3. Induction treatment variables: single agent versus multi-agent, doses, cycles, delay of treatments, progression or pseudoprogression.
4. Surgical approaches: open versus minimally invasive, conversion rates, completeness of resection.
5. Perioperative management: safety issues, complications, mortality.
6. Adjuvant therapy: treatment of residual disease, additional therapies based on marker status.
7. Pathologic/predictors of response: immunologic or next-generation sequencing that can correlate with histopathologic tumor kill and, if so, translation into durable survival.

The general thoracic community congratulates Tong and colleagues¹ for validating many of the perioperative concerns in a multi-institutional fashion seen with induction immunotherapy, particularly that of R0 resections, and their ability to maintain minimally invasive approaches despite the tissue reactions that has been observed with I-O therapy.² As noted in their summary table (Table 2) of current trials, we now await results of other multimodality paradigms of enhancing single agent I-O with combination

traditional chemotherapy and/or radiation. As perhaps an update, the results of the Check-Mate 816 trial were recently presented at the 2021 Annual American Association for Cancer Research Conference.³ This is the first phase 3 trial to show positive results using nivolumab plus a platinum-doublet with a significant improvement in pathologic complete response of 24% compared with 2.2% alone with chemotherapy. Neoadjuvant checkpoint inhibition is here to stay, but many questions remain unanswered, so we still have more work to go.

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See Article page 427.

Commentary: A new hope—neoadjuvant immunotherapy for resectable non-small cell lung cancer

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Compared with other malignancies, overall survival (OS) in non-small cell lung cancer (NSCLC) remains low even in early-stage disease.¹ In comparison, 5-year OS for localized

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CENTRAL MESSAGE

Immune checkpoint inhibitors have demonstrated remarkable efficacy across various malignancies. Their role in resectable lung cancers in particular is rapidly evolving and will change management paradigms.

colorectal and breast cancer ranges from 89% to 99%.^{2,3} There clearly is an unmet need to elucidate and target mechanistic pathways to improve survival in NSCLC. In the

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landmark LACE meta-analysis, adjuvant chemotherapy led to a modest 5.4% improvement in 5-year OS, primarily in stages II and III.⁴ For tumors <4 cm without lymph node involvement, adjuvant cytotoxic therapy does not improve survival and may even be harmful.^{5,6} Recently, immune checkpoint inhibitors (ICIs) targeting PD-1/PD-L1 have demonstrated remarkable efficacy in the management of advanced and metastatic NSCLC leading to their incorporation in standard treatment regimens.⁷ This has led to great enthusiasm for potential benefit in resectable disease, and multiple trials were launched exploring the role of ICIs in early-stage NSCLC, with promising early results.

In this issue of the *Journal*, Tong and colleagues⁸ report perioperative outcomes of neoadjuvant pembrolizumab in stage IB-IIIa NSCLC. In their well-designed phase II trial, neoadjuvant pembrolizumab demonstrated a favorable toxicity profile with minimal perioperative morbidity and no mortalities. Only one patient experienced a delay to surgery secondary to thyroiditis. Twenty-five out of 30 patients (83%) underwent resection, and 5 patients experienced disease progression. Twenty-three patients had an initial attempt at a minimally invasive approach, with 5 conversions to thoracotomy (21.7%). Only 3 patients (12%) required pneumonectomy. These results compare favorably to those in patients receiving neoadjuvant chemotherapy under current treatment regimens. Remarkably, 28% of the patients had a major pathologic response (MPR), defined as $\geq 10\%$ viable tumor cells in resected specimens.

This report from Tong and colleagues adds to the growing body of work evaluating the use of neoadjuvant ICIs alone or in combination with chemotherapy. There are more than 15 ongoing trials in this space, including 5 phase III trials.^{6,9} The first evidence in this space came from the landmark neoadjuvant nivolumab in stage I-IIIa NSCLC study.¹⁰ Similar to the Tong study, there were minimal side effects and no delays in surgery, and MPR was achieved in 45% of resected tumors.¹⁰ There were no delays to surgery, with 20 of 22 patients (91%) undergoing resection.¹¹ However, in contrast to the Tong study, 70% of resections were done in open fashion secondary to dense adhesions and intense inflammatory changes surrounding hilar nodes.¹¹

The inflammatory and desmoplastic effect of neoadjuvant ICIs is unclear, particularly in the presence of hilar nodal metastases. In the NEOSTAR trial, neoadjuvant nivolumab was compared with combination nivolumab + ipilimumab (CTLA-4 inhibitor) in operable NSCLC. The primary endpoint in this phase II randomized trial was MPR, which has been associated with overall survival and has potential as a surrogate of standard oncologic outcomes.¹² The dual inhibitor arm achieved an MPR of 50%, whereas the nivolumab alone arm achieved an MPR of 24%. Pathologic complete response was found in 10% and 38% of resected specimens in the single and dual

inhibitor arms, respectively. These data suggest combination ICI may have greater efficacy than single inhibitor therapy with the potential to dramatically improve oncologic outcomes in resectable NSCLC compared to standard chemotherapy. In the interim analysis of the LCMC3 trial, which is the largest ICI trial to date with 180 planned patients, neoadjuvant atezolizumab produced no major surgical delays, and achieved a tolerable toxicity profile with encouraging pathologic complete response and MPR rates.¹³

All in all, the current evidence for neoadjuvant PD-1/PD-L1 blockade for early-stage NSCLC is encouraging. Early trials have demonstrated excellent tolerability without major delays to surgical intervention, along with a remarkable pathologic response to treatment. Early data with the use of combination therapy also appears to show promising results. After several decades of status quo, the landscape of systemic therapy including neoadjuvant therapy is changing at a rapid pace. Perhaps this paradigm of checkpoint inhibition was the new hope we all needed.

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