EGFR mutations in lung cancer: not all equal in the eyes of the immune system?

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There were an estimated 2 million new lung cancer cases in 2018 [American Cancer Society, Cancer Facts and *Figures 2018* accessed 12 Aug 2019 https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf]. In this interesting paper Hastings *et al.* contribute to the knowledge of EGFR mutation (EGFRm) subtypes and response to immune checkpoint inhibitor (ICI) treatments in non-small cell lung cancer (NSCLC). This is a particularly important issue in the Asia-Pacific region where lung cancer is the leading cause of cancer deaths in women and the prevalence of lung cancers with driver EGFRm can be very high (1). As such, incremental gains in knowledge for this subset of lung cancer are relevant and timely, given the emergence of a proliferation of ICI therapies to the therapeutic armamentarium for lung cancer, and the question arises of treatment sequencing and best combinations (2).

It is generally thought that EGFRm tumors exhibit low response rates to immune checkpoint blockade overall, but some EGFRm tumors appear to respond. The Authors confirm that from their retrospective analysis of 171 cases of EGFRm NSCLC tumors, that EGFRm tumors do generally have a low response to ICIs, but outcomes can vary by the sensitising mutant allele. For example, the overall survival in the EGFR del19 group was reduced whereas EGFR L858R tumours had similar response rate and OS compared with the EGFR wildtype (EGFRwt) subgroup.

The strengths of this collaborative work (3) included making use of existing data sources including clinical trial and The Cancer Genome Atlas project, to which our Institution was privileged to contribute (4), resulting in a relatively large combined total study population and large enough subsets stratified by the sensitising allele to enable and understanding of ICI by EGFRm subtypes. Additionally, various ICIs were used which provides confidence in the generalisability of these results. Given the known inverse relationship of smoking to EGFRm status, and its link to the acquisition of a high tumour mutation burden (TMB)—which is a putative predictive biomarker of ICI response—it was important to note that this study did not identify a modifier effect of smoking on ICI response. In the same vein, pre-therapy PD-L1 expression, another putative ICI biomarker in some settings, also did not affect response. Indeed, neither did the presence of EGFR T790M mutations, a common acquired resistance mechanism to 1st and 2nd generation EGFR TKI treatments,

which has important clinical connotations.

Potential limitations include the retrospective design, and therefore the heterogeneity of lines of treatment, sequencing and timing which may have affected the patient outcomes. The heterogeneous nature of the ICIs used (which includes combination ICI therapy) also has an uncertain impact of the findings reported. Additional detail regarding the clinical settings where ICI therapies in this study would enable the reader to critically assess and determine their confidence in the applicability of the results in real life settings. Again, retrospectivity means that data are not universally available across all cases to avoid selection bias, e.g., incomplete data on TMB *vs.* PDL1 status in all cases. The authors acknowledge that molecular testing was not possible on the cohort receiving ICI, but we do not know if the results of EGFRm TMB status from a separate cohort reflects the differences seen here. TMB has also yet to be prospectively validated as an accepted biomarker in NSCLC patients. Of note, Bristol-Meyers has withdrawn its FDA application for first line ipilimumab + nivolumab in TMB high NSCLC from the Checkmate 227 study (5) whilst further data are awaited. We eagerly await further data too and the role that TMB (if any) will play in treatment selection in NSCLC patients. Despite the data presented here also coming from centres likely to have predominately Caucasian patients, it would have been very interesting to understand if there is any confounding by ethnicity or indeed differences in ethnicity.

Whilst this data of differential responses to ICI in EGFRm NSCLC is intriguing, cautious application of these finding needs to be made when translating this into a clinical decision about whether to proceed or not with an ICI in the face of limited treatment options after progression following TKIs and conventional chemotherapy. If sequential therapy proves to be the best approach, then the findings presented by Hastings and colleagues in this issues of the *Annals of Oncology* (3) requires prospective validation. Future trials of single agent ICI in EGFRm patients should consider $EGFR^{L858R}$ *vs.* $EGFR^{\Delta 19}$ as a potential stratification factor. Based on the results of the IMpower150 trial however, the likely positioning of ICI in the treatment of EGFRm NSCLC patients after progression of TKI therapy is combination chemotherapy plus a concurrent ICI (in this instance, atezolizumab) rather than a sequential approach. PFS was improved by the addition of atezolizumab to the chemotherapy backbone of carboplatin, paclitaxel and bevacizumab (median 9.7 *vs.* 6.1 months; hazard ratio, 0.59; 95% CI, 0.37–0.94) supporting this as a standard of care for EGFRm NSCLC patients. Of note EGFRm subset outcomes have not been reported. The concept of adding a doublet ICI (durvalumab and tremelimumab) to a platinum doublet chemotherapy is also currently being evaluated in the ILLUMINATE study (ACTRN12618001742268). The results of this trial are awaited to further understand the potential benefits of this up-front approach and any differential outcomes based upon EGFRm sub-class.

Overall, this paper has provided additional supportive and incremental knowledge in our understanding of how best to use modern medicines for targeting tumour vulnerabilities, as we continue to aim to improve outcomes in this rapidly-evolving field based on the personalised medicine paradigm.

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Footnote

Conflicts of Interest: The authors have 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.

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