Consensus

Expert consensus on perioperative treatment for non-small cell lung cancer

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Background

Non-small cell lung cancer (NSCLC) accounts for 85% of all newly diagnosed lung cancer cases. Among patients with NSCLC, about 20% are diagnosed with stage I and II, and 30% with stage III diseases (1). In recent years, the popularity of low-dose computed tomography (CT) screening for thoracic disease has resulted in a higher proportion of early-stage NSCLC cases being diagnosed. The mainstay of treatment for stages I–IIIA NSCLC is radical surgery coupled with neoadjuvant or adjuvant therapy in the appropriate setting (2). In patients with completely resected NSCLC, postoperative adjuvant chemotherapy has been associated with better overall survival (OS) in patients with early-stage disease. However, even for the patients with stage I NSCLC, the 5-year lung cancer-specific mortality rate after radical resection has remained unsatisfactory (3).

Platinum-based doublet chemotherapy is the standard adjuvant therapy for resected early NSCLC, but its efficacy is only modest, with an absolute 5-year OS increment of 5% from 40% to 45% (4,5). Clinicians urgently need better treatment strategies to improve the survival for these patients. The development of programmed cell death protein 1/programmed death ligand 1 (PD-1/PDL-1) checkpoint inhibitors has changed the therapeutic approach to the perioperative management of NSCLC. In recent years, neoadjuvant- and adjuvant-immunotherapy-containing regimens have gradually been adopted in early-stage NSCLC, with encouraging short- and long-term outcomes (6). In addition to immune checkpoint inhibitors (ICIs), targeted therapies have also been studied and proven to be beneficial to the appropriate populations in the perioperative setting. Despite many successful clinical studies and heated discussions, the perioperative precision treatment of NSCLC still currently lacks an expert consensus.

At present, perioperative precision management does not satisfy medical needs, and consistent progress and breakthroughs are urgently needed in standardized diagnosis and treatment strategies. Keeping in mind the development of preoperative therapy and postoperative therapy in NSCLC, as well as the increase in publication of phase III clinical trials in this area, the broad definition of perioperative period here will cover neoadjuvant therapy and adjuvant therapy within 3 years post-surgery. A consensus and guideline development panel consisting of thoracic surgeons and oncologists from around the world was established to decide the methodologies, processes, levels of evidence, and related recommendations. A comprehensive search was conducted on PubMed. Original articles published in English language before March 2022 were included. Combinations of the following terms were searched online: “NSCLC”, “non-small cell lung cancer”, “adjuvant”, “pathologic diagnosis”, “postoperative management”, “neoadjuvant”, “programmed cell death-1 (PD-1)”, “programmed cell death-ligand 1 (PD-L1)”, “chemotherapy”, “postoperative”, “perioperative”, “immunotherapy”, “target therapy”, “tyrosine kinase inhibitor (TKI)”, and “biomarker”. The most recent international conferences were also taken into account to ensure the treatment strategy was state of the art.

Table 1 Categories of evidence and consensus

Category	Evidence and consensus
Category 1	Based upon high-level evidence; there is uniform consensus that the intervention is appropriate
Category 2A	Based upon lower-level evidence; there is uniform consensus that the intervention is appropriate
Category 2B	Based upon lower-level evidence, there is consensus that the intervention is appropriate
Category 3	Based upon any level of evidence; there is major disagreement that the intervention is appropriate

The level of evidence, based on the National Comprehensive Cancer Network (NCCN) guideline, was defined according to the criteria outlined in *Table 1* (7). The strength of recommendations was classified as "strong" or "weak" according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system (8), and the recommendation statement was composed based on the real-world evidence. A "strong" recommendation generally refers to recommendations based on high-level evidence with consistency between clinical behavior and outcome expectancy; in contrast, a "weak" recommendation is typically based on low-level evidence with uncertainty between clinical behavior and outcome expectancy. After the first draft had been completed, all the panel members contributed to revising and finalizing this document.

Consensus 1: pathological diagnosis and biomarker testing

(I) Pathological diagnosis and biomarker testing of lung cancer is necessary (Category 1).

(II) For adjuvant therapy, detection of epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*), and other rare gene alterations is necessary to guide targeted adjuvant treatment. PD-L1 expression detection can be used as a companion diagnosis to guide the treatment decision of immunotherapy. Based on current evidence-based medical evidence, EGFR and PD-L1 are companion diagnostics to guide postoperative adjuvant therapy (Category 1).

(III) Next-generation sequencing (NGS) detection can simultaneously detect multiple biomarkers, which could be considered (Category 2B).

(IV) Molecular detection and PD-L1 assays are suggested for using approved assays (Category 1).

(V) For neoadjuvant therapy, pathological assessment of pathologic complete response (pCR) is required after surgery (Category 2A).

The type of immunotherapy and target therapy that has emerged in recent years represents a revolutionary breakthrough in the field of tumor treatment (9,10). The development and application speed of these therapies for NSCLC have improved significantly. However, how to select those individuals who would benefit most from treatment remains a significant challenge in the clinical application of this therapy. Comprehensive molecular biological testing information can provide a basis for the selection of immunotherapy for patients with lung cancer, prognostic judgment, and clinical trial enrollment.

In the future, through the full management of the clinical diagnosis and treatment information, genetic test results, and follow-up treatment plans, an individualized precision treatment platform for patients with NSCLC can be established while real-world data can be accumulated to continuously enrich and improve the panorama of individualized diagnosis and treatment of NSCLC patients. In addition, emphasizing the cooperation between oncologists and pathologists as well as that between molecular biology and bioinformatics experts while building a new multidisciplinary diagnosis and treatment model for the molecular oncology expert committee are also important development directions for oncology clinical and research.

Consensus 2: neoadjuvant therapy for NSCLC patients

(I) For patients with resectable stage II–IIIA NSCLC (without sensitive mutation), neoadjuvant immunotherapy combined with platinum-doublet chemotherapy or platinum-doublet chemotherapy alone may be considered before surgery. Neoadjuvant immunotherapy combined with platinum-doublet chemotherapy is preferred (Category 2A).

(II) For patients with potential resectable locally advanced NSCLC, neoadjuvant immunotherapy combined

Table 2 Neoadjuvant therapy for NSCLC

NCT	n	Stage	Surgical resection	Regimen	MPR [%]	pCR [%]	ORR [%]	Potential predictor	Pathological downstage [%]	>3 TRAEs [%]	Survival
NCTO2259621	22	I–IIIa	21 (R0: 20)	Nivolumab ×2 + S	9 [45]	2 [10]	2 [10]	TMB	8 [40]	1 [5]	18-mon RFS: 73%
ChiCTR-OIC-17013726	49	Ia–IIIb	37	Sintilimab + S	15 [40]	6 [16]	8 [20]	PET-CT SUV	14 [29]	4 [10]	NA
LCMC3 (NCT02927301)	101	Ib–IIIa	90	Atezolizumab ×2	15 [18]	4 [5]	NA	NA	NA	4 [4]	NA
IONESCO	46	Ib–IIIa	44	Durvalumab ×3 + S	8 [17]	3 [7]	4 [9]	NA	NA	NA	1-yr RFS: 78.2%; 1-yr OS: 89.1%
PRINCEPS (NCT02994576)	30	I–IIa	30 (R0: 29)	Atezolizumab ×1	4 [13]	0	2 [7]	PD-L1	NA	NA	NA
NEOSTAR Arm A (NCT03158129)	23	I–IIIa	21	Nivolumab + S	4 [17]	2 [9]	NA	NA	NA	1 death	NA
NEOSTAR Arm B (NCT03158129)	21	I-IIIa	16	(Nivolumab + Ipilimumab) + S	6 [29]	4 [21]	NA	NA	NA	NA	NA
NCT01820754 (TOP1201)	24	Ib–IIIa	13	CT ×1 + (Ipilimumab + CT) ×2 + S	NA	NA	14 [58]	NA	NA	11 [46]	mOS: 29.2 mon
NCT02716038	30	Ib–IIIa	29 (R0: 26)	(Atezolizumab + CT) ×2 + S	17 [57]	10 [33]	19 [63]	NA	19 [63]	15 [50]	mDFS: 17.9 mon
SAKK 16/14 (NCT02572843)	68	IIIa (N2)	55	(CT ×3 + Durvalumab ×2) + S	33 [60]	10 [18]	NA	NA	37 [67]	59 [88]	1-yr EFS: 73.3%
NADIM (NCT03081689)	46	IIIa (N2)	41	(Nivolumab + CT) + S	34 [83]	26 [63]	35 [76]	PD-L1	29 [63]	16 [34]	2-yr PFS: 77.1%; 2-yr OS: 89.9%

NSCLC, non-small cell lung cancer; MPR, main pathological response; pCR, pathological complete response; ORR, objective response rate; S, surgery; CT, chemotherapy; TRAES, treatment related adverse effects; TMB, tumor mutation burden; PET-CT, positron emission tomography-computed tomography; SUV, standardized uptake value; NA, not available; PD-L1, programmed cell death-ligand 1; RFS, recurrence-free survival; OS, overall survival; mOS, median overall survival; mDFS, median disease-free survival.

with platinum-doublet chemotherapy, neoadjuvant single-agent immunotherapy, or platinum-doublet chemotherapy alone may be considered to reduce the tumor burden and reassess the possibility of surgery after downgrading (Category 2A).

