

Changing landscape of advanced esophageal squamous cell carcinoma: Breakthroughs in systemic therapies (Review)

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Abstract. The treatment of advanced esophageal squamous cell carcinoma (ESCC) presents numerous challenges. Whereas conventional therapies such as chemotherapy, radiotherapy and targeted treatments have achieved some success. However, the substantial heterogeneity of the disease poses challenges in achieving comprehensive therapeutic coverage through a single treatment approach, because molecular subtyping remains insufficiently defined. Consequently, the response rate to targeted therapies is limited. Moreover, the issue of resistance to immunotherapy is becoming increasingly prominent, and reliable predictive biomarkers are lacking. Additionally, the regulatory mechanisms of the tumor microenvironment in metastatic lesions require further investigation. In recent years, the advent of immunotherapy and novel drug development has brought new hope, particularly with the clinical application of antibody-drug conjugates, bispecific antibodies, novel immune checkpoint inhibitors, new targeted therapies, and cell and vaccine therapies, which have markedly improved patient survival. The present review summarizes the current therapeutic landscape for advanced ESCC and discusses the potential of future treatment strategies. Despite improvements in survival rates with existing treatments, the integration of emerging therapies with precision medicine may become key to future ESCC management, through driving personalized treatment approaches and multidisciplinary collaboration, and ultimately improving patient quality of life and clinical outcomes.

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1. Introduction

Esophageal cancer (EC), a leading cause of cancer-related mortality worldwide, shows significant geographic variation in incidence and mortality. According to the International Agency for Research on Cancer, EC is the sixth deadliest cancer globally, and >510,000 new cases and >440,000 EC-related deaths were reported in 2020 (1,2). In Asia, particularly in China and parts of Iran and Africa, esophageal squamous cell carcinoma (ESCC) is the predominant type, accounting for >90% of all EC cases, whereas adenocarcinoma is more common in Western countries, and has a higher incidence in men than women (3,4).

The high incidence of ESCC is associated with multiple factors, including genetic susceptibility, dietary habits (for example, consumption of salted, hot foods, and smoking and alcohol use), and environmental pollution (5). Because of its insidious early symptoms, numerous patients are diagnosed in locally advanced or metastatic stages, when the tumor has limited responsiveness to standard treatments. Despite advances in therapeutic approaches, ESCC remains more challenging to treat than esophageal adenocarcinoma, and clinical hurdles such as drug resistance, recurrence and metastasis remain substantial (6). Thus, beyond early screening and diagnosis, developing effective new systemic therapies remains a major challenge.

The present review is aimed at providing a comprehensive evaluation of the current state of treatment for advanced ESCC, with a focus on novel drug development, clinical trial advancements, and future treatment directions. By summarizing current research progress, the authors hope to offer insights for future clinical research and drug development that may aid in further optimization of ESCC treatment strategies.

2. Current treatment landscape

Treatment for advanced ESCC typically involves a combination of various modalities, including chemotherapy, radiotherapy, targeted therapies and immunotherapy. Each treatment option has its own advantages and limitations, and treatment choice often depends on each patient's pathology, staging, overall health and individual characteristics (7,8).

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Chemotherapy. Chemotherapy remains a standard treatment for advanced EC, particularly for patients who are not candidates for surgery or who have experienced recurrence after surgery. Frequently used chemotherapy agents include platinum-based drugs (cisplatin and oxaliplatin), fluoropyrimidines (5-fluorouracil or capecitabine), docetaxel, paclitaxel and irinotecan (9). However, chemotherapy is associated with significant toxicity, and long-term use often leads to drug resistance and immunosuppression, thus affecting patient quality of life.

Platinum and fluoropyrimidine combination therapies are first-line treatments for advanced ESCC (10). Platinum compounds act by binding DNA, and subsequently inhibiting replication and repair, whereas fluoropyrimidines interfere with nucleic acid metabolism, thereby inhibiting cell division (11,12). This combination has demonstrated clinical efficacy in symptom relief and survival extension. Multiple trials have shown an overall response rate (ORR) of 40-55%, progression-free survival (PFS) of 5-6 months, and overall survival (OS) of 9-12 months with this regimen in treatment-naïve patients (13-15). Nevertheless, significant adverse effects, such as hematological toxicity (neutropenia 40-60% and anemia 30-50%), gastrointestinal reactions (cisplatin emesis rate 70-90%), cisplatin-related nephrotoxicity (20-30%) and oxaliplatin neurotoxicity (60-80%), limit its use, and numerous patients develop resistance over time (16). Other agents such as docetaxel, paclitaxel (microtubule inhibitors), and irinotecan (a topoisomerase I inhibitor) are frequently used second- or third-line treatments for advanced or metastatic ESCC (9,17,18). These drugs have been shown to provide limited clinical benefit in patients with resistant tumors, with response rates of 6-9%, a PFS of 2-3 months, and an OS of 6-7 months (19-21). However, these agents are also limited by their toxicity, including bone marrow suppression (neutropenia 40-80%, with grade ≥ 3 accounting for 15-40%), peripheral neuropathy (30-60%), allergic reactions (paclitaxel 10-30%), fluid retention (docetaxel 20-30%), delayed diarrhea (20-35%, with grade ≥ 3 accounting for 10-20%) and cholinergic syndrome (acute diarrhea/sweating, 30-50%).

Because chemotherapy effectiveness diminishes with continued use, patients often experience disease progression, whereas adverse effects significantly affect quality of life, particularly with high-dose regimens leading to severe bone marrow suppression and immunosuppression (22).

