Editorial

Exploring immune checkpoint inhibition in combination with anti-angiogenic therapy for patients with EGFR- or ALK-positive advanced non-small cell lung cancer

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International guidelines for the treatment of advanced non-small cell lung cancer (NSCLC) patients recommend an algorithm based on tumor biomolecular profile (1). The first-line proposed approach is dichotomic, based on an *ab initio* distinction between oncogene addicted versus non-oncogene addicted disease. In fact, the detection of driver genomic alterations has led to the development of specific tyrosine kinase inhibitors (TKIs) that radically changed the quality of life and the prognosis of oncogene-addicted NSCLC patients. Epidermal growth factor receptor (*EGFR*) mutations involving the exons 18–21 are carried by 10–40% of NSCLC patients, especially in Asian populations, and the most common alterations are represented by exon 19 deletions and exon 21 L858R point mutation (2). Other *EGFR* mutations account for approximately 10% of the total, commonly including *EGFR* exon 20 insertions (ex20ins) (2). First- and second-generation EGFR TKIs, such as gefitinib, erlotinib and afatinib, have been introduced in clinical practice in the last decade as upfront treatments (2). More recently, the third-generation EGFR-inhibitor osimertinib unseated the previous generation TKIs as first-line strategy demonstrating an antitumor activity covering the exon 20 T790M mutation, a typical mechanism of acquired resistance to first- and second-generation EGFR-TKIs (2).

Anaplastic lymphoma kinase (*ALK*) gene rearrangements are less frequent molecular alterations involving approximately 3–5% of nonsquamous NSCLC (3). Analogously to anti-EGFR TKIs, several ALK-TKIs have been tested and broadly approved during the last decade. In particular, the second-generation alectinib and brigatinib improved the survival outcomes of the first-ever approved crizotinib (3). Furthermore, lorlatinib has recently demonstrated to be effective either in patients previously treated with ≥1 ALK-TKI(s) or in naïve patients when compared to crizotinib (3).

To date, a platinum-based doublet is the treatment of choice at the exhaustion of standard targeted therapies for EGFR or ALK-positive patients. Oncogene-addicted NSCLC patients have been considered a poorly immunogenic population compared to the non-oncogene addicted counterpart, as supported by a low mutational load leading to less neo-antigen production and by the lack of benefit of immune-checkpoint inhibitors (ICI) in the early conducted trials (4). This, in turn, determined the presence of *ALK* or *EGFR* alterations as a typical exclusion criterion from immunotherapy clinical trials. Consistently with previous findings, the IMMUNOTARGET registry retrospectively confirmed poor survival outcomes previously treated, oncogene addicted advanced NSCLC patients (5).

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In particular, *ALK* rearrangements and *EGFR* mutations showed a disappointing median progression-free survival (PFS) of 2.5 months and 2.1 months, respectively. The ATLANTIC trial was a multicohort, phase 2 study assessing the efficacy of the anti PD-1 durvalumab, including 111 EGFR or ALK-positive patients (6). The median PFS in the oncogene-addicted cohort was not influenced by PD-L1 expression. Notably, a post hoc analysis investigated the outcomes of patients with PD-L1 ≥25% revealing no objective response among ALK-positive patients and an objective response rate (ORR) of 14.1% (95% CI: 6.6–25.0%) among EGFR-positive patients.

Camrelizumab (SHR-1210) is a humanized IgG4 monoclonal antibody directed against PD-1 that has proven to improve survival outcomes of advanced, non-oncogene-addicted NSCLC when associated with histology-driven platinum-based chemotherapy in squamous (7) and nonsquamous (8) histologies. Apatinib is a vascular endothelial growth factor receptor 2 (VEGFR2) inhibitor which demonstrated to be efficacious and safe for treating several advanced solid tumors. Further, preliminary clinical evidence suggests possible employment in treating pretreated advanced NSCLC patients (9,10).

With regard to the combination of camrelizumab and apatinib, a small open-label, phase 2 study investigated its clinical activity and safety profile among advanced, nonsquamous NSCLC patients (11). Based on prior evidence in the previously treated population (12), eligibility criteria included high tumor mutational burden (TMB) and absence of ALK or EGFR aberrations. The trial met its primary endpoint with an ORR of 40% (95% CI: 21.1–61.3%). Interestingly, the disease control rate (DCR) was 92.0% (95% CI: 74.0–99.0%), the median PFS was 9.6 months (95% CI: 5.5 months–not reached), and the median overall survival (OS) was not reached with a median follow-up of 19.5 months (range, 2.0–26.2 months). The 24-month OS rate was 82.5% (95% CI: 59.6–93.1%), with an exciting long-plateau within the survival curve. The safety profile was consistent with other similar combinations, with increased liver enzymes (12–24%) and hypertension (12%) as the most common grade 3–4 adverse events, leading to permanent treatment discontinuation in 4% of cases (11).

The results of a phase II trial evaluating the addition of albumin-bound paclitaxel for 4–6 cycles to the same combination of the PD-1 inhibitor and the VEGFR inhibitor in advanced nonsquamous NSCLC have been recently presented at the 2022 ASCO congress. Inclusion criteria included the absence of previous systemic treatment, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-1 and the negativity for EGFR mutations and ALK rearrangements (13). A promising median PFS of 10.9 months, which represented the primary endpoint of the trial, was documented. Encouragingly as well, ORR and DCR were respectively 73.8% (95% CI: 58.7–84.0%) and 98.1% (95% CI: 88.4–99.9%), and the safety profile did not show unexpected toxicities.

