Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide. Non-small cell lung cancer (NSCLC) represents 85% of newly diagnosed cases, of which 19% are localized, 24% are regional and 55% are distant (1,2). Properly staging the extent of disease at diagnosis influences the approach to treatment and prognosis. Despite ostensibly curative therapy for stage I–III NSCLC, 30–60% of patients go on to develop metastatic disease (3). Even with incremental advances in the treatment of NSCLC, the prognosis is poor: the median overall survival (OS) of metastatic NSCLC is approximately 12 months and the 5-year survival is only 1% (4). New therapies are urgently needed.

One of the most promising treatment modalities that has emerged in recent years is that of immunotherapy, specifically the use of immune checkpoint inhibitors (ICIs). These agents act on immune checkpoints that modulate the immune response, allowing for restoration of a T cell-mediated anti-tumor response. The immune checkpoint molecules in advanced clinical development include antibodies modulating cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed death 1 (PD-1), and programmed death ligand 1 (PD-L1); however, many others are on the horizon. CTLA-4 is expressed on the surface of...
T lymphocytes and acts centrally to inhibit T cell activation by binding to the peripheral membrane protein B7 on antigen-presenting cells, thereby preventing CD28 binding and stimulation of T cell activation (5). In contrast, the PD-1/PD-L1 checkpoint interaction occurs peripherally in the tumor microenvironment after T cell activation. PD-L1, expressed on the surface of tumor cells, binds to the PD-1 receptor on the T cell membrane and downregulates the immune response (6). Immunohistochemical expression of PD-L1 on tumor cell membrane and/or infiltrating immune cells is a biomarker of response to PD-(L)1 antibodies, and it is recommended that tumors from patients with newly diagnosed advanced NSCLC be tested for PD-L1 expression (7).

Multiple ICIs are currently approved in the treatment of advanced NSCLC. However, published ICI data are limited to locally advanced or metastatic disease at this time. Several phase II and III trials in advanced NSCLC have reported improved survival with PD-(L)1 antibodies, both when used alone and in combination with chemotherapy (Table 1). Collectively, the CheckMate trials, KEYNOTE trials and OAK study have led to FDA approval of nivolumab, pembrolizumab and atezolizumab, respectively, for the treatment of advanced or metastatic NSCLC. The various designs of these studies mean that anti PD-(L)1 antibodies are now indicated for untreated PD-L1 high (>50% expression) advanced or metastatic NSCLC patients, or previously treated advanced or metastatic NSCLC patients regardless of PD-L1 status. Not only have these well-tolerated agents improved response rates and OS, but the sustained duration of benefit in some patients suggests an ongoing anti-tumor response that could be beneficial in earlier stages of NSCLC with the goal of preventing tumor recurrence (14).

**Current treatment strategies for stage III NSCLC**

The current treatment for stage IIIA (T1–T4, N0–N2)
NSCLC is complex and dependent on locoregional disease burden found on cross-sectional imaging and mediastinal lymph node staging. Indeed, multi-disciplinary evaluation of these patients is crucial to determine the best sequence of therapy. As the overall therapeutic goal is surgical resection for potential cure, those patients with large tumors or with certain considerations such as location or invasion require neoadjuvant chemotherapy +/- radiation if they are felt to be surgical candidates (7). Adjuvant or neoadjuvant platinum-based chemotherapy should be considered for stage III NSCLC patients who are candidates for surgery, as a 2008 meta-analysis demonstrated that adjuvant chemotherapy decreased risk of death by 5.4% over 5 years compared to surgery alone (15,16). Adjuvant concurrent or sequential radiotherapy may also be warranted in certain situations, such as resections with positive surgical margins or pathologic N2 positive nodes where neoadjuvant therapy was not administered (17).

