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Review Article

Advancements in the research of immune checkpoint inhibitors for the treatment of advanced esophageal squamous cell carcinoma

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Abstract: Esophageal cancer (EC) has a high mortality rate and poor prognosis. Most patients are diagnosed at an advanced stage or with distant metastasis, making surgery impossible. Traditional curative radiotherapy and chemotherapy have limited efficacy. In recent years, with the development of clinical trials, immune checkpoint inhibitors (ICIs) have shown promising results in treating advanced and metastatic esophageal squamous cell carcinoma (ESCC) patients. ICIs have gradually become a primary therapeutic approach for EC. This review summarizes and provides an overview of the current research status and progress of ICIs in the treatment of advanced ESCC patients.

Keywords: Advanced esophageal squamous cell carcinoma, immune checkpoint inhibitors, targeted therapy

Introduction

EC is the seventh most common malignancy worldwide and the sixth leading cause of cancer-related deaths [1, 2]. Due to its invasiveness, EC's 5-year overall survival (OS) rate remains at 30-40% [3, 4]. However, the poor prognosis of EC is influenced by various factors such as disease recurrence, metastasis, and treatment complications. EC has two main subtypes, adenocarcinoma (AC) and squamous cell carcinoma (SCC), which account for over 90% of all cases [5-7].

Esophageal AC usually occurs in the lower one-third of the esophagus, known as Barrett's esophagus. In contrast, SCC primarily occurs in the upper part of the esophagus and is associated with smoking and alcohol consumption. SCC has the highest incidence rate globally compared to AC [8]. Traditional treatment modalities such as surgery, chemotherapy, and radiotherapy are insufficient for treating advanced esophageal tumors [9]. Therefore, it is crucial to explore innovative therapies to improve the prognosis of patients with advanced ESCC [10]. ICIs have been proven effective and safe for the treatment of advanced ESCC [11, 12], and several ICIs have been approved for first-line and second-line therapy for several cacners [13, 14]. The advent of immunotherapy has brought new hope for the survival of patients with advanced ESCC.

ICIs are monoclonal antibodies that restore anti-cancer immune responses by targeting immune checkpoint molecules [15]. So far, the most widely used ICIs in clinical practice target programmed cell death protein 1 (PD-1), programmed cell death protein 1 ligand (PD-L1), or cytotoxic T-lymphocyte antigen 4 (CTLA-4) [16, 17]. Traditional curative radiotherapy and che-

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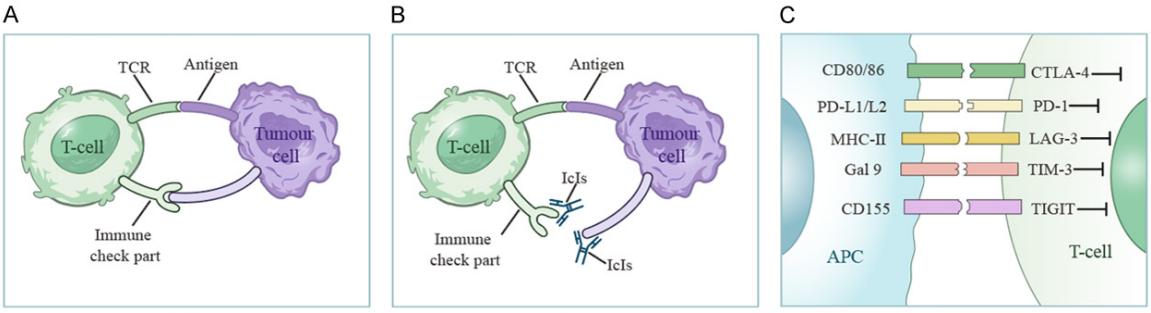

Figure 1. Immune Checkpoints (A) Tumor immune evasion, where immune inhibitory molecules on tumor cells bind to immune checkpoint receptors on T cells, suppressing the normal immune activity of T cells (using PD-1/PD-L1 as an example). (B) Mechanism of action of ICIs, where ICIs bind to immune checkpoint molecules and tumor cells, blocking their interaction and allowing T cells to continue their normal immune function, leading to the elimination of tumor cells (using PD-1/PD-L1 as an example). (C) Co-signaling pathways of T cell immune checkpoints.

motherapy have limited efficacy, are prone to recurrence, and have poor prognosis. The effectiveness and safety of ICIs in the treatment of advanced ESCC h ave been demonstrated, and several ICIs have been approved for first-line and second-line treatments. The advent of immunotherapy has brought more hope for survival to patients with advanced ESCC.

Immune checkpoint molecules

Immunotherapy for tumors is a treatment method that aims to combat tumors by repairing and enhancing the function of the body's immune system to control and kill tumor cells [18]. The characteristics of immunotherapy include inducing persistent clinical responses, lack of typical drug resistance, and the ability to cause autoimmune toxicity [19]. With a deeper understanding of the body's anti-tumor immune response and a better understanding of tumor immune escape mechanisms and the tumor microenvironment, new strategies and approaches for immunotherapy of ESCC has been further researched and expanded. Clinical trials have confirmed the effectiveness of immunotherapy in ESCC patients, with significant improvements in overall survival, disease-free survival, complete remission, partial remission, and overall response rate in patients receiving immunotherapy [20]. Since the approval of the first ICI, ipilimumab (an anti-CTLA-4 monoclonal antibody), by the US Food and Drug Administration (FDA) for the treatment of unresectable and metastatic melanoma in 2014, immunotherapy based on immune checkpoint blockade agents (ICBs) has been approved for the treatment of more types of tumors at early disease stages. The FDA has approved four types of ICIs (anti-PD-1, PD-L1, CTLA-4, and LAG-3 mAbs) for cancer treatment [21]. Other ICIs, such as TIM-3 and TIGIT inhibitors, have been extensively evaluated as treatment modalities in clinical trials for various solid tumors and leukemias (**Figure 1**) [22].

