Editorial

Atezolizumab for first-line treatment of metastatic nonsquamous non-small cell lung cancer: what makes the difference?

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The landing of immune checkpoint inhibitors (CKI) in the landscape of the primary treatment for non-small cell lung cancer (NSCLC) patients has been surely irrepressible, but burdened by a large selection limit, constituted by the percentage threshold of programmed death-ligand 1 (PD-L1) expression (1). Thus, while the media were exulting for the ouster of chemotherapy from the paradigm of treatment of lung cancer, the patients one by one came to the disappointing revelation that immunotherapy is not accessible to everyone, being reserved to those tumors expressing PD-L1 on at least 50% of cells. For all other tumors, a second chance with CKI is relegated as a rescue option, after progression of disease to first-line chemotherapy (2-4). Nevertheless, after further controversial results based on intermediate PD-L1 expression thresholds and depending on CKI type (or study design) as first-line (5,6), this fairly recent paradigm is already destined to be unhinged by the even more recent results obtained by CKI when combined with chemotherapy in this setting, irrespective of PD-L1. Some of such studies, testing immunotherapy combinations with standard drugs for untreated NSCLC patients, have now positive results, even showing for the first time that overall survival (OS) and progression free survival (PFS) can be both improved in lung cancer through immune checkpoint blockade (7-9).

On June 2018, the *New England Journal of Medicine* published the results of the Impower150 clinical trial, reported by Socinski *et al.* (8). This was a randomized, open-label, phase III study, enrolling patients with metastatic nonsquamous NSCLC who had not previously received chemotherapy, investigating in a 1:1:1 ratio, respectively: bevacizumab plus carboplatin plus paclitaxel (BCP group), atezolizumab plus bevacizumab plus carboplatin plus paclitaxel (ABCP group), and atezolizumab plus carboplatin plus paclitaxel (ACP group). In this first report, only the first two arms were analyzed, whilst data were not shown for the third. The co-primary endpoints of PFS and OS in the intention-to-treat population with wild-type (WT) genotype for *EGFR* and *ALK* were both met, as well as PFS in the WT population with high expression of an effector T-cell (Teff) gene signature in the tumor (a kind of surrogate of PD-L1 expression). Moreover, all the study subgroups had benefit from the addition of atezolizumab to standard therapy, irrespective of *EGFR* or *ALK* status, of PD-L1 expression on tumor cells or on immune cells, and of Teff signature. The 356 WT patients treated with ABPC scheme, consisting in an induction phase of two months with both chemotherapy and antibodies, followed by maintenance with bevacizumab and atezolizumab, had a longer PFS than the 336 WT patients treated with BCP, from 6.8 to 8.3 months, hazard ratios (HR) 0.62 [95% confidence interval (CI): 0.52–0.74], P<0.001. Such result as per investigator-assessment was completely confirmed as per independent review (8).

Beyond the statistical significance, one could argue about the slight clinical significance of a 1.5 months difference.

Nevertheless, we are aware of the limits of the traditional radiologic evaluation criteria (namely the RECIST1.1 as used in this trial) in estimating the real benefit from immunotherapy, as demonstrated by previous clinical trials in which a non-benefit in PFS resulted in a survival advantage (2,10). The IMpower150 investigators noted that a benefit with respect to PFS was in fact not observed in early phase studies with atezolizumab monotherapy in pretreated NSCLC patients (8). They justified the results of the current trial with the addition of bevacizumab, considering that both treatment arms included the same schedule of chemotherapy and that an improvement of PFS was not expected from atezolizumab. As alternative, they suggested that the earlier line of therapy may have made the difference (8). Although given the positive results of previous first-line immunotherapy trials also in terms of PFS (1) an "early line effect" could be plausible, in our opinion it is not likely that the only bevacizumab could make the difference. If so, how to explain the PFS improvement obtained with the addition of pembrolizumab to standard chemotherapy in the analogue first-line trial by Gandhi *et al.* (7)? Furthermore, how to justify the similar benefit on PFS recently announced for atezolizumab combined to different chemotherapeutic regimens in not less than three further phase III trials for NSCLC patients, namely IMpower130, 131 and 132 (9,11,12)? An explanation that has not been postulated, but that is plausible for all these trials, concerns the possible synergistic effect of chemotherapy with immune checkpoint blockade. The direct cytotoxic effect of the first on tumor cells could contribute to enhance the immune-stimulation by releasing wide amounts of tumor antigens (13), making the difference in terms of objective response rate (indeed raised from 48% to 63.5%, including 3.7% of complete response—tripled compared to the control arm) and improving PFS. On the other hand, the OS improvement from 14.7 to 19.2 months demonstrated at the interim analysis in the WT population (HR 0.78, 95% CI: 0.64–0.96, P=0.02) undoubtedly reaches the clinical significance in such a lethal malignancy, for which a gain in survival of 4.5 months represents an historical achievement (8).

The Teff signature assessment allowed to identify a subgroup more likely to derive wide benefit from the addition of atezolizumab, dramatically increasing the probability of PFS at 12 months from 18% to 46% as per the investigators' assessment (8). Nevertheless, considering that also Teff-low cases had statistically significant improvement of PFS, this explorative and quite complex method, unavailable for everyday clinical practice, is probably destined to remain an experimental tool. On the other hand, the preplanned subgroup analyses of the trial confirmed that PFS was in favor of ABCP in all subgroups, irrespective of the clinical features, of the mutational status and of the biomarkers' expression (8). These findings are potentially practice-changing, for the first time offering an effective immunotherapeutic approach also to oncogene-addicted tumors, as well as extending the possibility of primary immunotherapy also to patients with PD-L1 negative diseases.

Unfortunately, all that glitters are not all gold. Although the safety profile of ABCP was manageable and not-unexpected, with grade 1 or 2 treatment-related adverse events (AEs) even less frequent than in the control arm (35.9% *vs.* 45.4%) and grade 3 or 4 AEs occurring in 55.7% of cases *vs.* 47.7% for BCP, inevitable concerns should regard the toxic deaths occurred within this trial. Treatment-related deaths occurred in 11 patients (2.8%) in the ABCP arm and in 9 patients (2.3%) in the control arm, outlining a risky profile independently of the experimental drug. This latter consideration is also endorsed by the causes of such deaths, mostly constituted by thromboembolic or hemorrhagic events throughout both arms, with at least 12 deaths more likely due to the known toxicity profile of bevacizumab (lethal pulmonary hemorrhage, hemoptysis, pulmonary embolism, cerebrovascular accident and intestinal perforation), beyond the predictable deaths due to chemotherapy (febrile neutropenia, sepsis). Notably, no treatment-related deaths were directly attributable to immune-related events (8). Actually, in the pivotal trial published in 2006, investigating carboplatin and paclitaxel plus bevacizumab compared to chemotherapy alone in similar population and setting, the rate of toxic deaths was 3.6% in the experimental arm, compared to 0.4% of the control arm (14). This further element points bevacizumab as the potentially main responsible for the lethal toxicity.

The purpose of such big clinical trials should refrain from the temptation to maximize benefit in selected individuals, instead aiming to expand the magnitude of benefit for large groups of patients. Despite this trial undoubtedly offer a new possibility for primary treatment of nonsquamous NSCLC patients, both the clinicians and the regulatory entities should remember once again to look at the other side of the coin, facing any critical issues before translating new findings in clinical practice. In this light, the results of the third treatment arm of the trial, namely the group receiving atezolizumab plus chemotherapy, are eagerly

awaited to definitively clarify whether bevacizumab makes the difference, and if such difference is clinically significant enough to make the other side of the coin acceptable.

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Footnote

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

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