Chemotherapy + PD-1/PD-L1 Blockade Should Be the Preferred Option in the Neoadjuvant Therapy of NSCLC

Samuel Rosner, MD, Patrick M. Forde, MB, BCh*

Identifying the Clinical Need

Lung cancer remains the leading cause of cancer death worldwide.¹ Even for the earliest stages of NSCLC, survival is comparatively poor and lags behind surgical breast, colon, and prostate cancers by large margins. Over 20% of patients with stage I NSCLC, 50% with stage II, and a staggering 60% with stage IIIA are dead within 5 years—despite receiving curative-intent surgery.² In surgically resected patients, the risk of distant metastases may even be greater than the risk of local and regional recurrence,³ highlighting the need for earlier and better systemic control. Before very recent advances in the systemic therapy of early-stage lung cancer, medical oncologists were left with few therapeutic options to improve these poor survival rates. Recommended neoadjuvant and adjuvant chemotherapy (chemo) options for patients with resectable disease offered a real but, in truth, modest, 5% absolute improvement over surgery alone in 5-year overall survival (OS).⁴ During the golden age of lung cancer therapeutics from approximately 2008 onward, a disconnect emerged between advanced lung cancer (emergence of molecular-guided therapies, the immunotherapy revolution, and >20 new systemic therapy approvals) and resectable lung cancer (zero new therapies and a degree of therapeutic nihilism). Despite the fact that major therapeutic breakthroughs for advanced lung cancer have become almost routine, although few patients are actually cured of metastatic disease, standard treatment for a patient diagnosed with having stage II NSCLC in 2018 was essentially unchanged from 2008. This falls far short of the impressive expectations that have resulted from the molecular and immunotherapeutic advancements of the past decade and has left patients and clinicians with a clear unmet need in the field of early-stage lung cancer management.

Several recently reported neoadjuvant clinical trials (Table 1) incorporating immune checkpoint inhibitors (ICIs) either alone or in combination with chemo have presented promising results. This has pushed clinicians to rethink the treatment paradigm for early-stage NSCLC, and in doing so, has spurred welcome discussion and controversy over the optimal course of management.

Adjuvant Immune Checkpoint Blockade

Analogous to the recent advances in the neoadjuvant space, trials evaluating the safety and efficacy of ICIs in the adjuvant setting led to the approval of the Food and Drug Administration of adjuvant atezolizumab after definitive resection and subsequent adjuvant chemo, on the basis of data from IMpower010.⁵ In this randomized phase 3 multicenter study, eligible patients with stages IB to IIA (per seventh edition of the American Joint Committee on Cancer [AJCC] staging system) received 1 year of atezolizumab versus best supportive care, after completing definitive anatomical resection followed by adjuvant cisplatin-based chemo. In patients with resected stages II to IIA NSCLC and tumor programmed death-ligand 1 (PD-L1) expression of more than or equal to 1%, 36-month disease-free survival (DFS) was 60.0% in the treatment arm compared with 48.2% in the best supportive care group (hazard ratio [HR] = 0.66, 95% confidence interval: 0.50–0.88, p = 0.0039), meeting the complex preset hierarchical primary end point for the...
foundational understanding of the mechanism of ICIs have captured headlines and prolonged survival only for predecessors have watched on as novel systemic therapies patients dealing with resectable NSCLC, whose pre-existent excitement and hope for patients with more advanced NSCLC. Despite these caveats, this recent breakthrough brings much-needed improvement in DFS ($HR = 0.87 [0.60–1.26]$, respectively), suggesting much of the benefit was driven by the population of PD-L1 high-expressing tumors ($\geq 50\%$) in the treatment arm. The OS data from IMPower010 are still maturing and have yet to be reported, but will also provide added insight into the eventual prioritization of adjuvant atezolizumab versus emerging neoadjuvant chemo-immunotherapy options. In addition, the uncertain DFS benefit of adjuvant ICI for low PD-L1–expressing tumors and smaller tumors (IB and II) points to the continued need for further therapeutic development in early-stage NSCLC. Despite these caveats, this recent breakthrough has brought much-needed excitement and hope for patients dealing with resectable NSCLC, whose predecessors have watched on as novel systemic therapies have captured headlines and prolonged survival only for patients with more advanced NSCLC.

