JAMA Oncology | Review

Perioperative Immune Checkpoint Inhibition in Early-Stage Non–Small Cell Lung Cancer
A Review

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IMPORTANCE Although cancer-related mortality continues to decline, lung cancer remains the No. 1 cause of cancer deaths in the US. Almost half of the patients with non–small cell lung cancer (NSCLC) are diagnosed with early-stage, local or regional disease and are at high risk of recurrence within 5 years of diagnosis.

OBSERVATIONS Immune checkpoint inhibitors (ICIs) have improved outcomes for patients with metastatic NSCLC and have recently been tested in multiple clinical trials to determine their efficacy in the neoadjuvant or adjuvant setting for patients with local or regional disease. The landscape for perioperative ICIs in lung cancer is evolving rapidly, with recently reported and soon to mature clinical trials; however, the recent data highlight the potential of ICIs to increase response rates and decrease rates of relapse in early stages of lung cancer. Concurrently, novel applications of cell-free DNA may guide perioperative management strategies.

CONCLUSIONS AND RELEVANCE This article reviews the various approaches of incorporating perioperative use of immunotherapeutic agents for the treatment of early stages of NSCLC.

JAMA Oncol. 2023;9(1):135-142. doi:10.1001/jamaoncol.2022.5389
Published online November 17, 2022. Corrected on January 19, 2023.

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Lung cancer remains the leading cause of cancer-related mortality in the US, accounting for almost a quarter of all cancer deaths.[1] Stage I to III ("early stage") non–small cell lung cancer (NSCLC) accounts for 40% to 45% of all cases of lung cancer.[2] This number is likely to grow with increased adoption of low-dose computed tomography screening leading to increased identification of early-stage NSCLC.[3] For early-stage NSCLC, despite surgical resection, relapses and mortality are common. The addition of platinum-based chemotherapy regimens in the adjuvant setting has been the standard of care, with improved 5-year overall survival (OS) by 5.4%.[4]

Given that immunotherapy and targeted therapy have resulted in the biggest improvements in OS in the advanced-stage setting, it is of notable interest to determine the effectiveness of these approaches in early-stage NSCLC.[5,6] In December 2020, the results from the phase 3 ADAURA trial resulted in the first US Food and Drug Administration (FDA) approval of an adjuvant targeted therapy for NSCLC harboring an *EGFR* exon 19 deletion or exon 21 L858R mutation.[7] In the ADAURA trial, patients with *EGFR* mutation-positive stage IB to IIIA NSCLC who had received 1 to 4 cycles of cisplatin-based adjuvant chemotherapy were randomized to receive up to 3 years of adjuvant osimertinib or placebo. This study demonstrated a significant improvement in disease-free survival (DFS) in recipients of osimertinib,[8] thereby opening avenues for neoadjuvant and adjuvant use of tyrosine kinase inhibitors for early-stage lung cancer, with many trials currently underway.[9] There has also been a growing interest in incorporating immunotherapy in the neoadjuvant and adjuvant setting. With encouraging data from the pivotal phase 3 studies IMpower010,[10] KEYNOTE-091/PEARLS,[11] and CheckMate 816[12] and with multiple other studies underway, we have entered a new era in the treatment of early-stage NSCLC (**Figure 1**). This review focuses on the emerging data of using immunotherapy for improving outcomes for patients with resectable NSCLC.

