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EDITORIAL

Chinese Society of Clinical Oncology Non-small Cell Lung Cancer (CSCO NSCLC) guidelines in 2024: key update on the management of early and locally advanced NSCLC

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The Chinese Society of Clinical Oncology Non-small Cell Lung Cancer (CSCO NSCLC) guidelines were first published in 2016, ranking among the earliest-released guidelines within the CSCO series. In 2020 the CSCO published separate guidelines for NSCLC and small cell lung cancer (SCLC) for the first time to improve clinical usability. Compilation of the NSCLC guidelines takes into account the latest domestic and international research progress, including the accessibility of treatment options and regional development disparities specifically within China, further synthesizing expert opinions to provide rational, graded recommendations. The CSCO guidelines have become an essential reference and decision-making tool for clinicians in China since inception in 2016. With the advances and extension of treatment modalities and the emergence of new treatment models, significant breakthroughs have been achieved in the treatment of early-stage and locally advanced NSCLC. The 2024 CSCO guidelines have updated the recommended treatment regimens for these patients. By combining relevant clinical trial data, this article provides a detailed interpretation of the key updates on the treatment of early-stage and locally advanced NSCLC in the *Guidelines of CSCO non-small cell lung cancer.*

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Addition of NSCLC molecular typing: immunotherapy and targeted therapy in postoperative adjuvant treatment

The IMpower010 trial was designed to determine the efficacy of atezolizumab *vs.* best supportive care after adjuvant chemotherapy in resectable stage IB-IIIA NSCLC patients[1]. The study demonstrated that atezolizumab offers superior median disease-free survival (mDFS) benefits compared to best supportive care for patients with stage II-IIIA NSCLC and the degree of DFS benefit correlates with higher PD-L1 expression. The data indicated that the mDFS in the intention-to-treat (ITT) population [atezolizumab group *vs.* best supportive care group, not reached (NR) *vs.* 37.2 months, respectively, with a hazard ratio (HR) of 0.81], suggesting that atezolizumab reduces the risk of recurrence, new primary tumors, or death by 19% for all patients with II-IIIA NSCLC. A stratified analysis based on PD-L1 tumor cell (TC) expression showed the following: the mDFS in patients with a PD-L1 TC expression ≥ 1% [atezolizumab group *vs.* best supportive care group, not evaluable (NE) *vs.* 35.3 months, respectively, with an HR of 0.66; **Table 1**]; the mDFS in patients with a PD-L1 TC expression between 1% and 49% (atezolizumab group *vs.* best supportive care group, 32.8 *vs.* 31.4 months, respectively, with an HR of 0.87); and the mDFS in patients with a PD-L1 TC expression ≥ 50% (atezolizumab group *vs.* best supportive care group, NE *vs.* 35.7 months, respectively, with an HR of 0.43). Atezolizumab was approved by the China National Medical Products

Table 1 Some major randomized clinical trials with early and locally advanced NSCLC

Trials	Phases	Inclusion	Experimental groups	Control groups	Primary endpoint	Results of primary endpoints
IMpower010	Adjuvant (after chemotherapy)	Resectable stage IB-IIIA	Atezolizumab	Best supportive care	DFS	NR *vs.* 35.3 months (II-IIIA PD-L1 ≥ 1%)
ALINA	Adjuvant	Resectable stage IB-IIIA ALK+	Alectinib	Platinum-based chemotherapy	DFS	NR *vs.* 44.4 months (II-IIIA)
NCT03110978	Early-stage	Inoperable stage I-II or isolated parenchymal recurrences	Immunotherapy + SABR	SABR	4-year EFS rate	77% *vs.* 53%
KEYNOTE-671	Neoadjuvant + adjuvant	Resectable stage II-IIIB	Neoadjuvant: pembrolizumab + cisplatin-based chemotherapy Adjuvant: pembrolizumab	Neoadjuvant: placebo + cisplatin-based chemotherapy Adjuvant: placebo	EFS and OS	mEFS: NR *vs.* 17.0 months mOS: NR *vs.* 45.5 months
RATIONALE-315	Neoadjuvant + adjuvant	Stage II-IIIA	Neoadjuvant: tislelizumab + platinum-doublet chemotherapy Adjuvant: tislelizumab	Neoadjuvant: placebo + platinum-doublet chemotherapy Adjuvant: placebo	MPR rate	56.2% *vs.* 15.0%
AEGEAN	Neoadjuvant + adjuvant	Resectable stage II-III	Neoadjuvant: durvalumab + platinum-doublet chemotherapy Adjuvant: durvalumab	Neoadjuvant: placebo + platinum-doublet chemotherapy Adjuvant: placebo	pCR rates and EFS	pCR rates: 17.2% *vs.* 4.3% mEFS: NR *vs.* 25.9 months
CheckMate 77T	Neoadjuvant + adjuvant	Resectable stage IIA-IIIB	Neoadjuvant: nivolumab + platinum-doublet chemotherapy Adjuvant: nivolumab	Neoadjuvant: placebo + platinum-doublet chemotherapy Adjuvant: placebo	EFS	NR *vs.* 18.4 months
Neotorch	Neoadjuvant + adjuvant	Resectable stage II-III	Neoadjuvant: toripalimab + platinum-based chemotherapy Adjuvant: toripalimab	Neoadjuvant: placebo + platinum-based chemotherapy Adjuvant: placebo	EFS and MPR rate	mEFS: NR *vs.* 15.1 months MPR rate: 48.5% *vs.* 8.4%
TD-FOREKNOW	Neoadjuvant	Resectable stage IIIA-IIIB	Camrelizumab + chemotherapy (nab-paclitaxel and platinum)	Chemotherapy (nab-paclitaxel and platinum) alone	pCR rate	32.6% *vs.* 8.9%

