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

Carlos Aguado, Unai Jiménez Maestre, Xabier Mielgo-Rubio

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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.

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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-III 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-III 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.

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.

FOOTNOTES

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REFERENCES

- Forde PM, Spicer J, Lu S, Provencio M, Mitsudomi T, Awad MM, Felip E, Broderick SR, Brahmer JR, Swanson SJ, Kerr K, Wang C, Ciuleanu TE, Saylor GB, Tanaka F, Ito H, Chen KN, Liberman M, Vokes EE, Taube JM, Dorange C, Cai J, Fiore J, Jarkowski A, Balli D, Sausen M, Pandya D, Calvet CY, Girard N; CheckMate 816 Investigators. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. *N Engl J Med* 2022; **386**: 1973-1985 [PMID: 35403841 DOI: 10.1056/NEJMoa2202170]
- Forde PM, Spicer J, Lu S, Provencio M, Mitsudomi T, Awad MM, Felip E, Broderick S, Brahmer J, Swanson SJ, Kerr K, Wang C, Saylor GB, Tanaka F, Ito H, Chen K-N, Dorange C, Cai J, Fiore J, Girard N. Abstract CT003: Nivolumab (NIVO) + platinum-doublet chemotherapy (chemo) vs chemo as neoadjuvant treatment (tx) for resectable (IB-IIIa) non-small cell lung cancer (NSCLC) in the phase 3 CheckMate 816 trial. *Cancer Res* 2021; **81**: CT003-CT003 [DOI: 10.1158/1538-7445.am2021-ct003]
- Mielgo-Rubio X, Calvo V, Luna J, Remon J, Martín M, Berraondo P, Jarabo JR, Higuera O, Conde E, De Castro J, Provencio M, Hernando Trancho F, López-Ríos F, Couñago F. Immunotherapy Moves to the Early-Stage Setting in Non-Small Cell Lung Cancer: Emerging Evidence and the Role of Biomarkers. *Cancers (Basel)* 2020; **12** [PMID: 33233705 DOI: 10.3390/cancers12113459]
- Peters S, Kim AW, Solomon B, Gandara DR, Dziadziuszko R, Brunelli A, Garassino MC, Reck M, Wang L, To I, Sun SW, Gitlitz BJ, Sandler A, Rizvi N. IMpower030: Phase III study evaluating neoadjuvant treatment of resectable stage II-IIIb non-small cell lung cancer (NSCLC) with atezolizumab (atezo) + chemotherapy. *Ann Oncol* 2019; **30** Suppl 2: ii30 [DOI: 10.1093/annonc/mdz064.014]
- Tsuboi M, Luft A, Ursol G, Kato T, Levchenko E, Eigendorff E, Berard H, Zurawski B, Demedts I, Garassino MC, Yang J, Makarios K, Keller SM, Wakelee HA. 1235TiP Perioperative pembrolizumab + platinum-based chemotherapy for resectable locally advanced non-small cell lung cancer: The phase III KEYNOTE-671 study. *Ann Oncol* 2020; **31**: S801-S802 [DOI: 10.1016/j.annonc.2020.08.1437]
- Heymach JV, Mitsudomi T, Harpole D, Aperghis M, Jones S, Mann H, Fouad TM, Reck M. Design and Rationale for a Phase III, Double-Blind, Placebo-Controlled Study of Neoadjuvant Durvalumab + Chemotherapy Followed by Adjuvant

- Durvalumab for the Treatment of Patients With Resectable Stages II and III non-small-cell Lung Cancer: The AEGEAN Trial. *Clin Lung Cancer* 2022; **23**: e247-e251 [PMID: 34819266 DOI: 10.1016/j.clcc.2021.09.010]
- 7 **Herbst RS**, Giaccone G, de Marinis F, Reinmuth N, Vergnenegre A, Barrios CH, Morise M, Felip E, Andric Z, Geater S, Özgüroğlu M, Zou W, Sandler A, Enquist I, Komatsubara K, Deng Y, Kuriki H, Wen X, McClelland M, Mocchi S, Jassem J, Spigel DR. Atezolizumab for First-Line Treatment of PD-L1-Selected Patients with NSCLC. *N Engl J Med* 2020; **383**: 1328-1339 [PMID: 32997907 DOI: 10.1056/NEJMoa1917346]
 - 8 **Paz-Ares L**, O'Brien MER, Mauer M, Dafni U, Oselin K, Havel L, Esteban Gonzalez E, Isla D, Martinez-Marti A, Faehling M, Tsuboi M, Lee J-S, Nakagawa K, Yang J, Keller SM, Jha N, Marreaud SI, Stahel RA, Peters S, Besse B. VP3-2022: Pembrolizumab (pembro) vs placebo for early-stage non-small cell lung cancer (NSCLC) following complete resection and adjuvant chemotherapy (chemo) when indicated: Randomized, triple-blind, phase III EORTC-1416-LCG/ETOP 8-15 – PEARLS/KEYNOTE-091 study. *Ann Oncol* 2022 [DOI: 10.1016/j.annonc.2022.02.224]
 - 9 **Chaft JE**, Dahlberg SE, Khullar OV, Edelman MJ, Simone CB, Heymach J, Rudin CM, Ramalingam SS. EA5142 adjuvant nivolumab in resected lung cancers (ANVIL). *J Clin Oncol* 2018; **36**: TPS8581-TPS8581 [DOI: 10.1200/jco.2018.36.15_suppl.tps8581]
 - 10 **Calvo V**, Domine M, Sullivan I, Gonzalez-Larriba J-L, Ortega AL, Bernabé R, Sala MA, Campos B, De Castro J, Martín-Martorell P, Bosch-Barrera J, Mielgo X, Vilà L, Casal J, Ros S, Martínez Aguillo M, Padilla A, Sandiego S, Aires Machado J, Provencio-Pulla M. A phase III clinical trial of adjuvant chemotherapy vs chemoimmunotherapy for stage IB-IIIa completely resected non-small cell lung cancer (NSCLC) patients nadim-adjuvant: New adjuvant trial of chemotherapy vs chemoimmunotherapy. *J Clin Oncol* 2021; **39**: TPS8581-TPS8581 [DOI: 10.1200/jco.2021.39.15_suppl.tps8581]
 - 11 **Peters S**, Spigel D, Ahn M, Tsuboi M, Chaft J, Harpole D, Goss G, Barlesi F, Abbosh C, Poole L, May R, Dennis PA, Swanton C. P03.03 MERMAID-1: A phase III study of adjuvant durvalumab plus chemotherapy in resected NSCLC patients with MRD+ post-surgery. *J Thorac Oncol* 2021; **16**: S258-S259



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