KEYNOTE-590: Phase III study of first-line chemotherapy with or without pembrolizumab for advanced esophageal cancer

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Background: Treatment options for patients with advanced esophageal or esophagogastric junction (EGJ) cancer are limited. Current guidelines for first-line treatment of advanced esophageal or EGJ cancer recommend chemotherapy containing a platinum and a fluoropyrimidine agent. Pembrolizumab demonstrated antitumor activity in previously treated patients with advanced esophageal cancer and in patients with gastroesophageal junction cancer. **Aim:** To describe the design and rationale for the randomized, double-blind, placebo-controlled Phase III KEYNOTE-590 study, which will be conducted to investigate pembrolizumab in combination with chemotherapy as first-line treatment in patients with advanced esophageal or EGJ cancer.

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Esophageal cancer is the eighth most commonly diagnosed cancer worldwide and the sixth most common cause of cancer-related death (incidence, approximately 456,000; mortality, 400,000 in 2012) [1]. Incidence varies significantly between regions, with age-standardized rates ranging from 2.2 per 100,000 in the Middle East and Northern Africa to 10.2 per 100,000 in the Western Pacific region [2]. It is estimated that, in 2018, 17,000 people were diagnosed with esophageal cancer in the USA and almost 16,000 died of the disease [3]. The 5-year survival rate for patients with diagnosed esophageal cancer in the USA is only 18%, with poor outcomes attributed to late diagnosis and a propensity for metastases [4,5].

Most esophageal cancers can be categorized into two main histologic subtypes: squamous cell carcinoma (SCC) and adenocarcinoma. SCC is the most common esophageal cancer subtype diagnosed worldwide; however, there has been a shift in the past four decades toward an increasing incidence of adenocarcinoma in western populations [6,7].

Treatment options for patients with unresectable advanced or metastatic esophageal or esophagogastric junction (EGJ) cancer are limited. Current guidelines for the first-line treatment of advanced or metastatic disease recommend platinum-based chemotherapy in combination with fluoropyrimidine [8,9]. Although European Society for Medical Oncology guidelines recommend monotherapy or best supportive care as first-line therapy in patients with SCC [8], platinum doublet chemotherapy is commonly used without supportive evidence from randomized controlled trials in Asian countries, with response rates of only 20–50% [10]. For patients whose disease progresses on first-line therapy, there is no consensus on a second-line regimen, although docetaxel, paclitaxel and irinotecan are commonly used for both histologic subtypes [11–16]. The effectiveness of targeted agents has also been investigated. Results of the Trastuzumab for Gastric Cancer trial demonstrated that trastuzumab plus chemotherapy had antitumor activity in patients with HER-positive gastric or EGJ cancer but provided limited survival benefit to patients with low HER2 expression [17]. In two Phase III clinical trials, ramucirumab, a monoclonal antibody VEGFR2 antagonist, was effective only in patients with previously treated advanced or metastatic gastric or EGJ cancer [18,19]. Most patients in these trials to investigate targeted agents had gastric adenocarcinoma; only 17–26% had EGJ cancer [17–19]. Current guidelines recommend pembrolizumab for second-line or subsequent therapy for tumors with high microsatellite instability or deficient mismatch repair and for third-line or subsequent therapy for PD-L1-positive esophageal and EGJ adenocarcinoma [8]. Less evidence is available for esophageal SCC than for adenocarcinoma; platinum-containing chemotherapy provides response rates of 20–50% and median overall survival duration of 8–10 months [20,21]. Targeted agents have also been investigated as first-line therapy in patients with esophageal SCC, but these earlier attempts failed to demonstrate a clear benefit over chemotherapy alone [10,21,22]. Hence, there remains a significant need for novel therapeutic agents for the first-line treatment of advanced or metastatic esophageal or EGJ cancer.

KEYNOTE-590 trial

Herein, we describe the design and rationale for the randomized, double-blind, placebo-controlled Phase III KEYNOTE-590 study (ClinicalTrials.gov: NCT03189719), which will be conducted to evaluate the efficacy and safety of pembrolizumab plus chemotherapy compared with placebo plus chemotherapy as first-line treatment of patients with advanced esophageal or EGJ carcinoma.

