Clinical outcomes associated with tislelizumab in patients with advanced hepatocellular carcinoma who have been previously treated with sorafenib or lenvatinib in RATIONALE-208

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Background

- Tislelizumab is an anti-programmed cell death protein 1 (PD-1) monoclonal antibody with high affinity and binding specificity for PD-1, engineered to minimize Fc gamma receptor binding on macrophages to limit antibody-dependent cellular phagocytosis, a mechanism of T-cell clearance and a potential mechanism of resistance to anti-PD-1 therapy[1–3]
- Tislelizumab demonstrated clinical activity and was generally well tolerated in patients with previously treated advanced hepatocellular carcinoma (HCC) in the open-label, multicenter, Phase 2 RATIONALE-208 study (NCT03419897)[4]
  - After a median follow-up of 12.4 months (data cut-off: February 2020):[4]
    - Objective response rate (ORR) was 13.3% (95% CI: 9.3, 18.1)
    - Median progression-free survival (PFS) was 2.7 months (95% CI: 1.4, 2.8)
    - Median overall survival (OS) was 13.2 months (95% CI: 10.8, 15.0)
- At the time of this study, sorafenib (SOR) and lenvatinib (LEN) were recommended first-line treatments for patients with advanced HCC and continue to have an important role in the first-line treatment of HCC despite the recent approval of new immuno-oncology-based combinations (atezolizumab and bevacizumab) in some regions[5–7]
- We report the clinical outcomes of patients with advanced HCC who were previously treated with SOR/LEN

Methods

- Study design has been previously described; scan QR code to read full study methods
- In this descriptive-only secondary analysis, the following endpoints were evaluated in patients who had been previously treated with SOR/LEN and has received one or more doses of tislelizumab
  - Primary: ORR by independent review committee (IRC) (ORR_{IRC}) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
  - Secondary: Disease control rate (patients with a complete response [CR], partial response [PR], or stable disease [SD]) by IRC (DCR_{IRC}), duration of response by IRC (DoR_{IRC}), PFS by IRC (PFS_{IRC}), OS, and safety/tolerability

Results

Patient disposition

- As of February 2020, 249 patients were enrolled and 235 patients had received prior treatment with SOR/LEN
- Median follow-up duration for patients previously treated with SOR/LEN was 12.5 months (range: 0.1–21.3) and 30 (12.8%) of 235 patients were still on-treatment at data cut-off
- Baseline demographic and disease characteristics of patients previously treated with SOR/LEN are summarized in **Table 1**

Table 1. Baseline demographics and disease characteristics

		Patients (N=235)
Age, years	Median (range)	62.0 (29–90)
Sex, n (%)	Male	206 (87.7)
Race, n (%)	Asian	112 (47.7)
	White	96 (40.9)
ECOG PS, n (%)	0	121 (51.5)
	1	114 (48.5)
Prior lines of anticancer therapy, n (%)	1	126 (53.6)
	≥ 2	109 (46.4)
BCLC staging at study entry, n (%)	B	24 (10.2)
	C	211 (89.8)
Child-Pugh score at study entry,* n (%)	A	234 (99.6)
Extrahepatic spread, n (%)	Present	187 (79.6)
Macrovascular invasion, n (%)	Present	42 (17.9)
HCC etiology, n (%)	Hepatitis B	114 (48.5)
	Hepatitis C	36 (15.3)
	History of alcohol abuse	76 (32.3)
	NASH	42 (17.9)

*One patient had Child-Pugh B at study entry, but this was not expected to affect the study results. BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; NASH, non-alcoholic steatohepatitis

Conclusions

- Tislelizumab was investigated beyond the first-line setting, as effective second- and third-line treatment options are limited for patients with advanced HCC and there is an unmet medical need
- This analysis indicated that **tislelizumab was clinically active and well tolerated in patients with advanced HCC** who have received prior systemic treatment with SOR/LEN
  - After a median follow-up duration of 12.5 months, ORR_{IRC} was 13.6% (95% CI: 9.5, 18.7) and median OS was 13.5 months (95% CI: 10.9, 15.8)
  - Tislelizumab was generally well tolerated and adverse events were generally of low severity
- The results of this descriptive-only secondary analysis support the potential role of tislelizumab as a treatment option beyond the first-line setting for patients with advanced HCC

Efficacy: Tumor response

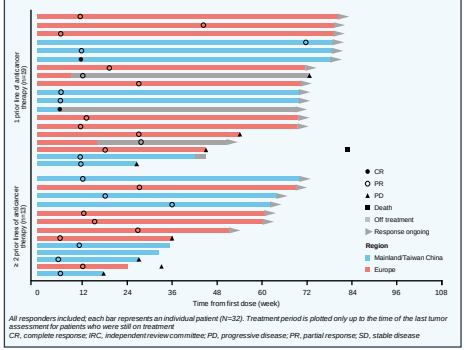
- Confirmed ORR_{IRC} in patients previously treated with SOR/LEN was 13.6% (95% CI: 9.5, 18.7), including two complete responses and 30 partial responses (**Table 2**)
- Disease control was achieved in 55.3% (95% CI: 48.7, 61.8) of patients and median DoR_{IRC} was not reached (**Table 2; Figure 1**)

