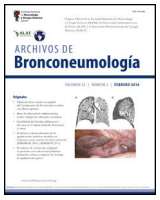
Archivos de Bronconeumología xxx (xxxx) xxx–xxx

Sociedad Española de Neumología y Cirugía Torácica SEPAR

ARCHIVOS DE
Bronconeumología

www.archbronconeumol.org



Editorial

Immunotherapy in Early-Stage Non-Small Cell Lung Cancer: A PRO/CON Debate

Introduction

The treatment landscape of early-stage non-small cell lung cancer (NSCLC) has evolved significantly with the introduction of immune checkpoint inhibitors (ICIs). Building on the success of immunotherapy in advanced disease, recent trials have explored its role in the perioperative setting for resectable NSCLC. These studies have shown promising improvements in pathological response and event-free survival, leading to regulatory approvals and integration into clinical guidelines [1–17]. However, as immunotherapy moves into earlier stages of disease, critical questions remain regarding its real-world applicability, long-term benefits, patient selection, and potential harms [21–28]. This editorial presents a balanced perspective on the use of immunotherapy in early-stage NSCLC, with arguments in favor and against its widespread implementation.

PRO position: immunotherapy in early-stage NSCLC

Given the poor prognosis of patients with non-metastatic, potentially curable lung cancer (stages II–IIIA) through surgery—very different from other tumors at the same stages—various strategies have been developed based on immuno- or chemoimmunotherapy: adjuvant (after surgery), neoadjuvant (before surgery), or perioperative (combining both).

The first study on neoadjuvant PD-1 blockade in resectable NSCLC was conducted by Forde et al. [1]. This study evaluated the feasibility of two cycles of nivolumab in 21 patients with early-stage (I–IIIA) NSCLC. Other monotherapy studies have also been tested, such as the Lung Cancer Mutation Consortium 3 (LCMC3) [2], another phase II trial involving 181 patients with resectable stage IB–IIIB (T3N2) NSCLC. Patients received two doses of atezolizumab before surgery. The primary endpoint was major pathological response (MPR), which was 20.4%.

Perioperative treatment with chemoimmunotherapy was pioneered by the NADIM study [3,4]. This was a phase II, single-arm, open-label, multicenter Spanish trial. It involved 46 patients with resectable stage IIIA N2 NSCLC. The goal was to assess the feasibility, safety, and efficacy of neoadjuvant chemotherapy with paclitaxel and carboplatin plus nivolumab every 3 weeks for 3 cycles before surgery, followed by 1 year of adjuvant nivolumab. The primary endpoint was 24-month progression-free survival (PFS), which was very high: 77.1%. Updated 5-year results published in Lancet Oncology show: overall survival (OS) of 81.2%, 5-year PFS of 69.4%, and R0 resection rates above 90% [5].

The NADIM II trial is a phase II, open-label, randomized, two-arm study that enrolled 90 patients with resectable stage IIIA–IIIB (8th edition) NSCLC to receive nivolumab plus chemotherapy (paclitaxel and carboplatin) or chemotherapy alone, followed by surgery. A total of 86 patients were randomized. The primary endpoint in the ITT population was pathological complete response (pCR) assessed by blinded independent central review. The pCR rate was 37% in the nivolumab plus chemotherapy group versus 7% in the chemotherapy group ($p = 0.0068$). The 24-month PFS was 67.2% in the experimental arm and 40.9% in the control arm (HR 0.47; 95% CI: 0.25–0.88). OS at 24 months was 85.0% in the nivolumab plus chemotherapy arm versus 63.6% in the chemotherapy arm (HR 0.43; 95% CI: 0.19–0.98) [6].

