



Immune checkpoint inhibitors in the first-line treatment of esophageal squamous cell carcinoma: Minireview for a big shift

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Abstract

Esophageal cancer is an aggressive malignancy often diagnosed at advanced stages, with esophageal squamous cell carcinoma being the predominant subtype worldwide. Standard first-line chemotherapy provides limited survival benefits, with a median overall survival of less than 1 year. Recent advancements in immunotherapy, particularly immune checkpoint inhibitors (ICIs), have transformed the treatment landscape, improving overall survival and progression-free survival. However, response rates remain variable, with programmed death ligand 1 (PD-L1) expression being the primary predictive biomarker. The variability in PD-L1 testing methods and immune microenvironment alterations after prior treatments complicate patient selection for ICIs. Several phase 3 trials, including KEYNOTE-590 and CheckMate 648, have demonstrated the efficacy of ICIs combined with chemotherapy, particularly in patients positive for PD-L1. Despite these advances, long-term survival remains low, emphasizing the need for better biomarkers and novel therapeutic strategies. This review explored current first-line treatment options for esophageal squamous cell carcinoma,

challenges in biomarker-based patient selection, and emerging therapeutic approaches.

Key Words: Esophageal squamous cell carcinoma; Immunotherapy; Immune checkpoint inhibitors; Programmed death ligand 1; First-line treatment

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Core Tip: This paper examined the evolving landscape of first-line treatments for esophageal squamous cell carcinoma, highlighting the transformative impact of immune checkpoint inhibitors. While immune checkpoint inhibitors combined with chemotherapy have improved survival, response rates remain inconsistent due to variability in programmed death ligand 1 testing and immune microenvironment changes. We critically analyzed landmark phase 3 trials (KEYNOTE-590, CheckMate 648) and discussed the limitations of current biomarkers. Addressing the urgent need for more precise patient selection and novel therapeutic strategies, this review provided insights into emerging approaches that could enhance long-term survival in esophageal squamous cell carcinoma.

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INTRODUCTION

Esophageal cancer (EC) is a highly aggressive malignancy that is frequently detected at advanced or metastatic stages. EC is the eleventh most common cancer worldwide with 511000 new cases in 2022 and the seventh-leading cause of cancer-related deaths with 445000 deaths in 2022[1]. There are two main subtypes of EC: Esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma. The risk factors and incidence vary between these two subtypes. ESCC is the most common histological subtype globally, accounting for more than 90% of all cases of EC, with particularly high incidence rates in Eastern Asia and Eastern Africa. The major risk factors for ESCC include smoking and alcohol consumption[2,3]. Spatial transcriptomic studies are exploring the mechanisms of progression from precancerous lesions to ESCC to find new biomarkers for early diagnosis and management[4,5].

The standard first-line chemotherapy regimen for advanced ESCC typically includes a platinum-based fluoropyrimidine doublet that offers a median overall survival (mOS) < 1 year[6]. In recent years, the treatment algorithm for unresectable, locally advanced, or metastatic ESCC has significantly evolved. Multiple randomized controlled trials have demonstrated a remarkable benefit from immune checkpoint inhibitors (ICIs), either alone or in combination with chemotherapy, in improving OS and progression-free survival (PFS)[7-12].

However, long-term survivors remain a small proportion of the total, with a 5-year OS around 10%. For most patients, prognosis remains poor, with a mOS of approximately 1 year[13]. The primary predictive factor for response to ICIs is the expression of programmed death ligand 1 (PD-L1). Nevertheless, for patients with low PD-L1 expression, the benefit of ICIs remains unclear, and a significant subset of these patients does not receive any advantage from immunotherapy[14]. The aim of this review was to explore the challenges in selecting the most appropriate therapeutic strategy for patients with ESCC, with a particular focus on first-line treatment options.

AVAILABLE BIOMARKERS

PD-L1 expression is currently the most established predictive biomarker for determining sensitivity to ICIs. For patients eligible for first-line treatment with ICIs, it is recommended to assess PD-L1 expression using immunohistochemistry (IHC). The clinical implementation of PD-L1 IHC testing is challenging due to the presence of multiple IHC assays, scoring systems, and cutoff thresholds. PD-L1 expression can be assessed using one of three main scoring methods: Tumor proportion score (TPS); combined positive score (CPS); or tumor area positivity (TAP).

TPS is calculated as the percentage of PD-L1-positive tumor cells relative to the total number of tumor cells, multiplied by 100. CPS is a cell-counting method that determines the ratio of the total number of PD-L1-positive cells (including tumor cells, mononuclear lymphocytes, and macrophages) to the total number of viable tumor cells, multiplied by 100. A minimum of 100 viable tumor cells must be present on the PD-L1-stained slide for a valid evaluation. TAP is a visually estimated scoring algorithm developed for the SP263 assay. It calculates the ratio of the area occupied by PD-L1-positive tumor and immune cells to the total tumor area. These scoring systems provide distinct approaches to quantifying PD-L1 expression and help guide therapeutic decisions in clinical practice.

