Safety, tolerability, and preliminary antitumor activity of sitravatinib plus tislelizumab in patients with unresectable locally advanced or metastatic hepatocellular carcinoma

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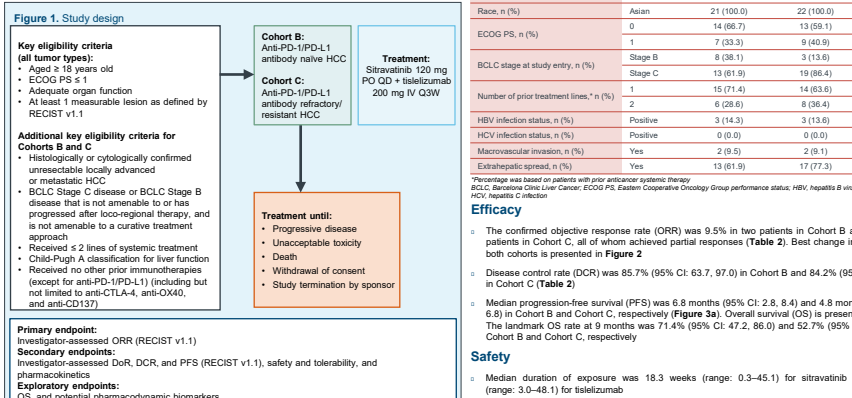
Background

- Combination therapy has shown promising activity in recent studies of patients with hepatocellular carcinoma (HCC).[1–3] However, some patients will not have a durable response.[3] Treatment options after prior immunotherapy in HCC remain a significant unmet medical need
- Tislelizumab is a humanized IgG4 anti-programmed cell death protein 1 (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.[4–6] 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.[7] This may help to overcome an immunosuppressive tumor microenvironment and augment antitumor responses
- This multi-cohort, 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 cohorts of patients with HCC receiving sitravatinib plus tislelizumab

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



Primary endpoint:
Investigator-assessed ORR (RECIST v1.1)
Secondary endpoints:
Investigator-assessed DoR, DCR, and PFS (RECIST v1.1), safety and tolerability, and pharmacokinetics
Exploratory endpoints:
OS, and potential pharmacodynamic biomarkers

Anti-PD-1/PD-L1 antibody refractory was defined as radiographic progression on or after anti-PD-1/PD-L1 therapy with a best response to anti-PD-1/PD-L1 of PD or SD for ≥ 6 weeks. Anti-PD-1/PD-L1 antibody resistant was defined as best response to anti-PD-1/PD-L1 therapy of CR or PR or SD lasting for > 6 weeks.
BCLC, Barcelona Clinic Liver Cancer; CD, cluster of differentiation; CR, complete response; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; IV, intravenously; 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; PR, partial response; QD, once a day; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

Results

Patients

- As of July 12, 2021, 43 patients across both cohorts were treated in the study, and 10 patients remained on treatment. Median follow-up time was 8.6 months (range: 0.7–10.6). In total, there were 43 patients in the safety analysis set, and 40 patients in the efficacy analysis set
- Baseline characteristics are summarized in **Table 1**

Conclusions

- Treatment with sitravatinib plus tislelizumab showed **efficacy** and a **manageable safety/tolerability profile** in patients with **pre-treated, advanced HCC**
- Sitravatinib plus tislelizumab demonstrated **antitumor activity** in previously treated patients with **anti-PD-1/PD-L1 antibody naive and refractory HCC,** with an ORR of 9.5% vs 10.5%, DCR of 85.7% vs 84.2%, and PFS of 6.8 months vs 4.8 months in Cohort B and Cohort C, respectively
- An **increase in sVEGF and IP-10,** and **decrease in sVEGFR2** was observed in both cohorts after treatment with tislelizumab plus sitravatinib
- **Further investigation** of sitravatinib plus tislelizumab in these patient populations is **warranted**

Table 1. Demographics and baseline characteristics (safety analysis set; N=43)

