Association of Tumor Response With Survival in Patients With Unresectable Hepatocellular Carcinoma Treated With First-line Tislelizumab Versus Sorafenib: Results From the RATIONALE-301 Study

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Conclusions

Objective tumor response was associated with higher overall survival (OS) and progression-free survival (PFS) landmark rates compared with nonresponse across treatment arms, but responders had a better survival benefit with tislelizumab compared with sorafenib.

For patients without objective response, OS rates were similar for both tislelizumab and sorafenib, with higher 6- and 12-month PFS rates for sorafenib compared with tislelizumab.

Background

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death worldwide[1]. The majority of patients present with advanced disease and, therefore, a poor prognosis.[2] Tislelizumab is a monoclonal antibody with high affinity and binding specificity for programmed cell death protein 1 (PD-1), engineered to minimize FcγR binding on macrophages.[3,4]

The phase 3 RATIONALE-301 study demonstrated noninferior OS with tislelizumab vs sorafenib as first-line monotherapy for unresectable HCC (median OS 15.9 vs 14.1 months, respectively; hazard ratio 0.85 [95% confidence interval (CI): 0.71, 1.02; *P*=0.0398]); OS superiority versus sorafenib was not met.[5]

It is not clear whether objective response is associated with increased survival following anti-PD-1 treatment. Here, we evaluated the association of tumor response with survival in patients from RATIONALE-301 (NCT03412773).

Methods

- The design of the randomized, open-label, phase 3 RATIONALE-301 study has been previously described[2]
- Systemic therapy-naïve adults with histologically confirmed HCC were randomized 1:1 to receive tislelizumab (200 mg intravenously every 3 weeks) or sorafenib (400 mg orally twice daily) until disease progression, intolerable toxicity, or withdrawal
- The primary endpoint was OS; secondary endpoints included PFS, objective response rate (ORR), and best overall response (BOR) by blinded independent review committee per RECIST v1.1.

Results

Baseline Characteristics

- Overall, 674 patients were randomized (tislelizumab, n=342; sorafenib, n=332)
- At the data cutoff (July 11, 2022), minimum study follow-up was 33 months in both treatment arms
- Baseline characteristics were generally similar across arms (**Table 1**)

Table 1. Baseline Characteristics (ITT Population)

	TIS (n=342)	SOR (n=332)
Mean (SD) age, years	60.2 (12.5)	59.3 (12.7)
Sex (male)	289 (84.5)	281 (84.6)
BCLC stage at study entry, B/C	70 (20.5)/272 (79.5)	80 (24.1)/252 (75.9)
EHS present	219 (64.0)	198 (59.6)
MVI present	51 (14.9)	49 (14.8)
Loco-regional therapy	265 (77.5)	250 (75.3)
AFP ≥400 ng/mL	135 (39.5)	116 (34.9)
Child-Pugh score, 5/6	263 (76.9)/77 (22.5)	248 (74.7)/84 (25.3)

Data are n (%) unless otherwise stated.
Abbreviations: AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; EHS, extrahepatic spread; ITT, intent-to-treat; MVI, macrovascular invasion; SD, standard deviation; SOR, sorafenib; TIS, tislelizumab.

Efficacy

- ORR with tislelizumab was 14.3% (95% CI: 10.8, 18.5) vs 5.4% (95% CI: 3.2, 8.4) with sorafenib
- Median duration of response was 36.1 months (95% CI: 16.8, not estimable) with tislelizumab vs 11.0 months (95% CI: 6.2, 14.7) with sorafenib
- Objective tumor response was associated with numerically higher OS rates (**Figure 1**) and longer median PFS in both the tislelizumab and sorafenib treatment arms (**Table 2**)
  - Median OS and median PFS were longer with tislelizumab vs sorafenib in patients who responded to treatment, but median PFS was longer with sorafenib than tislelizumab in those who did not respond
- For responders, 12-month PFS and 24-month OS and PFS rates were higher for tislelizumab than sorafenib (**Table 3**)
- In nonresponders, OS rates were similar across treatment arms while 6- and 12-month PFS rates were numerically higher with sorafenib vs tislelizumab

Table 2. Survival Outcomes Across BOR Categories (ITT Population)