Three major commercial IHC assays are commonly used to detect and quantify PD-L1 expression: Ventana PD-L1 SP263 (SP263); Dako PD-L1 IHC 22C3 pharmDx (22C3); and Dako PD-L1 IHC 28-8 pharmDx (28-8). Each assay employs a unique combination of antibody clone, staining platform, scoring algorithm, and cutoff for PD-L1 positivity. The variability in assays and cutoff thresholds (e.g., CPS $\geq 1/\geq 10$, TPS $\geq 1\%$) complicates the identification of patients most likely to benefit from treatment. Additionally, resource limitations in many pathology laboratories and the lack of comparative studies on PD-L1 assays for EC further challenge their clinical implementation[15].

Another challenge of PD-L1 assessment is that immune dynamics are significantly influenced by prior chemoradiotherapy in pretreated patients, both in esophageal adenocarcinoma[16] and ESCC. Single-cell RNA sequencing of ESCC tumors revealed that neochemoradiotherapy enhances CD8+ T cell infiltration and drives their exhaustion, potentially compromising long-term antitumor immunity[17]. The proportion of patients with tumors expressing high levels of PD-L1 in the first-line studies KEYNOTE-590 and CheckMate 649 were 51% with PD-L1 CPS ≥ 10 and 60% with PD-L1 CPS ≥ 5 , respectively. They were detected by different anti-programmed cell death protein 1 (anti-PD-1) antibody clones (22C3 and 28-8, respectively) and were higher than observed in the previous second-line study of pembrolizumab in patients with advanced esophageal cancer (KEYNOTE-181) and the third-line study of nivolumab in patients with advanced gastric or gastroesophageal junction cancer (Attraction-2)[8].

Similarly, immune profiling of 41 patients treated with neoadjuvant toripalimab and chemoradiotherapy demonstrated substantial shifts in immune cell composition, particularly an increase in CD86+ macrophage infiltration[18]. These findings highlight the evolving nature of the tumor immune microenvironment after treatment, complicating the accurate timing and interpretation of PD-L1 testing in pretreated patients.

Wang *et al*[18] conducted a study to evaluate inter-pathologist concordance for four PD-L1 antibodies in ESCC. Sixty-eight pathologists from 19 centers independently assessed the CPS for 22C3, SP263, SP142, and E1 L3N along with the Tumor Cell Positive Score and Immune Cell Positive Score. Fifty paraffin-embedded ESCC samples from patients at clinical stage T2-T4 were used. Results showed that except for SP263 CPS, Tumor Cell Positive Score for 22C3, SP142, and E1 L3N exhibited higher concordance with overall percent agreement values of 0.80, 0.85, and 0.86. The highest concordance was between SP263 and 22C3 (overall percent agreement 0.896). However, interchangeability between SP263 and 22C3 was not supported in standardized PD-L1 expression analyses[18].

EMERGING BIOMARKERS

ESCC is a highly aggressive malignancy with a poor prognosis, highlighting the urgent need for novel biomarkers to enhance early detection and treatment strategies. Recent research has identified several promising biomarkers. MicroRNA signatures have shown great potential, with an 8-microRNA panel demonstrating high diagnostic accuracy [19]. High hsa-miR-3665 promoter methylation levels have been proposed as a potential biomarker for ESCC progression [20]. Gene expression markers, such as PDZ-binding kinase, kinesin-13 family member 2C, and RAD51-associated protein 1, have exhibited high sensitivity in differentiating ESCC from normal tissues, further supporting their diagnostic and prognostic relevance[21].

DNA methylation plays a key role in ESCC by silencing apoptotic genes, impairing DNA repair, and altering the cell cycle, which together contribute to chemotherapy resistance with hypermethylated genes significantly influencing cancer response to chemotherapy, thus serving as valuable predictive markers for treatment outcomes[22]. Furthermore, spatial transcriptomics-derived markers, such as Deltex E3 ubiquitin ligase 3L and bone marrow stromal antigen 2, provide valuable insights into tumor heterogeneity and may serve as therapeutic targets, offering new avenues for precision medicine in ESCC[23]. Although these biomarkers show great potential, additional large-scale studies and clinical validation are necessary to translate these discoveries into better patient outcomes. Unfortunately, they are currently not available in clinical practice, neither from a diagnostic nor a predictive standpoint.

FIRST-LINE THERAPY OPTIONS

The landscape of first-line treatment for ESCC is undergoing rapid advancements, with phase 3 randomized controlled trials confirming the efficacy of anti-PD-1 inhibitors combined with chemotherapy. The main results are shown in Table 1. The first study that provided evidence of the benefit of combining immunotherapy with chemotherapy was the KEYNOTE-590 trial. It demonstrated significant OS and PFS improvements with chemotherapy (5-fluorouracil and cisplatin) plus pembrolizumab compared with the placebo. PD-L1 expression was assessed using the PD-L1 IHC 22C3 assay, with a CPS ≥ 10 considered positive. In patients with ESCC with PD-L1 CPS ≥ 10 , mOS was 13.9 months with pembrolizumab *vs* 8.8 months with placebo [hazard ratio (HR) = 0.57, 95% confidence interval (CI): 0.43-0.75; $P < 0.0001$]. Similar benefits were observed in the overall study population (12.4 months *vs* 9.8 months; HR = 0.73, 95% CI: 0.62-0.86; $P < 0.0001$). PFS was also significantly prolonged in patients with ESCC both with PD-L1 CPS ≥ 10 (7.5 months *vs* 5.5 months; HR = 0.51, 95% CI: 0.41-0.65; $P < 0.0001$) and in the overall population (6.3 months *vs* 5.8 months; HR = 0.65, 95% CI: 0.55-0.76; $P < 0.0001$). In the intent-to-treat (ITT) population, objective response rate (ORR) was 45.0% in the pembrolizumab plus chemotherapy group compared with 29.3% in the placebo plus chemotherapy group[8]. Based on these results, the Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy in the first-line setting.