Background & rationale

Pembrolizumab is a high-affinity, highly selective, humanized immunoglobulin G4- κ monoclonal antibody designed to block the interaction between PD-1 and its ligands, PD-L1 and PD-L2 [23,24]. Pembrolizumab has demonstrated robust, durable antitumor activity and a manageable safety profile against several advanced solid tumors and is approved in >60 countries for the treatment of one or more advanced cancers. The antitumor activity and safety of pembrolizumab in patients with esophageal carcinoma was previously investigated in the Phase Ib KEYNOTE-028 trial [25], the Phase II KEYNOTE-059 trial [26] and the Phase II KEYNOTE-180 trial [27].

The KEYNOTE-028 study included 23 patients with heavily pretreated, PD-L1-positive advanced esophageal cancer (78% SCC, 22% adenocarcinoma) who received pembrolizumab 10 mg/kg every 2 weeks for up to 2 years. After a median follow-up of 7 months, the objective response rate (ORR) was 30% (95% CI: 13–53%) with seven patients achieving confirmed partial response. ORR by histologic subtype was 28% (5/18 patients) for patients with SCC and 40% (2/5 patients) for those with adenocarcinoma. The median time to initial response was 4 months (range: 2–8 months), and the median duration of response was 15 months (range: 6 to ≥ 26 months) [25]. The KEYNOTE-059 study included 259 patients with previously treated gastroesophageal junction (51%) or gastric (49%) cancer who received pembrolizumab 200 mg intravenously every 3 weeks until disease progression. After a median follow-up of 5.8 months, the ORR was 11.6% (95% CI: 8–16%), with six (2.3%) patients achieving complete response; the median duration of response was 8.4 months (range: ≥ 1.6 to ≥ 17.3 months) [26]. The KEYNOTE-180 (ClinicalTrials.gov: NCT02559687) trial is an open-label, Phase II study to evaluate pembrolizumab monotherapy as third-line therapy in patients with advanced adenocarcinoma or SCC of the esophagus or advanced Siewert Type 1 adenocarcinoma of the EGJ. Patients in the current trial were treated with pembrolizumab 200 mg every 3 weeks for up to 2 years. After a median follow-up of 5.8 months, the ORR was 10% (95% CI: 5–17%), with 12 patients achieving confirmed partial response. In patients with PD-L1-positive

tumors, the ORR was 14% (95% CI: 6–25%), whereas in patients whose tumors were PD-L1-negative, the ORR was 6% (95% CI: 2–16%) [27].

In addition to the KEYNOTE-590 and KEYNOTE-180 studies, another clinical trial is underway to investigate the efficacy and safety of pembrolizumab in esophageal cancer. KEYNOTE-181 (ClinicalTrials.gov: NCT02564263) is a randomized, open-label, Phase III study to evaluate pembrolizumab monotherapy compared with physician's choice of standard therapy with paclitaxel, docetaxel or irinotecan in patients with advanced adenocarcinoma or SCC of the esophagus or advanced Siewert Type 1 adenocarcinoma of the EGJ that progressed after standard first-line therapy. The KEYNOTE-181 study has recently completed recruitment and is ongoing.

The promising antitumor activity demonstrated in the KEYNOTE-028 study in patients with heavily pretreated advanced esophageal cancer with both histologies and in the KEYNOTE-059 study in patients with pretreated gastroesophageal junction cancer and the continued unmet need for an effective treatment option for first-line advanced esophageal cancer support the early adoption of pembrolizumab as recommended third-line or subsequent therapy for PD-L1-positive esophageal and EGJ adenocarcinoma in recent US guidelines [28] and the investigation of pembrolizumab in patients with previously untreated advanced esophageal cancer. Furthermore, the addition of pembrolizumab to standard chemotherapy may translate to superior effectiveness and improved patient outcomes. It is known that platinum salts can have an iatrogenic impact on cancer evolution via the generation of neoantigens when tumor cells are destroyed [29], and, in esophageal cancers, these may be added to *de novo* mutations caused by common carcinogens, such as tobacco smoke and alcohol toxins [30]. Because the mutational landscape can determine sensitivity to PD-1 blockade, the presence of these neoantigens may increase pembrolizumab effectiveness and influence tumor regression [31,32]. Finally, in light of recent molecular classification data published by The Cancer Genome Atlas describing heterogeneous molecular subclasses [33], it is clear that biomarker analyses may provide information to assist in selecting those patients most likely to benefit from immunotherapy.

