

Clinical Benefit of First-Line Programmed Death-1 Antibody Plus Chemotherapy in Low Programmed Cell Death Ligand 1–Expressing Esophageal Squamous Cell Carcinoma: A Post Hoc Analysis of JUPITER-06 and Meta-Analysis

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abstract

PURPOSE Pembrolizumab or nivolumab plus chemotherapy was approved as a first-line treatment for high programmed cell death ligand 1 (PD-L1)–expressing esophageal squamous cell carcinoma (ESCC) by the European Medicines Agency, whereas the US Food and Drug Administration approved this regimen regardless of PD-L1 expression. The superiority of programmed death-1 (PD-1) antibody plus chemotherapy over chemotherapy alone in patients with low PD-L1–expressing ESCC remains debatable.

METHODS Post hoc analysis of the Chinese JUPITER-06 study focusing on efficacy stratified by PD-L1 tumor proportion score (TPS; using JS311 antibody) was conducted. Electronic databases were searched to identify eligible randomized controlled trials for meta-analysis. Study-level pooled analyses of hazard ratios (HRs) for overall survival and progression-free survival and odds ratios for objective response rate according to PD-L1 expression were performed.

RESULTS The post hoc analysis of JUPITER-06 showed more prominent clinical benefit with PD-1 antibody plus chemotherapy than with chemotherapy alone in both the high and low PD-L1–expressing subgroups. Five randomized controlled trials were included in the meta-analysis, and two PD-L1 expression scoring criteria, TPS ($\geq 1\%/< 1\%$) and combined positive score (CPS, $\geq 10/< 10$), were analyzed. Significant overall survival benefit by adding PD-1 antibody to chemotherapy was observed in both the TPS $< 1\%$ (HR, 0.74; 95% CI, 0.56 to 0.97) and CPS < 10 (HR, 0.77; 95% CI, 0.66 to 0.89) subgroups. Similarly, significantly prolonged progression-free survival was observed in both the TPS $< 1\%$ (HR, 0.66; 95% CI, 0.50 to 0.86) and CPS < 10 (HR, 0.63; 95% CI, 0.47 to 0.84) subgroups. In addition, the objective response rate of the TPS $< 1\%$ subgroup was significantly improved (odds ratio, 1.71; 95% CI, 1.27 to 2.29). In all high PD-L1–expressing subgroups, the pooled benefit of PD-1 antibody plus chemotherapy was significantly better than that of chemotherapy.

CONCLUSION This study provided novel evidence supporting the superiority of PD-1 antibody plus chemotherapy to chemotherapy alone in patients with advanced ESCC with low PD-L1 expression. Further studies of predictive biomarkers are warranted.

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Esophageal cancer was the seventh most frequently diagnosed cancer and the sixth leading cause of cancer-related death worldwide in 2020.¹ Esophageal squamous cell carcinoma (ESCC) and adenocarcinoma are the two most common histologic subtypes, of which 90% of esophageal cancer cases in Asia and sub-Saharan Africa are ESCC.² A large proportion of patients with ESCC are diagnosed at advanced stages because of the lack of distinguishing clinical indications and ultimately have poor prognosis, with the 5-year

survival rate ranging from 15% to 25%.³ In addition, the mainstay first-line therapy for patients with advanced or metastatic ESCC has been limited to platinum plus paclitaxel/fluorouracil chemotherapy over the past few decades despite an unsatisfactory median overall survival (OS) of < 12 months.^{4,5} Hence, there is an urgent need for novel regimens to improve treatment outcomes.

Since anti-programmed death-1 (PD-1) therapy has been shown to outperform traditional chemotherapy in the second-line treatment of advanced ESCC,⁶⁻¹⁰ new

CONTEXT

Key Objective

This study aimed to determine whether patients with advanced esophageal squamous cell carcinoma (ESCC) with low programmed cell death ligand 1 (PD-L1) expression would benefit from programmed death-1 (PD-1) antibody plus chemotherapy over chemotherapy alone in first-line settings.

Knowledge Generated

Post hoc analysis of JUPITER-06 according to tumor proportion score (TPS) subgroups showed prominent clinical benefit by adding PD-1 antibody to chemotherapy in both high and low PD-L1–expressing patients. A further meta-analysis of five phase III randomized controlled trials found significant overall survival, progression-free survival, and objective response rate improvement with PD-1 antibody plus chemotherapy over chemotherapy alone as first-line treatment for patients with advanced ESCC with low PD-L1 expression (TPS < 1% or combined positive score < 10).

Relevance (A.H. Ko)

This analysis offers further clarity regarding the benefit of using anti-PD-1 antibody therapy in combination with chemotherapy for patients with advanced ESCC whose tumors exhibit low (TPS < 1% or combined positive score < 10) and high PD-L1 expression.*

*Relevance section written by JCO Associate Editor Andrew H. Ko, MD.

clinical trials that explored more effective first-line strategies have recently established PD-1 antibody plus chemotherapy as a new standard.¹¹⁻¹⁵ For instance, in KEYNOTE-590, OS was significantly longer with pembrolizumab plus chemotherapy than chemotherapy alone in all randomly assigned patients with ESCC,¹¹ backing up the US Food and Drug Administration's approval regardless of programmed cell death ligand 1 (PD-L1) status. However, when it comes to subgroup analysis by PD-L1 combined positive score (CPS), pembrolizumab plus chemotherapy only benefits patients with ESCC with high PD-L1 expression (CPS \geq 10; median OS, 13.9 v 8.8 months; hazard ratio [HR], 0.57; 95% CI, 0.43 to 0.75) but not those with low PD-L1 expression (CPS < 10; median OS, 10.5 v 11.1 months; HR, 0.99; 95% CI, 0.74 to 1.32).¹¹ Similar observations were found in CheckMate 648 according to PD-L1 tumor proportion score (TPS) subgroups.¹² Comparatively, the European Medicines Agency only approved pembrolizumab plus chemotherapy in patients with advanced ESCC with PD-L1 CPS \geq 10, and nivolumab plus chemotherapy in patients with PD-L1 TPS \geq 1%. However, other studies, such as JUPITER-06, investigated the additional benefit of PD-1 antibody to chemotherapy in patients with advanced ESCC with different PD-L1 expression and reported contrasting results.¹³⁻¹⁵ Therefore, a much-debated question is whether patients with ESCC with low PD-L1 expression will truly benefit from PD-1 antibody plus chemotherapy. It is also still unclear whether PD-L1 expression could be used as an indicator to identify patients with advanced ESCC who would benefit more from anti-PD-1-chemotherapy combination or whether further biomarkers are needed.

To address these questions, we conducted a post hoc analysis of JUPITER-06 to determine the efficacy of

anti-PD-1-chemotherapy combination in subgroups stratified by PD-L1 TPS status. Furthermore, we also performed a meta-analysis on the basis of recent randomized controlled trials (RCTs) to comprehensively assess the clinical benefit of PD-1 antibody plus chemotherapy versus chemotherapy alone as the first-line treatment in advanced ESCC, especially in patients with low PD-L1 expression. Altogether, on the basis of the predominant clinical benefit for these patients from our post hoc analysis and meta-analysis, our findings provide additional evidence supporting the use of PD-1 antibody plus chemotherapy in patients with advanced ESCC with low PD-L1 expression (TPS < 1% or CPS < 10).