(III) The recommended number of cycles for neoadjuvant immunotherapy is 2–4, with an evaluation being performed every 2 cycles to formulate follow-up treatment plans. Preoperative staging and efficacy evaluation are required (Category 2A).

(IV) Use of multidisciplinary teams (MDTs) for treatment of all patients with stage III NSCLC is recommended (Category 2A).

Preoperative neoadjuvant chemotherapy only increases patients' 5-year OS rate after surgery by about 5% (11). In recent years, immunotherapy has shown better efficacy and lower toxicity than has chemotherapy in treating advanced NSCLC (*Table 2*). In the neoadjuvant setting, PD-1/PD-L1 monotherapy has been adopted, showing satisfactory efficacy. The Checkmate159 study (12) was the earliest exploration of neoadjuvant immunotherapy for NSCLC. In 2019, the investigators released the results of a follow-up at 34.6 months (13). Among the 20 patients who underwent surgery in the previous reporting period, 75% (15/20) of the patients did not relapse and were still alive. The 24-month recurrence-free survival (RFS) was approximately 69%, and only 1 long-term immune-related adverse event (AE) occurred (skin, grade 3). Mature RFS data are encouraging, and long-term AE data further confirm the safety and feasibility of neoadjuvant therapy with ICIs for resectable NSCLC. In another phase II monotherapy clinical trial (LCMC3), neoadjuvant atezolizumab was administered for

clinical IB–IIIA or selective IIIB stage resectable NSCLC patients (14). A total of 90 patients finally received surgical treatment. The major pathologic response (MPR) of the postoperative patients was 18%, the pCR was 5%, and the objective response rate (ORR) was 7%. A total of 29 patients had grade 3 to 4 AEs (6 cases were related to treatment), and 1 patient had delayed surgery due to grade 3 pneumonia. However, these data sets originate from phase II studies, and these encouraging results need to be confirmed in large, phase III randomized trials.

The NADIM (Neoadjuvant Chemotherapy and Nivolumab in Resectable Non-Small-Cell Lung Cancer) study was an exploration of neoadjuvant chemotherapy combined with immunotherapy in resectable stage IIIA NSCLC (15). The results showed that chemotherapy combined with nivolumab has a satisfactory outcome. In all, 46 patients received 3 cycles of nivolumab combined with paclitaxel and/or carboplatin chemotherapy before surgery, and nivolumab monotherapy was given as adjuvant therapy after surgery. The MPR of the postoperative patients was as high as 86.4%, the pCR was as high as 71.4%, and the ORR was 77.5%. Furthermore, 43 (93%) of 46 patients experienced treatment-related AEs during neoadjuvant treatment, and 14 (30%) experienced treatment-related AEs of grade 3 or worse; however, none of the AEs were associated with surgery delays or death. The most common grade 3 or worse treatment-related AEs were increased lipase (7%) and febrile neutropenia (7%). The primary relevance of this study lies in the high response rate to neoadjuvant chemotherapy plus immunotherapy.

The COLUMBIA study evaluated the efficacy and safety of atezolizumab combined with nab-paclitaxel plus carboplatin as neoadjuvant therapy in patients with resectable stage IB–IIIA NSCLC. The primary endpoint of the study was MPR. A total of 30 patients were enrolled in the study, the MPR rate was as high as 57%, the pCR rate was 33%, and the median OS has not yet been reached. The most common treatment-related grade 3–4 AEs were neutropenia (50%), increased alanine aminotransferase concentration (7%), increased aspartate aminotransferase concentration (7%), and thrombocytopenia (7%). There were no treatment-related deaths.

The NEOSTAR (Neoadjuvant Nivolumab or Nivolumab Plus Ipilimumab in Operable Non-Small Cell Lung Cancer) study showed that the addition of ipilimumab (1 mg/kg for 1 cycle) to nivolumab (3 mg/kg Q2W for 3 cycles) in the neoadjuvant setting improves clinical outcomes but that the adverse reactions (ARs) it causes may delay surgery (16). Dual agents resulted in a postoperative MPR of 33%, a pCR of 29%, and an ORR of 19% compared to 17%, 9%, and 22% in those receiving single agent nivolumab, respectively. In patients who achieved MPR, the ratio of partial response (PR) plus complete response (CR) assessed by imaging according to Response Evaluation Criteria in Solid Tumors (RECIST) was 60% in the dual-agent group. Five patients could not undergo surgery due to ARs and high surgical risks. The incidence of treatment-related ≥ grade 3 ARs was 13% and 5% in the dual and single agent group, respectively. The median time interval between patients undergoing surgical resection after neoadjuvant immunotherapy was 31 days. Among them, 22% (8 cases) of patients had surgery delayed by more than 42 days due to treatment-related ARs.

The CheckMate-816 trial was a phase 3 trial that compared nivolumab plus platinum-doublet chemotherapy (n=179) to platinum-doublet chemotherapy alone (n=179) in the neoadjuvant setting for no known sensitizing *EGFR* mutation and *ALK* alterations in patients with stage IB (≥4 cm)-IIIA [as per the American Joint Committee on Cancer (AJCC) seventh edition] NSCLC. The primary endpoints included event-free survival (EFS) and pCR, which were evaluated using independent blinded review, with the additional efficacy outcome measure being OS (17). The addition of nivolumab resulted in a statistically significant improvement in EFS, with a 37% reduction in the risk of progression, recurrence, or death [hazard ratio (HR) 0.63; 95% CI: 0.45–0.87; P=0.0052] compared to chemotherapy alone. Nivolumab plus chemotherapy yielded a median EFS of 31.6 months [95% CI: 30.2 to not reached (NR)] compared to 20.8 months for patients treated with chemotherapy alone (95% CI: 14.0–26.7). Additionally, 24% of patients treated with nivolumab plus chemotherapy achieved pCR (95% CI: 18.0–31.0), compared to 2.2% in those treated with chemotherapy only (95% CI: 0.6–5.6; estimated treatment difference 21.6; 95% CI: 15.1–28.2; P<0.0001). A prespecified interim analysis for OS resulted in an HR of 0.57 (95% CI: 0.38–0.87), which did not cross the boundary for statistical significance. The above data show that immune-based neoadjuvant combination therapy has a positive impact on deepening pathological remission and reducing the risk of tumor recurrence and is expected to bring long-term survival to patients.

More phase III clinical trials are being carried out globally—with more than 300 patients planned to be enrolled—including studies such as the IMpower 030 KEYNOTE-671, AEGEAN, and CheckMate 77T trials,

among others, which will further explore the application of ICIs in the neoadjuvant setting (*Table 3*).

Consensus 3: adjuvant target therapy for NSCLC patients with positive driver-gene mutations

(I) Patients with *EGFR* mutation-positive stage IA NSCLC should be regularly followed up after complete tumor resection, and adjuvant therapy is not recommended (Category 1).

(II) Osimertinib adjuvant therapy can be considered after complete tumor resection in high-risk (pleural invasion, nerve or vascular invasion, spread through air spaces, micropapillary etc.) with stage IB NSCLC and *EGFR*-sensitive mutations (Category 2A).

(III) For *EGFR* mutation-positive patients with stage IIA–IIB NSCLC EGFR-TKI [osimertinib, category 1 evidence; gefitinib, category 2B evidence; or icotinib (if available), category 1 evidence] adjuvant therapy is recommended after complete tumor resection with or without adjuvant chemotherapy (Category 1).

(IV) For *EGFR* mutation-positive patients with stage IIIA NSCLC, EGFR-TKI (osimertinib, category 1 evidence; gefitinib, category 1 evidence; icotinib, category 1 evidence; or erlotinib, category 2A evidence) adjuvant therapy is recommended after complete tumor resection, and adjuvant osimertinib is recommended first with or without adjuvant chemotherapy.

