Pembrolizumab for first-line treatment of advanced unresectable or metastatic esophageal or gastroesophageal junction cancer

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Abstract: Esophageal cancer (EC) is the seventh most common malignancy worldwide. Although systemic chemotherapy is the standard treatment for advanced EC, the available cytotoxic agents have limited efficacy. Pembrolizumab, a humanized monoclonal immunoglobulin G4 antibody that inhibits programmed cell death protein 1, has recently been developed for the treatment of patients with advanced EC. In the KEYNOTE-181 trial, pembrolizumab achieved a clinical meaningful overall survival benefit over chemotherapy alone when used as second-line treatment in patients with esophageal squamous cell carcinoma (ESCC) who had a combined positive score ≥10 for expression of programmed death ligand 1. Furthermore, KEYNOTE-590 showed that pembrolizumab + chemotherapy was more effective than chemotherapy alone as first-line chemotherapy for patients with advanced EC. Accordingly, immune checkpoint inhibitor (ICI) chemotherapy has become the standard first-line treatment for advanced EC. The use of ICIs in primary therapy has helped to improve the prognosis, especially for ESCC. Moreover, in CheckMate 577, patients who received postoperative nivolumab therapy had a reduced risk of recurrence, and the ability of preoperative ICI chemotherapy to reduce the incidence of recurrence is now under investigation. This review outlines the evidence for use of pembrolizumab as a first-line treatment for advanced unresectable or metastatic EC, summarizes the ongoing research on ICI combination chemotherapy, and discusses the associated issues.

Keywords: esophageal cancer, esophageal squamous cell carcinoma, immune checkpoint inhibitor, pembrolizumab, programmed cell death protein 1, combination therapy

Introduction

Esophageal cancer (EC) is the seventh most common cancer, accounting for 3.1% of all cancers, and the sixth leading cause of cancer deaths worldwide, accounting for 5.5% of all cases.[1] There are two main histological subtypes of EC, namely, esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). For most of the 20th century, ESCC comprised the vast majority of ECs globally. However, for the past three decades, the frequencies of EAC, esophagogastric junction (EGJ) cancer, and cancers of the gastric cardia have increased dramatically. Risk factor and incidence of EC differ between ESCC and EAC. ESCC is the most common histology in the worldwide, and has a particularly high incidence in Eastern Asia and Eastern Africa. In contrast, the incidence of EAC is markedly higher in Western countries.[2–5] Major risk factors for ESCC are smoking and alcohol consumption, whereas Barrett's esophagus with gastroesophageal reflux disease, obesity, and smoking are the main risk factors for EAC.[6]

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EC is a cancer with a poor prognosis. In advanced stages, it is detected symptomatically, but in early stages, it is undetected because of the absence of symptoms.[5] Previous report suggested that the prognosis of ESCC is worse than that of EAC.[7] However, despite ESCC and EAC being different disease entities with characteristic pathogenesis, epidemiology, tumor biology, treatment, and outcomes, there is ongoing debate regarding how histology influences the therapeutic approach. Moreover, although systemic chemotherapy is the standard treatment for patients with metastatic or recurrent EC who have no curative options, the chemotherapeutic agents available have limited efficacy.[8–10]

Although there is no evidence from randomized controlled trials that palliative chemotherapy confers a survival benefit over best supportive care as first-line treatment for patients with metastatic or recurrent EC, doublet chemotherapy consisting of platinum and a fluoropyrimidine has been recognized as first-line standard chemotherapy for several decades.[8–12] In one study, patients who received this treatment had an objective response rate (ORR) of 37.2%, median progression-free survival (PFS) of 4.8 months, and median overall survival (OS) of 10.4 months, indicating limited efficacy.[13] Furthermore, for several years now, taxane monotherapy has been used for second-line or later-line chemotherapy after refractoriness or intolerance to first-line chemotherapy[14,15] or irinotecan monotherapy.[8] Previous studies have reported ORRs of 10–40% and median OS rates in the range 8–10 months, indicating that these agents also have limited efficacy.

Recent clinical trials have demonstrated the clinical benefit of immune checkpoint inhibitor (ICI) therapy particularly in patients with metastatic or recurrent ESCC. The ATTRACTION-3 and KEYNOTE-181 trials, respectively, established the ICI inhibitors nivolumab and pembrolizumab as second-line treatments for metastatic or recurrent ESCC after refractoriness or intolerance to first-line chemotherapeutic agents.[16,17]

Following on from these results, the usefulness of combined chemotherapy and ICI therapy has been demonstrated in the first-line setting. The KEYNOTE-590 trial reported that pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy was effective in patients with metastatic or locally advanced EC or EGJ cancer who were not candidates for surgical resection or definitive chemoradiotherapy.[18]

Recent trials showed the efficacy of ICI and ICI-containing treatments, so we summarized the treatment based on pembrolizumab, which is first approved for patients with untreated EC regardless of histology, ESCC and EAC. In addition, some clinical trials related to pembrolizumab-containing treatments are ongoing. We focus on pembrolizumab for patients with advanced EC and discussed the issues of pembrolizumab and pembrolizumab-containing treatments.

