Perioperative Therapy for Resectable Non–Small-Cell Lung Cancer: Weighing Options for the Present and Future

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ABSTRACT

Anatomic surgical resection followed by cisplatin-based platinum-doublet adjuvant chemotherapy has been a long-standing standard of care for patients with early-stage, resectable non–small-cell lung cancer (NSCLC). More recently, incorporating of immunotherapy and targeted therapy in the perioperative setting has demonstrated improved disease-free or event-free survival in biomarker-defined subsets of patients. This article summarizes the results of major trials that led to approvals beyond chemotherapy in the perioperative setting. Alongside adjuvant osimertinib as a favored strategy for patients with *EGFR* mutation–positive NSCLC, there are competing potential standards of care for integrating immunotherapy in the neoadjuvant versus adjuvant setting, with advantages and disadvantages for each strategy. Emerging data in the coming years will provide further insight that may potentially lead to a combination of neoadjuvant and adjuvant treatment for many patients. Future trials should focus on clarifying the benefit of each component of treatment, defining an optimal treatment duration, and incorporating minimal residual disease to optimize treatment decisions.

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HISTORICAL BACKGROUND

Historically, complete anatomic surgical resection potentially followed by chemotherapy has been the standard of care for patients with early-stage resectable non–small-cell lung cancer (NSCLC). Up to four cycles of cisplatin-based adjuvant chemotherapy is routinely recommended for those with tumor size ≥4 cm and/or regional nodal involvement. However, the survival benefit offered by chemotherapy is modest, with the Lung Adjuvant Cisplatin Evaluation meta-analysis demonstrating a 5.4% absolute 5-year benefit in overall survival (OS) from adjuvant chemotherapy.[1] Despite surgery and adjuvant therapies, most patients with early-stage NSCLC die from disease recurrence. Efforts to improve outcomes by adding the antiangiogenic monoclonal antibody bevacizumab[2] or adjuvant postoperative radiation therapy[3] failed to confer a survival benefit, underscoring the ongoing need for better outcomes in this setting.

APPROVALS BEYOND CHEMOTHERAPY IN THE PERIOPERATIVE SETTING

The first strategy beyond conventional chemotherapy to shape the perioperative space in resectable NSCLC was adjuvant osimertinib for up to 3 years, on the basis of the dramatic improvement in disease-free survival (DFS) observed with postoperative osimertinib compared with placebo in patients with stage IB-IIIA *EGFR* mutation–positive NSCLC in the ADAURA trial.[4] This led to approval by the US Food and Drug Administration (FDA)[5] and European Commission,[6] with accompanying broad use as a standard of care, at least on the basis of the preliminary data presented and published thus far. However, a recent update shows that although the DFS benefit remains with 2 more years of follow-up, the DFS benefit begins to wane as soon as the 3-year period of treatment ends,[7] raising concern that therapy does not eradicate residual disease after surgery and raising the question of whether indefinite treatment with osimertinib may ultimately be favored. In the meantime, we eagerly await the results for OS with adjuvant osimertinib on the basis of this trial.

Most recently, immunotherapy has been incorporated into neoadjuvant and adjuvant regimens on the basis of data demonstrating improvement in event-free survival (EFS) and DFS, respectively, for early-stage, resectable NSCLC. To our knowledge, IMpower-010 is the first phase III trial that demonstrated a DFS benefit with immunotherapy, following complete surgical resection, adjuvant chemotherapy, and then up to a year of adjuvant atezolizumab in patients with PD-L1–positive, stage II-IIIA disease,[8] leading the FDA to approve atezolizumab for this population.[9] Of note, although the study demonstrated DFS benefit in patients with PD-L1–positive stage II-IIIA (stratified hazard ratio [HR], 0.66; 95% CI, 0.50 to 0.88), a post hoc analysis indicated that the benefit was driven overwhelmingly by patients with tumor PD-L1 expression ≥ 50%; HR, 0.87 and 0.43 for patients with PD-L1 1%-49% and ≥ 50%, respectively). Given the lack of benefit for PD-L1 of 1%-49%, the European Commission has approved atezolizumab only for patients with PD-L1 ≥ 50%.[10]

Notably, a recently reported interim analysis at the time of the first prespecified OS analysis at a median follow-up of 46 months showed a nonsignificant trend in favor of atezolizumab in PD-L1-positive patients with stage II-IIIA disease (HR, 0.71; 95% CI, 0.49 to 1.03) but not in all intention-to-treat populations, with OS benefit confined to patients with PD-L1 ≥ 50% (HR, 0.43) compared with those with PD-L1 1%-49% (HR, 0.95).[11]