Recently, the CheckMate 816 phase III, multicenter, randomized, open-label trial compared neoadjuvant nivolumab plus chemotherapy with chemotherapy alone in patients with resectable stage IB–IIIA NSCLC. Primary endpoints were event-free survival (EFS) and pCR. Median EFS was 31.6 months in the nivolumab plus chemo group vs. 20.8 months in the control group (HR 0.63; 97.38% CI: 0.43–0.91; $p = 0.005$). The pCR rate was 24% in the experimental group vs. 2.2% in the chemotherapy group (OR 13.94; 99% CI: 3.49–55.75; $p < 0.0001$) [7]. This treatment has been approved as a neoadjuvant option in the US and several other countries for adults with resectable NSCLC (tumors > 4 cm and/or node-positive) [8]. In Europe, the Committee for Medicinal Products for Human Use (CHMP) recommended nivolumab in combination with platinum-based chemotherapy as neoadjuvant treatment for resectable NSCLC with high recurrence risk in PD-L1 ≥ 1% tumors [9]. Recently, positive results from CM 816 in favor of overall survival (OS) have been announced via press release [10].

The KEYNOTE-671 trial also met its primary EFS endpoint in selected patients with resectable stage II, IIIA, and IIIB NSCLC. Results were presented at ASCO 2023 [11] and later published in NEJM [12]. A total of 797 patients were randomized. Median EFS was not reached in the study arm vs. 17 months in the control. OS was also significantly improved, leading to FDA approval [13].

On March 9, 2023, AstraZeneca announced that durvalumab significantly improved EFS in the AEGEAN trial for resectable NSCLC. This trial included 802 patients. Median EFS was not reached in the durvalumab group vs. 25.9 months in the control [14].

The Neotorch study also evaluated perioperative chemoimmunotherapy (with toripalimab), followed by 13 adjuvant toripalimab cycles. It showed significant improvement in EFS compared to chemotherapy alone [15,16].

https://doi.org/10.1016/j.arbres.2025.09.015

Please cite this article as: M. Provencio and F. Couñago, Immunotherapy in Early-Stage Non-Small Cell Lung Cancer: A PRO/CON Debate, Archivos de Bronconeumología, https://doi.org/10.1016/j.arbres.2025.09.015

CheckMate 77T is a phase III study evaluating the perioperative strategy in resectable NSCLC. It showed that neoadjuvant nivolumab + chemotherapy followed by adjuvant nivolumab improves outcomes. The CHMP has recommended this regimen [17].

The Spanish GECP consensus endorses perioperative treatment as a new standard in resectable NSCLC with nodal involvement [18].

CON position: immunotherapy in early-stage NSCLC

Despite compelling data from clinical trials, the real-world implementation of immunotherapy in early-stage non-small cell lung cancer (NSCLC) presents significant challenges. The universal adoption of this strategy may be premature, particularly when considering the current limitations in survival data, surgical completion rates, and the risk of overtreatment.

While trials like CheckMate 816 [7–10], KEYNOTE-671 [11–13] and NADIM II [6] have demonstrated overall survival (OS) gains, these results are not yet representative of the broader body of perioperative immunotherapy trials. The AEGEAN [14], NeoTORCH [15,16], and RATIONALE-315 [19] trials have reported improvements in pathological complete response (pCR) or event-free survival (EFS), but mature OS data remain pending. Furthermore, in the adjuvant setting, the BR31 trial [20] failed to show a disease-free survival (DFS) benefit in an unselected population.

Even in trials where survival gains have been reported, the context must be carefully considered. These studies involve highly selected patients, managed under strict protocols in academic centers with extensive resources. In routine clinical practice, patient populations are more heterogeneous, often with comorbidities, social barriers, and logistical challenges that may limit the applicability of trial results. Therefore, the efficacy demonstrated in trials may not translate to effectiveness in the real world [21].

A growing concern comes from real-world data showing that a significant proportion of patients do not proceed to surgery after receiving neoadjuvant immunotherapy. In a recent U.S. multicenter cohort study, only 63% of patients who began neoadjuvant immune checkpoint inhibitor (ICI) treatment ultimately underwent surgical resection. Reasons included disease progression, treatment-related toxicity, and functional decline [22]. Similarly, in a large study within the U.S. Veterans Affairs (VA) system, 27% of patients failed to complete surgery despite being initially deemed operable [23].

These findings are striking when contrasted with the >90% surgical completion rates typically reported in clinical trials. This discrepancy underscores a significant gap between controlled research environments and real-life clinical practice. If a key goal of neoadjuvant immunotherapy is to improve surgical outcomes, the failure of a substantial number of patients to reach surgery in everyday practice undermines this objective and may compromise curative intent.

