Clinical Trial Protocol

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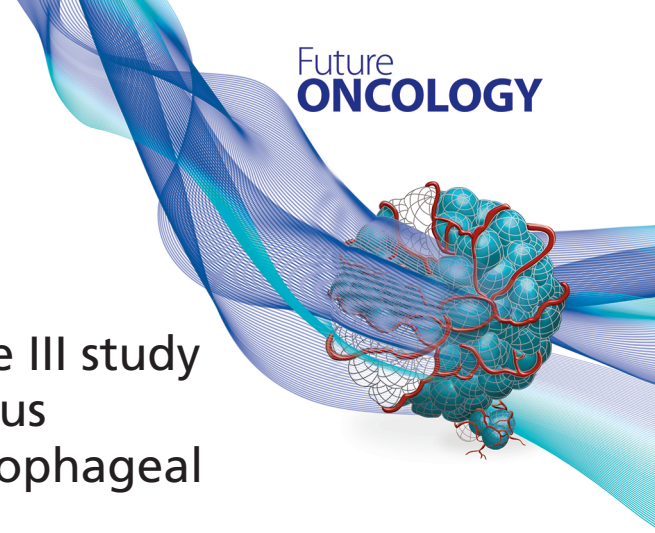

KEYNOTE-975 study design: a Phase III study of definitive chemoradiotherapy plus pembrolizumab in patients with esophageal carcinoma

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Despite curative-intent treatment, most patients with locally advanced esophageal cancer will experience disease recurrence or locoregional progression, highlighting the need for new therapies. Current guidelines recommend definitive chemoradiotherapy in patients ineligible for surgical resection, but survival outcomes are poor. Pembrolizumab is well tolerated and provides promising antitumor activity in patients with previously treated, advanced, unresectable esophageal/esophagogastric junction cancer. Combining pembrolizumab with chemoradiotherapy may further improve outcomes in the first-line setting. Here, we describe the design and rationale for the double-blind, Phase III, placebo-controlled, randomized KEYNOTE-975 trial investigating pembrolizumab in combination with definitive chemoradiotherapy as first-line treatment in patients with locally advanced, unresectable esophageal/gastroesophageal junction cancer. Overall survival and event-free survival are the dual primary end points.

Clinical trial registration: NCT04210115 (ClinicalTrials.gov)

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According to 2018 global estimates, esophageal cancer was the ninth most commonly diagnosed cancer worldwide (572,034 new cases) and the sixth most common cause of cancer-related death (508,585 deaths) [1]. The incidence of esophageal cancer varies substantially among geographic regions, with estimated age-standardized rates ranging from approximately 2.1 per 100,000 in Central America to approximately 24.7 per 100,000 in Eastern Asia [1]. The 5-year survival rates remain low at approximately 20% [2], with poor outcomes attributable to diagnosis occurring at advanced stages of the disease and the high propensity for metastases among patients with localized disease [3].

Esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) are the two primary histologic subtypes of esophageal cancer [2]. ESCC is the predominant subtype in most regions of the world,

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accounting for approximately 90% of all esophageal cancers, and typically results from direct contact between carcinogenic compounds, such as tobacco and alcohol, and the esophageal mucosa. Common risk factors for EAC are chronic gastroesophageal reflux disease, obesity, and male sex [2]. Responses to chemotherapy and radiotherapy differ between ESCC and EAC, which may in part be explained by the fact that the two subtypes are distinct biological entities with complex molecular features [4].

