Efficacy and safety of tislelizumab (TIS) plus lenvatinib (LEN) as first-line treatment in patients (pts) with unresectable hepatocellular carcinoma (uHCC): a single-arm, multicenter, phase II trial

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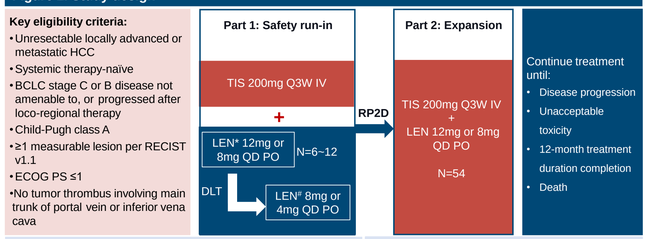
BACKGROUND

- Hepatocellular carcinoma (HCC) is estimated to be the sixth most prevalent cancer worldwide and the third leading cause of cancer-related death.[1]
- Tislelizumab, an anti-PD-1 monoclonal antibody with high binding affinity for PD-1 and with minimized Fcγ receptor binding on macrophages,[2,3] has demonstrated clinically meaningful overall survival (OS) benefit that is noninferior to sorafenib in first-line therapy of unresectable HCC (uHCC) in the international multicenter phase III RATIONALE-301 study.[4]
- Lenvatinib (LEN), a multikinase inhibitor, is a first-line treatment for uHCC based on the phase III REFLECT study.[5]
- Here, we report the primary analysis results from a phase II study of tislelizumab plus lenvatinib in patients with uHCC without previous systemic treatment.

METHODS

- BGB-A317-211 was a multicenter, open-label, single-arm phase II study (NCT04401800; **Figure 1**).
- The primary analysis was planned to be conducted at 6 months after the last patient was enrolled.

Figure 1. Study design



Primary endpoint: ORR per RECIST v1.1 by IRC

Secondary endpoints:

- Safety and tolerability
- ORR per RECIST v1.1 by investigators
- ORR per mRECIST and iRECIST by IRC and investigators, respectively
- DoR, DCR, and PFS per RECIST v1.1, mRECIST and iRECIST by IRC and investigators, respectively

Statistical assumption:

Based on the Simon's two-stage design, single-side α=0.025 and β= 0.05, >6 responders in EAS by IRC per RECIST v1.1 were needed in stage 1 (n=30) to continue the study, and ≥18 responders were needed by the end of stage 2 (n=60) to claim statistical superiority to a historical control ORR of 18.8% per RECIST v1.1(from LEN arm of phase 3 REFLECT study[5]) .

Safety analysis set (SAS): included all patients who had ≥1 dose of TIS or LEN;
Efficacy evaluable analysis set (EAS): included all dosed patients with measurable disease at baseline per RECIST v1.1 who had ≥1 post-baseline tumor assessment unless treatment was discontinued due to clinical disease progression or death before the first post treatment tumor assessment.
*Starting dose: 12mg (body weight ≥60 kg) or 8mg (body weight ＜60 kg).
#Reduced dose: 8mg (body weight ≥60 kg) or 4mg (body weight ＜60 kg).

RESULTS

Patients

- A total of 64 patients (**Table 1**) were enrolled (safety run-in part, n=6; expansion part, n= 58).
- At the data cutoff date (July 7, 2022), 14 (21.9%) patients were still undergoing study treatment.

Table 1. Baseline Characteristics (SAS, n=64)

Median age, years (range)		52.5 (28.0-70.0)	ECOG PS, n (%)	0	40 (62.5)
Male sex, n (%)		53 (82.8)		1	24 (37.5)
Region, mainland China, n (%)		64(100.0)	Child-Pugh score, n (%)	5	58 (90.6)
HCC etiology, HBV, n (%)		58 (90.6)		6	6 (9.4)
BCLC staging at study entry, n (%)	B	17 (26.6)	Macrovascular invasion, n (%)		7 (10.9)
	C	47 (73.4)	Extrahepatic spread, n (%)		37(57.8)
AFP ≥ 400 ng/ml, n (%)		26 (40.6)	Local regional therapy, n (%)		47 (73.4)

CONCLUSION

- **The study met its statistical superiority with tislelizumab plus lenvatinib vs historical data (lenvatinib arm of phase III REFLECT study) in the first-line setting in uHCC patients, with a confirmed ORR of 38.7% per RECIST v1.1 by IRC review.**
- **Tislelizumab plus lenvatinib showed a promising mPFS (9.6 months) and 6-month PFS rate (67.0%) per RECIST v1.1 by IRC review.**
- **Tislelizumab plus lenvatinib was generally well tolerated and no new safety signals were identified.**