### Biological and Clinical Rationales for Neoadjuvant Immune Checkpoint Blockade

Despite the recent advancement of adjuvant ICI, our foundational understanding of the mechanism of ICIs along with convincing preclinical evidence suggests improved efficacy of neoadjuvant compared with adjuvant immune therapy. It has been hypothesized that by initiating immune checkpoint blockade (ICB) while the tumor is “in situ,” this will leverage higher levels of endogenous tumor and tumor-associated antigen, thereby enhancing T-cell priming, leading to greater expansion of tumor-specific T-cell clones. These clones may persist even beyond time of resection to perpetuate immune surveillance and eliminate micrometastatic disease.

### Table 1. Neoadjuvant Immunotherapy Trials in NSCLC

<table>
<thead>
<tr>
<th>Journal/Conference</th>
<th>First Author</th>
<th>Year</th>
<th>Trial ID</th>
<th>Trial Phase</th>
<th>Primary End Point</th>
<th>Neoadjuvant Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Nature Medicine</em> (NeoStar)</td>
<td>Cascone et al.</td>
<td>2021</td>
<td>NCT03158129</td>
<td>II</td>
<td>MPR</td>
<td>Ipilimumab/nivolumab vs. nivolumab</td>
</tr>
<tr>
<td><em>Lancet Oncology</em> (NADIM)</td>
<td>Provencio et al.</td>
<td>2020</td>
<td>NCT03081689</td>
<td>II</td>
<td>PFS at 24 mo</td>
<td>Carbo/taxol + nivolumab</td>
</tr>
<tr>
<td>World Lung/ <em>Journal of Thoracic Oncology</em> (LCMC)</td>
<td>Lee et al.</td>
<td>2021</td>
<td>NCT02927301</td>
<td>II</td>
<td>MPR</td>
<td>Atezolizumab</td>
</tr>
<tr>
<td><em>Lung Cancer</em> (NEOMUN)</td>
<td>Eichhorn et al.</td>
<td>2021</td>
<td>NCT03197467</td>
<td>II</td>
<td>Safety</td>
<td>Pembrolizumab</td>
</tr>
<tr>
<td><em>AACR</em> (CheckMate 816)</td>
<td>Forde et al.</td>
<td>2020</td>
<td>NCT02998528</td>
<td>III</td>
<td>pCR</td>
<td>Nivolumab + chemotherapy</td>
</tr>
<tr>
<td><em>Journal of Thoracic Oncology</em></td>
<td>Gao et al.</td>
<td>2020</td>
<td>ChlCTR-OIC-17013726</td>
<td>Ib</td>
<td>Safety</td>
<td>Sintilimab</td>
</tr>
<tr>
<td><em>Lancet Oncology</em></td>
<td>Shu et al.</td>
<td>2020</td>
<td>NCT02716038</td>
<td>II</td>
<td>MPR</td>
<td>Atezolizumab + chemotherapy</td>
</tr>
<tr>
<td><em>ESMO</em></td>
<td>Lei et al.</td>
<td>2020</td>
<td>NCT04338620</td>
<td>II</td>
<td>pCR</td>
<td>Camrelizumab + chemotherapy</td>
</tr>
<tr>
<td><em>Oncoimmunology</em> (NeoTAP01)</td>
<td>Zhao et al.</td>
<td>2021</td>
<td>NCT04304248</td>
<td>II</td>
<td>MPR</td>
<td>Toripalimab + chemotherapy</td>
</tr>
<tr>
<td><em>Journal of Clinical Oncology</em></td>
<td>Rothschild et al.</td>
<td>2021</td>
<td>NCT02572843</td>
<td>II</td>
<td>1-y EFS</td>
<td>Durvalumab + chemotherapy</td>
</tr>
</tbody>
</table>

Carbo, carboplatin; EFS, event-free survival; ID, identification; MPR, major pathologic response; pCR, pathologic complete response; PFS, progression-free survival.
into early-stage disease. Proposed mechanisms behind this observation between tumor volume and ICI efficacy include the following: (1) poor T-cell immune infiltration into the tumor microenvironment owing to poor vascularization and heterogeneous fibrotic changes and (2) relative increased proportions of immune-suppressive cell populations, including myeloid-derived suppressor cells and tumor-associated macrophages, affecting both CD8+ T-cell trafficking and cytotoxic effects.

