay (21% in the study arm and 18% in the control arm), length of hospital stay, and the 90-day surgery-related complication rate showed no significant differences between the groups [28]. Based on the positive outcomes of the CheckMate 816 study, the FDA approved neoadjuvant immunotherapy combined with chemotherapy on March 4, 2022 [22].

Ongoing trials and novel approaches

In addition to the current landmark trial leading to regulatory approval, a number of phase III trials are ongoing in either neoadjuvant or adjuvant settings (Table 2).

A perioperative immunotherapy regimen has advanced survival benefits because it incorporates ICB treatment in both neoadjuvant and adjuvant settings. A promising outcome was observed in the NADIMII study, which included patients with stages IIIA and IIIB disease. In that study, patients received 3 cycles of nivolumab with chemotherapy, with 6 additional months of adjuvant nivolumab [29]. The

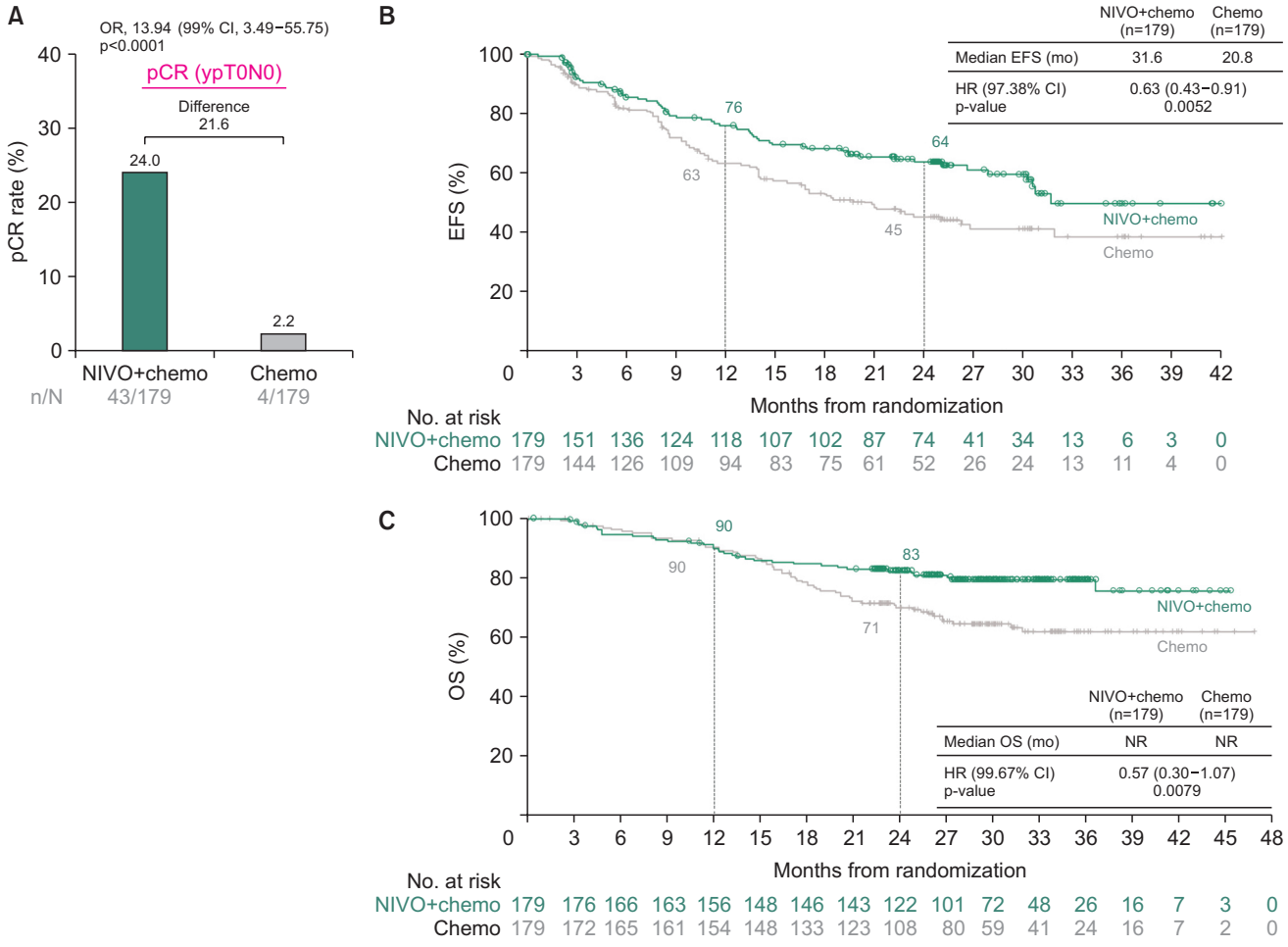


Fig. 2. Pathologic complete response (pCR) rate (A), event-free survival (EFS) (B), and overall survival (OS) (C) between the study and control arms. OR, odds ratio; CI, confidence interval; NIVO, nivolumab; Chemo, chemotherapy; HR, hazard ratio; NR, not reached.

