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: The potential advantage of combining anti-PD-1 antibodies with tyrosine kinase inhibitors has been revealed by several trials in advanced HCC. TIS, an anti-PD- 1 monoclonal antibody, has shown anti-tumor activity in HCC. LEN is a multikinase inhibitor approved for the first-line treatment of uHCC. This study aims to evaluate the efficacy and safety of TIS plus LEN in pts with uHCC.

Methods: Systemic treatment-naïve pts with uHCC received TIS (200 mg, IV, Q3W) and LEN (body weight 2:60 kg: 12 mg; <60 kg: 8 mg, PO, QD). Tolerability evaluated by assessing dose-limiting toxicities (DLTs) in the first 6 pts (Part 1) was the premise of the remaining enrollment (Part 2). Primary endpoint was objective response rate (ORR) assessed by Independent Review Committee (IRC) per RECIST v1.1. Based on the Simon's two-stage design, >6 responders were needed in stage 1 (n¼30) to continue, and 2:18 responders were needed by the end of stage 2 (n¼60) to claim statistical superiority to a historical control of 18.8% (from LEN arm of phase III REFLECT study) (a and b errors of 0.05).

Results: A total of 64 pts were enrolled and received TIS plus LEN (Part 1, n¼6; Part 2, n¼58) with 73.4% in BCLC stage C. As of 7 July 2022 (median follow-up, 12.5 months), 21.9% pts were on treatment. No DLTs were observed in the first 6 pts. The study met the statistical superiority criteria. There were 24 responders assessed by IRC per RECIST v1.1 in the efficacy evaluable analysis set (n¼62). Confirmed ORR and DCR were 38.7% (95% CI, 26.6-51.9) and 90.3% (95% CI, 80.1-96.4), respectively (Table). Median PFS was 9.6 months (95% CI, 6.8-NE), and 12-month PFS rate was 42.0% (95% CI, 25.7-57.4). Any grade of TRAEs occurred in 61 (95.3%) pts; 18 (28.1%) pts experienced Grade 2:3 TRAEs. Treatment related SAEs were reported in 6 (9.4 %) pts.

Conclusions: TIS plus LEN showed promising antitumor activity with acceptable safety profile as first-line treatment for uHCC.

Table: Confirmed tumor response per RECIST v1.1 (efficacy evaluable analysis set*, n = 62)

	IRC	Investigator review
Objective Response Rate, % (95% CI)	38.7 (26.6, 51.9)	41.9 (29.5, 55.2)
Best Overall Response, n (%)		
Complete Response	0 (0.0)	1 (1.6)
Partial Response	24 (38.7)	25 (40.3)
Stable Disease	32 (51.6)	27 (43.5)
Progressive Disease	5 (8.1)	8 (12.9)
Not Assessable	1 (1.6)	1 (1.6)
Disease Control Rate, % (95% CI)	90.3 (80.1, 96.4)	85.5 (74.2, 93.1)

*Include patients with measurable disease at baseline per RECIST v1.1 who had 2:1 dose of TIS or LEN, and had 2:1 post-baseline tumor assessment (included 1 patient who died with confirmed clinical disease progression before the first radiological assessment).