Neoadjuvant Immunotherapy in Resectable Non–Small Cell Lung Cancer

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Abstract: Lung cancer is the leading cause of cancer-related deaths worldwide and is associated with poor 5-year outcomes, even among the 20% to 25% of patients who present with operable disease. Cisplatin-based adjuvant chemotherapy has long been the standard of care for patients with resected non–small cell lung cancer (NSCLC). With the incorporation of immunotherapy, however, the treatment paradigm for NSCLC has changed dramatically. The introduction of immune checkpoint blockade has improved clinical outcomes in multiple phase 2 and 3 trials in both the neoadjuvant and adjuvant setting, resulting in new US Food and Drug Administration approvals in the management of early-stage resectable lung cancer.

This review explores the biological rationale for immune checkpoint blockade, both as monotherapy and in combination with chemotherapy, in conjunction with surgical management of patients with NSCLC. It also highlights the reported clinical trial data that have led to significant advances in the management of early-stage NSCLC. Additionally, this review summarizes ongoing key studies that will provide vital data on the clinical efficacy of these treatment approaches. The outcomes of ongoing trials and the associated biomarker-focused correlative studies will be critical to furthering the mechanistic understanding of immune checkpoint blockade in early-stage NSCLC. This, in turn, will help to uncover biomarkers of response and resistance in these patients.

Introduction

Lung cancer is the second most frequently diagnosed cancer among men and women, with an estimated 228,150 new cases occurring each year in the United States.[1] It is also the leading cause of cancer-related mortality, responsible for 23% of all cancer-related deaths.[1] Non–small cell lung cancer (NSCLC) accounts for 85%

of all lung cancer cases.[2] Despite increasing efforts in lung cancer screening, 50% of patients present with metastatic disease.[2] A further 30% of patients present with stage III locally advanced disease, and only 20% present with stage I or II disease.[2] Approximately 20% to 25% of patients have resectable disease at presentation.[3] However, 30% to 55% of patients who undergo curative surgery experience a recurrence and die of their disease.[4,5] The 5-year overall survival (OS) rate varies from 68% to 83% in stage I disease to 13% to 36% in stage III disease.[6]

Over the past 15 years, cisplatin-based adjuvant chemotherapy has been established as the standard of care for patients with resected stages II and III NSCLC. The pivotal Lung Adjuvant Cisplatin Evaluation (LACE) Collaborative Group meta-analysis, which was based on 5 studies with a total of 4584 patients and a median follow-up of 5.2 years, demonstrated that adjuvant chemotherapy was associated with a 5.4% decreased risk of death at 5 years for patients with stages II and III NSCLC disease (based on the 8th edition of the American Joint Commission on Cancer TNM staging system), with no benefit observed in stage I disease.[7] Studies of neoadjuvant chemotherapy demonstrated a comparable benefit from induction cisplatin-based chemotherapy, with 2 meta-analyses showing a 5% absolute survival improvement at 5 years.[8,9] The median major pathologic response (MPR) rate (defined as ≤10% residual viable tumor) reported after neoadjuvant chemotherapy is approximately 15%, and the historic pathologic complete response (pCR) rate (defined, with some variability, as the absence of tumor cells in all evaluated specimens) is 2% to 6%.[10] The decision between neoadjuvant and adjuvant cytotoxic chemotherapy varies significantly by institution, stage, and treatment team, but these 2 options are generally considered equivalent in terms of efficacy.

In the past 5 to 7 years, significant research efforts have been dedicated to improving the treatment paradigm for early-stage NSCLC, given the clear advances in systemic therapy for advanced disease and the significant recurrence rate in early-stage disease after surgery, an outcome that is eventually fatal for most patients. Immune checkpoint inhibitors (ICIs) have been approved for first- and second-line use in patients with metastatic NSCLC, and clinical experience with their safety and efficacy has been established.[11] This comprehensive review focuses on the rationale for perioperative immunotherapy in NSCLC. It also highlights the reported clinical trial data for immune checkpoint blockade in resectable NSCLC, and summarizes ongoing key phase 3 trials. Lastly, it explores biomarkers of response and future directions in the neoadjuvant treatment of early-stage NSCLC.

