Editorial Commentary

Will perioperative pembrolizumab treatment change perioperative treatment strategies for resectable non-small cell lung cancer?

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Surgical resection is the mainstay of treatment for early-stage (stages I–IIIA) non-small cell lung cancer (NSCLC), accounting for approximately 30% of lung cancer cases. However, even with complete resection, recurrence and metastasis occur (1), especially in the more advanced stages of early lung cancer. This may be due to the presence of distant micrometastases at the time of intervention. Therefore, to improve the prognosis of early-stage NSCLC, it is important to eliminate micrometastases using more effective systemic therapies.

Since the 1980s, several studies have shown that cisplatin-based adjuvant chemotherapy after surgical resection in patients with early-stage NSCLC improves surgical resection outcomes and is effective in increasing the 5-year survival rate by only 5% (2), thus being established as the central standard of care for patients with pathological stages II and III NSCLC. Regarding preoperative chemotherapy, many clinical trials were stopped prematurely because of the early establishment of postoperative chemotherapy (3,4); therefore, the efficacy of the latter has not been fully evaluated. However, a meta-analysis of numerous preoperative chemotherapy trials showed that it significantly improved overall survival (OS), time to distant recurrence, and recurrence-free survival (4). Previous preoperative and postoperative meta-analyses suggest that the effects on survival are similar; therefore, it is still unclear whether cisplatin-based chemotherapy should be administered as adjuvant or postoperative chemotherapy for patients with resectable NSCLC.

Recently, immune checkpoint inhibitors (ICIs) targeting the programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) signaling pathway have dramatically improved the prognosis of patients with locally advanced and metastatic NSCLC, changing the treatment framework. ICIs have produced durable responses and prolonged survival in 20–30% of patients with advanced NSCLC (5,6). These results have driven the rapid expansion of ICI-related treatment into perioperative therapy. Regarding perioperative treatment, preoperative ICI could maximize the efficacy of immunotherapy when the primary tumor is still present and has a high neoantigen burden. The presence of the whole tumor enables a broad T cell response owing to exposure to a large repertoire of tumor antigens (7). This approach theoretically allows intact tumors, lymphatic vessels, and draining lymph nodes to successfully prime T cells, efficiently activate systemic tumor immunity, and control small distant metastases (8). ICIs can be used in combination with chemotherapy in neoadjuvant therapy to enhance neoantigen release and promote a more robust immune response. This provides

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reason to expect a difference in the therapeutic effect of ICIs between postoperative and preoperative use, with interest in preoperative treatment growing once again. However, preoperative treatment has limitations that must be overcome. There are several risks, including missed resection in patients whose tumors have not responded to treatment and have progressed and the possibility that adverse events will complicate the continuation of subsequent treatment, including surgery. Losing the opportunity for surgery in operable lung cancer patients should be minimized. Therefore, the treatment strategy must balance the potential benefits and disadvantages of preoperative treatment. For neoadjuvant ICIs as the standard of care, they must be effective (pathologic regression) after induction therapy, safe, have few treatment-related serious adverse events (grade 3 or higher), have a low incidence of unresectable cases after induction therapy, and have little impact on perioperative morbidity and mortality.

Recently, Wakelee *et al.* reported a phase III study of perioperative pembrolizumab for early-stage NSCLC (KEYNOTE-671) (9). It was a double-blind phase III trial that enrolled patients with resectable stage II, IIIA, or IIIB (N2) NSCLC. In this study, 797 patients were randomized at a 1:1 ratio to receive neoadjuvant chemotherapy [cisplatin with gemcitabine (squamous histology type) or pemetrexed (non-squamous histology type)] plus pembrolizumab or placebo for 4 cycles, followed by surgery and adjuvant pembrolizumab or placebo for up to 13 cycles. The dual primary endpoints were event-free survival (EFS) and OS. The key secondary endpoints were pathological complete response (pCR) and major pathological response (MPR). The first interim analysis of EFS was initially reported with median follow-up time of 25.2 months (range, 7.5–50.6 months). The pembrolizumab plus chemotherapy group had a superior EFS at 24 months of 62.4% compared to 40.6% in the placebo group [hazard ratio (HR), 0.58; 95% confidence interval (CI): 0.46–0.72]. OS data were immature but not significant; however, 24-month OS was observed in 80.9% of the patients in the pembrolizumab group and 77.6% in the placebo group (HR, 0.73; 95% CI: 0.54–0.99). In resectable NSCLC, preoperative nivolumab in the CheckMate-816 (10), postoperative pembrolizumab in the KEYNOTE-091 (11), and postoperative atezolizumab in the IMpower-010 (12) studies have already shown efficacy. Perioperative pembrolizumab, may thus also become a new standard of care, but interesting questions remain as to whether ICIs as preoperative or postoperative treatment provide more substantial benefit, whether additional postoperative ICI therapy is necessary after preoperative ICI therapy, and, in the first place, whether preoperative and postoperative ICIs should be considered treatment strategies for the same stage group.

