Editorial Commentary

The beginning of the perioperative immunotherapy era in early-stage non-small cell lung cancer

Ivy Riano[1]^, Konstantin H. Dragnev[1], Joseph D. Phillips[2]

[1]Section of Hematology and Medical Oncology, Dartmouth Cancer Center, Dartmouth Health, Geisel School of Medicine at Dartmouth, Lebanon, NH, USA; [2]Section of Thoracic Surgery, Department of Surgery, Dartmouth Health, Geisel School of Medicine at Dartmouth, Lebanon, NH, USA
Correspondence to: Ivy Riano, MD. Section of Hematology and Medical Oncology, Dartmouth Cancer Center, Dartmouth Health, Geisel School of Medicine at Dartmouth, 1 Medical Drive Street, 03766 Lebanon, NH, USA. Email: ivy.riano@dartmouth.edu.
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The addition of an immune checkpoint inhibitor (ICI) to standard chemotherapy emerged as a promising therapeutic strategy in patients with advanced non-small cell lung cancer (NSCLC) resulting in significant longer overall survival (OS) and progression-free survival (PFS) compared to chemotherapy alone (1-3). As consequence, nivolumab and pembrolizumab were approved by the U.S. Food and Drug Administration (FDA) for second-line treatments of advanced NSCLC. Later, atezolizumab was confirmed for the same indication, and pembrolizumab was approved in first-line settings as a monotherapy for patients with NSCLC whose tumors have high programmed death ligand-1 (PD-L1) expression [tumor proportion score (TPS) ≥50%] and in combination with platinum-based chemotherapy for patients with metastatic non-squamous NSCLC, regardless of PD-L1 expression. Subsequently, the phase 3 PACIFIC trial demonstrated the efficacy and safety of concurrent chemoradiotherapy followed by consolidation durvalumab as a definitive treatment modality for unresectable, stage III NSCLC, as curable disease (4). This was the first treatment in decades to successfully improve survival in this clinical setting [median OS, 47.5 in durvalumab group *vs.* 29.1 months in placebo group; hazard ratio (HR) =0.72; 95% confidence interval (CI): 0.59–0.89] (5), increasing the need for coordinated decision-making among lung cancer specialists.

Surgery has been the cornerstone of curative treatment for early-stage NSCLC, demonstrating 5-year survival rates ranging from 41% for stage IIIA disease to 92% for stage IA1 (6). To improve those outcomes, adjuvant platinum-doublet chemotherapy became the standard-of-care for these settings. Although adjuvant therapy aims to decrease micrometastatic disease and prevent recurrence, the 5-year survival rates are only 4–5% higher than observation alone (7), leaving 'room' for clinical improvement.

The use of ICIs in perioperative settings (neoadjuvant and adjuvant) is dramatically transforming therapeutic practice patterns in patients with early-stage NSCLC without a targetable mutation (8-11). Currently, the FDA has approved separately adjuvant and neoadjuvant immunotherapy with platinum-doublet chemotherapy for resectable NSCLC (12,13), yet there is no consensus on the optimal sequence or duration, with multiple additional unanswered clinical questions. In this Editorial, KEYNOTE-671 trial will be discussed along with key phase 3 trials.

Adjuvant immunotherapy era

IMpower010 trial was the first phase 3 immunotherapy

^ ORCID: 0000-0002-3312-286X.

study to demonstrate a statistically significant disease-free survival (DFS) benefit with adjuvant atezolizumab *vs.* best supportive care in resected NSCLC following platinum-based chemotherapy (HR =0.79; 95% CI: 0.64–0.96; P=0.020) (14). More pronounced benefits were observed in the subgroup whose tumors expressed PD-L1 on ≥1% of tumor cells (TC) (HR =0.66; 95% CI: 0.50–0.88; P=0.0039). Grade 3–4 adverse events (AEs) occurred in 21.8% of patients in the atezolizumab arm *vs.* 11.5% in the chemotherapy-alone arm (15).

This study led to the FDA approval of adjuvant atezolizumab following resection and platinum-based chemotherapy in patients with stages II–IIIA NSCLC whose tumors express PD-L1 on ≥1% of TC (16). In contrast, the European Medicines Agency (EMA) considers patients for adjuvant atezolizumab if their PD-L1 levels are ≥50% without a targetable mutation (17). Updates on IMpower010 might clarify the characteristics of patients who would benefit from this approach. For now, results from the first interim OS analysis indicates a positive trend favoring atezolizumab in the PD-L1 ≥50% of TC in stages II–IIIA (HR =0.43; 95% CI: 0.24–0.78) (18). While the highest magnitude of OS was observed in patients whose TC had PD-L1 expression of ≥50%, patients with PD-L1 <50% would benefit from enrollment in clinical trials if possible. These results support that PD-L1 cutoff should be considered to select patients for adjuvant atezolizumab as well as the need to improve survival in the PD-L1 0% and 1–49% subgroups.