The similarly designed KEYNOTE-091 (PEARLS) trial also demonstrated improvement in DFS for patients with stage IB (≥4 cm) to IIIA NSCLC who received up to a year of adjuvant pembrolizumab,[12] and now has received FDA approval in this setting irrespective of PD-L1 expression.[13] Interestingly, there was no association of greater or lesser efficacy in the KEYNOTE-091 trial by PD-L1 expression: The HR for DFS with PD-L1 ≥ 50% was 0.82 (0.57-1.18) versus 0.76 (0.63-0.91) in the overall trial population,[12] a puzzling anomaly that remains unexplained. Given the added year of treatment required, the considerable financial cost, and the potential for even permanent immune-related toxicities from adjuvant immune checkpoint inhibitors,[14] risks and benefits should be discussed with the patient before offering adjuvant immunotherapy. We favor shared decision making before recommending adjuvant atezolizumab (for PD-L1-positive patients) or adjuvant pembrolizumab. The data from IMpower010 support limiting adjuvant atezolizumab to patients with PD-L1 ≥ 50%. We favor being judicious about recommending adjuvant therapy that has not demonstrated an improvement in survival while also recognizing that some well-informed patients will favor erring on the side of potential overtreatment if they consider their risk of recurrence high enough to justify pursuing a year of adjuvant immunotherapy.

In the neoadjuvant setting, the CheckMate-816 trial demonstrated an improvement in EFS with nivolumab plus chemotherapy for three cycles when compared with chemotherapy alone for patients with resectable stage IB-IIIA *EGFR* and *ALK* wild-type NSCLC[15] and also has received FDA approval.[16] Similar to the findings in IMpower010, the HR for EFS in CheckMate-816 was 0.85 (0.54-1.32), 0.58 (0.30-1.12), and 0.24 (0.10-0.61) for patients with PD-L1 expression <1%, 1%-49%, and ≥ 50%, respectively,[15] although the differences here were not enough to lead to changes in regulatory approval on the basis of tumor PD-L1 expression. Notably, improved EFS with chemotherapy/nivolumab was highly associated with the achievement of a pathologic complete response (pCR) (HR, 0.13 *v* no pCR).[17]

Importantly, the goal of perioperative chemotherapy is to eradicate potential micrometastatic disease and improve long-term survival. Although OS has remained the gold standard end point, the FDA has accepted DFS and EFS as reasonable end points to support approval, predicated on the assumption that delaying metastatic disease is a direct measure of a clinical benefit while awaiting OS results. Although this may seem a reasonable approach, especially in early-stage NSCLC cases for which extended follow-up is required for a mature OS data, we must continue to recognize the potential harms of overtreatment, both to patients and to broader society, as we develop new standards of care on the basis of surrogate end points. Ongoing phase III clinical trials with perioperative immune checkpoint inhibitors are summarized in Table 1.

PERIOPERATIVE ADJUVANT THERAPY FOR PATIENTS WITH A DRIVER MUTATION

Although adjuvant osimertinib remains a uniquely strong strategy for patients with *EGFR* mutation–positive NSCLC,[4] for those with most other driver mutations, we favor adjuvant chemotherapy alone, or enrollment in a clinical trial when available (Table 2). Not only has immunotherapy shown generally poor efficacy in the setting of advanced disease,[18] there may be an increased risk of immune-related adverse events when the patients are treated with tyrosine kinase inhibitors shortly after immune checkpoint inhibitors at the time of disease recurrence.[19,20]

Nevertheless, because such patients were eligible for IMpower010, PEARLS, and many other ongoing trials of immunotherapy in the perioperative setting, it is appropriate to present approved treatments such as atezolizumab as an option to be considered by shared decision making when such patients would otherwise be appropriate candidates.

NEOADJUVANT VERSUS ADJUVANT THERAPY: IDENTIFYING THE RIGHT TREATMENT FOR PATIENTS WITHOUT A DRIVER MUTATION

For those without a sensitizing driver mutation, there is an open question currently of whether to favor neoadjuvant chemotherapy/nivolumab or adjuvant atezolizumab after chemotherapy. Historically, neoadjuvant therapy in NSCLC has not been generally favored in patients with clearly resectable disease. This is largely because the majority of trials establishing OS benefit with perioperative chemotherapy incorporated a postoperative strategy,[21] and patients and some physicians may have a bias to resect all visible disease as readily as feasible, with additional but secondary modalities relegated to subsequent management. Additionally, neoadjuvant chemotherapy alone has demonstrated limited efficacy in inducing pathological response[22-24] and incurs some risk of progression that could preclude surgery.