Efficacy

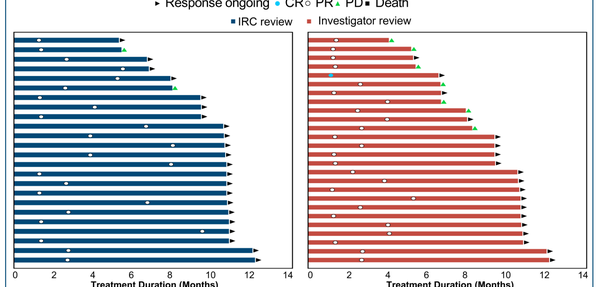
- As of cutoff date, the median study follow-up time was 12.5 months (range: 0.9, 22.1).
- Among the 62 patients in EAS, there were 23 responders in the first 60 patients, which met the statistical superiority criteria.
- Confirmed ORR per RECIST v1.1 by IRC and investigator review were 38.7% and 41.9%; DCR were 90.3% and 85.5% in EAS, respectively. The ORR per mRECIST and iRECIST were comparable with RECIST v1.1 (**Table 2**).
- Median DoR per RECIST v1.1 by IRC and investigator review were not reached (**Figure 2**); the 6-month event-free rates for DoR were 86.9% (95% CI: 56.5%, 96.6%) and 70.7%(95% CI: 47.6%, 85.0%), respectively.

Table 2. Tumor response by IRC and investigator review per RECIST v1.1, mRECIST and iRECIST (EAS, n=62)

	IRC review			Investigator review		
	RECIST v1.1	mRECIST	iRECIST	RECIST v1.1	mRECIST	iRECIST
Confirmed ORR, n (%) [95% CI[a]]	24 (38.7) [26.6, 51.9]	29 (46.8) [34.0, 59.9]	24 (38.7) [26.6, 51.9]	26 (41.9) [29.5, 55.2]	29 (46.8) [34.0, 59.9]	27 (43.5) [31.0, 56.7]
BOR/iBOR, n (%)						
CR/iCR	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.6)	1 (1.6)
PR/iPR	24 (38.7)	29 (46.8)	24 (38.7)	25 (40.3)	28 (45.2)	26 (41.9)
SD/iSD	32 (51.6)	27 (43.5)	32 (51.6)	27 (43.5)	24 (38.7)	28 (45.2)
PD	5 (8.1)	5 (8.1)	N/A	8 (12.9)	8 (12.9)	N/A
iUPD	N/A	N/A	2 (3.2)	N/A	N/A	3 (4.8)
iCPD	N/A	N/A	3 (4.8)	N/A	N/A	3 (4.8)
NA[b]	1 (1.6)	1 (1.6)	1 (1.6)	1 (1.6)	1 (1.6)	1 (1.6)
DCR, n (%)[95% CI[a]]	56 (90.3) [80.1, 96.4]	56 (90.3) [80.1, 96.4]	56 (90.3) [80.1, 96.4]	53 (85.5) [74.2, 93.1]	53 (85.5) [74.2, 93.1]	55 (88.7) [78.1, 95.3]

[a]The 95% CI was estimated using the Clopper-Pearson method.
[b]One patient received 1 dose TIS and LEN less than 1 cycle, died with confirmed clinical disease progression before the first radiological assessment.

Figure 2. Duration of response per RECIST v1.1 by IRC and investigator review



Each bar represents an individual responder (n=24 [per IRC review], left panel; n=26 [per investigator review], right panel).

Efficacy

- Reductions in tumor size of target lesion per RECIST v1.1 by IRC and investigator review were reported in 74.2% (46/62) and 80.6% (50/62) of patients in EAS, respectively (**Figure 3**).
- Median PFS (mPFS) per RECIST v1.1 by IRC and investigator review were 9.6 months (95% CI: 6.8, NE) and 8.5 months (95% CI: 5.3, NE), respectively (**Figure 4**).

Figure 3. Percentage change from baseline in Sums of diameters of target lesions per RECIST v1.1 by IRC and investigator review