Based on PEARLS/KEYNOTE-091 results (19), pembrolizumab was also approved by the FDA for adjuvant treatment following resection and platinum-based chemotherapy in stages IB–IIIA NSCLC (12). With this approval, pembrolizumab became the only immunotherapy accepted for NSCLC regardless of PD-L1 expression, in both, adjuvant and metastatic settings. PEARLS/KEYNOTE-091 phase 3 shown an improvement in the median DFS of 53.6 months [95% CI: 39.2–not reached (NR)] for patients who received pembrolizumab *vs.* 42.0 months (95% CI: 31.3–NR) for those who received placebo (HR =0.76; 95% CI: 0.63–0.91; P=0.0014). Grade 3–5 AEs occurred in 34% of the patients in the pembrolizumab arm *vs.* 26% in the placebo arm (19).

Notably, all these approvals were based on surrogate endpoints, with varying levels of OS data, some more promising than others. PEARLS/KEYNOTE-091 and IMpower010 trials provided valuable contributions into the field of adjuvant treatment of early-stage NSCLC. In contrast to IMpower010, PEARLS/KEYNOTE-091 showed no statistical benefit of pembrolizumab in patients with high tumor PD-L1 expression (HR =0.82; 95% CI: 0.57–1.18; P=0.14), neither benefit in patients with squamous NSCLC (HR =1.04) *vs.* nonsquamous NSCLC (HR =0.67) (19). Moreover, PEARLS/KEYNOTE-091 trial showed no benefit for patient with anaplastic lymphoma kinase (*ALK*) (20) translocation or epidermal growth factor receptor (*EGFR*) mutations regardless of the PD-L1 expression, whereas IMpower010 showed a benefit for patients with *EGFR* mutations if they had high PD-L1 levels. Certainly, there is no clear pattern of best benefit for those with higher tumor PD-L1 expression, as we have seen in many other trials of adjuvant therapy, and current data is not sufficient to support these conclusions. Thus, to determine whether adjuvant immunotherapy is beneficial, and for which patients, mature OS data is needed. In the meantime, the question remains as to how we can prioritize these available treatment options for the patients. We must therefore carefully discuss with our patients whether the benefits of immunotherapy justify the additional costs and risks.

Neoadjuvant immunotherapy

Neoadjuvant therapy in resected NSCLC aims to downstage tumors, increase R0 rates, and treat subclinical micrometastases at the earliest stage (17). CheckMate-816 was the first phase 3 trial to show a benefit of the neoadjuvant immunotherapy plus chemotherapy combination for resectable NSCLC over standard chemotherapy (9). As compared with previous preoperative strategies, CheckMate-816 trial showed a promising improvement in OS (HR =0.57; nonsignificant for OS at interim analysis) (9,21). The combination of neoadjuvant nivolumab and platinum based-chemotherapy also resulted in a significant improvement of event-free survival (EFS), pathological complete response (pCR) and major pathological response (MPR) (*Table 1*). Adding nivolumab did not increase AEs; 33.5% of patients in the nivolumab-plus-chemotherapy group *vs.* 36.9% in the chemotherapy-alone group experienced grade ≥3 AEs. Additionally, surgery-related AEs or surgical feasibility were not affected by the addition of nivolumab to chemotherapy (9). CheckMate-816 data granted the first FDA approval for neoadjuvant nivolumab in patients with resectable NSCLC; three cycles are now recommended for neoadjuvant chemo-immunotherapy. Yet, the duration has not been fully

elucidated.

Several other phase 1/2 trials have advanced neoadjuvant immunotherapy, including (I) neoadjuvant single-agent immunotherapy CheckMate-159, LCMC3, and TOP1501 trials, where immunotherapy was given for 2 cycles, and surgery performed 28–56 days after the first cycle; (II) neoadjuvant chemo-immunotherapy including NADIM, and SAKK 16/14 studies; and (III) dual immunotherapy in NEOSTAR trial administered for 2–4 cycles (17). The publication of these trials led to an increasing interest in perioperative immunotherapy, shifting the treatment paradigm of resectable NSCLC toward a neoadjuvant approach.