The combination of chemotherapy/nivolumab in the CheckMate-816 trial not only demonstrated improvement in EFS with the addition of immunotherapy but also demonstrated significant improvement in pathological response, including major pathological response (MPR) and pCR compared with chemotherapy alone.[15] Importantly, among patients with stage IIIA NSCLC, who comprised 64% of the patients on this trial, a greater percentage of patients who received neoadjuvant chemotherapy/nivolumab proceeded to definitive surgery and complete resection, with a greater

TABLE 1. Ongoing Phase III Clinical Trials With Perioperative Immune Checkpoint Inhibitors

Clinical Trial/NCT Identifier	Immunotherapy	Neoadjuvant	Surgery	Adjuvant Chemotherapy	Adjuvant Immunotherapy
KEYNOTE-671/NCT03425643	Pembrolizumab	CT + IO ✓	✓	×	✓
AEGEAN/NCT03800134	Durvalumab	CT + IO ✓	✓	×	✓
CheckMate 77T/NCT04025879	Nivolumab	CT + IO ✓	✓	×	✓
IMPOWER 030/NCT03456063	Atezolizumab	CT + IO ✓	✓	×	✓
BR.31/NCT02273375	Durvalumab	×	✓	✓	✓
MERMAID-1/NCT04385368	Durvalumab	×	✓	✓ CT + IO	✓
MERMAID-2[a]/NCT04642469	Durvalumab	×	✓	✓ CT + IO	✓
ANVIL/NCT02595944	Nivolumab	×	✓	✓	✓

Abbreviations: CT, standard of care platinum-doublet chemotherapy; IO, immune checkpoint inhibitor; NSCLC, non–small-cell lung cancer.
[a]Patients with NSCLC with minimal residual disease.

probability of minimally invasive surgery and lower risk of pneumonectomy for those with stage IIIA(N2) NSCLC when compared with chemotherapy alone.[25] These benefits were conferred with just three cycles of treatment administered over approximately 2 months, in contrast with the sequential approach of IMpower010 or PEARLS that entails 3 months of chemotherapy, followed by an additional year of atezolizumab or pembrolizumab after surgery.

A neoadjuvant strategy offers several other advantages over adjuvant therapy, such as the more reliable delivery of intended systemic therapy preoperatively compared with postoperatively.[26] Neoadjuvant treatment also provides the earliest opportunity for treatment of micrometastatic disease, administers immunotherapy while lymph nodes and lymphatic drainage remain intact, and allows direct assessment of treatment effects. We, therefore, favor neoadjuvant chemotherapy/nivolumab for patients with higher-risk disease, including those with stage IIIA disease and arguably those with stage II, node-positive NSCLC (American Joint Committee on Cancer [AJCC] 8th Edition Staging System). Additionally, data from NADIM II trial, a recently concluded phase II study for patients with stage IIIA-IIIB (AJCC 8th Edition Staging System) NSCLC, also demonstrated that 93% of patients receiving chemotherapy/nivolumab neoadjuvant therapy underwent definitive surgery compared with 69% of patients receiving neoadjuvant chemotherapy alone.[27] This study also demonstrated a remarkably high R0 resection rate with chemotherapy/nivolumab compared with chemotherapy (92.5% *v* 65.0%), supporting the particular utility of neoadjuvant chemotherapy with immunotherapy, particularly for those with higher-risk, node-positive disease.[27]

In contrast, the subset analysis of CheckMate-816 revealed a rather modest HR of 0.87 for EFS between chemotherapy/nivolumab versus chemotherapy alone among patients with stage IB-II (AJCC 7th Edition) disease. Given the high priority of addressing localized disease for lower-stage NSCLC, upfront surgery remains a compelling consideration in patients with node-negative disease.

HONING THE DURATION OF NEOADJUVANT AND ADJUVANT THERAPIES

The optimal duration of neoadjuvant and adjuvant therapy has yet to be defined, currently shaped by empiric estimates of a potential point of diminishing returns for chemotherapy and immunotherapy. Future trials should seek to define an optimal balance of efficacy in eradicating micrometastatic disease and optimizing clinical efficacy while avoiding overtreatment that incurs added costs, toxicity, and time of patients in longitudinal treatment.