In the current issue of Translational Lung Cancer Research, Gao *et al.* further expanded the knowledge on the combination of camrelizumab plus apatinib by publishing the preliminary results of a multicenter, phase 1b/2, open-label, multicohort trial investigating the efficacy and safety of this regimen in previously treated advanced EGFR or ALK-positive NSCLC patients (14).

Enrolment was restricted to a highly selected population of 18–70 years old patients, with a good ECOG PS of 0-1, without newly diagnosed brain metastases and treated with at least one anti-EGFR or anti-ALK targeted therapy. The primary endpoint was investigator-assessed ORR according to RECIST 1.1 criteria. The confirmed ORR was 18.6% (95% CI: 8.4–33.4%). The clinical benefit rate, including stable disease and responses lasting 24 weeks or longer, was set as secondary endpoints and was 27.9% (95% CI: 15.3–43.7%). Survival outcomes were also selected as secondary endpoints. The median PFS was 2.8 months (95% CI: 1.9–5.5 months), and the median OS was not reached (95% CI: 7.3 months–not reached) (14). The toxicity profile was similar to other experiences, reporting hypertension (16.3%), and proteinuria (11.6%) as the most frequent grade 3 adverse events.

The trial failed to meet the primary endpoint of 30% ORR with a 90% CI, demonstrating modest antitumor activity and a dismal PFS even with an acceptable safety profile.

The choice of ORR as the primary endpoint emphasizes the importance of radiological imaging assessment, for which a central review is preferable. Moreover, the population of EGFR-positive patients, although sharing a common unmet need, is widely heterogeneous as the treatment received by enrolled patients, ranging from different generations of EGFR TKIs to platinum-based chemotherapy alone in ex20ins EGFR-positive patients. Although the enrollment of the whole EGFR-mutant population is reasonable for the purpose of this kind of trials, this is a limit to consider for the interpretation of results.

Notably, none has achieved an objective response of

the only four ALK-positive patients enrolled in the trial. Despite the very small sample size, we should not be overly surprised as previously discussed studies have already aware of a lack of efficacy of ICI in this population (4), and a combined targeting of VEGFR might not serve as an immune trigger for ALK fusion-positive patients as it might be for those carrying EGFR mutations. Particularly, combining first- or subsequent-generation anti-ALK TKIs with single-agent immunotherapy produced safety concerns and unsatisfying efficacy results (15-17).

On the other hand, the population of 40 EGFR-positive patients obtained an ORR of 20% (95% CI: 9.1–35.6%), which was numerically different according to the subtype of EGFR mutation. Of note, the ORR was 13.6% (95% CI: 2.9–34.9%) among patients harboring exon 19 deletion, 21.4% (95% CI: 4.7–50.8%) among patients with exon 21 L858R point mutation, and 33.3% (95% CI: 0.8–90.6%) among those harboring ex20ins. This response trend was numerically also confirmed in terms of median PFS, which was longer for ex20ins (8.3 months), and was 5.3 months and 2.8 months for L858R and ex19del patients, respectively. Although it refers to small patients' subgroups, especially with regard to the least represented ex20ins *EGFR* mutation (n=3), this difference in terms of activity may represent the other side of the coin being hypothesis-generating. Given the unsatisfying immunotherapy efficacy for *EGFR*-mutant NSCLC, several early development trials investigated a strategy of combinations with TKIs (18,19). Nevertheless, the toxicity warning and the poor signals of clinical activity limited further development of this line of research (4). By contrast, this might not be the case for the camrelizumab plus apatinib combination, whose toxicity profile appeared to be acceptable and manageable.

EGFR- and ALK-positive patients have been enrolled in the IMpower 150 trial, which investigated the efficacy of carboplatin, paclitaxel, bevacizumab, and atezolizumab among treatment-naïve advanced NSCLC patients. 123 EGFR mutated patients were included in the intention-to-treat population (20). Among the 91 patients with sensitizing EGFR mutations, 78 have been previously treated with TKI. The atezolizumab-bevacizumab plus chemotherapy regimen improved survival outcomes more than bevacizumab plus chemotherapy among treatment-naïve patients with EGFR sensitizing mutations (HR: 0.60, 95% CI: 0.31–1.14) and among those who previously received TKI (HR: 0.74, 95% CI: 0.38–1.46). Interestingly, no overall survival benefit was found in the atezolizumab-bevacizumab-chemotherapy-treated group compared to the bevacizumab-chemotherapy group. These findings suggest a synergic action determined by immune-checkpoint and VEGF inhibition. Consistently, increased VEGF expression (21) and reduced T $CD8^+$ cells (22) are associated with EGFR mutations. Among the EGFR-mutant population, L858R EGFR positive NSCLC expressed an increased intratumoral T $CD8^+$ rate (23), which may suggest a different genomic susceptibility to immunotherapy. Unfortunately, IMpower 150 was not powered to evaluate the prognostic value of EGFR mutation subtypes. The survival outcomes of the 13 patients carrying ALK-rearrangements included were aggregated with that of EGFR-positive patients making the efficacy in this population difficult to interpret.

In conclusion, in absence of more active treatments following the failure of specific TKIs, combining immunotherapy with the VEGFR inhibition appears a reasonable approach warranting further investigation in the EGFR-positive NSCLC population, which primary aim might be the identification of predictive factors of response starting from the immunologic differences between EGFR mutation subtypes. Unfortunately, the same seems not applicable to the ALK-positive population, for which VEGFR inhibition might not be a significant enhancer of immunotherapy activity.

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