CTLA4

CTLA-4 is an inhibitory checkpoint molecule highly expressed in activated T cells and regulatory T cells (Tregs). CTLA-4 is closely related to CD28 but plays a different role in immune responses. CD28 is located on the surface of CD4+ and CD8+ T cells and acts as a co-stimulatory receptor. When it interacts with its ligands (B7), CD80 dimers, and CD86 monomers, it sends signals along with the signals from the T-cell receptor (TCR) to activate the entire cell. CTLA-4 is mainly present in intracellular vesicles compared to CD28. It has a higher affinity for CD80 and CD86 and competes with CD28 for ligand binding [23]. The binding of CTLA-4 to CD80/CD86 can inhibit the activation signal of T cells and prevent autoimmune diseases. Blocking CTLA-4 can directly target the inhibitory signals of effector T cells, reduce the suppressive effect of Tregs, and effectively enhance the anti-tumor activity of T cells [24].

PD-1/PD-L1

PD-1 is another inhibitory checkpoint molecule on T cells. It is expressed on the surface of T cells and is involved in cell apoptosis [17]. PD-1 belongs to the CD28 family and shares 23% amino acid homology with CTLA-4, but its

expression differs from CTLA-4 and is mainly expressed on activated T cells, B cells, and myeloid cells [25]. PD-1 has two ligands, PD-L1 and PD-L2. PD-L1 is primarily expressed in T cells, B cells, macrophages, and dendritic cells (DCs), and its expression can be upregulated on activated cells. PD-L2 is relatively limited in expression and is mainly expressed on antigen-presenting cells such as activated macrophages and dendritic cells [26]. Humanized anti-PD-1 monoclonal antibodies can specifically bind to PD-1, block the interaction between PD-1 and its ligands, and restore the immune response of T cells against tumors. PD-1/PD-L1 immune checkpoint inhibitors are currently highly anticipated cancer immunotherapy drugs that regulate the anti-tumor activity of T lymphocytes by blocking the PD-1/PD-L1 signaling pathway, and improving the patient's immune system response to tumors [17].

LAG-3

Lymphocyte activation gene 3 (LAG-3) is an inhibitory immune checkpoint protein that, like PD-1 and CTLA-4, is not expressed on naive T cells but can be induced on CD4+ and CD8+ T cells upon antigen stimulation, inhibiting T cell function [27]. LAG-3 has four ligands: Galectin-3, LSECtin, FGL1, and major histocompatibility complex II (MHC II). LAG-3 shares high homology with CD4 and has a higher affinity for binding to MHC II than CD4. LAG-3 competitively binds to MHC II (a shared ligand of LAG-3 and CD4), downregulating cytokine secretion and proliferative capacity of CD4+ T cells [28]. Additionally, LAG-3 can directly inhibit CD8+ T cells [29].

TIM-3

T-cell immunoglobulin and mucin domain 3 (Tim-3) is an inhibitory molecule expressed on the surface of T cells, including CD4+ Th1 cells, CD8+ cytotoxic T lymphocytes (CTLs), and Treg cells with enhanced suppressive function [30]. Like CTLA-4 and PD-1, TIM-3 is one of the most extensively studied immune checkpoint targets for immunotherapy. TIM-3 is also expressed in some innate immune cells, including DC cells, NK cells, monocytes, and macrophages. TIM-3 has four ligands: Galectin-9 (Gal-9), carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM-1), high mobility group box 1 (HMGB1), and phosphatidylserine (PtdSer). The binding of TIM-3 to its main ligand, Gal-9, inhibits the activity of helper T cells (Th1/Th17) and induces T cell exhaustion, thereby regulating T cell apoptosis and immune tolerance [31]. HMGB1 binds to DNA released from dying cells. It promotes the activation of innate immune cells through binding to receptors for advanced glycation end products (RAGE) and Toll-like receptors (TLRs), triggering innate immune cell activation and pro-inflammatory cytokine production. The binding of TIM-3 to HMGB1 can interfere with this process, thus inhibiting the activation of innate immune responses [32].

TIGIT

T-cell immunoglobulin and ITIM domain (TIGIT) is an immunoglobulin superfamily (IgSF) type I transmembrane protein. TIGIT can be expressed in T cells, regulatory T cells, memory T cells, and NK cells. TIGIT is a shared inhibitory receptor on T cells and NK cells and can inhibit the killing of tumor cells by NK cells and T cells. TIGIT has three ligands: CD155, CD112, and CD113, which are expressed on antigen-presenting cells (APCs) or tumor cells. Among the three ligands, TIGIT has the highest affinity for CD155 [33]. TIGIT inhibits T cells and NK cells through multiple mechanisms, with the most well-known mechanism being the binding of TIGIT to CD155, leading to phosphorylation of ITT-like motifs, recruitment of phosphatase 1 (SHIP-1), and ultimately inhibiting the production of IFN-gamma by NK cells. Therefore, blocking TIGIT can alleviate NK cell exhaustion and slow down tumor growth, resulting in effective anti-tumor immunity [34].

Immune-related adverse events (irAEs)

The rise of immune checkpoint inhibitors has brought hope to cancer patients. However, cancer immunotherapy is not a panacea, and it has been associated with a series of new irAEs during the treatment process. These adverse reactions are typically distinct from the well-known toxicities associated with traditional chemotherapy. In particular, the combination of immunotherapy and chemotherapy significantly increases the incidence of adverse events. Multiple meta-analyses have indicated that the toxicity rate of combination therapy with anti-PD-1, anti-PD-L1, and anti-CTLA-4 is significantly higher than that of monotherapy with anti-PD-1 or anti-PD-L1 drugs [35-37]. The inci-

dence of fatal ICI-related adverse reactions is estimated to be around 0.3% to 1.3%. Although the incidence is relatively low, these reactions often lead to devastating clinical consequences. For instance, cardiovascular complications caused by ICI treatment have a high mortality rate, frequently resulting in death due to refractory arrhythmias or cardiogenic shock. Therefore, in the future, further research on iRAEs specific to esophageal squamous cell carcinoma (ESCC) is still necessary.

Clinical trials of ICIs for the treatment of advanced ESCC

First-line treatment

Before the advent of immunotherapy, chemotherapy was the main treatment for advanced ESCC. Since 2019, with the tremendous success of clinical trials on immunotherapy, the era of immunotherapy for ESCC began. Numerous studies have been conducted on immunotherapy for advanced ESCC, constantly advancing the application of immunotherapy in ESCC treatment. Several phase III clinical trials, including ESCORT-1st, have successfully established immunotherapy as the standard first-line treatment for advanced ESCC. ESCORT-1st is a randomized, double-blind, placebo-controlled, multicenter, phase III trial. The primary endpoints were overall OS and progression-free survival (PFS). It included 596 patients from 60 hospitals in China and aimed to evaluate the efficacy and adverse events of camrelizumab combined with chemotherapy compared to placebo combined with chemotherapy as first-line treatment for advanced or metastatic ESCC. The results showed that in patients with advanced or metastatic ESCC, camrelizumab combined with chemotherapy significantly improved OS and PFS (median OS: 15.3 vs. 12 months; median PFS: 6.9 vs. 5.6 months) compared to placebo combined with chemotherapy [38].

