Safety, tolerability, and preliminary antitumor activity of sitravatinib plus tislelizumab in patients with unresectable locally advanced or metastatic gastric cancer/gastroesophageal junction cancer

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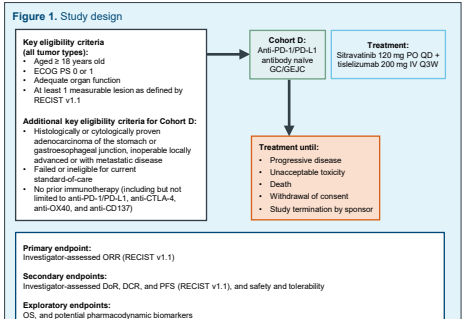
Introduction

- Patients with gastric cancer/gastroesophageal junction cancer (GC/GEJC) generally receive chemotherapy regimens containing platinum and fluoropyrimidine.[1,2] However, first-line chemotherapy typically does not exceed six months because of progressive disease or excessive toxicity[3–5]
- Immunotherapy with checkpoint inhibitors (CPIs) such as programmed cell death protein 1 (PD-1) provides meaningful initial response.[6] However, acquired resistance may lead to disease progression in patients with clinical responses.[7] Combining an immunotherapeutic PD-1 CPI with an agent that has both pleiotropic and antitumor properties could potentially enhance the antitumor efficacy observed with immunotherapy alone[8]
- Tislelizumab is a humanized IgG4 anti-PD-1 monoclonal antibody that has high affinity and specificity for PD-1, and was designed to minimize FcγR binding on macrophages to abrogate antibody-dependent phagocytosis, a potential mechanism of resistance.[9] Sitravatinib is a selective tyrosine kinase inhibitor targeting TAM (TYRO3, AXL, MER) and split tyrosine-kinase domain-containing receptors (vascular endothelial growth factor receptor 2 [VEGFR2], KIT) that can alter a tumor's immune landscape to favor immune checkpoint blockade and overcome resistance[10]
- A Phase 1/2 study (NCT03941873) is currently investigating treatment with sitravatinib plus tislelizumab in several solid tumor types. Here we report results from the Phase 2 study in a cohort of patients with unresectable locally advanced or metastatic, anti-PD-1/programmed death-ligand 1 (PD-L1) antibody naïve GC/GEJC

Methods

- An open-label, multicenter, non-randomized, multi-cohort, Phase 2 trial was conducted (NCT03941873)
- Study design and endpoints are summarized in **Figure 1**

Figure 1. Study design



CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; GC/GEJC, gastric cancer/gastroesophageal junction cancer; ORR, objective response rate; OS, overall survival; OX40, tumor necrosis factor receptor superfamily, member 4; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PO, orally; Q3W, every 3 weeks; QD, once a day; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1

Results

Patients

- As of July 12, 2021, 24 patients with GC/GEJC were treated in the study, and five patients remained on treatment
- Median follow-up was 5.2 months (range: 1.0–8.0). In total, there were 24 patients in the safety and efficacy analysis sets
- Baseline characteristics are summarized in **Table 1**

Conclusions

- Treatment with **sitravatinib plus tislelizumab** showed **efficacy and a manageable safety profile** in patients with **pre-treated, advanced GC/GEJC**
- Sitravatinib plus tislelizumab demonstrated antitumor activity in previously treated patients with anti-PD-1/PD-L1 antibody naive GC/GEJC, with an **overall ORR of 12.5%, DCR of 66.7%, and PFS of 3.4 months**
- A trend towards **increased sVEGF and IP-10**, and **decreased sVEGFR2** after treatment with tislelizumab plus sitravatinib was observed
- **Further investigation** of sitravatinib plus tislelizumab in this patient population is **warranted**

Table 1. Demographics and baseline characteristics (safety analysis set; N=24)

