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Treatments for resectable esophageal cancer: from traditional systemic therapy to immunotherapy

Yan Yan[1], Xijia Feng[2], Chengqiang Li[2], Toni Lerut[3], Hecheng Li[2]

[1]Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China;
[2]Department of Thoracic Surgery, Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China;
[3]Department of Thoracic Surgery, University Hospital Gasthuisberg, University of Leuven, Leuven 3000, Belgium.

Abstract

Esophageal cancer (EC) has a high incidence and poor prognosis. The two major histological types, squamous cell carcinoma and adenocarcinoma, differ in their epidemiology and treatment options. Patients with locally advanced EC benefit from multimodal therapy concepts including neoadjuvant chemotherapy, neoadjuvant chemoradiotherapy, and perioperative chemotherapy. Currently, immunotherapy for the solid tumor is a hot spot. Treatment with adjuvant immune checkpoint inhibitors (ICIs) is the first immunotherapy for resectable EC listed in the latest National Comprehensive Cancer Network Guidelines for the Esophageal and Esophagogastric Junction Cancers. Recent clinical trials have established ICIs for three treatment models of resectable EC. Their short-term results demonstrated ideal efficacy and tolerable toxicity, though some concerns remain. This review summarizes the novel data on the ICIs for resectable EC and lists the registered related clinical trials. Hopefully, this review can provide a reference for ongoing research on the treatment options for resectable EC.

Keywords: Esophageal cancer; Immune checkpoint inhibitor; Immunotherapy

Introduction

Esophageal cancer (EC) is a type of digestive system cancer with high incidence, high degree of malignancy, and high mortality. For both sexes combined, EC ranks the seventh (604,000 new cases, 3.1%) in terms of incidence and stands as the sixth (544,000 deaths, 5.5%) leading cause of cancer-related death worldwide in 2020.[1] Eastern Asia exhibits the highest regional incidence rates for both men (age-standardized incidence rate, 18.2/100,000) and women (age-standardized incidence rate, 6.8/100,000), partly because of the large burden in China. In 2012, 80% of EC-related deaths occurred in Asia.[2] The two major histological types of EC, squamous cell carcinoma (SCC) and adenocarcinoma (AC), differ greatly in their epidemiology. The treatment options for these two types are different to some extent.

Local and systemic treatments are the two major treatment options for EC. The histological type, location, extension, and size of the tumor can help to guide the treatment decisions. Endoscopic and surgical resection are the preferred options for localized and locally advanced EC. Because of the abundant lymphatic drainage in the esophageal submucosa, lymphatic node metastases appear early in EC, and the disease is often initially diagnosed at an advanced stage.[3] Although surgical techniques are constantly being refined, the prognosis of surgery alone for advanced EC is poor. Therefore, systemic treatment cannot be overlooked. The standard systemic treatment options for resectable EC include neoadjuvant chemoradiotherapy (NCRT), perioperative chemotherapy (PCT), and neoadjuvant chemotherapy (NCT).

Immunotherapy is currently the most active and promising research field in cancer treatment. Immune checkpoint inhibitors (ICIs) are widely used agents for immunotherapy that free immune cells to fight cancer by blocking the pathway that tumor cells use to shut down the anti-tumor immune response. Programed cell death protein 1 (PD-1) and its ligands are the main agents mediating tumor-induced immune suppression. Nivolumab, a PD-1 inhibitor, is the first ICI listed as preferred treatment option for resectable EC. Cytotoxic T lymphocyte antigen-4 (CTLA-4) and lymphocyte activation gene-3 (LAG-3) are also targeted negative regulatory checkpoints put into clinical trials besides PD-1 and its ligands.

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Correspondence to: Hecheng Li, Department of Thoracic Surgery, Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China
E-Mail: lihecheng2000@hotmail.com

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We summarized the novel data on ICIs for resectable EC and classified the registered related clinical trials into neoadjuvant immunotherapy, adjuvant immunotherapy, and perioperative immunotherapy. This brief review aims to provide a reference for the ongoing research of the treatment options for this disease.

Recommended Systemic Treatment Options for Resectable EC

According to the latest NCCN Guidelines for Esophageal and Esophagogastric Junction Cancers (Version 2.2022), the preferred treatment options for both localized SCC and AC staged as Tis-T2 (low-risk lesions: <3 cm, well-differentiated) without lymph node metastasis are single surgical approaches including endoscopic therapies and esophagectomy. Definitive chemoradiation is recommended for patients with unresectable EC.[4] Ongoing clinical research mostly focuses on locally advanced EC at a stage between preferred single surgery and recommended definitive chemoradiation. The recommended systemic treatment options differ between the two histological types and include NCT, NCRT, and PCT. Immunotherapy acts as an adjuvant treatment option.

Systemic treatment options for resectable esophageal squamous cell carcinoma (ESCC)

ESCC, which develops in the native esophageal epithelium, is the most common subtype of EC worldwide. In 2012, an estimated 456,000 people developed EC, of which 398,000 were diagnosed with ESCC.[2] Approximately 80% of global ESCC cases occurred in the Central and South-East Asian regions. China alone contributed to more than half of all global cases.

The chemoradiotherapy for EC followed by surgery study (CROSS study)[5] established NCRT as a first-line treatment option for resectable locally advanced ESCC. The CROSS study proved that NCRT could lead to a higher R0 resection rate (92% *vs.* 69%; $P < 0.001$), a better median overall survival (OS) (49.9 months *vs.* 24.0 months; HR, 0.657; 95% CI, 0.495–0.871; $P = 0.003$), and prolonged disease-free survival (DFS) (not reached *vs.* 24.2 months; HR, 0.498; 95% CI, 0.357–0.693; $P < 0.001$) compared with the surgery-alone group in patients with locally advanced EC. Pathological complete response (PCR) was observed in 18 of the 37 patients with ESCC (49%).[5] Hematologic toxic effects were the major treatment-related adverse events (TRAEs) in the NCRT group. Grade 3 hematologic toxic effects were observed in 7% of the patients and Grade 4 developed in one patient. This TRAE probably caused one patient to die while awaiting the surgery. All other TRAEs of Grade 3 or higher occurred in <13% of patients in the NCRT group.[5]

The regimen of the CROSS study combines the chemotherapy regimen, which involves carboplatin and paclitaxel, with radiotherapy. Another phase III multicenter, randomized, open-label clinical trial, NEOCRTEC 5010, confirmed the conclusion of the CROSS study with respect to ESCC. The group that received NCRT had a higher R0 resection rate (98.4% *vs.* 91.2%, $P = 0.002$), a better median OS (100.1 months *vs.* 66.5 months; HR, 0.71; 95% CI, 0.53–0.96; $P = 0.025$), and a prolonged DFS (100.1 months *vs.* 41.7 months; HR, 0.58; 95% CI, 0.43–0.78; $P = 0.001$) compared with the surgery-alone group.[6]

According to the 10-year outcome of the CROSS study and long-term efficacy of the NEOCRTEC 5010 study, the OS benefit in patients with locally advanced resectable ESCC who received the NCRT regimen of the CROSS study persisted for at least 10 years.[7,8] The 10-year outcome of the CROSS study suggested that NCRT resulted in a less isolated locoregional relapse (8% *vs.* 18%; HR, 0.39; 95% CI, 0.21–0.72) and synchronous locoregional and distant relapse (13% *vs.* 22%; HR, 0.43; 95% CI, 0.26–0.72), but not in less isolated distant relapse (27% *vs.* 28%; HR, 0.76; 95% CI, 0.52–1.13).[7] Relapse after NCRT is therefore an essential barrier to overcome.