Radiotherapy. For patients with locally advanced, unresectable ESCC, radiotherapy plays a key role in controlling symptoms such as dysphagia, pain and bleeding (23). Radiotherapy delivers high-energy radiation, which eliminates cancer cells and inhibits tumor growth, but also can damage surrounding tissues, thereby leading to severe complications including esophageal perforation and radiation-induced esophagitis (24). Chemoradiotherapy (CRT), the combination of radiotherapy with chemotherapy, is a frequently applied strategy for treating advanced ESCC. This approach enhances the cytotoxic effects of chemotherapy on tumor cells and provides additional therapeutic support when chemotherapy alone is insufficient (25). Common regimens include cisplatin or fluoropyrimidine-based CRT, which has been shown to improve treatment outcomes by mitigating the limitations of either modality used alone (26).

In the NEOCRTEC5010 phase III study, the R0 resection rate with neoadjuvant CRT combined with surgery was 98.4%, a value markedly higher than the 91.2% observed in the group receiving surgery alone ($P=0.002$); moreover, the combined treatment decreased the local and distant recurrence rates (27). In the TREC study, tislelizumab combined with radiotherapy achieved a pathological complete response rate (pCR) of 66.7% (28). In the phase II study of toripalimab combined with chemotherapy + radiotherapy in advanced ESCC, the objective response rate (ORR) was 57.7%, the 1-year PFS rate was 50%, and the 1-year OS rate was 76.9%, but a 9.1% rate of severe adverse reactions, such as esophageal fistula, was observed. In the TENERGY study, the clinical complete response (CR) rate after sequential atezolizumab following CRT was 42.1%, and the median OS was 31 months. The main adverse reactions of radiotherapy included acute reactions, such as radiation esophagitis (70-90%, grade ≥ 3 accounting for 15-30%), bone marrow suppression (leukopenia 30-50%), radiation pneumonitis (10-20%), and skin reactions (erythema/desquamation, 20-40%); the main late complications were esophageal stenosis (15-25%), pulmonary fibrosis (5-15%), and cardiac toxicity (5-10%, after mediastinal radiotherapy). Overall, the synergistic strategy of immunotherapy and radiotherapy has increased efficacy while maintaining an acceptable toxicity level and is gradually becoming an important treatment for locally advanced and advanced ESCC. However, more phase III data remain needed to support its role in first-line treatment.

Targeted therapy. Targeted therapy represents a major advancement in ESCC treatment. Targeted drugs specifically interact with molecular targets expressed in cancer cells, and inhibit tumor growth and spread with greater selectivity and fewer adverse effects than traditional chemotherapy (29). Unlike esophageal adenocarcinoma, for which human epidermal growth factor receptor2 (HER2)-targeted therapy is well-established, the lack of clearly defined and effective molecular targets in ESCC complicates treatment. Although no targeted therapies have been approved specifically for ESCC, drugs targeting broad-spectrum tumor types (such as entrectinib and larotrectinib for NTRK gene fusions, dabrafenib and trametinib for BRAF mutations, and selpercatinib for RET fusions) are being explored in second-line or later treatments for ESCC, but only a small subset of patients benefit from these therapies (30-32). The main adverse reactions of targeted therapy for ESCC vary by drug type: anti-EGFR drugs (such as cetuximab) commonly cause acneiform rash (60-80%, grade ≥ 3 accounting for 5-15%), diarrhea (30-50%), and hypomagnesemia (20-30%), whereas anti-angiogenic drugs (such as ramucirumab) may lead to hypertension (15-25%, grade ≥ 3 accounting for 5-10%), proteinuria (10-20%) and bleeding risk (3-8%) (33). With the advent of high-throughput sequencing technologies, researchers have identified several potential targets for ESCC, including epidermal growth factor receptor (EGFR), fibroblast growth factor receptor (FGFR), vascular endothelial growth factor (VEGF), yes associated protein 1 (YAP1) and cyclin-dependent kinase 4/6 (CDK4/6). Ongoing clinical trials are evaluating new therapies against these targets (34).

Immunotherapy. Immunotherapy has emerged as a promising strategy for advanced ESCC, particularly with the

introduction of immune checkpoint inhibitors (ICIs). ICIs, such as PD-1/PD-L1 inhibitors (nivolumab, pembrolizumab and dostarlimab), have shown significant progress in clinical applications, by blocking tumor immune escape mechanisms and reactivating the body's immune response to attack cancer cells (35). In ICI-naïve patients with cancer progression after first-line chemotherapy, nivolumab and pembrolizumab have shown groundbreaking results. With these agents, compared with other second-line conventional chemotherapies (paclitaxel/docetaxel/irinotecan), all patients benefit regardless of whether PD-L1 expression is high. Moreover, these agents have shown improvements in ORRs from 6-9% to 16-20%, and a survival benefit of OS extended from 6-7 months to 8-10 months, regardless of PD-L1 expression levels (35,36). Furthermore, phase III trials such as Keynote-590 and Checkmate-648 have established ICIs as part of a first-line ESCC treatment achieving an ORR as high as 65-70% and an OS of 15-17 months in combination with chemotherapy (37,38). The main adverse reactions of immunotherapy for ESCC (PD-1/PD-L1 inhibitors) are immune-related adverse events (irAEs), with an incidence rate of ~15-30% (grade ≥ 3 accounting for 5-10%). The most common adverse reactions include skin toxicity (rash/itching, 10-20%), endocrine abnormalities (hypothyroidism 5-10% and hypophysitis 1-3%), gastrointestinal toxicity (colitis 2-5% and hepatitis 1-3%), and pneumonia (1-5%). Severe but rare toxicities include myocarditis (<1%) and myasthenia gravis (<0.5%) (28).

