Editorial

From expert recommendations to multidisciplinary team decisions: a way to set out the novel perioperative options for patients with non-small-cell lung cancer

Giuseppe Luigi Banna[1,2], Jarushka Naidoo[3,4], Alfredo Addeo[5]

[1]Candiolo Cancer Institute, FPO-IRCCS, Candiolo, Turin, Italy; [2]Department of Oncology, Portsmouth Hospitals University NHS Trust, Portsmouth, UK; [3]Beaumont Hospital and RCSI University of Health Sciences, Dublin, Ireland; [4]Department of Oncology, Sidney Kimmel Comprehensive Cancer Center, Bloomberg-Kimmel Institute for Cancer Immunotherapy, Johns Hopkins University, Baltimore, MD, USA; [5]Department of Oncology, University Hospital of Geneva, Geneva, Switzerland

Correspondence to: Giuseppe Luigi Banna. Candiolo Cancer Institute, FPO-IRCCS, Candiolo, Turin, Italy; Portsmouth Hospitals University NHS Trust, Portsmouth, UK. Email: giuseppe.banna@nhs.net.

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.

Submitted Jul 12, 2022. Accepted for publication Jul 22, 2022.
doi: 10.21037/tlcr-22-517
View this article at: https://dx.doi.org/10.21037/tlcr-22-517

The progressive adoption of low-dose computed tomography (CT) screening for lung cancer is expected to increase the incidence of early-stage non-small-cell lung cancer (NSCLC) (1). The thrust to move effective systemic therapies from later to earlier disease phases, where cure rate remains unsatisfactory (2), alongside molecular profiling with next-generation sequencing (NGS) assays, has already started to reshape diagnostic and treatment algorithms for the early-stage NSCLC. Four milestone studies have changed our clinical practice in localised or locally advanced NSCLC and set the scene for new future research. First, the phase 3 PACIFIC study established maintenance immunotherapy with durvalumab following chemoradiotherapy for the unresectable stage III NSCLC (3). A sustained benefit in both progression-free survival (PFS) (more than tripled compared to placebo) and overall survival (OS) (with ten per cent more survivors in absolute terms) was reported at five years of follow-up (4). In patients with resectable stage IB to IIIA NSCLC according to TNM 7th edition, the phase 3 Checkmate816 study showed that three cycles of neoadjuvant chemotherapy plus nivolumab prolonged the median event-free survival (EFS) of about one-third in patients treated with this regimen, and led to more than ten-fold pathological complete response (pCR) compared with chemotherapy alone (5). A postoperative immunotherapy approach with adjuvant atezolizumab in patients with resected stage II-IIIA programmed-cell-death-ligand 1 (PD-L1) ≥1% NSCLC is the third major innovation and led to more than thirty per cent reduction in the risk of disease recurrence or death compared to best supportive care in the Impower010 phase 3 study (6). Lastly, in resected stage IB-IIIA with epidermal growth factor receptor (*EGFR*)-mutant NSCLC, a benefit in disease-free survival (DFS) was observed with adjuvant targeted therapy with osimertinib compared to placebo in the phase 3 ADAURA study, regardless of receipt of adjuvant chemotherapy (7). Taken together, there have been practice-changing advances in the perioperative management of NSCLC.

In the current issue, an international expert panel of thoracic surgeons and oncologists provide a consensus report on the perioperative management of NSCLC. To better understand the contribution to the existing knowledge, we first need to answer the question of whether a consensus on this topic is required. An expert consensus might be particularly needed when scant or low-level evidence is available for a clinically-relevant subject or conversely if the literature supports a different therapeutic approach (8,9). Alternatively, if a marginal benefit for a particular approach is seen, a meta-analysis might help to elucidate the next steps (10). In addition, Health Technology Assessments (HTA) by national agencies may provide

additional information on the potential risks and benefits of adopting new standards of care (11). In the setting of perioperative NSCLC, the need for an expert consensus is arising from the pace of the above-mentioned pivotal trials, the impact on current clinical diagnostic and therapeutic pathways, and the use of short-term or surrogate outcomes of benefit and often inconsistent biomarkers in some of these studies.

The important studies outlined above have utilised some novel and, in some cases, controversial endpoints, including pCR, major pathological response (MPR), EFS and DFS. The relationship between these endpoints and OS benefit is still debated (12). Furthermore, the definitions for these endpoints may differ across clinical trials. Regarding biomarkers, as in other disease settings, are crucial in the perioperative setting in order to identify which patients may benefit most from therapy (13) but also to prevent exposure to unnecessary treatment and side effects, avoid surgical delays and reduce associated costs (14). Surprisingly, although a high PD-L1 was established as a consistent predictive biomarker for immunotherapy in the advanced NSCLC (15) and appeared to associate with benefit in the neoadjuvant setting together with chemotherapy in both the Checkmate816 (5) and Phase 2 NADIM2 (16) studies, its predictive role was less clear in the phase 3 Keynote-091/PEARLS trial of adjuvant pembrolizumab (17) but confirmed in the same setting by the phase 3 Impower010 trial of atezolizumab utilising the SP263-based assay (6). Thus far, tumour mutational burden (TMB) was not predictive of the benefit of neoadjuvant chemoimmunotherapy, evaluated in the Checkmate816 study (5).