In addition to these logistical concerns, there is still uncertainty regarding the true benefit of immunotherapy in non-operable patients. Notably, the KEYNOTE-867 trial—evaluating pembrolizumab plus SBRT in medically inoperable stage I-II NSCLC—was recently discontinued due to lack of improvement in survival outcomes and increased toxicity [24]. This result highlights the risk of applying immunotherapy beyond well-established settings.

Another important consideration is the potential for overtreatment. The addition of ICIs introduces risks of immune-related adverse events (irAEs), including pneumonitis, adrenal insufficiency, thyroid dysfunction, and other endocrinopathies. These toxicities can delay surgery, impair postoperative recovery, or even require lifelong management. In patients with a low risk of recurrence—such as those with small, node-negative tumors—the incremental benefit of immunotherapy may not outweigh these risks [25].

The balance between benefit and harm becomes even more delicate in elderly patients or those with multiple comorbidities. These individuals are often underrepresented in clinical trials, yet they constitute a large proportion of the real-world early-stage NSCLC population. The introduction of neoadjuvant or adjuvant immunotherapy in these patients, without robust survival data, may result in reduced quality of life or treatment-related complications without clear oncologic benefit [26].

Furthermore, immunotherapy has shown limited efficacy in patients with oncogenic driver mutations, such as EGFR or ALK alterations, who represent a clinically significant subset of early-stage NSCLC. In these patients, targeted therapies remain the standard of care, and the benefit of adding ICIs is questionable and potentially harmful [27].

Moreover, access to immunotherapy remains uneven across healthcare systems, raising concerns about equity. High drug costs, limited infrastructure, and variability in multidisciplinary care may restrict access for patients in lower-resource settings, further widening disparities [28].

In summary, while the promise of immunotherapy in early-stage NSCLC is undeniable, its real-world application faces significant barriers. Surgical completion rates are substantially lower outside of trials, mature survival data are lacking for many regimens, and the risk of overtreatment and toxicity in certain subgroups is real. Until ongoing studies provide more definitive answers—and implementation strategies are optimized—it may be premature to adopt immunotherapy as a universal standard in early-stage NSCLC

Conclusions

Perioperative chemoimmunotherapy has been established as a new standard of care in early-stage resectable NSCLC by several international regulatory agencies, including the FDA and EMA, based on robust evidence from pivotal phase III trials demonstrating improvements in pathological response and event-free survival. These advances mark a significant shift in the management of resectable disease and offer new hope for improved long-term outcomes.

Nevertheless, successful implementation in routine clinical practice requires careful patient selection, awareness of potential barriers such as surgical attrition, and attention to specific subgroups—such as those with oncogenic driver mutations—in whom the benefit remains unclear. Continued follow-up of ongoing trials and real-world studies will be essential to optimize treatment algorithms and ensure equitable access to these promising therapies.

Authors' contribution

All authors have contributed substantially to obtaining the results and preparation of the manuscript in accordance with ICMJE criteria.

Artificial intelligence involvement

During the preparation of this work the author(s) used ChatGPT in order to improve language and readability. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sector.

Conflicts of interest

Felipe Couñago: Sponsored Research: Janssen, Recordati. Consulting, advisory role: Janssen, AstraZeneca. Lectures and educational activities: Janssen, Roche Farma, AstraZeneca, Astellas, Recordati. Ipssen. Travel, Accommodations, Expenses: AstraZeneca, Astellas, Janssen, Roche Farma, Recordati, Ipssen.

Mariano Provencio: Advisory council or committee: Amgen, Pfizer, Daiichi Sankyo, Johnson & Johnson, BMS, Takeda, AstraZeneca, Gilead, MSD, Guardant Health, Ipsen, Incyte Biosciences, Bayer; Honoraria: BMS, Astra Zeneca, MSD, Roche, Takeda, Eli Lilly, F. Hoffman-La Roche, Janssen, Pfizer, Amgen; Consulting fee: BMS, Astra Zeneca, MSD, Roche, Takeda, Eli Lilly, F. Hoffman-La Roche, Janssen, Pfizer, Amgen; Grants or funds: Research funding received from BMS, Astra Zeneca, MSD, Roche, Takeda, Pfizer, Takeda, Boehringer Ingelheim, Amgen, Instituto de Salud Carlos III, Spanish Ministry of Science and Innovation, European Commi.ssion, Eli Lilly, F. Hoffman-La Roche, Janssen, Phierre Fabre Pharmaceuticals.