Neoadjuvant Immunotherapy

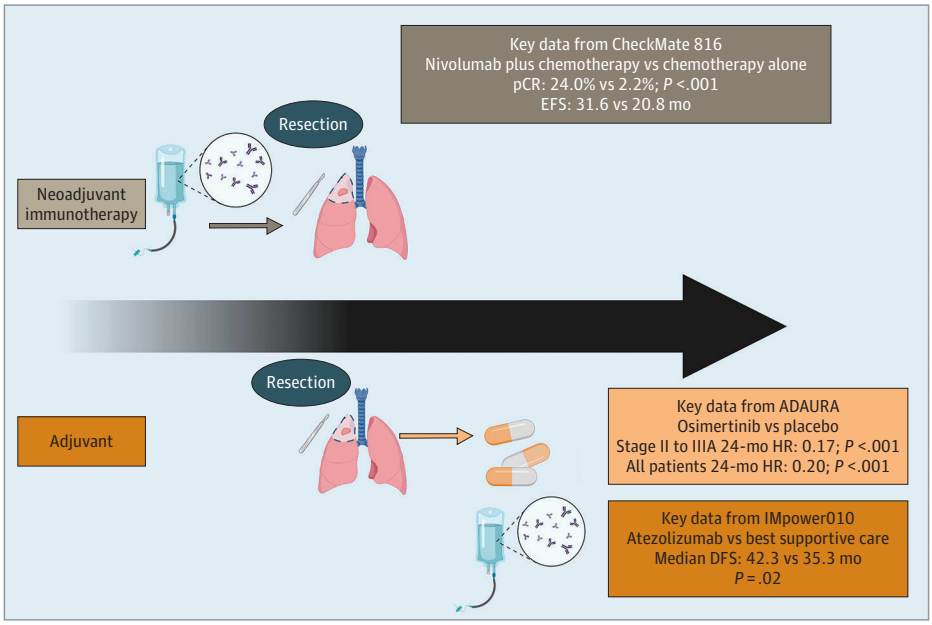
Neoadjuvant Chemotherapy and Immunotherapy Combination

The prospect of adding an immune checkpoint inhibitor (ICI) along with chemotherapy is of interest given the potential for chemotherapy to release antigens from dying tumor cells that stimulate and prime the expansion of antigen specific T cells, the action of which is augmented by an ICI.[13]

Given this, Shu and colleagues[14] conducted a single-arm phase 2 trial in which 30 patients received neoadjuvant atezolizumab with platinum doublet chemotherapy (carboplatin and nab-paclitaxel) for a total of 4 cycles. The primary end point was major pathological response (MPR) defined as presence of 10% or less residual viable tumor at the time of surgery, which occurred in 57% (17 of 30) of patients enrolled. Treatment-related adverse effects did not compromise surgical resection, and there were no treatment-related deaths.[14]

In the phase 3 randomized CheckMate 816 trial,[12] 358 patients were enrolled with newly diagnosed, resectable, stage IB to IIIA NSCLC without known *EGFR* or *ALK* alterations who were

Figure 1. Neoadjuvant and Adjuvant Treatment Approvals in Early-Stage Non–Small Cell Lung Cancer



Key data from the ADAURA trial,[8] IMpower010,[10] and CheckMate 816[12] have been encouraging in the neoadjuvant and adjuvant treatment of early-stage non–small cell lung cancer. DFS indicates disease-free survival; EFS, event-free survival; HR, hazard ratio; pCR, pathologic complete response.

randomly assigned to receive 3 cycles of neoadjuvant nivolumab with platinum-doublet chemotherapy or chemotherapy alone before definitive resection. The primary end points of the study were pathological complete response (pCR) (defined as 0% viable tumor in resected lung and lymph nodes) and event-free survival (EFS), with key secondary end points of MPR, OS, and time to death or distant metastases.[12] The median EFS was 31.6 months in the nivolumab and chemotherapy arm compared with 20.8 months in the chemotherapy alone arm (hazard ratio [HR], 0.63; *P* = .005). Moreover, 24% of patients in the nivolumab and chemotherapy arm achieved pCR vs 2.2% in the control arm (odds ratio, 13.94). The benefit of additional nivolumab was observed across all analyzed subgroups but was more pronounced for patients with the following features: younger than 65 years old, female, from Asia, Eastern Cooperative Oncology Group performance status of 0, stage IIIA disease, nonsquamous histology, never smoked, programmed cell death 1 (PD-1) ligand 1 (PD-L1) expression by tumor cells greater than 50%, and received carboplatin. Minimally invasive surgery was more common and pneumonectomy less common in patients who received chemoimmunotherapy, with no delays in surgery or substantial differences in treatment-related adverse events.[12] Based on these results, the FDA has approved neoadjuvant nivolumab plus chemotherapy.[15] The trial reported an interim analysis of OS in which median OS had not been reached in either treatment arm; mature OS data are eagerly awaited.