Adjuvant Immunotherapy in NSCLC

Several large studies are evaluating the efficacy of adjuvant ICIs following complete resection and/or chemotherapy in NSCLC. Two of these studies have resulted in US Food and Drug Administration (FDA) approvals for ICIs in the adjuvant setting. IMpower010 (N=1280) was the first phase 3 study to demonstrate a disease-free survival (DFS) benefit (hazard ratio [HR], 0.66; 95% CI, 0.50-0.88) with an ICI, specifically atezolizumab (Tecentriq, Genentech), in patients with stages II to IIIA NSCLC who had tumor programmed death ligand 1 (PD-L1) expression of at least 1%. The greatest benefit was seen in the subgroup of patients who had tumor PD-L1 expression of at least 50%.[12] The KEYNOTE-091 study (N=1177) found a significant improvement in DFS with adjuvant pembrolizumab (Keytruda, Merck) vs placebo after surgical resection in the intention-to-treat population (median DFS, 53.6 vs 42.0 months, respectively; HR, 0.76; 95% CI, 0.63-0.91; $P<.0014$). The researchers were surprised to see a lack of clear benefit among patients who had tumor PD-L1 expression of at least 50%.[13] Of note, 86% of patients in this study received adjuvant platinum-based chemotherapy prior to adjuvant pembrolizumab. The FDA has since approved both of these agents, with adjuvant atezolizumab approved for patients with resected stage II or III tumors that express PD-L1 on at least 1% of tumor cells, and adjuvant pembrolizumab approved for patients with resected stages II or III tumors, irrespective of PD-L1 status. Long-term follow-up for OS data in these trials is warranted.

Oncogene-Addicted NSCLC

ICI studies in NSCLC have largely excluded patients with epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase (*ALK*) oncogenic driver mutations because of the lack evidence of efficacy in advanced tumors with these mutations.[14] Additionally, treatment with molecularly targeted therapies is an area of expanding interest in oncogene-addicted NSCLC, with multiple active clinical trials ongoing in the adjuvant and neoadjuvant setting.

The ADAURA study demonstrated impressive results with adjuvant osimertinib (Tagrisso, AstraZeneca) in *EGFR*-mutant tumors, with an 80% reduction in the risk of disease recurrence or death and an 82% reduction in the risk of central nervous system progression or death among patients with resected stages IB to IIIA disease. These results led to a new standard of care in this patient population, which has been bolstered by a recent press release suggesting an OS benefit for osimertinib.[15,16] Building on these results, the role of osimertinib is being

Table 1. Phase 2 Trials of Neoadjuvant Immune Checkpoint Inhibitors

Trial (identifier)	Stage	No. of patients	Experimental arm (neoadjuvant phase)	Primary endpoint	MPR	pCR	Resection rate
SKCCC-JHU (NCT02259621)	IB-IIIA	21	2 cycles of nivolumab q 2 weekly	Safety	45% (9)	13% (3)	91% (21)
LCMC3[28] (NCT02927301)	IB-IIIB	181	2 cycles of atezolizumab q 3 weekly +/- adjuvant atezolizumab	MPR	21% (30)	7% (10)	88% (159)
NEOSTAR[30] (NCT03158129)	I-IIIA	23 monotherapy, 21 dual ICB	3 cycles of nivolumab q 2 weekly +/- 1 cycle of ipilimumab	MPR	22% (5) monotherapy, 38% (8) dual ICB	9% (2) monotherapy, 29% (6) dual ICB	89% (39)
MK 3475-223 (NCT02938624)	IB-IIIA	30	2 cycles of pembrolizumab q 3 weekly	Safety	28% (7)	8% (2)	83% (25)
IONESCO (NCT03030131)	IB-IIIA	46	3 cycles of durvalumab q 2 weekly	Complete surgical resection (R0)	17.5% (8)	7% (3)	89% (43)
PRINCEPS (NCT02994576)	I-IIIA	30	1 cycle of atezolizumab	Safety	14% (4)	0%	97% (29)
NeoCOAST (NCT03794544)	IB-IIIA	83	durvalumab (D) +/- oleclumab (O)[a] or monalizumab (M)[a] or danvatirsen (Da),[a] 1 × 28-day cycle	MPR	11% D (3), 19% D + O (4), 30% D + M (6), 31% D + Da (5)	3.7% D (1), 9.5% D + O (2), 10% D + M (2), 12.5% D + Da (2)	91.6% (76)

[a]Oleclumab is an anti-CD73 monoclonal antibody, monalizumab is an anti-NKG2A monoclonal antibody, and danvatirsen is an anti-STAT3 antisense oligonucleotide.