Pembrolizumab

Immune checkpoint inhibition
In many cancers, immunotherapy is dramatically changing conventional treatment. In particular, immunotherapy *via* the programmed cell death 1 (PD-1)/programmed death-ligand 1 (PD-L1) pathway has made a significant contribution. Inhibitory immune checkpoint molecules and stimulatory immune checkpoint molecules are important in maintaining immune homeostasis. Inhibitory immune checkpoint molecules include PD-1, cytotoxic T-lymphocyte-associated antigen 4, and lymphocyte activation gene-3, while stimulatory immune checkpoint molecules include CD40 ligand, OX40, and inducible T-cell costimulatory molecule. Cancer cells escape immune responses by aberrant expression of inhibitory immune checkpoint molecules, which is responsible for tumor progression.

Activated T cells, B cells, and natural killer cells expressed high levels of PD-1 that is an immunosuppressive receptor.[19] Interaction between PD-1 and PD-L1 or PF-l2 can mediate suppression of T-cell activity *via* negative regulation of the T-cell receptor and CD28 signaling (Figure 1(a)).[19] PD-L1 is highly expressed on many immune-related cells, including antigen-presenting cells, and PD-L1 expression is particularly increased in the tumor environment.[20] This suggests that the PD-1/PD-L1 pathway is upregulated in the tumor environment, resulting in a state of immunosuppression. PD-L1 is overexpressed in 18.4–82.8% of patients with ESCC, who have poor clinical outcomes.[21]
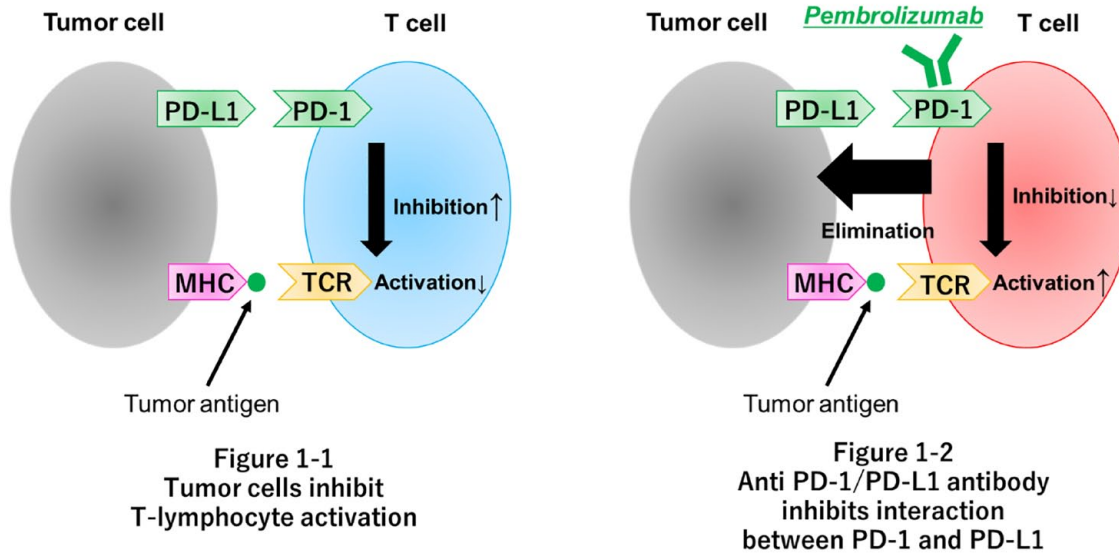
Figure 1. Mechanism of action of pembrolizumab.[15]
MHC, major histocompatibility complex; PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1; TCR, T-cell receptor.

