

# Perioperative Systemic Therapy for Resectable Non–Small Cell Lung Cancer

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## ABSTRACT

Despite remarkable treatment advancements in patients with advanced non–small cell lung cancer (NSCLC), recurrence rates for those with resectable, early-stage disease remains high. Immune checkpoint inhibitors and targeted therapies are 2 promising treatment modalities that may improve survival outcomes for patients with resected NSCLC when moved from the advanced stage to the curable setting. There are many clinical studies that have evaluated or are currently evaluating immunotherapy or targeted therapy in the perioperative setting, and recent trials such as CheckMate 816, ADAURA, and IMpower010 have led to new approvals and demonstrated the promise of this approach. This review discusses recent and ongoing neoadjuvant and adjuvant systemic therapy trials in NSCLC, and where the field may be going in the near future.

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**Lung cancer accounts for** the most deaths of any malignancy worldwide.<sup>1</sup> Non–small cell lung cancers (NSCLCs) constitute approximately 85% of all lung cancers. Most people with NSCLC are diagnosed at a metastatic or locally advanced stage, but 25% to 30% have resectable disease.<sup>2</sup> Surgical resection alone is not curative in many patients with early-stage NSCLC, with the rate of recurrence increasing with higher stage.<sup>3</sup>

Platinum-based adjuvant chemotherapy has been the standard of care for patients with resectable stage II–III disease, although the survival benefits are modest, with an increase in overall survival (OS) of approximately 5%.<sup>4,5</sup> Until recently, there have been no practice-changing advancements in perioperative systemic therapy (neoadjuvant or adjuvant) for almost a decade.<sup>6</sup>

Meanwhile, the widespread use of immunotherapy and targeted therapies has transformed the treatment of metastatic or unresectable NSCLC. These successes have further motivated research into using these treatment modalities in curable early-stage NSCLC.

This review outlines the important studies and data regarding neoadjuvant and adjuvant systemic therapies and highlights some ongoing trials.

## Perioperative Chemotherapy

Since the early 2000s, adjuvant chemotherapy with a platinum doublet has been a part of standard treatment for completely resected stage II–III NSCLC. In 2008, the Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis showed a 5-year absolute survival benefit of 5.4% (hazard ratio [HR], 0.89;  $P=.005$ ) in all patients. Breaking down outcomes by stage, IB disease did not have a significant improvement in OS (HR, 0.93; 95% CI, 0.78–1.10), and IA disease actually had a decrease in OS (HR, 1.41; 95% CI, 0.96–2.09). Both stage II and III disease had improved OS (HR, 0.83; 95% CI, 0.73–0.95, and HR, 0.83; 95% CI, 0.72–0.94, respectively).<sup>4</sup>

Despite meta-analyses showing a similar absolute survival benefit to adjuvant chemotherapy, use of neoadjuvant chemotherapy has typically been limited to patients with stage IIIA or IIIB N2+ disease, with the objective to downstage the tumor and make it more amenable to resection.<sup>5,7,8</sup> Some ongoing clinical trials evaluating immunotherapy or

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targeted drugs in the preoperative setting also include neoadjuvant chemotherapy.

### Perioperative Immunotherapy

Immune checkpoint inhibitors (ICIs) have dramatically changed the approach to advanced NSCLC and have become an integral part of first-line therapy in patients without a driver mutation. Checking a tumor's PD-L1 status is now a necessary part of workup in metastatic NSCLC to determine the most effective treatment strategy, as is molecular testing to exclude patients with driver oncogenes (eg, *EGFR*, *ALK*) who may not benefit from immunotherapy.

With the recent approvals of neoadjuvant and adjuvant ICIs in the United States, immunotherapy has finally made its way into the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for NSCLC management algorithm for early-stage disease.<sup>5</sup> There are still many ongoing trials further exploring the application of ICIs either as monotherapy or in combination with chemotherapy in the perioperative setting.

### Neoadjuvant Immunotherapy

Similar to the use of neoadjuvant chemotherapy, the goal of neoadjuvant immunotherapy would be to decrease the tumor size, improve the likelihood of complete resection, and eliminate any micrometastases. Immunotherapy before surgery also has the added benefits of providing an intact lymphatic system around the tumor and more neoantigens for the adaptive immune system to encounter and process. Preoperative treatment also allows for pathologic evaluation of the tumor response after immunotherapy.