KEYNOTE-590 is a randomized, double-blind, phase III clinical trial that included a total of 749 patients. Its objective was to evaluate the efficacy of pembrolizumab combined with chemotherapy compared to placebo combined with chemotherapy as first-line treatment for locally advanced EC or esophagogastric junction cancer, in patients with a PD-L1 combined positive score (CPS) ≥ 10. The primary endpoints were OS in ESCC patients with PD-L1 CPS ≥ 10, as well as OS and PFS in ESCC patients with PD-L1 CPS ≥ 10 and in all randomized patients. According to the mid-term analysis results published in The Lancet for KEYNOTE-590, in ESCC patients with PD-L1 CPS ≥ 10, the pembrolizumab combined with chemotherapy group significantly improved median OS (13.9 vs. 8.8 months) compared to chemotherapy alone. Furthermore, the median OS for the overall population of ESCC patients was extended by nearly 3 months (12.6 vs. 9.8 months). Significant benefits were also observed in the total population, including adenocarcinoma, and the population with PD-L1 CPS ≥ 10 [39]. The study results led to the approval of pembrolizumab combined with chemotherapy as a first-line treatment for unresectable locally advanced or metastatic EC or esophagogastric junction cancer, making pembrolizumab the first PD-1 inhibitor approved for first-line treatment of advanced EC globally and in China. It has been included in clinical practice guidelines recommended by organizations such as CSCO, ASCO, and ESMO and continues to be used. Subgroup analyses of KEYNOTE-590 for Japanese ESCC patients were also conducted, evaluating the efficacy in all Japanese patients as well as in patients with ESCC and a CPS score ≥ 10. The results showed that first-line pembrolizumab combined with chemotherapy improved overall survival and progression-free survival, with comparable safety between the treatment groups [40].

ASTRUM-007 is a randomized, double-blind, multicenter, placebo-controlled phase III clinical study led by Professor Jing Huang from the Cancer Hospital, Chinese Academy of Medical Sciences. It included 551 patients with previously untreated, locally advanced or metastatic ESCC and a PD-L1 CPS ≥ 1. The study compared sintilimab plus cisplatin plus 5-fluorouracil to placebo plus cisplatin plus 5-fluorouracil. The primary endpoints were PFS and OS. The results showed that compared to placebo plus chemotherapy, sintilimab plus chemotherapy significantly improved PFS (median PFS: 5.8 vs. 5.3 months; hazard ratio: 0.60; $P < 0.0001$) and OS (median OS: 15.3 vs. 11.8 months; hazard ratio: 0.68; $P = 0.0020$) in previously untreated PD-L1-positive advanced ESCC patients. Additionally, 201 patients (53%) in the sintilimab plus chemotherapy group and 81

patients (48%) in the placebo plus chemotherapy group experienced grade 3 or higher treatment-related adverse events. Sintilimab combined with chemotherapy significantly improved PFS and OS in previously untreated PD-L1-positive advanced ESCC patients, with manageable safety characteristics [41]. Based on the results of this study, CSCO also included sintilimab combined with chemotherapy (PD-L1 CPS ≥ 1) in the standard.

In addition, another Phase III clinical trial, RATIONNALE-306, evaluated the efficacy of camrelizumab combined with chemotherapy versus chemotherapy alone in patients with advanced or metastatic ESCC. The study enrolled 649 patients who were randomly assigned in a 1:1 ratio to the camrelizumab group or the placebo group. The combination chemotherapy group received either cisplatin/oxaliplatin plus fluorouracil or cisplatin/oxaliplatin plus paclitaxel. The chemotherapy group was selected based on stratification factors such as "geographical region" and "previous receipt of curative treatment" by the researchers. The primary endpoint of the study was OS in the intent-to-treat (ITT) population. The results showed that compared to placebo plus chemotherapy, the use of camrelizumab plus chemotherapy as first-line treatment for advanced or metastatic ESCC resulted in a significant and clinically meaningful overall survival benefit (median OS: 17.2 vs. 10.6 months; hazard ratio [HR]: 0.66; P < 0.0001). The safety profile of camrelizumab combined with chemotherapy was also manageable [42]. Based on these study results, the combination of camrelizumab and chemotherapy as first-line treatment was included in the "CSCO Guidelines for the Diagnosis and Treatment of EC (2023 edition)".

The JUPITER-06 trial was a multicenter, randomized Phase III study conducted in China for untreated advanced ESCC patients. The study compared the combination of tepotinib with chemotherapy versus chemotherapy alone as first-line treatment. The primary endpoints of the study were progression-free survival (PFS) and OS. The results showed that compared to chemotherapy alone, the combination of tepotinib with chemotherapy had higher PFS and OS as the primary endpoints (median PFS: 5.7 vs. 5.5 months; HR: 0.58) and (median OS: 17.0 vs. 11.0 months; HR: 0.58). Additionally, compared to chemotherapy alone, the combination of tepotinib with chemotherapy had a higher objective response rate (69.3% vs. 52.1%; P < 0.001). No new safety signals were observed compared to previously reported treatment methods using ICIs for advanced ESCC [43]. The study results were published in Cancer Cell in 2022, providing definitive evidence that ICIs are key drugs for first-line treatment of advanced esophageal squamous cell carcinoma.

