Phase 1b/2 Study of Sitravatinib Alone or With Tislelizumab in Advanced Hepatocellular Carcinoma and Gastric/Gastroesophageal Junction Cancer

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Conclusions

Sitravatinib with or without tislelizumab was generally well tolerated in patients with unresectable locally advanced or metastatic hepatocellular carcinoma (HCC) and gastric/gastroesophageal junction cancer (GC/GEJC).

Sitravatinib monotherapy demonstrated preliminary antitumor activity in patients with HCC with an objective response rate (ORR) of 25.0%. Sitravatinib with tislelizumab demonstrated preliminary antitumor activity in pretreated HCC (ORR=10.6%) and GC/GEJC (ORR=16.1%).

This study demonstrated sitravatinib as a potential treatment option for patients with advanced HCC or GC/GEJC, warranting further investigation of sitravatinib as monotherapy or combined with tislelizumab in these patient populations.

Background

Tislelizumab is a humanized, IgG4, monoclonal antibody with high affinity for programmed cell death protein 1 (PD-1).[1,2] Despite the promising antitumor activity of PD-1 inhibitors in solid tumors, response rates remain low, and many patients develop resistance.[3,4]

Sitravatinib is a selective tyrosine kinase inhibitor, targeting TAM (TYRO3, AXL, MER) and split tyrosine kinase domain containing receptors (VEGFR-2, KIT), which can alter a tumor's immune landscape to favor immune checkpoint blockade and overcome resistance.[5,6]

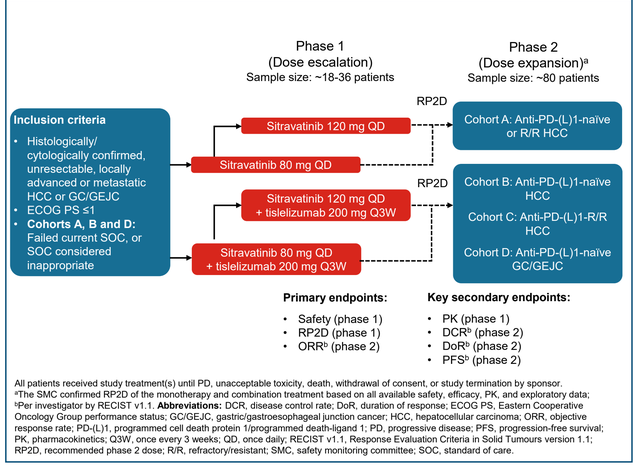
Combination of sitravatinib with tislelizumab may enhance the antitumor activity of the individual monotherapies;[7] this approach has demonstrated promising antitumor responses in advanced non-small cell lung cancer.[8]

Here we present safety and preliminary antitumor activity results from phase 1 and phase 2 of the SAFFRON-104 study of sitravatinib with or without tislelizumab in patients with advanced HCC or GC/GEJC.

Methods

- SAFFRON-104 is an open-label, multicenter, multicohort phase 1b/2 study (NCT03941873) (**Figure 1**)
- Phase 1 was designed to determine the recommended phase 2 dose (RP2D)
- Phase 2 was designed to further evaluate the safety and preliminary antitumor activity of sitravatinib with or without tislelizumab

Figure 1. SAFFRON-104 Study Design



All patients received study treatment(s) until PD, unacceptable toxicity, death, withdrawal of consent, or study termination by sponsor.
[a]The SMC confirmed RP2D of the monotherapy and combination treatment based on all available safety, efficacy, PK, and exploratory data; [b]Per investigator by RECIST v1.1. **Abbreviations:** DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GC/GEJC, gastric/gastroesophageal junction cancer; HCC, hepatocellular carcinoma; ORR, objective response rate; PD-(L)1, programmed cell death protein 1/programmed death-ligand 1; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; Q3W, once every 3 weeks; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; RP2D, recommended phase 2 dose; R/R, refractory/resistant; SMC, safety monitoring committee; SOC, standard of care.

