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

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

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Targeted treatment with a tyrosine kinase inhibitor (TKI) is associated with high response rates and significantly prolonged progression-free survival in the minority of patients (approximately 15–20%) with advanced non-small cell lung cancer (NSCLC) whose tumor harbors an epidermal growth factor receptor (*EGFR*) mutation, anaplastic lymphoma kinase (*ALK*) rearrangement or *ROS1* rearrangement (1). Consistently, an exceptional 5-year survival of 14.6% has been reported with the use of either gefitinib or erlotinib in *EGFR*-mutant cases, while an unprecedented 4-year survival rate of 56.6% has been observed in *ALK*-positive NSCLCs treated with first-line crizotinib (2,3). Furthermore, with the availability in clinical practice of novel second- and third-generation EGFR- and ALK-TKIs, that show activity even after the occurrence of acquired resistance to first-generation agents, the clinical outcome of oncogene-driven NSCLC patients is expected to improve further.

On the other hand, the oncologic community has recently witnessed another great therapeutic progress in NSCLC, with the introduction for clinical use of immune checkpoint inhibitors, termed immunotherapy, which has led to a substantial improvement in the outcome of patients with advanced disease, achieving a 5-year survival rate of 16% in a phase 1 study of the anti-programmed death protein 1 (PD-1) inhibitor nivolumab (4).

Within this scenario, the issue on whether immunotherapy is specifically active in the group of patients with oncogene-driven NSCLC is of utmost clinical relevance. To date, most of the data on the activity of immunotherapy in oncogene-driven advanced NSCLCs are derived from randomized phase 3 trials testing single-agent immunotherapy as salvage treatment of patients pretreated with platinum-based chemotherapy (5-7). In these studies, patients with *EGFR* mutation or ALK rearrangement were eligible only if pretreated not only with platinum-based chemotherapy but also with a targeted agent. As expected, the number of oncogene-addicted cases was quite low in

all the studies. Based on the results of these trials, a meta-analysis has clearly demonstrated that immunotherapy does not improve survival compared to docetaxel in the subgroup of *EGFR*-mutant patients [hazard ratio (HR) for survival =1.11, 95% CI: 0.80–1.53, P=0.54] as opposed to *EGFR* wild type patients, in which it provides a 33% reduction in the risk of death (HR for survival =0.67, 95% CI: 0.60–0.75, P<0.001) (8). More recently, useful insights into the activity of immunotherapy in oncogene-driven pretreated NSCLCs have been produced by the "ATLANTIC" trial (9). In detail, this was a phase 2 trial which included a cohort of 111 *EGFR*-mutant and *ALK*-positive patients who were treated with the anti-PD ligand 1 (anti-PD-L1) agent durvalumab. Importantly, in this oncogene-driven population pretreated with a TKI, the immune checkpoint inhibitor was associated with a very disappointing overall response rate (ORR), equal to 9.8%. Remarkably, even when the analysis was restricted to patients with a PD-L1 expression ≥25%, who—at least in principle—could benefit more from immunotherapy according to the predictive role of PD-L1 expression, response rate remained poor, being only 12.2%.

The above described results suggest that immunotherapy has scanty activity in *EGFR*-mutant and *ALK*-positive patients pretreated with a TKI. On the other hand, its efficacy as upfront treatment has yet to be determined, since oncogene-driven NSCLC patients have been generally excluded from the majority of clinical trials testing the efficacy of immunotherapy as first-line treatment (10). Despite this lack of data in the specific setting, there are a number of reasons why it is plausible that immunotherapy does not represent the ideal first-line treatment. First, a recent pooled analysis of 3,969 patients from 18 studies exploring the association between PD-L1 expression and *EGFR* mutation found that *EGFR*-mutant NSCLCs were less likely to be PD-L1-positive compared to EGFR wild type patients, with an odds ratio of 0.59 (95% CI: 0.39–0.92, P<0.02) (11). Second, tumor mutation burden (TMB), namely the total number of non-synonymous mutations per coding area of a tumor genome, has been found to be consistently reduced in *EGFR*-mutant and *ALK*-positive NSCLCs compared to the *EGFR* wild type genotype or other subtypes, such as *KRAS*-mutant tumors (12,13). This finding is particularly relevant, given the emerging evidence that suggests TMB be a more reliable biomarker of sensitivity to immunotherapy than PD-L1 expression (14,15). Last but not least, there are now data supporting the presence of an uninflamed tumor microenvironment in NSCLCs with *EGFR* mutations, which is characterized by the absence of T-cell infiltration and the presence of a poorly immunogenic tumor microenvironment with a higher proportion of $PD\text{-}L1^{-}/CD8^{-}$ tumor-infiltrating lymphocytes (TIL) compared to the *EGFR* wild type genotype (12). In addition, other authors have reported that the expression of the immunosuppressive CD73 molecule is induced in *EGFR*-mutant disease, which, in turn, may lead to a poorly immunogenic environment with reduced T-cell activation and interferon gamma signature (16). Therefore, also the relationship between EGFR pathway activation and over-expression of CD73 may be responsible for a reduced benefit from anti-PD-1/PD-L1 therapy.