Another exciting area of biomarker research in the perioperative setting includes circulating biomarkers. Cell-free circulating tumour (ct)DNA clearance was associated with pCR in the Checkmate816 study (5). However, ctDNA presence after surgery, albeit consistently prognostic, was not predictive of the benefit of immunotherapy in the Impower010 study (6,18), as DFS benefit from atezolizumab was observed in both patients with detectable ctDNA and without. In patients with oncogene-addicted NSCLCs, the DFS results reported by the ADAURA trial (7) in EGFR sensitising mutation-positive NSCLC can be considered a proof of principle for the adjuvant use of any next-generation TKIs in the oncogene-addicted NSCLC as long as they have proven to be very effective in the advanced stage. Moreover, the Impower010 study subanalysis of the *EGFR* and anaplastic lymphoma kinase (*ALK*) population showed a lack of benefit from adjuvant immunotherapy in these patients (6). This suggests that tumoral *EGFR* and *ALK* status must be known before planning adjuvant therapy for NSCLC. However, different tumour responses to immunotherapy can be observed within and across patients with oncogene-addicted NSCLCs. For instance, better outcomes are described among *EGFR* L858R or uncommon mutations compared to *EGFR* exon 19 deletions, in *KRAS*, *BRAF* and *MET vs. EGFR*, *ALK* and *ROS1*, or as the effect of the presence of co-mutations which may confer relative immunotherapy sensitivity (like *TP53*) or resistance (like *STK11*, *KEAP*, or *NFE2L2*) (19-23). This also remains a grey area for (neo)adjuvant treatments.

In this scenario, two key messages from the expert consensus represent a common thread of their recommendations that deserves emphasis. The first is that, in the perioperative setting, therapeutic planning of patients with NSCLC should be on a patient-by-patient basis and within a multidisciplinary specialist team. A patient's eligibility for surgery, in terms of tumour resectability and patient operability, is the first essential step and is a critical turning point to determining management as either localised or locally-advanced disease. Although cure is the primary objective in resectable and unresectable NSCLC, the ultimate goals of neoadjuvant chemoimmunotherapy are tumour downstaging aiming at more radical and potentially less invasive surgery and eradication of the micrometastatic disease. In unresectable NSCLC, chemoradiotherapy followed by immunotherapy remains the current standard to control the disease locally and prevent distant relapse. The second message relates to the interpretation of molecular testing, whether limited to the currently relevant molecular parameters (i.e., *EGFR*, *ALK* and PD-L1) or extended to all molecular drivers that may be detected by NGS profiling. Molecular results require discussion within multidisciplinary teams, including pathologists, molecular biologists and bioinformaticians, who can inform treatment planning or patient referral for clinical trials.

Some perioperative issues have not been discussed by the experts, such as the indication for adjuvant radiotherapy. Furthermore, the duration of perioperative treatments, including the length of the oncological follow-up, side-effects monitoring and the required professional specialities, will likely need appropriate focus. Nevertheless, this expert effort is commendable and spurs the oncology community to discuss and re-organise cancer services in the era of perioperative immunotherapy.

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: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-517/coif). GLB reports personal fees from AstraZeneca, Astellas, travel and conference expenses from Janssen, outside the submitted work. JN reports grants from Merck, AstraZeneca, personal fees from AstraZeneca, Bristol-Myers Squibb, Roche/Genentech, outside the submitted work. AA reports advisory board: MSD Oncology, Roche, Takeda, Pfizer, Bristol-Myers Squibb, AstraZeneca, Eli-Lilly, Roche; speaker bureau from Eli-Lilly, AstraZeneca, Amgen; SA consulting or advisory role from Bristol Myers Squibb, AstraZeneca, Boehringer Ingelheim, Eisai, Roche, Novartis, Merck Serono, MSD Oncology, Pfizer, Takeda, AbbVie; research funding from Boehringer Ingelheim, AstraZeneca, Bristol Myers Squibb, Eisai, Merck Serono, AbbVie; expert testimony from Roche, AstraZeneca, Bristol Myers Squibb; travels, accommodations, expenses from Roche Pharma AG, Lilly, Bristol Myers Squibb, AstraZeneca, Merck Sharp & Dohme, Amgen; outside the submitted work.

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.

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Cite this article as: Banna GL, Naidoo J, Addeo A. From expert recommendations to multidisciplinary team decisions: a way to set out the novel perioperative options for patients with non-small-cell lung cancer. Transl Lung Cancer Res 2022;11(7):1237-1240. doi: 10.21037/tlcr-22-517