For patients with clinically resectable, locally advanced ESCC or EAC, neoadjuvant chemoradiotherapy or postoperative chemotherapy offers a survival benefit over surgery alone, as demonstrated in the CROSS and JCOG9907 trials [5,6]. However, as many as 50–60% of patients with esophageal cancer are ineligible for curative resection [7]. For many of these patients, definitive chemoradiotherapy is recommended as a standard treatment option. The preferred chemotherapy regimens used with radiotherapy include 5-fluorouracil and cisplatin (FP), 5-fluorouracil and oxaliplatin or paclitaxel and carboplatin, each with similar efficacy [8–10]. Evidence supporting the use of these chemotherapy regimens as part of definitive chemoradiotherapy in the first-line setting were based on the results of pivotal randomized clinical trials in patients with locally advanced esophageal cancer. The landmark Radiation Therapy Oncology Group trial (RTOG-8501) established that definitive radiotherapy plus chemotherapy with FP was superior to radiotherapy alone in patients with localized esophageal cancer, demonstrating a survival benefit in the chemoradiotherapy group (median overall survival [OS]: 12.5 vs 8.9 months) [11]. The RTOG 94-05 (INT 0123) Phase III trial demonstrated that high-dose radiotherapy plus FP did not increase survival or local/regional control with a higher toxicity rate compared with standard-dose radiotherapy plus FP in patients with T1–T4N0/1M0 primary esophageal cancer [12]. In the Phase II/III PRODIGE5/ACCORD17 trial, the comparison of two definitive chemoradiotherapy regimens (leucovorin, 5-fluorouracil and oxaliplatin [FOLFOX] vs FP) showed no differences in survival outcomes (progression-free survival [PFS]: 9.7 vs 9.4 months; OS, 20.2 vs 17.5 months) or grade 3 or 4 adverse events (AEs) [13]. Recently, the RTOG 0113 Phase III trial demonstrated that paclitaxel plus fluorouracil did not significantly prolong OS compared with FP in definitive chemoradiotherapy in patients with locally advanced esophageal cancer [14]. Although these studies supported the use of FP and FOLFOX as part of a definitive chemoradiotherapy regimen, OS outcomes remain suboptimal, with the majority of patients dying of their disease. Therefore, a considerable need remains for novel therapeutic agents for the first-line treatment of advanced esophageal or gastroesophageal junction (GEJ) cancer.

Recent studies indicate that radiotherapy and chemotherapy can exert immunomodulatory effects that may result in synergistic treatment responses when combined with immunotherapy. For example, radiotherapy has been shown to upregulate expression of PD-L1 in the tumor microenvironment [15] and the combination of radiotherapy with anti-PD-1/PD-L1 treatments has led to improvements in the control of tumor growth and increased survival in various murine models [15–17]. Clinically meaningful improvements in disease-free survival with nivolumab compared with placebo were reported from the Phase III CheckMate-577 study in patients who had received neoadjuvant chemoradiotherapy for surgically resected stage II/III esophageal or gastroesophageal junction cancer [18]. Chemotherapy has also been shown to upregulate PD-L1 expression on tumor cells and dendritic cells, induce T-cell infiltration of tumor tissue and facilitate antigen uptake by dendritic cells [19–23]. Taken together with the findings of studies demonstrating the benefit of chemoradiotherapy in esophageal cancer (the RTOG-8501 [11], INT 0123 [12] and PRODIGE5/ACCORD17 [13] trials), the combination of chemoradiotherapy regimens with immunotherapies, such as immune checkpoint inhibitors, is a rational approach to enhancing antitumor responses and survival in patients with esophageal cancer.

Background & rationale

Pembrolizumab is a high affinity, highly selective, humanized immunoglobulin G4 kappa (IgG4κ) monoclonal antibody that binds to PD-1, thus inhibiting its interaction with PD-L1 and PD-L2 [24,25]. Pembrolizumab has demonstrated robust antitumor activity and a favorable safety profile in patients with multiple solid tumor types and is currently approved in more than 80 countries for the treatment of one or more advanced malignancies. Findings from the Phase Ib KEYNOTE-028 (ClinicalTrials.gov: NCT02054806) [26], the Phase II KEYNOTE-180 (NCT02559687) [27] and the Phase III KEYNOTE-181 (NCT02564263) [28] trials have demonstrated the antitumor activity and safety of pembrolizumab in patients with esophageal carcinoma. The ongoing Phase III KEYNOTE-590 (NCT03189719) trial is evaluating first-line pembrolizumab in patients with esophageal cancer [29] and met its primary end point with pembrolizumab plus chemotherapy compared with chemotherapy for OS and PFS [30].

The nonrandomized, multicohort, Phase Ib KEYNOTE-028 trial evaluated pembrolizumab monotherapy (10 mg/kg every 2 weeks for up to 2 years) in a cohort of 23 patients with heavily pretreated, PD-L1-positive esophageal carcinoma (ESCC in 78% of patients, EAC in 22%) [26]. After a median follow-up of 7 months, the objective response rate (ORR) was 30% (95% CI: 13–53) for all patients. The ORR by histologic subtype was 28% (5/18 patients) for patients with ESCC and 40% (2/5) for patients with EAC. The median time to initial response was 4 months (range: 2–8) and median duration of response was 15 months (range: 6–≥26). Median PFS and OS were 1.8 months (95% CI: 1.7–2.9) and 7.0 months (95% CI: 4.3–17.7), respectively. The safety profile of pembrolizumab monotherapy in this cohort with esophageal carcinoma was acceptable, with 39% of patients (9/23) experiencing grade 3 treatment-related AEs and no grade 4 or 5 treatment-related AEs.

