Editorial Commentary

Efficacy of the PD-1 inhibitor penpulimab in combination with chemotherapy for advanced lung squamous cell carcinoma: insights from a phase III multicenter study

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We would like to commend Dr. Zhong and colleagues on their well-designed and successfully completed study published in *The Lancet Respiratory Medicine*. This study reports the results of a multicenter, randomized, double-blind, placebo-controlled, phase III clinical trial evaluating the efficacy and safety of a novel therapeutic regimen combining penpulimab with paclitaxel and carboplatin for the treatment of advanced lung squamous cell carcinoma (LUSC) (1). Penpulimab is a new humanized anti-programmed cell death 1 (PD-1) antibody with a more stable structure and higher receptor occupancy compared to other anti-PD-1 antibodies (2). LUSC represents approximately 25–30% of all non-small cell lung cancers (NSCLCs) (3). Currently, pembrolizumab and atezolizumab are approved by the U.S. Food and Drug Administration as first-line therapies for advanced LUSC with programmed death-ligand 1 (PD-L1) expression levels exceeding 50% (4,5). Additionally, pembrolizumab in combination with chemotherapy is recommended as a first-line treatment for advanced LUSC (6,7). Other immunotherapies, such as nivolumab and ipilimumab, have also demonstrated significant improvements in outcomes for advanced LUSC (8-10). However, compared to lung adenocarcinoma, LUSC appears to exhibit lower responsiveness to current therapies (11). Notably, in the IMpower131 trial, the addition of atezolizumab to nab-paclitaxel and carboplatin did not significantly improve overall survival (OS) (12).

This study included 350 patients with locally advanced or metastatic LUSC from 74 hospitals in China. Eligible patients were those unsuitable for surgical resection, concurrent or sequential chemoradiation, and who had not previously received systemic chemotherapy. Patients with histologically confirmed LUSC were included despite the potential for adenocarcinoma contamination, whereas those with neuroendocrine tumors, *EGFR* mutations, or *ALK* fusions were excluded. No specific criteria or regulations were applied regarding PD-L1 expression levels. All patients received paclitaxel at 175 mg/m^2 and carboplatin

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with an area under the curve (AUC) of 5, combined with either penpulimab or a placebo. The 350 patients were randomized into two groups: 175 received penpulimab, and 175 received a placebo.

At the time of the final analysis (June 1, 2022), with a median follow-up of 24.7 months, patients in the penpulimab group showed a significantly improved progression-free survival (PFS) compared to those in the placebo group. The median PFS was 8.6 months [95% confidence interval (CI): 6.8–9.6] in the penpulimab group, which was significantly longer than the 4.2 months (95% CI: 4.2–4.3) observed in the placebo group (hazard ratio: 0.43, 95% CI: 0.33–0.56; P<0.0001). Notably, approximately 60% of the patients in the placebo group were switched to penpulimab monotherapy upon disease progression; nevertheless, a significant difference in PFS was still observed. In a subgroup analysis of the PD-L1-positive population, patients receiving penpulimab had better outcomes than those receiving placebo, with a median PFS of 8.1 months (95% CI: 5.7–9.7 months) versus 4.2 months (95% CI: 4.1–4.3) (hazard ratio: 0.37, 95% CI: 0.27–0.52, P<0.0001). A trend toward greater efficacy was observed with higher PD-L1 positivity. At this point, the median OS has not been reached in the penpulimab group, but a significant difference compared to the placebo group is anticipated in the future.

The incidence of grade 3 or higher treatment-related adverse events was similar between the penpulimab and placebo groups. However, immune-related pneumonitis was observed only in the penpulimab group, highlighting the need for careful monitoring when using penpulimab in combination with chemotherapy. The rate of treatment discontinuation due to adverse events was 6% with penpulimab, which is lower than the 12–30% reported in trials of other PD-1/PD-L1 inhibitors (6,12), suggesting that penpulimab in combination with chemotherapy is a well-tolerated treatment option for patients with lung cancer.