Table 1 Main results of randomized controlled trials investigating first-line treatment in advanced esophageal squamous cell carcinoma, focusing on the outcomes of the programmed death ligand 1 positive subgroups

	Phase	Experimental treatment	Enrollment	PD-L1 assay	PD-L1 cutoff	Median follow-up	Median OS PD-L1 positive subgroups	Median OS in overall population	Median PFS PD-L1 positive subgroups	Median PFS in overall population	ORR PD-L1 positive subgroups	ORR in overall population
KEYNOTE-590 [8], <i>n</i> = 749	3	Pembrolizumab + 5FU + cisplatin	Global	22C3 assay	PD-L1 CPS ≥ 10 (<i>n</i> = 383)	22.6 months (IQR: 19.6-27.1)	13.5 months <i>vs</i> 9.4 months (HR = 0.62, 95%CI: 0.49-0.78, <i>P</i> < 0.0001)	12.4 months <i>vs</i> 9.8 months (HR = 0.73, 95%CI: 0.62-0.86, <i>P</i> < 0.0001)	7.5 months <i>vs</i> 5.5 months (HR = 0.51, 95%CI: 0.41-0.65, <i>P</i> < 0.0001)	6.3 months <i>vs</i> 5.8 months (HR = 0.65, 95%CI: 0.55-0.76, <i>P</i> < 0.0001)	51.1% <i>vs</i> 26.9%	45.0% <i>vs</i> 29.3%
CheckMate 648 [24], <i>n</i> = 645	3	Nivolumab + 5FU + cisplatin	Global	28-8 assay	PD-L1 TPS $\geq 1\%$ (<i>n</i> = 97)	13 months ¹	15.4 months <i>vs</i> 9.1 months (HR = 0.54, 95%CI: 0.37-0.80, <i>P</i> < 0.001)	13.2 months <i>vs</i> 10.7 months (HR = 0.74, 95%CI: 0.58-0.96, <i>P</i> = 0.002)	6.9 months <i>vs</i> 4.4 months (HR = 0.65, 95%CI: 0.46-0.92, <i>P</i> = 0.002)	5.8 months <i>vs</i> 5.6 months (HR = 0.81, 95%CI: 0.64-1.04, <i>P</i> = 0.04)	53% <i>vs</i> 20%	47% <i>vs</i> 27%
CheckMate 648 [24], <i>n</i> = 649	3	Nivolumab + ipilimumab + 5FU + cisplatin	Global	28-8 assay	PD-L1 TPS $\geq 1\%$ (<i>n</i> = 97)	13 months ¹	13.7 months <i>vs</i> 9.1 months (HR = 0.64, 95%CI: 0.46-0.90, <i>P</i> = 0.001)	12.7 months <i>vs</i> 10.7 months (HR = 0.78, 95%CI: 0.62-0.98, <i>P</i> = 0.01)	4.0 months <i>vs</i> 4.4 months (HR = 1.02, 95%CI: 0.73-1.43, <i>P</i> = 0.90)		35% <i>vs</i> 20%	28% <i>vs</i> 27%
ESCORT-1 st [11], <i>n</i> = 596	3	Camrelizumab + paclitaxel + cisplatin	China	6E8 antibody	PD-L1 TPS $\geq 1\%$ (<i>n</i> = 329)	10.8 months (IQR: 7.3-14.3)	15.3 months <i>vs</i> 11.5 months (HR = 0.59, 95%CI: 0.43-0.80, <i>P</i> = 0.32)	15.3 months <i>vs</i> 12.0 months (HR = 0.70, 95%CI: 0.56-0.88, <i>P</i> = 0.001)	6.9 months <i>vs</i> 5.6 months (HR = 0.51, 95%CI: 0.39-0.67, <i>P</i> = 0.38)	6.9 months <i>vs</i> 5.6 months (HR = 0.56, 95%CI: 0.46-0.68, <i>P</i> < 0.001)	74.1% <i>vs</i> 65.6%	72.1% <i>vs</i> 62.1%
ESCORT-1 st [25], <i>n</i> = 596	3	Camrelizumab + paclitaxel + cisplatin	China	6E8 antibody	PD-L1 TPS $\geq 1\%$ (<i>n</i> = 329)	24 months ²	/ ⁵	15.6 months <i>vs</i> 12.6 months (HR = 0.70, 95%CI: 0.58-0.84, <i>P</i> = 0.0001)	/ ⁵	7.6 months <i>vs</i> 5.8 months (HR = 0.54, 95%CI: 0.45-0.65, <i>P</i> = 0.0001)	/ ⁵	/ ⁵
JUPITER-06 [26], <i>n</i> = 514	3	Toripalimab + paclitaxel + cisplatin	China	JS311 assay	PD-L1 CPS ≥ 1 (<i>n</i> = 401)	7.1 months ²	15.2 months <i>vs</i> 10.9 months (HR = 0.61, 95%CI: 0.44-0.87, <i>P</i> = 0.0056)	17 months <i>vs</i> 11 months (HR = 0.58, 95%CI: 0.43-0.78, <i>P</i> = 0.0004)	5.7 months <i>vs</i> 5.5 months (HR = 0.58, 95%CI: 0.44-0.75, <i>P</i> < 0.0001)	5.7 months <i>vs</i> 5.5 months (HR = 0.58, 95%CI: 0.46-0.74, <i>P</i> < 0.0001)		69.3% <i>vs</i> 52.1%
ORIENT-15 [27], <i>n</i> = 659	3	Sintilimab + paclitaxel + cisplatin	Global (> 97% China)	22C3 assay	PD-L1 CPS ≥ 10 (<i>n</i> = 381)	16 months (IQR: 12.3-19.4)	17.2 months <i>vs</i> 13.6 months (HR = 0.64, 95%CI: 0.48-0.85, <i>P</i> = 0.002)	16.7 months <i>vs</i> 12.5 months (HR = 0.63, 95%CI: 0.51-0.78, <i>P</i> < 0.001)	8.3 months <i>vs</i> 6.4 months (HR = 0.58, 95%CI: 0.45-0.75, <i>P</i> < 0.001)	7.2 months <i>vs</i> 5.7 months (HR = 0.56, 95%CI: 0.46-0.68, <i>P</i> < 0.001)	68% <i>vs</i> 49%	66% <i>vs</i> 45%
ASTRUM-007 [29]	3	Serplulimab + 5FU + cisplatin	China	/ ³	PD-L1 CPS ≥ 1 (<i>n</i> = 383)	14.9 months (IQR: 8.8-19.7)	15.3 months <i>vs</i> 11.8 months (HR = 0.68, 95%CI: 0.53-0.87, <i>P</i> = 0.0020) ³	/ ³	5.6 months <i>vs</i> 5.3 months (HR = 0.60, 95%CI: 0.48-0.75, <i>P</i> < 0.0001) ³	/ ³	57.6% <i>vs</i> 42.1%	
RATIONALE 306 [28], <i>n</i> = 645	3	Tislelizumab + cisplatin (or oxaliplatin) + capecitabine (or paclitaxel or 5FU)	Global	SP263 assay	PD-L1 TAP score $\geq 10\%$ (<i>n</i> = 223)	16.3 months (IQR: 8.6-21.8)	16.6 months <i>vs</i> 10.0 months (HR = 0.62, 95%CI: 0.44-0.87, <i>P</i> = 0.0029)	17.2 months <i>vs</i> 10.6 months (HR = 0.66, 95%CI: 0.54-0.80, <i>P</i> < 0.0001)		7.3 months <i>vs</i> 5.6 months (HR = 0.62, 95%CI: 0.52-0.75, <i>P</i> < 0.0001)		63% <i>vs</i> 42%