For resectable EC patients who remain at high risk for relapse after NCRT, ICI adjuvant treatment was designed and validated in the CheckMate-557 study.[9] This landmark achievement resulted in addition of adjuvant immunotherapy for resectable EC to latest NCCN Guidelines for the Esophageal and Esophagogastric Junction Cancers (Version 2.2022).[4] Adjuvant immunotherapy is the preferred treatment option for patients with ESCC staged as ypT-positive or N-positive after NCRT.[4]

Systemic treatment options for resectable esophageal adenocarcinoma (EAC)

EAC is typically located in the lower third of the esophagus and is also called esophagogastric junction cancer and gastroesophageal adenocarcinoma. Because it mainly occurs in patients with a history of gastroesophageal reflux disease, obesity is its major risk factor.[10] In high-income countries, approximately two-thirds of the histological types of EC is AC.[2] It has already become the most common histological type in seven high-income countries such as Australia, Canada, Denmark, Ireland, New Zealand, Norway, and the UK.[10]

The results of the CROSS study[5,7] and the CheckMate-557 study[9] also placed NCRT and adjuvant ICIs at the forefront for resectable EAC treatment, whereas better efficacy of NCRT emerged in SCC. Consequently, PCT and NCT are alternative strategies based on certain situations.

PCT is essential in the treatment of resectable EAC. The survival benefit of PCT in AC was first demonstrated in the milestone-like phase III Medical Research Council Adjuvant Gastric Infusion Chemotherapy (MAGIC trial).[11] This study established that PCT with epirubicin, cisplatin, and fluorouracil (FU) improved progression-free survival (PFS) (HR for progression, 0.66; 95% CI, 0.53–0.81; $P < 0.001$) and OS (5-year survival rate, 36% *vs.* 23%; HR for death, 0.75; 95% CI, 0.60–0.93; $P = 0.009$) in patients with non-metastatic AC. TRAEs in the MAGIC trial were more common than those in the CROSS study. The most prominent Grade 3–4 hematologic TRAE, granulocytopenia, occurred in 23.8% during preoperative chemotherapy period and 27.8% during postoperative

chemotherapy period.[11] The Grade 3–4 non-hematologic TRAEs were also reported.

A subsequent large phase II/III trial, the FLOT4 trial, used a docetaxel-based triplet FLOT (Fluorouracil plus Leucovorin, Oxaliplatin, and Docetaxel) regimen and showed a superior R0 resection rate (85% *vs.* 78%; $P = 0.0162$), OS (median OS, 50 months *vs.* 35 months; HR, 0.77; 95% CI, 0.63–0.94), and DFS (HR, 0.75; 95% CI, 0.62–0.91; $P = 0.0036$) compared with the regimen in MAGIC trial.[12] A recent score-matched study compared the therapeutic outcomes of NCRT and PCT.[13] The results exhibited that these two mainstream regimens showed no significant differences in tumor response and survival rates. TRAEs were more common after PCT (42/97 *vs.* 30/97; $P = 0.04$).

NCT is another acceptable treatment for resectable EAC. The Medical Research Council OEO2 trial demonstrated the survival advantage of preoperative fluorouracil and cisplatin (FC) compared to surgery alone.[14,15] The OS in 2 years was better in the cisplatin followed by surgical resection group (CS group) (HR, 0.79; 95% CI, 0.67–0.93; $P = 0.004$), and the survival benefit was maintained in a median follow-up of 6 years (HR, 0.84; 95% CI, 0.72–0.98; $P = 0.03$).[14,15] However, another large trial failed to demonstrate the same outcome.[16] In the OEO5 trial, triplet chemotherapy (epirubicin, oxaliplatin, and capecitabine, ECX) showed no OS advantage. Furthermore, it was also associated with higher toxicity than FC.[17] Consequently, NCT is rarely used.

Latest progress of the neoadjuvant treatment for resectable EC

Recently, there have been a few remarkable clinical trials on neoadjuvant treatment for resectable EC.

The NExT study plans to confirm the superiority of docetaxel, cisplatin plus 5-FU (DCF), and radiotherapy with cisplatin plus 5-FU over FC with regard to OS as a preoperative therapy for locally advanced ESCC.[18] At the 2022 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium, the research team reported the major outcome of this trial for the first time. DCF demonstrated superior OS with acceptable toxicity, pointing to a new standard treatment option for ESCC.[19]

A multicenter randomized clinical trial focused on the difference in safety between NCRT followed by minimally invasive esophagectomy (MIE) and NCT followed by MIE.[20] Initial results of the trial showed that the difference in safety between the two treatment models was not significant, but NCRT followed by MIE had better histopathologic outcomes.

The NEOadjuvant Trial in AC of the oEsophagus and oesophagoGastric Junction International Study (NeoAEGIS study) was designed to compare the efficacy of the MAGIC and CROSS regimens toward EAC.[21] The result awaits update.

In brief, exploration of a superior neoadjuvant treatment model for resectable EC is still underway. To achieve a better therapeutic effect and lower TRAEs rate, many clinical trials on the combination of ICIs and mainstream approaches for locally advanced resectable EC are going on.

Mechanisms of ICIs for the Treatment of EC

Effector T cell plays a key role in the anti-tumor immune response. During the T cell activation process, negative regulators are induced on the surface of T cell to maintain the balance of immune system. They are called immune checkpoints. Engagement of these immune checkpoints and their ligands during T cell receptor (TCR) signaling can impair T cell activation, function, proliferation, and survival,[22] promoting tumor immune evasion.

Compared with other types of solid tumor, EC has the hallmark of high number of tumor-infiltrating T cells and monocytes/macrophages.[23] Most of the tumor-infiltrating T cells are regulatory T cells (Tregs) and exhausted $CD8^+$ T cells. Tregs, together with tumor associated macrophages (TAMs), myeloid-derived suppressor cells, and cancer-associated fibroblasts, facilitate immunosuppressive tumor microenvironment (TME) of EC through mechanisms related to immune checkpoints.[24] $CD8^+$ T cells in the EC TME exhibit high level expression of immune checkpoint molecules including PD-1/programed cell death-ligand 1 (PD-L1), CTLA-4, and LAG-3 [Figure 1].

In essence, blockers of immune checkpoints have the potential to restore the effective anti-tumor response. Inhibitors of PD-1 have been approved for the treatment of EC. The antibodies of PD-L1, CTLA-4, and LAG-3 also entered clinical trials.

PD-1 and PD-L1

The function of PD-1 is best characterized in activated cytotoxic T cells and its major ligands. PD-L1 and PD-L2 are detected on the surface of antigen presenting cells (APCs) and cancer cells.[25,26] Engagement of PD-1 with its ligands leads to intracellular phosphorylation events, which promote T cell immune exhaustion in the TCR-CD28-dependent or independent mechanisms. The TCR-CD28-dependent mechanism involves two main downstream signaling pathways, which are phosphoinositide 3-kinase pathway and mitogen-activated protein kinase pathway.[27] The expression of B-cell-activating transcriptional factor is increased as well, which contributes to the T cell depression independent of TCR-CD28.

Consistently, $CD8^+$ T cells in EC TME obtain high PD-1 expression.[23] Results of a great many clinical trials suggested that the high expression level of PD-L1 in EC tumor cells was significantly associated with objective response from immunotherapy.[9,28-30] Therefore, PD-L1 expression level is one of the recommended biomarkers to identify the EC patients that may benefit from ICIs.[4] Besides tumoral or normal epithelial cells, TAMs are major components that express PD-1 ligands in EC TME.[31] M2 polarization increases PD-L2 expression in TAMs, resulting in immune evasion through PD-1 signaling pathway regulated by C-C motif chemokine ligand 2-C-C motif chemokine receptor 2 axis.[32] PD-1

