Commentary: Neoadjuvant immune checkpoint monotherapy for lung cancer: Has the train left the station?

Nasser K. Altorki, MD, and Jonathan Villena-Vargas, MD

In this issue of the Journal, Rusch and colleagues report the results of the Lung Cancer Mutation Consortium 3 (LCMC3) trial, the largest neoadjuvant trial of immune checkpoint inhibitor (ICI) monotherapy in patients with resectable stage IB to IIIB non–small cell lung cancer. Within 3 years, the investigators accrued 181 patients across 13 centers who received up to 2 preoperative cycles of the anti-programmed death-ligand 1 blocking antibody atezolizumab. The trial met its primary end point of major pathologic response (MPR), which was observed in 29 out of 143 resected patients (20%) whose tumors did not harbor EGFR mutations or Alk alterations. In addition, the authors report that neoadjuvant atezolizumab was well tolerated, had a safety profile consistent with that observed in other phase 2 and 3 neoadjuvant immunotherapy trials, and had no effect on postoperative pulmonary function.

So, what are the important lessons that thoracic surgeons should take away from this report? First, concerns about disease hyperprogression during neoadjuvant ICI monotherapy are wildly exaggerated. Disease progression occurred in 10% of patients, a proportion similar to that observed with preoperative chemotherapy alone. Second, the absence of a radiographic response does not signal a lack of pathologic response. Quite the opposite—25 of 29 patients with MPR had stable disease on posttreatment imaging. Third, although surgical resection can occasionally be technically challenging, it can be performed safely and frequently minimally invasively in nearly all patients. Finally, get acquainted with your immune-related postoperative adverse events. Fortunately, they are rare, for they can be quite serious.

With the spectacular results reported by CheckMate 816 investigators, one might be forgiven to ask, is it game, set, and match for neoadjuvant chemotherapy plus ICIs? Well, if you live and die by MPR, the answer would be “yes.” However, the LCMC3 investigators report a highly promising disease-free survival of 72% and overall survival of 80%. These impressive survival figures are simply not consistent with an MPR rate of only 20%. Is it possible that neoadjuvant atezolizumab induces an effective systemic antitumor immune response that eradicates micrometastases in some patients despite the absence of a pathologic response in the primary tumor? Very likely, the answer to this question is also “yes.” In fact, the results of IMpower010 and KEYNOTE-091 suggest as much. In both trials, primary resection followed by adjuvant chemotherapy then adjuvant ICIs was associated with a significant improvement in disease-free survival compared with adjuvant chemotherapy alone. We think it may be premature to discard neoadjuvant ICI monotherapy altogether. The trick, as is often the case, is to identify blood-based or tissue-based biomarkers that would allow us to select those patients who are most likely to benefit from the far less toxic and perhaps equally efficacious strategy of neoadjuvant ICI monotherapy. The work goes on.
Reference