Composition of pembrolizumab

Pembrolizumab is a genetically engineered human IgG4 monoclonal antibody specific for PD-1[22] and consists of four polypeptide chains, namely, two heavy chains with 447 amino acids each and two light chains with 218 amino acids each. It has a high affinity for PD-1 and inhibits the binding of both PD-L1 and PD-L2 to PD-1, which activates T cells and apoptosis of immune-mediated tumor cells as well as conversion of regulatory T cells to T effector cells.[22] Blockade of the PD-1 pathway can enhance the antitumor activity of T cells, thereby increasing immune control and killing tumor cells, and increases proliferation of tumor antigen-specific T cells and secretion of cytokines *in vitro* (Figure 1(b)). Pembrolizumab has been approved for the treatment of advanced non-small-cell lung cancer, melanoma, Hodgkin's lymphoma, and urothelial carcinoma, squamous cell carcinoma of the head and neck, cervical squamous cell cancer, microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) metastatic gastric and gastroesophageal cancer, MSI-H or dMMR metastatic colorectal cancer, and hepatocellular carcinoma.[23–32]

Combination chemotherapy

Chemotherapy has previously been reported to increase tumor immunogenicity and lead tumor cells to immunogenic cell death directly or indirectly.[33] Combination therapy with ICIs and chemotherapy is expected to more strongly induce immunogenic cell death of tumors by decreasing PD-L1 and PD-L2 expression,[19] promoting fewer myeloid suppressor cells[34] and antigen presentation by dendritic cells,[35] and decreasing regulatory T cells.[33] Platinum salts can increase generation of neoantigens on cancer cells when tumor cells are destroyed, so addition of pembrolizumab to standard chemotherapy may improve outcomes for patients.

Potential of combination with anti-vascular endothelial growth factor/vascular endothelial growth factor receptor therapies

Angiogenesis, the formation of new blood vessels from pre-existing vasculature, is an important process for tumor growth. The vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR) pathways have been reported to be important pathways leading to tumor angiogenesis.

VEGF-A is an endothelial cell growth and survival factor that binds to two receptor tyrosine kinases, VEGFR1 and 2. Upregulation of VEGF expression in tumor cells promotes neovascularization, solid tumor growth, and metastasis. Tumor cells consume large amounts of oxygen

and nutrients for rapid division and proliferation, resulting in hypoxia and acidosis in the tumor environment. Hypoxia further induces the secretion of angiogenic factors, including VEGF-A, to promote angiogenesis. Compared to normal physiological angiogenesis, tumors produce excessive amounts of angiogenesis-promoting factors, and the appropriate balance between promoting and inhibiting factors is lost.[36] As a result, disorganized angiogenesis continues within the tumor, exhibiting abnormal characteristics such as irregular shapes, dilation, meandering, abnormal branching, and dead ends.[37]

Tumor endothelial cells are also morphologically abnormal and poorly interconnected, resulting in vascular leakage. Tumor endothelial cells exhibit some of the characteristics of malignant cells, such as hyperproliferation and cytogenetic abnormalities.[38] Pericytes at the tumor periphery are also more loosely interconnected and less abundant than in normal vessels. Irregular perfusion of blood, hypoxia, hyponutrition, and acidosis in the tumor microenvironment are caused by these irregular structure of tumor vessels. These cause to reduced efficacy of anticancer drugs and further tumor growth.

This tumor microenvironment also contributes to immunosuppressive effects. *In vitro* and *in vivo* mouse models have reported that hypoxia leaded to upregulation of PD-L1, increased suppressor T regulatory cell activity, and inhibited effector T cell.[39] On the other hand, several studies suggested that angiogenic factors themselves could also have a number of effects on the immune system; VEGF directly upregulates PD-L1 expression on macrophages and dendritic cells and contributed to immune tolerance by reducing T-cell function and number.[40] Binding of VEGF to VEGFR2 on the surface of effector T cells upregulated PD-1 expression on CD8+ T lymphocytes, resulting in their downregulation and suppression of proliferation, which also contributed to immunosuppression. Binding of VEGF to VEGFR2 on bone marrow-derived suppressor cells (MDSCs) and Treg cells promoted the infiltration of these immunosuppressor cells.[41] This mechanism led to a state of immune tolerance by immune cells to tumor cells, which, in turn, led to tumor growth.

Anti-VEGF/VEGFR therapies, including bevacizumab, a neutralizing monoclonal antibody, and lenvatinib, a VEGFR multityrosine kinase, have demonstrated antitumor activity in clinical trials and are already approved for multiple indications in combination with standard chemotherapy or as single agents. Anti-VEGF/VEGFR therapy contributed to an improved tumor immune environment by significantly enhancing dendritic cell maturation and inhibiting the accumulation of MDSCs and Tregs in the tumor environment.[41] Sorafenib treatment has also shown to initiate regulation of VEGF expression and restore monocyte differentiation into dendritic cells.[42] These suggested that the combination of anti-PD-1 or anti-PD-L1 antibodies and anti-VEGF/VEGFR therapy might be mutually beneficial.

