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Neoadjuvant immunotherapy in non-small-cell lung cancer: times are changing—and fast

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Abstract

Recent data from a phase 3 trial have shown that the addition of immunotherapy to neoadjuvant chemotherapy improves event-free survival in patients with NSCLC. This is the first positive phase 3 trial in this setting, although several phase 3 trials are currently investigating the efficacy of neoadjuvant and adjuvant immunotherapy in resectable NSCLC.

TO THE EDITOR

The management of localized non-small-cell lung cancer (NSCLC) is set to undergo an important change in the first few months of this year (2022) due to the recent publication of the second primary endpoint—event-free survival (EFS)—from the Checkmate-816 trial. The data show that the combination of chemotherapy + nivolumab yielded a mean disease-free survival of 31.6 m in the experimental arm vs. 20.8 m (hazard ratio [HR]: 0.63) in the control arm (chemotherapy alone), with a 2 year-EFS rate of 64% vs. 45%, respectively [1]. These results, in addition to previously reported results showing an improvement in pathological complete response (pCR) of 24% vs. 2%, confirm the combination of three cycles of chemotherapy + neoadjuvant nivolumab as the new standard of care in resectable NSCLC [2].

This is the first time that pCR has been validated as a surrogate marker for survival in a randomized trial. In the experimental arm, the median EFS was 26.6 m in patients without pCR and not reached in those with pCR (HR: 0.13). Although the results in terms of overall survival are still immature, a trend towards better survival was observed in the experimental arm, in which 12% more patients were alive at 2 years (HR: 0.57).

This new change in clinical practice comes with several questions that need be resolved in the next few years, including the following: the role of adjuvant therapy; the selection of the most suitable candidates; comparison with adjuvant chemoimmunotherapy; the optimal approach in stage I-II disease; standardization of pathological response assessment; changes in resectability criteria; and changes in the preoperative algorithm.

The perioperative management of NSCLC will undoubtedly undergo a major transformation in the coming years due to the arrival of targeted therapy in this clinical setting, mainly the incorporation of pre- or post-operative immunotherapy [3]. The CheckMate 816 study was the first phase 3 trial to report positive results for the addition of immunotherapy to neoadjuvant chemotherapy [1]. However, other ongoing phase 3 trials evaluating other PD-1 axis inhibitors are expected to report results soon, such as the Impower-030 trial (atezolizumab) [4], KeyNote-671 trial (pembrolizumab) [5], and the Aegean trial (durvalumab) [6]. (Table 1). Likewise, atezolizumab has already obtained FDA approval for use in the adjuvant setting in patients with resected PD-L1 positive stage II-IIIA NSCLC [7], and positive results have also been reported from an interim analysis of the KeyNote-091 trial, showing the benefits of pembrolizumab in resected stage IB-IIIA NSCLC [8]. Nivolumab and durvalumab are also being evaluated in the adjuvant setting in several other phase 3 trials (ANVIL, NADIM-Adjuvant, Mermaid-1) [9-11]. (Table 2). As a result, the panorama for the treatment of early-stage NSCLC is becoming increasingly interesting, and the data suggest that it will be crucial to personalize treatment to offer the best treatment scheme for each individual patient.

These new options bring hope of a cure to a greater number of patients, but also new challenges for the multidisciplinary team and other professionals involved in the treatment of these patients. Once again, coordinated multidisciplinary work will be essential, especially among medical oncology, thoracic surgery, and radiation oncology.

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