Study design

The KEYNOTE-590 study is a randomized, double-blind, placebo-controlled Phase III study (Figure 1). Eligible patients will be randomly assigned in a 1:1 ratio to receive pembrolizumab 200 mg or placebo (normal saline) by intravenous (iv.) infusion every 3 weeks (Q3W) in combination with chemotherapy. The chemotherapy regimen for both arms will consist of cisplatin 80 mg/m² iv. Q3W (maximum six doses) plus 5-fluorouracil 800 mg/m² continuous iv. infusion on days 1–5 Q3W. Treatment will continue until confirmed radiographic progression, unacceptable toxicity, investigator or patient decision to withdraw, nonadherence to treatment or trial procedures or completion of 35 cycles of pembrolizumab or placebo (approximately 2 years).

Randomization will be performed using an interactive voice/web response system and will be stratified according to geographic region (Asia vs rest of world), histology (adenocarcinoma vs SCC), and Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1). Pembrolizumab or placebo assignment will be masked to patients and investigators.

Eligibility criteria

Eligibility criteria are described in Table 1. Briefly, men and women aged 18 years or older were eligible for enrollment if they had a histologically or cytologically confirmed diagnosis of locally advanced unresectable or metastatic adenocarcinoma or SCC of the esophagus or if they had advanced/metastatic Siewert Type 1 adenocarcinoma of the EGJ.

Planned sample size & study period

The planned sample size is approximately 700 patients. The study started in July 2017, and the estimated study completion date is 22 August 2021.

Outcome measures/end points

Primary end points are progression-free survival (PFS) and overall survival (OS) in all patients and in the subgroup of patients with a PD-L1 combined positive score (CPS) ≥ 10 . PFS is defined as the time from randomization to first documented disease progression per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) by blinded independent central review or death from any cause, whichever occurs first. OS is defined as the time from randomization to death from any cause. Secondary end points are safety and tolerability, ORR and duration of response per RECIST v1.1 by blinded independent central review and health-related quality of life

Figure 1. KEYNOTE-590 study design.

*Duration of cisplatin treatment will be capped at six cycles; however, treatment with 5-FU can continue per local standard.

5-FU: 5-fluorouracil; ECOG: Eastern Cooperative Oncology Group; EGJ: Esophagogastric junction; R: Randomization; SCC: Squamous cell carcinoma.

(assessed using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire [EORTC QLQ] core 30 items [C30] and esophageal module [OES18]) in all patients and in patients with PD-L1 CPS ≥ 10 . Exploratory end points include characterization of utilities using the EuroQol 5D 5-level (EQ-5D-5L) questionnaire and the evaluation of PFS per immune-related RECIST by blinded independent central review in all patients and in patients with PD-L1 CPS ≥ 10 . Additional biomarkers that may be indicative of clinical response or resistance, safety, pharmacodynamic activity or mechanism of action of pembrolizumab may also be investigated.

Study procedures

Tumor response and disease progression will be assessed using computed tomography or magnetic resonance imaging if computed tomography is contraindicated. Initial tumor imaging will be performed during screening (within 21 days before randomization). Thereafter, imaging will be performed every 9 weeks (or more often if clinically indicated) until disease progression (confirmed by subsequent imaging ≥ 4 weeks after first documentation of disease progression and verified by central review), start of new anticancer treatment, withdrawal of consent

Table 1. Eligibility criteria for KEYNOTE-590.

