Editorial Commentary

Optimizing the role of immunotherapy in the management of resectable non-small cell lung cancer

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Early-stage and regional (stages I–III) non-small cell lung cancer (NSCLC) represents approximately 40–45% of new NSCLC diagnoses in the United States (1). Surgical resection with curative intent is the cornerstone of therapy for early-stage NSCLC. However, recurrence and mortality rates remain high, with median survival historically ranging from 57 months for stage I–II disease to 12 months for stage III NSCLC (2). The addition of adjuvant platinum-based chemotherapy is associated with a modest 5% absolute improvement in overall survival (OS) and has remained the standard of care for several years (3). A similar magnitude of benefit is observed with neoadjuvant chemotherapy for resectable NSCLC (4). During the same period, the treatment paradigm for advanced NSCLC has evolved rapidly with the use of immunotherapy with or without chemotherapy, resulting in higher response rates and an improvement in survival (5). The spotlight now returns to early-stage and regional NSCLC with several trials underway to incorporate immune checkpoint inhibitors (ICIs) in the neoadjuvant, adjuvant, and perioperative settings.

The benefit of adding an ICI to multimodality therapy for non-metastatic NSCLC was first demonstrated by the randomized, placebo-controlled phase III PACIFIC trial, which evaluated the anti-programed death-ligand 1 (PD-L1) antibody, durvalumab, in patients with unresectable stage III NSCLC without disease progression after concurrent chemoradiotherapy, and showed an improvement in progression-free survival and OS compared with placebo (6,7). Subsequently, the phase III IMpower-010 and KEYNOTE-091 trials established a role for the ICIs, atezolizumab, and pembrolizumab, respectively, in the post-operative management of early-stage resected NSCLC due to a substantial improvement in disease-free survival compared with placebo (8,9).

Adding ICIs in the adjuvant setting can reverse the immunosuppressed environment associated with post-surgical stress (10), and potentially decrease the chances of disease recurrence by enhancing anti-tumor immunity, ultimately improving clinical outcomes as demonstrated in the IMpower-010 and KEYNOTE-091 trials (8,9). A strong case can also be made for using ICIs in the neoadjuvant setting. Potential advantages include enhanced antitumor immune response and improved tolerability in patients who have not previously received chemotherapy, earlier treatment of micrometastatic disease, the ability to downstage tumor and improve the chances of complete resection, and the ability to assess pathological response at the time of surgery (11). A more robust systemic antitumor immune response from neoadjuvant therapy can also potentially occur due to a higher tumor antigen load from an unresected tumor, which can generate a stronger tumor antigen-specific T cell response compared with the post-resection setting (12). Proof-of-concept was obtained

Table 1 Phase III trials evaluating perioperative immunotherapy for potentially resectable NSCLC

Trial name	Trial ID	Stage	Treatment	Primary endpoints	Median EFS (months)	pCR (%)	mPR (%)	Median OS (months)	ORR (%)	Participants undergoing in-trial surgery (%)
KEYNOTE-671	NCT03425643	II–IIIB	Pe + C > S > Pe; Pl + C > S > Pl	EFS and OS	Not reached; 17.0	18.1; 4.0	30.2; 11.0	Not reached; 45.5	NR; NR	82.1; 79.4
CHECKMATE 77T	NCT04025879	IIA–IIIB	N + C > S > N; Pl + C > S > Pl	EFS	Not reached; 18.4	25.3; 4.7	35.4; 12.1	NR	NR; NR	78.0; 77.0
AEGEAN	NCT03800134	II–IIIB	D + C > S > D; Pl + C > S > Pl	EFS and pCR	Not reached; 25.9	17.2; 4.3	33.3; 12.3	NR	56.3; 38.0	80.6; 80.7
NEOTORCH*	NCT04158440	II–III	T + C > S > T + C > T; Pl + C > S > Pl + C > Pl	EFS and mPR	Not reached; 15.1	24.8; 1.0	48.5; 8.4	NR	NR; NR	NR; NR

*, data reported for participants with stage III disease. NSCLC, non-small cell lung cancer; EFS, event-free survival; pCR, pathologic complete response; mPR, major pathologic response; OS, overall survival; ORR, objective response rate; Pe, pembrolizumab; C, chemotherapy; S, surgery; Pl, placebo; NR, not reported; N, nivolumab; D, durvalumab; T, toripalimab.