SKYSCRAPER-08 [30], n = 461	3	Tiragolumab + atezolizumab + paclitaxel + cisplatin	Asia	SP263 assay	PD-L1 TAP score $\geq$ 10% (n = 199)	14.6 months ⁴	18.9 months <i>vs</i> 10.5 months (HR = 0.70, 95%CI: 0.49-1.01)	15.7 months <i>vs</i> 11.1 months (HR = 0.70, 95%CI: 0.55-0.88, P = 0.0024)	6.2 months <i>vs</i> 5.4 months (HR = 0.56; 95%CI: 0.45-0.70, P = 0.0001)	59.7% <i>vs</i> 45.5%
MORPHEUS-EC [31], n = 152	1/2b	Tiragolumab + atezolizumab + 5FU + cisplatin	Asia	SP263 assay	PD-L1 TAP score $\geq$ 10% (n = 40)	10.9 months ⁴		16 months <i>vs</i> 9.9 months (HR = 0.64, 95%CI: 0.35-1.20)	6.9 months <i>vs</i> 4.1 months (HR = 0.52, 95%CI: 0.30-0.91)	67.7% <i>vs</i> 47.8%
MORPHEUS-EC [31], n = 152	1/2b	Atezolizumab + 5FU + cisplatin	Asia	SP263 assay	PD-L1 TAP score $\geq$ 10% (n = 40)	11.4 months ⁴		13.1 months <i>vs</i> 9.9 months (HR = 0.75, 95%CI: 0.40-1.39)	6.8 months <i>vs</i> 4.1 months (HR = 0.75, 95%CI: 0.44-1.26)	53.8% <i>vs</i> 47.8%

¹Minimum follow-up; the median follow-up was not provided in the study.

²Data at the minimum follow-up period of 24 months.

³The overall population coincides with the programmed death ligand 1 combined positive score $\geq$ 1. The study does not specify the assay for the programmed death ligand 1 analysis.

⁴Unavailable confidence interval of the median follow-up.

⁵In the final analysis, with a median follow-up of 24 months, data on objective response rate in both the overall population and programmed death ligand 1-positive subpopulation and progression-free survival and overall survival in the programmed death ligand 1-positive subpopulation were not reported.

PD-L1: Programmed death ligand 1; OS: Overall survival; PFS: Progression-free survival; ORR: Objective response rate; 5FU: 5-fluorouracil; HR: Hazard ratio; CI: Confidence interval; CPS: Combined positive score; IQR: Interquartile range; TPS: Tumor proportion score; TAP: Tumor area positivity.