(V) The adjuvant therapy duration of TKIs can be 24–36 months (Category 2A).

The introduction of EGFR-TKIs ushered in the era of precision treatment of NSCLC and significantly improved the survival time of patients with advanced NSCLC and the *EGFR*-sensitive mutation (18). Whether EGFR-TKIs can replace chemotherapy and become the preferred treatment plan for perioperative treatment of patients with operable NSCLC and how to achieve perioperative precision treatment have become research hotspots in recent years (*Tables 4*,*5*). The ADAURA trial was an international, multicenter, phase III, double-blind, randomized controlled registration clinical study, evaluating osimertinib in patients with *EGFR*-sensitive mutation-positive stage IB–IIIA (T3N2, AJCC7) non-squamous NSCLC after complete tumor resection (19). The primary endpoint was investigator-assessed disease-free survival (DFS). Based on the overwhelming efficacy advantage of adjuvant osimertinib, the ADAURA study was unblinded 2 years ahead of schedule. The use of adjuvant osimertinib resulted in a significantly lowered risk of disease recurrence or death by 83% in those with stage II–IIIA disease (HR 0.17, 99.06% CI: 0.11–0.26, P<0.001) and a significant 80% reduction in the risk of disease recurrence or death in those with stage IB–IIIA disease (HR 0.20, 99.12% CI: 0.14–0.30; P<0.001). The ADAURA study also found that adjuvant osimertinib reduced the risk of distant metastases, including brain metastases. Osimertinib adjuvant therapy was approved in the 2021 edition of the NCCN NSCLC guidelines (7) and is recommended for *EGFR*-sensitizing mutation-positive stage IB–IIIA (T3N2, AJCC7) patients with NSCLC.

The ADJUVANT study compared the efficacy of adjuvant gefitinib versus vinorelbine-platinum doublet in patients with stage II to IIIA NSCLC harboring the exon 19 deletion or exon 21 L858R mutation; the DFS improvement (HR 0.56, 95% CI: 0.40–0.79) indicated that the participants benefited significantly (20). Although there was no significant difference in OS between the two groups, the OS was numerically higher than that reported in previous studies for the gefitinib group.

The EVAN study (21) was a randomized controlled phase II study of erlotinib versus adjuvant chemotherapy for only patients with stage IIIA *EGFR*-positive NSCLC. The median follow-up was 33.3 months. The 2-year DFS rates, median OS, and 5-year OS rates for erlotinib versus chemotherapy were 81.35% versus 44.62% (HR 0.27, 95% CI: 0.14–0.53; P<0.001), 84.2 (95% CI: 78.1–NR) versus 61.1 (95% CI: 39.6–82.1) months and 84.8% versus 51.1%, respectively. Therefore, postoperative adjuvant erlotinib for patients with stage IIIA *EGFR*-positive NSCLC can significantly benefit survival.

The ADAURA study for the third-generation TKI (osimertinib) examined patients with stage IB to IIIA. A subgroup analysis of different stages showed that the higher the tumor-node-metastasis (TNM) stage of patients was, the greater the benefit (19). The ADJUVANT, EVAN, and ADAURA studies employed a subgroup analysis of the DFS benefit after adjuvant targeted therapy in different *EGFR* mutation subtypes.

The EVAN and ADJUVANT studies (16,18) both designed the adjuvant TKI treatment duration to be 2 years, and the treatment time for osimertinib in the ADAURA study (19) was 3 years. The postmortem analysis of the ADJUVANT study found that patients with an adjuvant treatment time ≥18 months benefitted more in terms of DFS (HR 0.38, 95% CI: 0.22–0.66) compared with those patients with an adjuvant treatment time <18 months (22).

Table 3 Ongoing trials of neoadjuvant therapy for NSCLC

Treatment	NCT	Regimen	Primary endpoint	Stage	N	Estimated completion date	Phase
Neoadjuvant ICI monotherapy	NCT04047186	Nivolumab + S	MPR	Multi-GGO	50	2024/12	2
	NCT03732664	Nivolumab/Pembrolizumab + S	Feasibility and safety	High-risk resectable NSCLC	40	2027/10	1
	NCT02818920 TOP1501	Pembrolizumab + S + Pembrolizumab	Feasibility and safety	Ib–IIIa	30	2026/3	2
	NCT02938624 MK3475-223	Pembrolizumab + S	Feasibility and safety	I–II	28	2021/4	1
	NCT03197467 NEOMUN	Pembrolizumab + S	Feasibility and safety	II–IIIa	30	2023/10	2
	NCT02994576 PRINCEPS	Atezolizumab + S	Feasibility and safety	Ib–IIIa	60	2022/12	2
	NCT03030131 IONESCO	Durvalumab + S	Surgical resection	Ib–IIIb	81	2019/8	2
	NCT04371796	Sintilimab + S	MPR	II–IIIa	20	2021/12	2
	NCT04197076	ICI ×2 + S	DFS, pCR	IIIa	200	2021/5	NA
	NCT03853187 DONAN	Durvalumab + S + RT/CT	Feasibility and safety	III	20	2022/4	2
Neoadjuvant ICI combine with chemotherapy	NCT04541251 TOP-LC1210	(Camrelizumab + CT) ×3	MPR	Ib–IIIa	40	2023/9	2
	NCT 04144608	(Toripalimab + CT) + S	Surgical resection	IIIa or IIIb	30	2020/12	2
	NC TO4304248 NeoTPD01	(Toripalimab + CT) ×3	pCR	III	30	2026/7	2
	NCT04586465 DYNAPET	(Pembrolizumab + CT) ×3	MPR, SUV	IIa–IIIb	23	2022/6	2
	NCT04379739	Camrelizumab + CT; Camrelizumab + Apatinib	MPR	II–IIIa	82	2026/12	2
	NCT04865705	Tislelizumab + CT	R0	III	33	2021/12	2
Neoadjuvant and adjuvant ICI	NCT04512430	(Atezolizumab + Bevacizumab + CT) + S + (Atezolizumab q4w ×6 mon)	MPR	IIIa (*EGFR*+)	26	2026/8	2
	NCT04465968 DEEP _OCEAN	(Durvalumab + RT + CT) + S + (Durvalumab/RT + CT)	3 yr OS	III	84	2030/8	3
	NCT04326153	Sintilimab + CT) + S + (Sintilimab ×8 + CT ×2)	2 yr DFS	IIIa	40	2022/12	2
	NCT03838159 NADIMII	(Nivolumab + CT) ×3 + S + (Nivolumab ×1 y)	pCR	III	90	2027/9	2
	NCT04379635 RATIONALE 315	(Tislelizumab 200 mg Q3W + CT) ×3 + S + (Tislelizumab 400 mg Q6W) ×8	MPR, EFS	II–IIIA	380	2021/2	3

Table 3 (*continued*)

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Treatment	NCT	Regimen	Primary endpoint	Stage	N	Estimated completion date	Phase
RCT	NCT02998528 CheckMate816	(Nivolumab + CT) + S; S + CT (Nivolumab + Ipilimumab) + S	EFS, pCR	Ib–IIIa	350	2028/11	3
	NCT03425643 KEYNOTE-671	(Pembrolizumab + CT) ×4 + S + (Pembrolizumab ×13); NAC + S	EFS, OS	II–IIIb (T3-4N2)	786	2026/6	3
	NCT03456063 IMpower030	(Atezolizumab + CT) + S + (Atezolizumab ×16); NAC + S	MPR, EFS	II–IIIb	450	2024/11	3
	NCT03800134 AEGEAN	(Durvalumab + CT) + S; NAC + S	MPR, EFS	II–III	800	2024/1	3
	NCT04025879	(Nivolumab + CT) + S + (Nivolumab); NAC + S	EFS	IIa (>4 cm)–IIIb (T3N2)	452	2024/9	3
	NCT04338620	Camrelizumab + CT) + S; NAC + S	pCR	III (N2)	94	2021/11	2
	NCT04379635	(Tislelizumab + CT) + S + (Tislelizumab); NAC + S	MPR, EFS	II–IIIa	380	2025/11	3
	NCT04422392	(ICI + CT) + S + (ICI + CT); NAC + S + CT	MPR	IIIa (N2)	90	2025/6	2
	NCT04061590	Pembrolizumab + S; (Pembrolizumab + CT) + S	TIL	I–IIIa	84	2022/4	2
	NCT04459611 neoSCORE	(Sintilimab + CT) ×2 + S + (CT ×2 + Sintilimab ×1 y); (Sintilimab + CT) ×3 + S + (CT ×1 + Sintilimab ×1 y)	MPR	Ib–IIIa	60	2023/7	2
	NCT03916627	Cemiplimab + S + (Cemiplimab + CT); (Cemiplimab + CT) + S + (Cemiplimab + CT); NAC + S + (Cemiplimab + CT)	MPR	NSCLC	94	2027/8	2
Neoadjuvant ICI + RT	NCT02904954	Durvalumab + S + Durvalumab ×1 y; (Durvalumab ×3 + RT) + S + (Durvalumab ×1 y)	MPR	Ib–IIIa	60	2022/4	2
	NCT03217071 PembroX	Pembrolizumab + S; (Pembrolizumab + RT) + S	TIL	I–IIIa	40	2021/12	2
	NCT03237377	(Durvalumab + RT) + S; (Durvalumab + Tremelimumab + RT) + S	Feasibility and safety	IIIa	32	2021/9	2
	NCT04245514 SAKK 16/18	Durvalumab ×1 + CT ×3 + RT) + S + (Durvalumab ×13 q4w)	EFS	T1-4 (>7 cm) N2	90	2025/3	2