One concern with neoadjuvant immunotherapy is the potential for adverse effects to delay surgery and increase the risk of progression. Adverse effects from immunotherapy may also cause complete resection to be more challenging.

### Neoadjuvant Immunotherapy as Monotherapy

CheckMate 159 was one of the first pilot studies evaluating the safety and feasibility of neoadjuvant immunotherapy monotherapy in NSCLC. The phase II trial evaluated 21 patients with stage I–IIIA who received preoperative nivolumab. All 21 underwent resection without delay; 20 underwent a complete resection (R0). Only 1 patient did not receive both planned doses of nivolumab prior to surgery. Because disease-free survival (DFS) and OS may take years to reliably evaluate, many neoadjuvant trials include tumor pathologic responses as a surrogate primary or secondary endpoint.<sup>9,10</sup> In CheckMate 159, a major pathologic response (MPR), where tumor viability was  $\leq 10\%$  in the surgical specimen, occurred in 45% of patients; 10% had a pathologic

complete response (pCR).<sup>11</sup> In comparison, the historical MPR rate with neoadjuvant chemotherapy has ranged from 16% to 21%.<sup>9,12–14</sup>

LCMC3 is a larger phase II trial evaluating neoadjuvant atezolizumab in 181 patients. Analysis showed good feasibility and safety (159/181 had surgery), but the MPR rate was only 21% and the pCR rate was 7%.<sup>15</sup>

Based on these smaller studies and others (Table 1), neoadjuvant immunotherapy as monotherapy appears to be somewhat effective in inducing a tumor response and does not interfere with surgical outcomes. Pathologic response rates and survival outcomes will need to be further evaluated in larger studies to determine a true benefit, but to date, response rates seem to be lower than those seen with combination immunotherapy and chemotherapy in unselected patients, which may limit its application.

### Neoadjuvant Immunotherapy in Combination With Chemotherapy

In a study by Shu et al<sup>16</sup> of 30 patients treated with neoadjuvant atezolizumab, nab-paclitaxel, and carboplatin, 57% had an MPR and 33% had a pCR. There were no surgical delays or postoperative complications due to the preoperative therapy.

The NADIM trial assessed patients with resectable IIIA disease treated with neoadjuvant chemotherapy and nivolumab. After resection, patients were also given adjuvant nivolumab for up to a year. Although 93% of patients experienced an adverse event, there were no treatment discontinuations, dose reductions, or delays in surgery; 3 of 46 patients had treatment-related adverse events that prevented them from receiving adjuvant nivolumab. The primary endpoint was progression-free survival (PFS) at 24 months, which was 77.1% in the modified intention-to-treat population. An MPR occurred in 83% of patients, and 67% had a pCR.<sup>17</sup>

SAKK 16/14 followed 67 patients with IIIA(N2) disease after treatment with neoadjuvant docetaxel, cisplatin, and durvalumab. Event-free survival (EFS) at 1 year, which was the primary endpoint, was 73%. MPR and pCR rates were 62% and 18%, respectively.<sup>18</sup>

The recently published CheckMate 816 trial is the first neoadjuvant immunotherapy study that has led to a new FDA approval. In this phase III study, 358 patients with resectable stage IB (tumors  $>4$  cm)–IIIA NSCLC without *EGFR* or *ALK* alterations were randomized to neoadjuvant nivolumab + platinum-based chemotherapy or chemotherapy alone. There were 2 primary endpoints: EFS and pCR—both were significantly improved with the combination therapy. Median EFS was 31.6 months with nivolumab + chemotherapy versus 20.8 months with chemotherapy alone (97.38% CI, 0.43–0.91;  $P=.005$ ), and 24% of patients had a pCR in the combination group compared with only