Neoadjuvant Immunotherapy Alone

In a proof-of-concept single-arm pilot study (n = 21), Forde and colleagues[16] demonstrated that 2 preoperative doses of nivolumab in adults with untreated, surgically resectable early-stage NSCLC had an acceptable adverse effect profile without any associated delays in surgery. They demonstrated that an MPR was achieved in 45% of patients, with 15% of patients achieving a pCR. Interestingly, radiologic response did not necessarily correlate to pathological response in this study. Additionally, neoadjuvant nivolumab increased tumor infiltration of CD8-positive/PD-1–positive immune cells. Higher tumor mutational burden, higher frequency of shared T-cell clones between intratumoral and peripheral compartments, and higher clonality of the T-cell population correlated with MPR.[16]

The phase 2 LCMC3 study evaluated preoperative treatment with up to 2 cycles of atezolizumab in 181 patients with untreated stage IB to IIIB resectable NSCLC.[17] Within the cohort without known *EGFR* or *ALK* alterations, 20.4% achieved MPR and 6.8% achieved a pCR, with MPR being achieved more commonly in patients with tumors showing tumor proportion score (TPS) of 50% or greater or high tumor mutational burden. Interestingly, this study found that *STK11/LKB1* and *KEAP1* mutations were more frequent in patients who did not achieve an MPR with atezolizumab. Similarly, fewer responses of cancer harboring *STK11* and *KEAP1* mutations have been described in context of *KRAS*-mutant advanced NSCLC, where these aberrations are correlated with low expression of immune response genes indicative of a cold tumor immune microenvironment.[18,19] More recently, a multiinstitution retrospective cohort study also demonstrated that *STK11* and *KEAP1* cancer mutations were associated with worse outcomes following ICI treatment among patients with *KRAS*-mutated advanced NSCLC but not among those with adenocarcinomas with wild-type *KRAS*.[20]

Besse and colleagues[21] reported the results of the single-arm, phase 2 PRINCEPS trial that administered a single dose of atezolizumab to 30 patients with clinical stage IA to IIIA (non-N2 only) NSCLC, with no MPRs observed. The authors concluded that the short delay between treatment with atezolizumab and surgery (which occurred 3-4 weeks after immunotherapy) might explain the absence of response in this particular study.[21] This phenomenon was also observed in the phase 1 study of neoadjuvant pembrolizumab in which all the patients who achieved MPR had a relatively long interval between first treatment and surgery.[22]

The single-arm, phase 2 IFCT-1601 IONESCO trial[21] studied the effect of neoadjuvant durvalumab with surgical resection between day 2 and 14 after the last infusion. The primary end point of the study was percentage of patients with complete resection (R0) while OS, DFS, overall response rate, and MPR were key secondary end points. Among the 46 eligible patients, 41 patients (90%) achieved an R0 resection, but the study was stopped due to excess 90-day postoperative mortality, likely related to postoperative complications rather than durvalumab toxicity.[23] Of the patients who had postoperative mortality, 75% of patients had cardiovascular comorbidities, likely contributing to poor outcomes.

Sintilimab, a monoclonal antibody that targets PD-1, was evaluated in the neoadjuvant setting in a phase 1b study that focused on safety as the primary end point, including a range of clinical and pathologic secondary end points. Eight of 40 patients achieved radiological partial response, resulting in an overall response rate of 20.0%. Among 37 patients who underwent surgery, 15 (40.5%) achieved MPR, including 6 patients (16.2%) with a pCR in primary tumor and 3 patients (8.1%) with a complete response in lymph nodes as well. The correlative analysis of maximum standardized uptake value from positron emission tomography imaging and PD-L1 expression showed improved pathologic responses with decreased posttreatment standardized uptake value uptake and higher baseline PD-L1 expression of stromal cells compared with tumor cells.[24]

Overall, outcomes with single-agent neoadjuvant immunotherapy vary widely, with an MPR ranging from 14% to 40% across studies that are relatively small but offer a proof of principle that neoadjuvant immunotherapy is generally safe and can be associated with meaningful radiographic and pathologic responses.

However, because only a limited and somewhat unpredictable subset of patients can be expected to respond well to ICI monotherapy, and progression or toxicity represent potential risks for those with immune-resistant cancers, this strategy has had more limited enthusiasm than trials for which a larger proportion of patients would be expected to demonstrate a good response, such as the aforementioned studies that combine ICI with a chemotherapy backbone or other trials that combine immunotherapy agents, as described below.

