# The path forward in early-stage lung cancer

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Editorial

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*Comment on:* Duan J, Tan F, Bi N, *et al.* Expert consensus on perioperative treatment for non-small cell lung cancer. Transl Lung Cancer Res 2022;11:1247-67.

**Keywords:** Early-stage lung cancer; perioperative strategy; perioperative immune checkpoint inhibition; perioperative targeted therapy

Submitted Jul 22, 2022. Accepted for publication Aug 29, 2022. Published online Dec 30, 2022.
doi: 10.21037/tlcr-22-546
**View this article at:** https://dx.doi.org/10.21037/tlcr-22-546

Lung cancer is the leading cause of cancer mortality worldwide, with 2.2 million new lung cancer patients (accounting for 11.4% of all cancer cases) and 1.8 million deaths (representing 18% of cancer deaths) in 2020 (1). Early-stage disease non-small cell lung cancer (NSCLC) has better outcomes, but the 5-year survival rates drop from 60% for stage IIA to 36% for stage IIIA disease (2,3). Adjuvant chemotherapy has shown to improve survival by 5.4% but is paired with clinically important toxicity (4).

Neoadjuvant chemotherapy is less extensively studied as adjuvant chemotherapy but has resulted a similar benefit of approximately 5% at 5-year (5).

Two new therapeutic strategies that revolutionized treatment of metastatic disease, have been introduced in the (neo)adjuvant field: targeted therapies and immune checkpoint inhibitors (ICIs). These have now led to a revival of interest for the treatment of non-metastatic lung cancer.

Of the tyrosine kinase inhibitor (TKI)'s, adjuvant osimertinib treatment significantly improved disease-free survival (DFS) after surgery for epidermal growth factor receptor (EGFR) mutated NSCLC (6). Soon after, adjuvant atezolizumab showed to improve outcome, with treatment benefit being most pronounced in patients with a high programmed death-ligand 1 (PD-L1) expression (7). In both trials higher disease stages benefited the most of this strategy, but all patients were still treated chemotherapy before randomization.

In earlier disease stages however, the improvement was less impressive. Adjuvant pembrolizumab similarly reached the primary endpoint of improved DFS, but no relation with PD-L1 expression was observed, leaving many of us puzzled behind (8).

Adoption of immunotherapy-based strategies were investigated in the neoadjuvant setting, due to several potential advantages over adjuvant therapies: (I) reduction of tumor burden before surgery allowing for less morbid resections; (II) to assess a potential therapeutic response on the resection specimen (pathological response); (III) to induce better immune-surveillance offering protection for disease recurrence. This strategy is in line with preclinical evidence in early disease, probably related to fitness of host immunity and presence of (sufficient) neo-antigens (9-11). Several trials looked at various endpoints such as safety, feasibility, efficacy, and pathological response rate of programmed death-1 (PD-1) inhibitors in monotherapy or combined with other ICIs or chemotherapy (12), all leading to the conclusion that neoadjuvant PD-1 inhibitor-based strategies are promising, safe, feasible and efficacious, leading to larger randomized trials.

In this edition of *Translational Lung Cancer Research*, an expert consensus on perioperative treatment for NSCLC

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is presented. Unique about this consensus meeting is the fact that the invited clinicians are mostly based in the Australasian and European countries, thereby introducing information of studies with new drugs. The paper covers all known studies and gives insight is the way different centers or countries have implemented the scientific data in their daily routine. It is clear that there are still many variations in patient management and questions to be addressed.

## Neo-adjuvant therapy

The choice of ICIs to be tested is nowadays immense and primary endpoints do vary. Is major pathological response (mPR) the best endpoint? How toxic will new combinations be and lead to a failure in performing the surgical resection? How many courses of therapy can be given in a safe way? Do we still need chemotherapy as standard of care (SoC)? Can you continue with ICI after surgery when it has shown to be successful?