METHODS

The JUPITER-06 Study and Post Hoc Analysis

JUPITER-06 was a recently published multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating the efficacy and safety of toripalimab, a PD-1 antibody, plus paclitaxel and cisplatin versus placebo plus paclitaxel and cisplatin as the first-line treatment for patients with advanced ESCC in China.¹³ The final progression-free survival (PFS) and interim OS analyses showed that the efficacy boundary for both PFS and OS was crossed, and the superiority of adding toripalimab to chemotherapy was observed across the prespecified PD-L1 subgroups (CPS \geq 1/< 1, CPS \geq 10/< 10).¹³ As the both PD-L1 scoring criteria, that is, CPS and TPS, were commonly reported in studies on ESCC,¹¹⁻¹⁵ we further performed a post hoc analysis according to TPS subgroups on the basis of the same patient-level data as of March 22, 2021.¹³ The end points of the present study included OS, PFS, objective response rate (ORR), and duration of response (DoR)

assessed by blinded independent central review per RECIST v1.1 in the intention-to-treat population.

In JUPITER-06, PD-L1 expression in tumor samples was stained and interpreted centrally in a blinded manner using an immunohistochemistry (IHC) kit with JS311 antibody, which showed satisfactory concordance with the widely used 22C3, 28-8, and SP263 antibodies.^{13,16,17} PD-L1 TPS was defined as the percentage of viable tumor cells with partial or complete membrane staining of PD-L1 in at least 100 viable tumor cells.

Literature Search, Data Extraction, and Meta-Analysis

To fully assess the clinical benefit of adding PD-1 antibody to chemotherapy as first-line treatment in patients with advanced ESCC with low PD-L1 expression, we performed an extensive literature search on PubMed, Embase, and Cochrane databases for RCTs published from January 1, 2010, to April 30, 2022, and data analysis began in May 2022. For details of the search strategy and inclusion criteria, see the Data Supplement (online only). Two authors (H.-X.W. and Y.-Q.P.) independently screened the trials for eligibility and extracted information from each trial. The included RCTs were additionally assessed for risk of bias using the Cochrane Risk of bias 2 tool, which yielded low risk for all studies included (Data Supplement).

Considering the distinct approval of US Food and Drug Administration and European Medicines Agency, two PD-L1 scoring criteria and their most commonly used cutoffs, TPS = 1% and CPS = 10, were investigated in the meta-analysis. Notably, in these trials, patients could be divided into two almost equal (both approximately 50%) subgroups with these two cutoffs to classify them as high and low PD-L1–expressing populations,¹¹⁻¹⁵ further supporting their value in stratifying patients on the basis of their PD-L1 expression levels.

Statistical Analysis

Post hoc analysis of treatment efficacy by PD-L1 TPS subgroups was performed among the intention-to-treat population of JUPITER-06 using SAS (version 9.3, SAS Institute). The unstratified Cox proportional hazards model was used to estimate the HR and 95% CI. The Kaplan-Meier method was used for median survival estimation. ORR differences were analyzed using the unstratified Cochran-Mantel-Haenszel test.

Unstratified (unless otherwise specified) HRs and odds ratios (ORs) with 95% CIs comparing PD-1 antibody plus chemotherapy with chemotherapy alone according to PD-L1 expression levels in the eligible studies were retrieved and synthesized to generate the overall treatment effects. Potential heterogeneity among studies was assessed using Cochrane's *Q* statistic and *I*² statistic. The random-effects models were used to calculate pooled HRs or ORs in the presence of significant heterogeneity ($P < .1000$ or $I^2 > 50\%$); otherwise, the fixed-effects models were applied. Meta-analysis was

performed using R 4.1.2 (The R Foundation). All *P* values were 2-sided, and $P < .05$ was considered statistically significant in the evaluation of pooled effects.

RESULTS

Post Hoc Analysis of JUPITER-06 According to PD-L1 TPS Subgroups

Results according to PD-L1 CPS of JUPITER-06 were previously reported, but there are few data from phase III trials investigating the concordance between TPS and CPS. Thus, to verify their comparability in classifying patients into low and high PD-L1 expression, we performed a concordance analysis and found that PD-L1 TPS showed a strong correlation with CPS (Spearman's ρ , 0.86 [95% CI, 0.83 to 0.89], $P < .0001$). In addition, when studied as binary variables, TPS also showed good concordance with CPS in some cases, such as TPS = 1% \times CPS = 5 (83.6%), TPS = 1% \times CPS = 10 (76.6%), and TPS = 5% \times CPS = 10 (89.0%) as shown in the Data Supplement.

PFS was significantly longer in the toripalimab arm than in the placebo arm in both PD-L1 subgroups (TPS \geq 1%/ $<$ 1%), with a median PFS of 5.7 months (95% CI, 5.6 to 7.0) versus 5.5 months (95% CI, 4.4 to 5.6) and an unstratified HR of 0.59 (95% CI, 0.44 to 0.79; $P = .0005$) in the TPS \geq 1% subgroup (Fig 1A) and a median PFS of 6.1 months (95% CI, 5.7 to 9.7) versus 5.7 months (95% CI, 5.4 to 5.8) and an unstratified HR of 0.59 (95% CI, 0.40 to 0.88; $P = .0089$) in the TPS $<$ 1% subgroup (Fig 1B). The 1-year PFS rates of the toripalimab arm versus the placebo arm were 26.5% versus 4.1% and 28% versus 7.6% in the TPS \geq 1% and TPS $<$ 1% subgroups, respectively.

Similarly, significant OS improvement by adding toripalimab was observed in both PD-L1 subgroups. In the TPS \geq 1% subgroup (Fig 1C), the median OS was 16.9 months (95% CI, 13.2 to not estimated) in the toripalimab arm versus 10.8 months (95% CI, 9.3 to 12.6) in the placebo arm, with an unstratified HR of 0.61 (95% CI, 0.42 to 0.90; $P = .0133$). In the TPS $<$ 1% subgroup (Fig 1D), the median OS of the placebo arm was 11.6 months (95% CI, 10.2 to 16.3), whereas that of the toripalimab arm had not been reached (95% CI, 12.6 to not estimated) at the time of data cutoff, with an unstratified HR of 0.63 (95% CI, 0.37 to 1.08; $P = .0913$). The 1-year OS rates of the toripalimab arm versus the placebo arm were 62.9% versus 42.1% and 67.4% versus 47.2% in the TPS \geq 1% and TPS $<$ 1% subgroups, respectively.