NSCLC, non-small cell lung cancer; MPR, main pathological response; pCR, pathological complete response; SUV, standardized uptake value; ICI, immune checkpoint inhibitor; S, surgery; RT, radiotherapy; CT, chemotherapy; NAC, neoadjuvant chemotherapy; OS, overall survival; EFS, event-free survival; TIL, tumor infiltrating lymphocyte; RCT, randomized controlled trial; GGO, ground-glass opacity; DFS, disease-free survival.

Table 4 Summary of randomized phase II/III trials of EGFR tyrosine kinase inhibitors in the adjuvant setting

Trial	Phase	Population	Arms	N	mDFS (months)	HR	mOS (months)	HR
RADIANT	III	IB–IIIA *EGFR*+	Erlotinib for 2 years	623	50.5	0.9	NR	1.09
			Placebo	250	48.2		NR	
BR19	III	IB–IIIA *EGFR*+	Gefitinib for 2 years	251	50.4	1.22	5.1	1.24
			Placebo	252	NR		NR	
CTONG1104/ ADJUVANT	III	II–IIIA *EGFR*+	Gefitinib for 2 years	111	30.8	0.56	75.5	0.92
			Cisplatin/vinorelbine	111	19.8		62.8	
EVAN	II	IIIA *EGFR*+	Erlotinib for 2 years	51	42.4	0.268	NR	0.165
			Cisplatin/vinorelbine	51	21		NR	
ADAURA	III	IB–IIIA *EGFR*+	Osimertinib for 3 years	339	NR	0.17	NR	0.4
			Placebo	343	20.4		NR	
EVIDENCE	III	II–IIIA *EGFR*+	Icotinib for 2 years	151	47.0	0.36	NR	0.91
			Intravenous chemotherapy	132	22.1		NR	

HR, hazard ratio; *EGFR*+, *EGFR*-mutated; mDFS, median disease-free survival; mOS, median overall survival; NR, not reached.

Table 5 Ongoing trials of neoadjuvant and adjuvant therapy with tyrosine kinase inhibitors

Trial	Phase	Therapy	Population	Arms	Primary endpoint
EMERGING	II	Neoadjuvant	IIIA *EGFR*+	Erlotinib for 6 weeks, then 1 year postoperatively cisplatin/gemcitabine	ORR
NCT03203590	II	Neoadjuvant	II–IIIA *EGFR*+	Gefitinib for 8 weeks carboplatin/vinorelbine	2-year DFS
NeoADAURA	II	Neoadjuvant	II–IIIA *EGFR*+	Osimertinib ± platinum/pemetrexed platinum/ pemetrexed	MPR
ALCHEMIST-ALK	III	Adjuvant	IB–IIIA *ALK*+	Crizotinib for 2 years placebo	OS
ALINA	III	Adjuvant	IB–IIIA *ALK*+	Alectinib for 2 years chemotherapy	DFS
NCT04302025	II	Neoadjuvant	IB–IIIB *ALK*+, *ROS1*+, *NTRK*+, *BRAF*+	Neoadjuvant ± adjuvant alectinib for 8 weeks entrectinib vemurafenib + cobimetinib	MPR
NCT03088930	II	Neoadjuvant	IA–IIIA *ALK*+ *ROS1*+, *MET*+	Crizotinib for 6 weeks	ORR
NCT01929200	II	Adjuvant	II–IIIA *EGFR*+	icotinib for 1-year adjuvant therapy vs. 2-year	RFS
NCT03349203	II	Neoadjuvant and Adjuvant	IIIB or oligometastasis *EGFR*+	Icotinib for 8 weeks before surgery and 2 years as adjuvant therapy	ORR
NCT03749213	II	Neoadjuvant	IIIA-N2 *EGFR*+	Icotinib for 8 weeks as neoadjuvant therapy and for 2 years as adjuvant therapy	ORR
NCT05165355	II	Adjuvant	IB–IIA *EGFR*+	Furmonertinib for 3 years as adjuvant therapy	2-year DFS
NCT04965831	II	Neoadjuvant and Adjuvant	IIIA–IIIB (N1-N2) *EGFR*+	Furmonertinib for 8 weeks before surgery and 2 years as adjuvant therapy	ORR
NCT04853342	III	Adjuvant	II–IIIA *EGFR*+	Furmonertinib versus placebo ± chemotherapy	DFS

ORR, overall response rate; DFS, disease-free survival; MPR, major pathological response; RFS, recurrence-free survival; OS, overall survival; *EGFR*+, *EGFR*-mutated; *ALK*+, *ALK*-rearranged; *BRAF*+, *BRAF*-mutated; *NTRK*+, *NTRK*-rearranged; *ROS1*+, *ROS1*-rearranged; *MET*+, *MET*-altered.

There is no standard for the duration of targeted adjuvant therapy. For this, we can refer to when resistance appears in the late first-line treatment of different TKIs.

The ADJUVANT and EVAN studies were direct assisted targeting strategies (i.e., EGFR-TKI was started directly after operation), while the ADAURA study allowed the option of sequential targeted therapy after adjuvant chemotherapy. It is worth investigating which strategy is better. In the ADAURA study (19), there was no difference in terms of the 24-month DFS rate between patients who started osimertinib treatment without adjuvant chemotherapy (45%) and those who received sequential osimertinib treatment after adjuvant chemotherapy (55%). On the other hand, the ADJUVANT study (18) analyzed the use of targeted therapy after disease progression. The response rate and longer OS suggest that from the perspective of the whole-process management of patients, targeted adjuvant therapy has more significant OS benefits than does sequential targeted therapy with adjuvant chemotherapy, which was especially apparent in the EVAN study (19). Patients with NSCLC with *EGFR*-sensitive mutations should be recommended to undergo targeted adjuvant therapy after surgery to enhance long-term benefit.

The incidence of *ALK*-positive NSCLC is about 3–7%, but its treatment effect is quite satisfactory (23). Crizotinib is the first targeted drug approved for the treatment of *ALK*-positive NSCLC (24). *ALK* inhibitors with or without chemotherapy have been studied as an options for neoadjuvant and adjuvant therapy. A small clinical study that included 11 N2M0 *ALK*-positive patients with NSCLC who received neoadjuvant crizotinib showed that 10 achieved PR, 2 achieved pCR, and 3 achieved downstaging after neoadjuvant therapy; the study further found that surgery successfully achieved R0 resection without surgery-related complications (25).

Alectinib is a highly selective, second-generation *ALK* inhibitor. The ALINA trial (NCT03456076) is an international, multicenter, open-label, randomized controlled phase III study intended to evaluate the efficacy and safety of adjuvant alectinib compared with platinum-based chemotherapy in patients with completely resected stage IB (tumors ≥4 cm) to stage IIIA (AJCC7) *ALK*-positive NSCLC (26). Enrolled patients will be randomly assigned in a 1:1 ratio to receive alectinib (600 mg) twice a day for 24 months or 4 cycles of platinum-containing doublet chemotherapy prescribed according to the local conditions of the research center. The primary endpoint of the study is investigator-assessed DFS, and secondary endpoints include OS, safety, and pharmacokinetics. The trial is now ongoing and expected to have the data released in 2023.

Consensus 4: adjuvant immunotherapy for NSCLC patients

(I) Platinum-based chemotherapy should be administered (Category 1).
(II) Atezolizumab is recommended in R0 patients with PD-L1 expression ≥1% II–IIIA stage NSCLC after platinum-based chemotherapy (Category 1).
(III) The duration of adjuvant immunotherapy is currently recommended for 1 year (Category 2A).

