



KEYNOTE-407: new hope for the treatment of lung squamous cell carcinoma

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Lung squamous cell carcinoma (SCC) accounts for approximately 25% of all cases of non-small cell lung cancer (NSCLC). Treatments vary a great deal between SCC and non-SCC. Platinum-based chemotherapy is the main treatment for lung SCC, and targeted therapies, such as epidermal growth factor receptor (EGFR) inhibitors and anaplastic lymphoma kinase (ALK) inhibitors, are effective for lung adenocarcinoma but not lung SCC; therefore, new treatment strategies for lung SCC are required. Novel tumor immunotherapies are becoming potential treatments for cancer patients. The results of the KEYNOTE-407 study on lung SCC are exciting. In this paper, we interpret and analyze the clinical implications of the KEYNOTE-407 study.

The KEYNOTE-407 study (1) is a multicountry, randomized, double-blind, placebo-controlled, phase III trial in treatment-naïve patients with stage IV squamous NSCLC (sq-NSCLC), including patients with negative expression of programmed death-ligand 1 (PD-L1). The primary endpoints are overall survival (OS) and progression-free survival (PFS). The secondary endpoints include overall response rate (ORR) and duration of response (DOR). A total of 559 eligible patients were randomly assigned at 1:1 to receive pembrolizumab 200 mg or placebo Q3W, for 35 cycles, combined with 4 cycles of carboplatin, area under curve (AUC) 6 mg/mL/min Q3W, and researchers' choice of either paclitaxel (PTX) 200 mg/m² Q3W or nab-PTX 100 mg/m² QW.

The results showed that pembrolizumab combined with carboplatin and PTX or nab-PTX significantly

improved ORR (57.9% *vs.* 38.4%), OS [hazard ratio (HR) 0.64, 95% confidence interval (CI): 0.49–0.85, P=0.0008], and PFS (HR 0.56, 95% CI: 0.45–0.70, P<0.0001) relative to placebo combined with carboplatin and PTX or nab-PTX. Regardless of the PD-L1 tumor proportion score (TPS), patients benefited from additional pembrolizumab therapy. In addition, pembrolizumab combined with carboplatin and PTX or nab-PTX showed a manageable safety profile.

In this study, we explore and analyze the effect of researchers' choice of either PTX (60.1%) or nab-PTX (39.9%), one of the stratification factors, on efficacy. Patients who received PTX or nab-PTX showed similar baseline characteristics. Pembrolizumab combined with carboplatin improved the outcomes, regardless of whether patients received PTX or nab-PTX. For the comparison between pembrolizumab combined with carboplatin and carboplatin only, the median OS (mOS) was 14.0 *vs.* 10.3 months for patients with PTX, with an HR of 0.67 (0.48–0.93), and were NR *vs.* 12.6 months for patients with nab-PTX, with an HR of 0.59 (0.36–0.98); the median PFS (mPFS) was 6.4 *vs.* 4.4 months for patients with PTX, with an HR of 0.52 (0.40–0.68), and were 6.5 *vs.* 5.9 months for patients with nab-PTX, with an HR of 0.65 (0.45–0.94); and the ORRs were 57.4% *vs.* 37.7% for patients with PTX and were 58.7% *vs.* 39.5% for patients with nab-PTX. For the comparison between pembrolizumab combined with carboplatin and placebo combined with carboplatin, in terms of grade 3–5 adverse events (AEs), the incidence rates were 63.9% *vs.* 59.3% for patients with

PTX and 78.9% *vs.* 81.4% for patients with nab-PTX; in terms of treatment discontinuation, the rates were 13.6% *vs.* 8.4% for patient with PTX and 12.8% *vs.* 3.5% for patients with nab-PTX; in terms of immune-related AEs, the incidence rates were 29.6% *vs.* 9.6% for patients with PTX and 27.5% *vs.* 7.1% for patients with nab-PTX; and in terms of steroids, the usage rates were 99.4% *vs.* 99.4% for patients with PTX and 88.1% *vs.* 86.7% for patients with nab-PTX. As first-line treatment for metastatic lung SCC, pembrolizumab combined with carboplatin and PTX was superior to placebo combined with carboplatin and PTX and significantly improved OS, PFS, and ORR, regardless of the specific type of PTX. Moreover, pembrolizumab combined with PTX or nab-PTX was well tolerated.

