# 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

Shu Kui Qin[1]; Josep Tabernero[2]; Eric Van Cutsem[3]; Charles S. Fuchs[4]; Yelena Yuriy Janjigian[5]; Pooja Bhagia[6]; Kan Li[6]; David Adelberg[6]; Yung-Jue Bang[7]

[1]PLA Cancer Centre of Nanjing Jinling Hospital, Nanjing, China; [2]Vall d'Hebron University Hospital and Institute of Oncology, Barcelona, Spain; [3]Leuven Cancer Institute, Leuven, Belgium; [4]Yale Cancer Center and Smilow Cancer Hospital, New Haven, CT, USA; [5]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [6]Merck & Co., Inc., Kenilworth, NJ, USA; [7]Seoul National University College, Seoul, South Korea

## 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)[1]
- Standard first-line 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[2]
  - Combination chemotherapy for advanced gastric/GEJ cancer provides a modest survival benefit compared with single-agent chemotherapy,[3] highlighting the need for more effective therapy
- The PD-1 inhibitor pembrolizumab has demonstrated antitumor activity and acceptable tolerability in patients with PD-L1–positive (combined positive score [CPS] ≥1) gastric/GEJ cancer when given as monotherapy in the first-line setting[4,5]
  - In cohort 3 of the phase 2 KEYNOTE-059 trial, the objective response rate (ORR) was 25.8%, the median duration of response (DOR) was 9.6 months, and median overall survival (OS) was 20.7 months; grade 3-5 treatment-related adverse events (TRAEs) were reported in 7 patients (22.6%)[4]
  - In the phase 3 KEYNOTE-062 trial, pembrolizumab monotherapy was noninferior to chemotherapy for OS (hazard ratio [HR], 0.91; 99.2% CI, 0.69-1.18; prespecified noninferiority margin, 1.2); grade 3-5 TRAE rates were 17% with pembrolizumab monotherapy and 69% with chemotherapy[5]
- Pembrolizumab + chemotherapy was also evaluated in KEYNOTE-062; compared with chemotherapy alone, pembrolizumab + chemotherapy in the CPS ≥1 population trended toward superior improvement in OS, although the magnitude of benefit appeared marginal (HR, 0.85; 95% CI, 0.70-1.03)[5]
- The KEYNOTE-859 trial (NCT03675737) is a randomized, multicenter, double-blind, phase 3 study to investigate pembrolizumab + chemotherapy versus placebo + chemotherapy as first-line therapy in patients with advanced HER2-negative gastric/GEJ cancer

## Objectives

### Primary

- To compare OS between pembrolizumab + chemotherapy and placebo + chemotherapy
- To compare progression-free survival (PFS) per RECIST v1.1 as assessed by blinded independent central review (BICR) between pembrolizumab + chemotherapy and placebo + chemotherapy

### Secondary

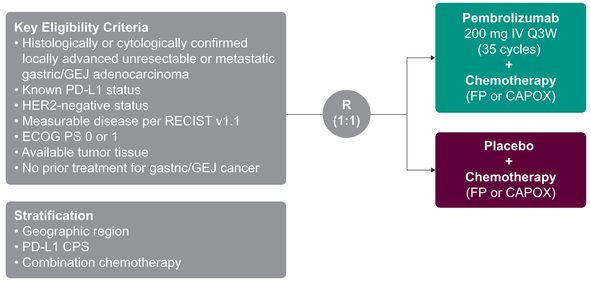
- To compare ORR and DOR per RECIST v1.1, as assessed by BICR, between pembrolizumab + chemotherapy and placebo + chemotherapy
- Safety and tolerability

## 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 is investigator's choice (before randomization) of 5-fluorouracil (5-FU) + cisplatin (FP) or capecitabine + oxaliplatin (CAPOX)
  - FP: continuous infusion of 5-FU 800 mg/m$^2$/day on days 1-5 of each cycle + IV cisplatin 80 mg/m$^2$ Q3W
  - CAPOX: oral capecitabine 1000 mg/m$^2$ twice daily on days 1-14 of each cycle + IV oxaliplatin 130 mg/m$^2$ on day 1 of each cycle Q3W
  - Duration of cisplatin or oxaliplatin may be capped at 6 cycles, per local country guidelines; treatment with 5-FU or capecitabine may continue per protocol
- Randomization will be stratified by the following
  - Geographic region (Europe/Israel/North America/Australia vs Asia vs rest of world)
  - PD-L1 tumor expression status
  - Combination chemotherapy (FP vs CAPOX)
- Patients will continue to receive treatment until disease progression, unacceptable toxicity, intercurrent illness that prevents further administration of treatment, noncompliance, or up to 35 administrations (~2 years) of study treatment