An important Phase III clinical trial for ESCC, CheckMate-648, was reported at the ASCO conference in 2023. This study focused on immunotherapy for ESCC patients and is the largest randomized controlled trial conducted to date for ESCC patients. A total of 970 patients with previously untreated, unresectable, advanced, recurrent, or metastatic ESCC were included in the study. The patients were randomly assigned in a 1:1:1 ratio to three groups (chemotherapy alone, nivolumab plus chemotherapy, nivolumab plus ipilimumab). The primary endpoints of the study were OS and PFS. The results showed that in patients with advanced ESCC, first-line treatment with nivolumab plus chemotherapy or nivolumab plus ipilimumab significantly prolonged overall survival compared to chemotherapy alone (median OS: 13.2 vs. 10.7 months; HR: 0.74; P = 0.002) and (median OS: 12.7 vs. 10.7 months; HR: 0.78; P = 0.01). It is worth noting that the treatment was more effective for patients with PD-L1 ≥ 1% (median OS: 15.4 vs. 9.1 months; HR: 0.54; P < 0.001) and (median OS: 13.7 vs. 9.1 months; HR: 0.64; P = 0.001). In patients with tumor cell PD-L1 ≥ 1%, the combination of nivolumab and chemotherapy also demonstrated a significant progression-free survival benefit compared to chemotherapy alone (HR: 0.65; P = 0.002), but the combination of nivolumab and ipilimumab did not show a more significant progression-free survival benefit than chemotherapy alone. The safety profile of immune combination therapy was also favorable, with adverse reactions observed being common immune-related adverse events. The potential occurrence of more severe adverse events was hypothyroidism [44]. Based on the results of the CheckMate-648 study, the nivolumab plus chemotherapy or nivolumab plus ipilimumab first-line treatment regimens were also includ-

ed in the "ASCO Guidelines for the Diagnosis and Treatment of EC (2023 edition)".

In summary, recent Phase III clinical trials have demonstrated the efficacy of immunotherapy and targeted therapy in the treatment of advanced ESCC. Camrelizumab, when combined with chemotherapy, showed a significant overall survival benefit compared to chemotherapy alone. Tepotinib, in combination with chemotherapy, also improved progression-free survival and overall survival compared to chemotherapy alone. Nivolumab, either in combination with chemotherapy or with ipilimumab, extended overall survival in ESCC patients compared to chemotherapy alone, particularly in patients with PD-L1 expression. These findings have led to the inclusion of these treatment regimens in the latest guidelines for the diagnosis and treatment of EC.

Second-line therapy

Second-line therapy for ESCC primarily targets ESCC patients who experience disease progression or develop intolerance after first-line treatment. ESCORT is a randomized, open-label, multicenter Phase III study conducted in China and the first Phase III study of immunotherapy specifically for the Chinese ESCC population. The main endpoint of the study was OS. The 457 enrolled patients were randomly divided into two groups: the camrelizumab monotherapy group and the chemotherapy-alone group. The study results showed that compared to chemotherapy, camrelizumab monotherapy as second-line treatment for ESCC significantly improved the median overall survival (mOS: 8.3 vs. 6.2 months; HR: 0.71) [45].

KEYNOTE-181 is the first large Phase III randomized controlled trial comparing pembrolizumab monotherapy to standard single-agent chemotherapy in second-line treatment for EC. The overall population data was first presented at the 2019 ASCO-GI Symposium. The study included 628 patients with advanced or metastatic EC or Siewert type I adenocarcinoma of the gastroesophageal junction. Among the 222 patients with PD-L1 CPS ≥ 10, the mOS was 9.3 months in the pembrolizumab group and 6.7 months in the chemotherapy-alone group, resulting in a 31% reduction in the risk of death (HR = 0.69, P = 0.0074). Among the 401 patients with squamous cell carcinoma, the mOS was 8.2 months in the pembrolizumab group and 7.1 months in the chemotherapy-alone group (HR = 0.78, P = 0.0095). In terms of safety, the pembrolizumab group had significantly lower rates of all drug-related adverse events (64.3% vs. 86.1%) and grade 3-5 adverse events (18.2% vs. 40.9%) compared to the chemotherapy-alone group, demonstrating good safety [46].

In addition, a study reported the pre-specified health-related quality of life (HRQoL) analysis results for patients with ESCC and PD-L1 CPS ≥ 10 from KEYNOTE-181. HRQoL was measured using the QLQ-C30, QLQ-OES18, and EQ-5D instruments. The study analyzed the mean change in global health status/quality of life, physical functioning, and symptom scales from baseline to week 9 in 387 patients, as well as the time to deterioration in specific scales. The results, reported at ASCO in 2021, showed no clinically meaningful differences in overall health status/quality of life scores between the treatment groups from baseline to week 9 (mean difference: 2.80; 95% CI: -1.48 to 7.08). Both treatment groups exhibited stable scores for physical functioning, QLQ-C30, and QLQ-OES18 symptoms from baseline to week 9. The time to deterioration in pain (HR: 1.22; 95% CI: 0.79 to 1.89), reflux (HR: 2.38; 95% CI: 1.33 to 4.25), and swallowing difficulties (HR: 1.53; 95% CI: 1.02 to 2.31) scales was similar between the two treatment groups. Based on this, the overall trend in HRQoL was expected to remain consistent at week 45, and the scores for global health status/quality of life were expected to remain stable over time [47]. These HRQoL data from KEYNOTE-181 provide additional evidence for the limited quality of life in advanced ESCC patients and strongly support pembrolizumab as a second-line treatment for advanced EC.

Following the KEYNOTE-181 study, Cao et al. performed a post-hoc subgroup analysis of Asian patients. This study included a total of 340 Asian patients with advanced or metastatic ESCC enrolled in KEYNOTE-181, including a Chinese cohort. Clinical characteristics, efficacy, and safety were compared between the pembrolizumab group and the chemotherapy-alone group. The efficacy of pembrolizumab monotherapy was also evaluated at different levels of PD-L1 CPS expression (< 1, 1, 5, and

10). The results showed that in all evaluated subgroups, pembrolizumab numerically improved overall survival compared to chemotherapy (mOS: 10.0 vs. 6.5 months, HR: 0.63, P < 0.0001). This improvement was particularly significant in PD-L1-positive tumor patients (lower risk of death in patients with a PD-L1 CPS cutoff value > 1. HR [95% CI]: CPS 1, 0.57 [0.44-0.75] [48].