Although immunotherapy offers distinct advantages in terms of selectivity, fewer adverse effects, and prolonged responses, not all patients benefit, and resistance remains a challenge. Additionally, irAEs, such as hepatitis and pneumonitis, require careful management (39). The therapeutic landscape for advanced ESCC continues to evolve, and novel approaches such as immunotherapy and targeted treatments are reshaping clinical practice. However, issues such as individual variability in treatment response, drug resistance, and adverse effects remain major challenges. Addressing these challenges requires further research, clinical trials, and the development of more effective, personalized therapies.

3. Advances and innovative therapies

Despite the high global incidence of ESCC, research and drug development for ESCC have lagged behind those for esophageal adenocarcinoma. However, in regions with high ESCC prevalence, such as Asia, clinical trials and research have increased. The unique biological and clinical characteristics of ESCC pose significant treatment challenges (3,8). Nevertheless, advancements in new drug development and innovative treatment strategies, including novel targeted therapies, immunotherapies, personalized treatments and cellular therapies, offer new hope for advanced ESCC.

Novel-targeted chemotherapy: ADC. Chemotherapy remains a frequently used approach for treating advanced EC. However, traditional chemotherapeutic agents, such as cisplatin and fluorouracil, often lead to drug resistance and significant toxicity after prolonged use. Consequently, interest in developing new chemotherapeutic agents that can enhance local drug concentration, overcome resistance, and reduce toxicity, is increasing.

A promising innovation in this area is antibody-drug conjugates (ADCs) (40,41). ADCs are composed of three key components: A monoclonal antibody with high specificity and affinity, a highly stable linker, and a potent cytotoxic small molecule drug. By leveraging the targeting ability of monoclonal antibodies, ADCs can precisely deliver cytotoxic drugs to tumor cells expressing specific antigens, thereby achieving targeted therapy (42). As of 2024, several ADCs have been approved globally, including enfortumab vedotin, brentuximab vedotin, trastuzumab emtansine, sacituzumab govitecan, mirvetuximab soravtansine, trastuzumab deruxtecan, and polatuzumab vedotin. However, none are currently approved for ESCC, although numerous clinical trials are underway.

At the 2023 EMSO conference, Daiichi Sankyo revealed results for B7H3-targeting ADC I-Dxd in pre-treated patients with ESCCs. Among 28 patients, six achieved partial response, with a confirmed ORR (cORR) of 21%, a median PFS (mPFS) of 2.7 months, and a median OS of 7 months (43). Grade ≥ 3 treatment-emergent adverse events (TEAEs) occurred in 43.7% of patients, whereas only 8% discontinued treatment because of TEAEs. The most common grade ≥ 3 TEAEs included anemia (19.0%), neutropenia (4.0%), nausea (3.4%), and lymphopenia (3.4%), and the safety and tolerability profiles were generally favorable. Additionally, Daiichi Sankyo initiated a phase III clinical trial (NCT06644781) focused on ESCC, which is expected to start in February 2025 with 510 participants. Several other B7H3 ADCs, such as HS-20093 and YL201, have shown promising early-phase results and are undergoing phase III trials (44).

Nectin-4, a protein expressed in multiple solid tumors, was a key focus at the 2024 ASCO conference. A phase I/II study has reported that in patients with ESCC who had previously received chemotherapy and immunotherapy, treatment with Nectin-4 ADC 9MW2821 at 1.25 mg/kg (n=30) led to an ORR of 30% and a disease control rate (DCR) of 73.3%. Treatment-related adverse events (TRAEs) occurred in 63.5% of patients (n=85), and 35.3% experienced grade ≥ 3 TRAEs (45). Similarly, a trial of the Nectin-4-targeting ADC SHR-A2102 by Hengrui Pharmaceuticals is actively recruiting patients. The TROP2-targeting ADC Trodelvy has shown limited efficacy in early studies in gastrointestinal tumors, including an ORR of only 5.3% in ESCC (46). However, Merck has initiated a clinical trial of TROP2 ADC in the treatment of ESCC (KEYMARKER-U06), whose results are awaited.

BL-B01D1, an ADC derived from bispecific antibodies targeting EGFR and HER3, was presented at the 2024 ESMO conference. In 74 evaluable patients with ESCC, the ORR was 35.1% (cORR: 32.4%), the DCR was 73.6%, and the median PFS was 4.3 months. At the recommended phase 2 dose of 2.5 mg/kg, the ORR was 44.2% (cORR: 40.4%), the DCR was 80.8%, the median PFS was 5.4 months, and the median duration of response was 6.6 months (47). The most common grades were TRAEs including anemia (28.3%), leukopenia (18.3%), thrombocytopenia (18.3%), neutropenia (16.7%) and lymphopenia (15.0%). Two cases of interstitial lung disease were observed, but no new safety signals were detected (48). A phase III randomized controlled trial (NCT06304974) for second-line treatment of ESCC has commenced enrollment, with a target of 488 patients with ESCC.

Table I. Novel antibody-drug conjugate therapies for esophageal squamous cell carcinoma.

First author/s, year	Drugs	Antibody	Payload	Line	Arm	Outcome	(Refs.)
Paz-Manrique <i>et al</i> , 2024	I-Dxd	B7H3	Dxd	≥2	Single arm	ORR, 21%; mPFS, 2.7 months; mOS, 7.0 months	(40)
Colombo <i>et al</i> , 2026	9MW2821	Nectin-4	MMAE	≥2	Single arm	ORR, 30%; DCR 73.3%	(42)
Patel <i>et al</i> , 2023	SKB264	Trop-2	SN-38	≥2	Single arm	ORR, 5.3%; mPFS, 3.4 months; mOS, 7.2 months	(43)
Ma <i>et al</i> , 2025	BL-B01D1	EGFR/ HER3	Ed-04	≥2	Single arm	ORR, 35.1%; DCR, 73.6%; mPFS, 4.3 months	(44)
Chalouni <i>et al</i> , 2018	YL201	B7H3	YL0014	≥2	Single arm	ORR, 25.0%; mPFS, 4.8 months	(41)

MMAE, microtubule inhibitors; Topo I inhibitors: Dxd, Ed-04, YL0014; B7H3: CD267; nectin-4, nectin cell adhesion molecule 4; Trop-2, trophoblast cell surface antigen-2; EGFR, epidermal growth factor receptor; HER3, human epidermal growth factor receptor 3; ORR, overall response rate; DCR, disease control rate; mOS, median overall survival; mPFS, median overall survival.