The CheckMate 648 trial assessed the efficacy of nivolumab combined with chemotherapy (fluorouracil and cisplatin), nivolumab with ipilimumab, or chemotherapy alone in patients with advanced, unresectable ESCC regardless of PD-L1 expression that was determined using the PD-L1 IHC 28-8 pharmDx assay, with a PD-L1 $\geq$ 1% considered positive. Among patients with PD-L1 $\geq$ 1%, mOS was 15.4 months for patients receiving nivolumab plus chemotherapy compared with 9.1 months for those treated with chemotherapy alone (HR = 0.54, 95%CI: 0.37-0.80; $P < 0.001$). Similarly, nivolumab plus ipilimumab improved survival, with a mOS of 13.7 months *vs* 9.1 months for chemotherapy alone (HR = 0.64, 95%CI: 0.46-0.90; $P = 0.001$). In the overall study population, mOS was 13.2 months for nivolumab plus chemotherapy compared to 10.7 months for chemotherapy alone (HR = 0.74, 99.1%CI: 0.58-0.96; $P = 0.002$), while nivolumab plus ipilimumab achieved a mOS of 12.7 months *vs* 10.7 months (HR = 0.78, 95%CI: 0.62-0.98; $P = 0.01$). PFS was significantly improved with nivolumab plus chemotherapy in patients with PD-L1 $\geq$ 1% with a median PFS (mPFS) of 6.9 months compared with 4.4 months with chemotherapy alone (HR = 0.65, 95%CI: 0.46-0.92; $P = 0.002$). In contrast, no significant difference in PFS was observed between the nivolumab plus ipilimumab group and the chemotherapy-alone group (4.0 months *vs* 4.4 months, HR = 1.02, 95%CI: 0.73-1.43; $P = 0.90$). ORR was notably higher with nivolumab plus chemotherapy than with chemotherapy alone, reaching 53% *vs* 20% in patients with PD-L1 $\geq$ 1% and 47% *vs* 27% in the overall population. Furthermore, in the nivolumab plus ipilimumab cohort, the ORR for patients with PD-L1 $\geq$ 1% was 35%[24].

Based on CheckMate 648, the FDA approved nivolumab in combination with fluoropyrimidine-based and platinum-based chemotherapy and nivolumab in combination with ipilimumab for the first-line treatment of patients with advanced or metastatic ESCC, irrespective of tumor PD-L1 status. EMA approval is restricted to patients with tumor cell PD-L1 expression of $\geq$ 1%.

The fully Asian ESCORT-1st trial showed efficacy of camrelizumab in combination with chemotherapy (paclitaxel and cisplatin) compared with placebo plus chemotherapy. PD-L1 expression was evaluated using a PD-L1 IHC kit (6E8

antibody: Abcam) and categorized based on the TPS. At a minimum follow-up of 24 months the results demonstrated a statistically significant improvement in OS (15.3 months *vs* 12.0 months, HR = 0.70, 95%CI: 0.56-0.88; $P < 0.0001$) and in PFS (6.9 months *vs* 5.6 months, HR = 0.51, 95%CI: 0.39-0.67; $P < 0.0001$) in the ITT population. At a median follow up of 10.8 months, HR for death was below 1 in those patients with PD-L1 expression $\geq 1\%$, both for mOS (15.3 months *vs* 11.5 months, HR = 0.59, 95%CI: 0.43-0.80; $P = 0.32$) and mPFS (6.9 months *vs* 5.6 months, HR = 0.51, 95%CI: 0.39-0.67; $P = 0.38$). This suggests a potential survival benefit also for patients with PD-L1 $< 1\%$, although the result was not statistically significant. ORR were observed in 72.1% of patients in the camrelizumab-chemotherapy group compared with 62.1% of patients in the placebo-chemotherapy group, showing a 10.1% difference between the groups (95%CI: 2.6%-7.6%; $P = 0.009$)[11,25]. Camrelizumab combination therapy for advanced or metastatic ESCC has been approved by National Medical Products Administration in China.

Similarly, the JUPITER-06 trial found toripalimab combined with paclitaxel and cisplatin *vs* placebo with paclitaxel and cisplatin significantly improved survival in Asian patients. PD-L1 expression was measured using the JS311 IHC assay, with PD-L1 CPS ≥ 1 considered positive and CPS ≥ 10 indicating high expression. PFS was significantly better in the toripalimab group, with a mPFS of 5.7 months compared to 5.5 months in the placebo group (HR = 0.58, 95%CI: 0.46-0.74; $P < 0.0001$). In the PD-L1 CPS ≥ 10 subgroup (HR = 0.65, 95%CI: 0.45-0.92; $P = 0.02$), and in the CPS < 10 subgroup (HR = 0.56, 95%CI: 0.41-0.78). In the overall population, OS was significantly improved in the toripalimab group, with 17 months in the experimental arm *vs* 11 months in the placebo group (HR = 0.58, 95%CI: 0.43-0.78; $P = 0.0004$), maintaining a positive trend in PD-L1 CPS ≥ 10 subgroup, though without reaching statistical significance (17.0 months *vs* 10.9 months, HR = 0.64, 95%CI: 0.40-1.03; $P = 0.06$)[26]. Toripalimab has received approval in China and Europe for the first-line treatment of advanced ESCC in combination with chemotherapy, demonstrating efficacy across various PD-L1 expression levels. However, it is not currently approved for this indication in the United States.