Recently the results of the CheckMate 816 phase III trial (CM816) were published, showing a benefit of combining chemotherapy plus nivolumab over chemotherapy alone. Both primary endpoints of improved event-free survival (EFS) and pathological response rate were met and did so with excellence (13). Just as in the adjuvant trials this approach appeared to be more advantageous in patients with higher disease stages (such as stage IIIA) and in patients with PD-L1 expression. This trial and other neoadjuvant PD-1 inhibitor-based trials, showed a significant proportion (approximately 15% in the CM816) of patients diagnosed with an operable NSCLC, that did not advance to surgery for various reasons (such as disease progression, toxicity, irresectability, …) (14).

## Adjuvant therapies

Most of the studies have not been able to introduce an arm where no chemotherapy is given. It is well known that not many patients are able to tolerate 3–4 courses of chemotherapy and subsequently can still be randomized to another agent or placebo. One must be careful of a potential selection bias when interpreting the adjuvant data. One clear message is echoed in this consensus meeting: Do preselect your patient for EGFR and anaplastic lymphoma kinase (ALK) mutation. This has major impact on the course of treatment. How long an adjuvant therapy like ICI or targeted agent must be given remains a question.

With the release of data from ongoing studies, we might be able to solve some of these questions, but time will usually tell.

From our and scientific point of view the path forward is to implement neo-adjuvant therapies, because this will identify those patients who benefit most and will most likely reduce the number of futile and expensive treatments in the adjuvant setting.

## Acknowledgments

*Funding:* None.

## Footnote

*Provenance and Peer Review:* This article was commissioned by the editorial office, *Translational Lung Cancer Research*. The article did not undergo external peer review.

*Conflicts of Interest:* Both authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-546/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



## References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
2. Eberhardt WEE, Mitchell A, Crowley J, et al. The IASLC lung cancer staging project: proposals for the revision of the M descriptors in the forthcoming eighth edition of the TNM classification of lung cancer. J Thorac Oncol

2015;10:1515-22.
3. Boyd JA, Hubbs JL, Kim DW, et al. Timing of local and distant failure in resected lung cancer: implications for reported rates of local failure. J Thorac Oncol 2010;5:211-4.
4. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008;26:3552-9.
5. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. Lancet 2014;383:1561-71.
6. Wu YL, Tsuboi M, He J, et al. Osimertinib in Resected EGFR-Mutated Non-Small-Cell Lung Cancer. N Engl J Med 2020;383:1711-23.
7. Felip E, Altorki N, Zhou C, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. Lancet 2021;398:1344-57.
8. Paz-Ares L, O'Brien MER, Mauer M, et al. VP3-2022: Pembrolizumab (pembro) versus 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;33:451-3.
9. McGranahan N, Furness AJ, Rosenthal R, et al. Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. Science 2016;351:1463-9.
10. Liu J, Blake SJ, Yong MC, et al. Improved Efficacy of Neoadjuvant Compared to Adjuvant Immunotherapy to Eradicate Metastatic Disease. Cancer Discov 2016;6:1382-99.
11. Blank CU, Rozeman EA, Fanchi LF, et al. Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma. Nat Med 2018;24:1655-61.
12. Chaft JE, Shyr Y, Sepesi B, et al. Preoperative and Postoperative Systemic Therapy for Operable Non-Small-Cell Lung Cancer. J Clin Oncol 2022;40:546-55.
13. Forde PM, Spicer J, Lu S, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. N Engl J Med 2022;386:1973-85.
14. Spicer J, Wang C, Tanaka F, et al. Surgical outcomes from the phase 3 CheckMate 816 trial: Nivolumab (NIVO)+ platinum-doublet chemotherapy (chemo) vs chemo alone as neoadjuvant treatment for patients with resectable non-small cell lung cancer (NSCLC). J Clin Oncol 2021;39:abstr 8503.

**Cite this article as:** Cuppens K, Baas P. The path forward in early-stage lung cancer. Transl Lung Cancer Res 2023;12(1):11-13. doi: 10.21037/tlcr-22-546