**Table 1. Select Completed Neoadjuvant Immunotherapy Trials**

Trial (ClinicalTrials.gov identifier)	Phase	Stage	Patients n	Treatment	Primary Results
CheckMate 159 <sup>11</sup> (NCT02259621)	II	I–IIIA	21	Nivo ×2 cycles	MPR, 45%; pCR, 10%
ChiCTR-OIC-17013726	II	I–IIIB	40	Sintilimab ×2 cycles	MPR, 40.5%; pCR, 16.2%
PRINCEPS <sup>41</sup> (NCT02994576)	II	I (≥2 cm)–IIIA	30	Atezo ×1 cycle	MPR, 14%
IONESCO (NCT03030131)	II	IB–IIIA (no N2)	46	Durva ×3 cycles	MPR, 18.6% Terminated due to 90-day mortality
NCT02259621	II	IB (≥4 cm)–IIIA	9	Nivo/lpi ×3 cycles	pCR, 22% Terminated due to toxicity
LCMC3 <sup>15</sup> (NCT02927301)	II	IB–IIIB	101	Atezo ×2 cycles → adjuvant Atezo (if response)	MPR, 21%; pCR, 7%
NEOSTAR <sup>42</sup> (NCT03158129)	II	I–IIIA	44	Nivo or Nivo/lpi ×3 cycles (lpi only ×1 cycle)	Nivo: MPR, 24%; pCR, 10% Nivo/lpi: MPR, 50%; pCR, 38%
NADIM <sup>17</sup> (NCT03081689)	II	IIIA	46	Nivo and carbo/paclitaxel ×3 cycles → adjuvant Nivo for 1 y	PFS at 24 mo, 77.1% MPR, 83%; pCR, 63%
SAK 16/14 <sup>18</sup> (NCT02572843)	II	IIIA (N2)	67	Durva and cisplatin/docetaxel ×3 cycles → adjuvant Durva for 1 y	EFS at 1 y: 73% MPR, 62%; pCR, 18%
NCT02716038 <sup>16</sup>	II	IB–IIIA	30	Atezo and carbo/nab-paclitaxel ×4 cycles (if no progression after 2 cycles)	MPR, 57%; pCR, 33%
NeoCOAST <sup>43</sup> (NCT03794544)	II	I (≥2 cm)–IIIA	84	Durva alone or with oleclumab, monalizumab, or danvatirsen ×1 cycle	MPR Durva: 11.1% Durva + O: 19.0% Durva + M: 30.0% Durva + D: 31.3%
NADIM II <sup>44</sup> (NCT03838159)	II	IIIA, resectable IIIB	87	Nivo and carboplatin/paclitaxel ×3 cycles → adjuvant Nivo for 6 mo vs chemo ×3 cycles	pCR Nivo + chemo: 36.2% Chemo: 6.8%
CheckMate 816 <sup>19</sup> (NCT02998528)	III	IB–IIIA	358	Nivo and chemo <sup>a</sup> ×3 cycles vs chemo ×3 cycles	Nivo + chemo: EFS, 31.6 mo; pCR, 24% Chemo: EFS, 20.8 mo; pCR, 2.2%

Abbreviations: Atezo, atezolizumab; Carbo, carboplatin; chemo, chemotherapy; D, danvatirsen; Durva, durvalumab; EFS, event-free survival; lpi, ipilimumab; M, monalizumab; MPR, major pathologic response; Nivo, nivolumab; O, oleclumab; pCR, pathologic complete response; PFS, progression-free survival.  
<sup>a</sup>Generic term “chemo” used when multiple regimens allowed in the study.

2.2% in the chemotherapy only group (99% CI, 3.49–55.75;  $P < .001$ ). Surgical outcomes were comparable with a trend toward fewer cancellations and more minimally invasive surgeries with the combination. The addition of nivolumab did not lead to increased issues with tolerability, feasibility, or timing of surgery.<sup>19</sup> The FDA approval is for patients with resectable NSCLC with any PD-L1 status, but the majority of the benefit was seen in patients with stage IIIA or a PD-L1 expression of ≥50%. The absence of clear EFS benefit for patients with a PD-L1 expression of <1% and for those with stage IB–II disease suggests that these patients may receive less benefit from the combination, although the study was not powered to examine subgroups, and all subgroups had significant improvements in pCR rates.

Similar trials evaluating other ICIs are currently underway (Table 2). As in advanced NSCLC, results of these trials will probably be similar and lead to the approval of several other immunotherapies in the neoadjuvant setting.