NEOSCORE, a phase II trial that randomly assigned patients with stage IB-IIIA (AJCC 8th edition) to either receive two or three cycles of the PD-1 inhibitor sintilimab plus chemotherapy in the neoadjuvant setting, followed by one or two cycles of adjuvant therapy, was terminated early after it demonstrated numerically better MPR and pCR rates with three cycles that were nevertheless not statistically significant.[28] Although these results corroborate the potentially emerging standard of three cycles of neoadjuvant chemoimmunotherapy that was incorporated into the CheckMate-816 trial and some others, it is worth underscoring that the far superior EFS for those who achieve a pCR was only attained by 24% of patients on CheckMate-816. This leaves us with an open question of whether we may achieve better clinical outcomes compared with three cycles of chemoimmunotherapy by intensifying preoperative therapy. The results of the KEYNOTE-671, IMpower-030, and CheckMate-77T trials, which all administer four cycles of neoadjuvant chemoimmunotherapy, will help provide data on this question, albeit without a direct comparison of treatment duration within a single trial.

In addition to these considerations for neoadjuvant therapy, it remains unknown whether or how to treat with additional systemic therapy postoperatively for those who do not achieve a pCR. Although it is understandable to be inclined to recommend additional chemotherapy and/or immunotherapy to these patients, the incremental benefit of further treatment with an approach identical or very similar to one

TABLE 2. Various Ongoing Clinical Trials With Perioperative Targeted Therapy for Resectable Non–Small-Cell Lung Cancer With a Driver Mutation

Clinical Trial/NCT Identifier	Neoadjuvant or Adjuvant	Stage	Mutation Subtype	Study Design	Study Phase	Primary End Point	Estimated Enrollment
NeoADAURA/ NCT04351555	Neoadjuvant	II-III B N2	*EGFR*	3 arms: Pb + CT *v* osimertinib + CT × 3 cycles *v* osimertinib for ≥9 weeks	III	MPR	328
Neolpower/NCT05104788	Neoadjuvant	II-IIIB	*EGFR*	Single arm: CT + icotinib × 2 cycles	II	MPR	27
FORESEE/NCT05430802	Neoadjuvant	IIIA-IIIB	*EGFR*	Single arm: Furmonertinib × 9 weeks + cisplatin + pemetrexed × 3 cycles	II	ORR	40
APPOINT/NCT04922138	Adjuvant	IA	*EGFR*	Aumolertinib until disease recurrence or completion of treatment or reaching the standard of discontinuation	II	2-year DFS	52
NCT05132985	Neoadjuvant and adjuvant	II-IIIB	*EGFR*	Neoadjuvant icotinib + carboplatin/cisplatin + pemetrexed × 2 cycles → adjuvant: CT (×2 cycles) + icotinib × 2 years	II	MPR	45
NOCE01/NCT05011487	Neoadjuvant	III N2	*EGFR*	Single arm: Osimertinib + CT × 2 cycles	II	Complete lymph node clearance rate	30
ANSWER/NCT04455594	Neoadjuvant	IIIA N2	*EGFR*	Almonertinib *v* erlotinib + CT	II	ORR	168
NCT02820116	Neoadjuvant and adjuvant	IIIA-IIIB	*EGFR*	Neoadjuvant icotinib × 8 weeks → adjuvant: Icotinib × 2 years	II	Complete resection rate	67
NCT05380024	Neoadjuvant	II-IIIB N2	*ALK*	Single arm: Ensartinib × 8 weeks	II	MPR	10
An ALCHEMIST treatment trial/NCT02201992	Adjuvant	IB-IIIA	*ALK*	Adjuvant crizotinib × 2 years *v* observation after surgery	III	OS	168
NCT03456076	Adjuvant	IB-IIIA	*ALK*	Adjuvant alectinib × 2 years *v* CT (×4 cycles)	III	DFS	257
NCT05241028	Adjuvant	IB-IIIA	*ALK*	Single arm: Ensartinib × 3 years	II	3-year DFS	80
ALNEO/NCT05015010	Neoadjuvant	III	*ALK*	Neoadjuvant alectinib × 8 weeks → adjuvant alectinib × 96 weeks	II	MPR	33
NCT05341583	Adjuvant	II-IIIB	*ALK*	Adjuvant ensartinib *v* placebo × 2 years	III	DFS	202
NCT04302025	Neoadjuvant and adjuvant	IB-III	Biomarker driven (non-IO arms) *ALK* *ROS1* *NTRK* *BRAF* *RET*	Neoadjuvant TKI × 8 weeks → adjuvant CT (×4 cycles) → TKI × 2 years Alectinib Entrectinib Entrectinib Vemurafenib + cobimetinib Pralsetinib	II	MPR	80
NCT05400577	Neoadjuvant	IB-IIIA	*KRAS G12C*	Single arm: Sotorasib for 4 weeks	II	MPR	25
Neo-Kan/NCT05472623	Neoadjuvant	IB-IIIA	*KRAS G12C*	Two arms: Arm A: Adagrasib × 6 weeks Arm B: Adagrasib × 6 weeks + nivolumab every 2 weeks for 3 doses	II	pCR	42
NCT05118854	Neoadjuvant	IIA-IIIB	*KRAS G12C*	Single arm: Sotorasib + cisplatin or carboplatin and pemetrexed for 4 cycles	II	Efficacy and safety of the combination	27