Treatment of stage III disease involving mediastinal lymph nodes (N2) varies due to limited data. Depending on tumor size, therapeutic options include surgical resection followed by adjuvant therapy with chemotherapy or sequential chemotherapy followed by radiation, or concurrent definitive chemoradiation followed by surgical consideration depending on response. However, the use of chemotherapy or chemoradiation as a neoadjuvant treatment in certain cases of N2 disease is an area of therapeutic complexity. The data are unclear about the survival benefit of surgery after neoadjuvant treatment compared to definitive chemoradiation; earlier phase II studies reported a potential benefit of surgery, but subsequent randomized phase III studies have not observed the same benefit (18-22). In the 2009 phase III study comparing concurrent chemoradiotherapy followed by surgery to concurrent chemoradiotherapy followed by continued radiotherapy, the median OS was 23 and 22 months, respectively (18). It should be noted that the treatment approach for poor-risk patients—those who exhibit poor prognostic features established in risk assessment models—with resectable stage III NSCLC who are not candidates for surgery or concurrent chemoradiation is less well defined. Definitive radiotherapy is currently a viable option, and studies have shown that using radiotherapy alone yielded a median survival of approximately 29 months (23).

Concurrent definitive chemoradiation has been established as the standard of care for unresectable stage IIIIB (N3 disease) NSCLC, with multiple studies showing a median OS of around 17 months (24,25).

The current therapeutic options for stage III disease are complex, and currently include surgery, radiation and classical cytotoxic chemotherapy. The long-term response and survival in these patients with current standard therapies however, is overall poor with a rate of 36% and 19% at 5 years for stages IIIA and IIIB, respectively (26).

### Survival/relapse risk for resectable disease: defining the unmet need

Well tolerated, effective neoadjuvant and adjuvant therapies for resectable lung cancer are therefore urgently needed. Even after curative resection of NSCLC, approximately 60% of patients with stage IIIA disease develop recurrence after 3 years (27). As discussed, both neoadjuvant and adjuvant chemotherapy have been shown to improve survival in resectable NSCLC (28,29). However, each option has its respective limitations. Neoadjuvant chemotherapy can delay surgery if treatment-related toxicities arise, increase complications during surgery, and in some cases possibly prevent surgical resection through tumor progression (30). Difficulties from adjuvant chemotherapy arise from treatment delays due to patient recovery after surgery and consequent poor compliance (31,32). Immunotherapy may fulfill this unmet need by providing a better tolerated treatment option when compared with conventional chemotherapy, while limiting the impact of treatment-related toxicities on surgical resection.

### Preclinical rationale for neoadjuvant immunotherapy

A recent study published in the preclinical setting supports the rationale for administering immunotherapy as a neoadjuvant treatment (33). Using an immunocompetent murine model of triple negative breast cancer (TNBC), it was demonstrated that mice treated with neoadjuvant anti-PD-1/anti-CD137 combination had a 100-day survival of 50% compared to 0% in mice treated with adjuvant anti-PD-1/CD137. The improved efficacy of neoadjuvant treatment was also demonstrated on a cellular level. Neoadjuvant anti-PD-1/anti-CD137 resulted in a sustained increase of tumor-specific CD8+ T cells in the blood even after the tumor had been removed; adjuvant anti-PD-1/anti-CD137 showed a significantly lower increase in CD8+ T cell percentage in blood (6% to 1.1%, P=0.0263). Levels of these tumor-specific CD8+ cells predicted long-term survival, with the majority of mice with high CD8+ levels...
surviving longer than 100 days (33). In addition, the authors also report that depleting T cells and natural killer cells in long-term survivors did not reduce survival as would be expected if the tumor was merely dormant, suggesting permanent tumor kill with neoadjuvant therapy.