### Adjuvant Immunotherapy

A number of completed and ongoing trials are solely looking at adjuvant immunotherapy involving each of the major ICIs (Table 3). The only large adjuvant study with published results to date is the phase III IMpower010. After receiving adjuvant platinum-based chemotherapy, 1,005 patients were randomized to adjuvant atezolizumab or best supportive care (BSC). The study’s primary endpoint, DFS, was tested hierarchically in 3 populations, and was

**Table 2. Select Ongoing Neoadjuvant Immunotherapy Trials**

Trial (ClinicalTrials.gov identifier)	Phase	Stage	Patients n <sup>a</sup>	Experimental Treatment	Primary Endpoint
KEYNOTE-671 (NCT03425643)	III	II–IIIA, resectable IIIB	786	Pembro and chemo <sup>b</sup> ×4 cycles → adjuvant Pembro ×13 cycles vs chemo ×4 cycles	EFS, OS
CheckMate 77T (NCT04025879)	III	II–IIIB	452	Nivo and chemo ×4 cycles → adjuvant Nivo for 1 y vs chemo ×4 cycles	EFS
TOP1501 (NCT02818920)	II	IB–IIIA	35	Neoadjuvant Pembro ×2 cycles → adjuvant chemo ×4 cycles → adjuvant Pembro ×4 cycles	MPR
IMpower030 (NCT03456063)	III	II–IIIB	451	Atezo and chemo ×4 cycles → adjuvant Atezo ×16 cycles vs chemo ×4 cycles	EFS
AEGEAN (NCT03800134)	III	II–IIIB	800	Durva and chemo ×4 cycles → adjuvant Durva ×12 cycles vs chemo ×4 cycles	EFS, pCR
NEOpredict (NCT04205552)	II	IB–IIIA	60	Nivo or Nivo/relatlimab ×2 cycles	Feasibility
NEO-DIANA (NCT04512430)	II	IIIA (EGFRm)	26	ABCP ×3 cycles and adjuvant Atezo for 6 mo	MPR

Abbreviations: Atezo, atezolizumab; ABCP, atezolizumab/bevacizumab/carboplatin/pemetrexed; chemo, chemotherapy; Durva, durvalumab; EFS, event-free survival; EGFRm, EGFR mutation; MPR, major pathologic response; Nivo, nivolumab; OS, overall survival; Pembro, pembrolizumab; pCR, pathologic complete response.

<sup>a</sup>Estimated number of patients for ongoing trials that are still recruiting.

<sup>b</sup>Generic term “chemo” used when multiple regimens allowed in the study.

found to be significantly improved in the stage II–IIIA population with PD-L1 expression  $\geq 1\%$  (HR, 0.66; 95% CI, 0.50–0.88;  $P=.0039$ ). DFS continued to remain significant in the stage II–IIIA population with any PD-L1 status (HR, 0.79; 95% CI, 0.64–0.96;  $P=.020$ ) but not in the total IB–IIIA population (HR, 0.81; 95% CI, 0.67–0.99;  $P=.040$ ).<sup>20</sup> OS results were still immature at the time of publication, but these results led to the accelerated approval of atezolizumab for adjuvant treatment in patients stage II–IIIA NSCLC and PD-L1 expression  $\geq 1\%$ .<sup>20,21</sup>

Interestingly, a subgroup analysis in the group with PD-L1 expression of 1%–49% showed that DFS was not significantly improved compared with the BSC arm, suggesting that the majority of benefit from adjuvant atezolizumab was driven by the group with PD-L1 expression  $\geq 50\%$ . Although not definitive for a lack of benefit in the subgroup with PD-L1 expression of 1%–49%, this suggests that until OS results are published, the high-PD-L1 group may be the best candidates for this approach.

### Perioperative Targeted Therapy

The established first-line treatment for metastatic NSCLC with actionable driver alterations, such as EGFR mutations, is often oral tyrosine kinase inhibitors (TKIs). Targeted therapy is significantly more effective than standard chemotherapy in this population, and ICIs typically have limited activity against many oncogene-addicted lung cancers regardless of PD-L1 status.<sup>22</sup>

The success of targeted therapy in advanced NSCLC inspired the search for their place in the perioperative setting. Most studies have involved EGFR-sensitizing

mutations (exon 19 deletions or L858 point mutations) because they are some of the most common actionable aberrations. This pursuit led to the ADAURA trial, which generated the first major advancement in perioperative treatment for NSCLC in more than a decade. These last sections review some of the chief studies involving neoadjuvant or adjuvant targeted therapy.

