Editorial Commentary

# New first-line treatment strategies for advanced lung squamous cell carcinoma

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Lung cancer has the highest prevalence among all malignancies, and is the leading cancer killer in both men and women worldwide. About 85% to 90% of lung cancers are non-small cell lung cancer (NSCLC), of which lung squamous cell carcinoma (LSCC) accounts for about 30% of all cases of NSCLC (1). While the practice of targeted therapy for NSCLC in the past decade has propelled NSCLC to the forefront of precision medicine, the cancer-driver mutations mainly present in adenocarcinoma and palliative chemotherapy remain the mainstream treatment for LSCC (2). Since the completion of the classic Eastern Cooperative Oncology Group (ECOG) 1594 study, platinum-based chemotherapy doublets have become the first-line treatment strategy for advanced LSCC, but the response rate and the median survival yielded from this study were only about 20% and about 8 months, respectively (3). Although the FLEX study demonstrated that combination of the chemotherapy with cetuximab improved the overall survival (OS), the regimen was associated with increased grade 4 or higher toxicities and was subsequently removed from the National Comprehensive Cancer Network (NCCN) guidelines (4). Therefore, the first-line treatment for advanced LSCC faces great difficulties, but some notable advances and breakthroughs in immunotherapy have been made.

## Immuno-monotherapy

KEYNOTE-024 was the first clinical trial that demonstrated the antitumor activity of immunotherapy as the first-line treatment for lung cancer. Up to 20% of subjects in this study had advanced LSCC, among whom the progression-free survival (PFS) and OS in the pembrolizumab group were superior to those in the standard platinum-based chemotherapy group. Also, it was found that advanced LSCC patients with PD-L1 TPS ≥50% could benefit from pembrolizumab monotherapy (5). Thus, a new era of immunotherapy for advanced LSCC began. It has been found that the expression rate of PD-L1 is higher in LSCC (6), and thus these patients may benefit more from immunotherapy. In the subgroup analysis of the KEYNOTE-042 study (7), LSCC showed significantly lower HR values than non-LSCC, which was consistent with the finding in the KEYNOTE 024 study. In addition to pembrolizumab, the CheckMate 026 study found that nivolumab had a higher disease response rate than chemotherapy for patients with a high tumor-mutation burden (8).

## Immunotherapy plus chemotherapy

In order to overcome the limitations of immuno-monotherapy, more research has investigated the strategies of combination immunotherapy, as demonstrated in the recently published studies including KEYNOTE-407 (9), IMpower 131 (10), and CheckMate 227 (11).

The KEYNOTE-407 study enrolled a full non-squamous population with any expression level of PD-L1 and treatment-naive patients with metastatic LSCC;

according to the double-blind principle, these subjects were equally randomized into a pembrolizumab 200 mg group or a placebo group; each treatment cycle lasted 3 weeks (up to 35 cycles). The treatment was also combined with 4 cycles of platinum-based doublet chemotherapy, in which the dose of carboplatin was 6 mg/mL/min, whereas the dose of paclitaxel (200 mg/m$^2$) or nanoparticle albumin-bound paclitaxel (nab-paclitaxel) (100 mg/m$^2$) was decided by the researchers. The authors also analyzed whether there was any efficacy difference between the 2 different chemotherapy regimens [i.e., paclitaxel (60.1%) *vs.* nab-paclitaxel (39.9%)] chosen by the researchers, which was also one of the stratification factors in the study. The results showed that, regardless of the PD-L1 expression levels detected by immunohistochemistry [tumor proportion score (TPS) ≥1% *vs.* <1%], the patients could always benefit from pembrolizumab plus chemotherapy. It was found that compared with placebo plus chemotherapy, pembrolizumab plus chemotherapy (carboplatin + paclitaxel or nab-paclitaxel) significantly increased overall response rate (ORR) (57.9% *vs.* 38.4%), prolonged OS (HR 0.64, 95% CI: 0.49–0.85, P=0.0008), and PFS (HR 0.56, 95% CI: 0.45–0.70, P<0.0001). In addition, pembrolizumab plus chemotherapy also showed manageable safety. The incidence of grade 3–5 toxicities was 63.9% and 59.3% in the pembrolizumab plus carboplatin + paclitaxel group and placebo plus carboplatin + paclitaxel group, respectively; in contrast, the incidence of grade 3–5 toxicities was 78.9% and 81.4% in the pembrolizumab plus nab-paclitaxel group and placebo plus nab-paclitaxel group, respectively. The incidence of immune-related toxicities was 29.6% *vs.* 9.6% in paclitaxel-treated patients and 27.5% *vs.* 7.1% in the nab-paclitaxel-treated patients.

The IMpower 131 study had a similar study design as the KEYNOTE-407 study. Patients with advanced squamous NSCLC with any expression level of PD-L1 were randomized 1:1:1 to Arm A (atezo 1,200 mg q3w + carbo AUC 6 q3w + pac 200 mg/m$^2$ q3w), Arm B (atezo + carbo + nab-pac 100 mg/m$^2$ weekly) or Arm C (carbo + nab-pac). According to the data released in the 2018 ASCO meeting, the median PFS was 6.3 months in Arm B *vs.* 5.6 months in Arm C. The one-year PFS rate was doubled (24.7% *vs.* 12.0%), and the risk of disease progression was reduced by 29% (HR =0.71). The PFS benefit was enriched in all PD-L1-positive subgroups and was most pronounced in populations with high PD-L1 expression (10.1 *vs.* 5.5 months). Although only preliminary OS data have been presented, the OS curves of these 2 study groups almost completely overlapped (12-month OS rate: 55.6% *vs.* 56.9%); at the time point of 24 months, the combination group had a significantly higher 2-year OS rate than the chemotherapy alone group (31.9% *vs.* 24.1%).