In the history of the development of preoperative and postoperative treatment with cytotoxic chemotherapy, both strategies the 5-year survival by 5%, with no difference between the two groups. Owing to this, there is still no consensus on the use of cytotoxic chemotherapy, with studies reporting different outcomes. In the NATCH study, treatment compliance differed by 90% in the preoperative group and 60% in the adjuvant chemotherapy group. Preoperative chemotherapy has been reported to be more effective in suppressing distant than local recurrence, suggesting that it reduces micrometastases and increases the likelihood of complete resection (4). Moreover, some preoperative treatment trials have suggested that preoperative chemotherapy has different therapeutic effects, depending on the stage of lymph node metastasis. In the chemotherapy for early stages trial (ChEST), the benefits of neoadjuvant chemotherapy were observed and were statistically significant only in the subgroup of stage IIB to IIIA (HR for OS 0.42; 95% CI: 0.25–0.71) but not in that of stage IB to IIA (HR for OS 1.02; 95% CI: 0.58–1.19) (3). These findings suggest that preoperative chemotherapy is preferred for patients with poor prognosis and larger more advanced-stage tumors who are potentially at a higher risk of micrometastases.

In the KEYNOTE-671 study, approximately 70% of patients were stage III and 45% were N2 cases, with a high proportion of more advanced resectable NSCLC. Subgroup analysis of EFS favored combination therapy with pembrolizumab and chemotherapy in all subgroups. By stage, patients with stage II disease had an HR of 0.65, and those with stage III disease had an HR of 0.54, showing a more pronounced effect in stage III, including N2. This trend was also observed in CheckMate-816. Sixty-four percent of the patients enrolled in the study had stage IIIA disease. From the subgroup analysis by stage, patients with stage IB–II had an HR of 0.87, and those with stage IIIA had an HR of 0.54, showing a more pronounced effect in stage IIIA. A meta-analysis of preoperative chemotherapy and the results of chemotherapy plus ICI in preoperative treatment suggested that preoperative therapy has greater benefit in patients with more advanced resectable NSCLC.

Preoperative treatment in patients with advanced disease is more likely to cause unresectability, which is associated

with treatment failure (10). For a treatment strategy to be successful in this patient population, preoperative treatment should have a stronger short-term therapeutic effect. Although no trials have directly compared ICI combination chemotherapy with ICI monotherapy in metastatic NSCLC, a network meta-analysis showed that the former tended to increase response rates, cause fewer progression events, and prolong progression-free survival (PFS) (13,14). Based on these data, it is reasonable to recommend ICI combination chemotherapy for patients who need to achieve a higher response rate and avoid early progression.

The greatest advantage of preoperative treatment, unlike postoperative treatment, is that the response of the tumor and surrounding tissue to therapy can be accurately evaluated using a surgical specimen, which is also a reference for postoperative treatment decisions. In the KEYNOTE-671 study, MPR occurred in 30.2% of patients in the pembrolizumab group and 11.0% of those in the placebo group, and pCR occurred in 18.1% and 4.0% of the patients, respectively. As in previous trials, ICI plus chemotherapy appeared to achieve higher MPR and pCR than chemotherapy alone. In-trial surgery was performed in 82.1% of patients in the pembrolizumab plus chemotherapy arm and 79.4% of those in the chemotherapy plus placebo group. Among them, 92% and 84%, respectively, achieved complete resection (R0). In addition, 3.8% and 6.5% of patients in the pembrolizumab plus chemotherapy and placebo plus chemotherapy arms, respectively, did not undergo in-study surgery because of disease progression. This suggests that the combination of preoperative chemotherapy and an ICI is unlikely to cause unresectability owing to disease progression.