Platinum-based adjuvant chemotherapy significantly improves survival in patients with NSCLC with a 5-year absolute OS benefit of 5.4% (4). In recent years, immunotherapy has achieved remarkable results in driver gene mutation-negative advanced NSCLC and has changed the treatment mode of these patients. Researchers are gradually turning their attention to neoadjuvant and adjuvant immunotherapy, hoping that immunotherapy can benefit more patients with early-stage NSCLC (*Table 6*). Several studies were designed to explore the efficacy of adjuvant immunotherapy after surgery for early-stage NSCLC (IMpower010, ANVIL, PEARLS, BR31, ALCHEMIST, MERMAID-1, MERMAID-2, CANOPY-A, and KEYNOTE-091).

The IMpower010 trial (27) was a randomized, open-label, global multicenter, phase 3 study that compared the efficacy of atezolizumab and best supportive care (BSC) in patients with early-stage NSCLC after complete resection and adjuvant chemotherapy. The primary endpoint of investigator-assessed DFS and secondary endpoint of OS were tested hierarchically: first DFS in the PD-L1 TC ≥1% (SP263) subgroup with stage II–IIIA disease, then DFS in all randomized patients with stage II–IIIA disease, DFS in the intention-to-treat (ITT) population (stage IB–IIIA), and finally OS in the ITT population. Atezolizumab showed statistically significant DFS benefit versus BSC in the PD-L1 TC ≥1% stage II–IIIA (HR 0.66, 95% CI: 0.50–0.88; P=0.0039) and all randomized stage II–IIIA populations (HR 0.79, 95% CI: 0.64–0.96; P=0.020). In the ITT population (stage IB–IIIA), the significance boundary was not crossed for DFS in the ITT population (stage IB–IIIA; HR 0.81, 95% CI: 0.67–0.99; P=0.040). It is worth noting that this study did not intentionally exclude patients with driver mutations.

The KEYNOTE-091 trial was a randomized, phase

Table 6 Postoperative adjuvant immunotherapy for NSCLC

Trial	Eligible patients	Intervention following surgery	Estimated enrolment (N)	Primary endpoint	Median follow-up	HR
IMpower 010	IB–IIIA NSCLC	Arm A: platinum doublet (4 cycles) followed by atezo (16 cycles). Arm B: platinum doublet (4 cycles) followed by best supportive care	1,280	DFS	32.8 m	0.66 (95% CI: 0.50–0.88) in PD-L1 + II–IIIA patients
PEARLS/ KEYNOTE-091	IB–IIIA NSCLC	Arm A: (optional chemotherapy) pembro (1 year). Arm B: (optional chemotherapy) placebo (1 year)	1,080	DFS	35.6 m	0.76 (95% CI: 0.63–0.91) in ITT patients. 0.82 (95% CI: 0.57–1.18) in PD-L1 TPS ≥50% patients
ANVIL	IB–IIIA NSCLC	Arm A: (optional chemotherapy and RT) nivolumab (1 year). Arm B: (optional chemotherapy and RT) observation	903	DFS/OS	NG	NG
BR31	IB–IIIA NSCLC	Arm A: (optional chemotherapy and RT if N2) duva (1 year). Arm B: (optional chemotherapy and RT if N2) placebo (1 year)	1,360	DFS	NG	NG
ALCHEMIST	IB–IIIA NSCLC	Arm A: platinum doublet (4 cycles). Arm B: platinum doublet (4 cycles) followed by pembrolizumab (17 cycles). Arm C: platinum doublet plus pembrolizumab (4 cycles) followed by pembrolizumab (additional 13 cycles)	1,263	DFS/OS	NG	NG

NSCLC, non-small cell lung cancer; atezo, atezolizumab; pembro, pembrolizumab; duva, durvalumab; DFS, disease-free survival; OS, overall survival; NG, not given; ITT, intention-to-treat; TPS, tumor proportion score; PD-L1, programmed cell death-ligand 1.

3 trial (ClinicalTrials.gov; NCT02504372) evaluating pembrolizumab compared to placebo for the adjuvant treatment of patients with stage IB (≥4 cm) to IIIA NSCLC following surgical resection and adjuvant chemotherapy (28). The dual primary endpoints were DFS in the overall population and in those whose tumors expressed PD-L1 [tumor proportion score (TPS) ≥50%]. The study randomized 1,177 patients (1:1) to receive either pembrolizumab (200 mg Q3W for 1 year, n=590) or placebo (n=587). The median DFS in the overall population was 53.6 months for pembrolizumab versus 42.0 months for placebo. Adjuvant pembrolizumab significantly improved DFS (HR 0.76, 95% CI: 0.63–0.91; P=0.0014) in patients with stage IB (≥4 cm) to IIIA NSCLC following surgical resection regardless of PD-L1 expression. However, the DFS difference in those with high PD-L1 expression (TPS ≥50%) did not reach statistical significance as per the prespecified statistical plan (HR 0.82, 95% CI: 0.57–1.18; P=0.14).

Based on recent breakthroughs in immunotherapy and targeted therapy, it is necessary to distinguish patients with adjuvant therapy in the future. For patients with *EGFR*-sensitive mutations, the evidence of target therapy is more sufficient. If the driver gene is negative, immunotherapy may provide a new treatment model with a large-scale phase III clinical study that has demonstrated significant benefits. The entire pattern of adjuvant treatment for early NSCLC represents a landmark change for clinical practice.

Consensus 5: perioperative patient management

(I) The AEs of perioperative target or immunotherapy should be taken seriously since they may lead to delay or cancellation of surgery, additional illness, and even death (Category 2A).

(II) Different ICIs and target therapy have different safety profiles. It is necessary to select ICIs with a high level of evidence and good security (Category 2B).

(III) Most immune-related (ir) AEs and targeted-related AEs can be managed effectively if detected and

treated early. An MDT approach is recommended for managing AEs. Emphasis should be placed on the education of patients and their families, the early identification of patients themselves, and the management of self-monitoring. For example, a patient self-report list can be made to monitor adverse reactions outside the hospital (Category 2A).

(IV) Regular monitoring should be conducted to detect any potential irAEs or targeted therapy-related AEs and to assess treatment response. The monitoring should be continued even after completion of neoadjuvant or adjuvant treatment (Category 1).

(V) Presence of a perioperative circulating tumor DNA (ctDNA)-positive status is a prognostic factor rather than a predictive factor. It is important to pay attention to the baseline of patients and to clarify the relevant screening items before neoadjuvant targeted therapy and neoadjuvant immunotherapy and whether there are corresponding risks of treatment, such as surgical complications or unsuitability for immunotherapy, etc. (Category 2B).

Targeted therapy and immunotherapy have dramatically changed the treatment landscape for patients with NSCLC. Nevertheless, targeted therapy and perioperative immunotherapy may be accompanied by serious AEs that can lead to delay or cancellation of surgery, additional illness, and even death. The severity of AEs can range from asymptomatic, severe, to life threatening (29).

A meta-analysis conducted by Lung Adjuvant Cisplatin Evaluation (LACE) and the NSCLC Collaborative Group showed that although grade 3–4 AEs for neoadjuvant immunotherapy were as high as 66% for chemotherapies (4,5), irAEs of pneumonia, cardiac toxicity, digestive tract toxicity, and other rare but serious toxicities seriously affected patient prognosis. Although there has been no head-to-head comparison study of AEs between PD-1 and PD-L1 inhibitors, a meta-analysis of 19 clinical trials indicated a higher incidence of pneumonitis with use of PD-1 inhibitors compared with PD-L1 inhibitors (30).

It is advised to adhere to the important principle of "prevention, assessment, inspection, treatment, and monitoring" for the management of ICIs to ensure early and accurate detection, diagnosis, and treatment of irAEs (31). Evaluation and routine screening of NSCLC patients before initiation of immunotherapy may be the most important component of irAE management because it allows the patients likely to be most susceptible to irAEs to be identified and flagged for early intervention (32). Before initiating ICI treatment, physicians should assess the current medical condition, past medical history (especially autoimmune disease, immunodeficiency disease, and special infection history), family history, and general condition, and perform baseline laboratory and imaging examinations. Regular monitoring should be conducted to detect any potential irAEs and to assess treatment response. The monitoring should be continued even if the treatment is stopped. Most irAEs can be managed effectively if detected and treated early.