DFS, disease-free survival; EFS, event-free survival; MPR, major pathologic response; NR, not reached; OS, overall survival; pCR, pathologic complete response.

Administration (NMPA) on 16 March 2022 as monotherapy for adjuvant treatment of stage II-IIIA NSCLC PD-L1-positive (TC ≥ 1%) patients who have undergone surgical resection and completed platinum-based chemotherapy based on the IMpower010 study findings[2]. Therefore, the guidelines have added "Postoperative stage II/III NSCLC should undergo PD-L1 expression testing to guide adjuvant immunotherapy" as a Class I recommendation. Additionally, updated data from the American Association for Cancer Research (AACR) on the IMpower010 trial indicated that the unstratified overall survival (OS) HR for the Asian ITT population was 0.73, which is consistent with the global HR of 0.71. Data from the 5-year follow-up evaluation of the Asian population in the IMpower010 study presented at the CSCO annual meeting in September 2024 showed that in the stage II-IIIA population with PD-L1 TC expression ≥ 1%, the mDFS in the atezolizumab group was not reached with an unstratified HR of 0.69. OS data were not mature in the second interim analysis. The 5-year OS rates in the stage II-IIIA Asian patients with PD-L1 TC expression ≥ 1% and stage II-IIIA Asian patients with PD-L1 TC expression ≥ 50% were 83.5% and 90.9%, respectively, confirming the excellent efficacy of atezolizumab as adjuvant therapy[3].

Even ALK-positive NSCLC patients receiving platinum-based adjuvant chemotherapy still experience a high recurrence rate post-surgery. The ALINA study, a global, phase III, open-label, randomized trial, aimed to determine the efficacy of alectinib *vs.* platinum-based chemotherapy in adjuvant treatment for patients with resectable stage IB-IIIA ALK-positive NSCLC[4]. The mDFS data were as follows: patients with stage II-IIIA NSCLC, NR *vs.* 44.4 months for the adjuvant alectinib *vs.* platinum-based chemotherapy group, respectively (HR = 0.24); and patients with stage IB-IIIA, NR *vs.* 41.3 months for the adjuvant alectinib *vs.* platinum-based chemotherapy group, respectively (HR = 0.24). The 2-year DFS for the alectinib group *vs.* the chemotherapy group was 93.8% *vs.* 63.0%, respectively, and the 3-year DFS was 88.3% *vs.* 53.3%, respectively. The 2-year DFS for the alectinib group *vs.* the chemotherapy group was 93.6% *vs.* 63.7%, respectively, in the ITT population. Additionally, alectinib demonstrated a benefit in the central nervous system-DFS compared to chemotherapy with an HR of 0.22. It is noteworthy that the indication for adjuvant alectinib treatment was approved by the U.S. Food & Drug Administration (FDA) in April 2024. Adjuvant alectinib treatment received approval from the European Commission and the NMPA in June 2024, achieving almost simultaneous global approval for adjuvant treatment of patients with stage IB-IIIA ALK-positive NSCLC based on the 8th edition of the *American Joint Committee on Cancer staging manual*. However, due to pharmacoeconomic considerations, the 2024 CSCO guidelines have added "For patients with postoperative pathologic detection of ALK fusion, adjuvant alectinib treatment after surgery" as a Class II recommendation for operable stage IIA-IIIB NSCLC treatment.