However, although the above-mentioned data suggest that immunotherapy could not work as upfront treatment of oncogene-driven NSCLC patients, research is now focusing on trying to associate targeted treatment and immunotherapy, in order to improve patients' outcomes compared to targeted therapy alone. Nevertheless, preclinical data support the fact that combining an EGFR- or ALK-TKI with an anti-PD-1 inhibitor does not result into a synergistic interaction (17,18). Even more importantly, clinical data from early phase 1 studies suggest that the combination of targeted therapy with immunotherapy may not be enough safe in either *EGFR*-mutant or *ALK*-positive patients. More in detail, the multi-arm phase 1b "TATTON" study evaluated the combination of the third-generation EGFR-TKI osimertinib (that is active also against the T790M mutation associated with resistance to first-generation TKIs) plus the anti-PD-L1 agent durvalumab (19). The trial consisted of a dose escalation part conducted in EGFR-TKI-pretreated patients (n=23) and a dose expansion part (n=11) performed in EGFR-TKI-naïve patients. The osimertinib/durvalumab combination showed some signs of activity (ORR of 66.7% and 21.4% in patients with T790M positive and T790M negative tumour status, respectively, and 70.0% in *EGFR*-mutant treatment-naïve patients). However, despite the single-arm design does not allow an estimation of the contribution of each drug to the activity of the combination, the observed ORRs are not necessarily better than the activity expected with EGFR-TKI alone. Furthermore, a 32% and 26% incidence of grade ≥3 treatment-related adverse events (TRAEs) attributed to osimertinib and durvalumab, respectively, was reported with this regimen. In addition, the trial was prematurely stopped, due to the

unacceptably high incidence of interstitial lung disease, which occurred in 38.2% of patients, being grade 3/4 in 14.7% of cases. Another trial (NCT02088112) tested the combination of gefitinib plus durvalumab in *EGFR*-mutant patients who were EGFR-TKI-naïve (20). This study showed a promising ORR of 78.9%, but again, a 55.0% incidence of grade ≥3 TRAEs was noted, being mainly liver toxicity (increased levels of transaminases). Interestingly, toxicity issues have been observed also with the combination of an ALK-TKI with immunotherapy. In fact, a recently published phase 1/2 trial exploring the combination of crizotinib plus nivolumab in untreated ALK-TKI-naïve patients reported an incidence of 38.5% (5/13) of grade ≥3 liver toxicity, which could have contributed to the two cases of toxic deaths that were observed in the trial (21). On this basis, enrollment was halted, due to unacceptable toxicity, and immunotherapy was discontinued in all study patients. With regard to activity, the combination of crizotinib and nivolumab produced an ORR of only 38.5%, which is much lower than the activity usually observed with crizotinib alone in the first-line treatment of *ALK*-positive advanced NSCLC patients (22). Also, in this case, beyond toxicity issues, the single arm design of the trial does not allow a definitive conclusion about comparative activity of the combination, but indirect comparison with single-agent TKI does not seem particularly encouraging.

In conclusion, there is evidence strongly suggesting that immunotherapy is not the most effective treatment in oncogene-driven patients pretreated with a TKI. Also, the presence of a low TMB along with an uninflamed tumor microenvironment does not support the use of immunotherapy as upfront treatment in oncogene-driven NSCLC. In addition, early phase 1/2 studies of the combination of targeted therapy with immunotherapy have often demonstrated unexpectedly relevant toxicity, which calls for extreme caution and thorough evaluation of the optimal schedule to adopt in combination regimens. Finally, with all the limitation of indirect comparisons, no obvious increase of ORR has been observed with the combination of a TKI and immunotherapy compared to TKI alone. On this basis, we conclude that, based on the evidence currently available, immunotherapy should not be integrated in the treatment of oncogene-driven NSCLCs.

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Footnote

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