The general principles of irAE treatment are as follows:

(I) ICI treatment should be suspended if irAEs of grade ≥2 occur; treatment can then be resumed if symptoms or laboratory tests are reduced to grade 1 or below. For symptoms persisting for >1 week, glucocorticoid (GC) treatment should be considered;

(II) Patients with grade 3–4 irAEs should be treated with GCs, which will generally reduce most AEs to grade 1 or below over 4–6 weeks;

(III) ICI treatment should be permanently discontinued for patients with grade 4 irAEs (or endocrine irAEs that can be controlled by alternative therapy). Permanent discontinuation of ICIs may be considered for patients with grade ≥2 irAEs lasting for more than 6 weeks, or if GC therapy cannot be reduced to <10 mg prednisone (or equivalent) within 12 weeks.

To maximize immunotherapy's efficacy, minimal residual disease (MRD) may become part of clinical practice in predicting and monitoring the therapeutic effects of the NSCLC treatment (33). In recent years, ctDNA has emerged as a potentially useful biomarker in a number of cancer types and settings. It is being investigated for use in screening and diagnosis, treatment selection, postoperative MRD detection, prognostics, and monitoring response and relapse (34).

The CheckMate 816 trial showed that ctDNA clearance was more frequent in patients who received neoadjuvant nivolumab plus chemotherapy (56%) than in those who received neoadjuvant chemotherapy alone (34%) (35). Additionally, patients with ctDNA clearance showed higher pCR rates than did patients without ctDNA clearance in both treatment groups: 46% *vs.* 0% in the nivolumab plus chemotherapy group, respectively, and 13% *vs.* 3% in the chemotherapy alone group, respectively. Exploratory analyses of biomarker subgroups from the Impower010 trial showed that treatment with atezolizumab, following surgery

and adjuvant chemotherapy, demonstrated an improvement in DFS in both ctDNA-positive (ctDNA+) and ctDNA-negative (ctDNA–) patients with PD-L1-positive stage II–IIIA NSCLC compared with best supportive care (BSC) (36). In ctDNA+ stage II–IIIA PD-L1-positive patients, the median DFS (mDFS) was 21.8 (atezolizumab) versus 7.2 months (BSC), with an HR of 0.54 (95% CI: 0.31–0.93). While in the ctDNA- stage II–IIIA PD-L1-positive patients, the mDFS was NR (atezolizumab) versus 37.3 months (BSC), with an HR of 0.57 (95% CI: 0.36–0.90). ctDNA positivity after surgery was strongly prognostic for a greater risk of disease recurrence or death, and it was more prevalent with a higher disease state, increased nodal status, and *EGFR*-positive status (37). Based on the current research data, the MRD detection based on ctDNA has shown its excellence in predicting postoperative disease recurrence in early NSCLC patients and hence could benefit NSCLC patient management.

OS is the gold standard efficacy endpoint in cancer treatment, but it will take a long time to evaluate OS in initial therapy. Therefore, appropriate alternative endpoints are needed to evaluate the efficacy of therapy in the early stage of cancer, which can be quickly introduced into the clinical practice (38). The most commonly used endpoints in neoadjuvant and adjuvant therapy studies include pCR, MPR, EFS, and DFS (39-41). One meta-analysis found DFS to be a valid surrogate endpoint for OS with adjuvant chemotherapy and radiotherapy in resectable early-stage NSCLC (42).

Discussion

Early-stage lung cancer is a malignant tumor that can still potentially be cured by surgical treatment. However, more than 50% of the patients treated only by surgery will experience recurrence or metastasis within 5 years (4,11). Even in patients with completed resected primary tumors smaller than 1 cm with no lymph node metastases, nearly 8% died of the disease within 5 years after surgery. To downstage the disease, improve the resectable rate, and reduce the tumor burden or postoperative recurrence—all for the ultimate purpose of prolonging survival to benefit more patients—a multitude of clinical trials that focused on neoadjuvant and adjuvant therapy were carried out in China and internationally in recent years (19-21). Some valuable clinical experience and research data have been obtained from these trials. Based on the status of perioperative treatment of early-stage lung cancer in China, this forum carried out in-depth discussions and exchanges on issues such as adjuvant and neoadjuvant therapy, biomarkers, efficacy evaluation indicators, and follow-up and finally reached an expert consensus.

While surgery is the main method for the treatment of early- and mid-stage lung cancer, this opportunity for surgery can be lost to patients with locally advanced disease unless there is effective neoadjuvant or adjuvant treatment (43). The past generation of adjuvant mainly involved chemotherapy, but many clinical studies and experiences have revealed its efficacy to be quite limited. In the past 5 years, through continuous exploration, targeted therapy and immunotherapy have achieved satisfactory efficacy in patients with advanced lung cancer. Besides, as an important part of management of NSCLC, radiation therapy is recommended to be assessed by a multidisciplinary team (MDT) after adjuvant therapy for patients with completely resected (R0) stage III N2 NSCLC. Therefore, it is also hoped that these approaches can be used in the preoperative treatment of lung cancer to help downstage lung cancer and increase the overall treatment efficacy. However, this process inevitably involves the issue of precise treatment; that is, how to improve the efficacy as much as possible on the premise of reducing toxicity and side effects. This is also an issue that has been paid close attention to in recent years.

In addition, the tumor itself can precipitate distant metastasis at a very early stage, and there is currently no method to detect tumor metastasis this early. Therefore, even patients with early-stage lung cancer are at risk of recurrence after surgical treatment although the risk for these patients is relatively low. In this regard, the current clinical postoperative adjuvant therapy is mainly performed for patients with a higher risk of recurrence, with the aim of reducing the recurrence risk of patients and further improving the effect of treatment. Guidelines recommend adjuvant chemotherapy for high-risk patients, but previous studies have shown that adjuvant chemotherapy improves OS by only about 5%. An inevitable problem in the process of adjuvant therapy is that in patients with a high risk of recurrence and metastasis, adjuvant therapy may not necessarily reduce the incidence of recurrence or metastasis. This is because, after the tumor tissue is removed, it is not completely clear whether the adjuvant therapy is effective, and this can only be determined after the final patients' survival results emerge.

Given the in-depth research being conducted in recent years, there is very good evidence to recommend the use

of targeted therapy and immunotherapy drugs for adjuvant treatment. Therefore, in the era of precision treatment, we can use scientific means to select those patients who can benefit from this therapy, which is also the goal that the majority of clinicians have been pursuing. There are still many problems in clinical practice that deserve further exploration. It is expected that current and future studies can support further optimization of adjuvant therapy strategies and bring more clinical benefits to patients with early and mid-stage resectable NSCLC.

Do you use chemotherapy before adjuvant TKI?

Stefano Bongiolatti: Adjuvant TKI therapy alone is not the standard of care in my country, and it could be administered in completely resected *EGFR* mutation-positive patients after traditional chemotherapy and/or in patients who are ineligible to receive platinum-based chemotherapy.

Alessandro Brunelli: Generally yes.

Alfonso Fiorelli: Two recent trials, ADJUVANT (20) and the EVAN (21), and one meta-analysis (44) showed that adjuvant TKIs compared to standard chemotherapy are associated with better DFS and lower toxicity in lung cancer patients harboring an *EGFR* mutation. The main limit of all these studies was the lack of data regarding OS. Thus, the improvement of the DFS alone supports the use of adjuvant TKIs, but cannot change the standard clinical practice of standard chemotherapy as first choice for adjuvant treatment.

Elisa Gobbini: Yes, when indicated and when patients are fit enough.

Cesare Gridelli: Yes, if patients are fit with no major comorbidities.

Thomas John: Yes.

Jae Jun Kim: The policy is different according to surgery. After surgery, we firstly use chemotherapy. If the response of chemotherapy is poor, we use TKIs. In the condition of advanced cases without surgery, we can firstly use adjuvant TKIs.

Steven H. Lin: Yes.

Giulio Metro: The ADAURA trial of adjuvant osimertinib versus placebo in completely resected stages IB–IIIA NSCLCs with a common del 19 or L858R *EGFR* mutation allowed 4 cycles of adjuvant platinum-based doublet prior to TKIs, but postoperative chemotherapy was not mandatory as per protocol (19). Interestingly, at a median follow-up of 22.1 months for osimertinib and 18.2 months for placebo, a prespecified subgroup analysis of DFS in the overall stage IB–IIIA population showed that a significant benefit in favor of osimertinib was seen either in patients who received adjuvant chemotherapy [N=410; HR =0.16 (0.10–0.26)] as well as in those who did not receive it [N=272; HR =0.23 (0.13–040)] (19,45). As a result, it seems that the DFS benefit of adjuvant osimertinib is independent of prior chemotherapy. However, since the cytocidal action of chemotherapy may add to the cytostatic effect of a TKI, it is my opinion that adjuvant platinum-based chemotherapy, if feasible, should always be considered before proposing osimertinib. Nevertheless, in selected cases chemotherapy may be omitted, but only after thorough discussion and shared decision. These cases include but are not limited to stage IB disease (where the therapeutic margin of chemotherapy is lower as compared to higher stages), elderly patients (who are more prone to develop chemotherapy-related adverse events), and refusal of chemotherapy from the patient.