Table 2. Summary of antitumor activity by IRC

	Total (N=235)
ORR (CR+PR), % (95% CI)	13.6 (9.5, 18.7)
Best overall response, n (%)	
CR	2 (0.9)
PR	30 (12.8)
SD*	98 (41.7)
PD	95 (40.4)
Not assessable†	10 (4.3)
DCR (CR+PR+SD), % (95% CI)	55.3 (48.7, 61.8)
Median DoR, months (95% CI)	NE (14.0, NE)

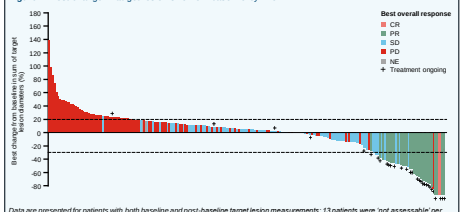
*Includes two patients assessed as non-CR/non-PD due to a lack of measurable disease per IRC; †No post-baseline assessment or an unevaluable post-baseline assessment. CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; IRC, independent review committee; NE, not evaluable; ORR, overall response rate; PR, partial response

Figure 1. Time to response and duration of response by IRC in patients who responded to tislelizumab



All responders included; each bar represents an individual patient (N=32). Treatment period is plotted only up to the time of the last tumor assessment for patients who were still on treatment
CR, complete response; IRC, independent review committee; PD, progressive disease; PR, partial response; SD, stable disease

Figure 2. Best change in target lesion size from baseline by IRC

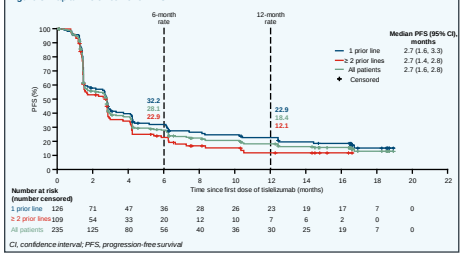


Data are presented for patients with both baseline and post-baseline target lesion measurements; 13 patients were 'not assessable' per IRC. Overall number of patients included: N=222
CR, complete response; IRC, independent review committee; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease

Efficacy: Survival estimates

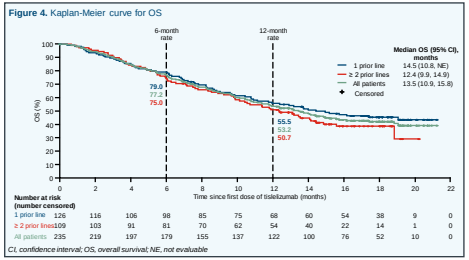
- Median PFS_{IRC} was 2.7 months (95% CI: 1.6, 2.8) in patients previously treated with SOR/LEN (**Figure 3**)
  - 6- and 12-month PFS_{IRC} rates were 28.1% (95% CI: 22.3, 34.2) and 18.4% (95% CI: 13.4, 24.0), respectively
- Median OS was 13.5 months (95% CI: 10.9, 15.8) in patients previously treated with SOR/LEN (**Figure 4**))
  - 6- and 12-month OS rates were 77.2% (95% CI: 71.2, 82.0) and 53.2% (95% CI: 46.6, 59.4), respectively

Figure 3. Kaplan-Meier curve for PFS



CI, confidence interval; PFS, progression-free survival

Figure 4. Kaplan-Meier curve for OS



CI, confidence interval; OS, overall survival; NE, not evaluable

Safety

- Tislelizumab was generally well tolerated in patients previously treated with SOR/LEN (**Table 3**)
- Immune-mediated treatment-emergent adverse events (TEAEs), based on sponsor assessment, occurred in 50 patients (21.3%) (**Table 4**)

Table 3. Summary of AEs

Patients, n (%)	All patients (N=235)
Any TEAE	223 (94.9)
Grade ≥ 3 TEAE	116 (49.4)
Serious TEAEs	87 (37.0)
TEAE leading to discontinuation	26 (11.1)
TEAE leading to dose delay	72 (30.6)
TEAE leading to death*	24 (10.2)
TEAEs reported in ≥ 15% of patients	
AST increased	70 (28.1)
ALT increased	52 (20.9)
Blood bilirubin increased	50 (20.1)
Decreased appetite	41 (16.5)
Asthenia	39 (15.7)

21 patients had disease progression reported as the primary cause of death. AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LEN, lenvatinib; SOR, sorafenib; TEAE, treatment-emergent AE

Table 4. Immune-mediated AEs

Patients, n (%)	All patients (N=235)
Any immune-mediated TEAE	50 (21.3)
Grade ≥ 3 TEAE	12 (5.1)
Immune-mediated TEAEs reported in ≥ 2% of patients (any grade)	
Hypothyroidism	16 (6.8)
Hyperthyroidism	6 (2.6)
Hepatic-related immune-mediated TEAEs reported in ≥ 1% of patients (any grade)	
AST increased	4 (1.7)
ALT increased	3 (1.3)
Hepatitis	3 (1.3)

Data are listed in order of decreasing frequency. AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent AE

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