As for antitumor response, the toripalimab arm also outperformed the placebo arm in both PD-L1 subgroups, with the ORR of 65.6% (95% CI, 57.5 to 73.0) versus 52.5% (95% CI, 43.9 to 60.9) and 74.4% (95% CI, 64.2 to 83.1) versus 54.4% (95% CI, 44.3 to 64.2) in the TPS \geq 1% and TPS $<$ 1% subgroups, respectively (Table 1). Similarly, longer DoR of toripalimab plus chemotherapy over placebo

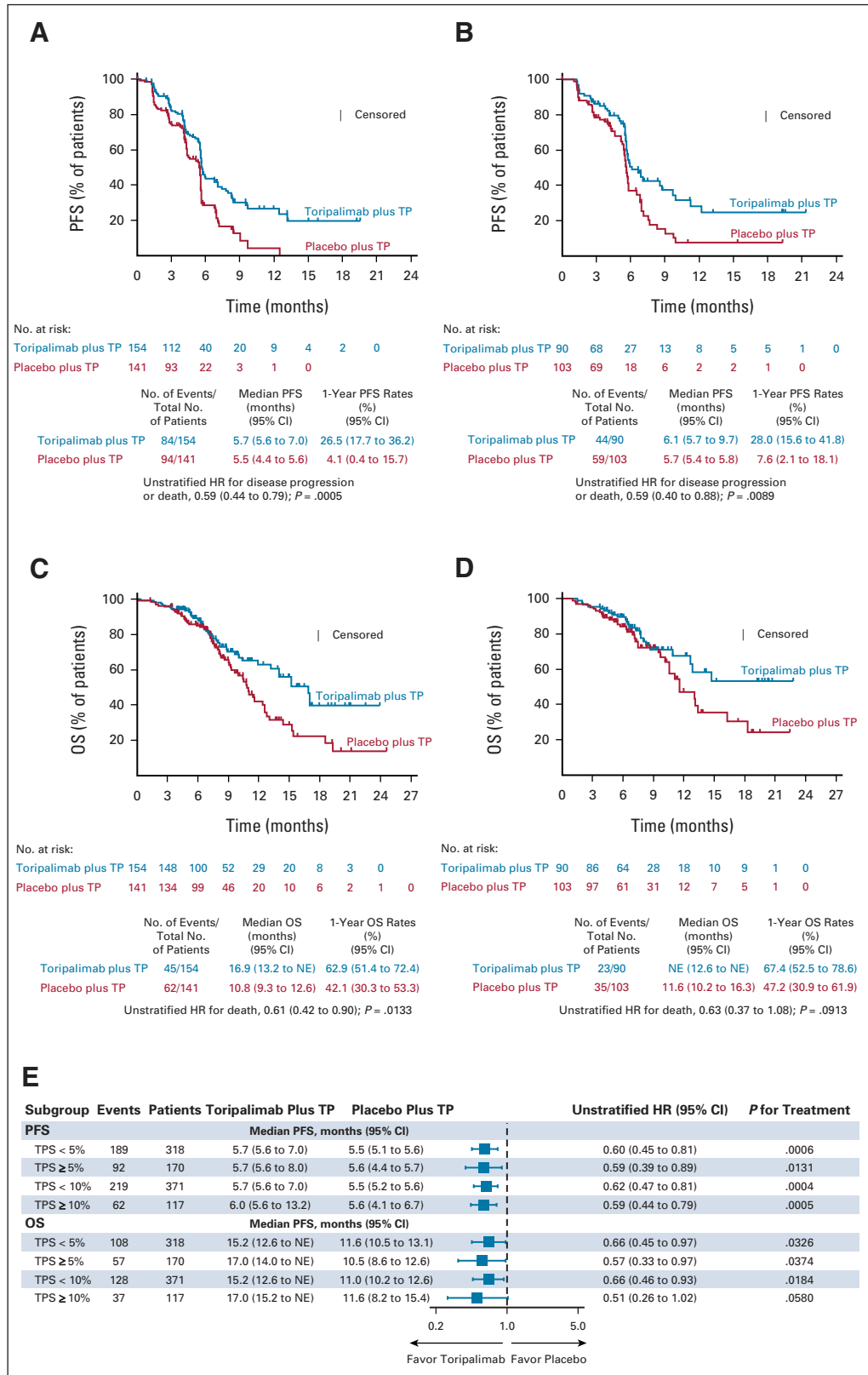


FIG 1. The post hoc analysis of the JUPITER-06 study according to PD-L1 TPS subgroups. Kaplan-Meier estimates of PFS in the (A) PD-L1 TPS ≥ 1% subgroup and (B) PD-L1 TPS < 1% subgroup (blinded independent central review-assessed PFS per RECIST v1.1 [ITT population]) and OS in (C) the PD-L1 TPS ≥ 1% subgroup and (D) the PD-L1 TPS < 1% subgroup (ITT population). (E) Forest plot summarizing results of (continued on following page)

FIG 1. (Continued). survival outcomes with toripalimab versus placebo in combination with chemotherapy in patients with high versus low PD-L1 expression according to TPS ($\geq 5\%$ v $< 5\%$, $\geq 10\%$ v $< 10\%$). HR, hazard ratio; NE, not estimated; OS, overall survival; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; TP, paclitaxel plus cisplatin; TPS, tumor proportion score.

plus chemotherapy was observed in both TPS $\geq 1\%$ and TPS $< 1\%$ subgroups (Data Supplement).

When using 5% or 10% as the TPS cutoff value of PD-L1 expression, significant improvements in PFS, OS, ORR, and DoR by adding toripalimab to chemotherapy were also observed in both the high and low PD-L1-expressing populations (Fig 1E, Table 1, and Data Supplement).

The above post hoc analysis of JUPITER-06 provided novel evidence supporting the superiority of toripalimab plus chemotherapy to chemotherapy alone in patients with advanced ESCC regardless of PD-L1 status. To further verify the benefit of adding PD-1 antibody to chemotherapy in the first-line treatment of advanced ESCC, we conducted the following meta-analysis.

Study Selection and Characteristics of the Eligible Trials

A total of 719 records were retrieved by database search. Five eligible phase III RCTs were finally included in the meta-analysis as shown in Figure 2, including KEYNOTE-590, CheckMate 648, ESCORT-1st, JUPITER-06, and ORIENT-15. The characteristics of these five studies are summarized in Table 2. Notably, in KEYNOTE-590, only the ESCC population was included. In addition, the nivolumab plus ipilimumab arm of CheckMate 648 was not included as it did not match the aim of this study. Almost all the included patients in these studies had available PD-L1 status (spanning 95%-100%); thus, a total of 2,908 patients were included in the meta-analysis. In regard to PD-L1 scoring criteria, KEYNOTE-590 only reported results according to CPS and ESCORT-1st only reported results according to TPS, whereas results according to CPS and TPS were available in the remaining three trials (PD-L1 TPS information of JUPITER-06 was reported in the aforementioned post hoc analysis). Among these trials, all primary end points were met except for PFS superiority in the overall population of CheckMate 648.