### Adjuvant Targeted Therapy

Initially, many adjuvant studies did not specifically select patients who were EGFR mutation–positive (EGFRm), because it was not known that EGFR mutations were a biomarker for effectiveness of EGFR TKIs. The RADIANT trial included patients whose tumors expressed the EGFR protein by immunohistochemistry or EGFR amplification by fluorescence in situ hybridization. A total of 973 patients with stage IB–IIIA resected disease were randomly assigned to 2 years of adjuvant erlotinib or placebo. There was no difference in DFS between the arms, but there was a trend toward improvement with TKIs in the EGFRm subgroup ( $P=.039$ ). The difference in this subgroup was not statistically significant given the hierarchical design of the study.<sup>23</sup>

SELECT was a single-arm phase II study evaluating the use of adjuvant erlotinib for 2 years in stage IA–IIIA EGFRm NSCLC. The primary endpoint, 2-year DFS, was 88%, an improvement compared with the historical control of 76% ( $P=.0047$ ). One concern with the use of adjuvant TKIs is the potential for early development of resistance, but SELECT noted that 26/40 patients were treated with erlotinib upon recurrence. There was likely

**Table 3. Select Adjuvant Immunotherapy Trials**

Trial (ClinicalTrials.gov identifier)	Phase	Stage	Patients n <sup>a</sup>	Treatment	Primary Results or Endpoint(s)
IMpower010 <sup>20</sup> (NCT02486718)	III	II–IIIB	1,280	After adjuvant chemo <sup>b</sup> → Atezo for 1 y vs BSC	Median DFS in stage II–IIIA, PD-L1 >1% Atezo: NE BSC: 35.3 mo
ANVIL (NCT02595944)	III	IB–IIIA	903	After adjuvant chemo for 1 y → Nivo vs BSC	DFS, OS
PEARLS <sup>45</sup> (NCT02504372)	III	IB (≥4 cm)–IIIA	1,177	After adjuvant chemo (if appropriate) → Pembro for 1 y vs placebo	Pembro: DFS in all, 53.6 mo; DFS in TPS ≥50% NR Placebo: DFS in all, 42 mo; DFS in TPS ≥50% NR
BR.31 (NCT02273375)	III	IB–IIIA	1,415	After adjuvant chemo (if appropriate) → Durva for 1 y vs placebo	DFS
MERMAID-1 (NCT04385368)	III	II–III (MRD+)	332	SoC and Durva ×4 cycles → maintenance Durva ×12 cycles vs SoC ×4 cycles → placebo	DFS
MERMAID-2 (NCT04642469)	III	II–III (MRD+)	284	After adjuvant chemo (if appropriate) → (if MRD+ within 96 wk postsurgery) Durva for 2 y vs placebo	DFS in PD-L1 TPS ≥1%
NADIM-ADJUVANT (NCT04564157)	III	IB–IIIA	210	Carbo/Paclitaxel ×4 cycles → Nivo ×6 cycles vs carbo/paclitaxel ×4 cycles	DFS

Abbreviations: Atezo, atezolizumab; BSC, best supportive care; Carbo, carboplatin; chemo, chemotherapy; DFS, disease-free survival; MRD, minimal residual disease; NE, not estimable; Nivo, nivolumab; NR, not reached; OS, overall survival; Pembro, pembrolizumab; SoC, standard of care; TPS, tumor proportion score.

<sup>a</sup>Estimated number of patients used for ongoing trials that are still recruiting.

<sup>b</sup>Generic term “chemo” used when multiple regimens allowed in the study.

minimal resistance created from the adjuvant therapy as the median duration of retreatment was 13 months, similar to the PFS with erlotinib in de novo metastatic disease.<sup>24,25</sup>

The phase III ADJUVANT/CTONG1104 trial compared gefitinib with adjuvant cisplatin/vinorelbine in patients with *EGFR*<sup>m</sup> stage II–IIIA NSCLC. Initial study results were promising, with a greater median DFS with gefitinib (28.7 vs 18 months;  $P=.0054$ ), but this superiority disappeared in the final analysis ( $P=.928$ ). There was also no significant improvement in OS.<sup>26,27</sup>

The ADAURA study included 682 patients with stage IB–IIIA *EGFR*<sup>m</sup> NSCLC who were randomized to osimertinib or placebo for 3 years, which was a longer duration than any of the prior studies. Osimertinib also had the advantage of a more favorable toxicity profile than first-generation TKIs, as well as increased central nervous system (CNS) activity. DFS in ADAURA at 24 months in the overall population was substantially better at 89% with osimertinib compared with 52% with placebo (HR, 0.20; 99.12% CI, 0.14–0.30;  $P<.001$ ). Also, it showed significantly fewer CNS recurrences in the TKI arm.<sup>6</sup> OS results are still pending, but given these large DFS differences, adjuvant osimertinib is now FDA-approved for patients with resected *EGFR*<sup>m</sup> NSCLC.