**Neoadjuvant Single- and Dual-Agent ICB**

One concern regarding incorporation of more aggressive combination regimens in the neoadjuvant space has been the potential risk of toxicity and delay of curative-intent surgery, particularly with some of the more dramatic immune-related adverse events that can occur with ICIs. To test the safety of ICI agents in this setting, an initial pilot study was first published evaluating safety and feasibility of two preoperative doses of nivolumab before definitive resection for patients with stages I to IIIA (per AJCC seventh edition) NSCLC. There were 21 patients enrolled, 20 of whom underwent complete tumor resection without treatment-related surgical delays, with the remaining patient found to have inoperable disease at time of surgery. Treatment-related adverse events (TRAEs) occurred in five of 22 patients, with only one event graded 3 or higher. Among the 20 patients’ tumors available for pathologic assessment, two (10%) achieved a pathologic complete response (pCR), defined as 0% residual tumor within the primary and nodal resection specimens. Major pathologic response (MPR), defined as no more than 10% viable tumor cells in the resected primary tumor, was noted in 9 of 20 patients (45%). Neoadjuvant nivolumab induced expansion of mutation-associated, neoantigen-specific T-cell clones in the peripheral blood, noted within 2 to 4 weeks after treatment. Extended follow-up data for this cohort of patients revealed a 24-month recurrence-free survival rate of 69%, with one long-term dermatologic immune-related adverse event reported. Since the initial publication of this neoadjuvant ICI trial in 2018, several early phase trials have assessed the safety and efficacy of single-agent or dual-agent ICI in NSCLC (Table 1). Most of the studies testing neoadjuvant single-agent ICI revealed it to be safe and feasible before curative-intent surgery. Nevertheless, a study reported by Reuss et al. of neoadjuvant ipilimumab plus nivo underwent early termination of the study arm. Although the combination was feasible, with all patients having received each scheduled dose, six of nine enrolled patients (67%) experienced TRAEs, with 33% being grade 3 or higher. In contrast, a phase 2 study by Cascone et al. evaluating efficacy of neoadjuvant ipilimumab plus nivo versus nivo monotherapy—with MPR as the primary end point—reported a total resectability rate of 89% among all enrolled patients with 100% undergoing R0 resection. Grade 3 to 5 TRAEs were 10% with ipilimumab plus nivo and 13% for nivo alone. These conflicting safety signals suggest the need for further investigation of neoadjuvant dual ICI to identify patient populations most likely to derive clinical benefit.

**Neoadjuvant Chemoimmunotherapy**

As we know from extensive clinical data in the advanced/metastatic setting, single-agent or even dual-agent ICI regimens—although capable of inducing impressive and durable responses—still leave most of the patients without significant clinical benefit. For this reason, strategies combining chemo with ICI have been explored to help boost response rates and offer benefit for patients less likely to respond to ICI alone—such as those with lower tumor PD-L1 expression scores or tumor mutational burden. Similarly, when evaluating ICIs in the neoadjuvant setting, although efficacy of these agents—measured largely by pathologic response data—has been encouraging, there are still many patients without deep tumor pathologic responses to single or dual ICI therapy. To further optimize outcomes, several studies have explored the safety and efficacy of combining neoadjuvant chemo with ICIs. Biological rationales for this combination strategy, as studied in the advanced/metastatic setting, include the recognition that chemo induces tumor lysis, leading to the release of tumor antigens, enhancing immune responses, and ultimately leading to improved rates of pathologic response and clinical outcomes. Among the first neoadjuvant chemoimmunotherapy trials was a single-arm, phase 2 trial of up to four cycles of atezolizumab in combination with nab-paclitaxel in patients with resectable stages IB to IIIA NSCLC reported by Shu et al. The study enrolled 30 patients, of whom 97% underwent surgery, with 87% undergoing successful R0 resection. pCR and MPR were reported at 33% and 57%, respectively, both of which are comparatively higher than historical rates after either neoadjuvant chemo or single-agent ICI. From a toxicity standpoint, grade 3 to 5 adverse events were mainly attributable to chemo, with neutropenia in 50% of patients. Building on this, several early-stage clinical trials have reported the safety and efficacy of neoadjuvant chemoimmunotherapy, with rates of pCR ranging from 9% to 63%, with particularly promising two-year follow-up data noted in the phase 2 NADIM trial. Some trials such as NADIM and SAKK 16/14—investigating three cycles of preoperative durvalumab combined with cisplatin and taxotere—have focused on
higher risk resectable patients, restricting enrollment to stage IIIA disease. At this time, it is unclear if there is improved benefit of neoadjuvant chemoimmunotherapy for lower risk (I/II) versus higher risk stage IIIA resectable patients, though this is certainly an area of interest which data from future larger scale, randomized studies may help elucidate.