Abbreviations: CT, platinum-pemetrexed chemotherapy; DFS, disease-free survival; IO, immune checkpoint inhibitor; MPR, major pathological response; ORR, overall response rate; OS, overall survival; Pb, placebo; pCR, pathologic complete response; TKI, tyrosine kinase inhibitor.

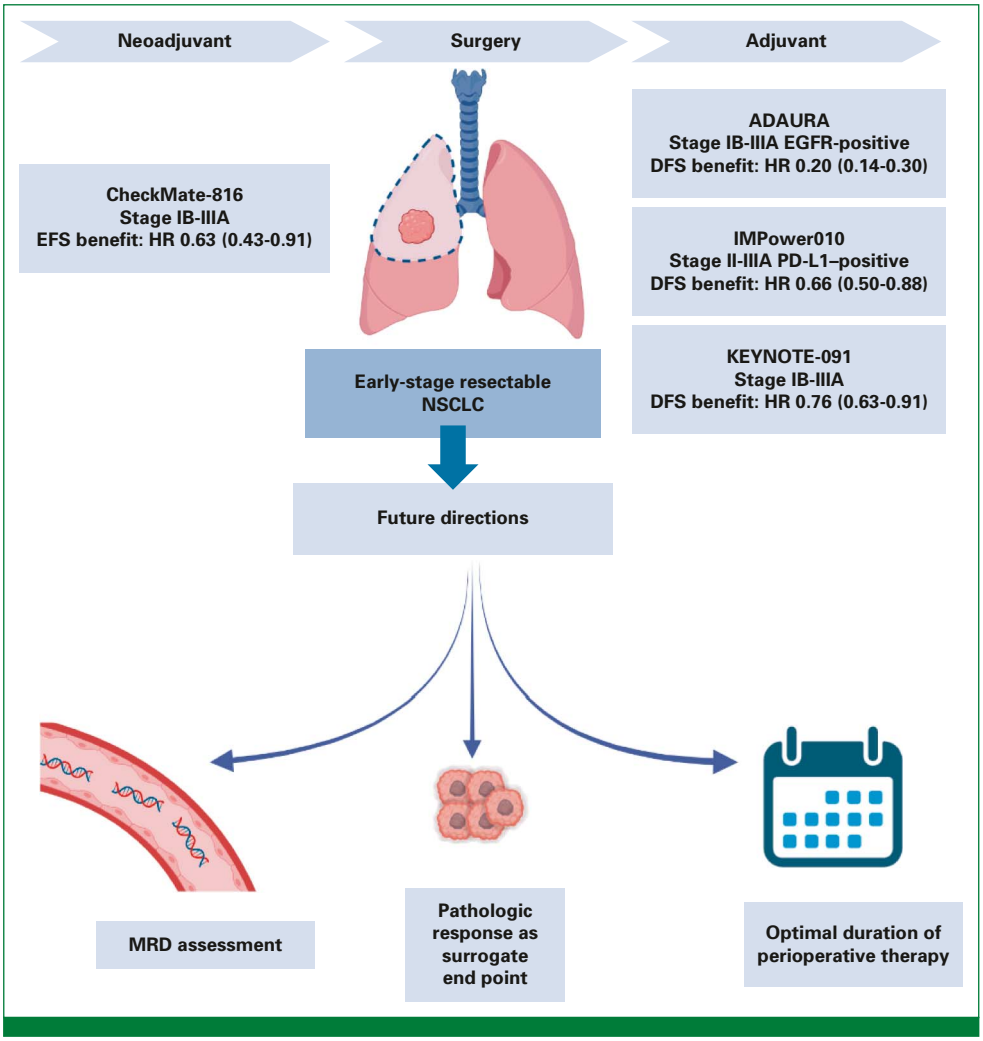

FIG 1. Simplified illustration of recent updates on systemic therapy beyond chemotherapy in the perioperative setting in early-stage resectable NSCLC and future directions. DFS, disease-free survival; EFS, event-free survival; HR, hazard ratio; MRD, minimal residual disease; NSCLC, non–small-cell lung cancer.

that left significant residual disease remains unclear. Ongoing trials that included both a neoadjuvant and adjuvant component should help clarify the contribution of postoperative therapy for the subset of patients in whom the preoperative therapy conferred disappointing results in the form of significant residual viable tumor, although none of these trials isolates the variable of adjuvant immunotherapy after neoadjuvant therapy as a controlled variable.

In the postoperative setting, future research will be required to define whether there may also be an opportunity to de-escalate from the current empirical approach of administering immunotherapy for a year after adjuvant chemotherapy. The duration of a year of immunotherapy conforms with the duration of consolidation durvalumab after chemoradiation in the curative setting for patients with unresectable stage III NSCLC,[29] but these trials demonstrate low rates of completion of a year of immunotherapy, with no evidence to suggest that patients who discontinue therapy for adverse effects or other reasons beyond disease progression have less favorable outcomes than those who complete a year of therapy; these points support the premise that the benefit conferred by immunotherapy may not be duration-dependent beyond a limited period of several months. Unfortunately, ongoing phase III trials will not provide direct assessment of the optimal duration of adjuvant immunotherapy.

INCORPORATING MINIMAL RESIDUAL DISEASE INTO DECISIONS AROUND PERIOPERATIVE THERAPY

