Editorial

Resectable non-small cell lung cancer: an evolving landscape

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The landscape of resectable non-small cell lung cancer (NSCLC) has changed dramatically in recent years, with the advent of neoadjuvant chemotherapy and evaluation of immunotherapy and targeted therapy in adjuvant and neoadjuvant settings. An international expert consensus, authored by Duan *et al.* (1), saliently summarises the existing therapeutic options for patients with resected NSCLC and the key trials supporting them, as well as recommendations on patient evaluation, selection and monitoring. It alludes also to the areas of active research to further improve outcomes. We offer our opinion on some of the areas discussed, in the hopes of promoting further fruitful discussion.

Upfront biomarker testing is considered standard in many areas of oncology. In resectable NSCLC, the consensus recognises that epidermal growth factor receptor (*EGFR*) mutations and programmed death ligand 1 (PD-L1) status actively guides postoperative adjuvant systemic therapy currently. However, it also suggests that detection of anaplastic lymphoma kinase (*ALK*) positivity and other rare molecular alterations "are necessary to guide adjuvant treatment" and that upfront next-generation sequencing (NGS) can be considered. The decision for upfront NGS over sequential targeted testing is a question that involves a complex interplay of turnaround time, tissue requirements, cost and utility. Whilst *EGFR* mutations are the most common actionable molecular alteration in NSCLC, approximately seven years were required from recruitment in the ADAURA study to U.S. Food and Drug Administration (FDA) approval of adjuvant osimertinib (2). Accrual and follow up of adjuvant NSCLC trials involving rarer genetic alterations will be significantly more challenging, and hence would unlikely be ready for prime time in the near future. Certain genetics aberrations, such as that in *EGFR*, *ALK* and Kirsten Rat Sarcoma (*KRAS*) are also nearly mutually exclusive in NSCLC (3) which may then favour sequential testing. Still, co-mutations may guide treatment, perhaps in the form of combination therapy of novel agents in a trial setting and hence should be strongly considered in patients who are trial fit.

Targeted therapy has gained traction in the treatment of resectable NSCLC, which is likely to expand in the years to come. The consensus paper makes a recommendation for adjuvant osimertinib, icotinib or gefitinib for patients with stage IIA-IIB disease who have undergone complete resection, with or without adjuvant chemotherapy. It also makes a recommendation for adjuvant osimertinib, icotinib, gefitinib or erlotinib for completely resected stage IIIA disease with or without adjuvant chemotherapy, with osimertinib being the preferred option. This invites the following questions: is adjuvant tyrosine kinase inhibitor (TKI) supplementary to the benefit of adjuvant chemotherapy or a less toxic alternative, and are the TKIs equivalent? Oncologists are now faced with the option of adjuvant chemotherapy followed by osimertinib TKI (4) or adjuvant TKI alone (as in EVAN, ADJUVANT-CTONG 1104 and EVIDENCE trials) (5-7). There is definite overall survival benefit with the use of adjuvant chemotherapy in resected NSCLC (8). Adjuvant cisplatin-based chemotherapy remains the recommendation for all stage IIA to IIIA resected lung cancer patients in recently updated American Society of Clinical Oncology (ASCO)

guideline recommendations (9). Despite data from phase III trials demonstrating significant disease-free survival (DFS) benefit (e.g., ADAURA, EVIDENCE) (4,6), due to immature follow up, overall survival (OS) has not been reported. Notably, these studies are also not powered for OS although many oncologists feel that OS impact would be most informative. The concern of using adjuvant *EGFR* TKIs alone as a replacement for adjuvant chemotherapy has been highlighted by many critics. In the randomised adjuvant trials such as ADJUVANT (5,10,11), the DFS curves would initially separate but then converge within two years of TKI cessation. This is unlike the persistent DFS curve separations seen usually with immunotherapy studies despite the patients being off therapy. Therefore, the benefit of adjuvant *EGFR* TKI alone without adjuvant chemotherapy remains unknown.

We recommend adjuvant osimertinib after adjuvant chemotherapy unless patients were either unfit or unwilling to receive adjuvant chemotherapy. Currently, only osimertinib is approved by US FDA, European Medicines Agency (EMA) and is recommended in ASCO, ESMO, and NCCN guidelines (9,12,13).

