Editorial

Operable non-small cell lung cancer: induction therapy, adjuvant therapy, or both?

Apostolos C. Agrafiotis^, Paul E. Van Schil

Department of Thoracic and Vascular Surgery, Antwerp University Hospital and University of Antwerp, Antwerp, Belgium

Correspondence to: Paul E. Van Schil, MD, PhD. Department of Thoracic and Vascular Surgery, Antwerp University Hospital, Drie Eikenstraat 655, B-2650 Edegem, Antwerp, Belgium. Email: Paul.VanSchil@uza.be.

Comment on: Shinohara S, Takahashi Y, Masago K, *et al.* The beginning of a new era in induction treatment for operable non-small cell lung cancer: a narrative review. J Thorac Dis 2023;15:747-58.

Keywords: Non-small cell lung cancer (NSCLC); neoadjuvant treatment; adjuvant therapy; immune checkpoint inhibitors (ICI); epidermal growth factor receptor (EGFR); tyrosine kinase inhibitors (TKI)

Submitted Apr 23, 2023. Accepted for publication Jun 09, 2023. Published online Jun 26, 2023.
doi: 10.21037/jtd-23-678
View this article at: https://dx.doi.org/10.21037/jtd-23-678

Shinohara *et al.* conducted a narrative review on neoadjuvant treatment of operable non-small cell lung cancer (NSCLC) for which there is currently a renewed interest in light of the promising results of recently performed phase II and III trials (1). The review focuses on randomized controlled trials conducted during the last 32 years. The authors investigate the efficacy of systemic induction therapy for operable NSCLC and the possible application of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) and immune checkpoint inhibitors (ICI).

Even if the benefit of neoadjuvant chemotherapy is undeniable for locally advanced NSCLC, its place in early-stage cases is still under debate. The authors underline another issue concerning the available body of literature: the studies included in their review cover an extensive period. During this period the staging modalities, the classification systems, and the surgical techniques have changed (1). This fact has to be taken into account when interpreting the different results. Another indisputable fact is the recent rapid development of new molecules that can be part of the treatment of NSCLC, such as the targeted agents and ICI. These molecules seem to be a real game-changer in the treatment not only of advanced NSCLC but also of resectable early-stage disease. Current areas of research include not only neoadjuvant therapy but also specific adjuvant therapy and a combination of both, as well neoadjuvant as adjuvant, so-called perioperative therapy. Precise treatment regimens have not been established. Best results have been reported in stage IIIA NSCLC although the optimal regimen remains to be determined, but early-stage NSCLC has also become a focus of specific interest.

Some trials included in the Shinohara *et al.* review should be underlined.

NADIM I is a single-arm phase II trial that investigated the efficacy of neoadjuvant nivolumab combined with chemotherapy in operable stage IIIA NSCLC followed by adjuvant nivolumab for 1 year. An impressive 3-year overall survival (OS) of 81.9% was reported (2). Another interesting finding of this trial is the use of circulating tumor DNA (ctDNA) as a surrogate marker of treatment success. More specifically, low pretreatment levels of ctDNA accounted for improved progression-free survival (PFS) and OS. In addition, undetectable ctDNA levels after neoadjuvant treatment proved to be a reliable biomarker for improved OS. These findings were confirmed in the randomized phase II NADIM II trial showing a significantly better PFS and OS in the combined chemotherapy/nivolumab arm in comparison with chemotherapy alone (3). It should be noted that in the NADIM I as well as in the experimental arm of NADIM II, nivolumab was continued for 1 year

^ ORCID: 0000-0002-7525-2080.

postoperatively; so, both these trials represent perioperative therapy.

Checkmate 816 is a randomized phase III study, which has already become a landmark trial (4). The addition of neoadjuvant nivolumab to chemotherapy was compared to chemotherapy alone in 358 subjects with resectable NSCLC who did not present EGFR/ALK mutations. Most of the enrolled patients were diagnosed with stage IIIA disease. In this trial no adjuvant immunotherapy was given and adjuvant chemotherapy and/or radiotherapy were optional. Regarding the results, an increased pathological response was found when neoadjuvant nivolumab was combined with chemotherapy. The primary endpoint of pathological complete response (pCR) significantly increased from 2.2% to 24%, independently of the disease stage, the histology, and the expression levels of PD-L1. Major pathological response (mPR) rates were respectively, 8.9% and 36.9%. In the arm of bimodal treatment, pCR was increased when the levels of PD-L1 expression were ≥1%. The second primary endpoint of event-free survival (EFS) was also considered to be acceptable in a press release on April 11, 2022 (5). Surgical outcomes were considered satisfactory. Operative time, R0 resection rates, the extent of resection, adverse events, complications, and length of stay were not influenced when nivolumab was added.

KEYNOTE-671 is a randomized, double-blind phase III trial that assessed neoadjuvant pembrolizumab plus chemotherapy, followed by adjuvant pembrolizumab as a single agent versus placebo plus neoadjuvant chemotherapy followed by adjuvant placebo in patients with resectable stage II, IIIA or IIIB (T3-4N2) NSCLC. In a press release published on March 1, 2023, pembrolizumab combined with chemotherapy resulted in a significant increase in EFS, pCR, and mPR over chemotherapy alone (6). The complete results are expected to be published soon.