		Cohort B (n=21)	Cohort C (n=22)	Total (N=43)
Age, years	Median (range)	62.0 (30, 70)	49.5 (29, 71)	55.0 (29, 71)
Sex, n (%)	Male	18 (85.7)	20 (90.9)	38 (88.4)
	Female	3 (14.3)	2 (9.1)	5 (11.6)
Race, n (%)	Asian	21 (100.0)	22 (100.0)	43 (100.0)
ECOG PS, n (%)	0	14 (66.7)	13 (59.1)	27 (62.8)
	1	7 (33.3)	9 (40.9)	16 (37.2)
BCLC stage at study entry, n (%)	Stage B	8 (38.1)	3 (13.6)	11 (25.6)
	Stage C	13 (61.9)	19 (86.4)	32 (74.4)
Number of prior treatment lines,* n (%)	1	15 (71.4)	14 (63.6)	29 (67.4)
	2	6 (28.6)	8 (36.4)	14 (32.6)
HBV infection status, n (%)	Positive	3 (14.3)	3 (13.6)	6 (14.0)
HCV infection status, n (%)	Positive	0 (0.0)	0 (0.0)	0 (0.0)
Macrovascular invasion, n (%)	Yes	2 (9.5)	2 (9.1)	4 (9.3)
Extrahepatic spread, n (%)	Yes	13 (61.9)	17 (77.3)	30 (69.8)

*Percentage was based on patients with prior anticancer systemic therapy
BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCV, hepatitis C infection

Efficacy

- The confirmed objective response rate (ORR) was 9.5% in two patients in Cohort B and 10.5% in two patients in Cohort C, all of whom achieved partial responses (**Table 2**). Best change in target lesion for both cohorts is presented in **Figure 2**
- Disease control rate (DCR) was 85.7% (95% CI: 63.7, 97.0) in Cohort B and 84.2% (95% CI: 60.4, 96.6) in Cohort C (**Table 2**)
- Median progression-free survival (PFS) was 6.8 months (95% CI: 2.8, 8.4) and 4.8 months (95% CI: 2.7, 6.8) in Cohort B and Cohort C, respectively (**Figure 3a**). Overall survival (OS) is presented in **Figure 3b**. The landmark OS rate at 9 months was 71.4% (95% CI: 47.2, 86.0) and 52.7% (95% CI: 23.2, 75.5) in Cohort B and Cohort C, respectively

Safety

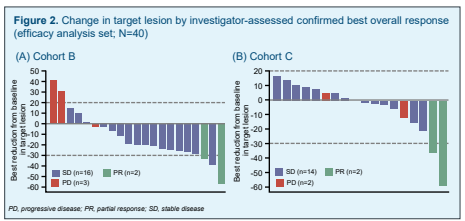
- Median duration of exposure was 18.3 weeks (range: 0.3–45.1) for sitravatinib and 18.3 weeks (range: 3.0–48.1) for tislelizumab
- In total, 42 patients (97.7%) had ≥ 1 treatment-emergent adverse event (TEAE), and 37 patients (86.0%) had ≥ 1 treatment-related AE (TRAE) (**Table 3**)
- There were two TRAEs leading to death (hepatic encephalopathy in Cohort B and unexplained death in Cohort C) (**Table 3**)
- In total, 26 patients (60.5%) experienced ≥ 1 TEAE leading to dose modification of sitravatinib; and 16 patients (37.2%) experienced ≥ 1 TEAE leading to dose modification of tislelizumab (**Table 3**). The TEAEs leading to sitravatinib discontinuation were hemoptysis, hepatic encephalopathy, pneumonia, and proteinuria and for tislelizumab discontinuation: death, hemoptysis, hepatic encephalopathy, and rash (all n=1, [2.3%])
- The most frequently observed TEAEs were increase in alanine aminotransferase (53.5%), increase in aspartate aminotransferase (53.5%), and palmar-plantar erythrodysesthesia (51.2%) (**Table 4**). The most frequently observed ≥ Grade 3 TEAEs were palmar-plantar erythrodysaesthesia (9.3%) and decrease in platelet count (7.0%)
- The safety profile of sitravatinib plus tislelizumab was similar across patients in Cohort B and Cohort C

Table 2. Analysis of confirmed disease response per RECIST v1.1 (efficacy analysis set; N=40)