In fact, the combination of lenvatinib and pembrolizumab has been reported to be effective in renal cell carcinoma, and these results are expected to be effective in other carcinomas, including EC.

Pivotal clinical trials

KEYNOTE-028
The first pivotal study was KEYNOTE-028, a multi-cohort, phase Ib trial that evaluated the efficacy and safety of pembrolizumab monotherapy (10 mg/kg every 2 weeks for up to 2 years) in patients with unresectable advanced EC who had already received more than two treatments.[43]

Pembrolizumab demonstrated promising antitumor efficacy as monotherapy with an ORR in seven patients (30%) [95% confidence interval (CI): 13–53] and a median duration of response (DOR) of 15 months (range, 6–26). Median PFS was 1.8 months (95% CI: 1.7–2.9) and median OS was 7.0 months (95% CI: 4.3–17.7). Nine patients (39%) experienced treatment-related adverse events (AEs); however, no grade 4 AEs or deaths were attributed to pembrolizumab.

In this trial, pembrolizumab monotherapy demonstrated potential efficacy in patients with heavily treated EC.

KEYNOTE-180
KEYNOTE-180 was a single-arm phase II trial that evaluated the efficacy and safety of pembrolizumab monotherapy (200 mg/kg, every 3 weeks) after failure of fluoropyrimidine-based, platinum-based, and taxane-based chemotherapy in

patients with unresectable advanced or recurrent EAC or ESCC.[44] This trial also evaluated biomarkers in tumor samples. The primary endpoint was ORR. The secondary endpoints included DOR, PFS, and OS as efficacy evaluations and AEs based on CTCAE version 4.0 as a safety assessment.

In all, 121 patients were enrolled in the study between 12 January 2016 and 21 March 2017. The median follow-up duration was 5.8 months and 58 patients (47.9%) had tumors that were PD-L1-positive [combined positive score (CPS) ≥ 10]. The Eastern Cooperative Oncology Group (ECOG) performance status (PS) score was 0 in 44 patients (36%) and 1 in 77 (64%). In all, 63 patients (52%) had histologically confirmed ESCC and 58 patients (48%) had histologically proven EAC. There were 106 patients (88%) who had received two previous therapies and 15 (12%) who had received ≥3 prior therapies.

Pembrolizumab monotherapy demonstrated promising antitumor efficacy with an ORR of 9.9% (95% CI: 5.2–16.7) in 12 patients by central assessment, and all patients had a partial response. The centrally assessed median DOR had not been reached as of the cutoff date, although it was anticipated to extend beyond 1.9–14.4 months.

Median OS was 5.8 months (95% CI: 4.5–7.2) and median PFS was 2.0 months (95% CI: 1.9–2.1). The ORR was 14.3% (95% CI: 6.7–25.4) in patients with ESCC (9/63) and 5.2% (95% CI: 1.1–14.4) in those with EAC (3/58). The ORR was 13.8% (95% CI: 6.1–25.4) in 8 of the 58 patients with PD-L1 positive tumors and 6.3% (95% CI: 1.8–15.5) in 4 of the 63 patients with PD-L1-negative tumors. The median DOR was not reached for patients with PD-L1-positive tumors (95% CI: 1.9–14.4 months) and was 4.4 (2.1–5.3) months for patients with PD-L1-negative tumors. PFS was similar between patients with ESCC and EAC and between those with PD-L1-positive and -negative tumors; however, OS was longer in patients with PD-L1-positive ESCC.

AEs were reported in 70 (57.9%) of the 121 patients, with grade 3 or 4 events in 14 (11%) and grade 5 AEs in one patient (1%). The most common AEs were fatigue (10%), rash (7%), pruritus (6%), hypothyroidism (6%), and diarrhea (5%). One death was attributed to treatment-related pneumonitis. Only five patients (4.1%) discontinued treatment with pembrolizumab because of AEs.

Although this trial included only patients with metastatic or recurrent ESCC with failure of two or more lines of therapy, the results for the efficacy endpoints, including ORR and OS, were very promising and the safety profile suggested that pembrolizumab monotherapy was tolerable. Furthermore, the findings of this study indicated that pembrolizumab is more effective in patients with ESCC than in those with EAC, which raised the possibility that the treatment strategies for ESCC and EAC may need to be different. In this trial, PD-L1 expression was evaluated using the CPS (number of PD-L1-positive tumor cells, macrophages, and lymphocytes divided by the total number of tumor cells) and found to show potential as a biomarker for pembrolizumab.