AEGEAN is a randomized, double-blind, multi-center, placebo-controlled global phase III trial that investigated durvalumab as a perioperative treatment for patients with resectable Stage IIA-IIIB NSCLC, irrespective of PD-L1 expression. A press release published on March 9, 2023, stated that neoadjuvant durvalumab in combination with chemotherapy followed by adjuvant monotherapy with durvalumab after surgery resulted in a statistically significant and clinically meaningful increase in EFS compared to neoadjuvant chemotherapy alone followed by surgical resection (7). The complete results are also expected to be presented soon.

The primary analysis of the phase III ADAURA trial revealed a clinically significant disease-free survival (DFS) advantage of adjuvant osimertinib versus placebo in stage IB-IIIA NSCLC harboring EGFR mutations after complete tumor resection (8). Osimertinib is a third-generation EGFR-TKI. On the whole population, DFS HR was 0.27 (95% CI: 0.21 to 0.34); the 4-year DFS rate was 73% (osimertinib) and 38% (placebo). Fewer local/regional and distant recurrences were observed in patients treated with osimertinib versus placebo. In a recent press release of March 9, 2023 also OS was found to be significantly longer in the osimertinib arm compared to placebo (9). These compelling results of adjuvant osimertinib reasonably led the researchers to investigate its efficacy in the neoadjuvant setting. Consequently, the phase III NeoADAURA study evaluates neoadjuvant osimertinib combined with or without chemotherapy compared to chemotherapy alone, in patients with resectable stage II–IIIB N2 EGFR-mutated NSCLC. The primary endpoint is mPR at the time of resection (10). Patient enrollment began on December 16, 2020, and the estimated primary analysis is scheduled for the first half of 2024.

The review of Shinohara *et al.* together with the "hot off the press" results of the most recent trials demonstrate that new therapeutic agents with promising results are added to the anticancer armamentarium. We are certainly moving towards a new era where surgery will be part of multimodality treatment, even for upfront resectable NSCLC. However, the optimal treatment regimen remains to be determined. Current clinical research focuses on specific subgroups of NSCLC to evaluate whether induction, adjuvant, or perioperative treatment with chemotherapy, immunotherapy, or targeted agents is the best option to yield excellent DFS and OS results. Undoubtedly, in the near future, a new standard of care algorithm will become available for resectable NSCLC. Thoracic surgeons will certainly have to adapt their surgical strategy accordingly!

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Thoracic Disease*. The article

did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-678/coif). PEVS has the following conflicts of interest to declare: (I) advisory board and/or honoraria for lectures from AstraZeneca, BMS, Roche, MSD and Janssen and (II) president-elect IASLC (International Association for the Study of Lung Cancer) and treasurer BACTS (Belgian Association for Cardiothoracic Surgery). ACA has 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. Shinohara S, Takahashi Y, Masago K, et al. The beginning of a new era in induction treatment for operable non-small cell lung cancer: a narrative review. J Thorac Dis 2023;15:747-58.
2. Provencio M, Serna-Blasco R, Nadal E, et al. Overall Survival and Biomarker Analysis of Neoadjuvant Nivolumab Plus Chemotherapy in Operable Stage IIIA Non-Small-Cell Lung Cancer (NADIM phase II trial). J Clin Oncol 2022;40:2924-33.
3. Provencio M, Serna R, Nadal E, et al. PL03.12 Progression Free Survival and Overall Survival in NADIM II Study. J Thorac Oncol 2022. Available online: https://doi.org/10.1016/j.jtho.2022.07.014
4. Forde PM, Spicer J, Lu S, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. N Engl J Med 2022;386:1973-85.
5. Bristol Myers Squibb - Neoadjuvant Opdivo (nivolumab) with Chemotherapy Significantly Improves Event-Free Survival in Patients with Resectable Non-Small Cell Lung Cancer in Phase 3 CheckMate -816 Trial (bms.com) (accessed on 07/04/2023).
6. Available online: https://www.merck.com/news/merck-announces-phase-3-keynote-671-trial-met-primary-endpoint-of-event-free-survival-efs-in-patients-with-resectable-stage-ii-iiia-or-iiib-non-small-cell-lung-cancer/
7. Available online: https://www.astrazeneca.com/media-centre/press-releases/2023/imfinzi-improved-efs-in-resectable-lung-cancer.html
8. Herbst RS, Wu YL, John T, et al. Adjuvant Osimertinib for Resected EGFR-Mutated Stage IB-IIIA Non-Small-Cell Lung Cancer: Updated Results From the Phase III Randomized ADAURA Trial. J Clin Oncol 2023;41:1830-40.
9. Tagrisso demonstrated strong overall survival benefit in the ADAURA Phase III trial for adjuvant treatment of patients with early-stage EGFR-mutated lung cancer. Accessed on 07/04/2023. Available online: https://www.astrazeneca.com
10. Tsuboi M, Weder W, Escriu C, et al. Neoadjuvant osimertinib with/without chemotherapy versus chemotherapy alone for EGFR-mutated resectable non-small-cell lung cancer: NeoADAURA. Future Oncol 2021;17:4045-55.

Cite this article as: Agrafiotis AC, Van Schil PE. Operable non-small cell lung cancer: induction therapy, adjuvant therapy, or both? J Thorac Dis 2023;15(7):3519-3521. doi: 10.21037/jtd-23-678