ICB, immune checkpoint blockade; MPR, major pathologic response; pCR, pathologic complete response.

evaluated as adjuvant therapy in earlier-stage disease (stages IA2 through IA3) in the ADAURA2 trial,[17] and in the neoadjuvant setting in the NeoADAURA study.[18] The LCMC4 LEADER trial from the Lung Cancer Mutation Consortium is conducting comprehensive molecular profiling in 1000 patients with stages IA2 through III NSCLC. The trial is designed to determine the proportion of these patients who possess any of 11 actionable oncogenic drivers mutations. The detection rate is expected to be approximately 33%.[19] Given the therapeutic implications of oncogene driver mutations, there is a need to ensure comprehensive biomarker testing in the management of patients with nonsquamous NSCLC across disease stages.

Rationale for Neoadjuvant Immunotherapy

Neoadjuvant ICIs are currently being evaluated as monotherapy or in combination with chemotherapy in more than 100 clinical trials across tumor types.[20] Several translational studies in animal models have demonstrated better efficacy of neoadjuvant immunotherapy compared with adjuvant immunotherapy in reducing distant metastases, an effect that was not observed with neoadjuvant chemotherapy alone.[21] There are several theoretical advantages to using ICIs in the neoadjuvant setting. The presence of the macroscopic tumor, the associated microenvironment, and the draining lymph nodes can provide a diverse range of tumor neoantigens and immune cells to activate and expand the immune response, which may contribute to more durable responses.[22] There is evidence that the primary tumor is important for T-cell priming and the draining lymph nodes are essential for antigen presentation, both of which are augmented by programmed death 1 (PD-1) blockade.[20] Additionally, neoadjuvant chemotherapy has been shown to increase PD-L1 expression on tumor cells and immune cell infiltrates, supporting potential synergy with immune checkpoint blockade.[23,24] Early induction of a broad and sustained immune response may facilitate eradication of micrometastatic disease, therefore reducing the risk of relapse.[20] Neoadjuvant therapies offer additional benefits compared with adjuvant approaches, most notably the ability to assess on-treatment response via pathologic response, which may in turn guide adjuvant treatment. Additional advantages include reduction in the tumor bulk prior to surgery, thereby potentially reducing

Table 2. Phase 2 Trials of Neoadjuvant Combination Chemotherapy + Immune Checkpoint Blockade

Trial (identifier)	Stage	No. of patients	Experimental Arm	Control arm	Primary endpoint	MPR	pCR	Resection rate
NADIM I[34] (NCT03081689)	IIIA (N2)	46	Nivolumab + CT, × 3 cycles q 3 weekly → adjuvant nivolumab × 1 y	None	24-mo PFS	83% (34)	63% (26)	89% (41)
NADIM II[37,38] (NCT03838159)	IIIA-IIIB	86	Nivolumab + CT, × 3 cycles q 3 weekly → adjuvant nivolumab × 6 mo	CT alone	pCR	52.6% (30)	36.8% (27)	85% (73)
Shu et al, Columbia University[41] (NCT02716038)	IB-IIIA	30	Atezolizumab + CT × 4 cycles q 3 weekly → SoC adjuvant therapy	None	MPR	57% (17)	33% (10)	97% (29)
SAKK 16/14[40] (NCT02572843)	IIIA (N2)	67	Durvalumab × 2 doses + CT × 3 cycles → adjuvant durvalumab	None	EFS at 1 y	60% (30)	18% (10)	82% (55)
NEOSTAR[30] (NCT03158129)	IB-IIIA	44	Nivolumab + CT + ipilimumab (22)	Nivolumab + CT (22)	MPR	50% (11) triplet arm, 32.1% (7) doublet arm	18% (4) in both arms	91% (20)