### Figure 1. Study Design




ECOG PS, Eastern Cooperative Oncology Group performance status; R, randomization.

### Patient Eligibility Criteria

| Key Inclusion Criteria | Key Exclusion Criteria |
|---|---|
| • Age ≥18 years<br>• Histologically or cytologically confirmed diagnosis of locally advanced unresectable or metastatic gastric/GEJ adenocarcinoma, with known PD-L1 expression status<br>• HER2-negative cancer<br>• Measurable disease per RECIST v1.1<br>• Archival tumor tissue sample or newly obtained core or excisional biopsy for PD-L1 expression and MSI biomarker analysis<br>• ECOG PS 0 or 1<br>• Adequate organ function | • Surgery, biopsy, or injury within 28 days of randomization<br>• Peripheral neuropathy grade >1<br>• Previous therapy for gastric/GEJ cancer<br>• Previous therapy with anti–PD-1, anti–PD-L1, or anti–PD-L2 or with an agent directed to another stimulatory or coinhibitory T-cell receptor<br>• Systemic anticancer therapy including investigational agents ≤4 weeks before randomization<br>• Radiotherapy ≤2 weeks before the first dose of study treatment<br>• Live vaccine ≤30 days before the first dose of study treatment<br>• Diagnosis of immunodeficiency or chronic systemic steroid/other immunosuppressive therapy ≤7 days before the first dose of study treatment<br>• Additional malignancy that is progressing or has necessitated active treatment within the past 5 years<br>• Active CNS metastases and/or carcinomatous meningitis<br>• Known history of HIV infection, hepatitis B, noninfectious pneumonitis, or active tuberculosis<br>• Known active hepatitis C, autoimmune disease, or infection<br>• Hypokalemia, hypomagnesemia, or hypocalcemia |

CNS, central nervous system; HIV, human immunodeficiency virus; MSI, microsatellite instability.

### Assessments and Follow-Up

- Responses will be assessed by computed tomography or magnetic resonance imaging during screening and subsequently every 6 weeks until progression of disease, start of new anticancer treatment, withdrawal of consent, or death
  - At 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 30 days after the last dose of study treatment (90 days for serious AEs), and severity will be graded according to the guidelines outlined in the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0

### Analyses

#### Efficacy

- Efficacy end points will be assessed in all randomly assigned patients in the intention-to-treat population
- OS and PFS will be estimated using the Kaplan-Meier method
- Differences in OS and PFS for pembrolizumab + chemotherapy versus placebo + chemotherapy will be assessed using a stratified log-rank test, with the magnitude of the treatment differences (ie, hazard ratio) and associated 95% CIs calculated using a stratified Cox model with Efron's tie-handling method

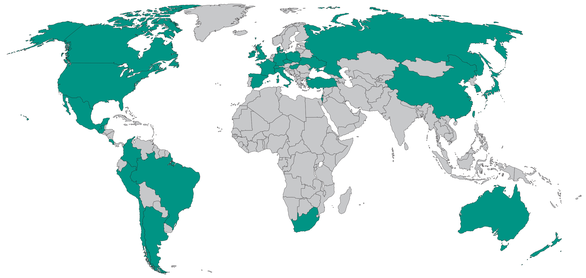
#### Safety

- Safety will be assessed in all randomly assigned patients who received ≥1 dose of study treatment

## Status

- KEYNOTE-859 enrollment is ongoing in 33 countries (Figure 2)

### Figure 2. Countries With Sites of Enrollment for KEYNOTE-859 (in green)

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## Disclosure

S. Qin has nothing to disclose.


## Contact Information

Contact the author at qinsk81@163.com for questions or comments.




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