Fabrizio Minervini: Yes, based on the ADAURA trial, chemotherapy is still part of adjuvant therapy.

Nuria M. Novoa: Before answering the questions, I would like to clarify that all these patients and specific treatments are discussed in the different MDT which I attend regularly being 1 of the 2 to 3 thoracic surgeons of my unit in charge. Therefore, we discuss evidences and pros and cons before deciding. Although the number of patients benefiting from surgery and receiving targeted therapies or immunotherapy is increasing, our experience is still limited.

Yes. Based on the evidence review, it was agreed that patients receive platinum-based treatment before using TKIs. Registered AEs were diverse in type and severity both after the classical chemotherapy and TKI treatment.

Maria Rodriguez: Following ADAURA trial (that allowed adjuvant chemotherapy prior to TKI therapy), we use chemotherapy followed by TKIs. Also, most guidelines recommend this.

Ichiro Sakanoue: No. Currently, we do not use adjuvant TKI in routine clinical practice. We are only using chemotherapy as an adjuvant therapy.

Kenichi Suda: Adjuvant TKI use is not approved yet in Japan. After the approval, I will try chemotherapy (but not mandatorily, I think) before osimertinib. Other TKIs, including gefitinib and erlotinib, have not been approved as adjuvant therapy in Japan.

Fabrizio Tabbò: Yes, based on the stage and risk profile of each single patient.

Terence Chi Chun Tam: (unless they are medically contraindicated) I personally would recommend patients

with stage IB–IIIA completely resected *EGFR*(+) tumors to undergo the standard 4 cycle of adjuvant chemotherapy and then a reassessment CT to confirm no early adjuvant failure before starting them on osimertinib.

Masanori Tsuchida: Yes. Adjuvant chemotherapy is a standard treatment option for the patients with pathological II and IIIA completely resected NSCLC at present. If recurrence is obvious, TKIs are proposed for patients with *EGFR* mutations.

Junji Uchino: Yes.

Luca Voltolini: Yes, we use chemotherapy for 4 cycles before adjuvant TKIs.

What is your preferred duration of adjuvant TKI therapy?

Stefano Bongiolatti: The results of the ADAURA study are remarkable, and so TKI therapy should be administered for 3 years after surgery to reduce disease relapse.

Alessandro Brunelli: Outside clinical trials, we generally reserve TKIs for when patients show relapse.

Alfonso Fiorelli: The best duration of adjuvant TKI treatment is still debated and several factors such as patient's compliance and cumulative toxicity may affect the length of treatment. In the ADJUVANT study (20), 80% of patients received treatment for 12 months, and 68% prolonged the therapy to more than 18 months. In the SELECT study (46), the treatment was preplanned for 24 months. However, 70% of patients completed 22 months of treatment, but in 40% of these, a reduction of planned dose was administered. In the era of second-generation EGFR-TKIs, an increase in the length of treatment is expected due to better compliance and lower toxicities compared to first-generation EGFR-TKIs.

Elisa Gobbini: 1 year.

Cesare Gridelli: 3 cycles.

Thomas John: 3 years on osimertinib.

Jae Jun Kim: The duration of usage of adjuvant TKI is not limited if the response is shown.

Steven H. Lin: According to ADAURA, it is maximum of 3 years or time of progression, whichever is earlier, so this is what we use and recommend.

Giulio Metro: Based on the ADAURA trial, current evidence suggests that the total duration of adjuvant osimertinib for completely resected, stages IB–IIIA *EGFR*-mutated NSCLCs should be up to 3 years (19).

Fabrizio Minervini: Based on the ADAURA trial, adjuvant osimertinib is approved for 3 years in Switzerland.

Nuria M. Novoa: In the cases we have operated on, TKI therapy was maintained up to 3 years, but most of the patients had it for 2 years. A decision was discussed and finally taken by medical oncologists of the MDT.

Maria Rodriguez: Following ADAURA evidence, we use TKIs for 3 years. Ichiro Sakanoue: Because of our current status stated above, I do not have a definitive answer for this question. However, based on the results from the ADAURA trial, I would prefer adjuvant TKI for at least 2 years.

Kenichi Suda: If approved, I will follow the ADAURA regimen (3 years).

Fabrizio Tabbò: 2–3 years.

Terence Chi Chun Tam: As per the AUDURA trial, 3 years.

Masanori Tsuchida: Although I do not use TKIs as an adjuvant therapy, I prefer 2 years.

Junji Uchino: 2 years.

Luca Voltolini: We use osimertinib for 3 years, when possible, in accordance with the protocol of the ADAURA trial.

How do you choose those patients most eligible for adjuvant PD-1/PD-L1?

Stefano Bongiolatti: Adjuvant immunotherapy alone is not the standard of care in my country, and can only be administered within a clinical trial. The selection criteria are different between study protocols, but immunotherapy could be administered in the absence of specific oncogenic drivers and variable expressions of PD-1/PD-L1.

Alessandro Brunelli: Those with PD-L1 mutations >1%.

Alfonso Fiorelli: Patients with resected stage II to IIIA NSCLC and with tumors having a PD-L1 expression of 1% or more are eligible for adjuvant PD-1/PD-L1 therapy. This is according to the results of the IMpower010 trial (27), showing that adjuvant atezolizumab was associated with significant improvement in DFS versus best supportive care after adjuvant chemotherapy. This difference was more evident in patients with PD-L1 expression on 50% or more of tumor cells.

Elisa Gobbini: Adjuvant immunotherapy has not entered clinical practice in France, but, if I had the possibility to use this drug, my choice would be driven by comorbidity (basically, all patients that do not have a contraindication for immunotherapy) regardless of the PD-1/PD-L1 status.

Jae Jun Kim: We choose patients based on PD-1/PD-L1 status and response of other adjuvant therapies.

Steven H. Lin: For all non-oncogene-driven tumors

(EGFR, ALK, ROS, RET), we would favor adjuvant PD-1/PD-L1 therapy.

Giulio Metro: Factors that should be taken into account in the decision process (beyond patient's clinical conditions) are the following: oncogene addiction status, PD-L1 expression ≥1%, disease stage, and receipt of adjuvant chemotherapy.

In the 2 studies that assessed the role of adjuvant PD-1/PD-L1 treatment (Impower010 and PEARLS) patients with *EGFR* mutations or *ALK* rearrangement were included, so we have clinical outcome data available on these subgroups from the forest plot analyses of both trials. However, since *EGFR*-mutated patient may derive a large benefit from osimertinib and *ALK*-rearranged patients have been shown to be unresponsive to ICIs (19,47), it is important that *EGFR* and *ALK* status should be known upfront in order to restrict adjuvant PD-1/PD-L1 treatment only to *EGFR*- and *ALK*-negative patients. In case other actionable drivers have been documented, the decision to offer adjuvant PD-1/PD-L1 treatment to patients with genetic alterations that, similarly to *EGFR* and *ALK*, are linked to little or no smoking history and have been associated with poor response to immune checkpoint inhibition in the advanced setting (i.e., *ROS1*, *RET*, *HER2*) should be made on a case-by-case basis.

In theory, PD-L1 expression may help select patients for adjuvant PD-1/PD-L1 therapy based on its predictive role demonstrated in the advanced setting. In line with this, in the Impower010 trial, adjuvant atezolizumab significantly improved DFS versus best supportive care in patients with stage II–IIIA NSCLC with PD-L1 expression ≥1% (27). Also, although DFS was significantly improved in all patients with stage II–IIIA NSCLC regardless of PD-L1 expression, forest plot analysis showed that this benefit was largely confined to patients with PD-L1 expression ≥1% [N=476; HR =0.66 (0.49–0.87)] as compared to PD-L1-negative [N=383; HR =0.97 (0.72–1.31)] (27). By contrast, in the PEARLS trial of adjuvant pembrolizumab, PD-L1 expression levels lacked predictivity. However, it is my opinion that longer follow-up in the latter study is needed to accurately assess the role of PD-L1 as a biomarker of benefit from anti PD-1/PD-L1 therapy (28).

Adjuvant PD-1/PD-L1 treatment may not be routinely administered in stage IB (tumor ≥4 cm) patients. In fact, we wait for more mature data in terms of follow-up, as the Impower010 DFS was not formally positive for the overall stage IB–IIIA population (27).

