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Commentary: I-O, I-O, there's still some work to go...

Stephen C. Yang, MD

In the classic scene of *Snow White and the Seven Dwarfs*, these fictional characters are singing and whistling the iconic song “Heigh-Ho” as they head off to work. Much like these famed heroes, physicians and patients continue to work on advancing the knowledge of immuno-oncology (I-O) and its role in resectable non-small cell lung cancer (NSCLC).

In this issue of the *Journal*, Tong and colleagues¹ present their perioperative outcomes from a multi-institutional prospective phase 2 trial using induction pembrolizumab for resectable stage IB-IIIa NSCLC. They conclude it is a safe regimen, with comparable morbidity compared with noninduction patients, no morbidity, and a respectable conversion rate of 21%, similar to other published induction strategies. Although programmed death-1/programmed cell death ligand 1 status was not available preoperatively for all patients and thus not reported, a major pathologic response rate of 28% was observed. However, some issues to note are as follows: a 57% squamous histology; disease progression in 4 patients (perhaps not appreciate at initial

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CENTRAL MESSAGE

Single-agent pembrolizumab appears safe, but much work remains in clarifying induction I-O strategies, effects on surgical tissue, and histopathologic predictors of tumor response to therapy.

evaluation); a 12% margin positivity that the authors feel likely would not have been avoided with an open operation; and, only a median follow-up of 11 months.

Although these findings do add to the growing outcome database using I-O for resectable NSCLC, it remains challenging to make definitive comparisons between studies due to the inconsistent reporting of perioperative metrics, as noted in Table 2 of their results. Much like the 7 personalities cross that bridge to work, we must keep constant the 7 areas in design and reporting of similar trials to adequately compare surgical outcomes:

1. Patient selection: histologic heterogeneity, demographics.
2. Pretreatment evaluation: preoperative imaging, invasive nodal evaluation, biologic marker status (eg, programmed death-1/programmed cell death ligand 1).

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

Ramiro Fernandez, MD, and Usman Ahmad, MD

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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