The ORIENT-15 trial demonstrated superiority of sintilimab combined with chemotherapy (cisplatin plus paclitaxel or cisplatin plus 5-fluorouracil) compared with placebo plus chemotherapy. PD-L1 expression was evaluated using the 22C3 pharmDx assay, considering both the TPS and CPS scoring systems. The primary endpoint was OS in both the overall population and the subgroup with PD-L1 CPS ≥ 10 . In the overall population, results demonstrated a significant improvement in OS for the sintilimab-chemotherapy group compared with the placebo-chemotherapy group, with a mOS of 16.7 months *vs* 12.5 months (HR = 0.63, 95%CI: 0.51-0.78; $P < 0.001$). Among patients with PD-L1 CPS ≥ 10 , mOS was 17.2 months in the sintilimab-chemotherapy group *vs* 13.6 months in the placebo group (HR = 0.64, 95%CI: 0.48-0.85; $P = 0.002$). Similarly, sintilimab-chemotherapy demonstrated significantly improved PFS (7.2 months *vs* 5.7 months (HR = 0.56, 95%CI: 0.46-0.68; $P < 0.001$), especially in PD-L1 CPS ≥ 10 subgroup (8.3 months *vs* 6.4 months, HR = 0.58, 95%CI: 0.45-0.75, $P < 0.001$)[27]. In summary, sintilimab has received approval from the National Medical Products Administration in China for use in combination with chemotherapy as a first-line treatment for ESCC, applicable to patients regardless of PD-L1 expression status. However, it has not yet been approved by the FDA or EMA for this indication.

Another trial that investigated a combination immunochemotherapy strategy was the RATIONAL306 trial comparing tislelizumab plus chemotherapy (oxaliplatin or cisplatin plus fluoropyrimidine or paclitaxel) *vs* placebo plus chemotherapy. PD-L1 expression status by TAP score was tested using the VENTANA PD-L1 (SP263) assay. mOS was 17.2 months in tislelizumab group *vs* 10.6 months in the placebo group (HR = 0.66, 95%CI: 0.54-0.80; $P < 0.000$). PD-L1 TAP score positivity thresholds of 10% showed significant differences in OS benefit (16.6 months *vs* 10.0 months, HR = 0.62, 95%CI: 0.44-0.87; $P = 0.0029$). Significant improvement in PFS was observed with tislelizumab plus chemotherapy *vs* placebo plus chemotherapy in the overall population (7.3 months *vs* 5.6 months, HR = 0.62, 95%CI: 0.52-0.75; $P < 0.0001$)[28].

Astrum-007 is a phase 3, double-blind, multicenter trial that assessed the effectiveness and safety of serplulimab combined with chemotherapy (fluoropyrimidine and cisplatin) *vs* chemotherapy alone in patients with advanced or metastatic ESCC and PD-L1 CPS ≥ 1 . The study demonstrated that mOS was significantly longer in the serplulimab plus chemotherapy group compared with the placebo plus chemotherapy group (15.3 months *vs* 11.8 months, HR = 0.68, 95%CI: 0.53-0.87; $P = 0.0020$). The mPFS was 5.8 months in the serplulimab group and 5.3 months in the control group (HR = 0.60, 95%CI: 0.48-0.75, $P < 0.0001$). In patients with PD-L1 CPS ≥ 10 , adding serplulimab to chemotherapy resulted in even greater survival benefits, both in mPFS and in mOS. Antitumor responses were also enhanced by serplulimab in both the PD-L1 CPS ≥ 10 and $1 \leq \text{CPS} < 10$ subgroups[29].

To overcome resistance to chemotherapy plus anti-PD-L1/anti-PD-1 therapies, studies, such as SKYSCRAPER-08 and MORPHEUS-EC trials, have been designed to incorporate new immunological targets. The phase 3 SKYSCRAPER-08 study evaluated the combination of tiragolumab (anti-TIGIT) plus atezolizumab with chemotherapy as a first-line treatment for advanced ESCC in an Asian patient population. TIGIT is an emerging inhibitory checkpoint expressed on activated T cells and natural killer cells, and tiragolumab may have the potential to enhance immune responses by working in synergy with other immunotherapeutic agents. A total of 461 patients were randomized to receive either tiragolumab and atezolizumab with chemotherapy or placebo with chemotherapy for up to six cycles, followed by maintenance therapy. At a minimum follow-up of 6.5 months, median independent review facility-assessed PFS was 6.2 months with tiragolumab *vs* 5.4 months with placebo (HR = 0.56, 95%CI: 0.45-0.70; $P < 0.0001$). The final OS analysis at 14.5 months showed a mOS of 15.7 months in the tiragolumab arm *vs* 11.1 months in the placebo arm (HR = 0.70, 95%CI: 0.55-0.88; $P = 0.0024$), confirming a significant and clinically meaningful survival benefit. These benefits were observed consistently across subgroups, regardless of PD-L1 expression levels[30].

In the MORPHEUS-EC phase Ib/II study a total of 152 patients were randomly assigned to one of three groups: Chemotherapy alone; atezolizumab plus chemotherapy; or tiragolumab plus atezolizumab with chemotherapy. mPFS was 4.1 months for chemotherapy, 6.8 months for atezolizumab plus chemotherapy, and 6.9 months for tiragolumab plus atezolizumab with chemotherapy. The survival benefit was consistent across various subgroups, including those based on PD-L1 status, with a trend toward improved OS in the tiragolumab arm[31].

