Impact of Baseline Liver Function on Overall Survival and Safety in Patients With Unresectable Hepatocellular Carcinoma Treated With First-line Tislelizumab: Results From the RATIONALE-301 Study

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Conclusions

Survival was similar between arms regardless of Child-Pugh score (CPS) or albumin-bilirubin (ALBI) grade. Additionally, tislelizumab showed a favorable safety profile compared with sorafenib, regardless of CPS or ALBI grade, supporting the primary analysis.

Patients with CPS 6 and ALBI grade 2 had poorer median overall survival (OS) than those with CPS 5 and ALBI grade 1, regardless of treatment, suggesting that patients with better liver function have more favorable outcomes.

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, which was engineered to minimize FcγR binding on macrophages.[3,4]

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

As liver function is a known predictor of survival in patients with HCC,[6] we evaluated baseline liver function and its impact on OS and safety in patients enrolled in 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
- In this exploratory analysis, OS and safety were assessed according to CPS (5 vs 6) and ALBI grade (1 vs 2)

Results

Baseline Characteristics

- At data cutoff (July 11, 2022), minimum study follow-up was 33 months
- Patient demographics were generally well balanced between treatment arms; however, there were some imbalances in baseline disease characteristics, with a slightly higher proportion of patients in the tislelizumab arm having advanced disease (**Table 1**)
- Regarding liver function, slightly more patients in the tislelizumab versus the sorafenib arm had CPS of 5 (76.9% vs 74.7%, respectively) and ALBI grade 1 (74.9% vs 68.1%, respectively)

Table 1. Baseline Characteristics (ITT Population)

	TIS (n=342)	SOR (n=332)	Total (N=674)
Mean (SD) age, years	60.2 (12.5)	59.3 (12.7)	59.8 (12.6)
Sex (male)	289 (84.5)	281 (84.6)	570 (84.6)
ECOG PS 1	159 (46.5)	151 (45.5)	310 (46.0)
BCLC stage			
Stage B	70 (20.5)	80 (24.1)	150 (22.3)
Stage C	272 (79.5)	252 (75.9)	524 (77.7)
HCC etiology			
HBV	203 (59.4)	206 (62.0)	409 (60.7)
HCV	46 (13.5)	39 (11.7)	85 (12.6)
Uninfected	82 (24.0)	80 (24.1)	162 (24.0)
EHS present	219 (64.0)	198 (59.6)	417 (61.9)
MVI present	51 (14.9)	49 (14.8)	100 (14.8)
AFP			
<400 ng/mL	206 (60.2)	213 (64.2)	419 (62.2)
≥400 ng/mL	135 (39.5)	116 (34.9)	251 (37.2)
CPS			
5	263 (76.9)	248 (74.7)	511 (75.8)
6	77 (22.5)	84 (25.3)	161 (23.9)
>6/missing	2 (0.6)	0 (0.0)	2 (0.2)
ALBI grade			
1	256 (74.9)	226 (68.1)	482 (71.5)
2	81 (23.7)	98 (29.5)	179 (26.6)
3/missing[a]	5 (1.5)	8 (2.4)	13 (1.9)
Loco-regional therapy	265 (77.5)	250 (75.3)	515 (76.4)
Distant metastasis	205 (59.9)	189 (56.9)	394 (58.5)

[a]Tislelizumab arm includes one patient of ALBI grade 3. No patients treated with sorafenib had ALBI grade 3.

Data are n (%) unless otherwise stated. **Abbreviations**: AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; CPS, Child-Pugh score; ECOG PS, Eastern Cooperative Oncology Group performance status; EHS, extrahepatic spread; HBV/HCV, hepatitis B/C virus; HCC, hepatocellular carcinoma; ITT, intent-to-treat; MVI, macrovascular invasion; SD, standard deviation; SOR, sorafenib; TIS, tislelizumab.