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> Male or female Age ≥ 18 years Histologically or cytologically confirmed locally advanced unresectable or metastatic adenocarcinoma or SCC of the esophagus or advanced Siewert Type 1 adenocarcinoma of the esophagogastric junction Measurable disease per RECIST v1.1 assessed by the local investigator ECOG performance status 0 or 1 Provide newly obtained (preferred) or archival tissue sample Negative urine or serum pregnancy test within 72 h before randomization (females) Willing to use an adequate method of contraception throughout the study and for 120 days after the last dose of study medication and up to 180 days after the last dose of cisplatin Adequate hematologic function, defined as ANC $\geq 1500/\mu\text{L}$, platelet count $\geq 100,000/\mu\text{L}$ and hemoglobin ≥ 9.0 g/dl or ≥ 5.6 mmol/l Adequate renal function, defined as creatinine $\leq 1.5 \times \text{ULN}$ or measured or calculated creatinine clearance ≥ 60 mL/min for those with creatinine levels $>1.5 \times \text{ULN}$ Adequate hepatic function, defined as total bilirubin $\leq 1.5 \times \text{ULN}$, or direct bilirubin $\leq \text{ULN}$ for those with total bilirubin levels $>1.5 \times \text{ULN}$, and ALT/AST levels $\leq 2.5 \times \text{ULN}$ Adequate coagulation function, defined as INR $\leq 1.5 \times \text{ULN}$ unless the patient is receiving anticoagulant therapy as long as PT or aPTT is within the therapeutic range Written informed consent 	<ul style="list-style-type: none"> Locally advanced esophageal carcinoma that is resectable or potentially curable with radiation therapy per local investigator Previous therapy for advanced disease Major surgery, open biopsy or significant traumatic injury within 28 days before randomization or anticipated need for major surgery during the study treatment period Known additional malignancy that is progressing or requires active treatment (except for BCC or SCC of the skin, <i>in situ</i> cervical cancer, <i>in situ</i> breast cancer that has undergone potentially curative treatment and <i>in situ</i> or intramucosal pharyngeal cancer) Known active CNS metastases and/or carcinomatous meningitis; patients with previously treated and radiologically stable brain metastases may be eligible Active autoimmune disease that has necessitated systemic treatment (other than replacement therapy) in the past 2 years Diagnosis of immunodeficiency, receiving chronic systemic steroid therapy >10 mg daily prednisone equivalent or any other form of immunosuppressive therapy within 7 days before the first dose of study treatment or history of organ transplant including allogeneic stem cell transplant Active infection necessitating systemic therapy History or current evidence of any condition, therapy or laboratory abnormality that might confound the study results or interfere with study participation Known psychiatric or substance abuse disorder that would interfere with cooperation with study requirements Pregnant or breastfeeding or expecting to conceive within the projected study duration Prior treatment with anti-PD-1, anti-PD-L1 or anti-PD-L2 agent or an agent directed to another stimulatory or coinhibitory T-cell receptor (e.g., CTLA4, OX40, CD137) Known hypersensitivity (grade ≥ 3) to any of the study drugs or their excipients Known history of HIV, HBV or HCV infection Known history of active tuberculosis Prior radiotherapy within 14 days of randomization Receipt of live vaccine within 30 days before the first dose of study treatment Participation in a study of an investigational agent or device within 4 weeks before the first dose of study treatment

ALT: Alanine aminotransferase; ANC: Absolute neutrophil count; aPTT: Activated partial thromboplastin time; AST: Aspartate aminotransferase; BCC: Basal cell carcinoma; ECOG: Eastern Cooperative Oncology Group; HBV: Hepatitis B virus; HCV: Hepatitis C virus; INR: International normalized ratio; PT: Prothrombin time; SCC: Squamous cell carcinoma; ULN: Upper limit of normal.

or death, whichever occurs first. Patients will be followed up for survival status by telephone approximately every 12 weeks until death, withdrawal of consent or the end of the study (whichever occurs first).