A further question would be whether all the TKIs are of equivalent efficacy as adjuvant treatment options. Erlotinib, gefitinib and icotinib are 1st generation TKIs, whereas osimertinib is a 3rd generation TKI. Central nervous system (CNS) relapse is not uncommon and often associated with significant morbidity, with a 10% rate of CNS recurrence reported in the placebo arm of ADAURA within the study period (4). Osimertinib has excellent CNS penetrance and was found to have efficacy in ADAURA to decrease CNS recurrence and prolong CNS disease-free survival, with only 1% of osimertinib treated patients having CNS relapse (4). In metastatic NSCLC, osimertinib has been shown to improve PFS in patients with CNS metastases compared to gefitinib or erlotinib (14). Icotinib also has a lower CNS penetrance rate at 6.1%, therefore raising concerns of potential CNS recurrence in comparison to osimertinib (15,16).

There are developing spaces for targeted therapy worth paying attention to. The ongoing ADAURA 2 study (NCT05120349) evaluates the role of adjuvant osimertinib in *EGFR* mutation-positive stage IA1-1A3 resected NSCLC which may impact on subsequent recommendations for stage 1A patients in the future. The use of adjuvant targeted therapies for other oncogene driven subtypes of resectable lung cancer such as *ALK* and *RET* are also being actively studied at the moment. Examples include the ALINA trial, a phase III study of adjuvant alectinib compared with platinum-based chemotherapy in patients with completely resected stage IB-IIIA *ALK*-positive lung cancer (17) and the LIBRETTO-432 trial, a phase III study of adjuvant selpercatinib in stage IB-IIIA *RET* fusion-positive NSCLC (18). Regarding the role of neoadjuvant targeted therapy for patients with resectable oncogene driven lung cancer, there is currently no high level evidence to support the use of TKIs and the consensus made no recommendations for its use. However, there has been emerging data to show that the neoadjuvant TKI approach may lead to downstaging and pathological response, with the randomised phase II EMERGING-CTONG 1103 study showing a non-statistically significant improved ORR of 54.1% in the neoadjuvant erlotinib arm compared to 34.4% in neoadjuvant chemotherapy arm (19). Readouts from the neoadjuvant trials of osimertinib with/or without chemotherapy (NeoADAURA, NCT04351555) and alectinib (ALNEO, NCT05015010) are eagerly awaited to determine the role of targeted therapies in this setting.

This consensus statement correctly identifies both neoadjuvant and adjuvant immunotherapy approaches as potential options for the peri-operative treatment of resectable NSCLC. Following the publication of IMpower010, which met its primary endpoint of improved DFS, the standard of care for adjuvant treatment now includes atezolizumab after platinum-based chemotherapy for patients with stage II-III resected NSCLC with PD-L1 expression of at least 1% (20). Recently, preliminary findings from PEARLS/KEYNOTE-091 were presented, showing that pembrolizumab after chemotherapy improved DFS regardless of PD-L1 status (21). These results lend further support to the benefit of sequential immunotherapy after chemotherapy, but leave open the question of whether concurrent treatment might provide even greater benefit. ALCHEMIST Chemo IO (ACCIO) is an ongoing adjuvant study in which patients are randomised to sequential or concurrent chemotherapy plus pembrolizumab following surgery, and results of this trial may provide additional insight into this issue (22).

In the neoadjuvant setting, nivolumab plus pre-operative chemotherapy was recently approved by the FDA based on CheckMate 816, which demonstrated significantly improved rates of pathological complete response (pCR), and longer event-free survival compared with pre-operative chemotherapy alone (23). There has been no direct comparison to determine whether immunotherapy is more beneficial when administered before or after