The biggest question is whether there is any benefit in adding postoperative adjuvant ICI therapy for patients who have achieved or not pCR with preoperative treatment. Although additional analysis of this study or another new study is needed to entirely answer this question, a hypothesis can be formulated from the results of this study. With all limitations of inter-trial comparison, an exploratory analysis of EFS by treatment showed that EFS in the group that achieved pCR was favorable in both the CheckMate-816 and KEYNOTE-671 trials, and there seemed to be no difference in the results between the two treatment strategies. Contrarily, in the patient population that did not achieve pCR, the HR of chemotherapy and ICI to chemotherapy alone was 0.84 (95% CI: 0.61–1.17) in the CheckMate-816 and 0.69 (95% CI: 0.55–0.85) in KEYNOTE-671. Of note, in the KEYNOTE-671 trial, patients who did not achieve pCR with pembrolizumab had a longer EFS than those who received placebo. These results suggest that the addition of adjuvant ICI therapy is more beneficial for patients who do not achieve pCR. Long-term follow-up data from these trials are needed to clarify this issue. However, one advantage of the KEYNOTE-671 regimen is that the pathological response to preoperative treatment can be confirmed before considering whether additional postoperative treatment is warranted.

Activation of immune cells by ICIs is a prerequisite for antitumor efficacy; however, over-activated immunity leads to specific side effects known as immune-related adverse events (irAEs). Severe irAEs sometimes require potent immunosuppressive therapy and can lead to the interruption of preoperative therapy, postponement of surgery, and sometimes fatal outcomes. In clinical trials using neoadjuvant ICI and chemotherapy, the distinction between treatment-related AEs (trAEs) and irAEs was unclear. In the KEYNOTE-671 trial, AEs of any cause occurred in 96.7% of patients in the pembrolizumab plus chemotherapy group and 95% of those in the placebo plus chemotherapy group. The incidence rates of grade 3 or higher trAEs were 44.9% and 37.3%, respectively. TrAEs led to the discontinuation of all study drugs in 12.6% of the patients in the pembrolizumab group and in 5.3% of those in the placebo group. Mortality rates from trAEs were 1.0% and 0.8% in the pembrolizumab and placebo arms, respectively. No new safety information has been reported for ICI and chemotherapy combination in the perioperative setting, with perioperative ICIs considered well-tolerated. However, the early detection and appropriate management of irAEs is necessary to maximize the therapeutic effects of this treatment strategy and minimize its clinical disadvantages. In actual clinical practice, when a trAE develops, it is sometimes difficult to decide whether to stop preoperative treatment and consider surgery or to treat the AE and continue preoperative treatment; however, every effort should be made to avoid jeopardizing the possibility of surgery. Because perioperative ICI therapy is accompanied by postoperative ICI administration, attention should also be paid to trAEs during postoperative ICI administration. In the KEYNOTE-671 study, 10% of patients experienced grade 3 or higher trAEs during postoperative pembrolizumab administration.

In summary, perioperative pembrolizumab was shown to increase pathological shrinkage as a short-term effect, contributing to prolonged disease-free survival (DFS) and potentially prolonged OS. The benefits of this treatment

strategy are greater in more advanced patients, such as those with pretreatment stage III NSCLC. Based on the results of this trial, this therapy has become a novel therapeutic strategy. Many trials targeting perioperative ICI and chemotherapy combination therapy in patients with clinical stage II or higher disease have been conducted (15,16). One of the greatest advantages of this approach is that the pathological findings from the preoperative treatment can be used as a reference for postoperative treatment. Neoadjuvant ICI therapy requires a disease management team including experts in oncology, surgery, and pathology. Given the early and high therapeutic efficacy of neoadjuvant ICI therapy, patients with large tumors and lymph node metastases who are not suitable for initial definitive surgery may be candidates for surgery after preoperative ICI therapy, with a potential for improved therapeutic outcomes.

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