



# Expert consensus on perioperative immunotherapy in non-small cell lung cancer: an editorial

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According to the latest estimations, approximately one out of three patients with a non-small cell lung cancer (NSCLC) diagnosis presents a localized disease (stage I–IIIA), for which a surgical procedure can be envisaged as the best treatment option (1). While the role of perioperative radiotherapy is still discussed, (neo)adjuvant, platinum-based chemotherapy is part of the treatment strategy depending on the precise disease stage, given the potential development of metastatic disease growing from micro-metastatic sites. Several strategies have been envisaged in the later years with agents other than chemotherapy [i.e., anti-angiogenic drugs, vaccines, early-generation EGFR tyrosine kinase inhibitors (TKIs) in unselected or in *EGFR*-mutant patients populations, tailored chemotherapy regimens] (2-5). Nevertheless, the standard of care of (neo)adjuvant chemotherapy has not changed, with an improvement of 5% in the 5-year survival rate compared to surgery alone (6). Considering the relative benefit and the toxicity related to platinum-based chemotherapy, potential predictive biomarkers have been proposed to address the clinical decision in this setting (7,8), but none has been validated.

Improving the outcomes of early NSCLC is a capital mission of current oncology. Two main aspects concur to defining this aim as pivotal. First, it is likely that the widespread introduction of lung cancer screening will provide an increase in NSCLC diagnosed at early stages. Second, NSCLC patients who undergo surgery for localized

disease are the ones for which a curative intent can be envisaged, and increasing the performance of perioperative systemic treatment translates into augmenting the chances of providing a cure.

Immune checkpoint inhibitors (ICIs; anti-PD-1/PD-L1) have revolutionized the treatment landscape of NSCLC (9). Following a classical drug development in advanced disease, after being shown active and effective in later therapy lines, they have been proven superior to chemotherapy in the second/third line and then have moved into the first-line setting, alone or in combination with chemotherapy according to PD-L1 expression levels. Given the substantial clinical benefit observed in advanced NSCLC, clinical trials have envisaged the role of ICIs in locally advanced disease, and the anti-PD-L1 durvalumab is now recommended and approved after definitive chemo-radiotherapy for non-surgical stage III NSCLC patients with PD-L1  $\geq 1\%$ . Therefore, the ultimate step is represented by the incorporation of ICIs in the treatment armamentarium in early, localized NSCLC suitable for surgical treatment. The survival rates observed with ICIs in advanced, pretreated NSCLC, inconceivable in the pre-immunotherapy era, established the concept of cure even in metastatic disease. The initial clinical trials results of perioperative NSCLC patients strongly support the role of ICI in early disease.

We have read with interest the expert consensus on perioperative immunotherapy provided by Qiu *et al.* (10), and we are delighted to comment on it for several reasons.

The amount of information and data (both available, both upcoming/eagerly awaited) on perioperative ICIs is significant and requires a thorough approach to assess a correct interpretation. The authors provide an organized and clear review of all the evidence. The topic is relatively complex, and as stated above, this is a clinical setting where the difference can be made for a relevant number of patients. Providing an in-depth discussion with international experts allows us to go beyond the data, share impressions and concerns and underline clinical trials' strengths and limitations. Detailing what is and what is not reported in the studies helps to translate the results in the clinical practice, following the best strategies.

We congratulate the authors for their proposal and the successful outcome of their project.

Considering the validity of the literature summary provided by the authors, we refer to the text for a comprehensive evaluation of the evidence emerging from clinical trials. We only add that the results of IMpower010, reporting the benefit in disease-free survival (DFS) of adjuvant atezolizumab after adjuvant chemotherapy in stage II–IIIA (according to the 7th edition of AJCC staging system) with PD-L1  $\geq 1\%$  have been recently published *in extenso* (11), prompting FDA approval. Studies are heterogeneous regarding disease stages included, treatment strategies proposed, and primary outcomes measures, accounting for the aforementioned challenges of a global interpretation.

Dealing with perioperative therapy requires serious considerations about several concepts involving different specialists and the basis of clinical oncology. Among these latter figures the relevance of correct and complete staging procedures and the inner significance of (neo)adjuvant therapies. It is worth to mention that, across the manuscript, neoadjuvant strategies seem to be fostered by thoracic surgeons too. Historically, with chemotherapy this was not the case, as surgical procedure was (appropriately) considered the backbone of treatment and delaying it was not easily accepted. Despite some technical challenges, this cultural shift is likely sustained by the good outcomes observed with neoadjuvant approaches.