Despite the limited development of ADCs for ESCC, other highly expressed molecular targets, such as Claudin 18.2, have shown efficacy in gastric cancer, and their potential to improve survival outcomes may soon be explored for ESCC. However, the heterogeneity of target expression in ESCC presents challenges for ADC efficacy because target levels may vary significantly between patients and tumor regions. Additionally, as with other targeted therapies and chemotherapies, ADCs might induce resistance, because tumor cells can alter target expression or enhance drug efflux mechanisms to evade treatment. Whereas ADCs offer precise delivery of cytotoxic agents to tumor cells, off-target effects may still occur and cause systemic toxicities, such as bone marrow suppression and liver damage (49,50). Identifying patients sensitive to ADCs, exploring combination therapies with immunotherapy, and developing novel linkers and cytotoxic drug combinations may expand the therapeutic potential of ADCs in ESCC (Table I).

Targeted therapies. Targeted therapy selectively eliminates cancer cells by focusing on specific tumor molecular characteristics, such as gene mutations or abnormal protein expression, while minimizing damage to normal cells. Although ESCC is biologically complex and highly heterogeneous, several targeted drugs have made significant progress in recent years.

EGFR/VEGF. The EGFR is a transmembrane receptor tyrosine kinase that is overexpressed in numerous epithelial-derived cancers, including ESCC. Activation of the EGFR signaling pathway promotes tumor proliferation, invasion and metastasis. In ESCC, EGFR overexpression is closely associated with tumor aggressiveness and poor prognosis. Afatinib, an anti-EGFR tyrosine kinase inhibitor, has demonstrated an ORR of 14.3%, a mPFS of 3.4 months, and a median OS (mOS) of 6.3 months in previously treated ESCC. Lartotinib improved the ORR to 20% and the mOS to 8 months, but did not significantly increase mPFS (51,52). Both treatments are undergoing further investigation (NCT04415853 and NCT04880811). Additionally, monoclonal antibodies (cetuximab and panitumumab) targeting EGFR combined with cisplatin and fluorouracil for ESCC have not shown

significant benefit (53-56). Amivantamab, a novel bispecific antibody binding both EGFR and cMET extracellular domains, has achieved an ORR of 10.7% and an mPFS of 4.1 months in patients with EGFR and/or MET overexpression, thus suggesting potential antitumor activity of bispecific targeted drugs (57).

VEGF is a critical factor in tumor angiogenesis. Anti-VEGF therapy limits tumor growth and metastasis by inhibiting new blood vessel formation and restricting the tumor's nutrient supply (58,59). Preliminary studies have shown that combining anti-VEGF therapy with chemotherapy can improve efficacy, although adverse effects such as hypertension and proteinuria remain concerns. Apatinib, a Chinese-developed small-molecule inhibitor targeting both VEGFR and HER2, has demonstrated an ORR of 12.5% and an mPFS of 3.9 months in previously treated ESCC. Clinical trials combining apatinib with camrelizumab or docetaxel are continued (60,61). Anlotinib, a multi-targeted small-molecule tyrosine kinase inhibitor, targets VEGFR, FGFR, RET and c-KIT. In a randomized controlled trial for advanced ESCC, the median PFS was 3.02 months in the anlotinib group and 1.41 months in the placebo group (62). Ongoing trials are evaluating anlotinib combined with paclitaxel and cisplatin (NCT04063683) or irinotecan (NCT03387904).

These findings highlight the efficacy and safety of angiogenesis-targeted therapies combined with chemotherapy for first-line treatment of ESCC, although large-scale randomized controlled trials are needed for further validation.

PI3K/AKT/mTOR. The mammalian target of rapamycin (mTOR) is a serine/threonine protein kinase that regulates protein synthesis, ribosomal protein translation, and cap-dependent translation. Dysregulation of mTOR signaling plays critical roles in tumorigenesis, angiogenesis, cell proliferation and metastasis (63,64). Buparlisib (BKM120), an oral PI3K inhibitor acting on mTOR, has demonstrated a DCR of 51.2% with an mPFS of 2.3 months and an mOS of 9.0 months in a multicenter phase II trial in 42 previously treated patients with ESCC. Common grade 3 or 4 adverse events include rash, anorexia, hyponatremia and liver dysfunction, and no treatment-related deaths were observed (65). The aforementioned

Table II. New targeted therapies for esophageal squamous cell carcinoma.