Safety will be monitored throughout the study and for 30 days after the end of treatment (90 days for serious adverse events). Safety analysis will include the incidence, causality and outcome of adverse events; changes in vital signs; and changes in laboratory values. Adverse events will be graded and recorded throughout the trial and follow-up period per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Patient-reported outcome assessments (EORTC QLQ-C30, EORTC QLQ-OES18 and EQ-5D-5L) will be administered electronically on day 1 (before drug administration, adverse event evaluation and disease status notification) of each cycle during cycles 1–9, every three cycles thereafter for up to 1 year, at the time of treatment discontinuation and at 30 days after treatment discontinuation. Tumor PD-L1 expression will be assessed by use of a Good Manufacturing Practice immunohistochemistry assay (PD-L1 IHC 22C3 pharmDx; Agilent Technologies, CA, USA). PD-L1 is measured as the CPS, or the number of PD-L1-positive cells (tumor cells, lymphocytes and macrophages) divided by the total number of tumor cells, multiplied by 100. Exploratory biomarker investigation may include genetic, RNA and proteomics analyses of blood and tumor samples.

Statistics

Efficacy will be assessed in the intent-to-treat population (all randomly assigned patients) and analyzed by randomized treatment group. Safety will be assessed in all randomly assigned patients who received at least one dose of study drug and will be analyzed by treatment received. The primary hypothesis for PFS and OS will be evaluated by comparing pembrolizumab plus chemotherapy with placebo plus chemotherapy using a stratified log-rank test. The study will be considered to have met its primary objective if at least one of the primary hypotheses is significant after controlling for multiplicity. Hazard ratios will be estimated using a stratified Cox proportional hazards regression

model using the same factors for randomization (geographic region, histology and ECOG performance status). Event rates over time will be estimated using the Kaplan–Meier method.

Interim analyses are planned. An external data monitoring committee will periodically review efficacy and safety results to determine whether the study will continue per prespecified criteria.

Conclusion

Pembrolizumab demonstrated promising antitumor activity in the esophageal cohort of the Phase Ib KEYNOTE-028 trial, which provided support for the further investigation of pembrolizumab in patients with advanced esophageal cancer. Preliminary data from the ongoing KEYNOTE-180 trial have also demonstrated promising antitumor activity in patients with previously treated, advanced/metastatic adenocarcinoma SCC of the esophagus or Siewert Type 1 adenocarcinoma of the gastroesophageal junction. In addition, the KEYNOTE-181 study is underway to investigate the safety and efficacy of pembrolizumab for previously treated advanced esophageal cancer. Herein, we described the methodology for the KEYNOTE-590 study, an ongoing Phase III study being conducted to investigate the safety and efficacy of pembrolizumab as first-line treatment for advanced esophageal carcinoma. The study aims to show that the combination of pembrolizumab with chemotherapy will provide improved effectiveness over chemotherapy alone and that the results from the KEYNOTE-590 study will help define the role of immunotherapy in patients with esophageal cancer, a patient population for whom treatment options are limited. In addition, biomarker data from this study may assist in determining the factors that influence the efficacy of immunotherapy and in selecting the patient subpopulations most likely to benefit from treatment with pembrolizumab.

Summary points

Introduction

- Treatment options for patients with unresectable advanced or metastatic esophageal or esophagogastric junction (EGJ) cancer are limited.
- Current guidelines for first-line treatment recommend chemotherapy containing a platinum and a fluoropyrimidine agent.

Background & rationale

- In the Phase Ib KEYNOTE-028 trial in patients with heavily pretreated, PD-L1-positive advanced esophageal carcinoma, pembrolizumab demonstrated promising antitumor activity (objective response rate: 30%) and a manageable safety profile.
- Pembrolizumab also demonstrated promising activity in the Phase II KEYNOTE-059 trial in patients with previously treated gastric or gastroesophageal junction cancer, thus supporting inclusion of pembrolizumab for third-line or subsequent therapy for PD-L1-positive esophageal and EGJ adenocarcinoma in the National Comprehensive Cancer Network Guidelines.
- Combining chemotherapy with pembrolizumab as first-line therapy may be beneficial for patients with advanced esophageal or EGJ cancer.