CT, chemotherapy; EFS, event-free survival; mo, months; MPR, major pathologic response; pCR, pathologic complete response; PFS, progression-free survival; SoC, standard of care.

the extent of surgery and improving R0 resection rates, and enhanced tolerability, resulting in increased rates of treatment completion.[25] Potential disadvantages of neoadjuvant approach include the risk of progression while on treatment, a delay in definitive local therapy secondary to toxicities, and the possibility of increased perioperative complications. Adjuvant treatment has the advantage of allowing the fastest time to surgery. It also provides more flexibility in timing of treatment and enables longer treatment duration.[26] Studies to date have sought to address these clinical concerns. A meta-analysis of 16 studies that involved 548 patients who received neoadjuvant immunotherapy, with 507 undergoing surgery, demonstrated the feasibility and safety of ICIs when given prior to surgery. It showed that 96% of patients underwent surgery after systemic treatment, with a surgical delay rate of 2.0%. The overall 30-day mortality rate was 0.6% across all 16 studies, and surgical morbidities were similar in type and frequency to contemporary data on thoracic resections without neoadjuvant immunotherapy.[27]

Neoadjuvant Immunotherapy: Monotherapy or Dual Checkpoint Blockade

ICIs have been evaluated in the neoadjuvant setting as monotherapy, as dual immune checkpoint inhibition with anti–PD-1/PD-L1 and anticytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) or antilymphocyte activation gene 3–encoded protein (LAG-3) antibodies, and in combination with chemotherapy. There are numerous ongoing phase 2 (Tables 1 and 2) and phase 3 (Table 3) trials investigating the efficacy of neoadjuvant immunotherapy in resectable NSCLC. In trial reports to date, neoadjuvant ICI monotherapy has been well tolerated, with MPR rates ranging from 18% to 45% and no significant delays to surgery. In the largest phase 2 study reported, the LCMC3 trial, 144 patients with stages IIA to IIIB NSCLC were enrolled and treated with 2 cycles of neoadjuvant atezolizumab given every 3 weeks, followed by 1 year of ICI postoperatively if a clinical benefit was seen. The primary endpoint was MPR.[28] Results showed that 20% of patients had a MPR (95% CI, 14-28) and among those patients, 7% experienced a pCR (95% CI, 3-12). There was an association between PD-L1 positivity and MPR. In this study, 11% of patients did not proceed to surgery and 6% of patients developed grade 3 or higher treatment-related adverse events (TRAEs).[28]

Two studies have examined combination immunotherapy with the anti–PD-1 antibody nivolumab (Opdivo, Bristol Myers Squibb) and the anti–CTLA-4 antibody ipilimumab (Yervoy, Bristol Myers Squibb). Reuss and colleagues halted their phase IB study early after enrolling 9 patients owing to a relatively high rate of side effects; however, 3 patients had a pCR.[29] The phase 2 NEOSTAR study enrolled 44 patients with resectable stages I to IIIA disease and randomly assigned them to receive either

neoadjuvant nivolumab monotherapy for 3 cycles or the same in combination with 1 cycle of ipilimumab.[30] The primary endpoint was MPR. The results showed the combination was superior in terms of pCR rates, with an MPR of 22% vs 38% and a pCR of 9% vs 29% in the monotherapy vs combination arms, respectively. In terms of tolerability in the overall study population, grade 3 to 5 TRAEs were reported in 13% (3/23) of patients treated with nivolumab and 10% (2/21) of patients treated with nivolumab plus ipilimumab. A total of 16% (n=7) of patients did not proceed to surgery on protocol, including 1 patient in each arm for toxicity-related reasons. However, 2 of the 7 patients (29%), including 1 patient with TRAE, eventually underwent surgery off protocol.[30,31]