The KEYNOTE-180 trial was an open-label, single-arm, Phase II study that evaluated pembrolizumab monotherapy (200 mg every 3 weeks [Q3W] for up to 2 years) in 121 patients with advanced or metastatic ESCC, EAC or Siewert Type 1 adenocarcinoma of the GEJ who had experienced disease progression while receiving two prior lines of standard therapy [27]. After a median follow-up of 5.8 months, ORR was 9.9% (95% CI: 5.2–16.7), with 12 partial responses. ORR was 14.3% (9/63 patients) in patients with ESCC and 5.2% (3/58) in patients with EAC. ORR was higher in patients with PD-L1-positive tumors compared with those with PD-L1-negative tumors (13.8% vs 6.3%). Median PFS and OS in the total population were 2.0 months (95% CI: 1.9–2.1) and 5.8 months (95% CI: 4.5–7.2), respectively. Pembrolizumab monotherapy was generally well tolerated in this third-line setting, with grade 3–5 AEs occurring in 12.4% of patients (15/121 patients), including one treatment-related death (pneumonitis).

The open-label, Phase III randomized KEYNOTE-181 trial evaluated pembrolizumab monotherapy (200 mg Q3W for up to 2 years) versus investigator's choice of single-agent docetaxel, paclitaxel or irinotecan in patients with advanced or metastatic ESCC, EAC or Siewert Type I adenocarcinoma of the GEJ [28]. The primary analysis was conducted on 628 patients, and median follow-up was 7.1 months in the pembrolizumab arm and 6.9 months in the chemotherapy arm. In the overall intention-to-treat population, no significant difference in median OS was observed between the pembrolizumab and chemotherapy groups (7.1 vs 7.1 months; hazard ratio [HR], 0.89; 95% CI: 0.75–1.05; p = 0.0560). A clinically meaningful but nonsignificant improvement in median OS was observed in patients with ESCC (8.2 vs 7.1 months; HR: 0.78; 95% CI: 0.63–0.96; p = 0.0095). Median OS was superior for pembrolizumab versus chemotherapy in patients whose tumors expressed PD-L1 with a combined positive score (CPS) ≥10 (9.3 vs 6.7 months; HR: 0.69; 95% CI: 0.52–0.93; p = 0.0074). Pembrolizumab was also associated with a more favorable safety profile, with fewer grade 3–5 AEs compared with chemotherapy (18% vs 41%).

Recently, the randomized, double-blind, Phase III, placebo-controlled KEYNOTE-590 trial was initiated [29], and it is evaluating the efficacy and safety of pembrolizumab (200 mg Q3W for up to 35 cycles) plus chemotherapy (FP) versus placebo plus chemotherapy as first-line treatment in patients with locally advanced or metastatic esophageal or GEJ carcinoma. Top-line results were positive in favor of pembrolizumab plus chemotherapy in the first-line treatment of esophageal carcinoma [30].

Taken together, findings from the KEYNOTE-028, KEYNOTE-180, and KEYNOTE-181 trials and the continued unmet need for effective treatment options in the first-line setting support the investigation of pembrolizumab combined with definitive chemoradiotherapy in patients with previously untreated esophageal cancer.

KEYNOTE-975

The KEYNOTE-975 study (NCT04210115) will evaluate the efficacy and safety of pembrolizumab plus definitive chemoradiotherapy compared with placebo plus definitive chemoradiotherapy as first-line treatment of patients with esophageal carcinoma.

Study design

The KEYNOTE-975 study is a double-blind, Phase III randomized placebo-controlled study (Figure 1). Eligible patients will be randomly assigned 1:1 to receive an intravenous (IV) infusion of pembrolizumab 200 mg Q3W (8 cycles) followed by 400 mg every 6 weeks (five cycles) or placebo (IV normal saline) in combination with definitive chemoradiotherapy. Pembrolizumab or placebo infusion will be administered first, followed by chemotherapy per local standard of care. The definitive chemoradiotherapy regimen will comprise one of three options chosen at the discretion of the study site investigator: FP (cisplatin 75 mg/m^2 IV infusion [day 1, weeks 1, 5, 8 and 11] plus 5-fluorouracil [1000 mg/m^2/day continuous IV infusion [days 1–4 for a total of 4000 mg/m^2 at weeks 1, 5, 8 and 11]) with radiotherapy at 50 Gy; FP with radiotherapy at 60 Gy; FOLFOX (oxaliplatin 85 mg/m^2 IV infusion

