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

Aguado C *et al*. Last news on neoadjuvant immunotherapy for NSCLC

Carlos Aguado, Unai Jiménez Maestre, Xabier Mielgo-Rubio

**Carlos Aguado,** Department of Medical Oncology, Hospital Universitario Clínico San Carlos, Madrid 28040, Spain

**Unai Jiménez Maestre,** Department of Thoracic Surgery, Hospital Universitario Cruces, Barakaldo 48903, Bizkaia, Spain

**Xabier Mielgo-Rubio,** Department of Medical Oncology, Hospital Universitario Fundación Alcorcón, Alcorcón 28922, Madrid, Spain

**Author contributions:** Aguado C, Jiménez U, and Mielgo-Rubio X wrote and revised the letter.

**Corresponding author: Carlos Aguado, MD, Consultant Physician-Scientist,** Medical Oncology, Hospital Universitario Clínico San Carlos, Calle del Prof Martín Lagos, Madrid 28040, Spain. carlos.aguado84@gmail.com

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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 non-small-cell lung cancer (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.

**Key Words:** Neoadjuvant; Immunotherapy; NSCLC; Perioperative; Checkmate-816; nivolumab; Chemo-immunotherapy

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**Core Tip:** Recent data from a phase 3 trial show that the addition of immunotherapy to neoadjuvant chemotherapy in patients with non-small-cell lung cancer (NSCLC) improves pathologic complete response and event-free survival. This is the first positive phase 3 trial in this setting, although several other phase 3 studies are currently investigating the efficacy of neoadjuvant and adjuvant immunotherapy in resectable NSCLC. We describe the results of the CheckMate-816 phase 3 trial, which found that neoadjuvant chemoimmunotherapy was superior to chemotherapy alone. We also briefly review the main phase 3 studies currently underway to evaluate the role of immunotherapy in the perioperative setting of 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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**Footnotes**

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**Table 1 Main phase 3 trials evaluating neoadjuvant chemoimmunotherapy in non-small-cell lung cancer**

|  |
| --- |
| **Neoadjuvant NSCLC** |
| **Study** | **IO agent** | **Strategy** | **Objective** | **Status** |
| CheckMate-816[1] | Nivolumab (anti-PD1) | ChT + IO | EFS and pCR | FDA approved |
| Impower-030[4] | Atezolizumab (anti-PD-L1) | ChT + IO | PFS and OS | Completed. Results pending |
| KeyNote-671[5] | Pembrolizumab (anti-PD1) | ChT + IO | EFS and OS | Active, not recruiting |
| Aegean[6] | Durvalumab (anti-PD-L1) | ChT+ IO | pCR and EFS | Recruiting |

IO: Immunotherapy; ChT: Chemotherapy; EFS: Event-free survival; pCR: Pathologic complete response; PFS: Progression-free survival; OS: Overall survival; FDA, Food and Drug Administration; NSCLC: Non-small-cell lung cancer.

**Table 2 Main phase 3 trials evaluating adjuvant immunotherapy in non-small-cell lung cancer**

|  |
| --- |
| **Adjuvant NSCLC** |
| **Study** | **IO agent** | **Strategy** | **Objective** | **Status** |
| Impower-010[7] | Atezolizumab (anti-PD-L1) | IO mono | OS in selected PD-L1 population | FDA approved in II-IIIA NSCLC PD-L1+ |
| KeyNote-091 (PEARLS)[8] | Pembrolizumab (anti-PD-L1) | IO mono | DFS | Interim analysis: positive in IB-IIIA NSCLC all corners |
| ANVIL[9] | Nivolumab (anti-PD1) | IO mono | OS and DFS | Active, not recruiting |
| NADIM-Adjuvant[10] | Nivolumab (anti-PD-1) | ChT + IO | DFS | Recruiting |
| Mermaid-1[11] | Durvalumab (anti-PD-L1) | ChT + IO | DFS in MRD+ | Recruiting |

IO: immunotherapy; mono: monotherapy; OS: overall survival; NSCLC: non-small-cell lung cancer; DFS: disease-free survival; ChT: chemotherapy; MRD: minimal residual disease; FDA, Food and Drug Administration; NSCLC: Non-small-cell lung cancer.