Relatlimab is an FDA-approved anti–LAG-3 antibody, which is licensed in combination with nivolumab (Opdualag, Bristol Myers Squibb) for the treatment of metastatic melanoma.[32] Schuler and colleagues conducted the first study in NSCLC evaluating preoperative dual immune checkpoint blockade with nivolumab and relatlimab, specifically in the phase 2 NEOpredict-Lung trial (N=60). The trial enrolled patients with stages IB to IIIA resectable NSCLC, who were randomized to 2 doses of preoperative nivolumab with or without relatlimab. The results demonstrated that the combination was safe and feasible, with all patients proceeding to surgery within 6 weeks. It also demonstrated an overall response rate of 27% vs 10% and an MPR of 30% vs 27% in the combination vs monotherapy arms, respectively.[33]

Neoadjuvant Immunotherapy in Combination with Chemotherapy

The combination of ICIs and chemotherapy appears synergistic based on preclinical data. The NADIM study was the first to evaluate this combination in patients. It enrolled 46 patients with stage IIIA disease in a single-arm, phase 2 study, where patients received nivolumab in combination with carboplatin and paclitaxel every 3 weeks for 3 cycles, followed by 1 year of adjuvant nivolumab after resection. The primary endpoint of progression-free survival at 24 months was met, with 77% of patients alive without a recurrence at 2 years (95% CI, 60-88). Pathological outcomes were superior to those seen with single-agent immunotherapy, with 83% of patients experiencing an MPR (95% CI, 68-93) and 63% experiencing a pCR (85% CI, 62-91).[34] Longer follow-up showed that the 3-year OS was 81.9% in the intention-to-treat population and 91% in the per-protocol population.[35] In terms of tolerability and surgical outcomes, 30% of patients experienced a grade 3 or higher TRAE. None of these TRAEs were associated with surgery delay or death, however, and 89% of patients underwent a surgical resection.[34] These phase 2 clinical trials, in combination with those shown in Tables 1 and 2, demonstrated the feasibility, safety, and promising signals of efficacy for neoadjuvant immunotherapy, either as monotherapy or in combination with chemotherapy or dual ICI, in early-stage NSCLC. This sets the stage for practice-changing phase 3 studies.

The CheckMate 816 trial was the first phase 3 study to show a benefit of neoadjuvant combination PD-1 blockade plus chemotherapy in early-stage NSCLC. It compared 3 cycles of neoadjuvant nivolumab plus platinum doublet chemotherapy vs neoadjuvant chemotherapy alone followed by resection. The primary endpoints were pCR and event-free survival (EFS).[36] The study enrolled 358 patients with stages IB to IIIA (primary tumor ≥4 cm) NSCLC based on the 7th edition of the American Joint Commission on Cancer TNM staging system. The study met its primary endpoints, with pCR achieved in 24% of patients in the combination arm (95% CI, 18.0-31.0) vs 2.2% of those in the control arm (95% CI, 0.6-5.6). This translated to a significant EFS benefit of 31.6 months (95% CI, 30.1 to not reached) vs 20.8 months (95% CI, 14.0-26.7) in the combination and monotherapy arms, respectively. The first interim analysis of the secondary endpoint of OS demonstrated an HR of 0.57 (95% CI, 0.38-0.87), which has not yet reached the prespecified margin for significance.[36] Surgical outcomes reported higher rates of minimally-invasive surgery, fewer pneumonectomies, more R0 resection, and shorter operations in the combination arm. CheckMate 816 is a neoadjuvant-only study, with no mandated postoperative treatment (although patients were permitted to receive adjuvant chemotherapy or radiation at investigator discretion). All other ongoing phase 3 trials in this population include an adjuvant immunotherapy phase. This trial resulted in a new standard of care following FDA approval in March 2022.[36] In terms of tolerability, overall TRAEs were similar in the combination and monotherapy arms, at 82% vs 89%, respectively, and 34% vs 37% for grade 3 or higher TRAEs, respectively.