Because some patients are cured with surgery alone, we know that not all the patients require further treatment, with this subset overtreated by the addition of systemic therapy. At the same time, the relatively low rates of actual delivery of adjuvant chemotherapy[30] (and possibly immunotherapy and targeted therapy in the future) may well reflect the ambivalence of patients who are wary about accepting the challenges of further treatment if there is no visible disease to follow and a recognized potential that they are cured without further intervention. Assessment for evidence of

minimal residual disease (MRD) as a biomarker may be especially helpful in such settings. A well-designed clinical study with circulating tumor DNA (ctDNA) assessment before and after the surgery, with or without adjuvant therapy for MRD-negative subset and with serial assessment of MRD to seek evidence of clearance with adjuvant therapy for those who are MRD-positive, would clearly illustrate the utility of this technology in refining which patients need additional therapy. Such a study would also clarify the trajectory of response by this parameter over the course of ongoing treatment. A phase II study using a ctDNA-guided approach in an analogous setting of stage II colon cancer demonstrated reduced adjuvant chemotherapy use without any compromise on recurrence-free survival.[31] Various trials (ClinicalTrials.gov identifier: NCT04238130, NCT04153526, NCT05254782, and NCT04367311) are investigating the potential use of perioperative ctDNA for MRD assessment in resectable NSCLC to guide the need of perioperative systemic therapy and other key questions in perioperative therapy for early stage NSCLC (Fig 1).

SURROGATE END POINTS IN TRIALS OF PERIOPERATIVE THERAPY FOR EARLY-STAGE RESECTABLE NSCLC

Surrogate end points such as MPR, pCR, DFS, and EFS are valuable to the extent that they correlate with and predict benefit in the gold standard of OS. If reliable in this regard, they afford an opportunity to change practice several years before OS data mature, improving clinical outcomes for thousands of patients in the interim. To improve consistency of pathologic assessment, the International Association for the Study of Lung Cancer has formulated a clear guidance in this setting.[32] Several studies have demonstrated a preliminary association between improved survival with resected NSCLC and MPR in the chemotherapy era.[33-36] We await longitudinal results from the current round of trials of more novel therapies to determine whether the surrogate end points presumed to predict OS benefit will ultimately prove to do so.