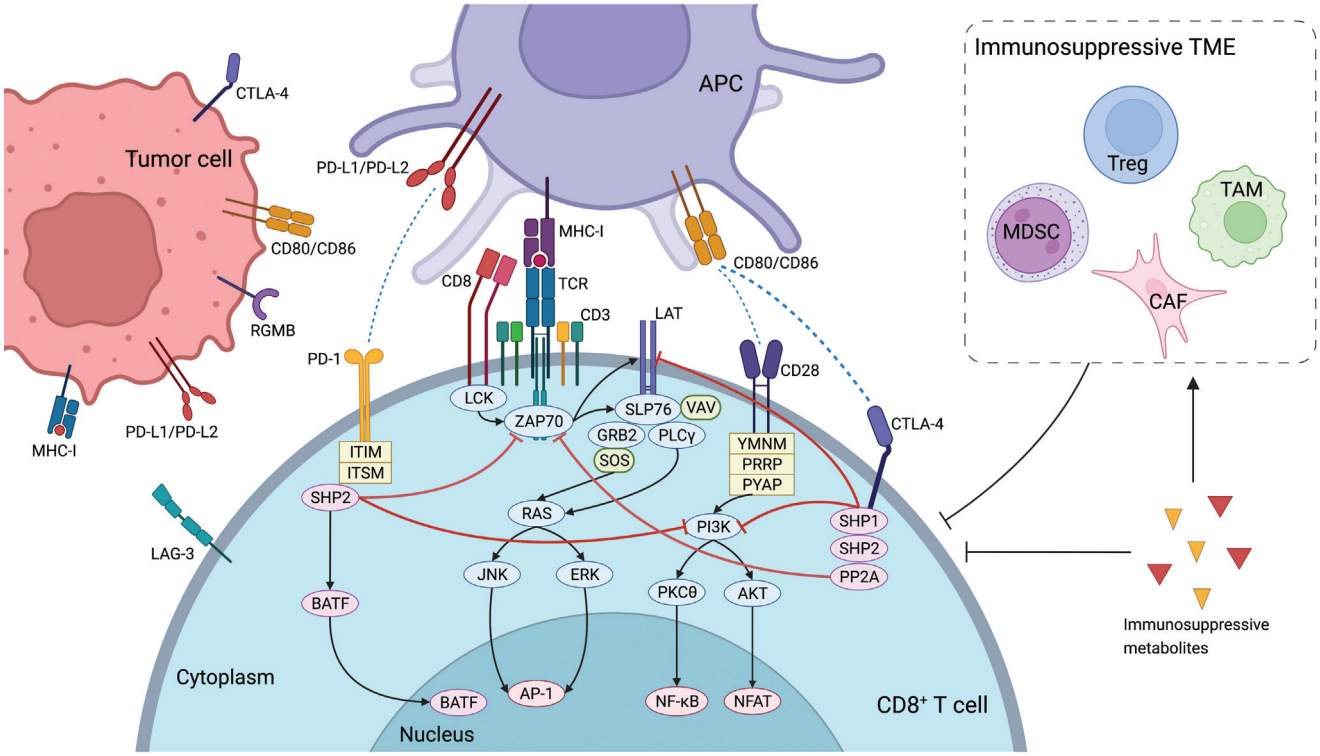

Figure 1: Immune checkpoints signaling in T cells of EC. AKT: Protein kinase B (PKB); AP-1: Activator protein-1; APCs: Antigen presenting cells; BATF: Basic leucine zipper transcriptional factor ATF-like; CAF: Cancer-associated fibroblast; CTLA-4: Cytotoxic T lymphocyte antigen-4; DCs: Dendritic cells; EC: Esophageal cancer; ERK: Extracellular-signal-regulated kinase; GRB2: Growth factor receptor-bound protein 2; ICIs: Immune checkpoint inhibitors; ITIM: Immunoreceptor tyrosine-based inhibitory motif; ITSM: Immunoreceptor tyrosine-based switch motif; JNK: c-Jun N-terminal kinase; LAG-3: Lymphocyte activation gene-3; LAT: Linker for activation of T-cells; LCK: Lymphocyte-specific protein tyrosine kinase; MDSCs: Myeloid-derived suppressor cells; MHC: Major histocompatibility complex; NF-κB: Neuclear factor-κB; NFAT: Nuclear factor of activated T cells; PD-1: Programed cell death protein 1; PD-L1: Programed cell death-ligand 1; PD-L2: Programed cell death-ligand 2; PI3K: Phosphoinositide 3-kinase; PKCθ: Protein kinase Cθ; PLCγ: Phospholipase Cγ; PP2A: Protein phosphatase 2A; PTPs: Protein tyrosine phosphatases; RGMB: RGM domain family member B; SHP-1: Src homology region 2 domain-containing phosphatase-1; SHP-2: Src homology region 2 domain-containing phosphatase-2; SLP76: Src homology region 2 domain-containing leukocyte phosphoprotein of 76 kD; SOS: Son of sevenless homolog; TAM: Tumor associated macrophage; TCR: T cell receptor; TME: Tumor microenvironment; Treg: Regulatory T cell; VAV: Guanine nucleotide exchange factor VAV; ZAP70: 70-kDa zeta-associated protein. This figure was created with Biorender.com.

expression was also observed on TAMs, which can lead to elevation of tumor cell PD-L1 expression.[24]

The responders in the clinical trials of PD-1 blockage therapies for EC demonstrated increased abundance of $CD8^+$ T cells in EC TME,[33-35] which suggests that the PD-1 inhibitors were capable of rescuing the exhausted T cells. These T cells home to the tumor and populate the EC TME to improve anti-tumor efficacy. In addition, the increase of $CD8^+$ T cell density was accompanied by a decreased proportion of M2-type TAMs,[35] which indicated that the successful usage of PD-1 blockage therapy for EC patients was closely relevant to other innate immune cells in the EC TME. Therapeutic outcomes of ICIs targeting PD-L1 not only rely on the PD-1/PD-L1 pathway, but also PD-L1-CD80 and PD-L2-repulsive guidance molecule family member B interactions.[36]

CTLA-4

T cell activation depends on the peptide-major histocompatibility complex (MHC) engagement of TCR and essential positive costimulatory signals provided by the engagement of CD28 on the surface of T cell and CD80 (also known as B7.1) or CD86 (also known as B7.2) on the surface of APCs. CTLA-4 brings damage to this process. During the early stage of T cell activation, intracellularly stored CTLA-4 is transported onto the surface of T cells and competitively engage with CD80 with stronger affinity, weakening the signal strength.[37] Intrinsically, upon engaging with CD80, CTLA-4 attenuates signals downstream of TCR by phosphorylation events.[36]

Dendritic cells act as the main professional APCs whose immune functions are impaired in patients with EC, accompanied by decreased CD80 and CD86 expression.[24] High level expression of CTLA-4 on the surface of Tregs in EC TME plays a vital role in the immunosuppression.[38] The upregulated expression of CTLA-4 not only occurs in effector T cells and Tregs of EC patients, it is also detected in ESCC tumor cells on the level of both mRNA and protein,[38] which further weakens anti-tumor immune response. The previous studies have proved that higher tumor cell CTLA-4 expression was associated with poor prognosis of ESCC patients,[38] whereas ESCC patients with a low tumor cell CTLA-4 expression level had longer OS.[39] Tumor infiltrating mononuclear cells (TIMCs) display positive CTLA-4 expression as well. Significant correlation between survival of ESCC patients and $CTLA\text{-}4^+$ TIMCs density in EC TME was discovered.[38] Moreover, it is proved that CD80 plays a protective role during

metaplasia in inflammatory esophageal carcinogenesis, which is closely related to EAC.[40]

Given these findings, scientists designed ICIs targeting CTLA-4 to boost anti-tumor immunity for EC. How CTLA-4 blockade therapy affects effector T cells and EC TME awaits to be revealed.

LAG-3

LAG-3 possesses a unique signaling pathway, which is not shared by other immune checkpoints, but the exact signaling mechanisms downstream of LAG-3 remain unknown. Since the structure of LAG-3 is similar to CD4, it is not surprising that MHC-II is the ligand of LAG-3. However, the binding between LAG-3 and MHC-II has a much higher affinity.[41] LAG-3 also impacts the function of $CD8^+$ T cell, suggesting the existence of additional LAG-3 ligands.

