Tislelizumab Versus Sorafenib in First-line Treatment of Unresectable Hepatocellular Carcinoma: The RATIONALE-301 European/North American Subgroup

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Conclusions

In the European/North American (EU/NA) subgroup, tislelizumab demonstrated numerically longer median overall survival (OS) and more durable antitumor response compared with sorafenib, as first-line treatment in patients with unresectable hepatocellular carcinoma (HCC). Tislelizumab had a favorable safety profile compared with sorafenib in the EU/NA subgroup. The results obtained in the EU/NA subgroup were consistent with published results from the overall study population.

Background

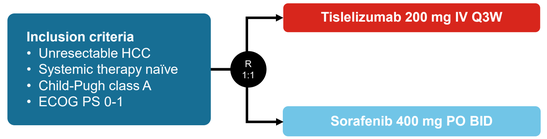
HCC is one of the most commonly diagnosed cancers globally.[1] Most cases occur in Asia, particularly in China, with 410,000 reported in 2020; however, the number of patients affected in other regions is also high, with over 87,000 HCC cases in Europe and 46,000 in North America in 2020.[2] Tislelizumab, a monoclonal antibody with high affinity and binding specificity for programmed cell death protein 1, was specifically engineered to minimize Fcγ receptor binding on macrophages.[3,4]

Tislelizumab demonstrated clinical activity and was generally well tolerated in patients with previously treated advanced HCC (NCT03419897).[5] In the RATIONALE-301 (NCT03412773) study in patients with unresectable HCC, tislelizumab showed noninferior OS vs sorafenib and demonstrated a favorable safety profile.[6] Here, we report data from the EU/NA subgroup in the RATIONALE-301 study.

Methods

- The study design has been previously described (**Figure 1**)[6,7]
- 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 a day until disease progression, intolerable toxicity, or withdrawal (**Figure 1**)
- The primary endpoint was OS; secondary endpoints included objective response rate (ORR), progression-free survival (PFS), duration of response (DoR) by blinded independent review committee per Response Evaluation Criteria in Solid Tumors version 1.1, and safety

Figure 1. RATIONALE-301 Study Design



Abbreviations: BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; IV, intravenously; PO, orally; Q3W, every 3 weeks; R, randomized.

Results

Baseline Characteristics

- Of 674 randomized patients, 172 (25.5%) were enrolled in the EU/NA subgroup (tislelizumab, n=89; sorafenib, n=83)
- Distribution of baseline characteristics was generally similar between the EU/NA subgroup and the overall population. Of note, the EU/NA subgroup had a higher number of patients with advanced-stage disease (Barcelona Clinic Liver Cancer [BCLC] Stage C) in the tislelizumab arm compared with the sorafenib arm, similar to the overall population (**Table 1**). In general, more patients in the EU/NA subgroup had less advanced disease (BCLC B) compared with the overall population (**Table 1**)
- At data cutoff (July 11, 2022), median OS follow-up in the EU/NA subgroup was 37.9 months in the tislelizumab arm and 38.5 months in the sorafenib arm

Efficacy

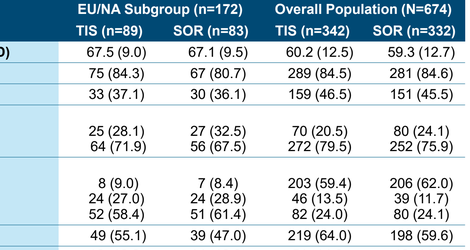
- In the EU/NA subgroup, tislelizumab demonstrated numerically longer median OS, which was consistent across most studied subgroups (**Figures 2 and 3**), similar median PFS (**Figure 4**), longer median DoR, and a higher ORR than sorafenib (**Table 2**). These results were similar to the overall population, with the exception of median PFS (**Table 2**)

