Gastroesophageal Junction Adenocarcinoma: KEYNOTE-859

A Randomized, Double-Blind, Phase 3 Study of Pembrolizumab Plus Chemotherapy as First-Line Therapy in Patients With HER2-Negative Advanced Gastric or Gastroesophageal Junction Adenocarcinoma: KEYNOTE-859

**Background**

- Gastric cancer is the sixth most diagnosed cancer worldwide (incidence, ~1,033,700) and the second most common cause of cancer-related deaths (mortality, ~782,700).
- Standard frontline therapy for patients with unresectable locally advanced, recurrent, or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction (GEJ) cancer includes a fluoropyrimidine + a platinum-based agent.
- Pembrolizumab + chemotherapy was also evaluated in KEYNOTE-062; compared with chemotherapy as first-line therapy in patients with HER2-negative, previously untreated, unresectable or metastatic gastric/GEJ cancer.
- Pembrolizumab + chemotherapy was also evaluated in KEYNOTE-062; compared with placebo in patients with PD-L1–positive (combined positive score [CPS] ≥1) gastric/GEJ cancer when given as monotherapy in the first-line setting.

**Objectives**

- **Primary**: To compare ORR and DOR per RECIST v1.1, as assessed by BICR, between pembrolizumab + chemotherapy and placebo + chemotherapy
- **Secondary**: To compare ORR and DOR per RECIST v1.1, as assessed by BICR, between pembrolizumab + chemotherapy and placebo + chemotherapy
- **Safety and tolerability**

**Methods**

**Study Design and Patients**

- This is a randomized, double-blind, phase 3 study of pembrolizumab + chemotherapy in patients with HER2-negative, previously untreated, unresectable or metastatic gastric/GEJ adenocarcinoma (Figure 1).
- Approximately 1542 patients will be randomly assigned 1:1 to receive intravenous (IV) pembrolizumab 200 mg every 3 weeks (Q3W) or placebo, both in combination with chemotherapy.
- Chemotherapy: investigator’s choice (before randomization) of 5-fluorouracil (5-FU) + cisplatin (FP) or capecitabine + oxaliplatin (CAPOX). FP: continuous infusion of 5-FU 800 mg/m² on days 1-5 of each cycle + IV cisplatin 80 mg/m² on day 1 of each cycle Q3W. Duration of cisplatin or oxaliplatin may be capped at 6 cycles, per local country.
- Patients will continue to receive treatment until disease progression, unacceptable toxicity, or patient withdrawal of consent.

**Key Inclusion Criteria**

- Age ≥18 years
- Histologically or cytologically confirmed diagnosis of locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma
- Known PD-L1 expression status
- HER2-negative cancer
- Measurable disease per RECIST v1.1
- Archival tumor tissue sample or newly obtained tissue sample or newly obtained tissue sample
- History of pneumonitis, or active tuberculosis
- Known active hepatitis C, autoimmune disease, or additional malignancy that is progressing or has been treated in the past 5 years
- Known history of hypokalemia, hypomagnesemia, or hypocalcemia

**Key Exclusion Criteria**

- Surgery, biopsy, or injury within 28 days of the first dose of study treatment
- Live vaccine ≤30 days before the first dose of study treatment
- Diagnosis of immunodeficiency or chronic systemic inflammatory immunosuppressive therapy 27 days before the first dose of study treatment
- Additional malignancy that is progressing or has necessitated active treatment within the past 5 years
- Active CNS metastases and/or carcinomatous meningitis
- Known history of HIV infection, hepatitis B, cervicoviral infections, or active tuberculosis
- Known active hepatitis C, autoimmune disease, or infection
- Hypokalemia, hypomagnesemia, or hypocalcemia

**Patient Eligibility Criteria**

**Efficacy**

- **Endpoints**
  - OS and PFS will be estimated using the Kaplan-Meier method.
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- **Statistical Methods**
  - OS and PFS will be estimated using the Kaplan-Meier method.
- **Assumptions**
  - Assumptions will be assessed by computed tomography or magnetic resonance imaging during screening and subsequently every 6 weeks until progression of disease.
  - Adverse events (AEs) will be monitored throughout the study from the time of randomization to 50 days after the last dose of study treatment (50 days after final study visit).
- **Study Drug Discontinuation, Imaging**
  - Study drug discontinuation, imaging will be performed within 4 weeks.
  - Adverse events (AEs) will be monitored throughout the study from the time of randomization to 50 days after the last dose of study treatment (50 days after final study visit).

**References**


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