Commentary: Real-world neoadjuvant immunochemotherapy for lung cancer: Additional data but still many questions

Valerie W. Rusch, MD, FACS

In recent years, immune checkpoint inhibitors (ICI) have revolutionized the treatment of lung cancer. Multicenter Phase 2 and 3 clinical trials have shown the safety and efficacy of ICI alone or in combination with chemotherapy in advanced non–small cell lung cancer (NSCLC),1,2 and as neoadjuvant and adjuvant therapy in combination with resection of locally advanced NSCLC.3,4 The superiority of neoadjuvant ICI and platinum-based chemotherapy versus chemotherapy alone has been reported in several large clinical trials testing multiple ICI that target either the programmed death-1 (PD-1) protein or its ligand, PD-L1.5-7 Consequently, neoadjuvant therapy with ICI and chemotherapy has become an approved treatment strategy in patients with stages IB-selected IIIB NSCLC.

Yang and colleagues8 compare outcomes after real world (ie, in routine practice outside the clinical trial setting) neoadjuvant ICI plus platinum-based chemotherapy to chemotherapy alone followed by resection in several hundred patients with clinical stages I through III NSCLC. As observed in clinical trials, the rate of pathologic complete response, the disease-free survival (DFS) and overall survivals were superior in patients receiving ICI plus chemotherapy. Patients also appeared to derive a benefit in DFS from the addition of various types of adjuvant therapy provided they had received at least 2 cycles of neoadjuvant therapy. These findings were confirmed after propensity score matching.

How do these real-world data contribute to the published literature? Evaluating therapies outside of clinical trials can demonstrate broad applicability to heterogeneous patient populations that potentially have a greater risk for treatment-related adverse events. Thus, the data reported here are reassuring to physicians and patients regarding expected outcomes after neoadjuvant ICI and chemotherapy in routine practice.

However, some results of this study differ from reported trials, and questions remain. The more favorable outcomes seen for squamous cell histology and female sex are not reported in other studies where there has been a lower prevalence of such characteristics.5,7 Small numbers of patients whose tumors contained oncogenic driver mutations such as epidermal growth factor mutations appeared to have better treatment responses to ICI and chemotherapy but such patients are now more effectively treated with targeted therapies. Pretreatment tumor testing for oncogenic driver mutations and for PD-L1 was not routinely performed but has become a standard part of initial assessment to guide the selection of neoadjuvant therapies.

Perhaps the issues that most require clarification in future studies are whether adjuvant therapy is beneficial in patients after neoadjuvant therapy and complete (R0) surgical resection, whether adjuvant therapy should be
given after a complete pathologic response as well as in patients who have residual viable tumor at resection, whether adjuvant ICI monotherapy is appropriate, the optimal duration of adjuvant therapy, and whether a biomarker such as circulating tumor DNA could guide the use of adjuvant therapy. The current study suggests that adjuvant therapy is associated with improved DFS in patients who received 2 cycles of neoadjuvant ICI and chemotherapy, but this could simply reflect the ability of some patients to tolerate more extended treatment. Prospective clinical trials are needed to answer these questions definitively and are already planned.

Conflict of Interest Statement
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