The NADIM II study further supports the combination of ICI and chemotherapy in the neoadjuvant setting.[37,38] This multicenter phase 2 study randomized 86 patients with stages IB to IIIB in a 2:1 ratio to receive either the combination of chemotherapy (carboplatin + paclitaxel) with nivolumab or chemotherapy alone, followed by surgical resection and 6 months of adjuvant nivolumab in the experimental arm. Of note, 34.5% and 36.8% of patients had multistation N2 disease in the monotherapy and combination arms, respectively. NADIM II reported a pCR rate of 36.8% in the combination arm vs 6.9% with chemotherapy alone, and an MPR rate of 52.6% in the combination arm vs 13.8% with chemotherapy alone. A total of 93% of the patients in the combination arm and 69% in the monotherapy arm proceeded to surgical resection, and grade 3 or higher AEs occurred in 25%

Table 3. Phase 3 Trials of Neoadjuvant Combination Chemotherapy + Immune Checkpoint Blockade

Trial (identifier)	Stage	No. of patients	Backbone	Intervention	Adjuvant ICI	Primary end-point(s)	pCR	EFS
CheckMate 816[36] (NCT02998528)	IB-IIIA (7th)	360	3 cycles of cisplatin or carboplatin + vinorelbine, pemetrexed, gemcitabine, docetaxel, paclitaxel	+/- nivolumab	None	pCR, EFS	24% vs 2.2%; *P*<.0001	31.6 vs 20.8 mo, HR 0.63, *P*=.0052
KEYNOTE-671[39] (NCT03425643)	IIA-IIIA (8th)	786	4 cycles of cisplatin + pemetrexed, gemcitabine	+ pembrolizumab or placebo	Pembrolizumab, placebo for 1 y	EFS, OS	Not reported	Reported as positive (press release)
IMpower030 (NCT03456063)	II-IIIB (8th)	450	4 cycles of cisplatin or carboplatin + pemetrexed, gemcitabine, nab-paclitaxel	+/- atezolizumab	Atezolizumab, BSC for 1 y	MPR, EFS	Not reported	Not reported
AEGEAN (NCT03800134)	IIA-IIIB (8th)	802	4 cycles cisplatin + gemcitabine, pemetrexed or carboplatin + pemetrexed, paclitaxel	+ durvalumab or placebo	Durvalumab, placebo for 1 y	pCR, EFS	17.2% vs 4.3%; *P*<.0001	Not reached vs 25.9 mo, HR 0.68, *P*=.0039
CheckMate 77T (NCT04025879)	II-IIIB (8th)	452	3-4 cycles cisplatin, carboplatin + pemetrexed, docetaxel, paclitaxel	+ nivolumab or placebo	Nivolumab, placebo for 1 y	EFS	Not reported	Not reported
NEOTORCH (NCT04158440)	II-IIIB (8th)	404	4 cycles cisplatin, carboplatin + pemetrexed, paclitaxel, docetaxel	+ toripalimab or placebo	Toripalimab, placebo for 1 y	EFS, MPR	24.8% vs 1%; *P*<.0001	Not reached vs 15.5 mo, stage III only; HR 0.40, *P*<.0001

7th, 7th edition of the American Joint Commission on Cancer TNM staging system; 8th, 8th edition of the American Joint Commission on Cancer TNM staging system; BSC, best supportive care; EFS, event-free survival; HR, hazard ratio; ICI, immune checkpoint inhibitor; mo, month(s); MPR, major pathologic response; OS, overall survival; pCR, pathologic complete response; y, year.

of those in the combination arm vs 10.3% of those in the monotherapy arm.[38] The 24-month OS data showed a 20% benefit for the chemoimmunotherapy arm, with 85.3% of patients who received chemoimmunotherapy still alive at 24 months vs 64.8% of those who received chemotherapy alone.[37] The results of ongoing phase 3 studies (see Table 3) are pending and are eagerly awaited, along with the results of associated translational studies.

Most recently, the phase 3 AEGEAN study, the first reported perioperative ICI trial, compared perioperative durvalumab (Imfinzi, AstraZeneca) plus neoadjuvant chemotherapy vs neoadjuvant chemotherapy alone in 802 patients with resectable, stages IIA to IIIB NSCLC. Durvalumab was given as 4 preoperative cycles and 12 postoperative cycles. This trial met both its coprimary endpoints: EFS and pCR. At a median follow-up of 11.7 months, median EFS was not reached in patients receiving perioperative durvalumab plus chemotherapy vs a median EFS of 25.9 months in the chemotherapy-alone arm (HR, 0.68; 95% CI, 0.53-0.88). The pCR rate also was better in the combination arm than in the chemotherapy-alone arm, at 17.2% vs 4.3%, respectively. A press release reported another phase 3 perioperative ICI trial, KEYNOTE-671, as showing improved EFS with pembrolizumab plus neoadjuvant chemotherapy vs chemotherapy alone.[39] Further data and longer follow-up

on these trial results are keenly awaited, especially in evaluating the effects of adjuvant immunotherapy after neoadjuvant chemoimmunotherapy.