		Total (N=24)
Age, years	Median (range)	62.5 (44–74)
Sex, n (%)	Male	20 (83.3)
	Female	4 (16.7)
Race, n (%)	Asian	24 (100.0)
ECOG PS, n (%)	0	2 (8.3)
	1	22 (91.7)
Number of prior treatment lines,* n (%)	1	14 (58.3)
	≥ 2	8 (33.3)
Primary location, n (%)	Gastroesophageal junction	7 (29.2)
	Stomach	17 (70.8)

*Percentage was based on patients with prior anticancer systemic therapy
ECOG PS, Eastern Cooperative Oncology Group performance status

Efficacy

- In the efficacy evaluable set (n=24), confirmed objective response rate (ORR) was 12.5% in three patients, all of whom achieved partial responses (**Table 2**). Best change in target lesion for all patients is presented in **Figure 2**
- Median duration of response was not evaluable (NE) (95% confidence interval [CI]: 3.5 months, NE)
- Disease control rate was 66.7% (95% CI: 44.7, 84.4)
- Investigator-assessed median progression-free survival (PFS) (RECIST v1.1) was 3.4 months (95% CI: 2.0, NE) (**Figure 3a**)
- Median overall survival (OS) was NE (95% CI: 4.7 months, NE) (**Figure 3b**). The landmark OS rate at 6 months was 71.3%

Safety

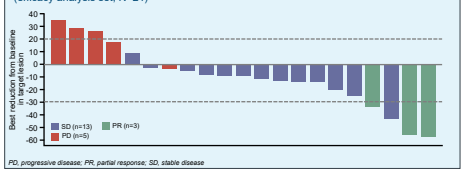
- Median duration of exposure was 11.4 weeks (range: 1.0–36.1) for sitravatinib and 12.1 weeks (range: 3.0–36.0) for tislelizumab
- Treatment-emergent adverse events (TEAEs) of any Grade and ≥ Grade 3 were reported in 95.8% and 50.0% of patients, respectively (**Table 3**)
- Serious TEAEs were observed in 45.8% of patients; the most common ≥ Grade 3 TEAEs included hypertension, upper abdominal pain, and respiratory failure (all n=2)
- Three patients experienced TEAEs leading to discontinuation of sitravatinib (proteinuria, deep vein thrombosis, pulmonary embolism, and upper gastrointestinal hemorrhage [all n=1]). Two patients experienced ≥ 1 TEAE leading to discontinuation of tislelizumab (deep vein thrombosis, pulmonary embolism, and upper gastrointestinal hemorrhage [all n=1])
- Six patients had their doses of sitravatinib reduced because of TEAEs. Five patients experienced ≥ 1 TEAE leading to death (unexplained death [n=2], myocardial infarction [n=1], and respiratory failure [n=2].) Three of these deaths were considered related to study treatment (unexplained death [n=2], and respiratory failure [n=1].) The most common TEAEs occurring in ≥ 10% of patients are listed in **Table 4**

Table 2. Analysis of confirmed disease response per RECIST v1.1 (efficacy analysis set; N=24)

	Total (N=24)
ORR, % (95% CI)	12.5 (2.7, 32.4)
Best overall response, n (%)	
Complete response	0 (0)
Partial response	3 (12.5)
Stable disease	13 (54.2)
Progressive disease	5 (20.8)
Not evaluated*	3 (12.5)
DCR, % (95% CI)	66.7 (44.7, 84.4)
Median DoR, months (95% CI)	NE (3.5, NE)

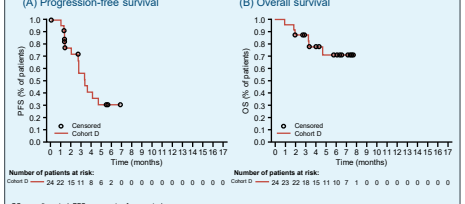
Three patients were not evaluated due to death before the first tumor assessment. CI, confidence interval; DCR, disease control rate; DoR, duration of response; NE, not evaluable; ORR, objective response rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1

Figure 2. Change in target lesion by investigator-assessed confirmed best overall response (efficacy analysis set; N=24)