KEYNOTE-590 study design & eligibility criteria

- KEYNOTE-590 is a randomized, double-blind, placebo-controlled, Phase III study to evaluate the efficacy and safety of pembrolizumab plus chemotherapy compared with placebo plus chemotherapy as first-line treatment for patients with advanced esophageal or EGJ cancer.
- Approximately 700 patients with previously untreated, locally advanced, unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the esophagus or advanced or metastatic Siewert Type 1 adenocarcinoma of the EGJ will be enrolled.
- Eligible patients will be randomly assigned to receive pembrolizumab or placebo in combination with chemotherapy (cisplatin plus 5-fluorouracil).

Outcome measures/end points

- The primary end points are progression-free survival and overall survival in all patients and in patients who have a PD-L1 combined positive score ≥ 10 .

Conclusion

- It is hoped that results from the KEYNOTE-590 trial will help define the role of immunotherapy in patients with esophageal cancer.

Supplementary data

An infographic accompanies this paper at the end of the references section. To download the infographic that accompanies this paper, please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/fon-2018-0609

Author contributions

All authors were involved in the conception, design or planning of the study and critically reviewed and revised the manuscript for important intellectual content.

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Ethical conduct of research

The authors state that they obtained appropriate institutional review board approval and followed the principles outlined in the Declaration of Helsinki for all human experimental investigations and that they received informed consent from the participants involved.