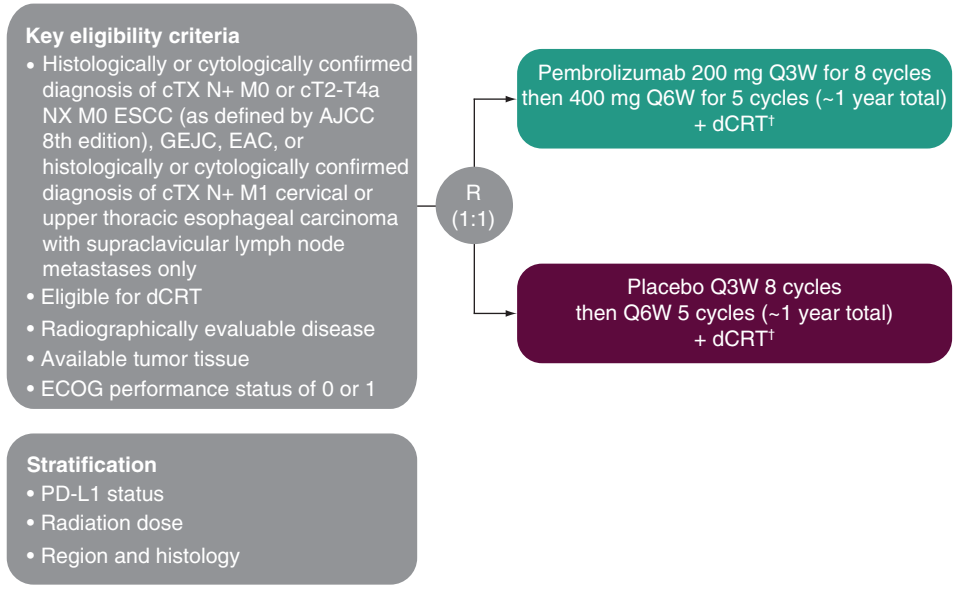

Figure 1. KEYNOTE-975 study design. Definitive chemoradiotherapy consists of definitive radiotherapy + concurrent chemotherapy.
†Patients in both treatment arms will receive a total of 50 Gy (FOLFOX) or 50 or 60 Gy (FP) radiotherapy over 5 weeks (6 weeks for 60 Gy). The choice of mandatory concurrent definitive chemoradiotherapy (FP with 50 Gy or 60 Gy or FOLFOX) will be at the discretion of the study site, but each investigational site must choose FP or FOLFOX and must use the same definitive chemoradiotherapy regimen for every patient at that site (i.e., a site will either be an 'FP 50 Gy site,' an 'FP 60 Gy site,' or a 'FOLFOX site').
EAC: Esophageal adenocarcinoma; dCRT: Definitive chemoradiotherapy; ECOG: Eastern Cooperative Oncology Group; ESCC: Esophageal squamous cell carcinoma; GEJC: Gastroesophageal junction cancer; FP: 5-Fluorouracil and cisplatin; QXW: Every 'X' weeks; R: Randomized.

[day 1, weeks 1, 3, 5, 7, 9 and 11] plus leucovorin 400 mg/m^2 or levoleucovorin 200 mg/m^2 IV infusion [day 1, weeks 1, 3, 5, 7, 9 and 11] plus 5-fluorouracil (400 mg/m^2 bolus IV [day 1, weeks 1, 3, 5, 7, 9 and 11] and 800 mg/m^2/day continuous IV infusion [days 1 and 2, weeks 1, 3, 5, 7, 9 and 11]) with radiotherapy at 50 Gy. Radiotherapy doses were selected based on global standard of care. Each investigational site must use the same definitive chemoradiotherapy regimen for every patient at that site (i.e., a site will either be an 'FP 50 Gy site,' an 'FP 60 Gy site,' or a 'FOLFOX site'). Treatment will continue until confirmed progression, unacceptable toxicity, intercurrent illness that prevents further administration of the study treatment, investigator or patient decision to withdraw, pregnancy of the patient, nonadherence to treatment or trial procedures, or completion of 13 cycles of pembrolizumab or placebo (~1 year).

Randomization will be performed using an interactive response technology system and will be stratified according to PD-L1 status (CPS ≥10 or CPS <10), radiation dose (50 or 60 Gy), and geographic region and histology (ESCC, East Asia; ESCC, all other regions; EAC, any region). Pembrolizumab or placebo assignment will be masked to patients, investigators and sponsor personnel.