Despite this change in practice, questions will surround the use of adjuvant TKIs and their clinical benefit until OS results are available. There are a handful of active

clinical trials, including those focusing on other driver alterations (Table 4), that will help provide more information on how to best use targeted therapy after surgery.

### Neoadjuvant Targeted Therapy

Neoadjuvant targeted studies have not had nearly as much interest to date as have adjuvant trials. EMERGING-CTONG 1103 has been the largest published neoadjuvant TKI trial. This was a phase II randomized study comparing erlotinib and chemotherapy in patients with stage IIIA(N2) *EGFR*<sup>m</sup> NSCLC. The primary end point of objective response rate was not statistically significant for improvement (54.1% vs 34.3%;  $P=.092$ ), but PFS results significantly favored erlotinib (21.5 vs 11.4 months;  $P=.001$ ).<sup>28</sup> Despite fewer data in this space, more trials are underway (Table 5).

### Discussion

After more than a decade of little change in the treatment of early-stage NSCLC, there have been 3 new FDA approvals since 2020: neoadjuvant chemotherapy + nivolumab, adjuvant atezolizumab, and adjuvant osimertinib. Although these advancements are exciting, the optimal application of these treatments is not completely straightforward.

One criticism of perioperative trials is the use of endpoints other than OS. Approvals of the above treatments were based on EFS, pCR, and DFS. This is not unique to NSCLC, given that other tumor types have also based

**Table 4. Select Adjuvant Targeted Therapy Trials**

Trial (ClinicalTrials.gov identifier)	Phase	Stage	Patients n <sup>a</sup>	Mutation	Treatment	Primary Results or Endpoint(s)
RADIANT <sup>23</sup> (NCT00373425)	III	IB–IIIA	973	EGFR expression by IHC EGFR amplification by FISH	E for 2 y vs PB	Median DFS E: 50.5 mo PB: 48.2 mo
SELECT <sup>24</sup>	II	IB (≥4 cm)–IIIA	100	EGFR	After adjuvant chemo (if appropriate) → E for 2 y	2-y DFS 88%
ADJUVANT/CTONG1104 <sup>26,27</sup> (NCT01405079)	III	II–IIIA	222	EGFR	G for 2 y vs cisplatin/vinorelbine ×4 cycles	5-y DFS G: 22.6% chemo: 23.2%
EVAN <sup>46</sup> (NCT01683175)	II	IIIA	102	EGFR	E for 2 y vs cisplatin/vinorelbine ×4 cycles	2-y DFS E: 81.4% chemo: 44.6%
ADAURA <sup>6</sup> (NCT02511106)	III	IB–IIIA	682	EGFR	OSI for 3 y vs PB	2-y DFS in II–IIIA OSI: 90% PB: 44%
ALCHEMIST-EGFR (NCT02193282)	III	IB–IIIA	420	EGFR	E for 2 y vs PB	OS
ALCHEMIST-ALK (NCT02201992)	III	IB–IIIA	168	ALK	Crizotinib for 2 y vs SoC	OS
ALINA (NCT03456076)	III	IB (≥4 cm)–IIIA	257	ALK	Alectinib for 2 y vs chemo <sup>b</sup> ×4 cycles	OS

Abbreviations: BSC, best supportive care; chemo, chemotherapy; DFS, disease-free survival; E, erlotinib; FISH, fluorescence in situ hybridization; G, gefitinib; IHC, immunohistochemistry; OS, overall survival; OSI, osimertinib; PB, placebo; SoC, standard of care.

<sup>a</sup>Estimated number of patients used for ongoing trials that are still recruiting.