Novel treatment option for inoperable early-stage NSCLC: radiotherapy combined with immunotherapy

Surgical resection has traditionally been the preferred standard treatment for patients with early-stage NSCLC. However, surgery is invasive and some patients may not tolerate radical surgical treatment. Stereotactic ablative body radiotherapy (SABR) is the standard treatment for early-stage lung cancer patients who are not candidates for surgery, providing an OS similar to surgical patients. Although the intrathoracic local control rate after SABR exceeds 90%, extrapulmonary recurrence is relatively common, indicating the necessity for combined systemic therapy with SABR. Combining SABR with immunotherapy increased the 4-year event-free survival (EFS) from 53% with SABR alone to 77% in a phase II randomized controlled trial involving patients with inoperable early-stage treatment-naive or lung parenchymal recurrent node-negative NSCLC[5]. The combination therapy regimen did not lead to the occurrence of ≥ 3 grade pneumonia or ≥ 4 grade adverse events. Therefore, combining immunotherapy with SABR represents a treatment option. Based on the above data, the guidelines have been updated to include "SABR combined with immunotherapy" as a Class II recommendation for treating inoperable stage IA and IB NSCLC (**Table 2**).

"The sandwich cookie" treatment paradigm: the era of combination perioperative immunotherapy and chemotherapy

The KEYNOTE-671 trial demonstrated that the mEFS in patients with resectable stage II-IIIB NSCLC receiving neoadjuvant pembrolizumab plus chemotherapy followed by

Table 2 Some major updates on immune combination therapy for early and locally advanced NSCLC

Staging	Stratification	Class I recommendation	Class II recommendation	Class III recommendation
Stage IA and IB	Unresectable	NA	SABR combined with immunotherapy	NA
Stage IIA and IIB	Resectable	NA	Platinum-based chemotherapy combined with pembrolizumab or tislelizumab for neoadjuvant and adjuvant treatment	Platinum-based chemotherapy combined with durvalumab for neoadjuvant and adjuvant treatment; Adjuvant nivolumab after neoadjuvant platinum-based chemotherapy combined with nivolumab treatment
Stage IIIA and IIIB	Resectable	Platinum-based chemotherapy combined with toripalimab for neoadjuvant and adjuvant treatment	Platinum-based chemotherapy combined with pembrolizumab, tislelizumab, or camrelizumab for neoadjuvant and adjuvant treatment	Platinum-based chemotherapy combined with durvalumab for neoadjuvant and adjuvant treatment; adjuvant nivolumab after neoadjuvant platinum-based chemotherapy combined with nivolumab treatment

NA, not available.

adjuvant pembrolizumab was 47.2 months compared to 18.3 months with chemotherapy alone with an HR of 0.59. The mOS was NR in the pembrolizumab group *vs.* 52.4 months in the chemotherapy-alone group with an HR of 0.72. The 36-month OS was 71% *vs.* 64% and the incidence of grade 3–5 treatment-related adverse events was 45% *vs.* 38%[6]. The U.S. FDA approved pembrolizumab in combination with chemotherapy for neoadjuvant treatment of resectable NSCLC (T ≥ 4 cm or N+), followed by adjuvant monotherapy with pembrolizumab post-surgery on 16 October 2023 based on the KEYNOTE-671 study findings.

The RATIONALE-315 study showed that the major pathologic response (MPR) with neoadjuvant tislelizumab plus chemotherapy followed by adjuvant tislelizumab *vs.* chemotherapy alone was 56.2% *vs.* 15.0% in patients with resectable stage II-IIIA NSCLC. The pathologic complete response (pCR) was 40.7% *vs.* 5.7%[7]. The NMPA approved a new indication of tislelizumab on 21 October 2024 based on the RATIONALE-315 study for combination platinum-containing chemotherapy as neoadjuvant treatment, followed by adjuvant monotherapy with tislelizumab after surgery for patients with resectable stage II or IIIA NSCLC.

The AEGEAN study findings suggested that combination neoadjuvant durvalumab with chemotherapy followed by adjuvant durvalumab *vs.* chemotherapy alone yields an mEFS of NR *vs.* 25.9 months (HR = 0.68) with a pCR of 17.2% *vs.* 4.3% in patients with resectable stage IIA-IIIB NSCLC, highlighting the advantages of perioperative immunotherapy[8].

The CheckMate 77T study showed that neoadjuvant nivolumab combined with chemotherapy followed by adjuvant nivolumab *vs.* chemotherapy alone results in an mEFS of NR *vs.* 18.4 months (HR = 0.58) in patients with resectable stage II-IIIB NSCLC, indicating that nivolumab before and after surgery significantly extends the mEFS[9].

