Editorial

Adjuvant TKI therapy in resected *EGFR*-mutant non-small-cell lung cancer—ready for prime time?

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The treatment landscape of metastatic non-small-cell lung cancer (NSCLC) in the 21st century was initially defined by the discovery of oncogene driver mutations and the promise of personalised therapy. Since the practice changing data from the IPASS study that showed EGFR inhibitors improve progression-free survival (PFS) in patients with sensitising *EGFR* mutations compared to platinum-doublet chemotherapy (1), multiple druggable oncogene driver alterations have been identified, including *ALK*, *ROS-1*, *RET* and *NTRK* rearrangements and *BRAF*, *KRAS*, *MET* and *HER2* mutations (2). Indeed, rapid advances have ensued in recent years with highly selective tyrosine kinase inhibitors (TKIs) demonstrating durable PFS and improved toxicity profiles. One such example is osimertinib, a third generation TKI which recently became the new first-line standard-of-care for the management of *EGFR*-mutant advanced NSCLC based on an improved overall survival (OS) compared to first generation EGFR TKIs (3).

However, despite improvement in PFS outcomes observed with these TKIs, only a subset of patients experience durable disease control and the majority inevitably succumb to disease progression as a consequence of drug resistance. While extensive research is currently underway to better understand mechanisms of circumventing drug resistance and developing highly potent TKIs, the current reality of 'cure' is confined to early stage lung cancers. In fact, with growing public awareness and adoption of lung cancer screening programmes, the proportion of early stage lung cancers is likely to increase in years to come. While surgery or stereotactic ablative radiotherapy are the mainstays of treatment, the risk of disease relapse from mirometastatic disease remains a concern. The LACE meta-analysis demonstrated a hazard ratio of death of 0.89 (95% CI, 0.82 to 0.96, P=0.005) and 5-year absolute benefit of 5.4% from adjuvant cisplatin-based chemotherapy (4), which tempered some of the results from individual studies. It is important to remember that these studies were from an era before molecular testing was routinely performed and when there was a high probability of disease understaging i.e., before PET scanning became more widely-adopted. Nevertheless, it is clear that adjuvant chemotherapy has a role in improving OS rates post-surgical resection.

What is unclear however is if novel therapies which have so elegantly demonstrated benefit in the advanced setting could have a survival impact in the early stage setting. To date, there have been a number of studies testing EGFR inhibitors in the adjuvant setting, all with their own limitations. The earlier clinical trials BR19 (gefitinib *vs.* placebo) and RADIANT (erlotinib *vs.* placebo) were designed prior to molecular selection by mutation status

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and subsequently both included patients regardless of *EGFR* mutation status. Although they were both negative studies, they were underpowered to draw any conclusions in subsequent post-hoc analyses (5,6). The ADJUVANT study (2 years of gefitinib *vs.* 4 cycles of cisplatin plus vinorelbine chemotherapy) and EVAN study (1 year of erlotinib *vs.* 4 cycles of cisplatin plus vinorelbine chemotherapy) were conducted in patients with *EGFR* mutations and demonstrated an improvement in PFS using TKIs (7,8). However, both these studies did not demonstrate an improvement in OS and the majority of relapses occurred after discontinuation of the TKIs. This raised two questions, firstly were EGFR TKIs merely delaying cancer progression through maintenance of a senescent state rather than apoptotic cell death and secondly was more time needed on adjuvant TKI therapy to effect a cure?

Furthermore, it is also important to appreciate that none of the reported adjuvant EGFR TKI studies have an arm where EGFR TKIs are started concurrently or post-chemotherapy. In fact, the rationale for combining chemotherapy with EGFR TKIs has confirmed efficacy in improving OS in the advanced setting compared to EGFR TKI monotherapy in two studies, one from Japan and one from India (9,10). It certainly would be intriguing to study this approach in the early stage setting. Indeed, there are a number of clinical trials which have not been reported yet and could illuminate this strategy including ALCHEMIST-EGFR (NCT02193282); adjuvant platinum-based chemotherapy followed by 2 years of erlotinib *vs.* placebo, WJOG6410L; adjuvant gefitinib for 2 years *vs.* combination gefitinib and chemotherapy in a Japanese population and ADAURA (NCT02511106); adjuvant platinum-based chemotherapy followed by 3 years of osimertinib *vs.* placebo. The latter study is especially important because in the advanced setting, osimertinib has become the new standard-of-care in advanced *EGFR*-mutant NSCLC and represents the most potent of the currently available TKIs. Having said that, the question being asked from the study is that of the advantage of osimertinib after chemotherapy, rather than a direct substitute for it (although the study does allow participants who are not suitable or who refuse chemotherapy and therefore will be a subgroup of interest). A recent press release has confirmed that this study is positive for disease-free survival, however the details are yet to be presented (11).