Neoadjuvant immunotherapy does not cause a delay in scheduled surgery in patients with early-stage lung cancer. Multiple clinical trials evaluating perioperative outcomes are required to determine the feasibility and safety of pulmonary resection following neoadjuvant immunotherapy (12). Pulmonary resection was feasible but cautioned against the development of mediastinal and

hilar fibrosis due to treatment response. Bott *et al.* (13) concluded that it was possible without causing undue morbidity, although pulmonary resection was difficult. Yang *et al.* (14) established that resection was safe and feasible, with perioperative outcomes comparable to those observed in a cohort of patients treated with neoadjuvant platinum-based chemotherapy. Pulmonary resection following neoadjuvant nivolumab therapy did not result in excessive morbidity or mortality. Despite the disease being radiographically stable, significant pathological responses were identified. A recent analysis of the National Cancer Database revealed that only 25.7% of such patients underwent lobectomy via a minimally invasive approach. Despite this, thoracotomy appears not to affect morbidity or early mortality rates (15).

Numerous trials are ongoing or in development, and neoadjuvant immunotherapies may eventually replace neoadjuvant chemotherapy as the standard of care for selected patients with locally and regionally advanced NSCLC. Nonetheless, there are several points to consider as we embark on this new paradigm. The selection of patients and the involvement of surgeons in trial enrolment are critical. Although minimally invasive procedures are possible, they may be technically challenging, and conversion should be considered if thoracoscopy does not allow for safe dissection. Pneumonectomy should be performed with caution until more safety data become available (16).

Taken together, the technical issues do not give rise to a higher complication rate, the ultimate readout in considering the benefit/risk ratio. The data supporting these assumptions derive from clinical trials, and the comprehensive acquisition of the specific competencies in the clinical practice will be crucial in order to obtain positive outcomes in the daily routine. Of note, the apparent discrepancies between the encouraging results of the first proof-of-concept of neoadjuvant nivolumab (17) and following results that are scaling down the enthusiasm have at least partially attributed to the potential sensitive patient selection in the first experience.

Except for IMpower010, all the results available thus far on this topic deal with neoadjuvant strategies and, after confirming safety and feasibility, the preliminary signs of activity rely on surrogate outcomes. Indeed, whether long-term survival outcomes (in terms of DFS and/or overall survival; OS) are the most significant, the encouraging data refer to pathological entities such as the achievement of major pathological responses (MPR; defined by  $\leq 10\%$  of

viable tumour cells in the surgical sample) and complete responses (pCR). While the pathological response to neoadjuvant chemotherapy has been validated as a reliable surrogate of survival outcomes in breast cancer (18), and moreover addresses adjuvant treatment (19), the evidence sustaining its role, as well its definition in NSCLC is less unequivocal (20-22). From a methodological point of view, the discussed and disappointing 5% benefit of (neo)adjuvant chemotherapy is referred to as a 5-year survival rate, so the final readout of perioperative immunotherapy strategies should recapitulate long-term survival outcomes. In the mentioned IMpower010, median follow-up was of 32.2 (interquartile range, 27.4–38.3) months and for resected II–IIIA, PD-L1  $\geq 1\%$  NSCLC, three-year DFS rate was of 60% *vs.* 48.2% in the atezolizumab and best supportive care, respectively (11).

Long-term results will actually clarify the true contribution of (chemo)immunotherapy in the management of early NSCLC. Nevertheless, the required long-term follow-up would delay the availability of treatments in the clinical practice, depriving patients from (potentially) useful therapy in the timeframe delimited by the report of surrogate outcomes (MPR) and landmark survival-rates.

We, therefore, agree with the observation provided almost unanimously by the panelists, who shared their enthusiasm about the available data, still waiting for survival information to drive definitive conclusions for a change in the clinical practice.

Together with the indirect pathological signs of neoadjuvant (chemo)immunotherapy activity and the lack of feasibility concerns, some clinical elements concur to sustain the role of ICIs in the perioperative NSCLC setting. Exposing patients to immunotherapy as early as possible during their disease course can be the right strategy, as ICIs benefit can be affected by performance status, concomitant medications (e.g., steroids, antibiotics), globally reflecting patients' fitness. On the other hand, correlations between lower tumour burden (such in localized disease) and undermined immunotherapy have not been reported. From this point of view, fostering the immune systems of early NSCLC, either in the neoadjuvant or in the adjuvant settings, can be interpreted as a suitable timeframe. Whether the presence of the tumour antigens (such as in the neoadjuvant strategy) may augment ICIs activity compared to the adjuvant setting is a question to be addressed ideally by head-to-head clinical trials, with accompanying translational research.