ATTRACTION-3 is a multicenter, randomized, open-label, Phase III trial. It aimed to evaluate the efficacy and safety of nivolumab compared to chemotherapy in patients with inoperable advanced or recurrent ESCC who were refractory or intolerant to fluoropyrimidine-based and platinum-based chemotherapy. The trial included 419 ESCC patients from 90 hospitals who were resistant or intolerant to fluoropyrimidine-based and platinum-based chemotherapy. The primary endpoint of the study was OS. The results showed a significant improvement in overall survival in the nivolumab group compared to the chemotherapy group (median OS: 10.9 vs. 8.4 months, hazard ratio: 0.77; P = 0.019). In terms of safety, the incidence of grade 3 or 4 treatment-related adverse events was significantly lower in the nivolumab group compared to the chemotherapy group (18% vs. 63%) [49]. Recently, Morihito et al. [50] reported the three-year follow-up results of ATTRACTION-3. The results showed that the 3-year overall survival rates were 15.3% and 8.7% in the two groups. Regardless of the best overall response (BOR), nivolumab demonstrated longer median overall survival compared to chemotherapy (partial response/complete response: 19.9 vs. 15.4 months; stable disease: 17.4 vs. 8.8 months; progressive disease: 7.6 vs. 4.2 months). In terms of safety, the proportion of grade 3 or higher treatment-related adverse events was lower in the nivolumab group compared to the chemotherapy group (19.1% vs. 63.9%). Compared to chemotherapy, nivolumab as a second-line therapy showed a clinically significant improvement in long-term overall survival in advanced ESCC patients previously treated with therapy, and it was well tolerated [50]. Based on the results of the ATTRACTION-3 trial, nivolumab has been established as the standard second-line treatment for advanced ESCC.

The RATIONALE-302 study is the first global Phase III study led by Chinese investigators, with Professor Lin Shen from Peking University Cancer Hospital as the principal investigator. It aimed to evaluate the efficacy and safety of trastuzumab deruxtecan compared to investigator's choice chemotherapy as second-line treatment for advanced or metastatic ESCC. The primary endpoint of the study was OS in the intention-to-treat (ITT) population. The study was conducted in 132 centers across 10 countries globally, with a total of 512 patients enrolled (404 Asian patients). The results showed a significant improvement in OS for patients in the trastuzumab deruxtecan group compared to chemotherapy (median OS: 8.6 vs. 6.3 months, hazard ratio: 0.70, one-sided P = 0.0001). In patients with a PD-L1 tumor proportion score (TPS) of ≥ 10%, the trastuzumab deruxtecan treatment group had a significantly longer median OS compared to the chemotherapy group (10.3 vs. 6.8 months), with a 46% reduction in the risk of death [51]. Van et al. assessed the health-related quality of life (HRQoL) and ESCC-related symptoms in patients from the RATIONALE-302 study. Changes from baseline to week 12 and week 18 were examined. The results showed that the trastuzumab deruxtecan group maintained overall health status/quality of life measured by the QLQ-C30, while the chemotherapy group experienced deterioration at week 12 and 18 (LS mean change difference: week 12: 5.8, P = 0.0028; week 18: 8.1, P = 0.0008). In addition, the trastuzumab deruxtecan group had less deterioration in physical functioning and fatigue, and there was also an improvement in reflux symptoms [52]. Kim et al. conducted a subgroup analysis of HRQoL in Asian patients from the RATIONALE-302 study, and the results were similar to those of Van et al. These post-hoc analysis results further support the benefits of trastuzumab deruxtecan in this patient population and suggest it as a potential new second-line treatment option for advanced or metastatic ESCC [53]. **Table 1** summarises the clinical trial information regarding the first-line and second-line treatment.

PD-L1 expression

Currently, a large number of research results and meta-analyses have confirmed the close correlation between PD-L1 expression and the efficacy of immune checkpoint inhibitors (ICIs) [54]. PD-L1 expression is an important indicator in clinical practice for guiding the selection

Table 1. Clinical trial information regarding the PD-1/PD-L1 inhibition

	Drug	Target	Phase	First/ Second Line	Sample Size	OS (months)	HR	PD-L1 Cutoff Value
ESCORT-1st	Carilizumab	PD-1	III	First Line	596	15.3 vs. 12.0	0.70	None
KEYNOTE-590	Pembrolizumab	PD-1	III	First Line	749	12.6 vs. 9.8	0.72	CPS ≥ 10
ASTRUM-007	Srilizumab	PD-1	III	First Line	551	15.3 vs. 11.8	0.68	CPS ≥ 1
RATIONNALE-306	Tislelizumab	PD-1	III	First Line	649	17.2 vs. 10.6	0.66	None
JUPITER-06	Trepelimumab	PD-1	III	First Line	514	17.0 vs. 11.0	0.58	None
CheckMate-648	Nivolumab +	PD-1 +	III	First Line	970	13.2 vs. 10.7	0.74, 0.78	TPS ≥ 1%
COMPASSION-03	Cadonilimab	PD-1/CTLA-4	I/II	First Line	22	9.4	None	None
ORIENT-15	Sindilizumab	PD-1	III	First Line	659	16.7 vs. 12.5	0.63	CPS ≥ 10
ESCORT	Carilizumab	PD-1	III	Second Line	457	8.3 vs. 6.2	0.71	None
KEYNOTE-181	Pembrolizumab	PD-1	III	Second Line	401	8.2 vs. 7.1	0.78	CPS ≥ 10
ATTRACTION-3	Nivolumab	PD-1	III	Second Line	419	10.9 vs. 8.4	0.77	None
RATIONALE-302	Tislelizumab	PD-1	III	Second Line	512	10.3 vs. 6.8	0.70	TAP ≥ 10%
CAP-02	Carilizumab	PD-1	II	Second Line	52	15.8	None	None