Neoadjuvant Immunotherapy Combinations

Based on the evidence demonstrating augmentation of antitumor immunity with dual checkpoint blockade through distinct and nonredundant cellular mechanisms, the combination of neoadjuvant nivolumab and ipilimumab (nivo/ipi) was tested in the phase 2 NEOSTAR trial, which included an arm for nivolumab monotherapy and for which MPR was the primary end point.[25] This trial demonstrated MPR rates of 22% and 38% in the nivolumab (n = 23) and nivo/ipi (n = 21) arms, respectively, each exceeding the prespecified boundary for success. The combination arm also had a higher pCR rate than nivolumab monotherapy (29% vs 9%, respectively). The modular platform design of this trial has enabled further investigation to evaluate the role of dual ICI added to neoadjuvant chemotherapy in other arms of the trial.[25] This trial and its planned correlative studies have the potential to better define the role of chemotherapy in the neoadjuvant setting when added to ICI, thereby enabling individualization of treatment selection.

Reuss and colleagues[26] conducted a similar study with neoadjuvant nivo/ipi over 6 weeks in patients with resectable NSCLC, focusing on safety, feasibility, and pathologic response as primary and secondary end points, respectively. This study was terminated early because 6 of the first 9 enrolled patients (67%) experienced treatment-related adverse events and 33% experienced grade 3 or greater treatment-related adverse events. Despite this substantial setback, pCR was observed in 33% of resected tumors, with 2 patients with pCR who remained disease free 24 months after surgery.

The global, randomized phase 2 NeoCOAST study[27] used durvalumab as an immunotherapy backbone and featured 4 different arms: durvalumab alone (n = 26), durvalumab with the anti-CD73 antibody oleclumab (n = 21), durvalumab with the anti-NKG2A antibody monalizumab (n = 20), and durvalumab with the anti-STAT3 antisense oligonucleotide danvatirsen (n = 16). These combinations with durvalumab were previously tested as consolidation therapy after chemoradiation in the phase 2 COAST trial of patients with stage III unresectable NSCLC.[28] The NeoCOAST study enrolled 84 patients with untreated, resectable (>2 cm), stage I to IIIA NSCLC, incorporating a primary end point of investigator-assessed MPR. The MPR and pCR rates were far more encouraging in the recipients of novel immunotherapy combinations. Based on these encouraging results and the recent approval of neoadjuvant nivolumab plus chemotherapy, a follow-up randomized clinical trial, NeoCOAST-2, has been launched, which will study these immunotherapy combinations given both in the neoadjuvant and adjuvant setting.

As detailed above, trials in the neoadjuvant setting have thus far focused on shorter-term efficacy end points such as MPR and pCR. Although data from the CheckMate 816 trial[12] demonstrated an association between pCR and EFS as an exploratory analysis and the NADIM study showed association of MPR with DFS,[29] further validation from multiple randomized studies is needed to validate this surrogate end point. It remains to be seen whether pCR is a reliable predictor of EFS, as well as whether EFS is a true surrogate marker of OS.[30]

Importantly, trials like CheckMate 816[12] incorporate early detection of driver mutations such as *EGFR* and *ALK* to exclude such patients from planned neoadjuvant chemoimmunotherapy. Some experts may well favor broad molecular marker testing to identify additional clinically relevant mutations such as *ROS1*, *RET*, *MET*, and potentially others that have demonstrated generally discouraging efficacy with immunotherapy. One of the challenges of implementing neoadjuvant therapy broadly will be the need for sufficiently rapid and broad molecular marker testing prior to committing to a plan for immunotherapy preoperatively.

Adjuvant Immunotherapy

Adjuvant cytotoxic chemotherapy has been the standard of care for patients with early-stage NSCLC and high-risk features, with a meta-analysis finding an improvement of 5.8% in DFS and 5.4% in OS at 5 years.[4] Based on the survival data with ICI seen in the metastatic setting[31] and after chemoradiotherapy in the PACIFIC trial,[32] clinical trials have tested whether these survival benefits could be extended to patients with resectable NSCLC. Several large phase 3 trials of adjuvant PD-L1 or PD-1 blockade in patients with resected NSCLC staged as IB with tumors 4 cm or larger to IIIA (7th edition TNM staging) have completed accrual, and 2 trials have been reported thus far.[11]