In conclusion, perioperative immunotherapy and targeted therapy have recently taken their place as potential additions to the current standard of care for patients with stage IB-IIIA NSCLC on the basis of a series of positive trials that offer a new range of options. Nevertheless, our current practice continues to evolve as we await more mature data from these studies and additional results that promise to help us better refine our understanding of an optimal duration of treatment and identify a reliable surrogate end point for OS. At the same time, there is an urgent need for biomarkers to help us recognize which patients will truly benefit while others may be safely observed.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
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REFERENCES

1. Pignon JP, Tribodet H, Scagliotti GV, et al: Lung adjuvant cisplatin evaluation: A pooled analysis by the LACE Collaborative Group. J Clin Oncol 26:3552-3559, 2008
2. Wakelee HA, Dahlberg SE, Keller SM, et al: Adjuvant chemotherapy with or without bevacizumab in patients with resected non-small-cell lung cancer (E1505): An open-label, multicentre, randomised, phase 3 trial. Lancet Oncol 18:1610-1623, 2017
3. Le Pechoux C, Pourel N, Barlesi F, et al: Postoperative radiotherapy versus no postoperative radiotherapy in patients with completely resected non-small-cell lung cancer and proven mediastinal N2 involvement (Lung ART): An open-label, randomised, phase 3 trial. Lancet Oncol 23:104-114, 2022
4. Wu Y-L, Tsuboi M, He J, et al: Osimertinib in resected EGFR-mutated non–small-cell lung cancer. N Engl J Med 383:1711-1723, 2020
5. US Food and Drug Administration: Approves osimertinib as adjuvant therapy for non-small cell lung cancer with eGFR mutations. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-osimertinib-adjuvant-therapy-non-small-cell-lung-cancer-egfr-mutations
6. European Medicines Agency: Tagrisso (Osimertinib). https://www.ema.europa.eu/en/medicines/human/EPAR/tagrisso
7. Tsuboi M, Wu Y-L, Grohe C, et al: Osimertinib as adjuvant therapy in patients (pts) with resected EGFR-mutated (EGFRm) stage IB-IIIA non-small cell lung cancer (NSCLC): Updated results from ADAURA. Ann Oncol 33:S808-S869, 2022
8. Felip E, Altorki N, Zhou C, et al: Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): A randomised, multicentre, open-label, phase 3 trial. Lancet 398:1344-1357, 2021
9. US Food and Drug Administration: FDA approves atezolizumab as adjuvant treatment for non-small cell lung cancer. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-atezolizumab-adjuvant-treatment-non-small-cell-lung-cancer
10. Globenewswire: European commission approves Roche's Tecentriq as adjuvant treatment for a subset of people with early-stage non-small cell lung cancer. https://www.globenewswire.com/news-release/2022/06/09/2459297/0/en/European-Commission-approves-Roche-s-Tecentriq-as-adjuvant-treatment-for-a-subset-of-people-with-early-stage-non-small-cell-lung-cancer.html