LAG-3 is significantly highly expressed in ESCC and its expression is one of the markers of exhausted $CD8^+$ T cells.[23,42] Positive LAG-3 expression was significantly associated with CTLA-4 expression in ESCC and acted as one of the predictors of worse recurrence-free survival (RFS) and OS of ESCC patients.[43] High level expression of LAG-3 featured a strong correlation with high amounts of $CD8^+$ tumor infiltrating lymphocytes (TILs) in EAC TME.[44] *LAG-3* gene showed associations with response to combined therapy of nivolumab and ipilimumab for unresectable EAC patients in a study.[45] It is believed that abundant LAG-3^+CD8^+ T cells in EAC TME represents prior-existing strong anti-tumor immune response, which is impaired by mechanisms related to PD-L1 and LAG-3.[45] ICIs are well-suited for the EAC patients who possess this characteristic of TME. Thus, LAG-3 is a new target of ICIs therapy for EC, garnering considerable interest.

Immune Checkpoint Therapy for Resectable EC

The most popular ICIs used in clinical trials for resectable EC are listed in Table 1. The details of the registered clinical trials of neoadjuvant, adjuvant, and perioperative immunotherapies for resectable EC are elaborated in the following sections [Figure 2].

Neoadjuvant immunotherapy

Among the registered clinical trials on immune checkpoint therapy for resectable EC, neoadjuvant immunotherapy is the dominant category. These trials involved multiple ICIs[46], including camrelizumab, pembrolizumab, tremelimumab, sintilimab, atezolizumab, tislelizumab, durvalumab, nivolumab, relatlimab, toripalimab, and IMC-001 [Table 2]. Neoadjuvant immunotherapies are often in combination with NCRT or NCT according to the regimen of CROSS study.

Camrelizumab

Camrelizumab is a PD-1 inhibitor approved by the National Medical Products Administration (NMPA) as a first-line treatment option for unresectable ESCC. As one of the most popular ICIs under investigation for clinical efficacy, a considerable number of clinical trials have focused on the neoadjuvant usage of camrelizumab for resectable locally advanced ESCC. Most of these trials have established a combination of camrelizumab with NCT and NCRT.

The NICE study (ChiCTR1900026240) is a single-arm, phase II study of neoadjuvant camrelizumab combined with chemotherapy in resectable thoracic ESCC with a primary outcome measure of PCR defined as ypT0N0. The research team announced their recent progress at the 2021 ASCO Annual Meeting. Among the 60 participants, 47 underwent complete NCT and radical surgery. The treatment resulted in 100% R0 resection. The PCR rate was 42.5%; five (10.6%) patients had PCR of the primary tumor but residual disease in the lymph nodes alone (ypT0N+). The Grade 3–5 TRAEs rate was 53.3%, and TRAEs resulted in a discontinuation rate of 6.7%. Common Grade 3–5 TRAEs included lymphopenia (50%), thrombocytopenia (10%), pneumonia (5%), and thyroid dysfunction (3.3%).[47] A phase III randomized controlled trial is required to further demonstrate possible improvements in survival.

Pembrolizumab

Pembrolizumab is a PD-1 inhibitor approved by the U.S Food and Drug Administration (FDA) as a first-line treatment option in combination with chemotherapy for unresectable ESCC and EAC. It has been tested clinically to treat both the resectable ESCC and EAC as neoadjuvant immunotherapy.

The PALACE I study (NCT03792347) is a phase Ib and single-arm study to test preoperative pembrolizumab with concurrent chemoradiotherapy (PPCT) for resectable locally advanced ESCC, setting safety as the primary outcome measure. Among the 20 participants, 19 (95%) received complete preoperative treatment and 18 (90%) underwent surgery. The reason for the incomplete neoadjuvant treatment was that the patient experienced Grade 3 leukopenia and lymphopenia and died while awaiting surgery. Discontinued surgery after complete neoadjuvant treatment in one participant was caused by the disease progression. During the neoadjuvant treatment period, all the 20 patients developed TRAEs of any grade. The most common TRAEs were leukopenia (100%), lymphopenia (100%), anemia (80%), esophagitis (55%), alopecia (55%), and fatigue (55%), most of which were of Grade 1 or 2. TRAEs of Grade 3 and higher were observed in 13 of the 20 patients (65%). The most frequent Grade 3 TRAE was lymphopenia (92%).[34] The R0 resection rate was 94%, with 56% PCR and 89% major pathological response (MPR). In a median postoperative follow-up of 6.6 months, all patients who underwent radical resection were free of disease recurrence.[34]

This phase Ib clinical trial verified the safety of PPCT. A further multicenter study with a larger sample size (143 participants) and PCR set as the primary outcome measure, PALACE II (NCT04435197), is ongoing.

Table 1: ICIs in clinical trials for resectable EC.

Drug	Brand name	Developer	Target	Approved cancer types	Approved treatment options for EC	Marketed date	Last revised
Nivolumab	Opdivo®	Bristol Myers Squibb	PD-1	Melanoma NSCLC RCC Hodgkin's lymphoma Urothelial cancer Colorectal cancer HCC EC Gastric cancer Malignant pleural mesothelioma	First-line therapy option for advanced or metastatic esophageal or EGJ adenocarcinoma (FDA) Adjuvant therapy option for patients with completely resected esophageal or EGJ tumors with residual pathologic disease who had received preoperative chemoradiation (FDA) Second-line therapy option for unresectable advanced, recurrent or metastatic ESCC after prior fluoropyrimidine- and platinum-based chemotherapy (FDA)	Dec. 22nd, 2014	Sep. 15th, 2021
Pembrolizumab	Keytruda®	Merck Sharp Dohme	PD-1	Melanoma NSCLC Hodgkin's lymphoma Primary mediastinal large B-cell lymphoma (PMBCL) Urothelial cancer Bladder cancer Colorectal cancer Gastric cancer EC Cervical cancer HCC MCC RCC Cancer of the endometrium CSCC Breast cancer	Second-line or subsequent therapy option for MSI-H/dMMR gastroesophageal tumors (FDA) Second-line therapy option for ESCC with PD-L1 expression levels by CPS of ≥10 (FDA and NMPA) First-line therapy option in combination with fluoropyrimidine- and platinum-based chemotherapy for locally advanced or metastatic esophageal or EGJ tumors (FDA)	Apr. 9th, 2014	Dec. 15th, 2021
Atezolizumab	Tecentriq®	Roche	PD-L1	Urothelial cancer NSCLC SCLC HCC Melanoma	-	May 16th, 2016	Nov. 15th, 2021
Avelumab	Bavencio®	Merck and Pfizer	PD-L1	MCC Urothelial cancer RCC	-	Mar. 23rd, 2017	Sep. 15th, 2020
Durvalumab	Imfinzi®	AstraZeneca	PD-L1	NSCLC ES-SCLC	-	May 1st, 2017	Apr. 15th, 2021
Toripalimab	TUOYI®	TopAllianc and Coherus-BioSciences	PD-1	FDA (orphan drug designation): NPC Mucosal melanoma Soft tissue sarcoma (STS) ESCC NMPA: Melanoma NPC Urothelial carcinoma ESCC	First-line therapy option for unresectable locally advanced, recurrent or distant metastatic ESCC (NMPA) Orphan drug designation for advanced or metastatic ESCC (FDA)	Dec. 17th, 2018	May 10th, 2022
Camrelizumab	AiRuiKa®	Hengrui	PD-1	NMPA: Melanoma NSCLC Hodgkin's lymphoma HCC ESCC	First-line therapy option for certain type of metastatic or locally advanced ESCC that advanced or unresectable after the first-line chemotherapy (NMPA)	May 29th, 2019	Oct. 10th, 2020
Sintilimab	Tyvyt®	Innovent Biologics	PD-1	NMPA: Hodgkin's lymphoma NSCLC	-	Dec. 24th, 2018	May 18th, 2021
Tislelizumab	BaiZeAn®	BeiGene	PD-1	FDA (application accepted for review): ESCC NMPA: Hodgkin's lymphoma NSCLC HCC	Application accepted for review for ESCC that cannot be removed, relapsed, locally advanced or has spread after the systemic therapy (FDA)	Dec. 26th, 2019	Sep. 13th, 2021
Tremelimumab	-	Chemstan	CTLA-4	FDA (orphan drug designation): HCC	-	-	-
IMC-001	-	ImmuneOncia Therapeutics	PD-L1	-	-	-	-
Relatlimab	-	Bristol Myers Squibb	LAG-3	-	-	-	-

The information in this table is based on the data on "National Medical Products Administration (NMPA)," "U.S. Food and Drug Administration (FDA)," and "MedlinePlus". CPS: Combined positive score; CSCC: Cutaneous squamous cell carcinoma; CTLA-4: Cytotoxic T lymphocyte antigen-4; dMMR: Deficiency of mismatch repair; EC: Esophageal cancer; EGJ: Esophagogastric junction; ESCC: Esophageal squamous cell carcinoma; ES-SCLC: Extensive-stage small cell lung cancer; HCC: Hepatocellular carcinoma; ICIs: Immune checkpoint inhibitors; LAG-3: Lymphocyte activation gene-3; MCC: Merkel cell carcinoma; MSI-H: Microsatellite instability-high; NMPA: National Medical Products Administration; NPC: Nasopharyngeal carcinoma; NSCLC: Non-small cell lung cancer; PD-1: Programed cell death protein 1; PD-L1: Programmed cell death-ligand 1; RCC: Renal cell carcinoma; SCLC: Small cell lung cancer; -: Not found.