Results

Patients

- At the data cutoff (March 31, 2023), 24 patients had received treatment in phase 1 and 87 patients in phase 2; no patients remained on the study
- Median study follow-up was 9.1 months (range: 0.7-36.9)
- Baseline characteristics are shown in **Table 1**

Table 1. Demographics and Baseline Characteristics (Safety Analysis Set)

	HCC			GC/GEJC[a]
Treatment	**Sitravatinib**	**Sitravatinib + tislelizumab**		**Sitravatinib + tislelizumab**
Prior anti-PD-(L)1 treatment	**Naïve or R/R (n=24)**	**Naïve (n=27)**	**R/R (n=24)**	**Naïve (n=32)**
Median age, years (range)	51.5 (31-70)	61.0 (30-70)	49.0 (29-71)	62.5 (44-74)
Male sex, n (%)	23 (95.8)	23 (85.2)	22 (91.7)	27 (84.4)
ECOG PS, n (%)				
0	10 (41.7)	14 (51.9)	13 (54.2)	3 (9.4)
1	14 (58.3)	13 (48.1)	11 (45.8)	29 (90.6)
PD-L1 TC score, n (%)[b]				
TC <1%	8 (33.3)	10 (37.0)	0 (0.0)	8 (25.0)
TC ≥1%	1 (4.2)	1 (3.7)	0 (0.0)	2 (6.3)
Unknown	15 (62.5)	16 (59.3)	24 (100.0)	22 (68.8)
Disease status, n (%)				
Unresectable locally advanced	1 (4.2)	5 (18.5)	4 (16.7)	1 (3.1)
Metastatic	23 (95.8)	22 (81.5)	20 (83.3)	31 (96.9)
Prior anticancer therapy,[c] n (%)	23 (95.8)	27 (100.0)	24 (100.0)	32 (100.0)
Median prior lines of therapy (range)	1.0 (1-2)	1.0 (1-2)	1.5 (1-2)	2.0 (0-6)
Prior CPI therapy	1 (4.2)	0 (0.0)	24 (100.0)	0 (0.0)

Data cutoff: March 31, 2023. [a]Four patients with GC/GEJC enrolled in phase 1 were not included in the efficacy or safety analysis by indication because they received sitravatinib monotherapy or were either anti-PD-1 or PD-L1 R/R; [b]PD-L1 status was evaluated with the VENTANA SP263 CDx assay; [c]Prior anticancer therapies included: tyrosine kinase inhibitors, immunotherapeutic agents, anti-HER2 agents, anti-VEGF(R) monoclonal antibody, and chemotherapeutic agents. **Abbreviations:** CPI, checkpoint inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; GC/GEJC, gastric/gastroesophageal junction cancer; HCC, hepatocellular carcinoma; HER2, human epidermal growth factor receptor 2; PD-(L)1, programmed cell death protein 1/programmed death-ligand 1; R/R, refractory/resistant; TC, tumor cell; VEGF(R), vascular endothelial growth factor (receptor).

Safety

- The RP2D of sitravatinib was determined to be 120 mg once daily as monotherapy and in combination with tislelizumab based on the results from phase 1
- A summary of safety results is presented in **Table 2**
- In patients receiving sitravatinib with tislelizumab, four treatment-related adverse events leading to death were reported: one caused by respiratory failure and three with unknown causes

Table 2. Summary of TRAEs (Safety Analysis Set)