Meta-Analysis According to PD-L1 TPS ($< 1\%$ / $\geq 1\%$)

The random-effects model was applied to calculate the pooled effects on survival as significant heterogeneity was observed among the four included studies ($P_{\text{heterogeneity}} = .0413$, $I^2 = 62\%$ for OS; $P_{\text{heterogeneity}} = .0145$, $I^2 = 69\%$ for PFS). Pooled analysis showed that adding PD-1 antibody to chemotherapy significantly improved the OS and PFS of patients with low PD-L1 expression (TPS $< 1\%$), with HRs of 0.74 (95% CI, 0.56 to 0.97; $P = .0312$) and 0.66 (95% CI, 0.50 to 0.86; $P = .0027$), respectively (Figs 3A and 3B). As for ORR, three trials were included in the pooled analysis as details of antitumor response according to TPS subgroups were

unavailable in ORIENT-15. A fixed-effects model was adopted ($P_{\text{heterogeneity}} = .3598$, $I^2 = 2\%$), and the results showed that the addition of PD-1 antibody significantly improved ORR in patients with low PD-L1 expression (TPS $< 1\%$) with an OR of 1.71 (95% CI, 1.27 to 2.29; $P = .0004$; Fig 3C). Pooled HRs of PFS and OS and pooled OR of ORR in the TPS $\geq 1\%$ subgroup were also evaluated, which unsurprisingly showed significant benefit by adding PD-1 antibody to chemotherapy (Data Supplement).

Meta-Analysis According to PD-L1 CPS (< 10 / ≥ 10)

The fixed-effects model was used to evaluate the pooled effects of OS ($P_{\text{heterogeneity}} = .1188$, $I^2 = 49\%$). We obtained a pooled HR of 0.77 (95% CI, 0.66 to 0.89; $P = .0007$), indicating that patients with low PD-L1 expression (CPS < 10) receiving PD-1 antibody plus chemotherapy still had significantly longer OS compared with those treated with chemotherapy alone (Fig 4A). As CheckMate 648 did not report PFS results according to PD-L1 CPS subgroups, the other three trials were included to generate a pooled HR of PFS using the random-effects model ($P_{\text{heterogeneity}} = .0533$, $I^2 = 65\%$) and significant improvement in PFS was also observed in patients with low PD-L1 expression (CPS < 10) receiving anti-PD-1-based therapy (Fig 4B; pooled HR, 0.63; 95% CI, 0.47 to 0.84; $P = .0016$). In terms of ORR, only ORIENT-15 reported CPS-stratified antitumor response (64% v 41% in patients with CPS < 10). In addition, pooled analysis of patients with high PD-L1 expression (CPS ≥ 10) also revealed significant clinical benefit by adding PD-1 antibody to chemotherapy (Data Supplement).

DISCUSSION

PD-1 antibody combined with chemotherapy is a promising treatment option for various solid tumors,¹⁸ and PD-L1 expression was examined as a predictive marker for response and efficacy.^{19,20} However, current evidence on the predictive value of PD-L1 expression in patients with treatment-naïve advanced ESCC is riddled with conflicts and ambiguity. Our previous study, JUPITER-06, demonstrated that regardless of the PD-L1 CPS level, PD-1 antibody plus chemotherapy was associated with significant PFS and OS benefit over placebo plus chemotherapy. In this post hoc analysis of JUPITER-06, we found that PD-1 antibody plus chemotherapy was superior to chemotherapy in terms of OS, PFS, ORR, and DoR in both high (TPS $\geq 1\%/5\%/10\%$) and low (TPS $< 1\%/5\%/10\%$) PD-L1-expressing subgroups, endorsing the application of this regimen in all populations, irrespective of PD-L1 TPS or CPS status. This additionally implied that PD-L1 expression

TABLE 1. Tumor Response With Toripalimab Versus Placebo in Combination With Chemotherapy in Advanced or Metastatic Esophageal Squamous Cell Carcinoma by BICR per RECIST v.1.1 in Patients With High Versus Low PD-L1 Expression According to TPS

PD-L1 Expression Response	TPS ≥ 1%		TPS < 1%	
	Toripalimab Plus TP (n = 154)	Placebo Plus TP (n = 141)	Toripalimab Plus TP (n = 90)	Placebo Plus TP (n = 103)
Best overall response, No. (%)				
CR	19 (12.3)	12 (8.5)	9 (10.0)	5 (4.9)
PR	82 (53.2)	62 (44.0)	58 (64.4)	51 (49.5)
SD	36 (23.4)	41 (29.1)	14 (15.6)	32 (31.1)
PD	11 (7.1)	22 (15.6)	7 (7.8)	10 (9.7)
Non-CR/non-PD ^a	1 (0.6)	1 (0.7)	0	1 (1.0)
NE	5 (3.2)	3 (2.1)	2 (2.2)	4 (3.9)
ORR				
ORR, % (95% CI)	65.6 (57.5 to 73.0)	52.5 (43.9 to 60.9)	74.4 (64.2 to 83.1)	54.4 (44.3 to 64.2)
Difference in ORR, % (95% CI)	13.1 (1.9 to 23.9)		20.1 (6.5 to 32.5)	
<i>P</i>	.0221		.0038	

PD-L1 Expression Response	TPS ≥ 5%		TPS < 5%	
	Toripalimab Plus TP (n = 90)	Placebo Plus TP (n = 80)	Toripalimab Plus TP (n = 154)	Placebo Plus TP (n = 164)
Best overall response, No. (%)				
CR	14 (15.6)	7 (8.8)	14 (9.1)	10 (6.1)
PR	50 (55.6)	41 (51.3)	90 (58.4)	72 (43.9)
SD	17 (18.9)	20 (25.0)	33 (21.4)	53 (32.3)
PD	7 (7.8)	9 (11.3)	11 (7.1)	23 (14.0)
Non-CR/non-PD ^a	0	1 (1.3)	1 (0.6)	1 (0.6)
NE	2 (2.2)	2 (2.5)	5 (3.2)	5 (3.0)
ORR				
ORR, % (95% CI)	71.1 (60.6 to 80.2)	60.0 (48.4 to 70.8)	67.5 (59.5 to 74.8)	50.0 (42.1 to 57.9)
Difference in ORR, % (95% CI)	11.1 (−3.1 to 24.9)		17.5 (6.7 to 27.8)	
<i>P</i>	.1272		.0015	

PD-L1 Expression Response	TPS ≥ 10%		TPS < 10%	
	Toripalimab Plus TP (n = 59)	Placebo Plus TP (n = 58)	Toripalimab Plus TP (n = 185)	Placebo Plus TP (n = 186)
Best overall response, No. (%)				
CR	11 (18.6)	6 (10.3)	17 (9.2)	11 (5.9)
PR	34 (57.6)	27 (46.6)	106 (57.3)	86 (46.2)
SD	9 (15.3)	15 (25.9)	41 (22.2)	58 (31.2)
PD	3 (5.1)	8 (13.8)	15 (8.1)	24 (12.9)
Non-CR/non-PD ^a	0	1 (1.7)	1 (0.5)	1 (0.5)
NE	2 (3.4)	1 (1.7)	5 (2.7)	6 (3.2)
ORR				
ORR, % (95% CI)	76.3 (63.4 to 86.4)	56.9 (43.2 to 69.8)	66.5 (59.2 to 73.2)	52.2 (44.7 to 59.5)
Difference in ORR, % (95% CI)	19.4 (2.3 to 35.0)		14.3 (4.3 to 23.9)	
<i>P</i>	.0262		.0049	

Abbreviations: BICR, blinded independent central review; CR, complete response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PD-L1, programmed cell death ligand 1; PR, partial response; SD, stable disease; TP, paclitaxel plus cisplatin; TPS, tumor proportion score.

