Editor's Note:
In the era of personalized medicine, a critical appraisal new developments and controversies are essential in order to derived tailored approaches. In addition to its educative aspect, we expect these discussions to help younger researchers to refine their own research strategies.

Controversies on Lung Cancer: Pros and Cons

PROS: should immunotherapy be incorporated in the treatment of oncogene-driven lung cancer?

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We have read with great interest our Colleagues' point of view suggesting that immunotherapy should not be integrated into the treatment of oncogene-driven non-small cell lung cancers (NSCLCs) based on currently available evidence. However, we would like to mention three points to challenge their recommendation.

The first one is about the prognosis of oncogene-driven NSCLCs. As mentioned by our Colleagues, the 5-year survival of patients with epidermal growth factor receptor (EGFR)+ NSCLC treated with gefitinib or erlotinib remains 14.6% (1). This doesn't seem to us of particular remark, but it reflects the ineluctable occurrence in these tumours of drug-resistance to both older and new-generation tyrosine kinase inhibitors (TKI) and possible chemotherapy, leading ultimately to cancer progression and patient death. This consideration on his own would eagerly warrant for new treatment approaches beyond TKIs and chemotherapy. Furthermore, at least 50% of patients with EGFR+ NSCLC is not candidate to a new-generation TKI due to the type of acquired resistance mechanism (2) and, so far as these new-generation drugs will come to the first line of treatment, most of the patients will not have valid TKI options in clinical practice at disease progression. On the other hand, as conceived by our colleagues, not all oncogene-driven NSCLCs may have similar prognosis when treated with TKIs. In particular, patients with anaplastic lymphoma kinase (ALK)+ tumours have a remarkable 4-year OS of 56.6% following first-line crizotinib (3), suggesting that a relevant difference in the response to TKIs and chemotherapy (4) may well exist between different oncogene-driven NSCLCs and this should be taken into account, but confirming at the same time that approximately fifty percent of patients still need further improvements in treatments.

The second aspect is about the possible lack of efficacy of immune checkpoint inhibitors (ICPIs) mentioned by our Colleagues. Notably, these data were limited to a meta-analysis of five randomized studies comparing ICPIs vs docetaxel in pre-treated patients with EGFR+ advanced NSCLCs (5) and data coming from cohorts

comparison within the phase II ATLANTIC study in pre-treated patients with EGFR+/ALK+ tumours (6). Both the studies assessed the role of ICPIs as monotherapy against chemotherapy, while we are currently celebrating the success of the combination of chemotherapy with ICPIs in the first line treatment of NSCLC (7) and the relevant progression-free survival (PFS) benefit observed even in patients with EGFR+/ALK+ tumours from the addition of antiangiogenic treatment to chemotherapy and ICPIs coming from the ImPower150 trial (8) suggest that combination of chemotherapy and ICPIs should be further investigated in TKI-resistant NSCLCs. However, in the ATLANTIC study (6), the independently centrally reviewed tumour objective responses were rather similar between patients with EGFR+/ALK+ and those with EGFR–/ALK– tumours. Furthermore, while the meta-analysis (5) did not consider predictive biomarkers of response to the ICPIs, the ATLANTIC study (6) reported higher OS in patients with at least 25% of tumour cells expressing PD-L1 compared to those below this value irrespective of EGFR or ALK status. Similarly, in the phase II BIRCH the activity in terms of the overall response rate of atezolizumab monotherapy as first-line or subsequent therapy in PD-L1+ (with ≥5% expressing tumour or immune cells) NSCLC patients, was independent by tumour EGFR mutation status (9).

The third aspect is about the role of tumour biomarkers potentially predictive of response to ICPIs. Preclinical and translational evidence about the expression of PD-L1 in EGFR+ tumours is controversial, with some indicating a cross-talking (10,11) and others supporting lesser frequency (but not the absence) of PD-L1 in these tumours (12,13). In our opinion there are three possible reasons to explain it: the intra- and inter-tumours heterogeneity (2); the tumour dynamism, especially under drug selective pressure, that could, for instance, explain the difference in the expression of PD-L1 reported in tumours developing a T790 mutation acquired resistance (14); and last the fact that not all mutations in oncogene-driven tumours have the same role and this regards the same gene (for instance, the presence of EGFR sensitive or resistant mutations) and even more so different genes [such as for the case of KRAS mutations that tend to overexpress tumour mutational burden (TMB) (15)]. This last point has been also suggested for TMB where the different capacity to produce neoantigens by specific tumour mutations should be considered, rather than only the rough number of nonsynonymous mutations (16). As a consequence of that: there is still a proportion of patients with EGFR+ tumours who overexpresses PD-L1 (6); the relatively higher expression of PD-L1 observed in ALK+ tumours does not match with objective disease response (6) and in patients with KRAS+ tumours, who seem more responsive to ICPIs, TMB is higher than in wild-type tumours (15).

Taken together all our considerations, we strongly believe that patients with TKI-resistant oncogene-driven NSCLCs should not be excluded *a priori* from trials investigation and clinical practice with ICPIs, especially if other predictive biomarkers (i.e., PD-L1 and/or TMB and/or TILs) suggest a possible response to ICPIs or if these drugs are combined with chemotherapy and possible antiangiogenic therapy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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