References

[1] Forde PM, Chaft JE, Smith KN, Anagnostou V, Cottrell TR, Hellmann MD, et al. Neoadjuvant PD-1 blockade in resectable lung cancer. N Engl J Med 2018;378(21):1976–86, http://dx.doi.org/10.1056/NEJMoa1716078.
[2] Rusch VW, Chaft JE, Johnson B, Wistuba II, Kwiatkowski DJ, Kris MG, et al. Surgical results of the Lung Cancer Mutation Consortium 3 trial: a phase II multicenter single-arm study to investigate the efficacy and safety of atezolizumab as neoadjuvant therapy in patients with stages IB-select IIIB resectable non-small cell lung cancer. J Thorac Cardiovasc Surg 2023;165(6):1802–13, http://dx.doi.org/10.1016/j.jtcvs.2022.10.007.
[3] Provencio M, Nadal E, Insa A, García-Campelo MR, Casal-Rubio J, Dómine M, et al. Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial. Lancet Oncol 2020;21(11):1413–22, http://dx.doi.org/10.1016/S1470-2045(20)30453-8.
[4] Cascone T, William WN Jr. Perioperative nivolumab results in favourable long-term outcomes in patients with locally advanced resectable non-small-cell lung cancer. Nat Rev Clin Oncol 2024, http://dx.doi.org/10.1038/s41571-024-00976-x. Epub ahead of print.
[5] Provencio M, Nadal E, Insa A, García-Campelo R, Casal J, Dómine M, et al. Perioperative chemotherapy and nivolumab in non-small-cell lung cancer (NADIM): 5-year clinical outcomes from a multicentre, single-arm, phase 2 trial. Lancet Oncol 2024;25(11):1453–64, http://dx.doi.org/10.1016/S1470-2045(24)00498-4.
[6] Provencio M, Nadal E, González-Larriba JL, Martínez-Martí A, Bernabé R, Bosch-Barrera J, et al. Perioperative nivolumab and chemotherapy in stage III non-small-cell lung cancer. N Engl J Med 2023;389(5):491–503, http://dx.doi.org/10.1056/NEJMoa2215530.
[7] Forde PM, Spicer J, Lu S, Provencio M, Mitsudomi T, Awad MM, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. N Engl J Med 2022;386(21):1973–85, http://dx.doi.org/10.1056/NEJMoa2202170.
[8] Neoadjuvant Opdivo (nivolumab) with chemotherapy provides benefits for patients with resectable non-small cell lung cancer across PD-L1 expression levels with three-year follow-up in CheckMate -816 trial. Bristol Myers Squibb Newsroom 2023. Available from: https://news.bms.com/news/details/2023/Neoadjuvant-Opdivo-Nivolumab-with-Chemotherapy-Provides-Benefits-for-Patients-with-Resectable-Non-Small-Cell-Lung-Cancer-Across-PD-L1-Expression-Levels-with-Three-Year-Follow-Up-in-CheckMate-816-Trial/default.aspx [cited 26.4.25].
[9] Bristol Myers Squibb receives European Commission approval for Opdivo (nivolumab) with chemotherapy as neoadjuvant treatment of resectable non-small cell lung cancer at high risk of recurrence in patients with tumor cell PD-L1 expression ≥1%. Bristol Myers Squibb Newsroom 2023. Available from: https://news.bms.com/news/details/2023/Bristol-Myers-Squibb-Receives-European-Commission-Approval-for-Opdivo-Nivolumab-with-Chemotherapy-as-Neoadjuvant-Treatment-of-Resectable-Non-Small-Cell-Lung-Cancer-at-High-Risk-of-Recurrence-in-Patients-with-Tumor-C [cited 26.4.25].
