Editorial

Neoadjuvant immunochemotherapy in resectable non-small cell lung cancer: the more cycles, the better?

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The selection of an optimal treatment strategy for resectable early and locally advanced non-small cell lung cancer (NSCLC) remains an area of active ongoing research. With the success of immune checkpoint-based immunotherapy in advanced NSCLC, numerous single-cohort and randomized controlled trials have been initiated to investigate its potential in the neoadjuvant setting for resectable NSCLC. The primary objectives of these trials have been to enhance tumor downstaging for achieving an R0 resection and to address any micro-metastasis. Neoadjuvant immunotherapy, either as monotherapy or in combination with chemotherapy and radiotherapy, has shown promising results in improving pathological response rates (1).

While neoadjuvant immunotherapy has demonstrated notable efficacy, questions have arisen regarding the optimal and safest number of treatment cycles. A shorter course of treatment may not sufficiently affect the tumor microenvironment, leading to a suboptimal treatment response. Conversely, an extended treatment course could carry the risk of treatment-related adverse events, potentially resulting in surgical delays or cancellations. Therefore, it is crucial to establish a consensus regarding the most effective and safest number of treatment cycles. Most clinical trials investigating neoadjuvant immunotherapy in NSCLC have focused on resectable stages I–IIIA, as stages IIIB–IIIC are commonly considered unresectable. However, there is an ongoing debate on whether these latter stages are genuinely ineligible for surgical resection, and this issue has drawn significant attention from researchers worldwide.

Recently, at the European Lung Cancer Congress 2023, updated results from the Checkmate-816 trial were presented (2). This phase 3 trial, employing a 1:1 randomized design, compared three cycles of neoadjuvant nivolumab plus chemotherapy with chemotherapy alone, with efficacy as the primary endpoint. The study enrolled a total of 358 patients with stages IB–IIIA NSCLC and without known Epidermal Growth Factor Receptor (EGFR) or Anaplastic Lymphoma Kinase (ALK) gene alterations. The nivolumab plus chemotherapy arm demonstrated a superior event-free survival of 57% compared to 43% in the chemotherapy-alone arm (HR 0.68; 95% CI: 0.49–0.93). Pathological complete response (pCR), defined as 0% viable residual tumor cells, was observed in 43/179 (24.0%) and 4/179 (2.2%) of patients receiving nivolumab plus chemotherapy and chemotherapy alone, respectively (3). Notably, this trial did not include patients with stage IIIB and IIIC, suggesting that these were considered unresectable and leaving the question whether these patients would have benefited from the study treatment unanswered.

In their retrospective study, Deng *et al.* sought

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to evaluate the real-world efficacy of neoadjuvant immunochemotherapy in stage III NSCLC, with a specific focus on the number of treatment cycles administered and the baseline peripheral immune markers as possible indicators of treatment response (4). The study included 115 patients with stage III NSCLC who received neoadjuvant immunochemotherapy followed by surgical resection. Among these patients, 61 (53.0%) had stage IIIA, 51 (44.3%) had stage IIIB, and 3 (2.6%) had stage IIIC disease. MPR was observed in 64 out of 115 patients (55.7%), of which 44 (38.3%) achieved a pCR. A *post-hoc* analysis indicated that patients receiving three or four treatment cycles had higher rates of MPR compared to those receiving only two cycles. However, extending the treatment duration beyond four cycles did not lead to further improvements in pathological response rates. The study did not report treatment-related adverse events but it is reasonable to assume that an extended treatment course would increase the risk of toxicities for these patients.

Based on their findings, the authors concluded that a neoadjuvant immunochemotherapy course consisting of 3–4 cycles is the most effective and safest approach for stage III NSCLC. Importantly, the study suggests that an even longer treatment course of more than four cycles does not confer higher chances of achieving a pathological response. The ongoing debate surrounding the definition of resectability for stage III NSCLC necessitates further investigation, particularly considering the influence of single- or multi-nodal involvement. Such insights could potentially lead to reconsideration of the neoadjuvant treatment course for these specific stage classifications. It is worth noting that the study by Deng *et al.* did not explore treatment-related adverse events. However, it is plausible that an extended treatment duration would increase the risk of adverse events in this patient population. Therefore, the balance between treatment efficacy and safety remains a crucial consideration.

Furthermore, while programmed death-ligand 1 (PD-L1) expression is currently the primary biomarker used to predict response to immunotherapy, there is pressing need for novel biomarkers. Deng *et al.*'s retrospective study demonstrated that baseline peripheral immune markers in blood samples, such as lymphocyte and monocyte counts, were higher in patients who achieved MPR, indicating their potential as biomarkers for predicting pathological response. Other studies have explored the predictive value of tumor-infiltrating lymphocytes in tumor biopsies for survival outcomes (5). Additionally, the scoring of PD-L1 on inflammatory immune cells, in addition to tumor cells alone, may provide useful information for predicting treatment response (6). Baseline immune cell presence, whether detected in peripheral blood or tumor biopsies, appears to play a critical role in determining the likelihood of response to immunotherapy treatment and should therefore be considered in future large-scale phase 3 trials.

In summary, the study by Deng *et al.* contributes valuable insights into the optimal treatment duration of neoadjuvant immunotherapy in locally advanced stage III NSCLC. Their findings support the use of a 3–4 cycle treatment course, which appears to offer the most favorable balance between efficacy and safety. However, further research is warranted to address the challenges associated with defining resectability for stage III NSCLC and to identify novel biomarkers that can accurately predict treatment response. Large randomized controlled trials specifically focused on (subdivisions of) stage III NSCLC are urgently needed to guide treatment decisions and optimize outcomes for these patients. In the pursuit of personalized medicine, the ongoing exploration of biomarkers, whether based peripheral immune markers or tumor tissue analysis, remains crucial for refining treatment strategies in the neoadjuvant setting.

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