In this context, Liang *et al.* present a consensus expert review and recommendations for post-surgical management of *EGFR*-mutant NSCLC (12). The consensus document was generated by a large global panel which consisted of experts from China. There was a further opinion piece from experts outside China specifically addressing the various recommendations made. Overall, there was equilibrium in opinions however there were varying levels of agreement with a few of the consensus statements.

The first consensus statement recommends that *EGFR* mutation testing be performed routinely in surgically resected non-squamous NSCLC. The rationale is that there is data for the use of EGFR TKIs in the adjuvant setting as outlined in this editorial. There was some disagreement by experts outside China questioning the strength of the data for adjuvant EGFR TKI therapy. Indeed, there should be a clinical justification for any investigation that is performed. Therefore, in the clinical setting where EGFR TKIs are not available as adjuvant therapy, there may not be a strong rationale for testing. Having said that, some of the advantages of performing oncogene mutation testing is for patient enrolment into adjuvant clinical trials, streamlining medical care (and therefore in the event of systemic disease relapse, there will not be a delay in initiating the appropriate systemic therapy) and the ability to perform targeted liquid biopsies as an adjunct investigation to monitor for disease relapse.

The second and third consensus statements recommend that EGFR TKIs could be used as a substitute for chemotherapy in patients with Stage 1B to 3A resected NSCLC. Unsurprisingly, there was disagreement amongst the experts outside China, mainly citing the lack of an OS advantage or an arm in any of the adjuvant studies combining chemotherapy with EGFR TKI therapy. Although EGFR TKI therapy represents a novel option with a biological rationale in this population, clinicians should exercise caution for these reasons and therefore chemotherapy should remain the standard-of-care for any post-operative oncogene driver mutation NSCLC patient outside a relevant clinical trial. Moreover, a number of crucial questions remain about using adjuvant EGFR TKI therapy, such as length of treatment and financial toxicity associated. Another important point is that there is a risk that by initiating the TKI early, there will be clonal selection and therefore a more resistant subtype or histological transformation at disease relapse. Outside more robust data, EGFR TKIs could be considered an option for patients with resected *EGFR*-mutant NSCLC who are ineligible or refuse to undergo chemotherapy as per the recommendations in consensus 4 and 5.

Next, consensus statement 6 recommends regular brain and bone imaging in patients with resected *EGFR*-mutant

NSCLC. Though intuitive given a small percentage of patients experience CNS disease relapse (13), a number of experts outside China had varying opinions. This is due to the lack of clinical trial data and in fact, the ADAURA study included chest, abdomen and pelvis CT staging (not brain) as part of the surveillance protocol. Nevertheless, it is important to always consider CNS relapse as a possibility in patients with resected *EGFR*-mutant NSCLC and clinicians should have a low threshold to institute brain imaging as clinically indicated.

Finally, consensus statements 7 and 8 suggest re-biopsying patient tumours at disease relapse and for the commencement of osimertinib *en spec*. Overall there was agreement for this approach from experts outside China. As discussed in this editorial, instituting TKI therapy early could result in clonal selection and relapsed tumours in this context are likely to behave differently from *de novo EGFR*-mutant tumours. For example, tumours which relapse after being treated with 1st line EGFR TKIs are more likely to have the *T790M* mutation but could also have other patterns of resistance such as a *MET* mutation or amplification or undergone small-cell transformation (14,15). Therefore, it is important to both histologically and molecularly evaluate relapsed disease in order to determine the most suitable treatment course as there could be a small percentage of patients of which osimertinib may not be the most suitable treatment option. Nevertheless, if re-biopsy of relapsed tumours is not possible, then instituting osimertinib based on Occam's razor applies.

As the era of precision medicine dawns upon the oncology community, so must our ongoing efforts to evaluate the role of currently available and novel therapies in varying clinical settings in both a systematic and robust way. This is important so that we can provide optimal care to our patients, which consists of an improvement in survival and quality-of-life weighed against the risks of drug and financial toxicities. As such, this consensus document by the Society of Translational Medicine on postoperative management of *EGFR*-mutant NSCLC is timely and educational. Nevertheless, the results from studies which have completed recruitment are awaited which will further inform us on the optimal management of this patient subpopulation. The positive ADAURA results may be the next step towards instituting molecular testing in this setting, although the magnitude of benefit will need to be considered when these data are available. Nonetheless, the primary endpoint for ADAURA was DFS in patients with Stage IB to IIIA resected NSCLC and many questions will remain unanswered for several years to come. Most importantly we will not know if the adjuvant third generation TKI (unlike the first generation TKIs) given for three years actually cures patients or simply delays disease progression. If it is the former, then there is no doubt that treatment paradigms should change to accommodate adjuvant TKIs, if it is the latter then we would argue that molecular subclassification will better enable researchers to design studies that impact cure by personalisation of therapy.

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