^aNon-CR/non-PD: Persistence of one to more nontarget lesions or stable, decreasing, or mild increase in uptake of bone lesions on bone scintigraphy.

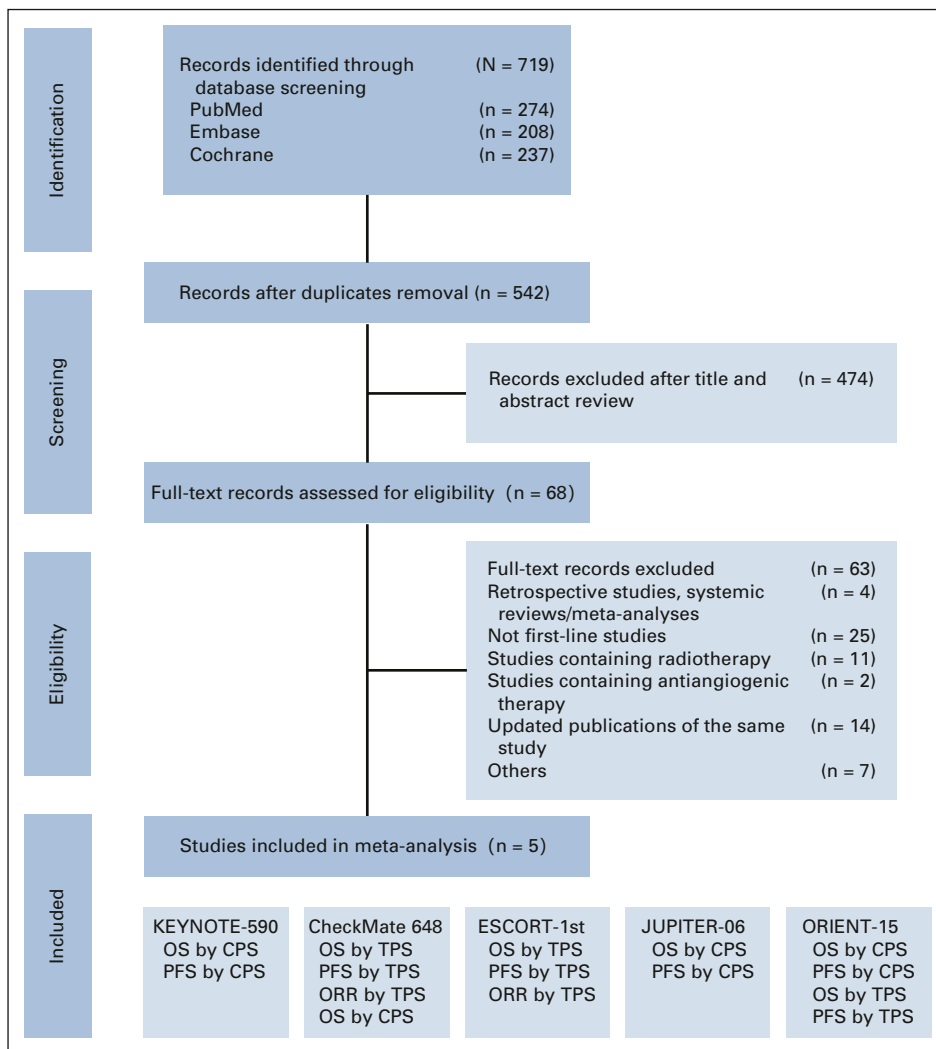


FIG 2. PRISMA flowchart of study inclusions and exclusions. CPS, combined positive score; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TPS, tumor proportion score.

was not an effective biomarker for patient selection under this certain condition.

Although JUPITER-06 and its post hoc analysis have shown the superiority of PD-1 antibody plus chemotherapy over chemotherapy alone in patients with low PD-L1-expressing ESCC, this issue remains controversial considering other similar trials.^{11,12,14,15} Therefore, a subsequent meta-analysis on the basis of these five RCTs was performed, and the results showed significantly better OS, PFS, and ORR by introducing PD-1 antibody to chemotherapy in both TPS < 1% and CPS < 10 populations. These pooled results further supported the superiority of PD-1 antibody combined with chemotherapy over chemotherapy alone regardless of PD-L1 status and provided novel evidence for using PD-1 plus chemotherapy in patients with treatment-naïve advanced ESCC with low PD-L1 expression (TPS < 1% or CPS < 10).

Higher levels of PD-L1 expression are apparently correlated with better outcomes in patients treated with anti-PD-1

monotherapy^{21,22} or investigated within a combinational therapy arm, but the predictive function of PD-L1 expression seems ambiguous in the setting of PD-1 antibody plus chemotherapy versus chemotherapy in patients with advanced ESCC considering existing evidence. According to the pooled meta-analysis, the clinical benefit of PD-1 inhibitor plus chemotherapy over chemotherapy alone was not only observed in patients with advanced ESCC with high PD-L1 expression (TPS ≥ 1% or CPS ≥ 10) but also in those with low PD-L1 expression (TPS < 1% or CPS < 10), a population for which single-agent PD-1 blockade seemed to have a small chance of benefit.^{7,21,22} Similarly, data from several other large cohort studies in patients with advanced-stage non-small-cell lung cancer showed that higher levels of PD-L1 expression were associated with better efficacy in patients treated with anti-PD-1 monotherapy,²³ whereas first-line PD-1 antibody combined with chemotherapy was superior to chemotherapy across all PD-L1 categories.^{24,25} Other widely accepted biomarkers

TABLE 2. Summary of the Trials Included in the Meta-Analysis

Trial, Year of Publication	Arm	Patients, No.	Patients With PD-L1 Status, No. (%) ^a	Treatment	PD-L1 Assay	PD-L1 Scoring Criteria Reported	Statistical Testing of Primary End Points ^b
KEYNOTE-590, ^c 2021	Test arm	274	264 (96)	Pembrolizumab plus PF, once every 3 weeks	IHC 22C3	CPS	(+) OS superiority in ESCC with CPS \geq 10 (+) OS superiority in ESCC (+) PFS superiority in ESCC
	Control arm	274	269 (98)	Placebo plus PF, once every 3 weeks			
CheckMate 648, ^d 2022	Test arm	321	321 (100)	Nivolumab once every 2 weeks plus PF once every 4 weeks	IHC 28-8	TPS and CPS	(+) OS superiority in ESCC with TPS \geq 1% (+) PFS superiority in ESCC with TPS \geq 1% (+) OS superiority in ESCC (-) PFS superiority in ESCC
	Control arm	324	322 (99)	PF, once every 4 weeks			
ESCORT-1st, 2021	Test arm	298	292 (98)	Camrelizumab plus TP, once every 3 weeks	IHC 6E8	TPS	(+) OS superiority in ESCC (+) PFS superiority in ESCC
	Control arm	298	293 (98)	Placebo plus TP, once every 3 weeks			
JUPITER-06, 2022	Test arm	257	244 (95)	Toripalimab plus TP, once every 3 weeks	IHC JS311	CPS and TPS ^e	(+) PFS superiority in ESCC (+) OS superiority in ESCC
	Control arm	257	244 (95)	Placebo plus TP, once every 3 weeks			
ORIENT-15, 2022	Test arm	327	327 (100)	Sintilimab plus TP/PF, once every 3 weeks	IHC 22C3	TPS and CPS	(+) OS superiority in ESCC with CPS \geq 10 (+) OS superiority in ESCC
	Control arm	332	332 (100)	Placebo plus TP/PF, once every 3 weeks			