Efficacy by CPS and ALBI Grade

- Median OS and 6- and 12-month OS rates were generally similar in patients treated with tislelizumab and sorafenib, and numerically greater in patients with CPS 5 vs 6, and ALBI grade 1 vs 2, regardless of treatment (**Table 2, Figure 1**)

Table 2. Efficacy by CPS and ALBI Grade (ITT Population)

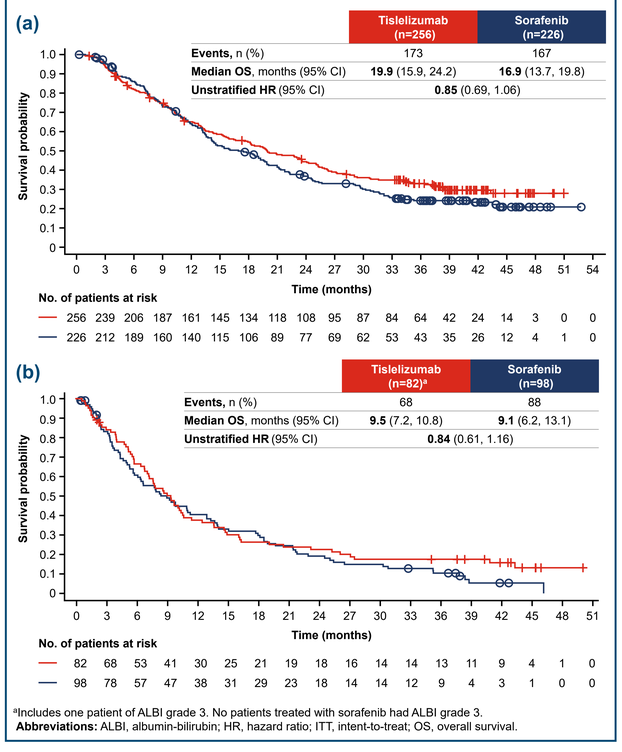
	CPS 5		CPS 6		ALBI Grade 1		ALBI Grade 2	
	TIS (n=263)	SOR (n=248)	TIS (n=77)	SOR (n=84)	TIS (n=256)	SOR (n=226)	TIS (n=81)	SOR (n=98)
Median OS, mo (95% CI)	19.5 (15.4, 23.5)	18.4 (14.5, 20.9)	8.7 (6.2, 12.3)	8.3 (5.6, 10.0)	19.9 (15.9, 24.2)	16.9 (13.7, 19.8)	9.5 (7.3, 10.8)	9.1 (6.2, 13.1)
Unstratified HR (95% CI)	0.88 (0.71, 1.08)		0.73 (0.52, 1.03)		0.85 (0.69, 1.06)		0.83 (0.60, 1.14)	
6-month OS, % (95% CI)	82.2 (76.9, 86.3)	85.6 (80.5, 89.5)	64.1 (52.2, 73.8)	57.3 (45.7, 67.3)	81.9 (76.6, 86.1)	86.0 (80.7, 89.9)	67.3 (55.8, 76.4)	60.7 (50.1, 69.8)
12-month OS, % (95% CI)	63.7 (57.4, 69.2)	66.5 (60.1, 72.2)	40.1 (29.0, 50.9)	29.3 (19.7, 39.5)	65.1 (58.8, 70.6)	64.1 (57.4, 70.1)	38.1 (27.5, 48.6)	40.5 (30.5, 50.2)

Abbreviations: ALBI, albumin-bilirubin; CI, confidence interval; CPS, Child-Pugh score; HR, hazard ratio; ITT, intent-to-treat; mo, months; OS, overall survival; SOR, sorafenib; TIS, tislelizumab.

Safety by CPS and ALBI Grade

- There were no notable differences in incidence of any grade treatment-emergent adverse events (TEAEs) or treatment-related adverse events (TRAEs) when comparing CPS 5 vs 6 or ALBI grade 1 vs 2. Patients treated with tislelizumab with ALBI grade 2 vs 1 experienced higher incidences of ≥grade 3 TEAEs (61% vs 44%) and TRAEs (36% vs 18%)
- Rates of ≥grade 3 TEAEs along with any grade and ≥grade 3 TRAEs were lower for patients treated with tislelizumab vs sorafenib across CPS and ALBI grade

Figure 1. OS for Patients With ALBI Grade (a) 1 and (b) ≥2 (ITT)



[a]Includes one patient of ALBI grade 3. No patients treated with sorafenib had ALBI grade 3.
Abbreviations: ALBI, albumin-bilirubin; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival.

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