Key eligibility criteria

Key eligibility criteria are described in Box 1. Briefly, men and women aged ≥18 years are eligible for enrollment if they have a histologically confirmed diagnosis of locally advanced unresectable (cTX N+ M0 or cT2-T4aNXM0) ESCC, GEJ cancer, EAC, or cervical or upper thoracic esophageal carcinoma with supraclavicular lymph node metastases only (cTX N + M1) and are candidates for first-line treatment with definitive chemoradiotherapy.

Planned sample size & study period

The planned sample size is approximately 600 patients. The study started in February 2020 and the estimated study completion date is February 2026.

Box 1. Eligibility criteria for KEYNOTE-975.

Inclusion criteria:

- Aged ≥18 years;
- Histologically confirmed cTX N+ M0 or cT2-4aNXM0 ESCC, GEJC, EAC or cTX N+ M1 cervical or upper thoracic esophageal carcinoma with supraclavicular lymph node metastases only;
- Deemed suitable for definitive chemoradiotherapy;
- Qualitatively evaluable disease upon radiographic assessment by the local investigator;
- Ineligible for curative surgery based on the documented opinion of a qualified medical/surgical/radiation oncologist;
- Not expected to require tumor resection during the course of the study;
- ECOG performance status 0 or 1;
- Adequately nourished and hydrated based on the investigator's judgement (a feeding tube is acceptable to maintain adequate nourishment);
- Provide tumor tissue sample adequate for PD-L1 and MSI biomarker analysis;
- Adequate hematologic function, defined as ANC ≥1500/μl, platelet count ≥100,000/μl and hemoglobin count ≥9.0 g/dl or ≥5.6 mmol/l;
- 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;
- Adequate hepatic function, defined as total bilirubin ≤1.5× ULN or direct bilirubin ≤ULN for those with total bilirubin >1.5× ULN and ALT/AST levels ≤2.5× ULN and albumin ≥3.0 g/dl;
- 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;
- Willing to use an adequate method of contraception throughout the study and for 120 days after the last dose of pembrolizumab and up to 180 days after the last dose of chemotherapy, whichever is greater;
- Negative urine or serum pregnancy test results within 24 h before the first dose of study intervention;
- Documented informed consent.

Exclusion criteria:

- Direct invasion of tumor into adjacent organs, such as the aorta or trachea (i.e., T4b disease);
- Prior chemotherapy or radiotherapy for esophageal cancer;
- Any prior systemic anticancer therapy for esophageal cancer;
- Weight loss of >20% in the previous 3 months;
- Major surgery other than for insertion of a feeding tube, open biopsy or significant traumatic injury within 28 days before randomization or anticipated need for major surgery during the study treatment period;
- Gastric or esophageal fistulae;
- Known additional malignancy that is progressing or has required active treatment within the past 3 years (except for BCC or SCC of the skin, *in situ* cervical cancer, *in situ* breast cancer that has undergone potentially curative treatment and localized prostate cancer that has undergone potentially curative treatment);
- Active autoimmune disease that has required systemic treatment (other than replacement therapy) in 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 solid organ/allogeneic stem cell transplant;
- Active infection requiring 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 an anti-PD-1, anti-PD-L1 or anti-PD-L2 agent or with an agent directed to another stimulatory or coinhibitory T-cell receptor (e.g., CTLA-4, OX40, CD137);
- Known severe 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;
- 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;
- History of noninfectious pneumonitis that required steroids, or current pneumonitis.

ANC: Absolute neutrophil count; aPTT: Activated partial thromboplastin time; BCC: Basal cell carcinoma; EAC: Esophageal adenocarcinoma; ECOG: Eastern Cooperative Oncology Group; ESCC: Esophageal squamous cell carcinoma; HBV: Hepatitis B virus; HCV: Hepatitis C virus; GEJC: Gastroesophageal junction cancer; INR: International normalized ratio; PT: Prothrombin time; MSI: Microsatellite instability; SCC: Squamous cell carcinoma; ULN: Upper limit of normal.