Another phase II trial (NCT04089904) plans to enroll 33 patients to determine the PCR rate in patients with cT1b-T2N0 EAC treated with neoadjuvant pembrolizumab, followed by surgical resection.

Tislelizumab

Tislelizumab is a PD-1 inhibitor. The FDA has accepted for review for its use for the treatment of ESCCs that cannot be removed, have relapsed, or have spread after systemic therapy.

The TD-NICE study (ChiCTR2000037488) is a phase II and single-arm clinical trial in which tislelizumab was used in conjunction with NCT. The primary outcome measure in this study was the MPR. A total of 36 of the 45 patients completed full neoadjuvant treatment and underwent surgery. The R0 resection rate was 80%, with 72% PCR and 50% MPR. The most frequent TRAEs were leukopenia (73%), anemia (51%), and thrombocytopenia (49%). Grade 3–4 TRAEs occurred in 19 (42.2%) of 45 patients. Postoperative complications occurred in 77.8% of the 36 patients. No treatment-related surgical delay or death occurred.[48]

Sintilimab

Sintilimab is another PD-1 inhibitor, which is approved by the FDA for the treatment of certain type of Hodgkin's lymphoma and non-small cell lung cancer (NSCLC). Sintilimab is mainly used for neoadjuvant treatment of ESCC.

The KEEP-G 03 study (NCT03946969) is a study of neoadjuvant sintilimab combined with triplet NCT of lipo-paclitaxel, cisplatin, and S-1 for resectable ESCC. The primary outcome measures of this study were safety and feasibility. At the 2020 European Society for Medical Oncology (ESMO) Annual Meeting, the research team updated the latest outcomes. Among the 17 enrolled patients, fifteen patients underwent complete neoadjuvant therapy and radical surgery. The R0 resection rate was 100%, with 26.7% PCR and 53.3% MPR. The most common TRAEs were Grade 1–2, and Grade 3–4 occurred in six (35.3%, 6/17) patients with decreased white blood cell count, decreased neutrophil count, and anemia. Grade 5 TRAEs were not observed. No surgical delays and unexpected surgical complications occurred.[49] Thus, the safety of this was confirmed. Further research is required to verify the feasibility of the proposed method.

Atezolizumab

Atezolizumab is a PD-L1 inhibitor approved by the FDA for the treatment of certain type of urothelial cancer, NSCLC, small cell lung cancer, hepatocellular carcinoma, and melanoma.

The PD-L1 Targeting in Resectable Esophageal Cancer study, shortened to the PERFECT study (NCT03087864), is a single-arm, phase II feasibility trial in which NCRT is combined with atezolizumab for resectable EAC. Feasibility, defined as the completion rate of atezolizumab treatment was the primary outcome measure of this study. Of the 40 patients, 34 (85%) completed all cycles of atezolizumab. The reasons for missing any cycle were autoimmune-related toxicity ($n = 3$), progression ($n = 2$), and death ($n = 1$).[33] The R0 resection rate was 100%, with 30% PCR. Median OS was 29.7 months and the median PFS was 19.4 months in the PERFECT trial.[33]

The most common TRAEs were fatigue (95%), mucositis (60%), nausea (53%), and anorexia (43%). Sixteen patients (40%) experienced a Grade 3–4 TRAE. The most common symptoms were anorexia (10%), nausea (8%), and syncope (8%). The aforementioned TRAEs occurred mainly during NCRT combined with ICI. A Grade 5 TRAE was observed in one patient who died because of a pulmonary embolus. Serious TRAEs leading to hospitalization or death were observed in 13 patients (33%).[33]

Toripalimab

In China, toripalimab was the first domestic anti-PD-1 monoclonal antibody approved for marketing. The FDA has approved the orphan drug designation of toripalimab for nasopharyngeal carcinoma, mucosal melanoma, ESCC, and sarcoma.

In a phase II trial (NCT04177797), 20 locally advanced resectable ESCC patients received neoadjuvant toripalimab in combined with chemotherapy. Among the 20 participants, 16 underwent surgery. The R0 resection rate was 87.5% (14/16), with 18.8% PCR (3/16) and 43.8% MPR (7/16).[35] TRAEs occurred in all patients, and four patients (22.2%) experienced Grade 3 or higher one. More importantly, this study revealed predictive values of potential prognosis factors reported by several prior studies, including proportion of M2-type TAMs and expression levels of related genes.

Other drugs

Except for the aforementioned clinical trials with newly updated results, the marketed PD-1 inhibitors nivolumab, the marketed PD-L1 inhibitor durvalumab, and the new PD-L1 inhibitor IMC-001 have all been tested clinically as agents for neoadjuvant immunotherapy. Their impacts on the prognosis of EC await reports. Besides PD1 and PD-L1 inhibitors, relatlimab, an antibody targeting LAG-3, is also used in clinical trials of neoadjuvant immunotherapy (NCT03044613).

Adjuvant immunotherapy

Immunotherapy with nivolumab has already been added to the guidelines for resectable EC as adjuvant immunotherapy for certain situation. The adjuvant tislelizumab has also entered clinical trials.

Nivolumab

The first immunotherapy added to the guidelines for resectable EC is adjuvant immunotherapy suited for both ESCC and EAC with R0 resection after NCRT but staged as