[10] Bristol Myers Squibb announces Opdivo plus chemotherapy as the first and only neoadjuvant-only immuno-oncology therapy to demonstrate statistically significant and clinically meaningful overall survival in resectable non-small cell lung cancer. Bristol Myers Squibb Newsroom 2025. Available from: https://news.bms.com/news/details/2025/Bristol-Myers-Squibb-Announces-Opdivo-Plus-Chemotherapy-as-the-First-and-Only-Neoadjuvant-Only-Immuno-Oncology-Therapy-to-Demonstrate-Statistically-Significant-and-Clinically-Meaningful-Overall-Survival-in-Resectable-Non-Small-Cell-Lung-Cancer/default.aspx [cited 26.4.25].
[11] Wakelee H, Altorki NK, Zhou C, Castellanos E, Felip E, Pérez-Garcia JM, et al. KEYNOTE-671: randomized, double-blind, phase 3 study of pembrolizumab or placebo plus platinum-based chemotherapy followed by resection and pembrolizumab or placebo for early-stage NSCLC. J Clin Oncol 2023;41 Suppl. LBA8000. Available from: https://meetings.asco.org/abstracts-presentations/225718
[12] Wakelee H, Altorki NK, Zhou C, Castellanos E, Felip E, Pérez-Garcia JM, et al. Perioperative pembrolizumab for early-stage non-small-cell lung cancer. N Engl J Med 2023;389(6):491–503, http://dx.doi.org/10.1056/NEJMoa2302983.
[13] FDA approves neoadjuvant/adjuvant pembrolizumab for resectable non-small cell lung cancer. U.S. Food and Drug Administration; 2023. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-neoadjuvant-adjuvant-pembrolizumab-resectable-non-small-cell-lung-cancer [cited 26.4.25].
[14] Imfinzi significantly improved event-free survival in AEGEAN Phase III trial for patients with resectable non-small cell lung cancer. AstraZeneca Press Release; 2023. Available from: https://www.astrazeneca.com/media-centre/press-releases/2023/imfinzi-improved-efs-in-resectable-lung-cancer.html [cited 26.4.25].
[15] Toripalimab plus chemotherapy improves event-free survival in resectable stage III NSCLC. The ASCO Post; 2023. Available from: https://ascopost.com/issues/june-10-2023/neotorch-trial-toripalimab-plus-chemotherapy-improves-event-free-survival-in-resectable-stage-iii-nsclc/ [cited 26.4.25].
[16] Ku S, Hu X, Wu L, Han B, Li W, Zhao J, et al. Perioperative toripalimab+platinum-doublet chemotherapy vs chemotherapy in resectable stage II/III non-small cell lung cancer (NSCLC): interim event-free survival (EFS) analysis of the phase III Neotorch study. J Clin Oncol 2023;41 Suppl.:425126, http://dx.doi.org/10.1200/JC.O.36.suppl.425126.
[17] Bristol Myers Squibb receives positive CHMP opinion for perioperative regimen of neoadjuvant Opdivo (nivolumab) and chemotherapy followed by surgery and adjuvant Opdivo for resectable non-small cell lung cancer in patients with tumor cell PD-L1 ≥1%. Bristol Myers Squibb Newsroom 2025. Available from: https://news.bms.com/news/corporate-financial/2025/Bristol-Myers-Squibb-Receives-Positive-CHMP-Opinion-for-Perioperative-Regimen-of-Neoadjuvant-Opdivo-nivolumab-and-Chemotherapy-Followed-by-Surgery-and-Adjuvant-Opdivo-for-Resectable-Non-Small-Cell-Lung-Cancer-in-Patients-with-Tumor-Cell-PD-L1—/default.aspx [cited 26.4.25].
[18] Ospina AV, Bolufer Nadal S, Campo-Cañaveral de la Cruz JL, González Larriba JL, Macía Vidueira I, Massutí Sureda B, et al. Multidisciplinary approach for locally advanced non-small cell lung cancer (NSCLC): 2023 expert consensus of the Spanish Lung Cancer Group GECP. Clin Transl Oncol 2024;26(7):1647–63, http://dx.doi.org/10.1007/s1.