The statistical analysis methods were similar across the studies. The Kaplan-Meier method was used to estimate OS, PFS, and duration of response. Differences in OS and PFS between groups were assessed using a stratified log-rank test, while HRs and 95% CIs were estimated using a Cox proportional hazards model. In KN590 the ORR differences were evaluated with the stratified Miettinen-Nurminen method[8]. In ORIENT-15 ORR and disease control rate were calculated using the normal approximation method with corresponding 95% CIs, and ORR differences between treatment groups were assessed using the Miettinen-Nurminen method[27]. In the RATIONALE-306 and ESCORT-1 study the Cochran-Mantel-Haenszel test was used to assess the ORR, with Clopper-Pearson 95% CIs[28,25].

The choice of chemotherapy varied across first-line chemoimmunotherapy trials, with paclitaxel plus cisplatin being more commonly used in studies focused on the Chinese population, whereas fluoropyrimidine plus cisplatin was the preferred regimen in global trials. Despite variations in chemotherapy protocols and PD-1 inhibitors, the survival benefits associated with adding a PD-1 inhibitor remained comparable across these studies[8,11,24-31]. Moreover, findings from the RATIONALE-306 trial indicated no significant difference in OS HR between patients treated with fluoropyrimidine plus cisplatin and those receiving paclitaxel plus cisplatin (0.66 *vs* 0.69)[28]. That said, key efficacy measures appeared to be more favorable in trials evaluating paclitaxel plus cisplatin plus PD-1 blockade compared with those assessing fluoropyrimidine plus cisplatin plus PD-1 blockade. While geographic factors (China *vs* other regions) may have influenced these results, they do not fully account for the observed differences.

Interestingly, in the Chinese subgroup of the KEYNOTE-590 trial, fluoropyrimidine plus cisplatin plus PD-1 blockade achieved a strong OS HR of 0.51, yet its median OS remained lower than that seen in Chinese trials using paclitaxel plus cisplatin[8]. One possible explanation is that paclitaxel in contrast to 5-fluorouracil has a greater potential to induce immunogenic cell death and enhance anti-tumor immune responses[32]. This characteristic may contribute to the superior efficacy observed with paclitaxel plus cisplatin plus PD-1 blockade. Furthermore, paclitaxel plus cisplatin is more convenient to administer than fluoropyrimidine plus cisplatin, making it a compelling option for further research in populations beyond China.

Regardless of the chemotherapy backbone, given these different treatment options, several researchers have focused on evaluating the cost-effectiveness of chemotherapy-immunotherapy combinations compared with monotherapy among currently approved regimens. The findings vary depending on the type of immunotherapy used. While the combination of toripalimab, sintilimab, and camrelizumab with chemotherapy has been shown to be cost-effective, the addition of serplulimab, pembrolizumab, or nivolumab to chemotherapy has not been considered a cost-effective option[33,34].

SAFETY PROFILE

The analysis of adverse events (AEs) across multiple studies shows no significant differences between treatment arms in terms of overall toxicity. In KN590, nearly all patients experienced AE, with grade 3 or higher events occurring at similar rates between the pembrolizumab group and the placebo group (86% and 83%, respectively)[8]. Likewise, treatment-related events were comparable in frequency and severity. The most common immune-mediated AEs were hypothyroidism, pneumonitis, and hyperthyroidism[8]. In CM648, grade 3-4 AEs were more common in the nivolumab plus chemotherapy arm (47%) than in the nivolumab plus ipilimumab (32%) arm or chemotherapy arm (36%), but treatment-related mortality remained low across all groups (about 2%)[24].

In patients receiving nivolumab plus chemotherapy, AEs were mainly chemotherapy-related, with nausea, decreased appetite, and stomatitis being the most common, along with some immune-mediated events. In contrast, nivolumab plus ipilimumab primarily led to immune-mediated AEs, most commonly rash, pruritus, and hypothyroidism[24]. The ESCORT-1 and JUPITER-06 studies reported high rates of treatment-related AEs, but severe toxicities (grade ≥ 3) were comparable between immunotherapy and placebo arms[11,25,26]. The most common immune-related AE with camrelizumab was reactive capillary endothelial proliferation (79.9% *vs* 10.8%)[11]. Similarly, in sintilimab and tislelizumab trials, AEs rates were similar between treatment groups, with immune-related toxicities being more frequent in immunotherapy arms but mostly mild (grade 1-2)[27,28].

In SKYSCRAPER-08, 98.2% of patients experienced treatment-related AEs, with a slightly higher incidence of grade 3/4 events in the tiragolumab + atezolizumab + chemotherapy group (59.6% *vs* 56.4%)[30]. However, grade 5 events were more frequent with tiragolumab (2.6% *vs* 0.9%). MORPHEUS-EC showed a similar trend, with grade 3-5 AEs occurring in 82.6% (chemotherapy), 83.1% (atezolizumab + chemotherapy), and 85.5% (tiragolumab + atezolizumab + chemotherapy), indicating a modest increase in serious AEs (SAEs) with the addition of tiragolumab[31]. Overall, while ICIs are generally associated with several immune-related toxicities, their safety profile remains comparable with chemotherapy, with most SAEs occurring at similar rates across treatment groups.