Perioperative immunotherapy (neoadjuvant + adjuvant)

The ultimate goal of early-stage NSCLC should be to improve OS. While previous data support the potential of neoadjuvant chemoimmunotherapy as a new standard of care in patients with early-stage NSCLC, the clinical value of immunotherapy in the postoperative setting remains unclear. As the CheckMate-816 trial did not include any immunotherapy as adjuvant treatment, several trials including the AEGEAN (10), Neotorch (11) and KEYNOTE-671 (8) have been designed to add this component in the postoperative period. However, only KEYNOTE-671, included OS as a co-primary endpoint.

The phase 3 AEGEAN trial enrolled patients to receive durvalumab in combination with neoadjuvant chemotherapy before surgery and as adjuvant monotherapy after surgery (10). This was a positive trial that showed a 32% improvement in EFS and a HR of 0.68. Furthermore, it showed statistically significant improvement in pCR of 17.2% in the perioperative durvalumab arm *vs.* 4.3% in the placebo group (difference 13.0%; 95% CI: 8.7–17.6%; P=0.000036) (10). The median follow-up was only 11.7 months, so the data are still preliminary. Although the AEGEAN results raised the question of how to use neoadjuvant and adjuvant therapy, as clinicians already use neoadjuvant therapy, they were not clearly superior to those of CheckMate-816 trial (9).

The phase 3 Neotorch trial, conducted in China, evaluated pre- and postoperative toripalimab, a monoclonal antibody against programmed death protein-1 (PD-1), plus chemotherapy followed by toripalimab maintenance in stages II–III NSCLC (11). An interim analysis conducted only in patients with stage III disease showed that perioperative toripalimab-plus-chemotherapy led to a 60% reduction in the risk of EFS as compared with perioperative chemotherapy alone (HR =0.40; 95% CI: 0.277–0.565; P<0.0001). Rates of MPR and pCR were significantly improved with the use of toripalimab (*Table 1*) (11). This study adds to data supporting the role of perioperative treatment with immunotherapy in patients with resectable NSCLC, but it does not clarify if the addition of adjuvant immunotherapy could achieve higher clinical benefits than neoadjuvant immunotherapy alone, as demonstrated with the CheckMate-816 trial (9).

The phase 3 KEYNOTE-671 trial was designed to answer a similar question with pembrolizumab. Patients with resectable, untreated stages II–IIIB (N2) NSCLC were enrolled to receive neoadjuvant pembrolizumab-plus-platinum-doublet chemotherapy (n=397) for 4 cycles or placebo (n=400) followed by surgery and adjuvant pembrolizumab therapy or placebo for up to 13 cycles. Baseline patients' characteristics were balanced between arms; approximately 70% of patients had stage III disease (8). Results demonstrated a clinically meaningful improvement in EFS at 25.2 months in the pembrolizumab group compared with the placebo group with a HR of 0.58 (62.4% *vs.* 40.6%, respectively; 95% CI: 0.46–0.72; P<0.001). The OS data was also encouraging, but there have not been enough events to make a statistical conclusion. Compared with chemoimmunotherapy alone, adding perioperative pembrolizumab was also associated with significant improvements in MPR (30.2% *vs.* 11.0%; P<0.0001), and pCR rates (18.1% *vs.* 4.0%; P<0.0001) (8). As a result of long follow-up, we may have a better understanding of the relative contribution of the adjuvant component to the perioperative immunotherapy regimen (8).

The benefits of perioperative pembrolizumab were also seen across all different subsets (8). For histology, the HRs were 0.58 for nonsquamous and 0.57 for squamous, both favoring pembrolizumab. There was a greater benefit in patients with high PD-L1 expression and in those with higher-stage disease. For instance, the improvement of EFS was more prominent in patients with PD-L1 status TC ≥1% compared with PD-L1 <1%. When stratified by stage, the patients with stage III had a trend toward significant better EFS (HR =0.54) as compared with stage II group (HR =0.65). While not statistically significantly different, these data at least raise the possibility that greater clinical benefit of perioperative immunotherapy may occur in tumors with PD-L1 status ≥1% and stage III disease (8). Although patients with stage III disease are most likely to benefit from

Table 1 Most-relevant phase 3 clinical trials with adjuvant and neoadjuvant immunotherapy components in patients with resectable NSCLC