from phase II clinical trials of neoadjuvant nivolumab with or without chemotherapy in resectable NSCLC, which demonstrated an improvement in pathological complete response (pCR) rates and survival compared with chemotherapy alone (13-15). These findings were confirmed by CheckMate-816, an open-label, randomized phase III study where patients with resectable stage IB–IIIA NSCLC received three cycles of platinum-doublet chemotherapy with or without nivolumab followed by definitive surgery. The co-primary endpoints were event-free survival (EFS) and pCR. Among the randomized patients, 83.2% underwent definitive surgery in the chemoimmunotherapy group *vs.* 75.4% in the chemotherapy-alone group. The EFS was 31.6 months with chemoimmunotherapy *vs.* 20.8 months with chemotherapy alone [hazard ratio (HR) =0.63; 97.38% confidence interval (CI): 0.43–0.91; P=0.005]. The pCR rate was 24% in the nivolumab-plus-chemotherapy arm *vs.* 2.2% in the chemotherapy-alone arm (odds ratio =13.94; 99% CI: 3.49–55.75; P<0.001) (16).

The next step in the development of ICIs for the management of resectable NSCLC is to identify the role of these drugs during the perioperative period. Several recently completed or ongoing trials have been designed to evaluate the use of ICIs in the neoadjuvant and adjuvant setting compared with the use of immune checkpoint inhibition during either period alone (*Table 1*).

Efficacy and safety data from a prespecified first interim analysis of the phase III, randomized, double-blind trial, KEYNOTE-671, were reported recently (17). Participants with resectable stage II–IIIB NSCLC received four cycles of neoadjuvant cisplatin-based chemotherapy with pembrolizumab or placebo, followed by surgical resection and adjuvant pembrolizumab or placebo for up to 13 cycles. The dual primary endpoints were EFS and OS. Secondary endpoints included major pathologic response (mPR), pCR, and safety. As observed in previous studies of chemoimmunotherapy in the neoadjuvant setting, approximately 80% of participants were successfully able to undergo surgery. Most participants underwent a lobectomy (78.8% *vs.* 75.1%), and the rate of complete resection was higher in the pembrolizumab arm (92% *vs.* 84.2%). With a median follow-up of 25.2 months, the 24-month EFS was 62.4% in the pembrolizumab group *vs.* 40.6% in the placebo group. Median EFS was not reached in the pembrolizumab group *vs.* 17 months in the placebo group (HR =0.58; 95% CI: 0.46–0.72; P<0.001). Estimated survival at 24 months was 80.9% in the pembrolizumab arm *vs.* 77.6% in the placebo group. Rates of pathological response were higher in participants who received chemoimmunotherapy (mPR 30.2% *vs.* 11%, pCR 18.1% *vs.* 4%). An exploratory analysis showed an EFS benefit in the chemoimmunotherapy arm regardless of the degree of pathologic response. Clinical benefit was observed across various subgroups, although the magnitude of benefit varied. Notably, participants with stage III disease and PD-L1-expressing tumors derived greater benefit with the addition of pembrolizumab (HR for event or death, 0.54 *vs.* 0.65, and 0.47 *vs.* 0.77, respectively). Treatment-

related adverse event (TRAE) rates were comparable; however, there were higher rates of adverse events (AEs) leading to discontinuation of all study treatments in the pembrolizumab arm (12.5% *vs.* 5.3%). Immune-related AEs (irAEs) and infusion reactions occurred more often in the pembrolizumab arm (25.3% *vs.* 10.5%). The most common irAEs were hypothyroidism, hyperthyroidism, pneumonitis, and skin rash.

