Editorial Commentary

First-line immune-chemotherapy combination: the right strategy to fight squamous non-small cell lung cancer?

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In *The New England Journal of Medicine*, Paz-Ares and colleagues published the results of KEYNOTE-407, a randomized phase III placebo-controlled trial, investigating the addition of pembrolizumab or placebo to first-line carboplatin-taxane chemotherapy, in patients with advanced squamous non-small cell lung cancer (NSCLC) (1). The study met its co-primary end-points, since immune-chemotherapy combination led to a significant longer overall survival (OS) and progression-free survival (PFS) as compared to placebo combination. In the intention to treat population, the median OS was 15.9 *vs.* 11.3 months [hazard ratio (HR): 0.64; 95% confidence interval (CI): 0.49 to 0.85], and the median PFS was 6.4 *vs.* 4.8 months (HR: 0.56; 95% CI: 0.45 to 0.70). The addition of pembrolizumab to platinum-chemotherapy resulted also in a significant increase of 1-year survival rate (65.2% *vs.* 48.3%), response rate (RR) (57.9% *vs.* 38.4%), and duration of response (7.7 *vs.* 4.8 months). The survival benefit was maintained in all subgroups of patients selected according to both clinical and pathological characteristics, including tumor programmed death ligand 1 (PD-L1) expression level. As expected, the number of patients who experienced immune-related adverse events (irAEs) and infusion reactions was significantly higher with immunotherapy than placebo (28.8% *vs.* 8.6%), with grade 3 or higher AEs reported to be 10.8% *vs.* 3.2%, respectively. Finally, the percentage of AEs leading to the discontinuation of any treatment components nearly doubled with pembrolizumab compared to placebo.

These findings led to the immediate approval of first-line immune-chemotherapy combination for patients with metastatic squamous NSCLC by regulatory authorities (U.S. Food and Drug Administration on October 30th, 2018, and European Medical Agency on March 14th, 2019). This approval marks a relevant milestone in the treatment of this lung cancer histotype, which accounts for 25–30% of all NSCLC, is almost always smoking-induced and associated to the lack of actionable mutations, therefore very difficult to treat with systemic therapies (2). Since the majority of recent advances in lung cancer treatment, including new chemotherapy agents, like pemetrexed, and targeted therapies, have been limited to non-squamous subtype, platinum-based combinations remained for a long time the backbone upfront therapy for squamous NSCLC, reaching a median survival plateau of 10–11 months (3). Combining the epidermal growth factor receptor (EGFR) inhibitor necitumumab with platinum-gemcitabine led only to a small improvement of OS (from 9.9 to 11.5 months) with an overall 16% reduction in the risk of death in the randomized phase III SQUIRE trial (4). Although patients with high tumor EGFR protein expression by immunohistochemistry (IHC), or EGFR copy number gain by fluorescence *in situ* hybridization (FISH), seem to gain longer survival benefit, however a validated predictive biomarker has not been established yet for clinical use. More recently, the KEYNOTE-024 study clearly demonstrated that single agent pembrolizumab is more effective and better tolerated