Trial	ICI	Phase	Arms	Staging	No. of patients	DFS (months, adjuvant); EFS (months, neoadjuvant)	MPR	pCR	OS	≥ Grade 3 adverse events	Adverse events leading to surgery cancellation
Key trials with adjuvant component											
IMpower010	Atezolizumab	3	After 4 cycles of platinum doublet chemotherapy, atezolizumab *vs.* best supportive care	IB to IIIA	1,280	Stage II–IIIA: HR 0.79; 95% CI: 0.64 to 0.96; P=0.020	–	–	mOS in ITT: not estimable; HR 0.995; 95% CI: 0.78 to 1.28. Stratified OS HRs 0.95; 95% CI: 0.74–1.24 in the stage II–IIIA, 0.71 (0.49–1.03) in the stage II–IIIA PD-L1 ≥1%, 0.43 (0.24–0.78) in the stage II–IIIA PD-L1 ≥50%	Atezolizumab-related grade 3 and 4 adverse events: 11%, and grade 5 events: 1%	–
PEARLS/ KEYNOTE-091	Pembrolizumab	3	Pembrolizumab *vs.* placebo	IB to IIIA	1,177	53.6 (95% CI: 39.2 to NR) *vs.* 42 (31.3 to NR) (HR 0.76; 95% CI: 0.63 to 0.91; P=0.0014)	–	–	–	34% *vs.* 26%	–
Key trials with neoadjuvant component											
CheckMate-816	Nivolumab	3	Nivolumab + platinum-based chemotherapy *vs.* chemotherapy alone, followed by resection	IB to IIIA	773	NR (31.6 to NR) *vs.* 20.8 (HR* 0.63; 97.38% CI: 0.43–0.91; P=0.005)	36.9% *vs.* 8.9% (OR 5.70; 95% CI: 3.16–10.26)	24.0% *vs.* 2.2% (OR 13.94; 99% CI: 3.49–55.75; P<0.001)	NR (HR 0.57; 99.67% CI: 0.30–1.07; P=0.079)	33.5% *vs.* 36.9%	2 *vs.* 1 patient
Key trials with neoadjuvant and adjuvant components											
AEGEAN	Durvalumab	3	Durvalumab + platinum-based chemotherapy *vs.* chemotherapy alone, followed by resection, and durvalumab for 1 year	II to IIIB	802	NR *vs.* 25.9 (HR 0.68; 95% CI: 0.53–0.88; P=0.0039)	33.3% *vs.* 12.3% (difference 21.0%; 95% CI: 5.1–26.9%)	17.2% *vs.* 4.3% (difference 13.0%, 95% CI: 8.7–17.6%; P=0.000036, based on interim analysis)	NR	42.3% *vs.* 43.4%	7 *vs.* 4 patients
Neotorch**	Toripalimab	3	Toripalimab + platinum-based chemotherapy *vs.* chemotherapy alone, followed by resection, and toripalimab for 1 year	II to III	404	NR *vs.* 15.1 (HR 0.40, 95% CI: 0.277–0.565, P<0.0001)	48.5% *vs.* 8.4%	24.8% *vs.* 1.0%	NR (HR 0.62, P=0.0502)	63.4% *vs.* 54.0%	Not reported
KEYNOTE-671	Pembrolizumab	3	Pembrolizumab + platinum-based chemotherapy *vs.* chemotherapy alone, followed by resection, and pembrolizumab for 1 year	II to IIIB	797	NR (34.1 to NR) *vs.* 17 (95% CI: 14.3–22.0) (HR* 0.58; 95% CI: 0.46–0.72; P<0.001)	30.2% *vs.* 11.0% (difference, 19.2%; 95% CI: 13.9–24.7%; P<0.0001)	18.1% *vs.* 4.0% (difference, 14.2%; 95% CI: 10.1–18.7%; P<0.0001)	NR (80.9% *vs.* 77.6%, 95% CI: NR, P=0.02)	44.9% *vs.* 37.3%	25 *vs.* 17 patients

*, HR for disease progression, disease recurrence, or death; **, analysis included only patients with stage III disease. NSCLC, non-small cell lung cancer; ICI, immune checkpoint inhibitor; DFS, disease-free survival; EFS, event free survival; MPR, major pathological response; pCR, pathological complete response; OS, overall survival; HR, hazard ratio; CI, confidence interval; mOS, median overall survival; ITT, intention-to-treat; PD-L1, programmed death ligand-1; NR, not reached; OR, odds ratio.

adjuvant systemic treatment (22), the optimal treatment in stage II remains controversial owing to its heterogeneity. Therefore, a multidisciplinary tumor board is needed to determine the appropriate goals of treatment prior to the initiation of neoadjuvant chemoimmunotherapy.