The IMpower010 trial was the first randomized phase 3 study to test the benefit of adjuvant atezolizumab after platinum-based chemotherapy in patients with completely resected stage IB to IIIA NSCLC.[10] A total of 1005 patients were randomized to receive atezolizumab every 3 weeks for up to 1 year (16 cycles) or best supportive care; the primary end point was investigator-assessed DFS tested hierarchically for different patient populations (≥1% expression of PD-L1 on tumor cells , all-randomized, and intention-to-treat population). After a median follow-up of 32.2 months in the stage II to IIIA population, atezolizumab treatment was shown to improve DFS compared with best supportive care in patients in the stage II to IIIA population whose tumors expressed PD-L1 on 1% or more of tumor cells (HR, 0.66; *P* = .004) and in all patients in the stage II to IIIA population (HR, 0.79; *P* = .02). In the intention-to-treat population, HR for DFS was 0.81 (*P* = .04). Notably, the greatest DFS benefit was observed patients with PD-L1 greater than 50% where the HR was 0.43, with a far more marginal DFS benefit for patients with PD-L1 of 1% to 49% (HR, 0.87). The DFS HR for patients with *EGFR* mutation-positive NSCLC (n = 43) was 0.57 (95% CI, 0.26-1.24) (vs 0.67 [95% CI, 0.45-1.00] for those with *EGFR* mutation-negative NSCLC [n = 248]), suggesting that patients with *EGFR* mutation-positive NSCLC may potentially benefit from adjuvant immunotherapy, although this finding is based on a small subset of the total study population. For those with ALK-positive NSCLC, the DFS HR was 1.05 (95% CI, 0.32-3.45), demonstrating no benefit from adjuvant immunotherapy. The OS data were not mature at the time of this writing, with the first prespecified interim analysis of OS showing a trend in favor of atezolizumab in the PD-L1 greater than 1% population (HR, 0.71 [95% CI, 0.49-1.03]) with most survival benefit seen in PD-L1 greater than 50% cohort (HR, 0.43 [95% CI, 0.24-0.78]).[10]

Among the 495 patients who received atezolizumab, immune-related grade 3 and 4 adverse events occurred in 53 (11%) patients and grade 5 events in 4 (1%) patients.[10] Overall, these results demonstrated no new safety concerns, although a minority, such as endocrine-related toxic effects, may be long-lasting. Based on the results of this study, the US FDA approved adjuvant treatment with atezolizumab (following resection and platinum-based chemotherapy) in patients with stage II to IIIA NSCLC with PD-L1 expression 1% or greater.

The randomized, placebo-controlled, phase 3 PEARLS study enrolled 1177 patients with confirmed stage IB to IIIA NSCLC after complete surgical resection with negative margins and provision of tumor tissue for PD-L1 testing.[11] Up to 4 cycles of adjuvant chemotherapy were permitted but not mandated, instead to be considered for patients with stage IB disease and strongly recommended for patients with stage II to IIIA disease. Patients were subsequently randomized to receive pembrolizumab or placebo every 3 weeks for up to 1 year. The trial had dual primary end points of DFS in the overall study population and the population with PD-L1 TPS 50% or greater.

With a median follow-up of 35.6 months, the estimated median DFS of the overall population was 53.6 months compared with 42.0 months in favor of pembrolizumab (HR, 0.76; *P* = .001), while the median DFS in the PD-L1 TPS 50% or greater population was not reached in either arm.[11] Subgroup analysis suggested that pembrolizumab was more beneficial in current smokers, patients with nonsquamous histology, and patients with *EGFR* alteration. Subgroup analysis with regard to chemotherapy showed higher DFS benefit for patients who received adjuvant chemotherapy (n = 1010; HR, 0.73 [95% CI, 0.60-0.89]) compared with those who did not (n = 167; HR, 1.25 [95% CI, 0.76-2.05]). Among those who received adjuvant chemotherapy, HR (95% CI) for DFS varied by number of cycles and chemotherapy regimen with greater and consistent benefit in those with 3 to 4 cycles (n = 943; HR, 0.74 [95% CI, 0.61-0.91]) and receiving carboplatin plus vinorelbine (n = 151; HR, 0.51 [95% CI, 0.31-0.83]).[33]

Surprisingly, a greater benefit was seen in patients with PD-L1 TPS 1% to 49% (HR, 0.67) than in those with PD-L1 TPS 50% or greater (HR, 0.82).[11] In terms of adverse events, grade 3 to 5 adverse events occurred in 34.1% of patients treated with pembrolizumab, compared with 25.8% with placebo. Overall, these data suggest that pembrolizumab may also have a role as another adjuvant treatment option for patients with stage I to IIIA NSCLC following complete resection and adjuvant chemotherapy regardless of PD-L1 expression. As of the time of this writing, pembrolizumab had not yet been approved by the FDA for this indication.