than first-line platinum-based chemotherapy in non-oncogene-addicted, metastatic NSCLC, with PD-L1 tumor proportion score of 50% or higher, reaching 30 months of median OS at the last follow-up (5), as compared to the 14.2 months of chemotherapy (HR: 0.63, 95% CI: 0.47–0.86). Following these results, pembrolizumab emerged as new standard of care for this subgroup of patients, which accounts for 30% of the overall NSCLC population. Conversely, an exploratory analysis of the KEYNOTE-042 trial (6), comparing pembrolizumab to platinum-chemotherapy in treatment-naive, EGFR/ALK wild-type, metastatic NSCLC, with at least 1% of tumor PD-L1 expression, revealed no survival differences among patients with PD-L1 expression between 1% and 49%, with median OS of 13.4 *vs.* 12.1 months (HR 0.92, 95% CI: 0.77–1.11), thus questioning the role of single agent immunotherapy in the subgroup of patients with intermediate PD-L1 expression. Recently the results of the phase 3 study KEYNOTE-189 (7), comparing pembrolizumab plus platinum-pemetrexed followed by pemetrexed and pembrolizumab maintenance versus placebo plus chemotherapy followed by placebo plus pemetrexed maintenance in non-squamous, treatment-naïve, advanced NSCLC without EGFR or ALK alterations, revealed the superiority of immune-chemotherapy combination even in this histological type. This clinical evidence revolutionized the old idea that chemotherapy just knocked down the patient's immune system, showing as platinum-combinations may help to trigger the anti-tumor immune response, thus increasing immune-checkpoint inhibitors' activity in individual patients. Of note, the clinical benefit observed with the addition of pembrolizumab to platinum-chemotherapy is at the cost of affordable toxicities. Indeed, the safety profile observed in the KEYNOTE-407 trial did not detach from the expected, being the majority of AEs manageable, without new identified toxicities. However, it should be noted that the discontinuation rate due to AEs nearly doubled in the experimental arm as compared to the placebo-arm (13.3% *vs.* 6.4%, respectively), so that, even if this could be partially related to the longer duration of treatment, it should be always kept in mind when selecting the triplet regimen. A subsequent exploratory analysis of the KEYNOTE-407 trial showed that the type of taxane (60.1% of patients in the study received paclitaxel, while 39.9% nab-paclitaxel) did not significantly influence the efficacy and safety of immuno-chemotherapy combination, revealing an interesting trend toward a longer survival and an increased incidence of grade ≥3 AEs in favour of nab-paclitaxel (8). One of the main raised criticisms concerns the study design. Indeed, the control arm included four cycles of carboplatin plus taxane, while a maximum of six cycles of platinum-chemotherapy is currently recommended by all international practice guidelines and represents the most adopted strategy in clinical practice. On the other side, a recent meta-analysis suggested that four versus six cycles of platinum-based first-line chemotherapy led to similar OS in advanced NSCLC patients (9), thus limiting to four the cycles of chemotherapy could be considered a rationale choice. Another limitation of the study design, which is common to other upfront chemo-immunotherapy combination trials in lung cancer, consists of the impossibility to assess whether final OS has been significantly influenced by the maintenance therapy with pembrolizumab. A final drawback of the current version of the published study is the short duration of follow-up (7.8 months), as a consequence of a preplanned event-driven, and not time-driven, second interim analysis, for declaring statistical significance. Therefore, long-term efficacy and safety data are currently lacking and longer follow-up is eagerly expected, especially when dealing with immunotherapy AEs, that might emerge even late. Although crossover to single agent checkpoint inhibitor for patients enrolled in the placebo-group was allowed by protocol design, the effective crossover rates were very low, reaching 31.7% in the intention-to-treat population and 42.8% among those patients who discontinued therapy, with the related causes not reported. Therefore, it remains still unclear whether combining immune-chemotherapy in first-line would be more effective than sequential strategy in squamous NSCLC. The percentage of patients receiving immunotherapy after platinum-chemotherapy will likely increase with additional follow-up, however, if this trend will be confirmed, more than half of patients with metastatic squamous NSCLC could never receive any second-line treatment. As regards the potential benefit of combination in patients with central nervous system (CNS) disease, the very low number included (20 and 24 patients in pembrolizumab- and placebo-combination arms, respectively) limited any evidence-based conclusion, highlighting a crucial point that warrant further investigation in dedicated trials. With respect to other studies, the KEYNOTE-407 interrupted the negative trend of upfront combinations in advanced squamous NSCLC, suggesting that the PD-1 inhibitor pembrolizumab is the best partner to combine with platinum-chemotherapy. Indeed, the addition of either ipilimumab (10), or

atezolizumab (11), to first-line carboplatin-taxane chemotherapy has recently failed to demonstrate any OS improvement in a similar naïve, PD-L1 unselected, squamous NSCLC population, and the biological, chemical, and pharmacological mechanisms underlying these different results are hot topics for translational research. Looking for immunotherapy predictive biomarkers remain a main objective for the academic, scientific community. Although the PFS of patients increased accordingly to the tumor PD-L1 expression levels, no relationship between OS benefit and PD-L1 tumor proportion score has been observed in this study, thus questioning the usefulness of biomarkers-based patients' selection for upfront combinations. Of course, the PD-L1 assessment remains crucial to identify patients with advanced NSCLC who are candidate to single agent pembrolizumab (12). In absence of direct comparison data, clinical decision of first-line therapy should be based on an individual basis, taking into account both tumor and patients' related characteristics, as well as benefit and risk associated to each treatment. Finally, a recent cost-effectiveness analysis estimated that the combining immunotherapy and chemotherapy will allow to nearly double life expectancy of patients with metastatic squamous NSCLC, with an incremental cost-effectiveness ratio (ICER) below $100,000/quality-adjusted life year (QALY), which makes such combination a cost-effective first-line option for this subgroup of patients (13).

In conclusion, the study of Paz-Ares *et al.* represents an important step forward in the treatment of patients with metastatic squamous NSCLC. Adding pembrolizumab to carboplatin-taxane allowed to reach a survival plateau never seen before at cost of a modest increase of irAEs, emerging as new standard of care for physicians, and more important, offering a new hope to a greater number of patients affected by this aggressive and difficult to treat disease. Additional follow-up of this trial will be crucial to establish the long-term efficacy and tolerability outcomes and definitively confirm first-line immune-chemotherapy combination as the right strategy to fight squamous NSCLC.

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Footnote

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

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