Promising data from early phase neoadjuvant chemoimmunotherapy trials have been followed by recently presented results of pathologic and surgical outcomes from the international, multicenter, randomized phase 3 study CheckMate 816 comparing neoadjuvant nivo with platinum-doublet chemo (nivo + chemo) versus chemo alone before definitive resection for patients with clinical stages IB to IIIA (per AJCC seventh edition) NSCLC. Results of the pathologic response primary end point revealed a statistically significant difference in pCR between nivo plus chemo versus chemo alone (24% versus 2.2%, respectively, OR = 13.94 [99% confidence interval: 3.49–55.75], p < 0.0001) and significantly deeper pathologic responses in the tumors resected from those patients who received chemoimmunotherapy. The addition of nivo to neoadjuvant chemo also led to higher rates of circulating-tumor (ct)DNA clearance, defined as change from detectable levels of ctDNA at cycle 1 to undetectable ctDNA levels at cycle 3, at 54% versus 34%. In terms of toxicity, nivo plus chemo did not increase TRAEs and led to zero treatment-related deaths, compared with three in the chemo arm. From a surgical perspective, patients who received nivo plus chemo were more likely to undergo surgical resection and had lower rates of pneumonectomy (17% versus 25%), a high-risk surgical procedure. Rates of R0 resection were numerically higher with the addition of nivo (83% versus 78%), and generally, similar to better surgical outcomes were noted with nivo plus chemo for all surgical metrics, including shorter duration of surgery, less blood loss, and no increase in postoperative hospitalization duration. These favorable surgical results may help mollify prior concerns from early reports highlighting fibrotic changes post-ICI making pulmonary resection more challenging. Although these intraoperative observations may occur as a result of ICI response, it seems that they do not impact surgical or clinical outcomes in aggregate, and in part may be representative of timing between neoadjuvant therapy and surgery, a potential future area of interest, particularly as neoadjuvant ICI becomes further incorporated into standard of care.

**Early Pathologic End Points**
Recent ongoing and previously reported early phase neoadjuvant NSCLC ICI trials have increasingly relied on pathologic end points such as pCR and MPR, with more established clinical end points such as event-free survival (for neoadjuvant trials), DFS, and OS still maturing. This has led to controversy over the utility and surrogacy of early pathologic end points when considering incorporation of neoadjuvant ICI into practice. Using historical data from studies evaluating neoadjuvant chemo, pathologic response has been correlated with survival outcomes, and therefore proposed as a clinically meaningful surrogate end point. Survival outcomes associated with pCR after neoadjuvant chemo have previously been reported, reinforcing its prognostic impact. In a pooled analysis of two French randomized phase 3 trials including patients with stages IB to IIIA NSCLC, the collective 8.3% of patients with pCR had an improved 80% five-year survival, compared with 56% in non-pCR patients (p = 0.0007). Certainly, as these new immunotherapeutic agents are explored in the neoadjuvant setting, these correlations between pathologic response and survival will need to be validated, and with multiple phase 3 neoadjuvant trials ongoing, there will be ample opportunity to do so. Nevertheless, given the underlying mechanism of response with ICIs—including continued immunosurveillance of micrometastatic disease—clinicians and patients may be encouraged by the collective interim results of these neoadjuvant chemoimmunotherapy trials, underscored and reinforced by a recent press report of positive event-free survival findings from CheckMate 816.

**Conclusions**
Conceptually, neoadjuvant therapy has clear clinical advantages over solely adjuvant therapy, given that early response to therapy can be evaluated both radiographically, with preimaging and postimaging of the intact primary tumor, and pathologically, at the time of resection. The recent approval of adjuvant atezolizumab, given for an entire year after surgery, mandates a long course of expensive and potentially toxic therapy for patients who may already have been cured of their cancer by surgery and perioperative chemo. In contrast, the benefit of a relatively short course of three to four cycles of neoadjuvant chemoimmunotherapy can be assessed in a multifaceted manner, by radiographic response, pathologic response at the time of surgical resection, and emerging technologies such as dynamic liquid biopsies that assess minimal residual disease after surgery. Postoperatively, after neoadjuvant therapy, the patient and clinician have time to regroup and consider the indication (or absence of indication) for further therapy. This has the potential to limit unnecessary treatment exposure to the same systemic agents for those patients who are unlikely to derive benefit (those
with minimal or no pathologic response) and for those who may have already achieved maximal benefit (tumors with pCR or near pCR). In turn, this can reduce the treatment-related toxicity (encompassing physical, psychosocial, and financial aspects) that ensues from a long course of adjuvant therapy in the absence of clinically apparent disease.

