



The KEY for chemo-immunotherapy combination: taking NOTES from squamous cell lung cancer

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Notes from a changing landscape

Lung cancer represents the most common cause of cancer death in the world. Non-small cell lung cancer (NSCLC) represents almost 85% of lung cancer cases. Unfortunately, diagnosis is often made at advanced or metastatic stage, with a 5-year survival rate between 0 and 5% with chemotherapy, that until a few years ago represented the only systemic treatment available (1,2). In this context, the primary goal of systemic therapy is to increase patients' survival, to reduce cancer symptom burden and to improve quality of life.

Over the past decade, together with the availability of targeted agents in oncogene-addicted cases, the development of immune checkpoint inhibitors, namely monoclonal antibodies anti-programmed death-1 (PD-1) and its ligand (PD-L1), has revolutionized the treatment of advanced NSCLC, establishing a new era in the treatment of lung cancer patients. Their efficacy has been demonstrated, initially, as second line therapy in patients affected by advanced, *EGFR* wild type and *ALK* not rearranged NSCLC, after a previous platinum-based chemotherapy. Afterwards, the efficacy of these drugs in the first-line setting has been explored: the randomized phase III study KEYNOTE-024, conducted in NSCLC patients with tumors characterized by PD-L1 expression equal to or higher than 50%, demonstrated that pembrolizumab is associated with a better outcome compared to standard platinum-based chemotherapy, in terms of both progression-

free survival (PFS) and overall survival (OS), getting the approval in this setting by regulatory agencies (3). Consequently, the determination of PD-L1 has become part of the baseline diagnostic evaluation, representing an important biomarker for the first-line patients' selection, although with the well-known limitations in both positive and negative predictive value.

Nevertheless, cases characterized by a PD-L1 expression equal to or higher than 50% represent just a minority (20–30%) of the entire population (4).

In order to expand the potential benefit from immunotherapy to a larger number of patients, several phase 3 studies combining the potential immunogenic effect of chemotherapy with PD-(L)1 blockade have emerged in rapid succession with positive results. For instance, the KEYNOTE-189 trial showed a significantly longer OS and PFS compared with chemotherapy alone in untreated advanced nonsquamous NSCLC patients (5).

Looking for the KEY (...NOTE-407)

With a design similar to the above described KEYNOTE-189, but in a different population in terms of tumor histology, the phase 3 trial KEYNOTE-407 evaluated the combination of the same immune checkpoint inhibitor with platinum-based chemotherapy as first-line treatment of advanced squamous NSCLC patients (6).

Overall, 559 patients were randomized 1:1 to receive chemotherapy plus placebo or chemotherapy plus pembrolizumab, without selection for PD-L1 expression. Chemotherapy backbone consisted of carboplatin, administered every 3 weeks in combination with either paclitaxel 3-weekly or nab-paclitaxel weekly (at investigator's choice), for 4 cycles. Pembrolizumab (or corresponding placebo) was administered at 200 mg every 3 weeks, for a maximum of 35 cycles, in addition to chemotherapy. The trial was designed with two co-primary endpoints, OS and PFS. The combination showed a clinically relevant benefit in all study endpoints. Namely, median OS was 11.3 months for patients assigned to control arm and 15.9 months for patients assigned to experimental arm [hazard ratio (HR) 0.46; 95% confidence interval (CI): 0.49–0.85; $P=0.0008$]. Median PFS was 4.8 months for patients assigned to control arm *vs.* 6.4 months for patients assigned to experimental arm (HR 0.56; 95% CI: 0.45–0.70; $P<0.0001$) and objective response rate (ORR) increased from 38.4% to 57.9%. The improvement in OS and PFS was consistent across all patients' subgroups divided according to PD-L1 [tumor proportion score (TPS) $<1\%$, $1-49\%$ and $\geq 50\%$]. Subgroup analysis according to the taxane chosen by investigators (paclitaxel *vs.* nab-paclitaxel) showed no significant differences in terms of OS, PFS and ORR (7). Incidence of treatment-related adverse events (AEs) was similar between the two treatment arms. A higher proportion of patients in the experimental arm discontinued treatment due to AEs: 13.3% compared to 6.4% of patients in the control arm. Furthermore, the addition of pembrolizumab to chemotherapy improved health-related global quality of life compared to chemotherapy alone, although no significant difference in time to deterioration of tumor symptoms (cough, chest pain, or dyspnea) was observed (8).