surgery. In theory, there are some potential advantages to the neoadjuvant approach. Neoadjuvant immunotherapy offers an early opportunity to treat micrometastatic disease, and the increased tumour bulk and presence of tumour antigens may result in deeper immune responses (24,25). Other advantages include tumour downstaging for surgery, increased rates of R0 resections, and reduced surgical time and invasiveness (23). In addition, neoadjuvant therapy can allow for prognostication via the assessment for pCR or major pathologic response (MPR), both of which have been demonstrated to strongly correlate with, and may serve as a surrogate marker for, survival outcomes (26,27). Given the remarkable tumoural response and improved surgical outcomes shown in CheckMate 816, it is tempting to wonder whether induction chemo-immunotherapy could play a role in locally advanced NSCLC with the goal of converting to resectability. In fact, 54% of patients in the NADIM study had multilevel N2 disease, which some may consider unresectable, and achieved good outcomes (28). While promising, the disadvantages of neoadjuvant immunotherapy should not be overlooked. These include a non-negligible risk of progression (6.7 percent in CheckMate 816) and known immunological toxicities, some of which may be long-term. It is therefore important to identify subgroups that would benefit best from this approach. Subgroup analysis from CheckMate 816 appeared to suggest that the magnitude of benefit was greater in patients with stage IIIA disease than in those with earlier stages, and in patients with PD-L1 expression of at least 1% than in those with a level of less than 1% (23). In NADIM, a PD-L1 expression of 25% or more was associated with MPR or pCR, although this was not a sensitive biomarker as 58% of patients with a PD-L1 expression of less than 25% also achieved MPR or pCR. In contrast, PD-L1 expression was not significantly associated with PFS or OS (28). Following promising outcomes in the phase II setting (28,29), a new generation of peri-operative immuno-chemotherapy trials will incorporate immunotherapy in both the neoadjuvant and adjuvant settings, and the treatment landscape is expected to change as new evidence becomes available (30-33).

The duration of adjuvant therapy remains a hot-button issue amongst oncologists, as we strive to strike the optimal balance between efficacy and toxicities. The expert consensus suggests adjuvant TKI duration of 12–24 months in resected *EGFR*-mutated NSCLC. This is shorter than durations used in trials that studied adjuvant erlotinib (RADIANT, EVAN, SELECT) (7,10,34) and adjuvant gefitinib (BR19, ADJUVANT) (5,35) where patients received two years of TKI, and osimertinib (4), where patients received three years of therapy. Treatment duration set by trials are somewhat arbitrary and longer durations of TKI come at the expense of potential toxicities, in patients who might otherwise have been cured by surgery. A study that looked at three months versus two years of adjuvant afatinib showed higher grade three toxicities and treatment discontinuation rates with longer durations of treatment (36). However until there are more definite answers from randomised controlled trials, we should continue to administer adjuvant TKI for durations used in the respective trials. As for immunotherapy, a duration of 1 year is currently practiced based on the IMpower010 and KEYNOTE-091 trials (20,21). However, a more nuanced method of determining therapy duration based on individual patient risk remains to be desired like assessing minimal residual disease (MRD) status.

To that end, ctDNA is an up-and-coming biomarker in multiple tumour types, with a recent multi-center phase II randomised controlled trial showing non-inferiority of a ctDNA-guided approach in determining the need for adjuvant chemotherapy in resected stage II colon cancer patients (37). In the realm of NSCLC, ctDNA appears also to have prognostic value. Exploratory analyses of the CheckMate 816 trial showed higher pCR rates in patients with ctDNA clearance after neoadjuvant therapy, and IMpower010 showed that patients with ctDNA-positivity after surgery and adjuvant therapy had poorer DFS outcomes (20,23). A small study also showed patients with detectable ctDNA 4 months post-treatment for stage I-III NSCLC have worse failure-free progression compared with patients with undetectable ctDNA (38). It is hence fathomable that ctDNA could be used, perhaps with other prognostic factors, to risk-stratify resected NSCLC patients to determine treatment duration.

There are however some challenges with use of ctDNA. Profiling of TRACERx study participants showed a ctDNA detection rate of only 19% in early-stage NSCLC (39). Timing also matters, with the DYNAMIC study showing that presence of ctDNA was associated with reduced recurrence-free survival when the ctDNA was measured at 3 days or 1 month post-resection, but not when measured within 1 day of resection (40). Whilst it is evident that ctDNA has prognostic value in treated early-stage NSCLC, questions that remain include the type of ctDNA technology to use, most suitable timepoints for ctDNA detection, as well as its predictive ability for treatment

decisions.

In summary, the consensus by Duan *et al.* highlights all the available treatment modalities and approaches available for resectable NSCLC. The decision for either neoadjuvant chemotherapy and nivolumab or adjuvant chemotherapy followed by atezolizumab is complex and should be made at a multi-disciplinary tumour board, taking into account patient factors and tumour characteristics. Adjuvant osimertinib should be considered for resected stage IB-IIIA NSCLC with *EGFR* mutations, ideally after the completion of adjuvant chemotherapy as indicated. We eagerly await further studies to guide how immunotherapy and targeted therapy can be incorporated into regimens to maximise benefits and minimise toxicities, and biomarker studies to determine individual patient risk.

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Footnote

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