Editorial Commentary

A new chapter in immune checkpoint inhibitor therapy: starting with advanced lung squamous cell carcinoma

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Lung cancer, which carries the highest morbidity and mortality rates of any malignant tumor, is associated with more than 2 million new cases and more than 1.7 million deaths every year (1). Squamous cell carcinoma (SCC), a subtype of non-small cell lung cancer (NSCLC), comprises one-quarter of these new lung cancer cases (2). Platinum-doublet chemotherapy has been considered as the standard first-line treatment for NSCLC since the milestone meta-analysis and pivotal randomized clinical trials were conducted (3,4). Owing to the widespread use of genetic and molecular techniques, a number of driver genes have been identified in patients with lung adenocarcinoma, another major pathological type of NSCLC, and patients can benefit from targeted therapy (5). Unfortunately, the proportion of SCC patients who have positive driver genes is small, and the treatment effect for SCC patients with positive driver genes is poor. Consequently, little progress has been made with first-line treatment for patients with advanced SCC in recent decades. However, after nearly 20 years of stagnation in SCC treatment, the emergence of immune checkpoint inhibitors (ICIs) has seemingly brought NSCLC treatment into a new era.

Studies such as KEYNOTE-010 (6), CheckMate 017/057/078 (7), POPLAR (8), and OAK (9) proved that ICIs can improve the prognosis of patients with advanced NSCLC, bringing about a new alternative for second-line treatment. Later, in a series of clinical trials that featured ICIs as a single agent, including KEYNOTE-024 (10), KEYNOTE-042 (11), and CheckMate 026 (12), ICIs consistently challenged platinum-doublet chemotherapy as the first-line treatment of advanced NSCLC. However, in contrast with the great success of immunotherapy as a second-line treatment for NSCLC, some of the studies failed to meet their primary endpoints in the first-line setting, and the studies that successfully demonstrated the superior performance of first-line immunotherapy were dependent on patients with a high level of PD-L1 expression being selected. This proposed the question of whether it was possible to find a new first-line treatment that could improve the survival of overall population with advanced SCC. Based on this, the KEYNOTE-407 (13) study was conducted to explore whether pembrolizumab combined with chemotherapy as a first-line treatment can improve the prognosis of patients with advanced SCC.

The double-blind (I:I) KEYNOTE-407 study randomized patients with treatment-naïve stage IV SCC to receive carboplatin-(albumin) paclitaxel combined with pembrolizumab or placebo followed by 200 mg of pembrolizumab or placebo every 3 weeks for up to 35 cycles. For the first four cycles, the patients were treated with carboplatin at a dose of AUC 6 mg/mL per minute and either paclitaxel at 200 mg/m^2 every 3 weeks or albumin-bound paclitaxel at 100 mg/m^2 once a week. Patients who received placebo-combination were eligible to crossover to the pembrolizumab-combination group and receive 200 mg of pembrolizumab every 3 weeks up to 35 cycles if their

disease progressed during or after the treatment. Overall, 40.1% patients in the placebo-combination group crossed over to the pembrolizumab-combination group, of whom 49.1% received subsequent anti-PD-(L) 1 therapy (13).

The enrolled patients needed to have an Eastern Cooperative Oncology Group (ECOG) performance score of 0 to 1, asymptomatic brain metastases, pneumonia without systemic glucocorticoid therapy, and be able to provide appropriate specimens for the measurement of PD-L1 expression level. Stratification factors included PD-L1 immunohistochemical expression level [tumor proportion score (the proportion of PD-L1 positive tumor cells, TPS), ≥1% *vs.* <1%, using PD-L1 IHC 22C3 pharmDx]; chemotherapy regimen (paclitaxel *vs.* albumin-paclitaxel); region of enrolment (East Asia *vs.* the rest of the world). The imaging evaluation was performed according to the RECIST 1.1 criteria (14).

The dual primary endpoints of the study were overall survival (OS) and progression-free survival (PFS); the secondary endpoints included objective response rate (ORR), duration of response (DoR), and patient safety. In the study, PFS2 was an exploratory endpoint, which was defined as the time from randomization to disease progression of the second-line of treatment or death from any cause. If disease progression was radiographically confirmed while clinical benefits were still evident, patients could continue to use open-label Pembrolizumab for a total of 35 cycles. During the course of treatment, the study could be stopped based on radiological disease progression, unacceptable toxicity, the investigator's decision, or the patient's withdrawal of consent.

The KEYNOTE-407 study included a total of 278 patients who received pembrolizumab plus chemotherapy and 281 patients who received placebo plus chemotherapy. The proportion of patients between groups by stratifying factors such as enrolment region (East Asia, 19.4% *vs.* 18.5%), PD-L1 expression level (<1%, 34.2% *vs.* 35.2%; 1–49%, 37.1% *vs.* 37.0%; ≥50%, 26.3% *vs.* 26.0%), and choice of chemotherapy regimen (Carboplatin, 60.8% *vs.* 59.6%) were well balanced.

In the total intention-to-treat population, pembrolizumab combined with chemotherapy reduced the risk of death by 29% compared to placebo plus chemotherapy [median OS, 17.1 months (95% CI: 14.4–19.9) *vs.* 11.6 months (95% CI: 10.1–13.7); HR 0.71 (95% CI: 0.58–0.88)], and reduced the risk of progression by 43% [median PFS, 8.0 months (95% CI: 6.3–8.4) *vs.* 5.1 months (95 % CI: 4.3–6.0); HR 0.57 (95% CI: 0.47–0.69)].