of patients who may benefit from immunotherapy. Based on the results of the KEYNOTE-181 trial and its subgroup analysis in Asian patients, both the National Medical Products Administration (NMPA) and the U.S. Food and Drug Administration (FDA) have approved pembrolizumab for the second-line treatment of PD-L1-positive (CPS ≥ 10), advanced or metastatic squamous cell carcinoma of the esophagus (ESCC). It is recommended that PD-L1 expression in cancer tissue be evaluated using the CPS scoring system. The PD-L1 (Dako 22C3) assay kit has been approved as a companion diagnostic for pembrolizumab treatment in ESCC, with a CPS ≥ 10 considered as a positive criterion. Based on the results of the KEYNOTE-590 study, the European Medicines Agency (EMA) has approved the use of pembrolizumab in combination with chemotherapy as a first-line treatment for advanced or metastatic ESCC, with a requirement of PD-L1 CPS ≥ 10. Based on the results of the CheckMate-648 study, EMA has approved the combination of nivolumab and ipilimumab as a first-line treatment for advanced or metastatic ESCC, with a requirement of PD-L1 (28-8) TPS ≥ 1%. For ESCC patients with low PD-L1 expression, Yap et al. conducted a meta-analysis of the low PD-L1 expression subgroup in previous clinical trials. A total of 4,752 patients from randomized clinical trials, including CheckMate-648, ESCORT-1st, KEYNOTE-590, ORIENT-15, KEYNOTE-181, ESCORT, RATIONALE-302, ATTRACTION-3, and ORIENT-2, were included in the analysis. The results showed that in the pooled analysis of first-line trials evaluating TPS (CheckMate-648 and ESCORT-1st), immune therapy did not significantly improve OS compared to chemotherapy in the subgroup of patients with TPS < 1% (HR: 0.91). In the pooled analysis of CPS trials (KEYNOTE-590 and ORIENT-15), immune therapy showed a significant but moderate OS benefit compared to chemotherapy in the subgroup with CPS < 10 (HR: 0.77). Therefore, in the subgroup with TPS < 1%, immune-based first-line treatment lacked survival benefits compared to chemotherapy alone [55].

The PD-L1 scoring systems used in clinical studies of ESCC immunotherapy include CPS, TPS, and TAP scores, and the 22C3, 28-8, and SP263 clones of antibodies are widely recognized internationally. In the KEYNOTE-181 study, PD-L1 IHC 22C3 pharmDx was used to detect CPS. In the CheckMate 648 study, PD-L1 IHC 28-8 pharmDx was used to determine TPS. In KEYNOTE-590, PD-L1 IHC 22C3 assay was used to determine CPS. In the RATIONALE 302 study, VENTANA PD-L1 (SP 263) detection and TAP scoring were used to evaluate PD-L1 expression [56]. The antibodies, detection methods, and cutoff values used for PD-L1 expression testing in different studies differ. Other factors may lead to variations in the test results, which ultimately affect the selection of treatment regimens. Currently, there have been several studies on the concordance of PD-L1 expression testing using immunohistochemistry in clinical analysis. However, the research on the consistency of PD-L1 expression testing

in ESCC patients is still limited and further research is needed [57, 58].

Resistance to ICIs

Combination therapy with ICIs

The use of ICIs in the second-line treatment and beyond for advanced ESCC has become a recommended option. However, the median survival is only 8.3 to 10.9 months, and compared to the chemotherapy group, the risk of death only decreases by about 22% to 30%. This indicates that there are still some patients who may not achieve significant survival benefits due to primary or acquired resistance [59]. Therefore, it is still necessary to explore more effective treatment options for these patients. Although drugs targeting PD-1 and CTLA-4 have been successful in the clinical treatment of various tumors, their efficacy is still unsatisfactory in some tumors, prompting researchers to continue exploring new immune checkpoints. TIGIT antibodies, as emerging immune checkpoints in recent years, are regarded as the most promising next-generation immune checkpoints. Currently, there are more than 10 TIGIT antibodies in clinical research, but no drugs targeting this immune checkpoint have been approved for marketing worldwide. Based on the current favorable clinical research results, TIGIT is expected to block the TIGIT signaling pathway in combination with PD-1/PD-L1 inhibitors. In this regard, two clinical studies for advanced ESCC patients are currently underway: NCT04732494 is a Phase II clinical trial aimed at evaluating the efficacy and safety of Arelituzumab in combination with ociperlimab (TIGIT antibody) compared to Arelituzumab monotherapy plus placebo as second-line treatment for unresectable, locally advanced, recurrent, or metastatic ESCC patients with PD-L1 tumor proportion score (TPS) ≥ 10%. The final results will be announced in 2024. NCT04543617 is a Phase III clinical trial aimed at evaluating the efficacy and safety of Atezolizumab in combination with or without Tiragolumab (TIGIT antibody) in the treatment of unresectable ESCC and synchronous definitive chemoradiotherapy (dCRT) non-progression patients. The final results will be announced in 2027. The combination therapy of LAG-3 and TIM-3 inhibitors with PD-1 inhibitors has been studied in several clinical Phase I/II trials in solid tumors or non-small cell lung cancer, exploring the issues of dosing and toxicity [60-64]. However, there is still a lack of clinical trials explicitly targeting advanced ESCC patients.

In addition, dual immune checkpoint inhibitors have also emerged as a novel immunotherapy in recent years. COMPASSION-03 is a multicenter, open-label, Phase Ib/II trial aimed at evaluating the safety and antitumor activity of Cardonilib, a dual-specific PD-1/CTLA-4 antibody, as monotherapy in patients with advanced solid tumors. Cardonilib is the world's first PD-1/CTLA-4 dual-specific antibody developed independently in China, targeting both PD-1 and CTLA-4 immune checkpoints. The study included patients who had previously failed systemic therapy and excluded patients who had received anti-PD-1, anti-PD-L1, or anti-CTLA-4 treatment. Among them, there were 22 ESCC patients. The safety and objective response rate of Cardonilib as monotherapy were observed in the Phase Ib and Phase II stages, respectively. The results showed that no dose-limiting toxicities occurred during the dose escalation phase of the Phase Ib trial, and Cardonilib demonstrated overall good safety. In the Phase II clinical trial, Cardonilib monotherapy achieved a median overall survival of 9.4 months in advanced ESCC patients who had previously failed no more than first-line systemic therapy. Therefore, Cardonilib showed promising tumor response rates and manageable safety, indicating its potential in the treatment of advanced solid tumors [65]. This study was published on October 3, 2023, in The Lancet Oncology and is the first multicenter clinical study targeting PD-1/CTLA-4 dual immune checkpoint inhibitors in the treatment of advanced solid tumors. Previously, the research team reported two-year follow-up data of a Phase Ib/II clinical study of Cardonilib in combination with chemotherapy as first-line treatment for gastric/gastroesophageal junction (G/GEJ) adenocarcinoma at the 2023 ASCO Annual Meeting, demonstrating excellent efficacy and manageable safety in populations with high, low, or negative PD-L1 expression. This study is expected to bring iterative therapies for first-line treatment of advanced ESCC, and dual immune checkpoint inhibitors such as PD-1/LAG-3, PD-1/TIM-3 have also been studied in Phase I clinical trials for solid tumors or hematological cancer, demonstrating

good safety [66, 67]. For advanced ESCC patients, a Phase II clinical trial is currently underway. NCT04785820 aims to evaluatethe efficacy and safety of the combination of Pembrolizumab (PD-1 inhibitor) and LAG525 (LAG-3 inhibitor) in patients with advanced ESCC who have progressed after first-line chemotherapy. The final results of this trial are expected to be announced in the future.