Open questions notes

The above described KEYNOTE-407 trial was not the first attempt to add an immune checkpoint inhibitor to first-line chemotherapy in advanced squamous NSCLC. However, the combination of ipilimumab (a cytotoxic T-lymphocyte-associated protein 4 inhibitor) with carboplatin plus paclitaxel was not successful, because it had not demonstrated an improvement in OS, compared with chemotherapy alone (9). On the contrary, based on the positive results of the above described KEYNOTE-407, regulatory agencies approved pembrolizumab in combination with carboplatin plus paclitaxel or nab-

paclitaxel, for patients candidates to receive first-line treatment for metastatic squamous NSCLC.

These data enrich the wide list of different studies with a similar design, which have evaluated the addition of an immune checkpoint inhibitor (either anti-PD-1 or anti-PD-L1) to first-line chemotherapy, leading to the authorization for this use in clinical practice both in squamous and non-squamous histology.

However, several issues remain not completely clear. In the IMpower-131 trial, the addition of the anti-PD-L1 atezolizumab to chemotherapy did not show a significant OS prolongation, even if a clinically meaningful OS improvement was observed in the high PD-L1 subgroup (10).

Based on these apparently discordant results, one hypothesis could be that different immune checkpoint inhibitors might not be completely interchangeable and that they do not perform in the same way. According to biology, anti PD-1 antibodies bind to PD-1 receptor, blocking its interaction with both ligands PD-L1 and PD-L2. On the other hand, anti PD-L1 blocks only the interaction between PD-1 and PD-L1 and this inhibition might be insufficient among low/negative PD-L1 patients (11). Recently, all randomized trials testing the combination of anti-PD-1 (nivolumab, pembrolizumab) or anti-PD-L1 inhibitors (atezolizumab) with first-line platinum-based chemotherapy in patients with metastatic NSCLC (both squamous and non-squamous histology) have been included in a literature-based meta-analysis (12). The pooled results of the meta-analysis showed a statistically significant and clinically relevant benefit both in terms of OS and PFS with the use of the combination of chemotherapy and immunotherapy, compared to chemotherapy alone. Subgroup analyses were performed, testing the interaction of treatment efficacy with the type of immune checkpoint inhibitor according to the level of PD-L1 expression. Notably, in the cases characterized by low PD-L1 expression, the benefit was statistically significant only with pembrolizumab (HR 0.56; 95% CI: 0.40–0.78), and not with atezolizumab (HR 0.92; 95% CI: 0.62–1.37), with a statistically significant interaction (12). However, this provocative result has several possible explanations: a true difference in efficacy between anti-PD-1 and anti-PD-L1 antibodies, or the longer follow-up of trials with pembrolizumab, compared to trials with atezolizumab, or the issues related to technical differences in terms of immunohistochemistry testing and scoring used in the trials for determining PD-L1 tumor expression. Overall, with the above-described limitations, these trials suggest that the first-line chemo-immunotherapy is a

successful strategy, in terms of efficacy, compared to the standard chemotherapy, at the price of greater side effects, higher costs and less personalized patients' selection.

PD-L1, indeed, that is the accepted biomarker for the selection of patients with advanced NSCLC eligible for first-line single agent pembrolizumab, given the significant association between PD-L1 expression and pembrolizumab efficacy (3,13,14), plays a far less clear role in the selection of patients for chemo-immunotherapy, considering that the benefit has been demonstrated across all subgroups of PD-L1 expression (6).

However, it is important to underline that in cases of PD-L1 expression greater than 50%, the current standard of treatment is single-agent pembrolizumab. In this subset of patients, no head-to-head comparison has been performed between immunotherapy alone and the combination of immunotherapy and chemotherapy (both strategies have documented an improvement in survival compared to chemotherapy), leaving open the question of what is the best approach and what are the factors that could guide patients' selection.

Conclusive notes

In conclusion, all these data certainly increase the number of potential upfront therapeutic options for patients with squamous cell lung cancer. However, the choice of the most appropriate treatment for each individual patient remains a challenge.

The available results from the different trials are rather heterogeneous in terms of differences in study populations, inclusion criteria, treatments schedules, stratification factors and other aspects.

Moreover, the choice of a second line in a population treated with a first line combined strategy remains a challenge. Thus, despite the KEYNOTE-407 results and the important progress in the management of squamous cell lung cancer with significant increase in response rate and survival, different questions remain open. In the era of personalized medicine, for example, a tailored approach seems to be evidently distant, especially if compared to non-squamous tumors. Ongoing trials, as the Lung-MAP, try to identify, based on molecular profiling, targeted strategies and will contribute to improve treatment management (15).

Therefore, further research—aimed to identify biomarkers (beyond PD-L1 expression) that predict response and allow selection for monotherapy versus combination therapy, to define treatment strategies to

overcome resistance and optimize efficacy—is required, with the ultimate purpose to offer the best treatment to every different patient affected by squamous cell lung cancer.

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Footnote

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