Neoadjuvant immunotherapy in other tumor types

The success of neoadjuvant immunotherapy in treating other cancers provides additional rationale for its use in stage III NSCLC. Currently established immunotherapies in advanced NSCLC first showed potential in treating melanoma patients, and preliminary results from neoadjuvant immunotherapy melanoma trials have been recently presented. The phase I OpACIN trial administered neoadjuvant nivolumab and ipilimumab in ten stage III melanoma patients and reported three complete responders and five partial responders, all of whom had not relapsed at a median follow-up of 45 weeks (34). Similarly, in a pooled clinical analysis of four ongoing clinical trials (NCT02437279, NCT02231775, NCT02519322, NCT01972347) from the International Neoadjuvant Melanoma Consortium, 21 patients received either neoadjuvant combined nivolumab/ipilimumab or nivolumab alone; eight complete responses with no recurrence were observed, and only three of the 13 remaining patients had recurring disease after neoadjuvant immunotherapy with surgery (35). The benefit of ipilimumab as neoadjuvant therapy has also been reported in case studies (36,37).

For locally advanced TNBC, the phase Ib KEYNOTE-173 study is examining combination pembrolizumab and chemotherapy in the neoadjuvant setting. Patients were assigned to either neoadjuvant pembrolizumab/ipilimumab or pembrolizumab alone; eight complete responses with no recurrence were observed, and only three of the 13 remaining patients had recurring disease after neoadjuvant immunotherapy with surgery (35). The benefit of ipilimumab as neoadjuvant therapy has also been reported in case studies (36,37).

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Neoadjuvant and adjuvant immune checkpoint inhibition in NSCLC: currently available data

Interim results from a phase II trial testing neoadjuvant nivolumab in newly diagnosed resectable Stage IIA–IIIB NSCLC (NCT02259621) were presented at the 2016 ESMO Congress and updated at the 2017 ASCO Annual Meeting. This study planned to administer two doses of nivolumab over 4 weeks prior to planned surgical resection. From 22 enrolled patients, 21 were deemed eligible and treated with neoadjuvant nivolumab and of these, 20 patients underwent surgical resection. The primary endpoints of feasibility and safety were met: administering nivolumab did not delay surgery, and treatment was well tolerated with one treatment-related grade 3 toxicity and no treatment-related grade 4 or 5 toxicities. Major pathologic response (MPR) was set as a secondary outcome and is defined as ≤10% residual viable tumor in the primary tumor. MPR captures treatment-specific anti-tumor activity and has been established as a potential surrogate of OS (39,40). Among the 21 per protocol patients 18 patients (85%) demonstrated stable disease, and 2 patients (10%) demonstrated a partial response while one patient had progressive disease. Notably, CT imaging underestimated the extent of nivolumab response, as MPR was reported in 9/21 cases (43%, 95% CI: 24–63%) (40). With a median follow-up of 12 months, 2/20 resected patients had experienced recurrence (41). Based on these encouraging data, this trial has expanded to examine combination neoadjuvant therapy with nivolumab and ipilimumab.

Durvalumab (anti-PD-L1) is now an FDA-approved option in unresectable stage III NSCLC. The phase III placebo-controlled PACIFIC trial (NCT02125461) (42) tested durvalumab after standard chemoradiotherapy and demonstrated a significant improvement in progression-free survival (PFS) (43).

Similarly, atezolizumab is being tested in the phase II DETERRED trial (NCT02525757) in patients with unresectable stage III NSCLC. In this study, atezolizumab is administered either concurrently with standard chemoradiation therapy followed by additional doses of atezolizumab during a consolidation phase, or solely during the consolidation phase after standard chemoradiation. The primary outcome is safety with a secondary outcome of PFS. Recently reported interim results of the consolidation only arm revealed a 20% (2/10) rate of high-grade immune-related adverse events. One patient who experienced grade 3 COPD exacerbation discontinued treatment after one dose of atezolizumab. Of the other 9 patients, 3 patients (30%) progressed after 6, 8, and 14 doses; the remaining patients remained on treatment at the time of report (44).