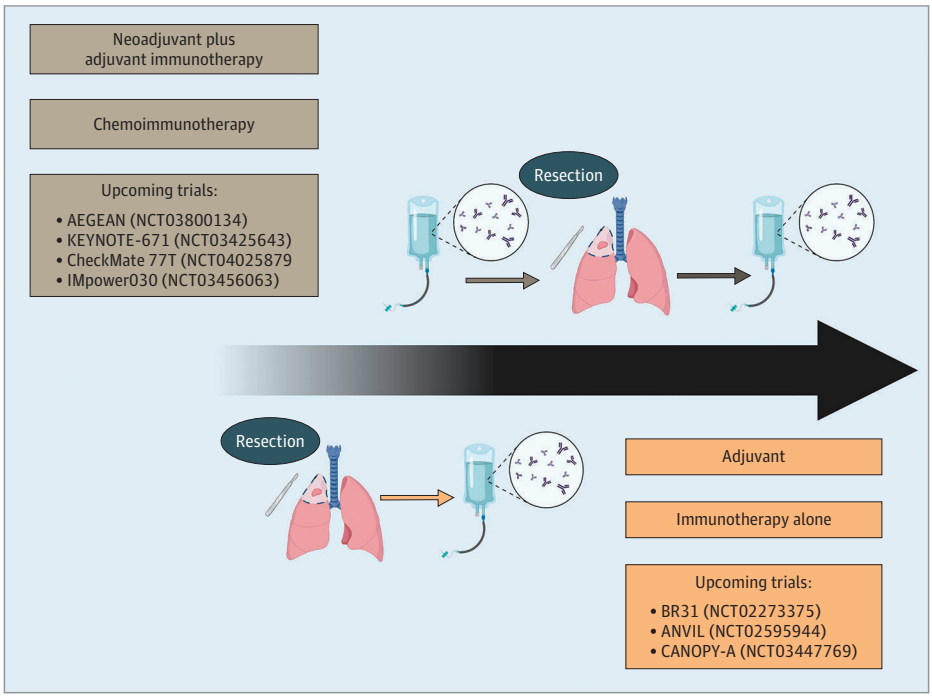
Both IMpower010[10] and the PEARLS[11] study clearly demonstrate a significant DFS benefit with adjuvant immunotherapy in some patients with early-stage NSCLC. However, important discrepancies are present between the 2 trials, including a greater number of patients with stage IIIA disease in IMpower010 (41.1% vs 28.8%) and a greater proportion of patients with PD-L1 expression of 1% or greater in PEARLS (60.5% vs 54.6%). Adjuvant chemotherapy was mandated only in IMpower010, and the control arm received best supportive care alone in IMpower010, whereas placebo was incorporated in the PEARLS study. The heterogeneity in PD-L1 expression–based responses from these 2 trials may be related to limitations of underpowered subgroup analyses, or the heterogeneity of PD-L1 expression in NSCLC.[34-37] However, these results bring into question the actual predictive ability of PD-L1 expression in the early-stage setting, routinely used for advanced NSCLC.[38] Further study will be required to reconcile the discordant but limited results seen thus far for adjuvant immunotherapy in early-stage NSCLC.

Along with these open questions, we still await the important OS results of these trials. Many additional phase 3 adjuvant immunotherapy trials are underway, including trials with novel immunotherapies, such as canakinumab (human IgGκ monoclonal antibody targeting IL-1β) in the CANOPY-A study.[39] We are optimistic that these ongoing studies will define the utility of ICIs in this setting, while also addressing questions of how modulation of the tumor microenvironment and incorporation of circulating tumor DNA for detection of minimal residual disease will correlate with the utility of adjuvant immunotherapy.