Outcome measures

The dual primary end points are OS and event-free survival (EFS) per blinded independent central review or biopsy in all patients, in the subgroups of patients with ESCC and in those whose tumors express PD-L1 with a CPS ≥10. OS is defined as the time from randomization to death due to any cause. EFS is defined as the time from randomization to an event defined as local, regional or distant recurrence of the treated esophageal cancer as assessed by blinded independent central review based on imaging or biopsy if indicated or death due to any cause. The secondary end point is safety and tolerability. Exploratory end points include assessment of health-related quality of life using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) core 30 items (C30) and EORTC QLQ Oesophageal module (OES18). Other exploratory end points include characterization of utilities using the European Quality of Life 5-dimension 5-level questionnaire. Molecular biomarkers (genomic, metabolic and/or proteomic) that may be indicative of clinical response or resistance, safety, pharmacodynamic activity or mechanism of action of pembrolizumab and other treatments may also be investigated.

Study procedures

Tumor imaging and assessment of disease will be conducted using computed tomography (or magnetic resonance imaging if computed tomography is contraindicated). Initial tumor imaging will be performed during screening (within 28 days before randomization). To monitor disease status, imaging will be performed at 8 weeks from the completion of radiation therapy (reference point for monitoring local recurrence), then every 9 weeks (or more often if clinically indicated) thereafter until 2 years postrandomization, then every 4 months thereafter until 3 years postrandomization, and then every 6 months thereafter until 5 years postrandomization. Tumor imaging will continue until disease recurrence, start of new anticancer treatment, withdrawal of consent, death or completion of 5 years of follow-up, whichever occurs first. Evaluation of tumor imaging for local, regional or distant disease recurrence will be performed by local investigators/radiologists and by blinded independent central review. Recurrences will be confirmed with a biopsy unless a biopsy is considered medically inappropriate. 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 AEs/serious adverse events, changes in vital signs and changes in laboratory values. AEs will be graded and recorded throughout the trial and follow-up period per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

The European Quality of Life 5-dimension 5-level, EORTC QLQ-C30 and EORTC QLQ-OES18 questionnaires will be administered electronically in the order listed (before drug administration, AE evaluation and disease status notification) on day 1 of each cycle during cycles 1–13, at the time of treatment discontinuation, and at the 30-day safety follow-up visit. Exploratory biomarker investigation may include genetic, microsatellite instability DNA, RNA and proteomic analyses of blood and tumor tissue samples.

PD-L1 expression will be assessed by use of a Good Manufacturing Practice immunohistochemistry assay (PD-L1 IHC 22C3 pharmDx; Agilent). PD-L1 expression is measured using CPS or the number of PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100.

Statistics

Primary efficacy analyses will be performed in the intention-to-treat population (all randomly assigned patients) and analyzed by randomized treatment group. Safety will be assessed in the all-patients-as-treated population, defined as all randomly assigned patients who received the study drug, and will be analyzed by treatment received. The primary hypotheses for OS and EFS will be evaluated by comparing pembrolizumab plus definitive chemoradiotherapy with placebo plus definitive chemoradiotherapy 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 met. HRs will be estimated using a stratified Cox proportional hazards regression model using the same stratification factors used for randomization (PD-L1 CPS; radiation dose; and geographic region and histology). Event rates over time will be estimated using the Kaplan–Meier method. Analyses using the Miettinen and Nurminen method will be performed when 95% CIs are provided for between-treatment differences in the percentage of patients with events.

Two interim analyses are planned to assess EFS and OS in patients with ESCC and in those whose tumors express PD-L1 with a CPS ≥10. An external data monitoring committee will review the interim analyses results

and periodically review efficacy and safety results to determine whether the study will continue per prespecified criteria.

Conclusion

Preliminary findings from the KEYNOTE-180, KEYNOTE-181 and KEYNOTE-590 trials indicate that pembrolizumab provides promising antitumor activity and has an acceptable safety profile in patients with previously treated, advanced esophageal cancer, including ESCC, GEJ cancer, EAC, or cervical or thoracic esophageal carcinoma with supraclavicular lymph node metastases only. Here, we describe the methodology for the Phase III KEYNOTE-975 study that will investigate the efficacy and safety of pembrolizumab in combination with definitive chemoradiotherapy as first-line treatment for locally advanced, unresectable esophageal carcinoma. The results from this study will help define the role of immunotherapy in the first-line setting for patients with esophageal cancer who are ineligible for curative surgery, a patient population for whom treatment options are limited.

Executive summary

- A substantial proportion of patients with locally advanced nonmetastatic esophageal cancer are ineligible for curative surgery at presentation.
- In these patients, definitive chemoradiotherapy is the recommended first-line treatment option, but survival outcomes associated with this treatment modality are poor.