11. Wakelee H, Altorki N, Felip E, et al: IMpower010: Overall survival interim analysis of a phase III study of atezolizumab vs. best supportive care in resected NSCLC. World Conference on Lung Cancer, Vienna, Austria, August 2022 (abstr#PL-03)
12. O'Brien M, Paz-Ares L, Marreaud S, et al: Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): An interim analysis of a randomised, triple-blind, phase 3 trial. Lancet Oncol 23:1274-1286, 2022
13. US Food and Drug Administration: FDA approves pembrolizumab as adjuvant treatment for non-small cell lung cancer. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-adjuvant-treatment-non-small-cell-lung-cancer
14. Patrinely JR Jr, Johnson R, Lawless AR, et al: Chronic immune-related adverse events following adjuvant anti-PD-1 therapy for high-risk resected melanoma. JAMA Oncol 7:744-748, 2021
15. Forde PM, Spicer J, Lu S, et al: Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. N Engl J Med 386:1973-1985, 2022
16. US Food and Drug Administration: FDA approves neoadjuvant nivolumab and platinum-doublet chemotherapy for early-stage non-small cell lung cancer. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-neoadjuvant-nivolumab-and-platinum-doublet-chemotherapy-early-stage-non-small-cell-lung
17. Girard N, Spicer J, Provencio M, et al: Abstract CT012: Nivolumab (NIVO) + platinum-doublet chemotherapy (chemo) vs chemo as neoadjuvant treatment for resectable (IB-IIIA) non-small cell lung cancer (NSCLC): Event-free survival (EFS) results from the phase 3 CheckMate 816 trial. Cancer Res 82:CT012, 2022
18. Calles A, Riess JW, Brahmer JR: Checkpoint blockade in lung cancer with driver mutation: Choose the road wisely. Am Soc Clin Oncol Educ Book 40:372-384, 2020
19. Schoenfeld AJ, Arbour KC, Rizvi H, et al: Severe immune-related adverse events are common with sequential PD-(L)1 blockade and osimertinib. Ann Oncol 30:839-844, 2019
20. Nishiyama A, Hattori Y, Takeuchi S, et al: Severe skin toxicity caused by sequential anti-PD-1 antibody and alectinib in non-small-cell lung cancer: A report of two cases and a literature review. Intern Med 61:1735-1738, 2022
21. Lim E, Harris G, Patel A, et al: Preoperative versus postoperative chemotherapy in patients with resectable non-small cell lung cancer: Systematic review and indirect comparison meta-analysis of randomized trials. J Thorac Oncol 4:1380-1388, 2009
22. Felip E, Rosell R, Maestre JA, et al: Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer. J Clin Oncol 28:3138-3145, 2010
23. Gilligan D, Nicolson M, Smith I, et al: Preoperative chemotherapy in patients with resectable non-small cell lung cancer: Results of the MRC LU22/NVALT 2/EORTC 08012 multicentre randomised trial and update of systematic review. Lancet 369:1929-1937, 2007
24. Nagai K, Tsuchiya R, Mori T, et al: Lung Cancer Surgical Study Group of the Japan Clinical Oncology Group: A randomized trial comparing induction chemotherapy followed by surgery with surgery alone for patients with stage IIIA N2 non-small cell lung cancer (JCOG 9209). J Thorac Cardiovasc Surg 125:254-260, 2003
25. Spicer J, Wang C, Tanaka F, et al: Surgical outcomes from the phase 3 CheckMate 816 trial: Nivolumab (NIVO) + platinum-doublet chemotherapy (chemo) vs chemo alone as neoadjuvant treatment for patients with resectable non-small cell lung cancer (NSCLC). J Clin Oncol 39:8503, 2021
26. Felip E, Rosell R, Maestre JA, et al: Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer. J Clin Oncol 28:3138-3145, 2010
27. Provencio M, Serna R, Nadal E, et al: Nivolumab + chemotherapy vs chemotherapy as neoadjuvant treatment for resectable IIIA-B NSCLC. World Conference on Lung Cancer, Vienna, Austria, August 2022
28. Qiu F, Fan J, Shao M, et al: Two cycles versus three cycles of neoadjuvant sintilimab plus platinum-doublet chemotherapy in patients with resectable non-small-cell lung cancer (neoSCORE): A randomized, single center, two-arm phase II trial. J Clin Oncol 40:8500, 2022
29. Antonia SJ, Villegas A, Daniel D, et al: Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med 377:1919-1929, 2017
30. Kehl KL, Zahrieh D, Yang P, et al: Rates of guideline-concordant surgery and adjuvant chemotherapy among patients with early-stage lung cancer in the US ALCHEMIST study (alliance A151216). JAMA Oncol 8:717-728, 2022
31. Tie J, Cohen JD, Lahouel K, et al: Circulating tumor DNA analysis guiding adjuvant therapy in stage II colon cancer. N Engl J Med 386:2261-2272, 2022
32. Travis WD, Dacic S, Wistuba I, et al: IASLC multidisciplinary recommendations for pathologic assessment of lung cancer resection specimens after neoadjuvant therapy. J Thorac Oncol 15:709-740, 2020
33. Cascone T, Gold KA, Swisher SG, et al: Induction cisplatin docetaxel followed by surgery and erlotinib in non-small cell lung cancer. Ann Thorac Surg 105:418-424, 2018
34. Chaft JE, Rusch V, Ginsberg MS, et al: Phase II trial of neoadjuvant bevacizumab plus chemotherapy and adjuvant bevacizumab in patients with resectable nonsquamous non-small-cell lung cancers. J Thorac Oncol 8:1084-1090, 2013
35. Pataer A, Kalhor N, Correa AM, et al: Histopathologic response criteria predict survival of patients with resected lung cancer after neoadjuvant chemotherapy. J Thorac Oncol 7:825-832, 2012
36. William WN Jr, Pataer A, Kalhor N, et al: Computed tomography RECIST assessment of histopathologic response and prediction of survival in patients with resectable non-small-cell lung cancer after neoadjuvant chemotherapy. J Thorac Oncol 8:222-228, 2013

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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