KEYNOTE-181

Based on the promising results of KEYNOTE-028 and KEYNOTE-180, the phase III KEYNOTE-181 trial was performed to confirm that pembrolizumab monotherapy (200 mg every 3 weeks) was superior to chemotherapy (paclitaxel or docetaxel, irinotecan) in terms of efficacy in patients with metastatic or recurrent ESCC or EAC refractory to a fluoropyrimidine and platinum.[17]

Patients were randomly assigned (1:1) to pembrolizumab monotherapy or the investigator's choice of chemotherapy (paclitaxel 80–100 mg/m² once per week for 3 weeks then 1 week off; docetaxel 75 mg/m² every 3 weeks; or irinotecan 180 mg/m² every 2 weeks). Randomization was also stratified according to histology (ESCC or EAC) and geographic region (Asia *versus* rest of the world).

The primary endpoint was OS in patients with PD-L1-positive tumors (CPS ≥ 10), in those with ESCC, and in all patients. The secondary endpoints were investigator-assessed PFS and ORR in patients with PD-L1-positive ESCC and in all patients.

In total, 628 patients was enrolled between 8 December 2015 and 16 June 2017 and assigned

to pembrolizumab monotherapy ($n = 314$) or chemotherapy ($n = 314$). At the time of data cut-off on 15 October 2018, median OS was 6.9 months in the pembrolizumab group and 7.1 months in the chemotherapy group. The patient background characteristics were follows: ECOG PS 0/1, 39%/61%; histologically confirmed ESCC/EAC, 401 patients (64%)/227 patients (36%); CPS ⩾10/⩽10/not evaluated, 35%/63%/2%; metastatic disease, 576 patients (92%); and 0/1/⩾2 previous treatments, 0.3%/98%/2%. Median OS was 9.3 months for patients with PD-L1-positive tumors (CPS ⩾10) in the pembrolizumab group and 6.7 months in their counterparts in the chemotherapy group [hazard ratio (HR) 0.69, 95% CI: 0.52–0.93; $p = 0.0074$], 8.2 months and 7.1 months, respectively, in the patients with ESCC (HR: 0.78, 95% CI: 0.63–0.96; $p = 0.0095$), and 7.1 months and 7.1 months in all patients (HR: 0.89, 95% CI: 0.75–1.05; $p = 0.0560$). Although statistically significant differences were not found for pembrolizumab in all groups, an unplanned subgroup analysis showed a favorable median OS of 10.3 months in patients with ESCC and 6.7 months in patients with PD-L1-positive tumors (HR: 0.64, 95% CI: 0.46–0.90). However, there was no statistically significant difference in median OS between patients with EAC and those with PD-L1-positive tumors (6.3 months *versus* 6.9 months; HR: 0.93, 95% CI: 0.52–1.65). There were fewer grade 3 or higher treatment-related AEs in the pembrolizumab group than 40.9% in the chemotherapy group (18.2% *versus* 40.9%).

Although the trial endpoint was not met, pembrolizumab demonstrated a median OS benefit over chemotherapy alone as second-line treatment for PD-L1-positive ESCC. Accordingly, the US Food and Drug Administration and Japanese Pharmaceuticals and Medical Device Agency approved pembrolizumab as second-line chemotherapy for patients with advanced or metastatic PD-L1-positive (CPS ⩾10) ESCC.

KEYNOTE-590 trial
KEYNOTE-590 was a randomized phase III trial that compared the efficacy of pembrolizumab + 5-fluorouracil and cisplatin (CF) with that of placebo + chemotherapy in patients with previously untreated, unresectable, or metastatic EAC or ESCC.[18]

Patients were randomly assigned (1:1) to receive either pembrolizumab (200 mg every 3 weeks) or placebo, plus CF (5-fluorouracil 800 mg/m² on Days 1–5 and cisplatin 80 mg/m² on Day 1) once every 3 weeks for up to 35 cycles. Randomization was also stratified by geographic region, histology (ESCC or EAC), and PS. The primary endpoints were OS in patients with ESCC and PD-L1-positive tumors (CPS ⩾10) and OS and PFS in patients with ESCC, PD-L1-positive tumors, and in all randomized patients. The secondary endpoints included safety and ORR and DOR in all patients and in PD-L1-positive patients. A total of 749 patients were enrolled and assigned to pembrolizumab + CF ($n = 373$) or placebo + CF ($n = 376$). The patient background characteristics were as follows: ECOG PS 0/1, 40%/60%; histology ESCC/EAC, 73%/27%; CPS ⩾10/⩽10/not evaluated, 51%/46%/3%; and metastatic disease/unresectable locally advanced, 91%/9%.