A goal in the setting of perioperative immunotherapy

is, in line with all oncological treatments, to administer the best treatment according to each patient and disease characteristics. Although this statement could seem quite utopistic, as an absolute and perfect match between treatment and patient is hard to envisage with current biomarkers, some elements favoring the oncological community and treating physicians can be considered. As stated by the authors and emerged from the consensus panelists, early-stage NSCLC management is currently influenced by molecular status, similar to advanced disease. Osimertinib has become the standard of care in the adjuvant setting of *EGFR*-mutated NSCLC and is now evaluated in the neoadjuvant setting (23,24). It is expected that other oncogene-driven diseases as well could benefit from targeted agents in the perioperative setting. Therefore, it has become crucial to assess the molecular status of NSCLC even in the early stages, considering both the potential of kinase inhibitors (as clinical practice or clinical trials) and the disappointing results of immunotherapy strategy in oncogene-addicted, advanced NSCLC (25). The last statement should nevertheless be interpreted with caution, as a large amount of available data refer to single-agents PD-1/PD-L1 inhibitors administered in later treatment lines. With particular regard to *KRAS*- and *BRAF*-altered lung cancers, potentially sensitive to ICIs, both strategies could be envisaged, and a potential mixed approach (targeted agents in neoadjuvant, adjuvant immunotherapy, as the inverted sequence can lead to enhanced toxicities) may be of interest in peculiar cases (25).

Some panelists referred to PD-L1 expression as a valuable biomarker to address patients to immunotherapy alone or combined chemo-immunotherapy, moving the threshold of  $\geq 50\%$  of positive tumour cells from advanced to early NSCLC stages. Still, a large majority of the panelists expressed potential concern with regard to neoadjuvant PD-1/PD-L1 single-agent, as the phenomenon of hyper-progression could frustrate the surgical approach (26). Notably, if the risk of hyper-progression is acceptable in the advanced setting, considered the benefit/risk ratio, in curative, early stages, it could be more difficult to accept by patients and physicians. From this perspective, we agree with panelists that chemo-immunotherapy combinations in the neoadjuvant setting could be a reasonable option, given the limited occurrence of hyper-progressions according to evidence from first-line treatment, observed both directly and from Kaplan-Meier curves of registration studies (27,28).

Moving to the “pure” adjuvant setting, the evaluation of

minimal residual disease by measuring circulating tumour DNA, correctly evoked by the authors, will hopefully help address patients to adjuvant therapy in the next future. However, its role is not currently defined in clinical practice.

Another relevant issue that emerged in the consensus deals with immune-related toxicities in the perioperative setting. Indeed, the adverse events may not only be severe and condition patients in a long-term timeframe, but in the specific scenario of early NSCLC, the risk of surgery delay should be taken into account and the potential need for high-dose steroids for managing autoimmune toxicities. Again, patient selection would likely play a pivotal role. Even with the lack of valid biomarkers to predict patients more likely to develop immune-related adverse events, a multidisciplinary evaluation should be performed with particular regard to patients with underlying autoimmune disease, again for a thorough assessment of the benefit/risk ratio (29).

Concerning additional, minor considerations provided by authors and panelists, we think that  $^{18}\text{F}$ -FDG PET should continue to be an essential element for disease staging. However, we are more challenged about its role in evaluating systemic, immunotherapy-containing therapy in the perioperative setting. Its role is still not defined, and it is not commonly used in clinical routine, so its utilization could add complexities in response interpretation. CT-scan based RECIST should remain the criteria of reference.

In conclusion, we are thankful to the authors for their rigorous and complete work of synthesis. Moreover, we truly believe that sharing visions and concerns internationally is an extraordinary and timely effort. Indeed, even if perioperative immunotherapy is still not incorporated into NSLC guidelines and clinical practice, the rapidity of the development of these strategies and the availability of data prompt us to foresee it in the next future. Discussions like the one proposed in this consensus are of great utility, both in terms of information and in light of moving the results of clinical trials into daily practice. As emerged from the consensus and as we have tried to recapitulate, the potential availability of multiple treatment opportunities in the perioperative setting of NSCLC would require the knowledge of expected outcomes and the ability to select each patient to the right strategy. Now that the stakes deal with the patients' cure, all the efforts should be made, in a multidisciplinary environment, to always chasing all the chances.

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