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Central Message: This paper from Feldman et al. presents data from the NEOSTAR trial, evaluating surgical outcomes in patients receiving chemotherapy and nivolumab with and without ipilimumab.

Central Picture Legend: Matthew J. Bott, M.D.
Recent trials evaluating perioperative chemoimmunotherapy have revolutionized the treatment of patients with locally advanced, surgically resectable lung cancer. In this issue of *The Journal of Thoracic and Cardiovascular Surgery*, Feldman and colleagues present additional data from a prospective clinical trial evaluating combination T-cell checkpoint inhibition and chemotherapy in patients with stage IB to IIIA non-small cell lung cancer (NSCLC).¹ The NEOSTAR trial used a sequential, single-arm, phase 2 study design to evaluate neoadjuvant nivolumab (nivo), nivo plus ipilimumab (ipi), nivo plus platinum-based chemotherapy (chemo), or the combination of nivo, ipi, and chemo. While the primary findings of the study have been previously published, the analysis described here focuses specifically on surgical outcomes in the latter two groups (nivo/chemo and nivo/ipi/chemo).

The safety and efficacy of the nivo/chemo regimen have been demonstrated in a randomized phase III trial; however, surgical results after the nivo/ipi/chemo regimen have not been previously described, and further analysis of this group may provide unique insights.² In general, outcomes in both treatment groups were on par with expected outcomes of surgical resection after neoadjuvant therapy.

Complete resection was obtained in the vast majority of cases (nivo/chemo, 91%; nivo/ipi/chemo; 95%), there was no 90-day operative mortality in either cohort, and grade 3 complications were infrequent (~20%) in both groups. The majority of patients in each group underwent open thoracotomy (95% in nivo/chemo vs. 80% in nivo/ipi/chemo), and surgical complexity scores indicated that 50% of cases in each group were more difficult than a standard lobectomy.

Several subtle differences were noted between the groups. For instance, nivo/ipi/chemo patients had longer operative times and received more blood transfusions. Similarly, although
rates of grade 3 complications were similar, the overall 30-day complication rate was 65% in nivo/ipi/chemo patients, compared with 32% in nivo/chemo patients. These complications were primarily respiratory and cardiac in nature. Rates of complications were higher despite a numerically higher performance status in the triple-therapy group (70% of nivo/ipi/chemo patients had an Eastern Cooperative Oncology Group performance status of 0, compared with 45.5% of nivo/chemo patients). These findings are in line with published data from both the locally advanced and metastatic settings, suggesting that combination CTLA-4/PD-L1 blockade may be associated with higher rates of toxicity—in particular, immune-related adverse events.\(^3,4\)

However, despite these potential challenges, oncologic outcomes with the triple-therapy regimen were highly encouraging. For instance, the nivo/ipi/chemo regimen was associated with a major pathologic response (MPR) rate of 50% in the intent-to-treat population and 62.5% in patients who were noted to have wild-type EGFR or ALK. This compares favorably with the MPR rates of 32.1% (intent to treat) and 41.2% (EGFR or ALK wild-type) seen in the nivo/chemo arm of this study and 36.9% after nivolumab plus chemotherapy in Checkmate 816.\(^2,5\) Whether this higher MPR rate translates to better disease control and patient survival will need to be assessed in subsequent analyses.

Additional studies are needed to clarify the role of combination regimens beyond chemotherapy and PD-1/PD-L1 inhibition; however, the authors should be congratulated for this groundbreaking clinical trial. Multiagent combination chemoimmunotherapy may ultimately represent the future of induction therapy for locally advanced lung cancer. In particular, regimens targeting multiple T-cell checkpoints may be well-suited for tumor types that have been associated with lower response rates to PD-1/PD-L1 inhibition, such as those with PD-L1 <1%
or with molecular alterations, such as *STK11* mutations.\(^3\) If successful, these strategies have the potential to significantly improve oncologic outcomes for these patients.
References


