Safety, Tolerability, and Preliminary Antitumor Activity of Sitravatinib Plus Tislelizumab in Patients With Unresectable Locally Advanced or Metastatic Gastric Cancer or Gastroesophageal Junction Cancer

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Objectives: Sitravatinib is a selective tyrosine kinase inhibitor targeting TAM and VEGFR2 that reduces the number of myeloid-derived suppressor and regulatory T cells and increases the ratio of M1/M2-polarized macrophages. This may help to overcome an immunosuppressive tumor microenvironment and augment antitumor responses. Tislelizumab, an anti-programmed cell death protein-1 (PD-1) antibody designed to minimize binding to FcγR on macrophages and abrogate antibody-dependent phagocytosis, has shown activity in patients with multiple advanced solid tumors. This multicohort, phase 1/2 study assessed the safety/tolerability and efficacy of sitravatinib alone or with tislelizumab (BGB-900-104; NCT03941873). We report results from the phase 2 gastric cancer/gastroesophageal junction cancer (GC/GEJC) cohort receiving sitravatinib plus tislelizumab.

Methods: Eligible patients were aged ≥18 years, had inoperable locally advanced or metastatic GC/GEJC, had failed or were ineligible for current standard of care, must not have received prior immunotherapy, had an ECOG PS of 0-1, and ≥1 measurable lesion (RECIST v1.1). Patients received sitravatinib 120 mg orally once daily and tislelizumab 200 mg intravenously every 3 weeks. The primary endpoint was objective response rate (ORR) (RECIST v1.1; by investigator). Secondary endpoints included duration of response (DoR), disease control rate (DCR), progression-free survival (PFS) (all per RECIST v1.1; by investigator), and safety and tolerability. Exploratory endpoints included overall survival (OS).

Results: As of July 12, 2021, 24 patients were treated. Median age was 62.5 years (range: 44-74), 83.3% of patients were male, and 62.5% of patients had received ≥2 prior lines of systemic therapy. Median study follow-up was 5.2 months (range: 1.0-8.0); five patients (20.8%) remained on treatment. Confirmed ORR was 12.5% in three patients (95% CI: 2.7-32.4), all of whom achieved partial responses. Median DoR was not estimable (95% CI: 3.5 months-NE), DCR was 66.7% (95% CI: 44.7-84.4), and median PFS was 3.4 months (95% CI: 2.0-NE). Median OS was not estimable (95% CI: 4.7 months-NE); the landmark OS rate at 6 months was 71.3% (95% CI: 46.1-86.3). Treatment-emergent adverse events (TEAEs) of any grade/grade ≥3 were reported in 95.8%/50.0% of patients. Serious TEAEs were observed in 45.8% of patients (n=11). The most common grade ≥3 TEAEs included hypertension, upper abdominal pain, and respiratory failure (all n=2; 8.3%). In total, three patients (12.5%) experienced ≥1 TEAE leading to discontinuation of sitravatinib, and two patients (8.3%) experienced ≥1 TEAE leading to discontinuation of tislelizumab. Dose reductions of sitravatinib due to TEAEs occurred in six patients (25.0%).

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Conclusions: The combination of sitravatinib plus tislelizumab showed preliminary antitumor activity, and a manageable safety profile, in patients with pre-treated, advanced GC/GEJC. Further investigation in this patient population is warranted.