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<p>Article details</p> <p> Title of article KEYNOTE-590: Phase III study of first-line chemotherapy with or without pembrolizumab for advanced esophageal cancer</p> <p> Authors Ken Kato, Manish A Shah, Peter Enzinger, Jaafar Bennouna, Lin Shen, Antoine Adenis, Jong-Mu Sun, Byoung Chul Cho, Mustafa Ozguroglu, Takashi Kojima, Vladimir Kotorov, Cinta Hierro, Ying Zhu, Lee Anne McLean, Sukrut Shah and Toshihiko Doi</p> <p> Article URL www.futuremedicine.com/doi/10.2217/fo-2018-0609</p> <p> Trial registration number NCT03189719</p>	<p>Study design and treatment including planned sample size, planned study period and study procedures (cont)</p> <p>Eligible patients will be randomly assigned in a 1:1 ratio to receive pembrolizumab 200 mg or placebo (normal saline) by iv. infusion Q3W in combination with chemotherapy. The chemotherapy regimen for both arms will consist of cisplatin 80 mg/m² iv. Q3W (capped at 6 doses) plus 5-FU 800 mg/m² continuous iv. infusion on days 1–5 Q3W. Treatment will continue until confirmed radiographic progression, unacceptable toxicity, investigator or patient decision to withdraw, nonadherence to treatment or trial procedures or completion of 35 cycles of pembrolizumab or placebo (~2 years)</p> <p>Randomized patients will be stratified according to geographic region (Asia vs rest of world), histology (adenocarcinoma vs SCC), and ECOG performance status (0 or 1). Pembrolizumab or placebo assignment will be masked to patients and investigators.</p> <p>The planned sample size is ~700 patients. The study started in July 2017, and the estimated study completion date is August 22, 2021.</p>
<p>Primary objective/rationale</p> <p> Primary objective Compare between treatment arms PFS per RECIST 1.1, as determined by blinded independent central review, and OS in all patients whose tumors are PD-L1 CPS ≥10</p> <p> Secondary objectives Evaluate between treatment arms in all patients whose tumors are PD-L1 CPS ≥10: • ORR per RECIST 1.1, as determined by blinded independent central review • DOR per RECIST 1.1, as determined by blinded independent central review • Changes from baseline in HRQOL using the EORTC QLQ-C30 and the EORTC QLQ-OES18</p>	<p>Key eligibility criteria</p> <p>Age ≥18 years, male or female</p> <p>Histologically or cytologically confirmed diagnosis of locally advanced unresectable or metastatic adenocarcinoma or SCC of the esophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the EGJ</p> <p>Measurable disease per RECIST v1.1 assessed by the local investigator</p> <p>ECOG performance status 0 or 1</p> <p>Provide newly obtained (preferred) or archival tissue sample</p> <p>Negative urine or serum pregnancy test within 72 h before randomization (females)</p> <p>Willing to use an adequate method of contraception throughout the study and for 120 days after the last dose of study medication and up to 180 days after the last dose of cisplatin</p> <p>Adequate hematologic function, defined as ANC ≥1500/μl, platelet count ≥100,000/μl and hemoglobin ≥9.0 g/dl or ≥5.6 mmol/l</p> <p>Adequate renal function, defined as creatinine ≤1.5 × ULN or measured or calculated creatinine clearance ≥60 ml/min for those with creatinine levels >1.5 × ULN</p> <p>Adequate hepatic function, defined as total bilirubin ≤1.5 × ULN or direct bilirubin ≤ULN for those with total bilirubin levels >1.5 × ULN, and ALT/AST levels ≤2.5 × ULN</p> <p>Adequate coagulation function, defined as INR ≤1.5 × ULN unless the patient is receiving anticoagulant therapy as long as PT or aPTT is within the therapeutic range</p> <p>Written informed consent</p>
<p>Study design and treatment including planned sample size, planned study period and study procedures</p> <p>Global Placebo-controlled Multicenter Two-arm study Randomized 1:1</p> <p>Phase III Target enrollment: ~700 patients</p> <p>Stratification factors</p> <ul style="list-style-type: none"> Geographic region (Asia vs non-Asia) Histology (adenocarcinoma vs SCC) ECOG performance status (0 or 1) <p>Eligibility criteria</p> <ul style="list-style-type: none"> Confirmed advanced adenocarcinoma or SCC of the esophagus or Siewert Type 1 adenocarcinoma of the EGJ <p>R (1:1) n ≈ 700</p> <p>Placebo + 5-FU + cisplatin*</p> <p>Pembrolizumab + 5-FU + cisplatin*</p> <p>Disease progression or unacceptable toxicity</p> <p>*Duration of cisplatin treatment will be capped at six cycles; however, treatment with 5-FU can continue per local standard.</p>	<p>Outcome measures/end points</p> <p>Primary end points</p> <p>PFS and OS in all patients and in the subgroup of patients with PD-L1 CPS ≥10. PFS is defined as the time from randomization to first documented disease progression per RECIST v1.1 by blinded independent central review or death from any cause, whichever occurs first. OS is defined as the time from randomization to death from any cause</p> <p>Secondary end points</p> <p>Safety and tolerability, ORR and duration of response per RECIST v1.1 by blinded independent central review and health-related quality of life (assessed using the EORTC QLQ C30 and esophageal module) in all patients and in patients with PD-L1 CPS ≥10</p> <p>Exploratory end points</p> <p>Utilities using EQ-5D-5L questionnaire, PFS per immune-related RECIST by blinded independent central review in all patients and in patients with PD-L1 CPS ≥10, molecular biomarkers that might be indicative of response, resistance, safety, pharmacodynamic activity or mechanism of action of pembrolizumab</p>
	<p>Glossary</p> <p>ALT: Alanine aminotransferase; ANC: Absolute neutrophil count; aPTT: Activated partial thromboplastin time; AST: Aspartate aminotransferase; CPS: Combined positive score; DOR: Duration of response; ECOG: Eastern Cooperative Oncology Group; EGJ: Esophagogastric junction; EORTC QLQ-C30: EORTC Quality of Life Questionnaire C30; EORTC QLQ-OES18: EORTC Quality of Life Questionnaire Oesophageal Module; EORTC: European Organisation for the Research and Treatment of Cancer; EQ-5D-5L: EuroQol 5-dimension 5-level; INR: International normalized ratio; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; Q3W: Every 3 weeks; RECIST v1.1: Response Evaluation Criteria in Solid Tumors version 1.1; SCC: Squamous cell carcinoma; ULN: Upper limit of normal</p>