Abbreviations: CPS, combined positive score; ESCC, esophageal squamous cell carcinoma; IHC, immunohistochemistry; OS, overall survival; PD-L1, programmed cell death ligand 1; PF, fluorouracil plus cisplatin; PFS, progression-free survival; TP, paclitaxel plus cisplatin; TPS, tumor proportion score.

^aPercentage of patients with available PD-L1 status.

^b(+) indicates that the test met the prespecified boundary for significance, whereas (-) indicates the opposite.

^cOnly patients with ESCC were included.

^dThe nivolumab plus ipilimumab group was not included.

^ePost hoc analysis of JUPITER-06 on PD-L1 TPS subgroups is reported in the present study.

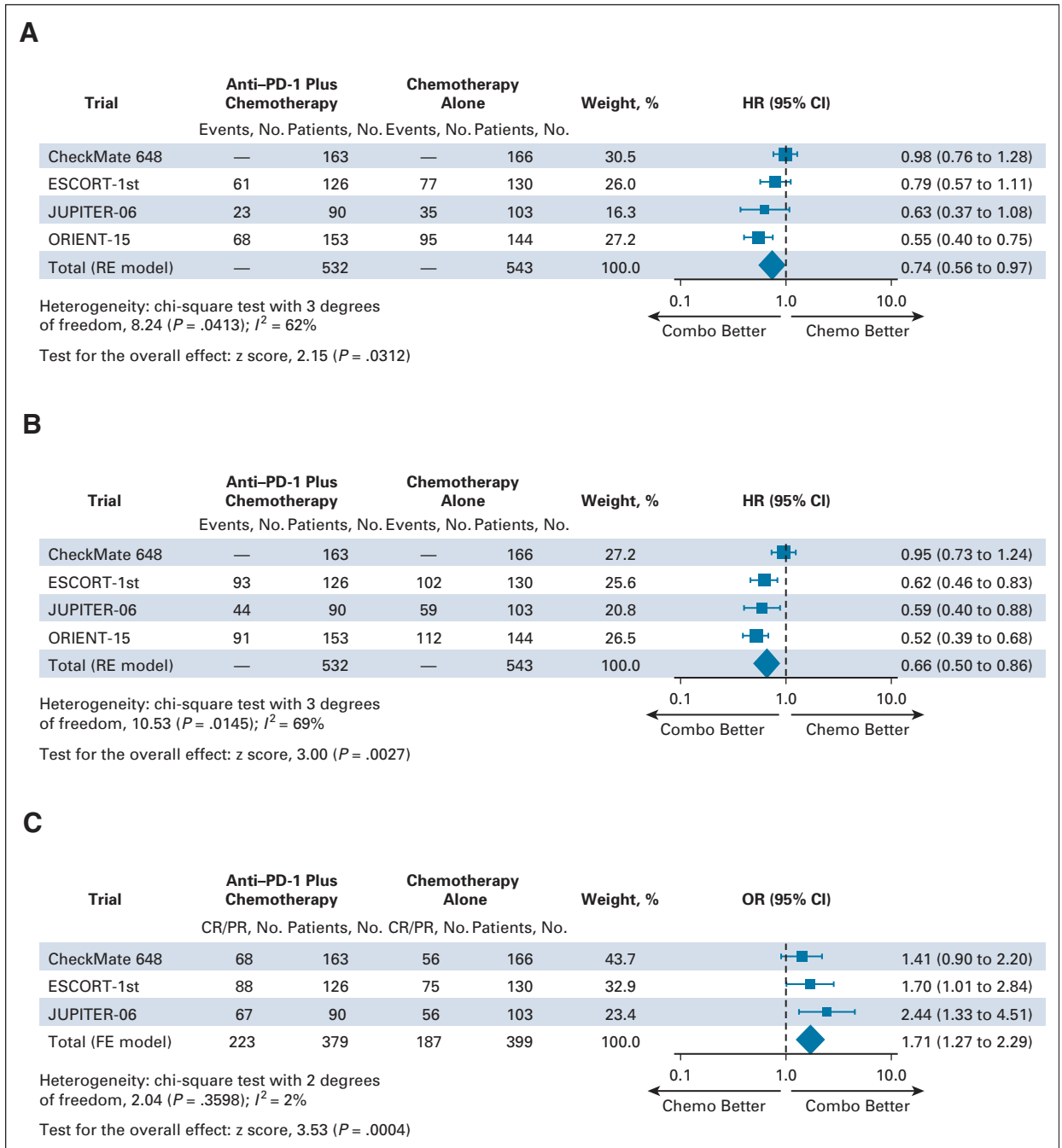


FIG 3. Meta-analysis of clinical benefit with PD-1 antibody plus chemotherapy versus chemotherapy alone in the PD-L1 TPS < 1% subgroup. The forest plots show HRs for (A) OS, (B) PFS, and (C) OR for objective response with PD-1 antibody plus chemotherapy as compared with chemotherapy alone in the PD-L1 TPS < 1% subgroup. Percentages may not total 100 because of rounding. Chemo, chemotherapy; Combo, combinational treatment of PD-1 antibody and chemotherapy; CR, complete response; FE, fixed-effects; HR, hazard ratio; OR, odds ratio; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PR, partial response; RE, random-effects; TPS, tumor proportion score.

predicting the efficacy of anti-PD-1 monotherapy, such as tumor mutational burden,²⁶ also became less valuable in identifying a beneficial population when it comes to the combinational setting.²⁷ This phenomenon indicates that peculiar predictive biomarker(s) may exist in the setting of combinational therapy, and further biomarker studies are

warranted to identify patients with treatment-naïve advanced ESCC who could benefit most from PD-1 antibody plus chemotherapy. We anticipate further efforts to develop novel approaches to uncover more convincing biomarker-response relationships. Also, after JUPITER-06, we are performing whole-exome sequencing on tumor tissue