Neoadjuvant immune checkpoint inhibition in NSCLC: ongoing trials

A comprehensive list of ongoing trials investigating the use of ICIs in the neoadjuvant treatment of stage III NSCLC can be found in Table 2.
In addition to the neoadjuvant nivolumab study with interim results mentioned earlier, two other trials are currently studying combination nivolumab with ipilimumab (anti-CTLA-4) in the neoadjuvant setting. CheckMate 816 is a randomized, open label phase III trial (NCT02998528) comparing neoadjuvant combination nivolumab and ipilimumab or platinum doublet plus nivolumab versus standard neoadjuvant platinum doublet chemotherapy in stage IB (≥4 cm)–IIIA NSCLC. The rationale for combination nivolumab and ipilimumab in CheckMate 816 is based on results from CheckMate 012, a phase I study in stage IIIIB/IV NSCLC patients that demonstrated a higher objective response rate and PFS with combination therapy compared to nivolumab monotherapy (45). Similarly, chemotherapy-anti-PD-1 combination therapy has demonstrated promising efficacy in advanced NSCLC (11). The primary endpoint of this study is pCR rate measured at the time of surgery. The efficacy of combination nivolumab and ipilimumab compared to nivolumab monotherapy for stage I-III A NSCLC in the neoadjuvant setting is being evaluated in the NEOSTAR trial (NCT03158129).

TOP 1501 (NCT02818920), a phase II trial, is evaluating the surgical feasibility rate in patients following neoadjuvant pembrolizumab and also includes consolidation pembrolizumab following adjuvant therapy. Other adjuvant trials look to increase the versatility of pembrolizumab as a therapeutic option.

Atezolizumab is being studied in many ongoing clinical trials, as detailed in Table 2:

**Table 2 Ongoing trials using neoadjuvant immunotherapy in NSCLC**

<table>
<thead>
<tr>
<th>NCT identifier</th>
<th>Phase</th>
<th>Arms</th>
<th>Target accrual</th>
<th>Primary endpoint</th>
<th>Status</th>
<th>Projected study completion date</th>
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<td></td>
<td></td>
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<td>NCT02927301</td>
<td>II</td>
<td>Neoadjuvant atezolizumab</td>
<td>180</td>
<td>Major pathological response</td>
<td>Open</td>
<td>July 2023</td>
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<tr>
<td>NCT02994576</td>
<td>II</td>
<td>Neoadjuvant atezolizumab</td>
<td>60</td>
<td>Major toxicity or morbidity</td>
<td>Open</td>
<td>May 2021</td>
</tr>
<tr>
<td>NCT02716038</td>
<td>II</td>
<td>Neoadjuvant atezolizumab + platinum-doublet chemotherapy</td>
<td>30</td>
<td>MPR</td>
<td>Open</td>
<td>December 2020</td>
</tr>
<tr>
<td>NCT03102242</td>
<td>II</td>
<td>Induction atezolizumab with chemotherapy + radiation followed by consolidation chemotherapy and adjuvant atezolizumab</td>
<td>63</td>
<td>Disease control rate</td>
<td>Open, not yet recruiting</td>
<td>March 2020</td>
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<tr>
<td>Durvalumab</td>
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<tr>
<td>NCT02572843</td>
<td>II</td>
<td>Neoadjuvant chemotherapy + durvalumab</td>
<td>68</td>
<td>Event free-survival</td>
<td>Open</td>
<td>December 2021</td>
</tr>
<tr>
<td>Nivolumab</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>NCT03081689</td>
<td>II</td>
<td>Neoadjuvant nivolumab and chemotherapy followed by adjuvant nivolumab</td>
<td>46</td>
<td>PFS</td>
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<td>June 2022</td>
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<tr>
<td>Nivolumab/ipilimumab</td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>NCT02259621</td>
<td>II</td>
<td>Neoadjuvant nivolumab + ipilimumab; Neoadjuvant nivolumab</td>
<td>30</td>
<td>Safety</td>
<td>Open</td>
<td>January 2023</td>
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<tr>
<td>NCT02998528</td>
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<td>326</td>
<td>Major pathological response</td>
<td>Open</td>
<td>March 2024</td>
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<td>NCT02818920</td>
<td>II</td>
<td>Neoadjuvant pembrolizumab followed by adjuvant chemotherapy then pembrolizumab</td>
<td>32</td>
<td>Surgical feasibility rate</td>
<td>Open</td>
<td>January 2027</td>
</tr>
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</table>