The ORR of patients in the pembrolizumab-combination group was 62.6%, and the ORR of the placebo-combination group was 38.40% (P<0.0001). The median DoR of the pembrolizumab plus chemotherapy group was 8.8 months (95% CI: 1.3–28.4), almost twice of that of placebo plus chemotherapy group with 4.9 months (95% CI: 1.3–28.3).

In patients with negative PD-L1 expression (TPS, <1%), the OS hazard ratio of pembrolizumab plus chemotherapy *vs.* placebo plus chemotherapy was 0.79 (95% CI: 0.56–1.11), the PFS hazard ratio was 0.67 (95% CI: 0.49–0.91), the ORR was 67.4% *vs.* 41.4%, the median DoR was 6.9 months *vs.* 5.7 months, and the PFS2 hazard ratio was 0.61 (95% CI: 0.44–0.85).

In patients with a PD-L1 expression level (TPS) of 1–49%, the OS hazard ratio of pembrolizumab plus chemotherapy *vs.* placebo plus chemotherapy was 0.59 (95% CI: 0.42–0.84), the PFS hazard ratio was 0.52 (95% CI: 0.38–0.71), ORR was 55.3% *vs.* 42.3%, the median DoR was 10.4 months *vs.* 4.8 months, and the PFS2 hazard ratio was 0.51 (95% CI: 0.37–0.72).

In patients with a highly positive PD-L1 expression level (TPS, ≥50%), the OS hazard ratio of pembrolizumab combined with chemotherapy *vs.* placebo combined with chemotherapy was 0.79 (95% CI: 0.52–1.21) without progression. The PFS hazard ratio was 0.43 (95% CI: 0.29–0.63), the ORR was 64.4% *vs.* 30.1%, the median DoR was 9.2 *vs.* 4.6 months, and the PFS2 hazard ratio was 0.61 (95% CI: 0.40–0.91).

By analyzing various subgroups, it can be established that at different PD-L1 expression levels, pembrolizumab combined with chemotherapy was superior to placebo combined with chemotherapy in all aspects including median OS, median PFS, median PFS2, ORR, and DoR.

In terms of safety, the incidence of grade 3–5 adverse reactions was roughly the same between the pembrolizumab plus chemotherapy group and the placebo plus chemotherapy group, with rates of 74% and 70%, respectively. The incidence of adverse reactions of any grade was 99% and 98%, respectively, and the difference was not significant. In the pembrolizumab treatment group, the incidences of adverse reactions and grade 3–5 adverse reactions related to immunization and infusion were 35% and 13%, respectively. The treatment-related mortality was 4% and 2%, respectively.

A significant level was reached for the exploratory endpoint PFS2, despite the ability of the patients to crossover. The median PFS2 was 13.8 months (95% CI: 12.2–15.9) in the monoclonal antibody plus chemotherapy

group and 9.1 months (95% CI: 8.2–10.2) in the chemotherapy only group. The risk of disease progression was reduced by 41% (HR 0.59, 95% CI: 0.49–0.72) in the monoclonal antibody plus chemotherapy group.

In the Chinese cohort extension study (15), the pembrolizumab plus chemotherapy group comprised a total of 65 patients, and the placebo plus chemotherapy group included a total of 60 patients. In the overall intention-to-treat population in this cohort, pembrolizumab plus chemotherapy reduced the risk of death by 56% [median OS, 17.3 months; 95% CI: 14.1–not reached (NR) *vs.* 12.6 months; 95% CI: 9.6–NR; HR 0.44 (95% CI: 0.24–0.81)] and reduced the risk of progression by 68% [median PFS, 8.3 months (95% CI: 6.2–10.3) *vs.* 4.2 months (95% CI: 4.0–4.4); HR 0.32 (95% CI: 0.21–0.49)]. For the pembrolizumab plus chemotherapy group, the ORR was 78.5%, compared with 41.7% for the placebo plus chemotherapy group. The median DoR of the pembrolizumab plus chemotherapy and placebo plus chemotherapy groups was 8.9 and 3.5 months, respectively.

Collectively, KEYNOTE-407 has presented a new option for the first-line treatment of patients with advanced SCC. More importantly, unlike the previous studies such us KEYNOTE-024 (7) and KEYNOTE-042 (8), KEYNOTE-407 has demonstrated the survival improvement offered by ICI-based therapy for SCC patients, regardless of PD-L1 expression level, and has thus opened up the benefit of immunotherapy to all patients with advanced SCC.

As described above, even though 49.1% of the patients in the chemotherapy-combination group received subsequent ICI therapy, which improved the survival of this control group, pembrolizumab plus chemotherapy still exhibited significant prolonged PFS and OS, therefore further supporting the superior role of pembrolizumab plus chemotherapy as a first-line treatment for patients with advanced SCC. Further investigation is warranted to provide more evidence regarding the first-line treatment strategy for SCC patients.

With the benefits offered by the use of pembrolizumab combined with chemotherapy as a first-line treatment, it is the first treatment option that has imposed on platinum-doublet chemotherapy's status as the first-line treatment for advanced SCC. Undoubtedly, there are still many factors that need to be taken into account in the decision-making process for first-line treatment, one example of which is PD-L1 expression level. Based on the KEYNOTE-024/042 studies, patients with positive PD-L1 expression (TPS ≥50% or TPS ≥1%) who received pembrolizumab monotherapy benefited from superior ORR compared with those who received traditional platinum-doublet chemotherapy regimens. The treatment choice between ICI monotherapy and ICI-based combination therapy for this group of patients is still unclear, and further exploration is needed.

With striking efficacy, ICIs have stirred the third revolution in treatment for NSCLC, following the paths of chemotherapy and targeted therapy. It is important to note that our current knowledge of ICIs is still in its infancy, and more research is needed to help us determine the timing and approach to the application of ICIs in clinical practice.

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Footnote

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