<sup>b</sup>Generic term “chemotherapy” used when multiple regimens allowed in the study.

practice changes on these surrogate endpoints.<sup>29–31</sup> Use of these endpoints is attractive from a practical standpoint because they take less time to evaluate and allow patients faster access to new treatments. Pathologic response after neoadjuvant therapy has been associated with improved survival in NSCLC in prior studies, although the FDA has made it clear that pathologic response alone is not adequate for approval at this time.<sup>32–34</sup> Adjuvant trials are more difficult to assess because there is currently no way to evaluate disease response after treatment. DFS was found to have a good correlation with OS in adjuvant chemotherapy studies.<sup>35</sup> Thus DFS, if of a sufficient magnitude, will have to serve as an OS surrogate for the time being, but perhaps this is an area in which biomarkers such as circulating tumor DNA (ctDNA) to identify patients at higher risk of recurrence would be useful.

The ADAURA trial’s first interim analysis was published at an unplanned time point due to the magnitude of the DFS benefit discovered. Based on the 2-year DFS results (90% vs 44%), it is standard of care to give adjuvant osimertinib after adjuvant chemotherapy (for stage II–IIIA) to patients with resected stage IB–IIIA disease and a sensitizing *EGFR*m. Assuming OS is eventually proven to be better as well, we think that it will not be much longer before other presently used TKIs in advanced disease will be used for their respective oncogenes (eg, *ALK*, *ROS1*, *RET*) in resectable disease.<sup>6</sup>

The necessary duration of osimertinib for optimal benefit is not as clear. Currently, adjuvant osimertinib is given for 3 years, as in the ADAURA trial. This time frame was based on prior studies showing increased recurrences in the third year after treatment for 2 years postsurgery, and the finding that adjuvant targeted treatments in other diseases, such as gastrointestinal stromal tumor, benefitted from longer duration of treatment.<sup>36,37</sup> However, the optimal duration of treatment is unknown and it will be critical to analyze patterns of recurrence in the ADAURA osimertinib arm after stopping treatment. Although we may be overtreating patients who would have had similar outcomes with just 1 or 2 years of osimertinib, it is also possible that longer or indefinite treatment may be necessary. Hopefully, further studies will evaluate the efficacy of different treatment durations, while risk-adjusted treatment based on ctDNA minimal residual disease (MRD) may also help.

Results of the IMpower010 study with adjuvant atezolizumab were groundbreaking, but it was not even a year later that the positive results for neoadjuvant nivolumab were published from the CheckMate 816 trial. Now, we run into the conundrum of deciding between neoadjuvant chemotherapy + immunotherapy and adjuvant immunotherapy when there have not been any head-to-head comparisons. Some immunotherapy trials, including KEYNOTE-786, include both neoadjuvant and adjuvant immunotherapy, potentially causing further confusion

**Table 5. Select Neoadjuvant Targeted Therapy Trials**

Trial (ClinicalTrials.gov identifier)	Phase	Stage	Patients n <sup>a</sup>	Mutation	Treatment	Primary Results or Endpoint(s)
ESTERN <sup>47</sup> (NCT01217619)	II	IIIA (N2)	25	EGFR	E for 56 d → surgery if response	Radical resection rate 60%
NCT00600587 <sup>48</sup>	II	IIIA (N2)	24	EGFR	E if EGFR <sup>m</sup> for 42 d or carboplatin/gemcitabine if EGFR <sup>w</sup> ×3 cycles	RR E: 58.3% chemo: 25%
NCT01217619 <sup>49</sup>	II	IIIA	31	EGFR	E if EGFR <sup>m</sup> for 4–7 wk or chemo <sup>b</sup> if EGFR <sup>w</sup> ×2 cycles	ORR E: 67% chemo: 19%
EMERGING-CTONG 1103 <sup>28</sup> (NCT01407822)	II	IIIA (N2)	72	EGFR	E for 42 d → adjuvant E for 1 y vs cisplatin/gemcitabine ×2 cycles → adjuvant cisplatin/gemcitabine ×2 cycles	ORR E: 54.1% BSC: 34.3
NEO-ADAURA (NCT04351555)	III	II–IIIB	328	EGFR	OSI for 9 wk vs OSI and chemo ×3 cycles vs chemo ×3 cycles	MPR
NOCE01 (NCT05011487)	II	IIIA (N2)	30	EGFR	OSI for 60 d and cisplatin/pemetrexed ×2 cycles	LN clearance rate
ALNEO (NCT05015010)	II	III	33	ALK	Alectinib for 8 wk → adjuvant alectinib up to 96 wk	MPR
NAUTIKA (NCT04302025)	II	II–IIIB	80	ALK, ROS1, NTRK, BRAF V600, or RET	Alectinib/entrectinib/vemurafenib with cobimetinib, or pralsetinib for 8 wk → adjuvant chemo ×4 cycles → continued treatment with TKI (if response) for 2 y	MPR