First author/s, year	Drugs	Target	Line	Arm	Outcome	(Refs.)
Ma <i>et al</i> , 2024	Afatinib	EGFR (TKI)	≥2	Single arm	ORR, 14.3%; mPF, 3.4 months; mOS, 6.3 months	(48)
Fantacuzzi <i>et al</i> , 2024	Larotininib	EGFR (TKI)	≥2	Single arm	ORR, 20.0%; mOS, 8.0 months	(49)
Li <i>et al</i> , 2024	Cetuximab	EGFR (mAb)	1L	Cetuximab + Chem vs. Chem	ORR, 19.0% vs. 13.0%; mPFS, 5.9 vs. 3.9 months; mOS, 9.5 vs. 5.5 months	(50)
Hong <i>et al</i> , 2020	Panitumumab	EGFR (mAb)	1L	Panitumumab + Chem vs. Chem	ORR, 35.6% vs. 37.0%; mPFS, 5.3 vs. 5.8 months; mOS, 9.4 vs. 10.2 months	(51)
Moehler <i>et al</i> , 2020	Amivantamab	EGFR/c-Met (BSAB)	≥2	Single arm	ORR, 10.7%; mPFS, 4.1 months	(54)
Lorenc <i>et al</i> , 2024; Rodon <i>et al</i> , 2024	Apatinib	VEGFR2/HER2 (TKI)	≥2	Single arm	ORR, 12.5%; mPFS, 3.9 months	(58,70)
Katari <i>et al</i> , 2024	Anlotinib	VEGFR/FGFR/PDGFR/RET (TKI)	≥2	Anlotinib vs. placebo	mPFS, 3.02 vs. 1.41 months	(59)
Huang <i>et al</i> , 2021	Buparlisib	PI3K	≥2	Single arm	DCR, 51.2%; mPFS, 2.3 months; mOS, 9.0 months	(62)
Wang <i>et al</i> , 2024	Futibatinib	FGFR	≥2	Single arm	ORR, 13.7%	(64)
Kojima <i>et al</i> , 2022; Angerilli <i>et al</i> , 2023	Palbociclib	CDK4/6	≥2	Single arm	ORR, 0%; mPFS, 1.8 months; mOS 3.0 months	(65,66)

BSAB, bispecific monoclonal antibody; mAb, monoclonal antibody; Chem, chemotherapy; TKI, tyrosine kinase Inhibitor; EGFR, epidermal growth factor receptor; VEGFR2, vascular endothelial growth factor receptor 2; HER2, human epidermal growth factor receptor 2; FGFR, fibroblast growth factor receptor; PDGFR, platelet-derived growth factor receptor; RET, rearranged during transfection; PI3K, phosphoinositide 3-Kinase; CDK4/6, cyclin-dependent kinase 4/6; ORR, overall response rate; mOS, median overall survival; mPFS, median overall survival.

study highlights the potential of PI3K/AKT/mTOR inhibition to serve as an effective ESCC target, although further studies are necessary to overcome resistance to PI3K/AKT/mTOR inhibitors.

Other pathways in targeted therapy. Monoclonal antibodies to FGFR2 specifically bind the receptor and effectively block its signal transduction, thus inhibiting tumor cell proliferation and survival (66). A phase I trial of futibatinib has demonstrated an ORR of 13.7% in patients with FGF/FGFR mutations in ESCC, although more extensive data are required for validation (67). CDK4/6 amplification occurs in 10-20% of ESCC cases, and CDK4/6 inhibitors modulate the immune microenvironment by enhancing antigen presentation, upregulating PD-L1 expression, and inducing immunogenic cell death (68). However, the NCI-MATCH trial of palbociclib, a CDK4/6 inhibitor, did not show objective responses in EC, thus leading to disappointing clinical outcomes (69). Consequently, research is moving toward combination therapies, and trials combining CDK4/6 inhibitors with targeted and immunotherapies are currently underway (NCT05865132 and NCT04866381). Additionally, treatments targeting MAT2A/PRMT5, YAP1, and other pathways are in development, although no breakthrough result has been reported to date (70-72).

Targeted therapy remains an important direction for advanced ESCC. Future clinical trials will focus on discovering and validating new targets. Targeted drugs for these pathways may become new treatment options for advanced ESCC. Researchers will also explore how to maximize the efficacy of combination therapies to improve patient survival (Table II).

Immunotherapy and combination therapies. Immunotherapy activates the patient's immune system to recognize and attack cancer cells, primarily by reversing immunosuppressive mechanisms. Given its high mutational burden and strong heterogeneity, ESCC may be readily recognized by the immune system; consequently, immunotherapy is particularly promising for this type of cancer. Current immunotherapeutic strategies for ESCC focus primarily on ICIs, particularly PD-1/PD-L1 inhibitors.

Tumor cells can evade immune surveillance through the binding of PD-L1 to PD-1 on T cells and subsequent suppression of T cell function. PD-1 inhibitors block this interaction, thereby alleviating the immune suppression and restoring T cell antitumor activity (73). Nivolumab and pembrolizumab have demonstrated efficacy in several clinical trials and gained

global approval (37,38). However, other inhibitors targeting the same pathway have not shown significant advantages over these approved drugs. Consequently, a new generation of ICIs, such as anti-cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), anti-lymphocyte-activation gene 3 (LAG-3) and anti-T cell immunoglobulin domain and mucin domain-3 (TIM-3), are emerging (74,75). CTLA-4, a member of the immunoglobulin superfamily, inhibits T cell differentiation by binding B7 ligands, and subsequently suppressing both cellular and humoral immune responses. Moreover, CTLA-4 enhances the immunosuppressive function of cytotoxic T cells, thereby promoting tumor immune escape and hindering immune system activation (76). In the CheckMate 648 trial, combining nivolumab with the anti-CTLA-4 drug ipilimumab extends the median OS by 2 months (12.7 months vs. 10.7 months) and decreases the risk of death by 22%, while maintaining manageable safety (77). LAG-3 plays a key role in regulating the signaling pathways of T lymphocytes and antigen-presenting cells, and consequently contributes to adaptive immune responses (78). New anti-LAG-3 antibodies, such as efitlagimod alpha, have shown promising results in squamous cell carcinomas of the head and neck and non-small cell lung cancer, and further studies in ESCC are awaited. TIM-3, another key molecule in immune evasion, is being targeted in clinical trials of the humanized IgG4 antibody TQB2618, aimed at overcoming the low response rate and resistance to current ICIs (79). Additionally, bispecific antibodies targeting these pathways are under development.