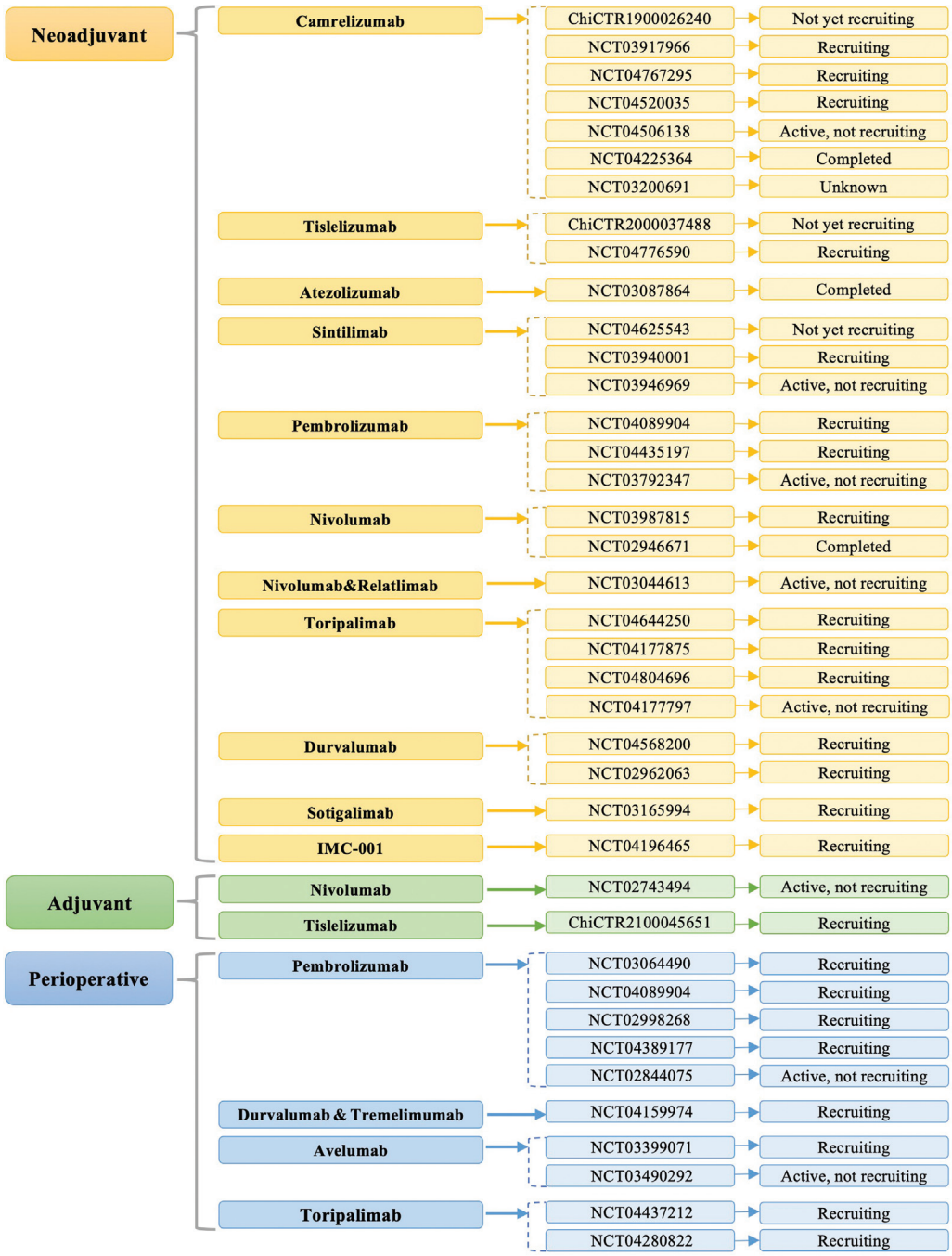

Figure 2: Registered clinical trials of ICIs for resectable EC. Registered clinical trials of ICIs for resectable EC are classified as neoadjuvant, adjuvant, and perioperative immunotherapies. Their identifiers and recruitment status are shown in this figure. The data in this figure are based on the "clinicalTrials.gov" and "Chinese Clinical Trial Registry." EC: Esophageal cancer; ICIs: Immune checkpoint inhibitors.

ypT-positive and/or N-positive. The ICI used in this regimen is nivolumab, a PD-1 inhibitor. This breakthrough was based on the CheckMate-557 study (NCT02743494), a global, randomized, double-blind, placebo-controlled phase III trial.[50] In the short-term outcome for a 24.4-month median follow-up, the DFS was significantly longer among 532 patients who received nivolumab adjuvant therapy than among 262 patients who received placebo (22.4 months *vs.* 11.0 months).[9] Nivolumab continued to demonstrate clinically meaningful efficacy with another 14-month follow-up in the CheckMate-557 study. Nivolumab reduced the risk of recurrence or death by 33% and distant recurrence or death by 29%, resulting in prolonged DFS and distant metastasis-free survival.

TRAEs should not be neglected. In the short-term study, TRAEs were more common with nivolumab than with placebo including Grade 3–4 events (13% *vs.* 6%, respectively) and events leading to discontinuation (9% *vs.* 3%, respectively). Longer follow-up showed that TRAEs in the nivolumab arm occurred earlier, although they resolved for most patients.

Table 2: Clinical trials of neoadjuvant immunotherapy for resectable EC.

Trial registration	Phase	Type	Start and complete date	Enrollment	Arm	Drug	Intervention/treatment	Primary outcome measure
ChiCTR1900026240	Phase II	ESCC	Oct. 2019 to Sep. 2021	60	Single arm	Camrelizumab	Camrelizumab + NCT (albumin-bound paclitaxel + carboplatin)	PCR
NCT03917966	Phase II	ESCC	Apr. 2020 to Oct. 2022	60	Single arm	Camrelizumab	Camrelizumab + NCT (docetaxel + nedaplatin)	ORR MPR
NCT04506138	Phase I/II	ESCC	Aug. 2020 to Dec. 2025	46	Single arm	Camrelizumab	Camrelizumab + NCT (albumin-bound paclitaxel + carboplatin)	PCR MPR
NCT04767295	Phase II	ESCC	Mar. 2021 to Mar. 2023	28	Single arm	Camrelizumab	Camrelizumab + NCT (albumin-bound paclitaxel + carboplatin)	ORR PFS OS DCR PCR
NCT04225364	Phase II	ESCC	Jan. 2020 to Jan. 2021	56	Single arm	Camrelizumab	Camrelizumab + NCT (albumin-bound paclitaxel + cisplatin)	PCR
NCT04520035	Phase II	ESCC	Aug. 2020 to Dec. 2021	60	Single arm	Camrelizumab	Camrelizumab + NCT (albumin-bound paclitaxel + cisplatin)	PCR
NCT03200691	Phase II	ESCC	Aug. 2017 to Jul. 2020	21	Single arm	Camrelizumab	Camrelizumab + neoadjuvant radiotherapy	PCR
ChiCTR2000037488	Phase II	ESCC	Dec. 2020 to May 2022	45	Single arm	Tislelizumab	Tislelizumab + NCT (albumin-bound paclitaxel + carboplatin)	MPR
NCT04776590	Phase II	ESCC	Jan. 2021 to Dec. 2024	30	Single arm	Tislelizumab	Tislelizumab + NCRT (albumin-bound paclitaxel + carboplatin)	PCR
NCT03087864	Phase II	AC	Mar. 2017 to May 2020	40	Single arm	Atezolizumab	Atezolizumab + NCRT (paclitaxel + carboplatin)	Feasibility
NCT03946969	Phase Ib/II	ESCC	May 2019 to Nov. 2021	40	Single arm	Sintilimab	Sintilimab + NCT (lipo-paclitaxel + cisplatin + S-1)	Safety
NCT03940001	Early phase I	ESCC	May 2019 to May 2022	20	Single arm	Sintilimab	Sintilimab + NCRT (paclitaxel + carboplatin)	Unacceptable toxicity PCR MPR
NCT04625543	Phase II	ESCC	Dec. 2020 to Sep. 2023	100	Double arms	Sintilimab	Sintilimab + NCT (paclitaxel + carboplatin)	MPR
NCT03792347	Phase Ib	ESCC	Jan. 2019 to Jun. 2020	20	Single arm	Pembrolizumab	Pembrolizumab + NCRT (paclitaxel + carboplatin)	Safety
NCT04435197	Phase II	ESCC	Aug. 2020 to Jun. 2025	143	Single arm	Pembrolizumab	Pembrolizumab + NCRT (paclitaxel + carboplatin)	MPR
NCT04089904	Phase II	AC	Oct. 2019 to Feb. 2025	33	Single arm	Pembrolizumab	Pembrolizumab alone	PCR
NCT03044613	Phase I	ESCC or AC	Jul. 2017 to Feb. 2024	32	Double arms	Nivolumab relatlimab	Immunotherapy + NCRT (paclitaxel + carboplatin)	Number of participants with TRAEs
NCT03987815	Phase II	ESCC	Aug. 2019 to Jul. 2022	20	Single arm	Nivolumab	Nivolumab alone	MPR
NCT02946671	Phase I	ESCC	Mar. 2016 to Mar. 2020	16	Three arms	Nivolumab	Nivolumab + mogamulizumab (three different doses)	Number of patients with adverse events including intraoperative and postoperative complications; Rate of Foxp3-positive patients in tumor by immunohistochemical analysis
NCT04177797	Phase II	ESCC	Mar. 2020 to Dec. 2023	20	Single arm	Toripalimab	Toripalimab + NCT (paclitaxel + carboplatin)	PCR
NCT04644250	Phase II	ESCC	Sep. 2020 to Mar. 2024	32	Single arm	Toripalimab	Toripalimab + NCT (lipo-paclitaxel + cisplatin)	PCR
NCT04177875	Phase II	ESCC	May 2019 to Apr. 2022	44	Single arm	Toripalimab	Toripalimab + NCT (docetaxel/albumin-bound paclitaxel + cisplatin)	MPR ORR
NCT04804696	Phase II	ESCC	Apr. 2021 to Mar. 2024	53	Single arm	Toripalimab	Toripalimab + NCT (docetaxel/albumin-bound paclitaxel + cisplatin)	PCR
NCT04568200	Phase II	ESCC	Jun. 2020 to Dec. 2023	60	Double arms	Durvalumab	Arm A durvalumab + NCT (paclitaxel + carboplatin) Arm B placebo	TR PR
NCT02962063	Phase I/II	AC	Nov. 2016 to Nov. 2023	78	Single arm	Durvalumab	Durvalumab + NCRT (paclitaxel + carboplatin)	Unacceptable toxicity PCR
NCT03165994	Phase II	ESCC or AC	May 2017 to Apr. 2024	30	Single arm	Sotigalimab	Sotigalimab + NCRT (paclitaxel + carboplatin)	PCR
NCT04196465	Phase II	ESCC or AC	Dec. 2019 to Sep. 2026	48	Single arm	IMC-001	IMC-001 alone	MPR Objective response (ORR)