Predictive Biomarkers of Response

Despite advances in treatment options for resectable NSCLC, a significant proportion of patients do not benefit and outcomes remain poor despite multimodal treatment. There is a clinical need for biomarkers to identify patients most likely and unlikely to benefit from neoadjuvant therapy. PD-L1 expression, tumor mutational burden (TMB), and immunophenotype have been proposed as potential biomarkers and evaluated in clinical studies.

The evidence for the use of expression levels of PD-L1, as assessed by immunohistochemistry, as a biomarker for response has yielded mixed results across the neoadjuvant ICI trials to date. The LCMC3, NADIM I, and NEOSTAR studies showed an association between MPR rate and PD-L1 expression.[25,28,30,34] However, no significant association was seen between MPR rate and PD-L1 expression in a study by Shu and colleagues and in the SAKK 16/14 trial.[40,41] In NADIM II, patients with a pCR had a higher PD-L1 score than non-pCR patients, and the pCR rate rose across increasing PD-L1 scoring categories (<1%, 14.3%; 1%-49%, 41.7%; ≥50%, 61.1%; P=.008).[38] Similarly, pCR rates after chemoimmunotherapy in the CheckMate 816 trial were augmented with increasing PD-L1 expression, with the greatest benefit observed in patients with a PD-L1 expression level of at least 50% (a pCR rate of 45%).[36] Therefore, the PD-L1 level has the potential to be informative in the clinical setting, and should be evaluated in all patients who are newly diagnosed with NSCLC.

Multiple trials have assessed TMB as a biomarker, and mixed results have been seen both in early-stage and advanced NSCLC. TMB is not a viable biomarker for patient selection at present. Although an early-phase trial demonstrated an association between high TMB and MPR at surgery in 11 patients,[42] multiple subsequent studies with larger sample sizes, including LCMC3 and CheckMate 816, showed no significant correlation with survival or pathologic response.[36,43]

The current use of PD-L1 expression and TMB as biomarkers for the use of ICIs in the management of NSCLC remains controversial in current clinical practice,[44] as their power to identify patients achieving an MPR or pCR is modest. The immunophenotype is the evaluation of the composition and phenotype of peripheral immune cell subpopulations and plasma factors in the peripheral blood, and has been evaluated as a potential complementary biomarker.[45] In the NADIM and LCMC3 trials, patients achieving a pCR seem to have a distinctive peripheral blood immune status at diagnosis, even showing different immune response to treatment.[45,46] Ongoing studies are evaluating the role of immunophenotyping, but it remains experimental.

Assessment of Response

Accurate assessments of tumor response to treatment that predict long-term outcomes are essential for effective and efficient patient care. Several ways to assess response to treatment based on pathology, imaging, and liquid biopsy have been developed, although their respective roles in neoadjuvant NSCLC treatment remain to be fully elucidated.

There is a strong association between pCR and survival following neoadjuvant chemotherapy that has been shown across studies (HR for survival, 0.49; 95% CI, 0.43-0.56).[47] Pathologic responses may guide future treatment decisions, and biospecimens obtained during surgery enable translational studies that may guide future drug and biomarker development. Both pCR and MPR are being studied as possible surrogate endpoints for OS in early-stage NSCLC, with retrospective analyses showing a correlation between MPR and long-term survival.[48] The benefits of surrogate endpoints include shorter study duration and smaller sample size requirements. They also led to earlier trial reporting, which allows more rapid improvements in patient care and outcomes. The follow-up and mature data from the studies presented in Tables 1 to 3 will aid in the validation of these endpoints for potential surrogacy.