	Cohort B (n=21)	Cohort C (n=19)	Total (N=40)
ORR, % (95% CI)	9.5 (1.2, 30.4)	10.5 (1.30, 33.1)	10.0 (2.8, 23.7)
Best overall response, n (%)			
Complete response	0 (0.0)	0 (0.0)	0 (0.0)
Partial response	2 (9.5)	2 (10.5)	4 (10.0)
Stable disease	16 (76.2)	14 (73.7)	30 (75.0)
Progressive disease	3 (14.3)	2 (10.5)	5 (12.5)
Not evaluated*	0 (0.0)	1 (5.3)	1 (2.5)
DCR, % (95% CI)	85.7 (63.7, 97.0)	84.2 (60.4, 96.6)	85.0 (70.2, 94.3)

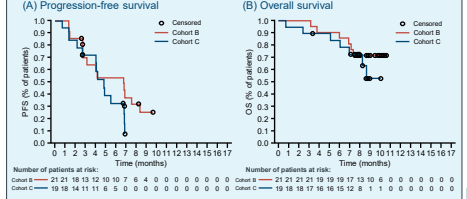
*One patient was not evaluated for best overall response due to "unexplained death" before the first tumor assessment
CI, confidence interval; DCR, disease control rate; ORR, objective response rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1

Figure 2. Change in target lesion by investigator-assessed confirmed best overall response (efficacy analysis set; N=40)



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

Figure 3. Progression-free survival and overall survival (efficacy analysis set; N=40)



OS, overall survival; PFS, progression-free survival

Table 3. Combined summary of AEs in Cohorts B and C (safety analysis set; N=43)

Patients, n (%)	TEAEs	TRAEs
Patients with ≥ 1 AE	42 (97.7)	37 (86.0)
Serious	12 (27.9)	7 (16.3)
≥ Grade 3	21 (48.8)	17 (39.5)
≥ Grade 3 serious	9 (20.9)	6 (14.0)
AEs leading to death	3 (7.0)	2 (4.7)
AEs leading to sitravatinib discontinuation	4 (9.3)	4 (9.3)
AEs leading to tislelizumab discontinuation	4 (9.3)	4 (9.3)
AEs leading to sitravatinib dose modification*	26 (60.5)	24 (55.8)
AEs leading to tislelizumab dose modification†	16 (37.2)	13 (30.2)

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

Table 4. Combined summary of TEAEs with ≥ 15% frequency in Cohorts B and C (safety analysis set; N=43)

Event, n (%)	Any Grade	≥ Grade 3
Alanine aminotransferase increased	23 (53.5)	1 (2.3)
Aspartate aminotransferase increased	23 (53.5)	1 (2.3)
Palmar-plantar erythrodysesthesia	22 (51.2)	4 (9.3)
Proteinuria	20 (46.5)	1 (2.3)
Diarrhea	18 (41.9)	1 (2.3)
Hypertension	14 (32.6)	1 (2.3)
Blood creatine phosphokinase increased	10 (23.3)	1 (2.3)
Blood thyroid stimulating hormone increased	10 (23.3)	0 (0.0)
Decreased appetite	10 (23.3)	0 (0.0)
Platelet count decreased	9 (20.9)	3 (7.0)
Hypoalbuminemia	8 (18.6)	0 (0.0)
Vomiting	8 (18.6)	0 (0.0)
White blood cell count decreased	8 (18.6)	0 (0.0)
Abdominal pain upper	7 (16.3)	0 (0.0)
Alpha hydroxybutyrate dehydrogenase increased	7 (16.3)	0 (0.0)
Blood bilirubin increased	7 (16.3)	0 (0.0)
Blood lactate dehydrogenase increased	7 (16.3)	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 an increase in soluble VEGF (sVEGF) and interferon gamma-induced protein 10 (IP-10), and a decrease in sVEGFR2 was observed after treatment with tislelizumab combined with sitravatinib in both cohorts at all post-treatment visits (**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
Cohort B	sVEGF	2.9 (2.0, 4.1)	18	2.6 (1.6, 4.3)	16
	sVEGFR2	0.7 (0.6, 0.8)	18	0.8 (0.7, 0.9)	16
	IP-10	1.5 (1.2, 1.8)	18	1.4 (1.1, 1.7)	16
Cohort C	sVEGF	3.8 (2.9, 5.0)	15	3.6 (2.4, 5.4)	13
	sVEGFR2	0.6 (0.6, 0.7)	15	0.7 (0.6, 0.7)	13
	IP-10	1.2 (0.8, 1.6)	15	1.4 (1.0, 1.9)	13

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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