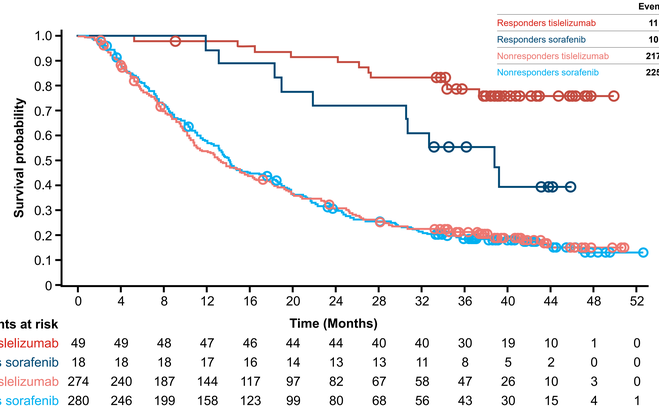
	Median OS, months (95% CI)		Median PFS, months (95% CI)	
	TIS (n=342)	SOR (n=332)	TIS (n=342)	SOR (n=332)
Responders	(n=49) NE (NE, NE)	(n=18) 38.8 (21.9, NE)	(n=49) 38.2 (21.7, NE)	(n=18) 15.9 (10.4, 32.4)
	HR 0.34 (95% CI: 0.14, 0.80)		**HR 0.38 (95% CI: 0.18, 0.79)**	
Nonresponders[a]	(n=274) 13.3 (11.0, 15.9)	(n=280) 14.1 (13.1, 17.4)	(n=274) 2.1 (2.1, 2.1)	(n=280) 2.5 (2.1, 4.1)
	HR 1.00 (95% CI: 0.83, 1.21)		**HR 1.43 (95% CI: 1.18, 1.73)**	
CR	(n=10) NE (NE, NE)	(n=1) NE (NE, NE)	(n=10) NE (28.2, NE)	(n=1) NE (NE, NE)
	HR NE (95% CI: NE, NE)		**HR NE (95% CI: NE, NE)**	
PR	(n=39) NE (NE, NE)	(n=17) 38.8 (19.0, NE)	(n=39) 29.5 (13.1, 45.0)	(n=17) 13.3 (10.4, 19.0)
	HR 0.41 (95% CI: 0.17, 0.96)		**HR 0.50 (95% CI: 0.24, 1.04)**	
SD	(n=94) 24.0 (19.4, 29.3)	(n=139) 19.1 (15.2, 21.7)	(n=94) 4.9 (4.2, 6.2)	(n=139) 6.5 (6.2, 8.2)
	HR 0.73 (95% CI: 0.54, 1.00)		**HR 1.23 (95% CI: 0.88, 1.71)**	
PD	(n=169) 9.9 (8.6, 10.9)	(n=121) 10.4 (7.6, 13.4)	(n=169) 2.0 (2.0, 2.1)	(n=121) 2.1 (2.0, 2.1)
	HR 1.05 (95% CI: 0.81, 1.35)		**HR 1.13 (95% CI: 0.89, 1.42)**	

Presented HRs are unstratified HRs for TIS vs SOR. Patients were determined as not assessable (tislelizumab, n=19; sorafenib, n=34) if a postbaseline scan was not available, and were not included in the analysis. [a]Includes patients determined as non-CR/non-PD (tislelizumab, n=8; sorafenib, n=10) and not evaluable (tislelizumab, n=3; sorafenib, n=10).
Abbreviations: BOR, best overall response; CI, confidence interval; CR, complete response; HR, hazard ratio; ITT, intent-to-treat; NE, not estimable; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; SOR, sorafenib; TIS, tislelizumab.

Limitations

- The results of this exploratory analysis of the RATIONALE-301 study, including treatment effects on PFS and OS, should be interpreted with caution as the subgroups were defined by a postbaseline variable (i.e., BOR) and the sample size was small

Figure 1. OS Rates for Responders and Nonresponders to Treatment (ITT population)



Abbreviations: CI, confidence interval; ITT, intent-to-treat; NE, not estimable; OS, overall survival.

Table 3. 6-, 12-, and 24-Month OS and PFS Rates (ITT Population)

	OS, % (95% CI)						PFS, % (95% CI)					
	6 months		12 months		24 months		6 months		12 months		24 months	
	TIS (n=342)	SOR (n=332)	TIS (n=342)	SOR (n=332)	TIS (n=342)	SOR (n=332)	TIS (n=342)	SOR (n=332)	TIS (n=342)	SOR (n=332)	TIS (n=342)	SOR (n=332)
Responders	98.0 (86.4, 99.7)	100 (100, 100)	98.0 (86.4, 99.7)	94.4 (66.6, 99.2)	91.7 (79.4, 96.8)	72.2 (45.6, 87.4)	97.9 (86.1, 99.7)	100 (100, 100)	79.7 (64.5, 88.9)	70.1 (42.3, 86.4)	64.7 (48.3, 77.1)	25.8 (6.9, 50.4)
Nonresponders	78.2 (72.8, 82.7)	81.5 (76.4, 85.6)	53.9 (47.8, 59.7)	58.1 (52.0, 63.7)	31.3 (25.9, 40.0)	30.6 (25.3, 36.2)	16.5 (12.1, 21.5)	32.8 (26.7, 39.1)	7.7 (4.6, 11.7)	14.2 (9.2, 20.3)	3.9 (1.7, 7.6)	4.4 (1.6, 9.5)
CR	100 (100, 100)	100 (100, 100)	100 (100, 100)	100 (100, 100)	100 (100, 100)	100 (100, 100)	100 (100, 100)	100 (100, 100)	100 (100, 100)	100 (100, 100)	100 (100, 100)	NE (NE, NE)
PR	97.4 (83.2, 99.6)	100 (100, 100)	97.4 (83.2, 99.6)	94.1 (65.0, 99.2)	89.5 (74.5, 95.9)	70.6 (43.2, 86.6)	97.4 (82.8, 99.6)	100 (100, 100)	73.7 (55.4, 85.4)	68.2 (39.5, 85.4)	54.4 (36.0, 69.6)	24.5 (6.4, 48.7)
SD	92.6 (85.0, 96.4)	92.0 (86.1, 95.5)	78.7 (69.0, 85.7)	68.1 (59.6, 75.2)	51.0 (40.5, 60.6)	39.5 (31.3, 47.6)	44.7 (33.5, 55.4)	64.3 (53.9, 72.9)	18.4 (10.3, 28.2)	25.9 (16.3, 36.7)	7.2 (2.3, 16.2)	6.7 (1.9, 15.6)
PD	70.5 (62.9, 76.8)	69.2 (60.0, 76.8)	39.0 (31.5, 46.4)	45.9 (36.6, 54.6)	19.6 (13.9, 26.1)	19.0 (12.5, 26.7)	0.0 (NE, NE)	0.0 (NE, NE)	0.0 (NE, NE)	0.0 (NE, NE)	0.0 (NE, NE)	0.0 (NE, NE)

Abbreviations: CI, confidence interval; CR, complete response; ITT, intent-to-treat; NE, not estimable; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; SOR, sorafenib; TIS, tislelizumab.

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