For patients with advanced LUSC, the combination of anti-PD-1 antibody therapy and chemotherapy may provide superior efficacy compared to the combination with anti-PD-L1 antibody therapy. As shown in *Table 1*, an indirect comparison of the KEYNOTE-407 and IMpower131 phase III randomized trials in advanced LUSC demonstrated that pembrolizumab, an anti-PD-1 antibody, combined with chemotherapy (KEYNOTE-407) was associated with better OS and PFS than atezolizumab, an anti-PD-L1 antibody, combined with chemotherapy (IMpower131) (13). Specifically, among patients with high PD-L1 expression, pembrolizumab plus chemotherapy and atezolizumab plus chemotherapy achieved similar OS and PFS. However, in patients with low or negative PD-L1 expression, pembrolizumab plus chemotherapy was superior to atezolizumab plus chemotherapy in terms of OS and PFS. Anti-PD-1 antibodies bind to PD-1 and inhibit the interaction between PD-1 and its ligands (PD-L1 and PD-L2), whereas the PD-1/PD-L2 axis remains intact with anti-PD-L1 antibodies. In patients with low or negative PD-L1 expression, PD-L2 expression is increased, and the spectrum of immune molecule expression may be more complex (14,15). As a result, anti-PD-L1 antibodies may not exert sufficient anti-tumor effects in PD-L1 low/negative patients compared to anti-PD-1 antibodies. Additionally, PD-L1 staining appears to be a less reliable predictor of treatment response in LUSC compared to lung adenocarcinoma (16). Indeed, anti-PD-1 antibodies have been selected over anti-PD-L1 antibodies in recent clinical trials for LUSC (17). The combination therapy of nivolumab, an anti-PD-1 antibody, and ipilimumab, an anti-CTLA-4 antibody, demonstrated favorable OS outcomes in advanced LUSC in the CheckMate 227 trial. Additionally, the KEYNOTE-407 trial did not show significant OS improvement in PD-L1-negative patients, whereas the CheckMate 227 trial did. The combination of penpulimab and chemotherapy significantly improved PFS irrespective of PD-L1 expression levels, with similar improvements in OS anticipated. These findings highlight the efficacy of penpulimab, an anti-PD-1 antibody, in patients with advanced LUSC.

In conclusion, the combination of penpulimab with paclitaxel and carboplatin represents a promising new primary treatment option that significantly improves both PFS and OS in patients with advanced LUSC. The findings of this study support the efficacy of penpulimab, even in patients with low PD-L1 expression, and warrant consideration for its further clinical application. However, as this study exclusively involved Chinese patients, future studies are necessary to evaluate the clinical benefits of

Table 1 Clinical trial outcomes for immunotherapy-based treatments in lung squamous cell carcinoma

Trial	Treatment	OS		PFS		References
		OS value	HR (95% CI)	PFS value	HR (95% CI)	
KEYNOTE-407	Pembrolizumab + carboplatin + (paclitaxel or nab-paclitaxel) *vs.* chemotherapy	Pembrolizumab arm: 17.2 months, chemotherapy arm: 11.6 months	0.71 (0.59–0.85) for all patients	Pembrolizumab arm: 8.0 months, chemotherapy arm: 5.1 months	0.62 (0.52–0.74) for all patients	(5,6)
			0.68 (0.47–0.97) for patients with PD-L1 TPS ≥50%		0.48 (0.33–0.69) for patients with PD-L1 TPS ≥50%	
			0.61 (0.45–0.83) for patients with PD-L1 TPS 1–49%		0.60 (0.45–0.81) for patients with PD-L1 TPS 1–49%	
			0.83 (0.61–1.13) for patients with PD-L1 TPS <1%		0.70 (0.52–0.95) for patients with PD-L1 TPS <1%	
Impower 131	Atezolizumab + carboplatin + nab-paclitaxel *vs.* chemotherapy	Atezolizumab arm: 14.2 months, chemotherapy arm: 13.5 months	0.88 (0.73–1.05) for all patients,	Atezolizumab arm: 6.3 months, chemotherapy arm: 5.6 months	0.71 (0.60–0.85) for all patients,	(11)
			0.48 (0.29–0.81) for patients with PD-L1 TC3 or IC3		0.41 (0.25–0.68) for patients with PD-L1 TC3 or IC3	
			0.72 (0.52–1.00) for patients with PD-L1 TC2/3 or IC2/3		0.53 (0.39–0.72) for patients with PD-L1 TC2/3 or IC2/3	
			0.86 (0.67–1.11) for patients with PD-L1 TC1/2/3 or IC1/2/3		0.61 (0.48–0.77) for patients with PD-L1 TC1/2/3 or IC1/2/3	
			1.08 (0.81–1.45) for patients with PD-L1 TC1/2 or IC1/2		0.70 (0.54–0.91) for patients with PD-L1 TC1/2 or IC1/2	
			0.87 (0.67–1.13) for patients with PD-L1 TC0 and IC0		0.82 (0.65–1.04) for patients with PD-L1 TC0 and IC0	
CheckMate 227 (subanalysis of LUSC)	Nivolumab + ipilimumab *vs.* chemotherapy	Data not available	0.69 (0.52–0.91) for PD-L1 positive patients	Data not available	Data not available	(7-9)
			0.52 (0.34–0.82) for PD-L1 negative patients			

OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; PD-L1, programmed death-ligand 1; TPS, tumor proportion score; TC, tumor cell; IC, immune cell; LUSC, lung squamous cell carcinoma.

penpulimab in non-Asian populations.

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Footnote

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