The Neotorch study indicated that the mEFS with neoadjuvant toripalimab combined with chemotherapy followed by adjuvant toripalimab *vs.* chemotherapy alone is NR *vs.* 15.1 months (HR = 0.40) in patients with resectable stage II or III NSCLC, respectively. The MPR was 48.5% *vs.* 8.4%, respectively, and the pCR was 24.8% *vs.* 1.0%, respectively. The Neotorch study primarily reported results of patients with stage IIIA-IIIB NSCLC[10]. The NMPA approved combination toripalimab with chemotherapy for neoadjuvant treatment followed by adjuvant toripalimab monotherapy for adult patients with resectable stage IIIA-IIIB NSCLC on 26 December 2023 based on the Neotorch study findings.

The TD-FOREKNOW study showed that the pCR with neoadjuvant camrelizumab combined with chemotherapy followed by adjuvant camrelizumab *vs.* chemotherapy alone is 32.6% *vs.* 8.9% and MPR is 65.1% *vs.* 15.6% in patients with stage IIIA or IIIB NSCLC, respectively, indicating that camrelizumab is a potential treatment option for perioperative NSCLC[11].

The results of these studies confirmed that "sandwich cookie" perioperative therapy combines the advantages of neoadjuvant and adjuvant immunotherapy, which offers

greater benefits. This approach initiates antitumor immunity in the presence of primary tumors and lymph node metastases and helps eliminate residual micrometastases before and after surgery. The guidelines have been updated based on the data from the above clinical studies, as follows: resectable stage IIA and IIB NSCLC, (1) "platinum-based chemotherapy combined with pembrolizumab or tislelizumab for neoadjuvant and adjuvant treatment" was added as a Class II recommendation, (2) "platinum-based chemotherapy combined with durvalumab for neoadjuvant and adjuvant treatment" was added as a Class III recommendation, and (3) "adjuvant nivolumab after neoadjuvant platinum-based chemotherapy combined with nivolumab treatment" was added as a Class III recommendation; and patients with resectable stage IIIA or IIIB NSCLC, (1) "platinum-based chemotherapy combined with toripalimab for neoadjuvant and adjuvant treatment" was added as a Class I recommendation, (2) "platinum-based chemotherapy combined with pembrolizumab, tislelizumab, or camrelizumab for neoadjuvant and adjuvant treatment" was added as a Class II recommendation, (3) "platinum-based chemotherapy combined with durvalumab for neoadjuvant and adjuvant treatment" was added as a Class III recommendation, and (4) "adjuvant nivolumab after neoadjuvant platinum-based chemotherapy combined with nivolumab treatment" was added as a Class III recommendation (**Table 2**). However, it remains unclear whether the efficacy of this treatment model is significantly correlated with PD-L1 expression. Therefore, testing for PD-L1 expression prior to treatment is not recommended.

The presence of EGFR mutations or ALK fusions is a contraindication for neoadjuvant/perioperative and adjuvant immunotherapy. Therefore, it is important to perform molecular profiling (ideally in a multiplex platform) in early-stage NSCLC.

Conclusions

The 2024 CSCO NSCLC guidelines have undergone significant updates for early and locally advanced NSCLC. The updates primarily focus on targeted therapy and immunotherapy (especially the latter), reflecting the recent trends in drug development. The inclusion of atezolizumab adjuvant therapy based on PD-L1 expression and alectinib adjuvant therapy based on ALK fusion detection have led to more precise molecular typing-based NSCLC treatment. The combination of immunotherapy, such as nivolumab, with radiotherapy offers a new therapeutic option for inoperable stage IA and IB NSCLC. Based on the results of several perioperative immunotherapy clinical studies, the "neoadjuvant plus adjuvant" treatment model has become the predominant approach, building upon the previous "neoadjuvant" or "adjuvant" therapy models. Pembrolizumab, tislelizumab, durvalumab, toripalimab, and camrelizumab have become the agents recommended for this treatment model, heralding a new era of "sandwich cookie" perioperative combined immunotherapy and chemotherapy for NSCLC.

The timely incorporation of these new findings into guidelines is essential to provide clinicians in China with a reference for clinical practice, which is the essence of guideline development. We believe that the CSCO NSCLC guidelines will continue to be grounded in evidence-based practice, starting from the actual circumstances of patients in China, and progressively enhancing the international influence.

Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Zhijie Wang, Boyang Sun.
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Contributed data or analysis tools: Siyuan Chen, Boyang Sun.
Performed the analysis: Siyuan Chen, Boyang Sun.
Wrote the paper: Siyuan Chen, Boyang Sun, Zhijie Wang.

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