Median OS in patients with ESCC and PD-L1-positive tumors was significantly longer in the pembrolizumab + CF group than in the placebo + CF group (13.9 months *versus* 8.8 months; HR: 0.57, 95% CI: 0.43–0.75; $p < 0.0001$). Median OS was 12.6 months *versus* 9.8 months (HR: 0.72 95% CI: 0.60–0.88; $p < 0.0006$) in patients with ESCC, 13.5 months and 9.4 months (HR: 0.62, 95% CI: 0.49–0.78; $p < 0.0001$) in those with PD-L1-positive tumors, and 12.4 months and 9.8 months (HR: 0.73, 95% CI: 0.62–0.86; $p < 0.0001$) for the study population overall.

Median PFS was also significantly longer in patients with ESCC in the pembrolizumab + CF group than in their counterparts in the placebo + CF group (6.3 months *versus* 5.8 months; HR: 0.65, 95% CI: 0.54–0.78; $p < 0.0001$). Median PFS was significantly longer in patients with PD-L1-positive tumors in the respective groups (7.5 months *versus* 5.5 months; HR: 0.51, 95% CI: 0.41–0.65; $p < 0.0001$) and in all patients (6.3 *versus* 5.8 months; HR: 0.65, 95% CI: 0.55–0.76; $p < 0.0001$), indicating a significant increase in all populations. The secondary endpoint of ORR was also significantly prolonged in all patients (45.0% in the pembrolizumab + CF group and 29.3% in the placebo + CF group; $p < 0.0001$). Furthermore, subgroup analysis showed a trend toward longer median OS and PFS in patients with EAC.

Grade 3 or higher treatment-related AEs occurred in 86% of patients in the pembrolizumab + CF group and in 83% of those in the placebo + CF group (leukopenia, 24% *versus* 17%; anemia, 17% *versus* 22%; neutropenia, 15% *versus* 16%), with no significant between-group differences. The AE profile was consistent with that reported previously, with 7% of patients in the pembrolizumab + CF group experiencing grade 3 or higher immune-related AEs. Therefore, pembrolizumab + CF was well tolerated with an acceptable safety profile.

The results of KEYNOTE-590 suggested that pembrolizumab + doublet chemotherapy could be a standard first-line treatment in patients with metastatic or recurrent EC. The US Food and Drug Administration approved pembrolizumab + platinum and fluoropyrimidine-based chemotherapy as a first-line regimen for patients with advanced EC regardless of histology or PD-L1 expression on March 23, 2021.

Ongoing clinical investigations of pembrolizumab

Pembrolizumab + doublet chemotherapy consisting of a fluoropyrimidine and platinum has become the new first-line standard treatment for patients with advanced EC. However, median OS is still reported to be 12 months. The phase III LEAP-014 trial (NCT04949256) is presently evaluating the efficacy and safety of a new investigational regimen consisting of pembrolizumab and a fluoropyrimidine, platinum, and lenvatinib in an effort to improve clinical outcomes in patients with advanced ESCC (Table 1).

Definitive chemoradiotherapy is the standard treatment for unresectable locally advanced EC without metastasis, similar to for unresectable locally advanced lung cancer. A phase III trial known as PACIFIC has demonstrated the efficacy of ICI therapy administered after chemoradiotherapy in patients with unresectable locally advanced lung cancer.[45] This finding has led to some ongoing phase III trials investigating a strategy consisting of definitive chemoradiotherapy followed by or combined with an ICI in patients with unresectable and/or resectable locally advanced EC. KEYNOTE-975 (NCT04210115) is a phase III trial that is comparing concurrent use of pembrolizumab + definitive chemoradiotherapy consisting of a fluoropyrimidine and platinum regimen *versus* placebo + definitive chemoradiotherapy in patients with locally advanced ESCC or EAC (Table 2).

Preoperative chemoradiotherapy followed by surgery is now one of the standard treatment options for patients with resectable locally advanced ESCC, based on the results of the CROSS trial, in which OS was significantly longer in a group that received preoperative adjuvant chemoradiotherapy than in a group that underwent surgery alone (49.4 months *versus* 24.0 months.[46] Some trials are underway to evaluate a new investigational treatment of preoperative chemoradiotherapy + ICI therapy (Table 2). The phase I PALACE-1 study found that pembrolizumab in combination with preoperative chemoradiotherapy was safe with a pathological complete response rate of 55.6% in patients with resectable ESCC.[47] However, in a phase II trial conducted in Korea, the pathological complete response rate for pembrolizumab combined with preoperative chemoradiotherapy was poor at 23.1%.[48] Therefore, further investigations are needed to determine the efficacy of preoperative chemoradiotherapy + ICI therapy.