Background & rationale

- In the esophageal cohort of the Phase Ib KEYNOTE-028 trial, pembrolizumab was associated with durable antitumor activity and a manageable safety profile in heavily pretreated, PD-L1+ advanced esophageal carcinoma.
- Preliminary findings from the Phase II KEYNOTE-180 and Phase III KEYNOTE-181 trials in patients with previously treated advanced or metastatic esophageal cancer support the use of pembrolizumab as second- and third-line therapy for patients with PD-L1+ disease.

KEYNOTE-975 study design & eligibility criteria

- KEYNOTE-975 is a double-blind, Phase III randomized placebo-controlled trial that will evaluate the efficacy and safety of pembrolizumab plus definitive chemoradiotherapy versus placebo plus definitive chemoradiotherapy as first-line treatment of patients with locally advanced, unresectable esophageal cancer.
- Approximately 600 patients with previously untreated, locally advanced, unresectable esophageal squamous cell carcinoma, gastroesophageal junction cancer, esophageal adenocarcinoma, or cervical or upper thoracic esophageal carcinoma with supraclavicular lymph node metastases only, who are candidates for definitive chemoradiotherapy, will be enrolled.
- Eligible patients will be randomly assigned 1:1 to receive pembrolizumab or placebo in combination with definitive chemoradiotherapy.

Outcomes

- The dual primary end points are overall survival and event-free survival in all patients, esophageal squamous cell carcinoma patients and patients whose tumors express PD-L1 with a combined positive score $\geq$10.

Conclusion

- The results of KEYNOTE-975 will help define the role of immunotherapy as a first-line treatment option in patients with esophageal cancer who are not eligible for curative surgery.

Supplementary data

An infographic accompanies this paper at the end of the references section. To download the infographic and the supplementary data that accompanies this paper, please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2020-0969

Author contributions

Conception, design or planning of the study was done by MA Shah, J Bennouna, T Doi, L Shen, K Kato, A Adenis, H Mamon, M Moehler, BC Cho, CS Shih, A Desai, and P Enzinger. Analysis of the data was performed by BC Cho and S Bordia. Acquisition of the data by MA Shah, T Doi, L Shen, M Moehler, X Fu, BC Cho and S Bordia. Interpretation of the results was done by M Moehler, BC Cho and P Bhagia. Drafting of the manuscript was done by MA Shah, M Moehler, BC Cho, S Bordia and A Desai. Critically reviewing or revising the manuscript for important intellectual content was done by MA Shah, J Bennouna, T Doi, L Shen, K Kato, A Adenis, H Mamon, M Moehler, X Fu, S Bordia, P Bhagia, CS Shih, A Desai and P Enzinger. Final approval was given by all authors.

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Ethical conduct of research

The authors state that appropriate institutional review board approval from each participating site will be obtained, and this study will follow the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent will be obtained from the participants involved prior to any study procedures.

Data sharing statement

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., NJ, USA (MSD) is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the US and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

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KEYNOTE-975: a Phase III study of definitive chemoradiotherapy plus pembrolizumab in patients with esophageal carcinoma

Authors
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Trial registration number
NCT04210115