Abbreviations: BSC, best supportive care; chemo, chemotherapy; DFS, disease-free survival; E, erlotinib; EGFR<sup>m</sup>, mutated EGFR; EGFR<sup>w</sup>, wild-type EGFR; LN, lymph node; MPR, major pathologic response; ORR, overall response rate; OSI, osimertinib; RR, response rate; TKI, tyrosine kinase inhibitor.

<sup>a</sup>Estimated number of patients used for ongoing trials that are still recruiting.

<sup>b</sup>Generic term “chemotherapy” used when multiple regimens allowed in the study.

regarding perioperative management. Also, as mentioned previously, in both of these trials certain groups seem to be deriving most of the benefit. In particular, the group with PD-L1 expression of  $\geq 50\%$  in IMpower010 (HR, 0.43; 95% CI, 0.27–0.68) and patients with either stage IIIA or PD-L1 expression  $\geq 50\%$  in CheckMate 816 (HR, 0.24; 95% CI, 0.10–0.61, and HR, 0.54; 95% CI, 0.37–0.80, respectively).<sup>19,20</sup>

Using the information currently available, we feel it would be most beneficial to recommend neoadjuvant nivolumab + chemotherapy over adjuvant atezolizumab in patients with stage II–IIIA disease with PD-L1 expression  $\geq 1\%$ . Patients with PD-L1 expression  $< 1\%$  may also be offered neoadjuvant chemotherapy + immunotherapy but with a more nuanced discussion of the risks in the setting of a likely lower level of benefit. Neoadjuvant therapy allows for tumor assessment and thus the ability to evaluate efficacy of treatment. In an exploratory analysis in CheckMate 816, a pCR was associated with a longer EFS.<sup>19</sup> Importantly, the regimen also calls for only 3 cycles of chemotherapy + immunotherapy compared with a whole year of atezolizumab after 4 cycles of adjuvant chemotherapy. Finally, neoadjuvant treatment avoids the issue that fewer patients are likely to receive adjuvant therapy due to issues with recovery from surgery or follow-up after resection. The concerns with neoadjuvant treatment about delayed surgeries from adverse events or cancelled

surgeries due to progression do not seem to be a major issue.<sup>19</sup>

We still feel there may be a place for adjuvant immunotherapy, although where exactly is unclear. Certainly, patients with high PD-L1 expression derive benefit, and it makes sense for patients with early-stage NSCLC who are upstaged postoperatively. Adjuvant immunotherapy may eventually be given in combination with neoadjuvant immunotherapy pending results of other studies, or perhaps there is a subset of patients who may benefit more based on either pathologic response or MRD levels postoperatively. As outcomes for early-stage NSCLC improve, management will become more complex and nuanced.

## Conclusions

Adjuvant platinum-based chemotherapy has been the mainstay of perioperative treatment for NSCLC for years, although the recent FDA approvals for both new neoadjuvant and adjuvant therapies have dramatically changed this in only a few short years.

The ADAURA trial with osimertinib may only be the beginning of a series of practice-changing findings in perioperative targeted therapy, whereas immunotherapy has proven to be feasible, safe, and effective perioperatively. However, challenges remain in refining these advances.

One of the main challenges will be to confidently identify which patients should receive perioperative systemic therapy. Biomarkers such as ctDNA might be one answer. For example, checking for MRD postresection to determine the need for adjuvant therapy is a promising strategy that is currently being validated in trials. Studies have already shown that the presence of ctDNA after definitive treatment can be predictive of recurrence.<sup>38–40</sup> Other challenges include the optimal timing and duration of perioperative therapy, and the widespread adoption of biomarker testing in patients with early-stage NSCLC. While we await ongoing and future trials to better define the use of perioperative targeted therapy, we can state with confidence that the advances of the

preceding decade are finally making their way beyond advanced disease into earlier, curable stages of lung cancer.

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