GEMSTONE-304: A Phase III Study of Fluorouracil and Cisplatin (FP) with CS1001 (Sugemalimab), an Anti-PD-L1 Antibody, or Placebo in Unresectable Locally Advanced, Recurrent or Metastatic Esophageal Squamous Cell Carcinoma (ESCC)

Gastrointestinal Cancers Symposium

TPS255

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BACKGROUND

- In 2018, 572,000 patients were diagnosed with esophageal cancer worldwide and it caused 509,000 deaths, ranking 7th in new malignant tumors and 6th in deaths, respectively[1]. More than half of newly diagnosed cases and deaths were in China (307,000 and 283,000, respectively)[2], of which 86.3% are esophageal squamous cell carcinoma[3].
- Immunotherapy including anti-PD-(L)1 monoclonal antibodies (mAb) that target PD-(L)1 pathway has made great progress in various advanced malignancies. For advanced ESCC, the regimen of immune checkpoint inhibitor in combination with chemotherapy as first-line therapy has been explored in a Phase III study KEYNOTE-590, where pembrolizumab plus FP regimen demonstrated statistically significant improvement in median overall survival (OS) (12.6 vs 9.8 months; HR: 0.72; 95% CI, 0.60-0.88; P = 0.0006) compared to chemotherapy alone[4].
- CS1001 (sugemalimab) is a full-length, fully human programmed death ligand-1 (PD-L1) targeted immunoglobin G4 (IgG4, s228p) mAb.
  - *In vitro,* sugemalimab specifically binds to PD-L1, competitively blocks the binding of human PD-L1 with PD-1 and CD80, which leads to CD4+ T lymphocyte proliferation and enhances the production of interferon-γ[5].
  - Sugemalimab lacks antibody-dependent cellular mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC), but retains antibody -dependent cellular phagocytosis (ADCP), which can mediate direct killing of tumor cells by macrophages.
- Sugemalimab plus platinum-based chemotherapy demonstrated promising efficacy and tolerable safety in patients with unresectable locally advanced, recurrent or metastatic ESCC in Phase Ib of GEMSTONE-101 study (NCT03312842)[6] .
- GEMSTONE-304 (NCT04187352, protocol No. CS1001-304) is a multi-center, double-blind, randomized, Phase III study to evaluate the efficacy and safety of CS1001 in combination with FP as the first-line therapy in subjects with unresectable locally advanced, recurrent or metastatic ESCC.

OBJECTIVES

Primary Objective

- To compare PFS using RECIST v1.1 assessed by Blinded Independent Central Review Committee (BICR) and OS in all patients between the following treatment: CS1001 plus FP versus placebo plus FP.

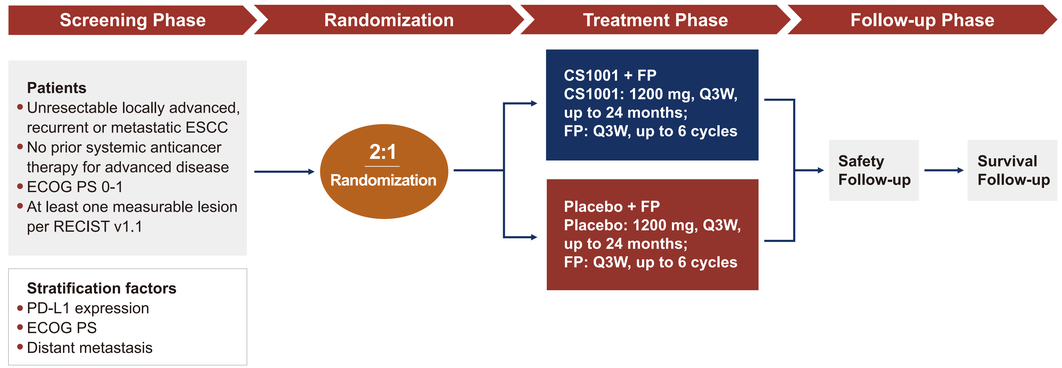
Secondary Objectives

- To compare investigators-assessed PFS, BICR and investigators-assessed ORR and DoR between CS1001 plus FP and placebo plus FP.
- To evaluate the safety and tolerability profile between the patients taking CS1001 plus FP versus placebo plus FP.
- To characterize the pharmacokinetics and immunogenicity of CS1001.