Primary objectives/rationale

Primary objective

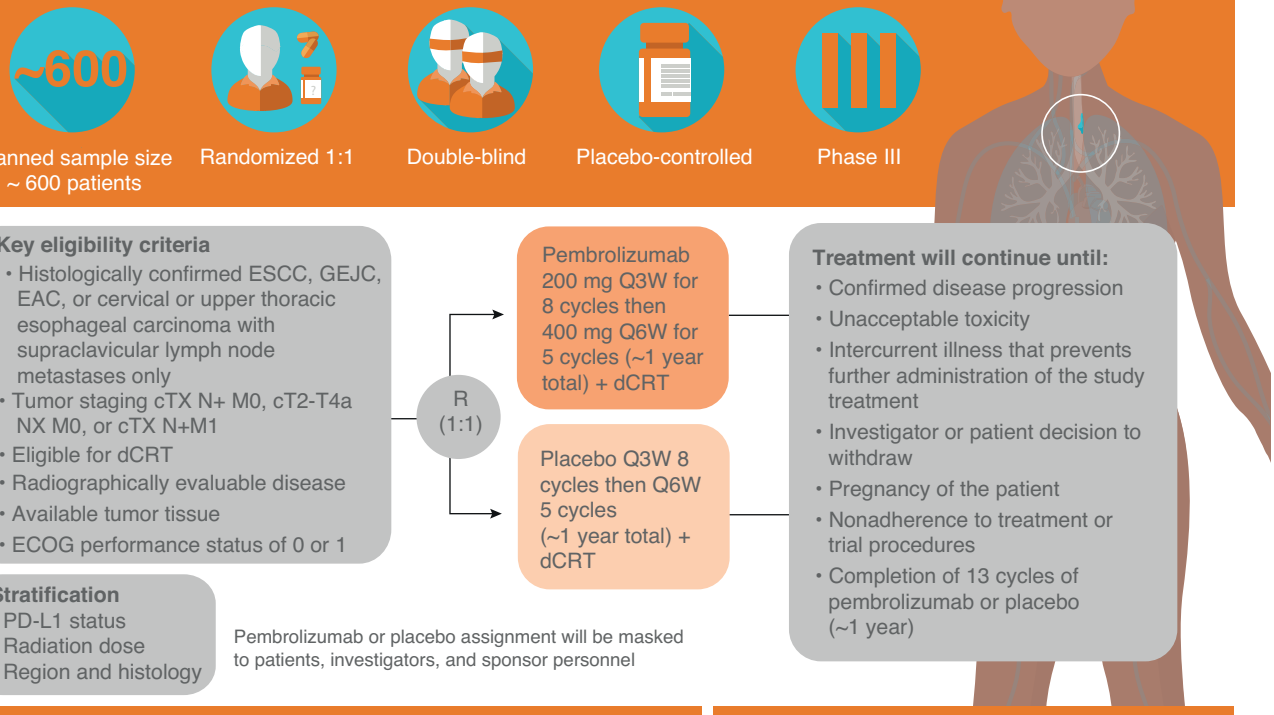
Compare OS between pembrolizumab plus dCRT and placebo plus dCRT in all patients, in the subgroups of patients with ESCC and in those whose tumors express PD-L1 (CPS ≥10)

Compare EFS between pembrolizumab plus dCRT and placebo plus dCRT in all patients and in the subgroups of patients with ESCC and those whose tumors express PD-L1 (CPS ≥10)

Secondary key objectives

Evaluate the safety and tolerability of pembrolizumab plus dCRT

Study design & treatment



Key eligibility criteria

- Histologically confirmed ESCC, GEJC, EAC, or cervical or upper thoracic esophageal carcinoma with supraclavicular lymph node metastases only
- Tumor staging cTX N+ M0, cT2-T4a NX M0, or cTX N+M1
- Eligible for dCRT
- Radiographically evaluable disease
- Available tumor tissue
- ECOG performance status of 0 or 1

R (1:1)

Pembrolizumab 200 mg Q3W for 8 cycles then 400 mg Q6W for 5 cycles (~1 year total) + dCRT

Placebo Q3W 8 cycles then Q6W 5 cycles (~1 year total) + dCRT

Treatment will continue until:

- Confirmed disease progression
- Unacceptable toxicity
- Intercurrent illness that prevents further administration of the study treatment
- Investigator or patient decision to withdraw
- Pregnancy of the patient
- Nonadherence to treatment or trial procedures
- Completion of 13 cycles of pembrolizumab or placebo (~1 year)

Stratification

- PD-L1 status
- Radiation dose
- Region and histology

Pembrolizumab or placebo assignment will be masked to patients, investigators, and sponsor personnel

Outcome measures/end points

Primary end points:
OS (defined as the time from randomization to death due to any cause)

EFS (defined as the time from randomization to an event, defined as local, regional, or distant recurrence of the treated esophageal cancer or death due to any cause) between pembrolizumab plus dCRT and placebo plus dCRT in all patients and in the subgroups of patients with ESCC and those whose tumors express PD-L1 with a CPS ≥10

Secondary end points:
Safety and tolerability

Exploratory end points:

- HRQoL (assessed using the EORTC QLQ-C30 and EORTC QLQ-OES18 questionnaires)
- Characterization of utilities (assessed using the EQ-5D-5L questionnaire)
- Molecular biomarkers

Glossary

CPS: Combined positive score; dCRT: Definitive chemoradiotherapy; EAC: Esophageal adenocarcinoma; EFS: Event-free survival; EGJ: Esophagogastric junction; EORTC QLQ-C30: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire core 30 items; EORTC QLQ-OES18: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Oesophageal Cancer Module; EQ-5D-5L: European Quality of Life 5D 5-level; ESCC: Esophageal squamous cell carcinoma; GEJC: Gastroesophageal junction cancer; HRQoL: Health-related quality of life; IV: Intravenously; OS: Overall survival; PD-L1: Programmed death ligand 1; Q3W: Every 3 weeks