Immune checkpoint inhibitors combined with targeted therapy

Immune evasion plays a crucial role in the occurrence and progression of ESCC [68]. Therefore, it is necessary to implement a multidisciplinary combined treatment that targets the mechanisms of ESCC immune evasion. Currently, another treatment option for patients resistant to immunotherapy is the combination of immunotherapy and targeted therapy [69]. Targeted therapy, as a novel treatment approach, has been proven to play an important role in the treatment of ESCC.

Although ESCORT has demonstrated the potential of camrelizumab in the second-line treatment of advanced ESCC, the results are still unsatisfactory. The objective response rate (ORR) of second-line immunotherapy as a single agent for ESCC is only about 13-20%, and the improvement in OS is not significant, even in the population with positive PD-L1 expression, the OS improvement is only 3 months. Therefore, a phase III study of immunotherapy for Chinese ESCC patients, called CAP 02, has been conducted. This study is a single-arm, open-label, phase II clinical trial. It still includes ESCC patients who have failed first-line immunotherapy and aims to evaluate the efficacy and safety of camrelizumab combined with apatinib in the immunotherapy-treated population. The primary endpoint of the study is the investigator-assessed confirmed objective response rate. The study results showed a confirmed ORR of 34.6%, median progression-free survival (mPFS) of 6.8 months, and median overall survival (mOS) of 15.8 months. It confirmed the potential antitumor activity and safety of camrelizumab combined with apatinib [70]. At the same time, the results of CAP 02 suggest that anti-tumor angiogenesis and inhibition of tumor immune escape have a synergistic effect, and multi-target tyrosine kinase inhibitors (TKIs) targeting angiogenesis are a promising choice for immunotherapy combination regimens.

Anlotinib is a novel multi-target TKI targeting VEGFR1-3 and is a potential first-line combination therapy and second-line monotherapy drug for Chinese ESCC patients. It is also recommended by CSCO as a recommended drug for the second-line and subsequent treatment of advanced ESCC. A single-arm, multicenter, open-label phase II clinical trial (ALTER-E003) investigated the efficacy and safety of TQB2450 combined with anlotinib as first-line treatment for advanced ESCC (TQB2450 is a novel PD-L1 inhibitor developed in China). The primary endpoint was ORR. The interim results showed that among the 23 evaluable patients included in the study, the best overall response evaluation was as follows: partial response (PR) in 14 cases (60.9%), stable disease (SD) in 8 cases (34.8%), and unevaluable (NE) in 1 case (4.4%). The preliminary ORR was 60.9%, and the disease control rate (DCR) was 95.7%. As of the data cutoff date, no patients had disease progression, and the safety analysis showed tolerability without generating new safety signals [71]. Therefore, preliminary results suggest that the combination of anlotinib and TQB2450 as first-line treatment for advanced ESCC has encouraging efficacy and manageable adverse events. However, these conclusions still need to be confirmed in subsequent trials.

In 2022, ESMO reported a phase II study of regorafenib combined with nivolumab in the treatment of recurrent and metastatic solid tumors. Regorafenib is also a small molecule TKI that activates and enhances the functions of natural killer cells and CD8+ T cells while inhibiting the functions of tumor-associated macrophages. The study results showed an objective response rate (ORR) of 43% and a median progression-free survival (mPFS) of 6.9 months among the 29 evaluable patients. The ORR was 71% in 7 PD-L1-positive patients and 36% in 14 PD-L1-negative patients, without the generation of new safety signals [72]. Therefore, the regimen of regorafenib combined with nivolumab is feasible for the treatment of patients with recurrent and metastatic solid tumors. The publication of these trial results will also support future clinical trials on the combination use of regorafenib.

In addition to TKIs, the combination of fibroblast growth factor receptor (FGFR) inhibitors and immune checkpoint inhibitors (ICIs) is also being explored as a new strategy for cancer patients. FGFR inhibitors can enhance the sensitivity of ICIs by directly acting on cancer cells or the tumor microenvironment (TME) [68]. These findings suggest that the combination of FGFR inhibitors and ICIs, such as futibatinib and pembrolizumab, may have potential as a treatment option for advanced ESCC. Overall, Immune checkpoint inhibitors combined with targeted therapy shows a promising effect on the advance ESCC (**Table 2**).

The efficacy and safety of ICIs in the treatment of advanced ESCC

Since the advent of ICIs, significant clinical benefits have been observed for patients with advanced ESCC. The results of the aforementioned clinical studies (**Table 1**) and related meta-analyses indicate that the use of ICIs in first-line, second-line, and subsequent treatments significantly improves patients' overall survival (OS). Moreover, ICIs demonstrate better safety profiles with fewer grade 3-5 treatment-related adverse events (TRAEs) [73]. In first-line treatment, ESCC patients receiving ICIs (immune checkpoint inhibitors) combined with paclitaxel/platinum (TP) exhibit significantly higher objective response rates (ORR), disease control rates (DCR), progression-free survival (PFS), and overall survival (OS) rates compared to patients receiving ICIs combined with fluoropyrimidine/platinum (FP). The pooled incidence of treatment-related deaths does not show a significant statistical difference between the two groups. ICIs combined with TP demonstrate higher rates of hematological toxicity but lower rates of gastrointestinal toxicity compared to ICIs combined with FP. Therefore, for patients with advanced ESCC, first-line treatment with ICIs combined with TP may result in better clinical outcomes [74, 75]. In second-line chemotherapy, PD-1 inhibitors have shown significant improvements in overall survival (OS) and objective response rate (ORR) for patients with advanced ESCC, particularly in those who are PD-L1 positive. However, there is no significant improvement observed in progression-free survival (PFS) and disease control rate (DCR) [76].