The data in this table are based on the "ClinicalTrials.gov" and "Chinese Clinical Trial Registry." AC: Adenocarcinoma; DCR: Disease control rate; EC: Esophageal cancer; ESCC: Esophageal squamous cell carcinoma; Foxp3: Forkhead box P3; MPR: Major pathological response; NCRT: Neoadjuvant chemoradiotherapy; NCT: Neoadjuvant chemotherapy; ORR: Objective response rate; OS: Overall survival; PCR: Pathological complete response; PFS: Progression free survival; PR: Pathological response; TR: Tumor response; TRAEs: Treatment-related adverse events.

Tislelizumab

Neoadjuvant tislelizumab therapy was performed as described above. This is also a possible option for adjuvant immunotherapy.

An open-label, randomized, controlled phase III trial (ChiCTR2100045651) is ongoing in China to test the validity and safety of R0 resected ESCC with a high risk of recurrence. The primary outcome measure is DFS and the secondary outcome measures are OS, the incidence of TRAEs, and severe adverse events. The results of this trial are needed to confirm whether adjuvant tislelizumab is another potential agent.

Perioperative immunotherapy

Perioperative immunotherapy is another popular treatment model for resectable EC. The targets of perioperative ICIs in clinical trials are PD-1, PD-L1, and CTLA-4. The ICIs used for perioperative application include pembrolizumab, toripalimab, avelumab, durvalumab, and tremelimumab [Table 3].

Pembrolizumab

As one of the most popular ICIs used in clinical trials, pembrolizumab is also used in the perioperative period for both ESCC and EAC. This drug is often used in combination with NCRT and NCT. Its safety and feasibility are still being assessed clinically.

A phase II trial (NCT02844075) of NCRT combined with perioperative pembrolizumab for ESCC is ongoing, and its primary outcome measure is PCR. The research team published the latest outcome at the 2019 ASCO Annual Meeting. Among the 28 enrolled participants, 26 underwent esophagectomies. Two patients did not undergo surgery due to death or withdrawal of consent. The PCR rate was 46.1%. OS rates of 6 and 12-month were 89.3% and 82.1%, respectively. The most common TRAEs were neutropenia (50.0%) and liver enzyme elevation (30.8%) during the neoadjuvant and adjuvant periods.[51] The addition of perioperative pembrolizumab to NCRT for ESCC demonstrated promising efficacy with acceptable toxicity. Based on these results, further investigation is warranted in phase III clinical trials.

Perioperative pembrolizumab was also added to NCT (NCT04389177) for locally advanced ESCC in a phase II and single-arm trial (KEYSTONE-001). The primary outcome measure of this study is MPR.

Pembrolizumab, radiotherapy, and chemotherapy in neoadjuvant treatment of malignant esophagogastric diseases, referred to as the PROCEED study (NCT03064490), is a phase II trial of the combination of perioperative pembrolizumab and NCRT for resectable EAC. The primary outcome measure of this trial is PCR. The estimated primary completion date for this study is March 2025. We look forward to progress updates in the near future.

Toripalimab

Apart from the neoadjuvant ICIs therapy, the results of perioperative toripalimab for EC patients were presented as well.

At the 2020 ESMO Annual Meeting, the latest advances in a clinical trial on perioperative toripalimab combined with NCT for ESCC were reported. This trial used MPR as the primary outcome measure. Among the 24 enrollments, 18 patients underwent surgical resection, four patients were awaiting the operation, and two patients were unavailable for surgery. The PCR and MPR rates were 16.7% and 50.0%, respectively.[52] More data are needed to update the long-term efficacy of this regimen.

Avelumab

Avelumab, a PD-L1 inhibitor, has been approved for Merkel cell carcinoma, urothelial cancer, and renal cell carcinoma.

The safety and efficacy of NCRT in combination with avelumab in the treatment of resectable esophageal and gastroesophageal junction cancer are being evaluated in a two-part clinical trial (NCT03490292). The results of the first part, a run-in phase for safety evaluation, were published at the 2019 ASCO Annual Meeting. The primary outcome measure for this part was dose-limiting toxicity (DLT).[53] Six EAC patients were enrolled in this part of the study and five participants reached R0-resection. One patient had R1 resection due to tumor extension to the linked adventitial surface without invasion of the surrounding structure. No DLTs were seen in the first five patients; therefore, the expansion cohort is open to enrollment. No Grade 3 or higher TRAEs were observed. The research team concluded that PCRT with avelumab was well tolerated with no unexpected toxicities.[53] The second part with a primary outcome measure of PCR, will enroll an additional 18 patients with ESCC or EAC to further confirm efficacy.

Other drugs

Tremelimumab is a CTLA-4 inhibitor. A double-arm, phase II study (NCT04159974) is ongoing to test the safety and efficacy of the combination of perioperative tremelimumab and durvalumab for resectable EAC. This may provide a new strategy for achieving better therapeutic outcome.

Summary and Prospect

This review lists the registered clinical trials of immune checkpoint therapies for resectable EC and demonstrates their novel progress categorized according to the treatment period during which the immunotherapies were administered. The ICIs used in these trials are also summarized.

From the aspect of treatment models, neoadjuvant ICIs are mostly aimed at ESCC patients, while EAC patients are often treated with perioperative ICIs. This might be due to the better pathological outcome of NCRT for ESCC than for EAC in previous studies.[5]

Table 3: Clinical trials of perioperative immunotherapy for resectable EC.