As an example, and focusing on cost, recent Medicare prices in the United States would suggest that a full course of adjuvant therapy using the dose and schedule of atezolizumab studied in IMpower010 costs approximately $200,000 (flat dose of 1200 mg for 16 cycles at $12,524.64) whereas three doses of neoadjuvant nivo, delivered with chemo as in CheckMate 816, is a relative bargain at about $31,000 (flat dose of 360 mg for three cycles at $10,281.24). Of course, we must await definitive results from CheckMate 816 (and from the many other ongoing neoadjuvant and adjuvant trials), and cost is not the sole determinant of therapy; however, financial toxicity is a key factor for both patients and health care systems. Increased awareness regarding the toll of financial toxicity is certainly important, and formal cost-effectiveness studies evaluating different perioperative treatment strategies are warranted.

We hope that ongoing and future studies will focus on both enhanced efficacy and optimal de-escalation of therapy for those patients who may be cured by surgery and short courses of perioperative therapy ideally given in the neoadjuvant setting.

In terms of prioritization of neoadjuvant ICB (either dual or monotherapy) alone versus with chemo, evidence thus far reveals a doubling in rate of pCR with the addition of chemo. As stated before, it is plausible that this improved pCR will also translate into long-term survival benefits. Nevertheless, further exploration of predictive biomarkers (i.e., PD-L1 or tumor mutational burden) is needed to find if certain patients may derive similar benefit from ICB alone, without the addition of chemo—under a similar paradigm to metastatic NSCLC. Additional biomarkers, such as ctDNA clearance, can aid in the perioperative treatment setting. Correlative studies from the initial pilot neoadjuvant nivo study revealed concordance between ctDNA clearance and pathologic response (≥30% reduction in viable tumor), highlighting its potential utility.

Separate, but related to the purview of this commentary includes the parallel field of neoadjuvant-targeted therapy for oncogenic-driven NSCLCs. Many of the neoadjuvant ICB and chemoimmunotherapy trials exclude patients with EGFR- or ALK-sensitizing mutations, given their inferior outcomes with immunotherapy for advanced lung cancer. As the list of effective targeted therapies against these oncogene drivers grows, it will be increasingly important to implement clinical trials investigating their utility in the neoadjuvant and/or adjuvant setting. Neoadjuvant trials, such as NEOADAURA (EGFR) and LCMC4 (multiple targeted therapy arms), are ongoing to address this question. Integral to this will be the need for earlier broad-based genomic testing to properly categorize a patient’s tumor and select the appropriate neoadjuvant approach. We are still in the early days of this shift in treatment paradigm, but certainly, the writing is on the wall.

Early-stage NSCLC carries a high rate of recurrence and mortality, despite treatment with curative-intent surgery and additional perioperative chemo options. Results from adjuvant ICI trials, including IMpower010, are quite encouraging and practice changing for some patients; however, they still leave many patients at risk for recurrence. There is a strong biological rationale for incorporating immunotherapy into neoadjuvant treatment, which has been supported by results from several early phase clinical trials. The addition of chemo to anti-PD-1 in this setting increases pathologic responses dramatically, improves surgical outcomes compared with chemo alone, and is clearly safe and feasible. Most importantly, neoadjuvant therapy delivers an early assessment of therapeutic benefit allowing informed decision-making in the postoperative phase and avoiding potential unnecessary toxicity from long courses of adjuvant therapy delivered to many patients but curing relatively few. As such, chemo plus PD-1 pathway blockade is the preferred option in the neoadjuvant therapy of NSCLC.

CRediT Authorship Contribution Statement
Samuel Rosner, Patrick M. Forde: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing.

References


29. Forde PM, Spicer J, Lu S. Nivolumab (NIVO) + platinum-doublet chemotherapy (chemo) vs chemo as neoadjuvant treatment (tx) for resectable (IB-IIIa) non-small cell lung cancer (NSCLC) in the phase 3 CheckMate 816 trial. Cancer Res. 2021;81(suppl 13):CT003.