Clinically, it remains unclear whether adding a year of ICI therapy postoperatively is beneficial compared to 3–4 cycles of neoadjuvant chemoimmunotherapy. Moreover, do adverse events occur at higher rate during the neoadjuvant or adjuvant portion of treatment? Unfortunately, neither the incremental benefit nor added side effects of an additional year of immunotherapy can be determined from the trial results. Adjuvant immunotherapy administered every 3 weeks is associated with more frequent clinic visits, elevated health care costs, and potential cumulative immune-related toxicities. Ultimately, every patient should have an evidence-based discussion with their clinicians to decide whether to pursue additional adjuvant immunotherapy or continue with surveillance only.

Surgical considerations

The use of ICIs before surgery remains a topic of ongoing discussions with some uncertainties surrounding surgical feasibility. In the neoadjuvant setting, the advantage of allowing patients enough time to respond to preoperative therapy is paramount, but not at the expense of overly extending loco-regional disease control or potentially curative surgical therapy (23). Neoadjuvant immunotherapy has been shown to be both safe and feasible before curative surgery in most studies (8,10,11). Notably, a high number of patients in the KEYNOTE-671 trial did not undergo in-study surgery (71 patients in the pembrolizumab arm *vs.* 82 in the placebo arm) (8). Physicians' decision, AEs, and radiographic disease progression accounted for this. Yet, some patients receiving neoadjuvant immunotherapy were not initially considered for surgery (stage IIIB N2 node), thus the exclusion for surgical resection could be less.

Additionally, Forde *et al.* (NCT02259621) showed that 2 preoperative doses of nivolumab given to patients with resectable NSCLC were not associated with delays in surgery (24). Similar findings were reported in a phase 2 study (NCT02818920) (25) where 2 cycles of neoadjuvant pembrolizumab were safe and well tolerated. Its use was not associated with excess surgical morbidity or mortality. Pembrolizumab delayed surgery only in one patient due to thyroiditis, and the most common postoperative AEs was atrial fibrillation (24%) (25). Moreover, the phase 2 NADIM study showed a greater percentage of patients in the neoadjuvant nivolumab-plus-chemotherapy group than in the control group who underwent surgery (93% *vs.* 69%), and worse survival outcomes were not observed among patients with N2 disease than among those with N0 or N1 disease (26).

In conclusion, neoadjuvant immunotherapy does not seem to jeopardize the outcomes and feasibility of the surgery. 'Surgical resectability' should be reevaluated after the treatment. Importantly, thoracic surgeons should be actively involved in trial design considering that clinical outcomes will be heavily influenced by patient selection and surgical expertise. Therefore, a multidisciplinary participation in designing this type of trials is encouraged.

Biomarkers

There are no confirmatory biomarkers that uniformly identify patients with resectable NSCLC who might benefit most from neoadjuvant or adjuvant immunotherapy. KEYNOTE-671 trial included patients with known driver mutations (*EGFR* mutations/*ALK* translocations), who historically have been excluded from previous trials. Although the sample was too small (n=33) to make definitive conclusions, EFS was consistently improved in those with *EGFR* mutation (8). Based on current data, it is recommended that neoadjuvant/adjuvant immunotherapy should not be used routinely in patients with *EGFR* mutations/*ALK* fusions (17). Particularly considering the significant benefit of osimertinib in patients with *EGFR* mutations.

Additionally, CheckMate-816 trial showed that ctDNA clearance after neoadjuvant nivolumab had a higher pCR rate, suggesting that ctDNA could be predictive of tumor response (9). In contrast, IMpower010 reported that regardless of whether ctDNA-minimal residual disease was positive or negative, adjuvant atezolizumab could provide DFS benefit (14). Thus, ctDNA remains controversial as a predictive tool. Further research is needed to inform more personalized treatment decisions in neoadjuvant settings.

Conclusions

Results from phase 3 KEYNOTE-671, AEGEAN, and Neotorch trials are not identical, but support the benefits of perioperative ICIs for patients with early-stage NSCLC. The KEYNOTE-671 data supports pembrolizumab as a treatment option in this clinical setting. The positive

news for patients is that there are more regimens that improve clinical outcomes, even though neoadjuvant pembrolizumab has not yet been approved. It will be critical to collect mature survival data to define the role of neoadjuvant immunotherapy in reducing recurrences and curing early-stage cancers. Immune-related AEs are generally manageable and do not exclude patients from surgery. Balancing potential efficacy benefits with toxicity is a shared decision-making with patients and clinicians. Multidisciplinary tumor board discussions are vital for determining the best treatment approach for each patient, considering node involvement, performance status, comorbidities, and geographical disparities. Perioperative immunotherapy for resectable NSCLC is not currently available in some clinical practice worldwide due to the lack of approval or reimbursement, with more experiences coming from clinical trials.

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