Treatment, n (%)	**Sitravatinib (n=27)**	**Sitravatinib + tislelizumab (n=84)**
Any grade TRAE	27 (100.0)	76 (90.5)
Grade ≥3 TRAE	14 (51.9)	42 (50.0)
Serious TRAE	6 (22.2)	18 (21.4)
TRAEs leading to death	0 (0.0)	4 (4.8)
TRAEs leading to treatment discontinuation	1 (3.7)	9 (10.7)
TRAEs leading to dose modification[a]	18 (66.7)	53 (63.1)
Most frequent TRAEs by preferred term		
Proteinuria		
Any grade Grade ≥3	15 (55.6) 0 (0.0)	46 (54.8) 3 (3.6)
Aspartate aminotransferase increased		
Any grade Grade ≥3	14 (51.9) 2 (7.4)	38 (45.2) 0 (0.0)
Alanine aminotransferase increased		
Any grade Grade ≥3	14 (51.9) 2 (7.4)	38 (45.2) 0 (0.0)
Palmar-plantar erythrodysesthesia syndrome		
Any grade Grade ≥3	19 (70.4) 3 (11.1)	30 (35.7) 5 (6.0)

Data are n (%). Data cutoff: March 31, 2023. Adverse events were classified based on Medical Dictionary for Regulatory Activities version 25.0. [a]TRAEs leading to dose modification included dose reduction, dose interruption, or dose delay.
Abbreviation: TRAE, treatment-related adverse event.

Efficacy

- In the efficacy analysis set, the ORR with sitravatinib monotherapy was 25.0% in patients with advanced HCC (95.8% were pretreated, only one of whom had received checkpoint inhibitors) (**Table 3**)
- The ORR with sitravatinib plus tislelizumab in patients with pretreated, anti-PD-1/programmed death-ligand 1 (PD-L1)-naïve HCC was 11.5%, with a median progression-free survival (PFS) of 6.8 months
- In patients with pretreated, anti-PD-1/PD-L1-naïve GC/GEJC who were treated with sitravatinib plus tislelizumab, the ORR was 16.1%, with a median PFS of 3.6 months

Table 3. Pooled Efficacy Results

	HCC				GC/GEJC[a]
Treatment	**Sitravatinib**		**Sitravatinib + tislelizumab**		**Sitravatinib + tislelizumab**
Prior anti-PD-(L)1 treatment	**Naïve or R/R**	**Naïve**	**R/R**	**Subtotal**	**Naïve**
Efficacy analysis set	**(n=20)**	**(n=26)**	**(n=21)**	**(n=47)**	**(n=31)**
ORR, n (%)	5 (25.0)	3 (11.5)	2 (9.5)	5 (10.6)	5 (16.1)
DCR, n (%)	18 (90.0)	22 (84.6)	17 (81.0)	39 (83.0)	22 (71.0)
Median DoR, mo (95% CI)[b]	7.7 (2.8, NE)	5.7 (4.1, NE)	NR (5.4, NE)	5.7 (4.1, NE)	5.5 (2.7, NE)
Safety analysis set	**(n=24)**	**(n=27)**	**(n=24)**	**(n=51)**	**(n=32)**
Median PFS, mo (95% CI)[b]	6.8 (4.0, 7.4)	6.8 (2.8, 8.3)	4.2 (2.7, 6.8)	4.8 (4.0, 6.8)	3.6 (2.8, 4.7)
Safety analysis set (phase 2 only)	**(n=20)**	**(n=21)**	**(n=22)**	**(n=43)**	**(n=24)**
Median OS, mo (95% CI)[b]	26.7 (9.1, NE)	20.5 (7.4, NE)	12.4 (7.0, 14.1)	12.8 (8.2, 26.5)	8.9 (4.7, 16.0)

Data cutoff: March 31, 2023. [a]Four patients with GC/GEJC enrolled in phase 1 were not included in this analysis because they either received sitravatinib monotherapy or were anti-PD-1 or PD-L1 R/R; [b]Medians were estimated by the Kaplan-Meier method with 95% CIs estimated using the Brookmeyer and Crowley method with log-log transformation. **Abbreviations:** CI, confidence interval; DCR, disease control rate; DoR, duration of response; GC/GEJC, gastric/gastroesophageal junction cancer; HCC, hepatocellular carcinoma; mo, months; NE, not estimable; NR, not reached; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed cell death protein 1/programmed death-ligand 1; PFS, progression-free survival; R/R, refractory/resistant.

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