Combined Perioperative Strategy With Neoadjuvant and Adjuvant Immunotherapy

Other clinical trials have incorporated an ICI into both neoadjuvant and adjuvant settings. The TOP1501 single-arm trial administered neoadjuvant pembrolizumab for 2 cycles to 30 patients with early-stage NSCLC, followed by surgery, then up to 4 cycles of adjuvant chemotherapy were strongly encouraged, followed by 4 cycles of adjuvant pembrolizumab offered. Seven of 22 (28%) MPRs and at least 2 pCRs were observed, demonstrating the potential efficacy of neoadjuvant and adjuvant pembrolizumab.[40] This study also

Figure 2. Neoadjuvant and Adjuvant Treatment Approaches Being Studied in Early-Stage Non–Small Cell Lung Cancer



demonstrated that pembrolizumab was safe and well tolerated in the neoadjuvant setting, and its use was not associated with excess surgical morbidity or mortality.

Similarly, the Swiss Group for Clinical Cancer Research (SAKK) reported the benefit of perioperative durvalumab treatment in a single-arm trial with 2 doses preoperatively after neoadjuvant chemotherapy followed by adjuvant therapy for 1 year in 67 patients with resectable stage IIIA (N2 node-positive) disease.[41] Of the 55 patients who underwent resection, 34 (62%) achieved an MPR, and 10 (18%) had a pCR, with postoperative nodal downstaging occurring in 37 patients (67%).[41] This study also saw an encouraging rate of 1-year EFS of 73%.

The single-arm, phase 2 NADIM trial out of Spain enrolled 46 patients with stage IIIA NSCLC to receive neoadjuvant nivolumab along with platinum doublet chemotherapy for 3 cycles before surgical resection, followed by adjuvant nivolumab for 1 year.[42] The primary end point was PFS at 24 months, which was 77.1%, and the 24-month OS was 90%. The 3-year update from this trial showed promising survival results, with 36-month OS rates of 81.9% and 91.0% in the intention-to-treat and per-protocol populations, respectively, thus markedly exceeding the historical 3-year OS rates that have remained at approximately 30% over several decades. At 42 months, those treated per protocol showed a DFS of 81.1% and OS of 87.3%.[42] Subsequently, the randomized phase 2 NADIM II trial recently demonstrated that neoadjuvant nivolumab plus chemotherapy (n = 57) significantly improved the primary end point of pCR compared with the chemotherapy arm (n = 29) in patients with resectable stage IIIA to IIIB NSCLC (36.8% vs 6.9%).[43] At 24 months, secondary end points demonstrated benefit with chemoimmunotherapy approach with improved PFS (66.6% vs 42.3%) and OS (84.7% vs 63.4%).[44]

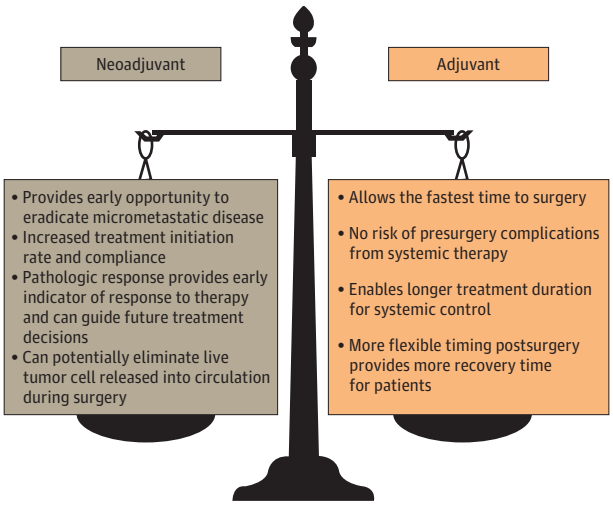
Several phase 3 studies are underway using different ICIs to determine whether sequential neoadjuvant chemoimmunotherapy and adjuvant immunotherapy improve survival (**Figure 2**), though no data have yet been reported from these trials. Questions on further correlations with improved EFS and the true value of EFS in predicting OS remain to be elucidated.