Discussion

Nowadays, there are two important clinical questions related to ICI therapy for patients with advanced EC. The first concerns the optimal first-line treatment for advanced EC. Like KEYNOTE-590, CheckMate 648 is a phase III trial and compared the efficacy of nivolumab + CF, nivolumab + ipilimumab, and CF alone as first-line treatment in patients with previously untreated, unresectable or metastatic ESCC.[49] In that study, patients were randomly assigned (1:1:1) to receive nivolumab (240 mg every 2 weeks) + CF, nivolumab (3 mg/kg every 2 weeks) + ipilimumab (1 mg/kg every 6 weeks), or CF alone. The primary endpoints were PFS and OS in all patients and ORR in patients with PD-L1-positive ESCC [tumor proportion score (TPS) ⩾ 1] and in all patients. In total, 970 patients were randomized (1:1:1), and about 50% were PD-L1 positive (TPS ⩾ 1). For patients with PD-L1-positive ESCC, median OS was significantly longer in the nivolumab + CF group than in the CF group (15.4 months *versus* 9.1 months; HR: 0.54, 95% CI: 0.37–0.80; *p* < 0.0001) and also significantly longer in the nivolumab + ipilimumab group than in the CF group (13.7 months

versus 9.1 months; HR: 0.64, 95% CI: 0.46–0.90; $p = 0.0010$). For all patients, median OS was significantly longer in the nivolumab + CF group than in the CF group (13.2 months *versus* 10.7 months; HR: 0.74, 95% CI: 0.58–0.96; $p = 0.002$) and was also significantly longer in the nivolumab + ipilimumab group than in the CF group (12.7 months *versus* 10.7 months; HR: 0.78, 95% CI: 0.62–0.98; $p = 0.01$).

For patients with advanced PD-L1-positive ESCC, median PFS was significantly longer in the nivolumab + CF group than in the CF group (6.9 months *versus* 4.4 months; HR: 0.65, 95% CI: 0.46–0.92; $p = 0.002$). However, median PFS was not significantly longer in the nivolumab + ipilimumab group than in the CF group (4.0 months *versus* 4.4 months; HR: 1.02, 95% CI: 0.73–1.43; $p = 0.90$). For all patients, median PFS was not significantly longer in the nivolumab + CF group than in the CF group (5.8 months *versus* 5.6 months; HR: 0.81, 95% CI: 0.64–1.04; $p = 0.0355$).

Given these results, clinicians would be required to select one of the following three options for patients with advanced ESCC: pembrolizumab + CF, nivolumab + CF, or nivolumab + ipilimumab. However, there are presently no data that can aid selection of the best treatment. EAC was included in only KEYNOTE-590, and pembrolizumab + CF is the treatment of choice for EAC. We believe that nivolumab + ipilimumab would be an option for with advanced ESCC who are not suitable for chemotherapy. In particular, patients with renal or cardiac dysfunction might benefit from treatment with ICIs alone. However, these frail patients were excluded in the CheckMate 648 trial and require further investigation. Biomarkers might be helpful for selecting optimal treatments, such as molecular targeted therapies. PD-L1 expression is recognized as one of the promising biomarker candidates for predicting the efficacy of ICI-containing regimens. PD-L1 expression was considered in the pivotal clinical trials for ICI therapy in patients with EC. KEYNOTE-181 examined PD-L1 expression based on the CPS and suggested a benefit in patients with a CPS ≥ 10.[16] CheckMate-577 also reported the usefulness of the CPS.[50] A retrospective trial at our hospital found that PFS tended to be better at a higher CPS cutoff point (CPS: 5, HR: 1.33; CPS: 10, HR: 0.85, and CPS: 20, HR: 0.70).[51] Therefore, it is expected that CPS will be confirmed as a biomarker for patients with advanced ESCC treated with ICI therapy at the 2022 ASCO-GI meeting. However, CPS alone is not sufficient for accurate prediction of the efficacy of ICI therapy, and further studies are needed.

The second question concerns the optimal treatment for patients who have previously received ICI therapy. The phase III CheckMate 577 trial evaluated adjuvant nivolumab monotherapy compared with placebo in patients with resectable EC or EGJ cancer who had received preoperative chemoradiotherapy and had residual pathological disease.[50] Patients were randomly assigned (2:1) to nivolumab monotherapy ($n = 532$; at dose of 240 mg every 2 weeks for 16 weeks followed by nivolumab at dose of 480 mg every 4 weeks) or to placebo ($n = 262$). The primary endpoint was disease-free survival (DFS). A pre-specified interim analysis showed that postoperative nivolumab monotherapy achieved a statistically significant improvement in median DFS compared with placebo [22.4 months (95% CI: 6.6–34.0) *versus* 11.0 months (95% CI: 8.3–14.3); HR: 0.69, 95% CI: 0.56–0.86; $p = 0.0003$]. In the histological subgroup analysis, median DFS tended to be better in the nivolumab group than in the placebo group for patients with ESCC (29.7 months *versus* 11.0 months; HR: 0.61) than for those with EAC (19.4 months *versus* 11.1 months; HR: 0.75).