Results from three other phase III trials of perioperative chemoimmunotherapy show similar results. The CheckMate 77T trial is a randomized, double-blind, phase III trial evaluating four cycles of platinum-doublet chemotherapy with nivolumab or placebo, followed by surgery and one year of adjuvant nivolumab or placebo in 461 participants with untreated, resectable stage IIA (>4 cm) –IIIB (N2), *EGFR/ALK* wild-type NSCLC (18). A prespecified interim analysis shows an improvement in EFS with chemoimmunotherapy [mEFS not reached *vs.* 18.4 months (HR =0.58; 97.36% CI: 0.42–0.81; P=0.00025)] and pCR rate (25.3% *vs.* 4.7%, odds ratio =6.64; 95% CI: 3.40–12.97). A similar proportion of participants in both arms were able to undergo definitive surgery and no new safety signals were observed. The AEGEAN trial is a randomized, double-blinded, phase III study evaluating four cycles of platinum-based chemotherapy with either durvalumab or placebo, followed by surgery and up to 12 cycles of adjuvant durvalumab or placebo in 802 individuals with stage IIA–IIIB NSCLC with no documented *EGFR* or *ALK* alterations (19). Treatment was associated with a manageable safety profile and 77.6% of participants in the chemoimmunotherapy arm completed surgery as planned. There was a marked improvement in EFS and pCR rate for participants receiving chemoimmunotherapy [mEFS not reached *vs.* 25.9 months (HR =0.68; 95% CI: 0.53–0.88; P=0.004), pCR 17.2% *vs.* 4.3%]. The Neotorch trial is a randomized, double-blind, placebo-controlled, phase III trial underway in China to evaluate the safety and efficacy of the anti-PD-L1 antibody, toripalimab with chemotherapy as neoadjuvant therapy for resectable stage II–III NSCLC without *EGFR* and *ALK* alterations followed by surgical resection and toripalimab maintenance *vs.* placebo for 13 cycles (20). Results from a planned interim analysis of EFS in 404 participants with stage III NSCLC showed an improvement in EFS in the toripalimab arm (median EFS not reached *vs.* 15.1 months; HR =0.40; 95% CI: 0.277–0.565; P<0.0001). Rates of pathological response were also higher in participants receiving toripalimab (pCR 24.8% *vs.* 1.0%; mPR 48.5% *vs.* 8.4%). A higher proportion of participants enrolled in this trial had squamous histology (77%) and N2 nodal involvement (70%) in comparison to similar trials. An improvement in EFS was observed across all subgroups. OS results are reported to show a trend in favor of the toripalimab arm.

Taken together, these emerging data support a role for ICIs in the perioperative management of resectable NSCLC without actionable genomic alterations. However, despite these promising results, several issues need to be addressed to further improve patient outcomes and realize the full potential of perioperative immune checkpoint inhibition. First, compared with chemotherapy alone, chemoimmunotherapy is associated with a greater risk of high-grade AEs, including TRAEs that result in discontinuation of treatment in approximately 10% of patients (17,20). Approximately 18–20% of patients in the chemoimmunotherapy arms of trials evaluating perioperative immune checkpoint inhibition were unable to undergo surgery as planned. In the KEYNOTE-671 trial AEs were responsible for more than a third of these cases (17). Since surgical resection with curative intent is a major predictor of long-term outcomes in patients with early-stage NSCLC, the inability to undergo surgery as planned after chemoimmunotherapy is a matter of concern. An analysis of AEs from ongoing trials that resulted in discontinuation of treatment or delay in surgery can help in determining if baseline evaluation of blood counts or serological markers can identify patients at risk for severe irAEs, and in developing preemptive strategies for the management of these toxicities. For example, an early decrease in circulating B-cells has been shown to be associated with an increased risk of developing irAEs (21). Second, although clinical benefit is observed across subgroups in ongoing trials evaluating perioperative ICIs, the magnitude of benefit is variable and only a minority of patients achieve a pathologic response at the time of surgery. These issues highlight the need to improve patient selection in order to identify individuals most likely to benefit from treatment and several avenues are ripe for consideration. An improved understanding of the molecular determinants of response to ICIs and routine use of next-generation sequencing to uncover the genomic profile of NSCLC supports mandatory molecular testing prior to consideration of perioperative immunotherapy and a prospective evaluation for mutations such as *KEAP1* and *STK11* that are known to confer resistance to immunotherapy (22). The use of novel combinatorial strategies should also be considered to improve the clinical

activity of perioperative immunotherapy. Pre-clinical and clinical data show increased antitumor activity of ICIs in combination with anti-angiogenic agents (23). Future clinical trials for resectable NSCLC should investigate the role of anti-angiogenic therapy in combination with chemoimmunotherapy in the perioperative setting. Third, the use of circulating tumor DNA (ctDNA) to accurately identify response to chemoimmunotherapy can also be considered. Results from the CheckMate-816 trial showed that patients with ctDNA clearance had a longer EFS and a greater likelihood of achieving an mPR (16). Finally, a shared limitation of ongoing trials of perioperative chemoimmunotherapy is that the study design does not permit assessment of the relative contribution of the preoperative and postoperative phases of treatment to clinical outcomes. Future trials should be designed to address this question to help optimize the treatment regimen, especially as it relates to the duration of therapy in the postoperative period. In the meantime, the results of the KEYNOTE-671 trial support a role for ICIs in the perioperative management of resectable NSCLC, and data from other ongoing trials of perioperative immunotherapy will be eagerly awaited.

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