Supplementary material

Study protocol

PD-1 antibody (Camrelizumab) in EBV positive metastatic gastric cancer patients.

Background

Several studies have reported the safety and efficacy of programmed cell death-1 (PD-1) inhibitors in mGC patients, with an ORR ranging from 11% to 23.3%. EBV positivity was identified as a distinct molecular subtype of GC by The Cancer Genome Atlas (TCGA) Research Network. EBV positive tumor accounts for 9% according to the TCGA study and approximately 5% in China. In June 2018, Panda et al. reported that one EBVaGC patient with low TMB and microsatellite stability (MSS) achieved partial response (PR) after treatment with a PD-L1 inhibitor. Another study reported a 100% ORR with PD-1 inhibitor in EBV-positive mGC patients but the sample size was relatively small (n=6). Camrelizumab (also known as SHR-1210) is a selective, humanized, high-affinity immunoglobulin G4 κ monoclonal antibody against PD-1. Camrelizumab was reported to have encouraging efficacy in mGC patients in China, with an ORR of 23.3%. In the present study, we will assess the efficacy and safety of camrelizumab as salvage treatment in EBV-positive mGC patients.

Study design

This is a single-center, single-arm, open-label, prospective phase 2 study (ClinicalTrials.gov, Identifier NCT03755440) conducted at the Sun Yat-sen University Cancer Center (Guangzhou, China).

EBV positive metastatic GC patients who fail to standard chemotherapy will receive therapy of single agent, PD-1 antibody, Camrelizumab (also known as SHR-1210), 200 mg, every 2 weeks. The primary endpoint is response rate. Secondary endpoint is progress free survival, overall survival, safety and quality of life.

Sample size was determined using Simon's optimal two-stage design, with a significance level of 5% and power of 80%. P0=15% (null hypothesis) was based on the results of previously published studies using ORR with anti-PD-1 antibody in mGC (11-23%). P1=45% or higher (alternative hypothesis) was considered as a success in EBV-positive mGC. The presence of at least 1 response (CR or PR) in the 6 patients enrolled in the first stage allowed the trial to proceed to the second stage, in which another 13 patients would be enrolled. Considering a drop-out rate of 5%, a total of at least 20 patients were needed for this two-stage trial.

Patients provided either newly biopsy-obtained or archival tumor samples for the assessment of PD-L1 expression, mismatch repair (MMR) status, and whole-exome sequencing.

Criteria

Inclusion criteria: 1) Histologically confirmed Recurrent/Metastatic gastric adenocarcinoma; 2) EBER positive; 3) Failed from first-line platinum and fluorouracil based chemotherapy and second-line chemotherapy; or could not tolerate systematic chemotherapy; 4) ECOG performance status of 0 or 1; 5) Life expectancy ≥12 weeks; 6) Subjects must have measurable disease by CT or MRI per RECIST 1.1 criteria; 7) Can provide either a newly obtained or archival tumor tissue sample; 8) Adequate laboratory parameters during the screening period as evidenced by the following: Absolute neutrophil count ≥1.5×10^9/L; Platelets ≥90×10^9/L; Hemoglobin ≥9.0 g/dL; Serum albumin ≥2.8 g/dL; Total bilirubin (TBIL) ≤1.5× upper limit of normal (ULN), ALT and AST ≤1.5× ULN Creatinine clearance ≥50 mL/min; 9) Female of child bearing potential, a negative urine or serum pregnancy test result within 72 h before study treatment. Participants of reproductive potential must be willing to use adequate contraception for the course of the study through 60 days after the last dose of SHR-1210. Male subjects must be willing to use adequate contraception for the course of the study through 120 days after the last dose of SHR-1210; 10) Subjects must be willing to participate in the research and sign an informed consent form (ICF).

Exclusion criteria: 1) Subjects with any active autoimmune disease or history of autoimmune disease; 2) Subjects having clinical symptoms of metastases to central nervous system (such as cerebral edema, requiring steroids intervention, or brain metastasis progression); 3) Has a known additional malignancy within the last 5 years before study treatment with the exception of curatively treated basal cell and squamous cell carcinoma of the skin and/or curatively resected in-situ cervical cancers; 4) Uncontrolled clinically significant heart disease, including but not limited to the following: (1) > NYHA II congestive heart failure; (2) unstable angina; (3) myocardial infarction within the past 1 year; (4) clinically significant supraventricular arrhythmia or ventricular arrhythmia requirement for treatment or intervention; 5) Concurrent medical condition requiring the use of cortisol (>10 mg/day Prednisone or equivalent dose) or other systematic immunosuppressive medications within 14 days before the study treatment. Except: inhalation or topical corticosteroids. Doses >10 mg/day prednisone or equivalent for replacement therapy; 6) Has received prior anti-cancer monoclonal antibody (mAb), chemotherapy, targeted small molecule therapy within 4 weeks prior to first dosing or not recovered to ≤CTCAE 1 from adverse events (except for hair loss or neurotoxic sequelae from prior platinum therapy) due to a previously administered agent; 7) Palliative irradiation finished within 2 weeks; 8) Active infection or an unexplained fever >38.5°C before two weeks of first dosing (subjects with tumor fever may be enrolled at the discretion of the investigator); 9) Known Human Immunodeficiency Virus (HIV) infection-active Hepatitis B or Hepatitis C; 10) Currently participating or has participated in a study within 4 weeks of the first dose of study medication; 11) Pregnancy or breast feeding; 12) Prior therapy with a PD-1, anti-PD-Ligand 1 (PD-L1) or CTLA-4 agent; 13) Subjects are known to have a history of psychiatric substance abuse, alcoholism, or drug addiction; 14) According to the investigator, other conditions that may lead to stop the research.

Study drug

Camrelizumab (Also known as SHR-1210) is provided by Jiangsu Hengrui Pharmaceuticals Co., Ltd. It is freeze-dried powder injection. It is 200 mg/20 ml per dose.

Potential benefit and risk

(1) Benefit: EBV positivity was identified as a distinct molecular subtype of GC by The Cancer Genome Atlas (TCGA) Research Network. EBV positivity may be a biomarker to predict response to PD-1 inhibitors. Camrelizumab was reported to have encouraging efficacy in mGC patients in China, with an ORR of 23.3%. You will receive Camrelizumab for free. Insurance will be covered.

(2) Risk: The side effect profiles for camrelizumab included reactive cutaneous capillary endothelial proliferation, rash, hypothyroidism, hyperthyroidism, fatigue, elevated transaminase et al. Most of the side effects were grade 1 or 2 and tolerable.

Ethics approval and consent to participate

This study was conducted at Sun Yat-sen University Cancer Center (Guangzhou, China). It was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Sun Yat-sen University Cancer Center (No. B2018-058-01).