The combination of immunotherapy with chemotherapy and targeted therapies is a current research hotspot. Immunotherapy combined with traditional treatments offers complementary effects and enhanced therapeutic efficacy. Immunotherapy combined with chemotherapy has already been approved as a first-line ESCC treatment benefiting patients regardless of PD-L1 expression levels. Ongoing studies continue to focus on combinations of different PD-1/PD-L1 inhibitors with chemotherapy, such as serplulimab, toripalimab and camrelizumab, although no new breakthroughs or targets have emerged (80-82). The efficacy and safety of these immunotherapy-chemotherapy combinations are well-established, thus leading to further exploration of whether adding targeted therapy can enhance the effectiveness of these combinations. However, research combining immunotherapy with targeted therapies for ESCC remains limited. At the 2023 ESMO conference, a phase II trial demonstrated that the combination of PD-1 inhibitors with anlotinib and chemotherapy resulted in ORRs of 90, 43.3, and 26.7%, respectively, for first-line treatment of ESCC. The median PFS in the three groups was 13.4, 7.2, and 4.8 months, and the median OS was not yet reached (83). A single-arm phase I study evaluating camrelizumab combined with apatinib as a second-line treatment of advanced ESCC showed an ORR of 34.6%. On the basis of these findings, the NCT03603756 trial led to the advancement of camrelizumab plus apatinib and chemotherapy to first-line treatment of ESCC, on the basis of an ORR of 80.0%, an mPFS of 6.85 months, and a DCR of 96.7% (84,85). Overall, immunotherapy has made significant progress in ESCC, and as clinical trials and combination therapies are increasingly explored, immunotherapy is expected to further improve outcomes for patients with advanced ESCC.

In recent years, multiple clinical trials have evaluated the efficacy and safety of combined immunotherapy and radiotherapy ($\pm$ chemotherapy) for locally advanced or metastatic ESCC. In the EC-CRT-001 phase II study, 42 patients with unresectable locally advanced disease received toripalimab combined with concurrent CRT. The 3-year OS rate was 44.8%, and the 3-year PFS rate was 35.7%. Patients who achieved a CR induced by treatment had improved prognosis, and those with irAEs showed a higher PFS (86). Another single-arm study (ChiCTR2100046715) indicated that, in the treatment of previously untreated advanced ESCC, the median PFS of the toripalimab + chemotherapy regimen with added radiotherapy was 9.8 months, with a 1-year PFS rate of 41.9%, a 1-year OS rate of 69.7%, and an ORR of 45.5%. The safety was favorable, the severe adverse reactions were controllable, and no treatment-related deaths were observed (87). In a phase II randomized trial of locally advanced disease, no significant differences in PFS/OS were observed between the induction and consolidation toripalimab + concurrent CRT group and the CRT alone group (median PFS 10.0 vs. 17.8 months; HR=1.57; P=0.228) (88). These findings suggested this treatment's potential as a supplementary strategy to standard treatment. However, further validation through large-sample randomized phase III trials is still needed.

Despite progress, ICIs are not effective for all patients, and some develop resistance after an initial response. Immunotherapy can also cause a range of irAEs, such as inflammation of the skin, liver, intestines and lungs. In severe cases, these irAEs can lead to serious outcomes (89,90). Moreover, although PD-L1 expression is currently the main biomarker for immunotherapy, its predictive value is not absolute. Further research is needed to develop more accurate and comprehensive biomarkers to guide the use of immunotherapy (Table III).

Chimeric antigen receptor (CAR)-T cell therapy. CAR-T cell therapy is an innovative immunotherapy that involves genetically engineering a patient's own T cells to express receptors that can recognize and eliminate cancer cells. Although CAR-T cell therapy has achieved remarkable success in hematologic malignancies, its application in solid tumors, particularly ESCC, remains largely in the preclinical stage (91,92). Researchers are currently developing CAR-T cells targeting surface antigens in EC, and preliminary studies have shown that these therapies significantly inhibit tumor growth and spread in some patients

CAR-T cell therapy for ESCC is in early stages of clinical exploration, primarily in phase I trials assessing safety and preliminary efficacy. Most existing studies have used CAR-T cells targeting tumor-associated antigens such as EGFR, MUC1, or HER2. In single-arm trials, some patients experienced transient tumor shrinkage or disease stabilization, but the overall ORR was relatively low ($<20\%$), and the median PFS was typically 2-4 months (93,94). The efficacy is far from meeting the standards for widespread application in solid tumors. Challenges include: i) the 'cold tumor' characteristics of the ESCC immune microenvironment, wherein tumor suppressive factors (such as TGF- β) limit CAR-T cell infiltration and activity; ii) heterogeneity in target expression and tumor antigen escape; and iii) treatment-related toxicities

Table III. Novel immunotherapy and combination therapies for esophageal squamous cell carcinoma.