In addition, current evidence is against the use of adjuvant PD-1/PD-L1 treatment in resected patients who are not candidates for adjuvant chemotherapy based on the fact that it was mandatory in the Impower010 trial and that in the PEARLS trial, adjuvant pembrolizumab appeared to be detrimental versus placebo for patients who did not receive adjuvant chemotherapy [N=167; HR =1.25 (0.76–2.05)] (28).

Nuria M. Novoa: Selection is based on the pathological positivity report. We moved from considering the possibility of using it when positivity was >50% toward lower levels. It is currently being considered from >1%.

Maria Rodriguez: In adjuvant therapy, following evidence of the IMpower010 trial, only atezolizumab is approved by the FDA. We use it only in PD-L1-positive patients following 4 cycles of adjuvant chemotherapy.

Ichiro Sakanoue: Obviously, we need to confirm the percentage of PD-L1 using resected lung tissue/tumor samples, but based on our current practice, we do not use PD-L1 in the adjuvant setting. Also, I think we need to confirm that the patients do not have idiopathic pulmonary fibrosis in pathology and radiology findings.

Kenichi Suda: For patients with pathological stage II–III diseases without EGFR/ALK, PD-L1 staining seems to be important, especially for the IMpower 010 regimen (atezolizumab). Platinum doublet should be used prior to adjuvant PD-1/PD-L1.

Fabrizio Tabbò: In our country it is still not possible to use adjuvant ICIs; however, I would consider patient's conditions and comorbidities, disease stage, PD-L1 status and previous adjuvant chemotherapy.

Terence Chi Chun Tam: I personally would recommend patients with stage IIB–IIIA completely resected *EGFR* and *ALK* (–) tumor to undergo the standard 4 cycles of adjuvant chemotherapy and then a reassessment CT to confirm no early adjuvant failure before starting them on 1 year of atezolizumab. Unless patients are very keen, I do not offer atezolizumab to stage IIA patients.

Masanori Tsuchida: Adjuvant platinum-based chemotherapy is a standard treatment option for the patients with pathological II and IIIA completely resected NSCLC at present. If recurrence is obvious, the patients with PD-1 expression >1% are candidates for immune therapy.

Junji Uchino: Stage IB with tumor ≥4 cm, stage II–IIIA NSCLC after complete surgical resection with resection margins proved microscopically to be free of disease (R0).

In addition, it will probably be targeted at patients with a negative for an oncogenic driver.

Luca Voltolini: We cannot use adjuvant PD-1/PD-L1 outside clinical trials.

Do you use chemotherapy before adjuvant PD-1/PD-L1?

Stefano Bongiolatti: Traditional adjuvant chemotherapy is the standard of care, and immunotherapy is neither recommended nor funded by the National Health System in this setting; it can only be administered within clinical trials.

Alessandro Brunelli: Generally yes.

Alfonso Fiorelli: Postoperative platinum-based chemotherapy remains the standard of care in most of the world for resected lung cancer. Thus, adjuvant PD-1/PD-L1 should be administered after standard chemotherapy. The IMpower010 trial (27) and ANVIL trial (48) randomized patient to adjuvant PD-1/PD-L1 or observation after completion of surgical resection and adjuvant chemo- or radiotherapy.

Elisa Gobbini: Yes, when indicated and when patients care fit enough.

Cesare Gridelli: Yes, if patients are fit with no major comorbidities.

Thomas John: Yes.

Jae Jun Kim: Regardless of whether patients undergo surgery or not, we firstly use chemotherapy.

Steven H. Lin: Yes, we would opt for chemotherapy before starting PD-1/PD-L1 as indicated by the IMPower010 trial.

Giulio Metro: In the 2 studies that assessed the role of adjuvant PD-1/PD-L1 treatment, the Impower010 included the use of adjuvant chemotherapy as mandatory prior to adjuvant atezolizumab, while the PEARLS trial of adjuvant pembrolizumab also included patients who had not received adjuvant chemotherapy (27). However, in the latter study the forest plot analysis of DFS suggested that adjuvant pembrolizumab could be detrimental for patients who did not receive adjuvant chemotherapy [N=167; HR =1.25 (0.76–2.05)]. Conversely, adjuvant pembrolizumab was associated with a significant DFS benefit in patients who had received postoperative chemotherapy [N=1010; HR =0.73 (0.60–0.89)] (28). These data are in line with the biological rationale that chemotherapy might enhance subsequent immune response to ICIs by inducing tumor lysis and releasing tumor antigens (49).

Therefore, while we wait for more data on this topic from ongoing and future studies, it is my opinion that, if adjuvant PD-1/PD-L1 treatment is to be used, it should always be anticipated by adjuvant chemotherapy.

Fabrizio Minervini: Yes, based on the IMPOWER-010 trial and the Swiss label for atezolizumab, which mandates chemotherapy.

Nuria M. Novoa: Yes, we have followed the same strategy of the NADIM study (when the study was closed) which includes platinum-based chemotherapy + nivolumab in the neoadjuvant setting and nivolumab alone for the adjuvant setting.

Maria Rodriguez: Yes, following evidence of the IMpower010 trial we use it following 4 cycles of adjuvant chemotherapy.

Ichiro Sakanoue: Currently, we do not use adjuvant TKIs as a routine adjuvant therapy. We only use chemotherapy as an adjuvant therapy. Therefore, I do not have a definitive answer for this question.

Kenichi Suda: Probably yes (it is expected that chemotherapy is "required" before atezolizumab adjuvant therapy based on the IMPOWER 010 study). Subgroup analysis of the PEARLS trial also showed a worse outcome for pembrolizumab in patients without adjuvant chemotherapy.

Fabrizio Tabbò: In our country, it is still not possible to use adjuvant ICIs; however I would use chemotherapy when indicated based on disease and patient features.

Terence Chi Chun Tam: Yes, as per the IMPOWER010 trial unless they are medically contraindicated. In such patients, if they accept that it is a deviation from currently available best evidence, I do offer them direct atezolizumab adjuvant therapy for 1 year.

Masanori Tsuchida: Yes.

Junji Uchino: Yes.

Luca Voltolini: If we could use adjuvant PD-1/PD-L1, we would use chemotherapy for 4 cycles before.

What is your preferred duration of adjuvant PD-1/PD-L1 therapy?

Stefano Bongiolatti: I cannot answer this question due to the lack of recommendations from our health system about adjuvant immunotherapy.

Alessandro Brunelli: Outside clinical trials, we generally start immune-oncology when patients show relapse.

Alfonso Fiorelli: To maximize patient outcomes, the treatment decision should be based on treatment efficacy, safety, and surgery rate. The selection of patient remains unclear, as there are no standardized biomarkers to select patient who will benefit from adjuvant PD-1/PD-L1 therapy or who will develop AEs. In the IMpower010 trial (27) and ANVIL trial (48), patients received adjuvant PD-1/PD-L1 up to 1 year.

Elisa Gobbini: 1 year.

Cesare Gridelli: 12 months.

Thomas John: 12 months.

Jae Jun Kim: We usually use adjuvant PD-1/PD-L1 when the response is shown.

Steven H. Lin: Up to 1 year.

Giulio Metro: In both studies that assessed the role of adjuvant PD-1/PD-L1 treatment (Impower010 and PEARLS), the duration of adjuvant PD-1/PD-L1 treatment was 1 year. Therefore, if adjuvant PD-1/PD-L1 therapy is to be used, it should last up to 1 year.

Fabrizio Minervini: Adjuvant atezolizumab is approved for 1 year maximum.

Nuria M. Novoa: Following the NADIM strategy, 1 year after surgery is the standard time.

Maria Rodriguez: For atezolizumab, 1 year. With pembrolizumab, following the recent evidence of the PEARLS trial (not approved yet, and effective regardless of PD-L1 status), 1 year. However, in our setting, it seems the European Medicines Agency will only approve pembrolizumab in PD-L1-positive patients.

Ichiro Sakanoue: Based on the recent promising results in clinical trials, I would prefer to use adjuvant PD-L1 for at least 1 year.

Kenichi Suda: If approved, I will follow the trial designs (IMPOWER010 or PEARLS).

Fabrizio Tabbò: In our country it is still not possible to use adjuvant ICIs; however I'd say for one year totally.

Terence Chi Chun Tam: One year as per the IMPOWER010 trial.

Masanori Tsuchida: I do not have a specific preference.

Junji Uchino: One year.

Luca Voltolini: Looking at the trials on adjuvant PD-1/PD-L1, we will use it, when possible, for 1 year.

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Footnote

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