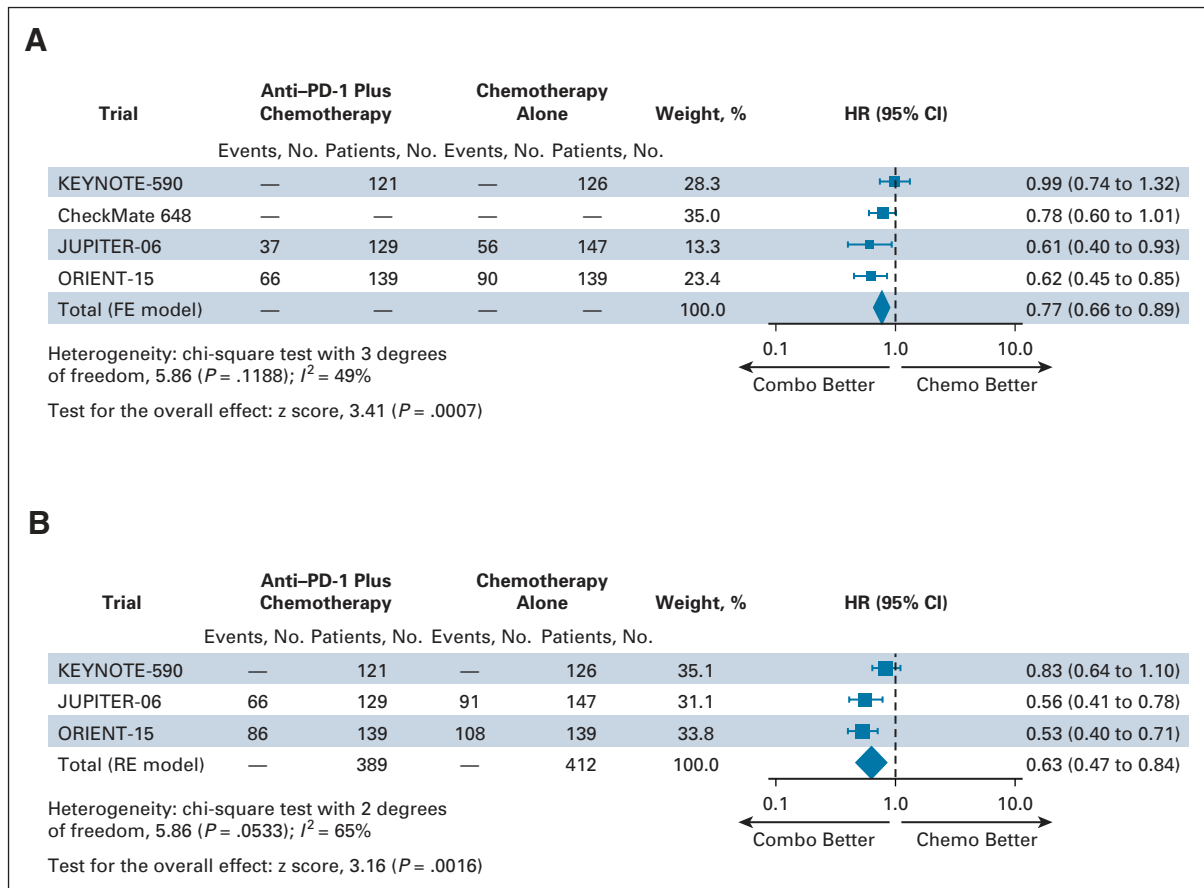


FIG 4. Meta-analysis of clinical benefit with PD-1 antibody plus chemotherapy versus chemotherapy alone in the PD-L1 CPS < 10 subgroup. The forest plots show HRs for (A) OS and (B) PFS with PD-1 antibody plus chemotherapy as compared with chemotherapy alone in the PD-L1 CPS < 10 subgroup. Percentages may not total 100 because of rounding. Chemo, chemotherapy; Combo, combinational treatment of PD-1 antibody and chemotherapy; CPS, combined positive score; HR, hazard ratio; FE, fixed-effects; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; RE, random-effects.

samples ($n = 486$) obtained from patients with ESCC to identify biomarker(s) for more potentially precise guidance on the application of PD-1 antibody plus chemotherapy.

Some heterogeneity among the five RCTs inevitably limits the generalizability and the comparability of the results, which should be noted in the cross-trial interpretation of immunotherapy-chemotherapy combination in ESCC. The first one is geographical disparity, and ESCORT-1st,¹⁴ JUPITER-06,¹³ and ORIENT-15 (approximately 97%)¹⁵ recruited almost only Asian patients, whereas more than 30% of patients in CheckMate 648¹² and KEYNOTE-590¹¹ were from regions other than Asia. Researchers have shown that Asian patients with ESCC have typical genetic and clinical characteristics different from White patients and may have greater immunotherapy response rates,²⁸ which could be one of the reasons that the two global trials did not show substantial benefit in the low PD-L1-expressing population, whereas the three Asian-only trials did. Notably, the most recently released data of RATIONALE-306 also showed prolonged OS of tislelizumab plus chemotherapy over chemotherapy in patients

with low PD-L1-expressing ESCC in a global manner,²⁹ which was in line with the results of our meta-analysis. Second, different chemotherapy backbones, fluorouracil/paclitaxel plus cisplatin, were distinctively adopted in these trials, but actually, the survival outcomes with these two chemotherapies were comparable among studies, which was also confirmed directly in RATIONALE-306 that incorporated both regimens.²⁹ Finally, different PD-L1 antibodies and scoring systems were used in various trials as shown in Table 2, which may also contribute to the heterogeneity among studies and pose a challenge to the pooled meta-analysis. This could be partially alleviated by the efforts to prove the comparability between different PD-L1 IHC assays. For instance, the analytic performance of the Dako 22C3 and 28-8 assays was proved to be highly comparable with no significant difference in the efficacy of dividing populations using a TPS cutoff of 1%,^{30,31} whereas for the JS311 antibody used in JUPITER-06, it was cross-compared with 22C3 and 28-8 for PD-L1 IHC staining in multiple tumor tissues, including tissues from melanoma, urothelial cancer, ESCC, and non-small-cell lung cancer, and demonstrated an overall concordance of approximately 80%-90% although

binding to an epitope on the cytoplasmic rather than the extracellular domain.^{13,16,17} Thus, we believed that it might be reasonable and acceptable to use the same cutoff value in this meta-analysis despite the different antibodies and scoring methods. As the pooled results from our meta-analysis showed, PD-1 antibody plus chemotherapy tended to be superior to chemotherapy alone in both TPS < 1% and CPS < 10 populations, which ought to be recommended for clinical application in consideration of its robust long-term survival benefit, which may not be fully demonstrated by the interim results of these RCTs.