First author/s, year	Drugs	Target	Line	Arm	Outcome	(Refs.)
Ooki <i>et al</i> , 2023	Pembrolizumab	PD-1	1L	Pembrolizumab + Chem vs. Chem	Overall: ORR, 43.8% vs. 31.0%; mPFS, 6.3 vs. 5.8 months; mOS, 12.3 vs. 9.8 months; CPS ≥ 10 : ORR, 51.0% vs. 28.0%; mPFS, 7.5 vs. 5.5 months; mOS, 13.9 vs. 8.8 months	(34)
Alsina <i>et al</i> , 2024	Nivolumab	PD-1	1L	Nivolumab + Chem vs. Chem	Overall: ORR, 47.0% vs 27%; mPFS, 5.8 vs. 5.6 months; mOS, 13.2 vs. 10.7 months; PD-L1 $\geq 1\%$: ORR, 53.0% vs. 20%; mPFS, 6.9 vs. 4.4 months; mOS, 15.4 vs. 9.1 months	(35)
Martínez-Pérez <i>et al</i> , 2024	Toripalimab	PD-1	1L	Toripalimab + Chem vs. Chem	ORR, 69.3% vs. 52.1%; mPFS, 5.7 vs. 5.5 months; mOS, 17.0 vs. 11.0 months	(78)
Zhang <i>et al</i> , 2020	Sintilimab	PD-1	1L	Sintilimab + Chem vs. Chem	Overall: mPFS, 7.2 vs. 5.7 months; mOS, 16.7 vs. 12.5 months; CPS ≥ 10 : mPFS, 8.3 vs. 6.4 months; mOS, 17.2 vs. 13.6 months	(85)
Zhang <i>et al</i> , 2024	Camrelizumab	PD-1	1L	Camrelizumab + Chem vs. Chem	Overall: mPFS, 7.6 vs 5.8 months; mOS, 15.6 vs. 12.6 months; TPS ≥ 1 : mPFS, 6.9 vs. 5.6 months; mOS, 16.9 vs. 12.7 months	(79)
Wang <i>et al</i> , 2024	Tislelizumab	PD-1	1L	Tislelizumab + Chem vs. Chem	mPFS, 7.3 vs. 5.6 months; mOS, 17.2 vs. 10.6 months	(86)
Wang <i>et al</i> , 2024	Serplulimab	PD-1	1L	Tislelizumab + Chem vs. Chem	Overall: mPFS, 5.8 vs. 5.3 months; mOS, 15.3 vs. 11.8 months CPS ≥ 10 : mPFS, 7.1 vs. 5.3 months; mOS, 18.6 vs. 13.9 months	(86)
Wu <i>et al</i> , 2022	Sugemalimab	PD-L1	1L	Sugemalimab + Chem vs. Chem	mOS, 15.3 vs. 11.5 months; mPFS, 6.2 vs. 5.4 months	(87)
Alsina and Fleitas-Kanonnikoff, 2024	Ipilimumab	CTLA-4 + PD-1	1L	Ipilimumab + Nivolumab vs. Chem	ORR 18% vs. 27%; mPFS, 2.9 vs. 5.6 months; mOS, 12.7 vs. 10.7 months	(35)
Xu <i>et al</i> , 2024	Tiragolumab	TIGHT + PD-L1	1L	Tiragolumab + Atezolizumab + Chem vs. Chem	ORR, 59.7% vs. 45.5%; mPFS, 6.2 vs. 5.4 months; mOS, 15.7 vs. 11.1 months	(88)

BSAB, bispecific monoclonal antibody; mAb, monoclonal antibody; Chem, chemotherapy; CTLA-4, cytotoxic T lymphocyte associate protein-4; TIGHT, T cell immunoreceptor with Ig and ITIM domain; ORR, overall response rate; mOS, median overall survival; mPFS, median overall survival.

(such as cytokine release syndrome and off-target effects), which are difficult to predict and control (91). Future development directions include constructing dual-target/multi-target CAR-T cells, combining immunomodulators or local radiotherapy to improve the tumor microenvironment (TME), and developing controllable switchable CAR-T systems to enhance safety. Currently, this therapy does not meet the conditions for standard treatment, but it may be explored as an individualized therapy in specific populations. Despite the challenges, such as the complexity of the TME and T cell tolerance, ongoing

advancements in technology hold promise for the future of CAR-T therapy in EC.

Vaccine therapy. Cancer vaccines are aimed at enhancing the body's immune response against tumor-specific antigens, thereby eliminating or inhibiting tumor progression (77). These vaccines typically target tumor-associated antigens, which are overexpressed in cancer cells or expressed at low levels in normal cells. By introducing these antigens into the patient's body, vaccines can stimulate a specific immune