The Neoadjuvant vs Adjuvant Immunotherapy Debate

The platform of neoadjuvant immunotherapy allows for unique benefits, including early eradication of micrometastases,[45] a higher treatment initiation rate as well as higher patient adherence,[46] the possibility of surgical downstaging, a potential decrease in need for more extensive procedures (such as pneumonectomy or open thoracotomy), and the ability to assess pathologic responses, which may serve as a predictor of survival and inform decisions about future treatment (**Figure 3**).[47] Similarly, measuring changes in circulating tumor DNA, specifically changes in variant allele frequency, can predict clinical benefit, PFS, and OS.[48] Such approaches could be used as adjunct measurement of disease and potentially as a surveillance mechanism.

In contrast, adjuvant therapy allows for the fastest time to surgery and eliminates any risks of complications of systemic therapy prior to surgery.[49] In addition, adjuvant therapy allows for a longer treatment duration for systemic control, while more flexible postsurgery time potentially affords more time to recover for patients. During recovery, testing for molecular alterations can be pursued, likely with adequate specimens to help guide selection of adjuvant therapy.[50] Given the current state of molecular

Figure 3. Pros and Cons of Neoadjuvant and Adjuvant Approaches in Treatment of Early-Stage Non–Small Cell Lung Cancer



testing, adjuvant therapy also obviates the need for rapid molecular determination to rule in or out neoadjuvant therapy with ICI.

Although the full significance of pCR is yet to be realized, the value of adjuvant therapy in patients who achieve pCR might be expected to be diminished. Circulating tumor DNA has been widely adopted for the detection of molecular drivers in patients with metastatic NSCLC. Whether it can be used to detect minimal residual disease after resection and guide use of adjuvant therapy remains uncertain, as the sensitivity of the current approaches may not suffice for an earlier stage of disease.[51,52]

Conclusions

While the pattern of positive trials of adjuvant chemotherapy for resectable NSCLC has made the adjuvant setting the default treatment pattern for patients with early-stage NSCLC over most of the past 2 decades, new data, approvals and ongoing trials are rapidly changing the standards of care. It is possible that immunotherapy for early-stage NSCLC may follow the pattern established in advanced NSCLC, where survival has been significantly improved for most patients. However, the benefits in the early-stage setting must be weighed against the adverse effects and risks of adding immunotherapy, including the substantial financial toxicity with these expensive therapies.[53] The optimal timing, duration, and sequence of immunotherapy with other systemic therapies are only now beginning to be defined.

ARTICLE INFORMATION

Accepted for Publication: August 30, 2022.

Published Online: November 17, 2022. doi:10.1001/jamaoncol.2022.5389

Correction: This article was corrected on January 19, 2023, to fix data errors and clarify text in the Adjuvant Immunotherapy section.

Author Contributions: Dr Desai had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Desai and Adashek contributed equally to the work.
Concept and design: All authors.
Acquisition, analysis, or interpretation of data: Adashek, Reuss.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
Administrative, technical, or material support: Desai, Reuss, Mansfield.
Supervision: Reuss.

Conflict of Interest Disclosures: Dr Reuss reported grants to institution from Genentech/Roche and Verastem; personal fees (advisory board) from Genentech/Roche, Sanofi/Genzyme, and Personalis; and personal fees from AstraZeneca outside the submitted work. Dr West reported personal fees from AstraZeneca and Merck (advisory board, consultant, speaker) and Regeneron (consultant) during the conduct of the study. Dr Mansfield reported grants to institution from Novartis and Verily; other to institution from Rising Tide Foundation (grant reviewer) and Triptych Health Partners (think tank); honoraria to institution for participation in advisory boards from Janssen, BeiGene, Chugai Pharmaceutical (Roche), and Ideology Health; personal fees from Miami International Mesothelioma Symposium (presentation), Antoni van Leeuwenhoek Kanker Instituut (CME presentation), and AXIS Medical Education (CME presentation, to institution); and other from Johnson & Johnson Global Services (steering committee, to institution), Intellisphere LLC (CME presentation, to institution), Answers in CME (CME presentation, to institution), Roche (travel support), AbbVie (advisory board, to institution), AstraZeneca (advisory board, to institution), Bristol Myers Squibb (advisory board, to institution), Genentech/Roche (advisory board, to institution), and Mesothelioma Applied Research Foundation (nonremunerated director) outside the submitted work. No other disclosures were reported.

Disclaimer: Dr West is Web Editor of *JAMA Oncology* but was not involved in any of the decisions regarding review of the manuscript or its acceptance.

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