NSCLC, non-small cell lung cancer; MPR, major pathologic response; PFS, progression-free survival.
trials in the neoadjuvant setting. Neoadjuvant atezolizumab is in phase II testing, and two trials are administering atezolizumab as monotherapy. The PRINCEPS trial (NCT02994576) gives patients one dose of neoadjuvant atezolizumab, while another trial (NCT02927301) gives two neoadjuvant doses and then follows adjuvant chemotherapy with potential consolidation atezolizumab for up to 1 year (46).

As previously mentioned, durvalumab has not yet been the Food and Drug Administration (FDA)-approved for treatment of NSCLC. One major clinical trial outside the US, however, is investigating durvalumab as both a neoadjuvant and adjuvant therapy. This phase II study in Switzerland combines durvalumab with neoadjuvant chemotherapy followed by adjuvant durvalumab in patients with stage IIIA disease (NCT02572843). In the US, two phase III trials of durvalumab in stage III NSCLC are currently open. As mentioned previously, results from the PACIFIC trial in unresectable stage III NSCLC have demonstrated promising efficacy (43).

**Adjuvant immune checkpoint inhibition in NSCLC: ongoing trials**

Ongoing trials investigating the use of ICIs in the adjuvant setting of stage III NSCLC can be found in Table 3. With many of these studies, along with the neoadjuvant studies mentioned earlier, set to be completed in the next 3–5 years, the body of evidence supporting the use of immunotherapy for early stage NSCLC may grow.

Nivolumab is being studied in the adjuvant and consolidation settings in two phase III trials. The ANVIL trial (NCT02595944) is studying adjuvant nivolumab after surgical resection, and enrollment is ongoing (47). In the consolidation setting, nivolumab is also being compared against placebo in patients with unresectable stage III NSCLC after receiving chemoradiation (NCT02768558).
Along with the previously mentioned neoadjuvant nivolumab/ipilimumab trials, the results of these studies may lead to immunotherapy indications for early stage NSCLC.

Pembrolizumab is being evaluated in the adjuvant treatment of early stage NSCLC. The phase III PEARLS trial (NCT02504372) compares efficacy of pembrolizumab to placebo following surgical resection and standard adjuvant therapy. A phase I trial is examining the maximum tolerated dose and safety of pembrolizumab when combined with concurrent chemoradiation therapy in unresectable stage III disease (NCT02621398).

Also, in patients with unresectable stage III NSCLC, Alliance Foundation Trials is administering induction atezolizumab with chemoradiotherapy, followed by consolidation chemotherapy with adjuvant atezolizumab (NCT03102242). The phase III IMpower010 trial (NCT02486718), focuses on consolidation atezolizumab compared to placebo following adjuvant chemotherapy (48).

Finally, IONESCO (NCT02273375) is a phase III study of adjuvant durvalumab compared to placebo in completely resected NSCLC.

Conclusions
The numerous ongoing clinical trials of ICIs in the neoadjuvant and adjuvant settings demonstrate the promising future of immunotherapy in the complex management paradigm of stage III NSCLC. Even though currently available data are limited, the interim reports suggest that perioperative use of PD-(L)1 antibodies is well tolerated and may have efficacy. For unresectable stage III NSCLC, the PACIFIC trial have met its primary endpoint of improved PFS with durvalumab with recent FDA approval in this treatment setting. In addition to nivolumab, atezolizumab is being studied as neoadjuvant therapy; four phase II studies are currently open with results to be released over the next 3–6 years. With multiple trials investigating each of these ICIs in large patient cohorts, we eagerly await the results of these studies to determine their role in the management of stage III NSCLC.

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None.

Footnote
Conflicts of Interest: The authors have no conflicts of interest to declare.

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