The CheckMate 227 study also compared the efficacy and safety of platinum-based doublet chemotherapy, nivolumab monotherapy, duplicate, nivolumab plus ipilimumab, and nivolumab plus platinum-based doublet chemotherapy in treatment-naive patients with advanced or recurrent NSCLC. The study was divided into 2 parts, of which Part 1 has shed light on the role of two-drug combination immunotherapy in treating these malignancies. The OS benefit was also observed in patients with a PD-L1 expression level of less than 1%, with a median duration of 17.1 months with nivolumab plus ipilimumab and 14.9 months with chemotherapy, which reached the primary endpoint. The OS benefit was more prominent in the LSCC group [HR: 0.69 (0.52–0.92)], and was also seen in patients with PD-L1 TPS <1% (HR 0.62; 95% CI: 0.48–0.78).

## Problems and perspectives

Although these clinical studies have reshaped the patterns of treatment for advanced LSCC, certain uncertainties still linger.

First, the treatment strategy for patients with different expression levels of PD-L1 should be reasonably decided upon. It has been well recognized that immunotherapy plus chemotherapy is the preferred treatment for patients with low expression levels of PD-L1. For advanced LSCC patients with PD-L1 TPS ≥50%, however, it is unclear whether pembrolizumab monotherapy or immunotherapy plus chemotherapy should be the first-line treatment. For these patients, immuno-monotherapy seems to have been able to bring remarkable survival benefits, and so it is uncertain if combination with chemotherapy would bring added advantages or simply be a superfluous addition (12,13). Due to the lack of head-to-head clinical trials, some meta-analyses for indirect comparisons have offered preliminary evidence that pembrolizumab plus chemotherapy is significantly superior to pembrolizumab monotherapy in terms of ORR and PFS, although the OS of the meta-analysis showed no significant difference. Therefore, for patients with PD-L1 ≥50%, either monotherapy or combination therapy may be feasible, and the decision can be made mainly based on clinical features including tumor burden and medication tolerance.

 

Immunotherapy plus chemotherapy may achieve faster tumor remission in patients with high tumor burden and severe symptoms and/or in patients who can well tolerate chemotherapy. In contrast, immuno-monotherapy may be a more rational option when the cost and toxicities of the combination therapy are problematic for the patient. Furthermore, there is no consensus concerning whether pembrolizumab (based on the KEYNOTE-042 study) or NIVO + IPI (based on the CheckMate 227 study) should be the preferred first-line chemotherapy-free treatment strategy for patients with PD-L1 TPS ≥1%. While further studies are needed to resolve this question, some research has supported the use of NIVO+IPI in patients with PD-L1 TPS <1%.

Second, the specific first-line drugs for advanced LSCC should also be reasonably chosen during immunotherapy plus chemotherapy. It is not clear, for example, what the advantages and disadvantages of anti-PD-1 and anti-PD-L1 monoclonal antibodies are. Subgroup analysis in a meta-analysis showed that the efficacies of anti-PD-1 or anti-PD-L1 monoclonal antibody were significantly different when combined with chemotherapy as the first-line treatment for NSCLC (OS; HR: 0.56 *vs.* 0.85, P<0.001) (14). However, since few clinical trials on PD-L1 inhibitors have been carried out and no head-to-head studies have compared the roles of anti-PD-1 and anti-PD-L1, the selection of either drug should be done with caution. Third, the choice of chemotherapy drugs such as nab-paclitaxel and ordinary paclitaxel also warrants further investigation. Socinski compared the efficacy of carboplatin/nab-paclitaxel with that of carboplatin/paclitaxel for advanced NSCLC. The results showed that patients with LSCC had higher ORRs after treatment with nab-paclitaxel (ORR: 41% *vs.* 24%, RR =1.68, 95% CI: 1.27–2.22) (15). On the other hand, nab-paclitaxel can overcome the disadvantage (i.e., requiring hormonal pretreatment that may weaken the efficacy of immunotherapy) of other taxanes and thus can exert a synergistic effect with immunotherapy. However, there is still insufficient evidence to guide clinical choices and more head-to-head comparison data are needed.

Finally, some ongoing studies are actively exploring new combination strategies for immunotherapy in the treatment of lung cancer, which include the combination of immunotherapy with anti-angiogenesis drugs (for improving the tumor microenvironment) (16), with targeted therapy (17), with IDO1 inhibitors (18), or with radiotherapy (19). However, these studies have yet to yield promising results.

In summary, treatment of advanced LSCC has entered the era of immunotherapy in recent years. Immune checkpoint inhibitors have dramatically improved the OS of lung cancer patients and even offer the possibility of a cure. However, only a limited proportion of patients can benefit from this revolutionary treatment. At present, there is no precise and perfect molecular marker for screening those patient populations that will receive most benefit from these therapies. Given the above, avenues of future research may include (I) the integration of internal factors of tumors with tumor microenvironment-related factors for exploring efficient and accurate systems for predicting the treatment response, and (II) identifying patient populations that may benefit from the combinations of immunotherapy with other therapeutic methods.

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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.2020.03.14). The authors have no conflicts of interest to declare.

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