On November 23, 2019, Prof. Ying Cheng of Jilin Cancer Hospital presented the results of an interim analysis of the KEYNOTE-407 China extension study, including extension cohorts, at the 2019 European Society for Medical Oncology in Asia (ESMO Asia) conference (2).

A total of 125 treatment-naïve patients in China with histologically confirmed stage IV sq-NSCLC and no symptomatic brain metastases were enrolled at Chinese centers and randomly assigned at 1:1 to receive 4 cycles of pembrolizumab (200 mg, Q3W) + carboplatin (AUC 6, Q3W) + PTX (200 mg/m², Q3W)/nab-PTX (100 mg/m², QW) or placebo + carboplatin + PTX/nab-PTX, followed by maintenance therapy with pembrolizumab or placebo. Patients with cancer progression in the control group could crossover to receive pembrolizumab monotherapy. The primary endpoints were PFS and OS, and the secondary endpoint was ORR. Moreover, protocol-defined subgroup analyses were performed to analyze OS, PFS, and ORR per PD-L1 tumor expression status (TPS ≥50% *vs.* 1% to 49% *vs.* <1%) to evaluate the benefits of pembrolizumab combined with carboplatin in the Chinese population and to compare with the results of the global population.

After a median follow-up of 10.4 months, the results showed that mOS was 17.3 months in the pembrolizumab group and 12.6 months in the control group, indicating that pembrolizumab combined with carboplatin reduced mortality by 56%; for mPFS, the figures were 8.3 and 4.2 months, respectively, indicating that pembrolizumab combined with carboplatin reduced the risk of progression or mortality by 68%. Moreover, pembrolizumab combined with carboplatin improved the ORR by 36.8% (78.5% *vs.* 41.7%). As of May 2019, 35 patients in the control group crossed over to receive pembrolizumab monotherapy, and 31 patients (48%) in the pembrolizumab group and

4 patients (7%) in the control group were still receiving treatments.

The overall incidence of AEs (any grade) was 100% in both groups; for grade 3–5 AEs, the rates were similar in the two groups, 89% and 87%. Major immune-related AEs included hyperthyroidism, hypothyroidism, infusion reactions, myositis, pneumonitis, thyroiditis, and type 1 diabetes.

The results of the KEYNOTE-407 China extension study are consistent with those of the global KEYNOTE-407 study. First-line treatment with pembrolizumab combined with carboplatin significantly improves the OS and PFS of patients with metastatic sq-NSCLC and demonstrates a manageable safety profile, indicating that the regimen brings more benefits to Chinese patients with lung SCC.

It should be noted that taxanes are used in the KEYNOTE-407 study. Our analysis of conventional PTX *vs.* nab-PTX showed that nab-PTX achieved similar outcomes and caused fewer adverse reactions; more importantly, it eliminated steroid pretreatment, a step required for conventional PTX. Currently, there is no definitive evidence to suggest that high-dose steroids affect the efficacy of immunotherapy; however, some retrospective analyses and basic research have shown that steroids may negatively affect immunotherapy. Thus, eliminating this risk can improve the confidence of patients and physicians regarding the regimen. Moreover, this study does not use gemcitabine, a standard treatment for SCC, or radiotherapy, which eliminates the risk of radiation injury.

In summary, as first-line treatment for metastatic lung SCC, pembrolizumab combined with carboplatin and PTX/nab-PTX, significantly improves OS, PFS, and the ORR and is well tolerated. For the Chinese population, first-line treatment with pembrolizumab combined with carboplatin and PTX/nab-PTX significantly improves the OS and PFS of patients with metastatic sq-NSCLC with a manageable safety profile.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tlcr.2020.03.12>). The authors have no

conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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