The rate of treatment-related AEs leading to treatment discontinuation was 9% in the nivolumab group and 3% in the placebo group. Therefore, postoperative nivolumab monotherapy was well tolerated with an acceptable safety profile.

Accordingly, the US Food and Drug Administration and Japanese Pharmaceuticals and Medical Device Agency approved postoperative nivolumab therapy for patients who have undergone preoperative radiation chemotherapy and complete resection but failed to achieve a pathological complete response.

Optimal treatment of patients with early recurrence during or after postoperative nivolumab therapy has not been established. Given the data to date, ICI-containing regimens are not expected to be effective if the patient relapses during postoperative nivolumab therapy or

Table 1. Clinical trials of pembrolizumab in patients with metastatic or recurrent EC.

Clinical trial	Phase	Histology	Line	Patients, n	Regimen	ORR (%)	PFS (months)	OS (months)
KEYNOTE-180	II	ESCC, EAC	Third or later	121	Pembrolizumab	9.9	2.0	5.8
KEYNOTE-181	III	ESCC, EAC	Second	628	Pembrolizumab	13.1	2.1	7.1
KEYNOTE-590	III	ESCC, EAC	First	749	CF + pembrolizumab *versus* CF alone	45	6.3	12.4
LEAP-014	III	ESCC	First	Recruiting	CF + pembrolizumab ± lenvatinib	NA	NA	NA

CF, cisplatin + 5-fluorouracil; EAC, esophageal adenocarcinoma; EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; NA, not assessed; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Table 2. Clinical trials related to pembrolizumab in patients with locally advanced EC and EAC.

Clinical trial	Phase	Histology	Line	Patients, n	Regimen	pCR (%)	PFS (months)	OS (months)
KEYNOTE-975	III	ESCC, EAC	dCRT	Recruiting	dCRT ± pembrolizumab	NA	NA	NA
PALACE-1 (NCT03792347)	I	ESCC	Preoperative	20	Preoperative CRT + pembrolizumab	55.6	NA	NA
ACTS-29 (NCT02844075)	II	ESCC	Perioperative	28	Preoperative CRT + pembrolizumab Postoperative pembrolizumab	23.1	NA	NA
KEYNOTE-585	III	Gastric and EGJ AC	Perioperative	Recruiting	5-FU + platinum ± pembrolizumab	NA	NA	NA

AC, adenocarcinoma; CRT, chemoradiotherapy; dCRT, definitive chemoradiotherapy; EAC, esophageal adenocarcinoma; EGJ, esophagogastric junction; ESCC, esophageal squamous cell carcinoma; NA, not assessed; OS, overall survival; pCR, pathological complete response; PFS, progression-free survival.

shows early progression thereafter. Hence, the regimens selected would include the conventional cytotoxic agents, such as 5-fluorouracil, platinum, and taxanes without use of preoperative chemotherapy. These agents are key drugs for EC and might be candidates for use as palliative chemotherapy. Furthermore, platinum-based chemotherapy might alter the immune environment after cytotoxic chemotherapy.[33] Therefore, ICI rechallenge after such chemotherapy may be considered. The efficacy of ICI rechallenge has been reported for patients with non-small-cell lung cancer.[52] However, if patients received preoperative docetaxel + CF and postoperative nivolumab and showed early recurrence, the efficacy was limited. Therefore, new agents are needed. JCOG1804E (the FRONTiER trial) has evaluated the safety and efficacy of nivolumab in combination with CF or docetaxel + CF as preoperative chemotherapy in patients with resectable EC.[53] A pathological complete response rate of 33.3% was reported in patients treated with preoperative docetaxel + CF + nivolumab. These results suggest that this regimen is promising and that an ICI could be used for preoperative chemotherapy in the future. The development of treatment for patients who have relapsed after such therapy also requires consideration in the future.

Conclusions

Based on the results of KEYNOTE-590, pembrolizumab + chemotherapy has become the standard first-line chemotherapy for patients with metastatic or recurrent EC. The results of CheckMate 648 also suggest that nivolumab + chemotherapy and nivolumab + ipilimumab might become standard first-line chemotherapy for patients with metastatic or recurrent ESCC. These ICI-containing therapies have contributed to prolonging life expectancy in these patients when used first line. Studies of new investigational therapies are already underway. This is an area that will require further attention in the future.

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