In the ASTRUM-007 study, the incidence of AEs of any grade was similar between the ITT population (98%) and the control population (98%). Immune-related AEs occurred in 35% of patients in the serplulimab plus chemotherapy group and 18% in the placebo plus chemotherapy group. The most frequent immune-related AEs were hypothyroidism, dermatitis, and hyperthyroidism[31].

ONGOING TRIALS

In the context of these findings, ongoing trials continue to explore combination therapies aimed at improving treatment outcomes in advanced ESCC. Among the ongoing studies, we highlight a series of promising trials from a therapeutic perspective as they combine immunotherapy with chemotherapy alongside other molecules, potentially overcoming the

primary resistance to current treatment regimens. The LEAP-014 (NCT04949256) is a phase 3 randomized trial assessing the efficacy and safety of pembrolizumab plus lenvatinib and chemotherapy compared with pembrolizumab plus chemotherapy alone.

Another multicenter phase II trial (NCT05013697) is investigating the combination of benmelstobart (a novel humanized anti-PD-L1 monoclonal antibody) with anlotinib (a multitargeted tyrosine kinase inhibitor) or placebo, in combination with paclitaxel and cisplatin as a first-line treatment for advanced ESCC. A phase II clinical study (NCT05322499) is evaluating the efficacy and safety of camrelizumab combined with chemotherapy or anlotinib in patients with advanced ESCC who have previously received first-line immunotherapy.

A two-arm, open-label, multicenter study (NCT05522894) is assessing the efficacy and safety of AK104 (anti-PD-1/CTLA-4 bispecific antibody) alone or combined with cisplatin and paclitaxel in treating advanced ESCC without prior systemic therapy. A phase I/II study (NCT06532799) is examining the safety and efficacy of autologous tumor-infiltrating lymphocyte therapy combined with pembrolizumab immunotherapy in patients with advanced or metastatic refractory gastric and EC. Lastly, the ANSWER study (NCT05214222) is an open-label, phase II trial investigating the combination of penpulimab (an anti-PD-1 antibody) and chemotherapy with or without anlotinib as a first-line treatment for advanced ESCC.

CONCLUSION

Choosing the optimal first-line treatment for metastatic ESCC is becoming increasingly complex due to the expanding range of therapeutic options. The decision-making process involves a careful evaluation of biomarker assessments, response rates, mechanisms of resistance, and the integration of next-generation ICIs. One of the current challenges is the variability in the PD-L1 scoring methods, TPS, CPS, and TAP. These scoring systems are not always concordant, making it difficult to consistently stratify patients and select the most effective therapy. Furthermore, response rates among patients who are positive for PD-L1 vary widely, reinforcing the need for improved biomarker-driven treatment approaches[15].

Resistance to PD-1/PD-L1 inhibitors remains a significant hurdle in ESCC treatment, requiring novel strategies to enhance immune responses. The inhibition of TIGIT, an emerging checkpoint target, has shown the potential to strengthen anti-tumor immunity by complementing the PD-L1/PD-1 axis. Early clinical data suggest that adding anti-TIGIT agents to existing regimens can lead to superior responses compared with both chemotherapies alone and traditional chemoimmunotherapy involving PD-L1 blockade[35].

Another key factor influencing treatment selection is the choice of chemotherapy backbone. There is no globally accepted standard regimen, and geographical preferences vary between platinum/fluoropyrimidine and platinum/taxane combinations. Preclinical evidence indicates that these regimens exert different immunomodulatory effects, potentially altering the efficacy of concurrent PD-1 inhibition[32]. Fluoropyrimidines influence dendritic cell maturation, while paclitaxel promotes the depletion of myeloid-derived suppressor cells, both of which may impact the immune response against tumors. However, direct comparisons between these chemotherapy backbones in the context of immunotherapy remain limited. Most clinical trials have allowed only one platinum doublet, with the notable exception of the ORIENT-15 study, where both paclitaxel and fluorouracil-based regimens were included. However, since 93% of patients in that trial received paclitaxel, it remains difficult to draw definitive conclusions about the comparative efficacy of these regimens[27].

Despite concerns about immune-related toxicities, the overall safety profile of chemoimmunotherapy appears to be comparable with chemotherapy alone in terms of SAEs. Across multiple studies, the incidence of AEs greater than grade 3 do not seem to be significantly higher in arms incorporating ICIs. This suggests that while checkpoint inhibitors introduce distinct toxicity profiles, they do not necessarily add to the overall burden of SAEs, if patients receive appropriate monitoring and management.

Given these complexities, selecting the most appropriate first-line treatment for metastatic ESCC requires a personalized approach that considers patient characteristics, biomarker status, resistance mechanisms, chemotherapy backbone, and safety concerns. The emergence of anti-TIGIT agents offers an exciting opportunity to improve patient outcomes by enhancing immune responses beyond PD-1/PD-L1 blockade. However, further studies are necessary to refine treatment strategies and establish the most effective therapeutic combinations in this rapidly evolving landscape. The ongoing clinical trials are essential to explore these innovative therapies and to provide more insight into their potential to overcome current treatment limitations and improve patient survival in metastatic ESCC.

FOOTNOTES

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