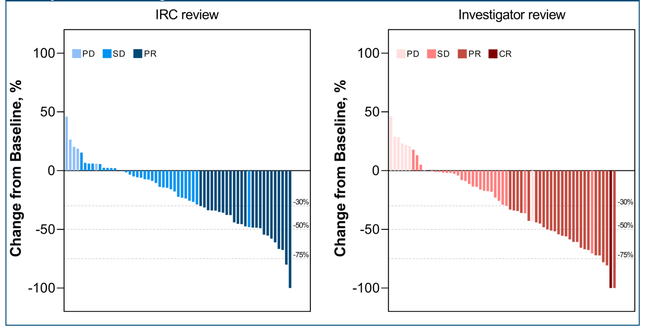
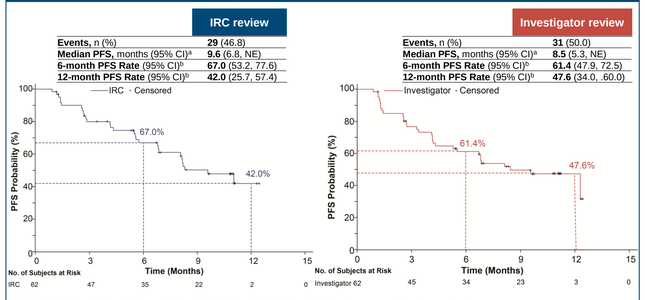


Figure 4. Kaplan-Meier plot of PFS per RECIST v1.1 by IRC and investigator review (EAS, n=62)



[a]Estimated by the Kaplan-Meier method with 95% CI calculated using the Brookmeyer and Crowley method.
[b]Estimated by the Kaplan-Meier method with 95% CIs calculated using the Greenwood formula.

Safety and tolerability

- No dose-limiting toxicity (DLT) was observed in the first 6 patients.
- Treatment-related adverse events (TRAEs) at grade ≥3 were 28.1%; treatment-related serious adverse events (SAEs) were 9.4% (**Table 3**).
- The most common (>10%) TRAEs included proteinuria, hypertension and hypothyroidism, etc. The majority were mild and moderate (**Table 4**).

Table 3. Summary of TRAEs and potential imAEs (SAS, n=64)

TRAEs, n (%)	**61 (95.3)**
Grade ≥3	18 (28.1)
Serious	6 (9.4)
Led to treatment discontinuation	2 (3.1)
Led to death	1 (1.6)
Led to treatment modification[a]	34 (53.1)
Potential imAEs, n (%)	**36 (56.3)**
Grade ≥3	8 (12.5)
Serious	3 (4.7)
Led to tislelizumab discontinuation	0 (0.0)
Led to death	0 (0.0)
Led to tislelizumab modification[b]	7 (10.9)
Treated with systemic corticosteroids	4 (6.3)

Potential imAEs are extracted from the Clinical Database based on the MedDRA look-up table from AEs reported up to 90 days after the last dose of tislelizumab.
[a]Treatment modification included an interrupted/ delayed or reduced dose.
[b]Tislelizumab modification included an interrupted/ delayed dose.

Table 4. Most common (>10%) TRAEs (SAS, n=64)

TRAEs	All grades*	Grade 3
Proteinuria	28 (43.8)	0 (0.0)
Hypertension	23 (35.9)	2 (3.1)
Hypothyroidism	20 (31.3)	0 (0.0)
Aspartate aminotransferase increased	15 (23.4)	0 (0.0)
Platelet count decreased	14 (21.9)	4 (6.3)
Palmar-plantar erythrodysaesthesia syndrome	13 (20.3)	4 (6.3)
Weight decreased	13 (20.3)	0 (0.0)
Blood creatine phosphokinase MB increased	10 (15.6)	0 (0.0)
Blood lactate dehydrogenase increased	10 (15.6)	0 (0.0)
Lipase increased	10 (15.6)	2 (3.1)
Amylase increased	9 (14.1)	0 (0.0)
Blood bilirubin increased	8 (12.5)	0 (0.0)
Alanine aminotransferase increased	7 (10.9)	0 (0.0)
Dysphonia	7 (10.9)	0 (0.0)
Haematuria	7 (10.9)	0 (0.0)
Rash	7 (10.9)	0 (0.0)
White blood cell count decreased	7 (10.9)	1 (1.6)

*There was no TRAEs at grade 4 or grade 5 with frequency over 10%

Abbreviations

TIS, tislelizumab; LEN, lenvatinib; Q3W, every 3 weeks; QD, once a day; IV, intravenous injection; PO, orally; DLT, dose limiting toxicity; RP2D, recommended phase 2 dose; HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; AFP, alpha-fetoprotein; IRC, independent review committee; ORR, objective response rate; BOR, best overall response; DoR, duration of response; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; SAS, safety analysis set; EAS, efficacy evaluable analysis set; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; mRECIST, modified Response Evaluation Criteria in Solid Tumors; iRECIST , immune Response Evaluation Criteria in Solid Tumors; "i" indicates immune responses assigned using iRECIST; iBOR=BOR; iCR=CR; iPR=PR; iSD=SD; iUPD=unconfirmed progression; iCPD=confirmed progression; NA, not assessable; N/A, not applicable; NE, not estimable.

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