[19] Yue D, Wang W, Liu H, Chen Q, Chen C, Liu L, et al. Perioperative tislelizumab plus neoadjuvant chemotherapy for patients with resectable non-small-cell lung cancer (RATIONALE-315): an interim analysis of a randomised clinical trial. Lancet Respir Med 2025;13(2):119–29, http://dx.doi.org/10.1016/S2213-2600(24)00269-8.
[20] Butts C, Shepherd FA, Tsao MS, Ding K, Seymour L, Ellis PM, et al. LBA48 CCTG BR.31: a global, double-blind placebo-controlled, randomized phase III study of adjuvant durvalumab in completely resected non-small cell lung cancer (NSCLC). Ann Oncol 2024;35 Suppl. 7:S1234–5, http://dx.doi.org/10.1016/S0923-7534(24)03869-9.
[21] Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. N Engl J Med 2000;342(25):1887–92, http://dx.doi.org/10.1056/NEJM200006223422507.
[22] Bott MJ, D'Amico TA, Yang CJ, Berry MF, Riely GJ, Tan KS, et al. Perioperative chemotherapy and immune checkpoint inhibitors for resectable non-small cell lung cancer: real-world outcomes and challenges to surgery. J Thorac Oncol 2024;19(6):970–80, http://dx.doi.org/10.1016/j.jtho.2024.02.020.
[23] Lin J, Scholz C, Meziani L, Schuler M, Chaft JE, Hellmann MD, et al. Outcomes of neoadjuvant chemoimmunotherapy followed by surgery versus definitive chemoradiation plus durvalumab in potentially resectable stage III non-small-cell lung cancer. Cancer Immunol Immunother 2025;74(5):1471–84, http://dx.doi.org/10.1007/s00262-025-03961-0.
[24] Pircher A, Sótér S, Galffy G, Kowalski D, Hata A, Valdivia Bustamante AA, et al. Stereotactic body radiotherapy (SBRT) with pembrolizumab (pembro) for unresected stage I/II non-small-cell lung cancer (NSCLC): the randomized, double-blind, phase 3 KEYNOTE-867 study. Ann Oncol 2024;35 Suppl. 1:S117O, http://dx.doi.org/10.1016/j.annonc.2024.09.117O.
[25] Barcellini L, Nardin S, Sacco G, Ferrante M, Rossi G, Barletta G, et al. Immune checkpoint inhibitors and targeted therapies in early-stage non-small-cell lung cancer: state-of-the-art and future perspectives. Cancers (Basel) 2025;17(4):652, http://dx.doi.org/10.3390/cancers17040652.
[26] Matsukane R, Oyama T, Tatsuta R, Kimura S, Hata K, Urata S, et al. Real-world prevalence and tolerability of immune-related adverse events in older adults with non-small cell lung cancer: a multi-institutional retrospective study. Cancers (Basel) 2024;16(11):2159, http://dx.doi.org/10.3390/cancers16112159.
[27] Zhou C, Wu L, Fan Y, Wang Q, Zhang L, Liu Y, et al. Efficacy of immunotherapy in patients with oncogene-driven non-small-cell lung cancer: a systematic review and meta-analysis. Ther Adv Med Oncol 2023;15:17588359231225036, http://dx.doi.org/10.1177/17588359231225036.

[28] Polite BN, Adams-Campbell LL, Brawley OW, Bickell NA, Carethers JM, Flowers CR, et al. Immune-based cancer treatment: addressing disparities in access and outcomes. J Clin Oncol 2021;39(17):1881–8, http://dx.doi.org/10.1200/JCO.21.00203.

Mariano Provencio [a,*], Felipe Couñago [b,c,d,e]
[a] *Mariano Provencio, Medical Oncologist, Chief of Medical Oncology, Hospital Universitario Puerta de Hierro, Madrid, Spain*
[b] *Radiation Oncologist, GenesisCare, Spain*
[c] *Hospital Universitario San Francisco de Asís, Madrid, Spain*
[d] *Hospital Universitario La Milagrosa, Madrid, Spain*
[e] *Department of Medicine, Faculty of Medicine, Health and Sport Sciences, Universidad Europea de Madrid, Madrid, Spain*

Corresponding author.
E-mail address: mprovenciop@gmail.com (M. Provencio).