DESIGN

- NCCN guidelines recommend the fluoropyrimidine in combination with platinum regimens as the first-line therapy for unresectable locally advanced, recurrent or metastatic esophageal cancer. Stronger evidences support combination with cisplatin than other platinum agents[7].
- As shown in the figure below, approximately 540 patients will be randomized in a 2:1 ratio to receive the treatment of CS1001 + FP or placebo + FP. CS1001 or placebo treatment will continue until disease progression, unacceptable toxicity, withdrawal of informed consent, reaching the maximum duration of treatment per protocol or end of study, whichever occurs first.

Schema of Study Design



ECOG= Eastern Cooperative Oncology Group; ESCC=Esophageal Squamous Cell Carcinoma; FP=Flurouracil+Cisplatin; PS=Performance Status; Q3W=every 3 weeks; RECIST=Response Evaluation Criteria in Solid Tumors.

Study Population

Key Inclusion Criteria	Key Exclusion Criteria
• ≥ 18 years and ≤ 75 years on the day of signing ICF. • Histologically or cytologically confirmed unresectable locally advanced, recurrent or metastatic ESCC. • Not be eligible for curative therapy such as chemoradiotherapy or surgery. • Have not received any systemic anti-tumor therapy as the main regimen for locally advanced or metastatic ESCC. • ECOG PS 0 or 1. • Have at least one measurable lesion as evaluated by the investigator according to RECIST v1.1, and the baseline imaging assessment must be performed within 28 days prior to the first dose of investigational product. • Palliative treatment (e.g. radiotherapy) for local lesion must be completed ≥ 14 days prior to the first dose of investigational product.	• Adenocarcinoma, mixture of adenocarcinoma and squamous cell carcinoma, or other pathological type of esophageal cancer. • With active CNS metastasis and/or carcinomatous meningitis. • With documented gastrointestinal bleeding, perforation, or esophageal fistula within 6 months prior to randomization. The lesion has high risk of bleeding, gastrointestinal perforation or esophageal fistula assessed by the investigators. • Subjects who have previously received any treatment of antibody or drug that targets at T-cell coregulatory pathways or immune checkpoint pathways, e.g., antibodies targeting at PD-1, PD-L1, CTLA-4, OX-40, CD137, TIM-3, LAG-3, etc. Subjects who have received cell-based immunotherapy, e.g., CIK, CAR-T, etc.

CAR-T=Chimeric Antigen Receptor T Cell; CIK=Cytokine-induced Killer Cell; CNS=Central Nervous System; CTLA-4=Cytotoxic T Lymphocyte-associated Antigen 4; ECOG=Eastern Cooperative Oncology Group; ESCC=Esophageal Squamous Cell Carcinoma; ICF=Informed Consent Form; LAG-3=Lymphocyte Activation Gene 3; PD-1=Programmed Death-1; PD-L1=Programmed Death-ligand 1; PS=Performance Status; RECIST=Response Evaluation Criteria in Solid Tumor; TIM-3=T Cell Immunoglobulin Mucin Molecule 3.

Assessments

- The efficacy assessment will be performed by BICR and investigators based upon RECIST v1.1 every 6 weeks (± 7 days) from the first dose for the first year; and then every 12 weeks (± 7 days) until BICR confirmed progressive disease, subject withdraws from the study, or the end of study, whichever occurs first.
- The safety assessment will be performed throughout the study and during the follow-up period. AEs and laboratory test results will be graded per National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.
- The pharmacokinetics and immunogenicity assessments will be performed at Cycle 1, 2, 3, 4, 8 and every 8 cycles thereafter and at end-of-treatment visit.

STATUS

- The study is actively enrolling patient, and enrollment is expected to take place in 65 sites in China.

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