Table 2. The current ongoing representative perioperative phase III adjuvant and/or neoadjuvant trials of immune checkpoint inhibitors

Setting	Study	NCT	Stage	Regimen	Duration
Adjuvant	IMpower010	NCT02486718	IB (≥4 cm)–IIIA	Atezolizumab	1 Year
Adjuvant	Pearls/KN091	NCT02504372	IB (≥4 cm)–IIIA	Pembrolizumab	1 Year
Adjuvant	ANVIL	NCT02273375	IB (≥4 cm)–IIIA	Nivolumab	1 Year
Adjuvant	ALCHEMIST	NCT02194738.	IB (≥4 cm)–IIIA	Pembrolizumab+chemotherapy (4 cycles)	1 Year+4 cycles
Adjuvant	BR.31	NCT02273375	IB (≥4 cm)–IIIA	durvalumab	1 Year
Neoadjuvant	CheckMate-816	NCT02998528	IB (≥4 cm)–IIIA	Nivolumab+platinum doublet	3 Cycles
Neo & adjuvant	CheckMate-77T	NCT04025879	IIA–IIB (T3N2)	Nivolumab+platinum doublet; (adjuvant) nivolumab	(Neoadjuvant) 3 cycles; (adjuvant) 1 year
Neo & adjuvant	KN671	NCT03425643	IB–IIIA	Pembrolizumab+platinum doublet; (adjuvant) pembrolizumab	(Neoadjuvant) 4 cycles; (adjuvant) 1 year
Neo & adjuvant	IMpower030	NCT0345606	II–IIIB (T3N2)	Atezolizumab+platinum doublet; (adjuvant) atezolizumab	(Neoadjuvant) 4 cycles; (adjuvant) 1 year
Neo & adjuvant	Aegean	NCT03800134	IB (≥4 cm)–IIIB	Durvalumab+platinum doublet; (adjuvant) atezolizumab	(Neoadjuvant) 4 cycles; (adjuvant) 1 year

NCT, National Clinical Trial.

control arm in that study received only 3 cycles of cytotoxic chemotherapy before surgery. Although the study population included patients with advanced-stage NSCLC, the pCR rate was higher (36.8% versus 6.9%), and PFS was significantly longer in the study arm (not reached versus 18.3 months; HR, 0.48; 95% CI, 0.25–0.91; p=0.025). Additionally, OS also showed a clear separation between the groups, showing an HR of 0.40 (95% CI, 0.71–0.93; p=0.0034) after 26.1 months of follow-up. Based on this promising outcome, data from ongoing phase III trials comparing perioperative immunotherapy, such as CheckMate 77T (NCT04025879), IMpower 030 (NCT03456063), and AEGEAN (NCT03800134), are awaited. Lastly, there are ongoing studies evaluating ICB combination regimens without cytotoxic chemotherapy, which require further validation with a larger number of patients [30].

Discussion

Immunotherapy for the treatment of early-stage NSCLC has become a standard practice. However, the introduction of novel therapies has raised multiple questions that require further elucidation. Since both adjuvant-only and neoadjuvant-only regimens were approved at a similar time point, practical decisions regarding selection of ICB treatment either before or after surgery become essential. The treatment decision also needs to be made based on data showing that 21.5% of patients were not able to receive adjuvant therapy after surgery with adjuvant cytotoxic chemotherapy. Moreover, whether applying adjuvant ICB for an additional 12 months, as in the IMpower 010 study, is sufficient has yet to be determined. In terms of biomarkers, some studies have suggested patient selection based on high expression of the PD-L1 protein in the tumor [20]. However, another study did not determine the clinical benefit of choosing treatment based on PD-L1 protein expression [24]. Lastly, whether the magnitude of clinical benefit could be achieved by incorporating ICB both before and after surgery still requires further evidence.

Since increasingly many patients are exposed to ICB in the perioperative setting, the following issues will cause challenges in the current clinical practice. First, although multiple adjuvant trials have succeeded in preventing disease relapse, the OS benefit was limited. Although the results of neoadjuvant therapy currently seem more likely to lead to a survival benefit compared with other studies, long-term follow-up results have not yet been published. Second, before immunotherapy was approved as a perioperative regimen, ICB was the core backbone of treatment in the palliative setting. For this reason, if patient relapses after ICB is used for curative intent, no definitive clinical evidence indicates whether an ICB re-challenge should be performed with palliative aims. Lastly, the safety profile of adjuvant therapy cannot be overemphasized. Unlike minor immune-related AEs, such as hypothyroidism or hyperthyroidism, an acceptable trade-off for clinical efficacy in the palliative setting regarding these adverse events should be weighed considering these patients as potentially curable candidates. For the same reason, severe immune-mediated AEs, such as pneumonitis, meningitis, or Guillain-Barré syndrome, might be major hurdles for perioperative immunotherapy despite their very rare incidence.

As perioperative strategies have become more complicat-

ed, a multidisciplinary team approach has become more important. Other than the initial evaluation of resectability by the surgeon, other components, such as *EGFR* and *ALK* mutation status, the PD-L1 expression profile, and tolerability of immunotherapy should be carefully considered in the treatment decision. Hence, it is more important than ever for other relevant specialists, particularly medical oncologists, to participate in the perioperative decision-making process with surgeons to achieve the best treatment outcomes.

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Author contributions

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Conflict of interest

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