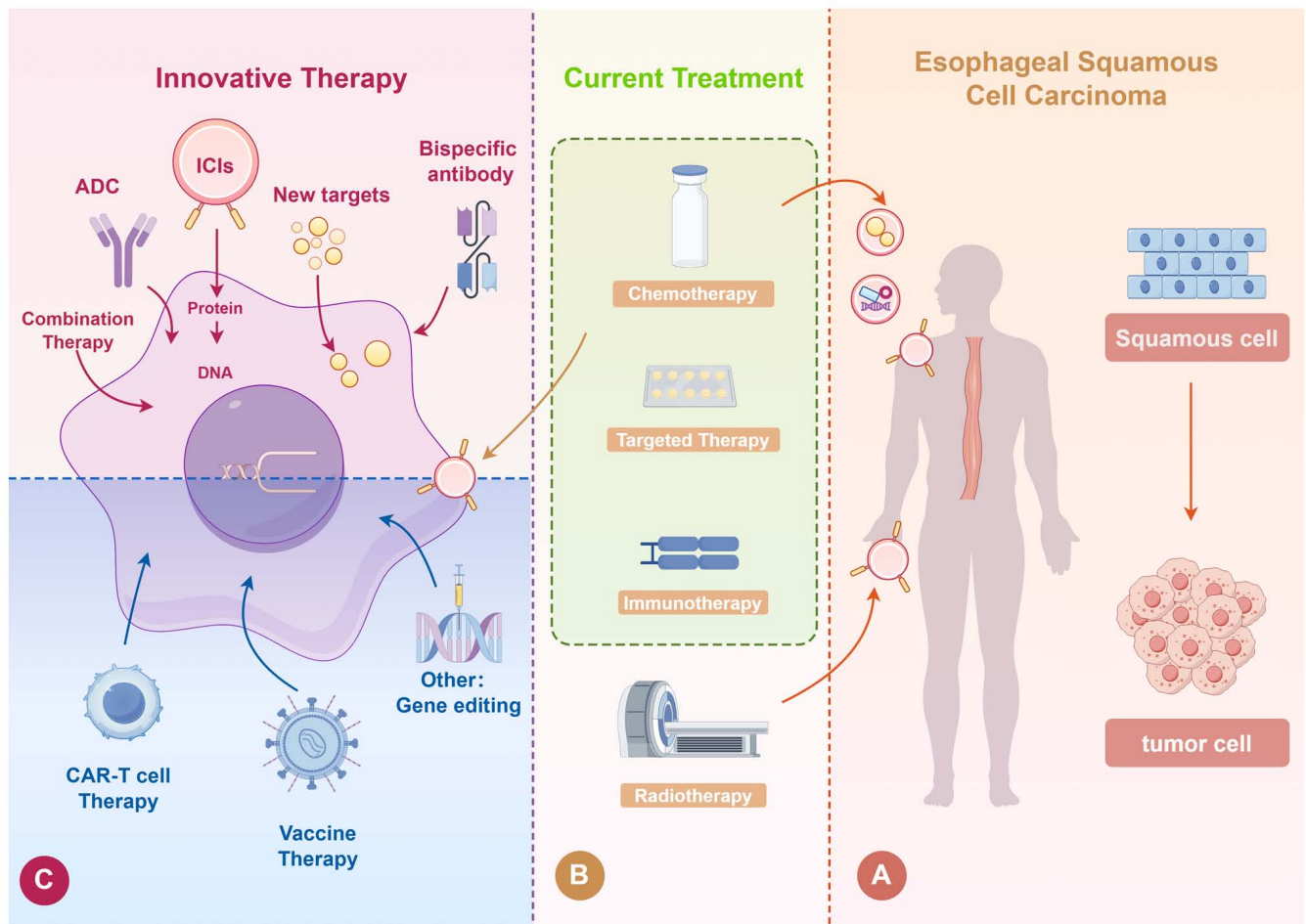


Figure 1. Treatment overview of advanced ESCC. Comprehensive overview of the key therapeutic strategies for advanced ESCC, encompassing traditional chemotherapy, immunotherapy, targeted therapy, ADCs and emerging treatment modalities. ADCs integrate targeted monoclonal antibodies with cytotoxic agents and selectively deliver chemotherapy to cancer cells. Immunotherapy and targeted therapy currently have numerous highly effective and safe novel targets, thus enhancing immune responses while disrupting tumor growth pathways. Additionally, dual-specificity antibodies, cellular therapies and vaccine-based approaches are under active development. Emerging directions include personalized treatment regimens based on genetic profiling and innovative clinical trials exploring novel drug combinations to improve patient outcomes. ESCC, esophageal squamous cell carcinoma; AD, antibody-drug conjugate; ICIs, immune checkpoint inhibitors; CAR-T cell, chimeric antigen receptor T cell. Created by Figdraw.

response, inducing T cells to attack and destroy tumor cells bearing the same antigen. Current cancer vaccine approaches focus on peptide vaccines, DNA vaccines and dendritic cell (DC) vaccines (95). Early results have shown that some patients develop immune responses to the vaccines, and combining vaccines with ICIs or chemotherapy appears to enhance their efficacy (94).

Vaccine therapy in ESCC involves peptide vaccines (such as WT1, NY-ESO-1 and p53) and individualized vaccines based on DCs (96). Some small-scale clinical studies have shown that vaccines can induce specific T-cell responses and achieve disease control in some patients, with DCR reaching 30-40%, but the ORR is generally low (<10%), and no definitive evidence has indicated survival improvements (95,97). The main challenges include: (i) ESCC lacking high-frequency and widely expressed immunogenic tumor antigens; (ii) the immune status of patients being impaired, and the immune response induced by vaccines not being persistent; and (iii) immune suppression mechanisms in the TME (such as Tregs and myeloid-derived suppressor cells) weakening vaccine effect (98). Future directions include combination treatment

with ICIs to relieve immune suppression, development of new delivery platforms (such as nanoparticles or RNA vaccines) to enhance antigen presentation efficiency, and integration of tumor neoantigen screening for individualized vaccine design. Although its current efficacy is limited, vaccine therapy has potential prospects in the control of early or postoperative minimal residual disease and is worthy of further development. In the future, combining vaccines with ICIs (such as PD-1/PD-L1 inhibitors) may further expand T cell recognition and attack of tumor antigens, thereby enhancing the overall effectiveness of immunotherapy (99). Current innovative therapies are shown in Fig. 1.

4. Challenges and future perspectives

As new drugs and therapeutic strategies continue to emerge, future clinical trial designs will become more diverse and precise. Optimizing therapeutic outcomes and integrating new drugs with existing treatment regimens will be central to future clinical research. For example, combination therapies involving immunotherapy and chemotherapy have already

achieved significant results in several clinical trials, and future research may identify optimal combination strategies through deeper mechanistic studies. A proposed priority is a multicenter study comparing nivolumab + FOLFOX with pembrolizumab + carboplatin/paclitaxel in PD-L1-positive patients. Furthermore, the combination of immunotherapy and targeted therapies remains an important research direction. The authors recommend focusing on EGFR/HER2 inhibitors combined with PD-1 blockers in molecularly selected populations, leveraging liquid biopsy for real-time resistance monitoring. Although current treatment methods have improved patient survival and quality of life to some extent, challenges such as resistance, adverse effects and limited efficacy remain to be addressed.

In summary, the future treatment of EC is expected to further improve patient survival and quality of life through multidisciplinary collaboration, precision medicine, and the continuing development of new drugs, with an emphasis on the aforementioned proposed strategies. This will offer new hope for the clinical treatment of advanced EC.

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Availability of data and materials

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Authors' contributions

YL and JL conceived and designed the study. YL and WM wrote and edited the manuscript, constructed the figures, and performed the literature review. YL, JL and XX revised the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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