Computed tomography and ^{18}F-fluorodeoxyglucose–positron emission tomography/computed tomography are considered the gold-standard imaging modalities for staging and assessing response in NSCLC using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. These modalities remain pivotal in assessing treatment outcomes. However, accurate measurement by imaging remains challenging with immunotherapy because changes in tumor size may be affected by immune infiltration and/or stromal and inflammatory cell responses.[49] Therefore, discontinuation of ICI treatment on the basis of RECIST criteria alone is premature. For example, in the NEOSTAR trial, 16% of patients treated with ICIs had "nodal immune flare" on preoperative imaging, with radiologically abnormal nodes following therapy that upon pathologic evaluation were devoid of cancer and demonstrated de novo noncaseating granulomas.[30] Several studies have shown that clinical responses based on imaging are poorly associated with pathologic response or long-term survival.[50,51] Advances in artificial intelligence and imaging techniques may lead to improved accuracy in

the future and aid in clinical decision-making.

The analysis of circulating tumor DNA (ctDNA) is evolving in many cancer types, and is emerging as a potential surveillance and predictive tool in the perioperative setting. The CheckMate 816 group showed that clearance of ctDNA was more likely when nivolumab was given with chemotherapy (56%) vs chemotherapy alone (34%). Additionally, pCR was more likely to be achieved with clearance of ctDNA (46% pCR rate in patients with ctDNA clearance vs 13% in those without it). Furthermore, patients with pCR and clearance of ctDNA were more likely to undergo complete surgical resection.[36] In the NADIM phase 2 trial, both pre- and post-treatment ctDNA levels were significantly associated with progression-free survival and OS.[52] ctDNA levels after neoadjuvant treatment outperformed radiologic assessment of response (by RECIST criteria) in predicting survival.[52] In the adjuvant setting, IMpower010 investigators reported that the detection of ctDNA after resection and before adjuvant therapy was significantly correlated with inferior DFS.[53] However, the optimal methods to quantify ctDNA and to counteract issues such as clonal hemopoiesis are not well established. Therefore, measurement of ctDNA levels is not yet directly applicable to clinical care of patients with early-stage lung cancer, and additional translational research is warranted to define the role of ctDNA in this setting.

Future Directions

A rapidly evolving treatment landscape is unfurling in the management of early-stage NSCLC, with many questions yet to be resolved. These include defining the optimal neoadjuvant regimens, the duration of the neoadjuvant phase prior to the planned surgical resection, the role of adjuvant therapy, and the significance of predictive biomarkers in patient selection. Additionally, as successful neoadjuvant therapies are evaluated in locally advanced NSCLC, the debate over what is considered technically and medically resectable disease becomes increasingly complicated, highlighting the importance of multidisciplinary tumor boards in case-by-case treatment planning. Furthermore, the validation of surrogate endpoints, such as MPR and pCR, will hopefully allow a significantly more rapid translation of research advances into standard patient care. A promising future lies ahead of findings that have growing potential to further tailor and personalize treatment.

Conclusion

In conclusion, neoadjuvant immunotherapy represents a major advance in the management of early-stage NSCLC and has been shown to be safe, efficacious, and feasible. Preoperative chemoimmunotherapy induces a pCR in 24% of patients, with a median EFS benefit approaching 1 year. It also has the potential to make marginally resectable tumors, which may have originally required pneumonectomy, eligible for lung-sparing surgery without increased drug toxicity. Although adjuvant immunotherapy has become a new standard of care for some patients, more data are needed for appropriate patient selection. To effectively manage our patients with lung cancer, institutional processes must ensure timely biopsy and sufficient tissue acquisition. These changes will enable PD-L1 expression testing and NGS for oncogene driver alterations, primarily in *EGFR* and *ALK*, in all patients with NSCLC given the therapeutic implications. Our treatment paradigm will continue to evolve based on the outcomes of ongoing trials, mature data from reported trials, and the outcomes of the extensive translational work. The potential benefit of these advances should be amplified by the adoption of lung cancer screening programs, with an expected increase in early-stage diagnoses of NSCLC. After a long period of therapeutic stagnation in early-stage disease, these advances offer a significant step forward and a chance to cure more patients with NSCLC by reducing the mortality and morbidity associated with resectable lung cancer.

Disclosures

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