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ASO PERSPECTIVES

Neoadjuvant and Adjuvant Pembrolizumab for the Treatment of Early-Stage Resectable Non-small Cell Lung Cancer An Editorial Regarding the Interim Data Analysis of the KEYNOTE-671 Phase III Trial of Neoadjuvant and Adjuvant Pembrolizumab

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Among patients who undergo surgery for locally advanced non-small cell lung cancer (NSCLC) with curative intent, a substantial portion will experience recurrence and succumb to their disease. The addition of chemotherapy provides limited benefit with an absolute improvement in overall survival of 5% over 5 years.[1] Recent trials combining immune checkpoint inhibition and chemotherapy in the neoadjuvant setting for patients with locally advanced NSCLC have shown dramatic responses and sparked excitement in the thoracic oncology community.

In 2022, the CHECKMATE-816 trial was published in the *New England Journal of Medicine* (*NEJM*). This was the first phase III trial of neoadjuvant checkpoint inhibition in NSCLC and demonstrated that the addition of nivolumab to neoadjuvant cisplatin- or carboplatin-based chemotherapy increased the likelihood of complete pathological response (no viable tumor in the resected lung or lymph nodes) from 2.2 to 24.0%, with an associated improvement in event-free survival from 45 to 64% at 24 months from surgery.[2] Results of this trial have led to approval of nivolumab in combination with chemotherapy in the neoadjuvant setting by the US Food and Drug administration as well as recommendation in the guidelines of the National Comprehensive Cancer Network (NCCN).[3] This effective combination of chemotherapy and immunotherapy for patients with resectable (stage IB–IIIA) tumors provides hope that we can improve upon disappointing rates of recurrence and mortality for patients with non-small cell lung cancer (NSCLC).

More recently, an interim analysis of the KEYNOTE-671 phase III trial of neoadjuvant and adjuvant pembrolizumab for early-stage (II, IIIA, or IIIB) NSCLC was also published in *NEJM* and provides further evidence that immunotherapy is an effective partner to chemotherapy for the treatment of resectable NSCLC.[4] Participants were randomized to receive neoadjuvant pembrolizumab (200 mg) or placebo, with all receiving cisplatin-based neoadjuvant chemotherapy. Following surgery, participants received either adjuvant pembrolizumab (for those who had received pembrolizumab as a neoadjuvant therapy) or placebo. This planned interim analysis was performed 5 months after the last participant underwent randomization, with a median participant follow-up time of 25.2 months. At 24 months, participants assigned to the pembrolizumab group had significantly better event-free survival (62.4% versus 40.6%, HR 0.58, 95% 0.46–0.72, $p<0.001$), pathological complete response rate (18.1% versus 4.0%, $p < 0.0001$), and major pathological response rate (30.2% versus 11.0%, $p < 0.0001$). At this early timepoint, the estimated difference in overall survival between the pembrolizumab group and the placebo group did not meet the prespecified threshold for statistical significance (80.9% versus 77.6%, $p = 0.02$). Though there does appear to be an early signal toward improved overall survival, we await mature data for this outcome. The interim data do note that six patients in the pembrolizumab group versus two in the placebo group died within 30 days of surgery, a concerning finding that will need to be reevaluated in the complete study data.

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It is difficult to directly compare the CHECKMATE-816 and KEYNOTE-671 trials, given differences in inclusion criteria (stages IB–IIIA versus II–IIIB), protocol (three versus four cycles of neoadjuvant therapy, approved chemotherapy regimens, addition of adjuvant immunotherapy), and maturity of data (complete versus interim analyses). However, it is important to note that the inferences from these trial data are consistent: the pathologic complete response rate and major pathologic response rate in the KEYNOTE-671 trial were similar to those observed CHECKMATE-816, and the addition of immunotherapy demonstrated a significant event-free survival advantage over chemotherapy alone. Indeed, this growing body of evidence suggests that neoadjuvant chemoimmunotherapy should be the standard of care for locally advanced, resectable NSCLC in the absence of targetable mutations. However, uncertainty remains as to the benefit of additional checkpoint inhibition in the adjuvant setting. In this regard, the KEYNOTE-671 trial will provide important information on the effectiveness of perioperative immunotherapy versus neoadjuvant only, with the AEGEAN, CHECKMATE-77T and NEOTORCH trials adding to that body of evidence.[5,6]

All of the recently published trials and those to come over the next few years will have a profound impact on the practice of thoracic surgical oncology. It is imperative that thoracic surgeons are familiar with the existing data supporting neoadjuvant checkpoint inhibition and collaborate closely with other members of multidisciplinary team. Careful staging at the time of initial diagnosis will facilitate identification of patients who will benefit from this novel treatment paradigm. Tissue acquisition and molecular testing at diagnosis is critical to facilitate efficient decision-making. Surgeons should be aware of immune-related adverse events and screen for these in the preoperative setting. Finally, we should be reassured that, while treatment and associated response may result in inflammatory changes in the pulmonary hilum and nodal basins, the early phase and phase III data accumulated to date have not shown an adverse perioperative safety signal.

The existing portfolio of neoadjuvant and perioperative trials have provided a solid foundation for this novel therapeutic approach, and enthusiasm continues to grow within the lung cancer community. However, many questions remain unanswered. Are there patients who do not benefit from adjuvant checkpoint inhibition after neoadjuvant therapy? Are there patients in whom chemotherapy can be omitted? What is the optimal duration of therapy? What is the optimal timing of surgery following neoadjuvant checkpoint inhibition? Are there potentially patients in whom surgery can be omitted? Improved biomarkers and correlative studies from the growing number of clinical trials will hopefully allow us to answer these and other questions in the near future. It is paramount that thoracic surgeons remain engaged in both the standard-of-care and clinical trial settings as this paradigm evolves.

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