Discussion

In summary, the combination of immune checkpoint inhibitors (ICIs) with targeted therapies has shown promise in the treatment of ESCC. Clinical trials have evaluated various combinations, including ICIs with angiogenesis inhibitors, PD-L1 inhibitors with multi-target tyrosine kinase inhibitors (TKIs), and ICIs with FGFR inhibitors. These combinations have demonstrated encouraging efficacy and manageable safety profiles. However, further trials and research are needed to establish the optimal treatment regimens and to validate the results obtained from these early studies.

More than 50% of ESCC patients have overexpression of the epidermal growth factor receptor (EGFR) [77]. Nimotuzumab, a fully recombinant humanized anti-EGFR monoclonal antibody, is the first monoclonal antibody used for the treatment of malignant tumors in China. Many studies have confirmed its effectiveness and safety in increasing sensitivity to chemotherapy and radiotherapy. In 2022, ASCO released a partial research summary on the efficacy and safety of nimotuzumab combined with concurrent chemoradiotherapy compared to placebo in unresectable locally advanced ESCC (NXCEL1311). A mid-term analysis of short-term efficacy and safety was conducted after 6 months of follow-up. The results showed that the objective response rate (ORR) in the nimotuzumab group was significantly higher than in the placebo group (93.8% vs. 72.0%); the complete response rate (CR) was also significantly higher in the nimotuzumab group (32.5% vs. 12.2%) [78]. Based on the mid-term results, it can be concluded that nimotuzumab combined with chemoradiotherapy is safe and can improve the complete response rate (CRR) and ORR in treated patients. OS results still need further follow-up for final analysis. In addition, the LEAP-014 study is currently underway, which uses a combination of chemotherapy, immunotherapy, and the anti-vascular endothelial growth factor (VEGF) drug lenvatinib. We also look forward to the further survival benefits that the four-drug combination regimen may bring to patients.

In conclusion, with the advent of the immunotherapy era, immune checkpoint inhibitors (ICIs) have brought new hope for the treatment

Table 2. Immune checkpoint inhibitors combined with targeted therapy

Trial Name/ID	Phase	Design Type	Study Arm	Control Arm	Primary Endpoints	Start Date	Estimated End Date
SKYSCRAPER 08	III	Two-arm	Tiragolumab + Atezolizumab + Paclitaxel + Cisplatin	Atezolizumab + Placebo + Paclitaxel + Cisplatin	OS, PFS	2020.10	2025.8
ESCORT-RWS	Real-world	Observational	Carilizumab	None	Adverse Events (AE)	2020.12	2026.12
AdvanTIG-203	II	Two-arm	Tislelizumab + Ociperlimab	Tislelizumab + Placebo	Objective Response Rate (ORR)	2021.3	2024.2
SKYSCRAPER-07	III	Three-arm	Atezolizumab + Tiragolumab	Atezolizumab + Tiragolumab-equivalent placebo/Atezolizumab-equivalent placebo + Tiragolumab-equivalent placebo	PFS, OS	2020.9	2027.3
NCT04785820	II	Three-arm	Lomvastomig (RO7121661)/Tobemstomig (RO7247669)	Nivolumab	OS	2021.6	2025.6
ALTER-E003	II	Single-arm	Anlotinib + TQB2450	None	ORR	2022.3	2024.9
LEAP-014	III	Two-arm	Pembrolizumab + Lenvalinib + Investigator's Choice Chemotherapy (Cisplatin, 5-FU, Oxaliplatin, Capecitabine, Leucovorin, Paclitaxel)	Pembrolizumab + Investigator's Choice Chemotherapy (Cisplatin, 5-FU, Oxaliplatin, Capecitabine, Leucovorin, Paclitaxel)	Dose-limiting Toxicities (DLT), AE, Number of Participants Discontinuing Treatment Due to AE, OS, PFS	2021.7	2025.12
NXCEL1311	III	Two-arm	Nintedanib + Radiotherapy + Chemotherapy (Paclitaxel + Cisplatin)	Placebo + Radiotherapy + Chemotherapy (Paclitaxel + Cisplatin)	OS	2015.3	2021.12

of advanced and metastatic diseases. Unprecedented clinical responses have changed the treatment landscape for various malignancies, including EC, as well as malignant melanoma, metastatic lung cancer, and metastatic renal cancer, driving ICIs to the forefront of treatment. However, a significant portion of patients still do not show substantial responses to ICI immunotherapy. The mechanisms of primary and acquired resistance to immune therapy are not yet clear. Further research is needed on tumor microenvironment, response molecular mechanisms, and ICI resistance. In addition, better biomarkers need to be identified to provide prognostic information for precise patient selection and the choice of the most suitable treatment strategy.

ESCC exhibits high heterogeneity, and there are significant biological and clinical differences between Eastern and Western patients, which pose challenges to clinical research. For example, the subgroup analysis of Asian patients in the KEYNOTE-181 study showed a significantly higher degree of benefit in the Asian subgroup, indicating that patients from different countries and regions can achieve varying degrees of benefit. Therefore, future hierarchical analyses should consider more influencing factors. In addition, as a country with a high incidence of EC, China has a great clinical demand for ESCC drug treatment, so more research is needed on Chinese ESCC patients to develop treatment strategies that are more suitable for the Chinese population. Currently, research on advanced and metastatic ESCC patients in China is gradually becoming more specific. Researchers are focusing more on studying treatment strategies that are more in line with Chinese ESCC patients, such as the ESCORT-RWS real-world study, post-analysis of Asian subgroups in other global studies, and Chinese cohorts.

ICIs have shown very positive effects in the treatment of advanced ESCC patients. Researchers are also constantly exploring multidisciplinary combination treatments with immunotherapy as the core. The success of dual immune therapy in the CheckMate-648 study and immune combination targeted therapy in the CAP-02 study suggests that "chemotherapy-free" approaches can also provide significant survival benefits and are more suitable for advanced ESCC patients who are intolerant to chemotherapy. Therefore, exploring more drug combination treatments is essential. Immune combination therapy regimens or monotherapy with dual immune checkpoint inhibitors are emerging treatment strategies and one of the main directions of future research. However, the simultaneous use of multiple drugs can also lead to greater side effects, so the associated adverse effects of drug combination therapy should not be overlooked. In summary, the optimization of the combination mode and dosage of different drugs to maximize efficacy and minimize adverse reactions is the leading research direction for the future of ICIs, providing more personalized treatment options for patients with advanced ESCC.

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Disclosure of conflict of interest

None.

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