PD, progressive disease; PR, partial response; SD, stable disease

Figure 3. (A) Progression-free survival and (B) overall survival (efficacy analysis set; N=24)



OS, overall survival; PFS, progression-free survival

Table 3. Summary of AEs (safety analysis set; N=24)

Patients, n (%)	TEAEs	TRAEs
Any AE	23 (95.8)	21 (87.5)
≥ Grade 3 AE	12 (50.0)	10 (41.7)
Serious AE	11 (45.8)	8 (33.3)
≥ Grade 3 serious	10 (41.7)	7 (29.2)
AE leading to death	5 (20.8)	3 (12.5)
AE leading to sitravatinib discontinuation	3 (12.5)	2 (8.3)
AE leading to tislelizumab discontinuation	2 (8.3)	1 (4.2)
AE leading to sitravatinib dose modification*	12 (50.0)	12 (50.0)
AE leading to tislelizumab dose modification†	5 (20.8)	5 (20.8)

AE leading to sitravatinib dose modification included dose reduction and/or interruption; †AE leading to tislelizumab dose modification included dose delay and/or interruption. AE, adverse event; TEAE, treatment-emergent AE; TRAE, treatment-related AE

Table 4. TEAEs with ≥ 10% frequency (safety analysis set; N=24)

Event, n (%)	Any Grade	≥ Grade 3
Hypoalbuminemia	10 (41.7)	0 (0.0)
Anemia	9 (37.5)	1 (4.2)
Blood creatine phosphokinase increased	9 (37.5)	0 (0.0)
Proteinuria	9 (37.5)	1 (4.2)
Aspartate aminotransferase increased	8 (33.3)	0 (0.0)
Alanine aminotransferase increased	7 (29.2)	0 (0.0)
Weight decreased	7 (29.2)	0 (0.0)
Hypertension	6 (25.0)	2 (8.3)
Platelet count decreased	6 (25.0)	0 (0.0)
Blood alkaline phosphatase increased	5 (20.8)	0 (0.0)
Palmar-plantar erythrodysaesthesia	4 (16.7)	0 (0.0)
Decreased appetite	4 (16.7)	1 (4.2)
Abdominal pain upper	4 (16.7)	2 (8.3)
Hypothyroidism	4 (16.7)	0 (0.0)
Fatigue	4 (16.7)	1 (4.2)
Diarrhea	3 (12.5)	0 (0.0)
Blood bilirubin increased	3 (12.5)	1 (4.2)
Nausea	3 (12.5)	0 (0.0)
Hyperthyroidism	3 (12.5)	0 (0.0)
Asthenia	3 (12.5)	0 (0.0)

TEAE, treatment-emergent adverse event

Pharmacodynamic biomarkers

- Changes from baseline (Cycle 1 Day 1, [C1D1]) in blood-based biomarkers were assessed. A trend towards increased soluble VEGF (sVEGF) and interferon gamma-induced protein 10 (IP-10), and decreased sVEGFR2 was observed at both C2D1 and C3D1 after treatment with tislelizumab combined with sitravatinib (**Table 5**)

Table 5. Change from baseline in pharmacodynamic biomarkers

	C2D1		C3D1	
Biomarker	Estimated mean fold change from C1D1 (95% CI)	Patients, n	Estimated mean fold change from C1D1 (95% CI)	Patients, n
sVEGF	2.5 (1.8, 3.3)	17	2.1 (1.5, 3.1)	12
sVEGFR2	0.7 (0.6, 0.7)	17	0.7 (0.6, 0.7)	12
IP-10	1.6 (1.3, 2.0)	17	2.0 (1.4, 2.9)	12

Baseline was at C1D1. The mean fold change was estimated from a linear mixed model of repeated measurements. An increase from baseline was a fold change of > 1 at C2D1 or C3D1; a decrease from baseline was a fold change of < 1 at C2D1 or C3D1
C, cycle; CI, confidence interval; D, day; IP-10, interferon gamma-induced protein 10; sVEGFR2, soluble vascular endothelial growth factor receptor 2.

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