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EQUAL CONTRIBUTION

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REFERENCES

- Sung H, Ferlay J, Siegel RL, et al: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 71:209-249, 2021
- Rustgi AK, El-Serag HB: Esophageal carcinoma. *N Engl J Med* 371:2499-2509, 2014
- Pennathur A, Gibson MK, Jobe BA, et al: Esophageal carcinoma. *Lancet* 381:400-412, 2013
- Ajani JA, D'Amico TA, Bentrem DJ, et al: Esophageal and esophagogastric junction cancers, version 2.2019, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 17:855-883, 2019
- Lagergren J, Smyth E, Cunningham D, et al: Oesophageal cancer. *Lancet* 390:2383-2396, 2017
- Kato K, Cho BC, Takahashi M, et al: Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): A multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 20:1506-1517, 2019
- Kojima T, Shah MA, Muro K, et al: Randomized phase III KEYNOTE-181 study of pembrolizumab versus chemotherapy in advanced esophageal cancer. *J Clin Oncol* 38:4138-4148, 2020
- Huang J, Xu J, Chen Y, et al: Camrelizumab versus investigator's choice of chemotherapy as second-line therapy for advanced or metastatic oesophageal squamous cell carcinoma (ESCORT): A multicentre, randomised, open-label, phase 3 study. *Lancet Oncol* 21:832-842, 2020

In conclusion, our study provides further evidence supporting the superiority of adding PD-1 antibody to chemotherapy as a first-line treatment for patients with advanced ESCC with low PD-L1 expression. On the basis of the post hoc analysis of JUPITER-06 and a meta-analysis, we presented novel evidence in response to this highly disputed issue. Furthermore, our findings also indicate the necessity of multiomics research to uncover more effective biomarkers that could be used to identify patients with ESCC who might benefit from immunotherapy-chemotherapy combination.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

All requests for data from JUPITER-06 will be reviewed by the Sun Yat-sen University Cancer Center and the sponsor, Shanghai Junshi Biosciences. Requests for patient-level data can be submitted at wangfeng@sysucc.org.cn with a detailed proposal for approval.

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9. Xu J, Li Y, Fan Q, et al: Clinical and biomarker analyses of sintilimab versus chemotherapy as second-line therapy for advanced or metastatic esophageal squamous cell carcinoma: A randomized, open-label phase 2 study (ORIENT-2). *Nat Commun* 13:857, 2022
10. Shen L, Kato K, Kim SB, et al: Tislelizumab versus chemotherapy as second-line treatment for advanced or metastatic esophageal squamous cell carcinoma (RATIONALE-302): A randomized phase III study. *J Clin Oncol* 40:3065-3076, 2022
11. Sun JM, Shen L, Shah MA, et al: Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): A randomised, placebo-controlled, phase 3 study. *Lancet* 398:759-771, 2021
12. Doki Y, Ajani JA, Kato K, et al: Nivolumab combination therapy in advanced esophageal squamous-cell carcinoma. *N Engl J Med* 386:449-462, 2022
13. Wang ZX, Cui C, Yao J, et al: Toripalimab plus chemotherapy in treatment-naïve, advanced esophageal squamous cell carcinoma (JUPITER-06): A multi-center phase 3 trial. *Cancer Cell* 40:277-288.e3, 2022
14. Luo H, Lu J, Bai Y, et al: Effect of camrelizumab vs placebo added to chemotherapy on survival and progression-free survival in patients with advanced or metastatic esophageal squamous cell carcinoma: The ESCORT-1st randomized clinical trial. *JAMA* 326:916-925, 2021
15. Lu Z, Wang J, Shu Y, et al: Sintilimab versus placebo in combination with chemotherapy as first line treatment for locally advanced or metastatic oesophageal squamous cell carcinoma (ORIENT-15): Multicentre, randomised, double blind, phase 3 trial. *BMJ* 377:e068714, 2022
16. Sheng X, Chen H, Hu B, et al: Safety, efficacy, and biomarker analysis of toripalimab in patients with previously treated advanced urothelial carcinoma: Results from a multicenter phase II trial POLARIS-03. *Clin Cancer Res* 28:489-497, 2022
17. Wang Z, Ying J, Xu J, et al: Safety, antitumor activity, and pharmacokinetics of toripalimab, a programmed cell death 1 inhibitor, in patients with advanced non-small cell lung cancer: A phase 1 trial. *JAMA Netw Open* 3:e2013770, 2020
18. Meric-Bernstam F, Larkin J, Tabernero J, et al: Enhancing anti-tumour efficacy with immunotherapy combinations. *Lancet* 397:1010-1022, 2021
19. Doroshow DB, Bhalla S, Beasley MB, et al: PD-L1 as a biomarker of response to immune-checkpoint inhibitors. *Nat Rev Clin Oncol* 18:345-362, 2021
20. Wang F, Wei XL, Wang FH, et al: Safety, efficacy and tumor mutational burden as a biomarker of overall survival benefit in chemo-refractory gastric cancer treated with toripalimab, a PD-1 antibody in phase Ib/II clinical trial NCT02915432. *Ann Oncol* 30:1479-1486, 2019
21. Huang J, Xu B, Mo H, et al: Safety, activity, and biomarkers of SHR-1210, an anti-PD-1 antibody, for patients with advanced esophageal carcinoma. *Clin Cancer Res* 24:1296-1304, 2018
22. Shah MA, Kojima T, Hochhauser D, et al: Efficacy and safety of pembrolizumab for heavily pretreated patients with advanced, metastatic adenocarcinoma or squamous cell carcinoma of the esophagus: The phase 2 KEYNOTE-180 study. *JAMA Oncol* 5:546-550, 2019
23. Garon EB, Rizvi NA, Hui R, et al: Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med* 372:2018-2028, 2015
24. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al: Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med* 378:2078-2092, 2018
25. Paz-Ares L, Luft A, Vicente D, et al: Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med* 379:2040-2051, 2018
26. Carbone DP, Reck M, Paz-Ares L, et al: First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. *N Engl J Med* 376:2415-2426, 2017
27. Paz-Ares L, Langer CJ, Novello S, et al: LBA80—Pembrolizumab (pembro) plus platinum-based chemotherapy (chemo) for metastatic NSCLC: Tissue TMB (tTMB) and outcomes in KEYNOTE-021, 189, and 407. *Ann Oncol* 30:v917-v918, 2019
28. Deng J, Chen H, Zhou D, et al: Comparative genomic analysis of esophageal squamous cell carcinoma between Asian and Caucasian patient populations. *Nat Commun* 8:1533, 2017
29. Yoon H, Kato K, Raymond E, et al: LBA-1 RATIONALE-306: Randomized, global, placebo-controlled, double-blind phase 3 study of tislelizumab plus chemotherapy versus chemotherapy as first-line treatment for advanced or metastatic esophageal squamous cell carcinoma (ESCC). *Ann Oncol* 33:S375, 2022
30. Tsao MS, Kerr KM, Kockx M, et al: PD-L1 immunohistochemistry comparability study in real-life clinical samples: Results of blueprint phase 2 project. *J Thorac Oncol* 13:1302-1311, 2018
31. Hirsch FR, McElhinny A, Stanforth D, et al: PD-L1 immunohistochemistry assays for lung cancer: Results from phase 1 of the blueprint PD-L1 IHC assay comparison project. *J Thorac Oncol* 12:208-222, 2017



AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Clinical Benefit of First-Line Programmed Death-1 Antibody Plus Chemotherapy in Low Programmed Cell Death Ligand 1–Expressing Esophageal Squamous Cell Carcinoma: a Post Hoc Analysis of JUPITER-06 and Meta-Analysis

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