Trial registration	Phase	Type	Start and complete date	Enrollment	Arm	Drug	Intervention/treatment	Primary outcome measure
NCT03064490	Phase II	AC	Oct. 2017 to May 2023	38	Single arm	Pembrolizumab	Neoadjuvant period: pembrolizumab + NCRT (paclitaxel + carboplatin) Adjuvant period: pembrolizumab	PCR
NCT02844075	Phase II	ESCC	Jan. 2017 to May 2022	18	Single arm	Pembrolizumab	Neoadjuvant period: pembrolizumab + NCRT (paclitaxel + carboplatin) Adjuvant period: pembrolizumab	PCR
NCT02998268	Phase II	AC	Mar. 2017 to Apr. 2025	42	Double arms	Pembrolizumab	Arm A: Induction period: chemotherapy (paclitaxel + carboplatin) Neoadjuvant period: pembrolizumab + NCRT (paclitaxel + carboplatin) Adjuvant period: pembrolizumab Arm B: Induction period: pembrolizumab + chemotherapy (paclitaxel + carboplatin) Neoadjuvant period: pembrolizumab + NCRT (paclitaxel + carboplatin) Adjuvant period: pembrolizumab	DFS
NCT04389177	Phase II	ESCC	Jul. 2020 to Dec. 2024	50	Single arm	Pembrolizumab	Neoadjuvant period: pembrolizumab + NCT (paclitaxel + cisplatin) Adjuvant period: pembrolizumab	MPR
NCT04089904	Phase II	AC	Oct. 2019 to Feb. 2025	33	Single arm	Pembrolizumab	Pembrolizumab alone	PCR
NCT04159974	Phase II	AC	Sep. 2019 to Jun. 2024	56	Double arms	Durvalumab and tremelimumab	Arm A: durvalumab Arm B: durvalumab + tremelimumab	Safety and efficacy
NCT03490292	Phase I/II	ESCC or AC	May 2018 to Mar. 2022	24	Single arm	Avelumab	Neoadjuvant period: avelumab + NCRT (paclitaxel + carboplatin) Adjuvant period: avelumab	Part 1: DLT Part 2: PCR
NCT03399071	Phase II	AC	Jul. 2017 to Aug. 2025	40	Single arm	Avelumab	Neoadjuvant period: avelumab + NCT (FLOT) Adjuvant period: avelumab + adjuvant chemotherapy (FLOT)	PCR
-	-	ESCC	Apr. 2020 to Sep. 2020	24	Single arm	Toripalimab	Neoadjuvant period: toripalimab + NCT (nab-paclitaxel + S-1) Adjuvant period: toripalimab + adjuvant chemotherapy (nab-paclitaxel + S-1)	MPR
NCT04437212	Phase II	ESCC	Jul. 2020 to Dec. 2023	20	Single arm	Toripalimab	Neoadjuvant period: toripalimab + NCRT (paclitaxel + cisplatin) Adjuvant period: toripalimab	MPR
NCT04280822	Phase III	ESCC	Apr. 2020 to Mar. 2028	400	Double arms	Toripalimab	Arm A: Neoadjuvant period: toripalimab + NCT (paclitaxel + cisplatin) Adjuvant period: toripalimab Arm B: NCT (paclitaxel + cisplatin)	EFS

The data in this table are based on the "clinicalTrials.gov" and "Chinese Clinical Trial Registry." AC: Adenocarcinoma; DFS: Disease-free survival; DLT: Dose-limiting toxicity; EC: Esophageal cancer; EFS: Event-free survival; ESCC: Esophageal squamous cell carcinoma; FLOT: Docetaxel + oxaliplatin + leucovorin + fluorouracil; MPR: Major pathological response; NCRT: Neoadjuvant chemoradiotherapy; NCT: Neoadjuvant chemotherapy; PCR: Pathological complete response; -: Not found.

Most of the mentioned clinical trials are in phase II, and few have entered phase III. Limitations common to phase II trials should be noted, including small sample size and lack of a control group. Except for the multicenter study CheckMate-557, trials for ESCC mostly took place in a single Asian country, especially China, whereas all the trials for EAC were located in a single western country. This finding is highly correlated with the epidemiology of this type of cancer. Hence, the results of the clinical trials described above should only provide reference values for certain populations. In general, the trials on combination of ICIs with NCRT, NCT, and PCRT for resectable EC are still at a very early stage. Credibility and generality are inadequate and must be improved in the future. We suggest multi-centric (if possible, multinational) initiatives to overcome these limitations.

All the mentioned trials had a satisfactory R0 resection rate. However, in some studies, particularly in trials targeting ESCC, the PCR rate was lower than that in the CROSS study with NCRT alone. As the research of ICIs for EC was initiated not long ago, further follow-up to evaluate the long-term DFS and OS, in other words, the efficacy of the therapy, is awaited.

The response assessment methods and criteria have varied in different trials for preoperative systemic treatment, and very few studies have reported the details. The PALACE I study took advantage of the positron emission tomography-computed tomography scan and set complete metabolic response as their criteria.[34] How to better assess the response and define the situation suited for the surgery needs to be verified to help decide the treatment option.

Although an acceptable incidence of TRAEs has been reported, they still threaten the safety of ICIs treatment regimens. TRAEs were reported in all the above studies, and TRAEs-related surgical delay or death occurred in some cases. The safety of the ICIs is expected to improve desperately.

Blocking the PD-1/PD-L1 pathway is the major approach of immunotherapy for resectable EC patients, which has shown remarkable anti-tumor effects. However, ICIs therapy was useless for some patients and drug resistance appeared in some cases. The PD-L1 expression of ESCC and microsatellite instability-high (MSI-H)/deficiency of mismatch repair are two current guideline-recommended indicators for successful ICIs therapy.[4] Unfortunately, the advantage of PD-L1-positive ESCC on objective response for ICIs therapy was not significant in a clinical trial.[54] What is more, the MSI-H only occurs in about 7% EAC patients.[55] Their prognostic values are limited. How to better identify the beneficial EC patients for PD-1 blockade therapy is an urgent problem to be solved. To be noted, advancing our understanding of the regulatory mechanisms of this pathway and the EC TME can bring imperative benefits to this barrier.

Signaling process of PD-1/PD-L1 pathway contains a series of events including genomic alternations, transcriptional and post-transcriptional mechanisms regulating the expression of molecules, and post-translational

modification of molecules.[56,57] With the continuous development of gene analysis technology, scientists illustrated several EC specific immune-related genes and genomic alternations such as *CCR5*,[58] *TSPAN2*,[58] *PTEN*,[59] *TIM-3*,[60] *LAMININ*-γ2,[61] and chromosome 11q13.3 amplification.[62] These are all potential biomarkers for PD-1/PD-L1 blockade therapy responders of EC. Immune-related long non-coding RNA signature of this pathway in ESCC was identified as well,[63] which could be employed as an independent predictor for ESCC immunotherapy prognosis.

Currently, studies reported that immune infiltration frequency was associated with PD-L1 expression within EC TME and was responsible for effectiveness of PD-1/PD-L1 blockade treatment. The clinical outcome-related components include frequencies of TILs, TAMs, $CD8^+$ T cells, and Tregs.[64-66] The latest outcomes of a prior-mentioned trials confirmed this finding.[33-35]

Furthermore, the metabolic reprograming of TME also provides useful avenues to the determination of suitable EC patients for ICIs. Serum lactate dehydrogenase, C-reactive protein, and relative eosinophil count serve as useful biomarkers to optimize clinical decisions and predict the response of EC patients to treatment with anti-PD-1 drugs.[67,68]

Unlike PD-1/PD-L1 blockade therapy, ongoing clinical trials of anti-CTLA-4 immunotherapy for resectable EC are few in number. Efficacy of CTLA-4 blockade therapy for several solid tumors was limited by severe TRAEs, which were mostly immune-related adverse events (irAEs). CTLA-4 is a Tregs intrinsic immune checkpoint against fatal autoimmune disease. Boosting cancer immunity by inhibiting CTLA-4 also leads to the upregulation of auto-immune responses, resulting in irAEs. Some scientists concluded that one should preserve rather than block CTLA-4 checkpoint for safer and more effective immune checkpoint therapy.[69] Others overcame this barrier by engineering TME specific anti-CTLA-4 antibody.[70] Whether CTLA-4 targeted ICI should be approved for cancer immunotherapy is still an open question.

For LAG-3, its immunosuppressive mechanism is a brand-new field of research which has gained broad attention. A recent study demonstrates that fibrinogen-like protein 1 (FGL1) was a major LAG-3 functional ligand independent of MHC-II. It was highly produced by human cancer cells, and an elevated FGL1 expression in the plasma of cancer patients is associated with a poor prognosis and resistance to anti-PD-1 therapy.[71] The outcome of the clinical trial using combined therapy of nivolumab and relatlimab for resectable EC may help in answering the mystery.

Undoubtedly, recent satisfactory outcomes of immunotherapy for resectable EC offer hope for a breakthrough, but the deficiencies still need to be conquered. Prompt solutions to these concerns will perfect ICIs treatment for resectable EC with reliable effect and good safety in the coming days.

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Conflicts of interest

None.

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