Table 1. Baseline Characteristics

	EU/NA Subgroup (n=172)		Overall Population (N=674)	
	TIS (n=89)	SOR (n=83)	TIS (n=342)	SOR (n=332)
Age, years, mean (SD)	67.5 (9.0)	67.1 (9.5)	60.2 (12.5)	59.3 (12.7)
Male	75 (84.3)	67 (80.7)	289 (84.5)	281 (84.6)
ECOG PS 1	33 (37.1)	30 (36.1)	159 (46.5)	151 (45.5)
BCLC staging				
Stage B	25 (28.1)	27 (32.5)	70 (20.5)	80 (24.1)
Stage C	64 (71.9)	56 (67.5)	272 (79.5)	252 (75.9)
Hepatitis etiology				
HBV	8 (9.0)	7 (8.4)	203 (59.4)	206 (62.0)
HCV	24 (27.0)	24 (28.9)	46 (13.5)	39 (11.7)
Uninfected	52 (58.4)	51 (61.4)	82 (24.0)	80 (24.1)
EHS present	49 (55.1)	39 (47.0)	219 (64.0)	198 (59.6)
MVI present	16 (18.0)	14 (16.9)	51 (14.9)	49 (14.8)
PVTT present	10 (11.2)	12 (14.5)	34 (9.9)	33 (9.9)
ALBI score				
1	70 (78.7)	49 (59.0)	256 (74.9)	226 (68.1)
≥2	18 (20.2)	33 (39.8)	82 (24.0)	98 (29.5)
Missing	1 (1.1)	1 (1.2)	4 (1.2)	8 (2.4)
Posttreatment anticancer therapy				
Systemic	55 (61.8)	53 (63.9)	185 (54.1)	199 (59.9)
Immunotherapy	7 (7.9)	16 (19.3)	33 (9.6)	87 (26.2)

Data cutoff: July 11, 2022. Data are n (%) unless otherwise specified. **Abbreviations**: ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; EHS, extrahepatic spread; EU/NA, European/North American; HBV/HCV, hepatitis B/C virus; MVI, macrovascular invasion; PVTT, portal vein tumor thrombus; SD, standard deviation; SOR, sorafenib; TIS, tislelizumab.

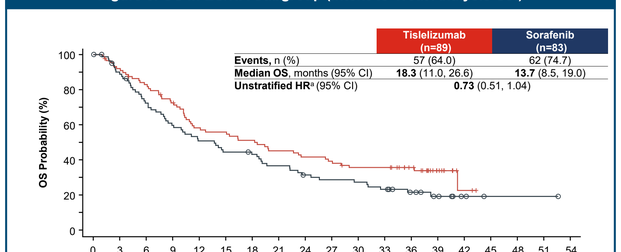
Figure 2. OS by Baseline Characteristics in the EU/NA Subgroup (Intent-to-Treat Analysis Set)



Subgroup	No. of Events/ No. of Patients	Hazard Ratio for Death (95% CI)	OS (months) Median (95% CI) TIS	OS (months) Median (95% CI) SOR
ECOG PS				
0	68/109	0.66 (0.41, 1.06)	26.3 (16.4, NE)	18.8 (1.0, 25.6)
1	51/63	0.82 (0.47, 1.43)	9.8 (6.5, 11.4)	8.1 (4.8, 13.7)
BCLC stage				
Stage B	32/52	0.55 (0.27, 1.13)	26.3 (16.4, NE)	22.2 (8.5, 25.6)
Stage C	87/120	0.79 (0.52, 1.20)	12.1 (9.8, 23.5)	11.8 (5.9, 18.5)
Hepatitis etiology				
HBV	14/21	0.70 (0.24, 2.05)	16.4 (10.2, NE)	14.2 (2.1, NE)
HCV	32/48	0.62 (0.31, 1.27)	27.1 (9.8, NE)	14.7 (8.2, 23.7)
Uninfected	73/103	0.80 (0.50, 1.26)	18.6 (10.2, 26.3)	10.1 (6.2, 22.2)
Baseline AFP				
<400 ng/ml	81/120	0.68 (0.44, 1.05)	23.2 (15.4, 41.2)	14.7 (1.0, 23.2)
≥400 ng/ml	38/51	0.72 (0.38, 1.37)	9.8 (6.1, 18.3)	6.5 (4.0, 13.7)

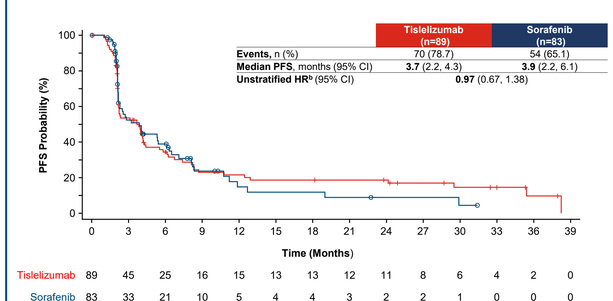
Data cutoff: July 11, 2022. **Abbreviations:** AFP, alpha fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; EU/NA, European/North American; HBV/HCV, hepatitis B/C virus; NE, not estimable; OS, overall survival; SOR, sorafenib; TIS, tislelizumab.

Figure 3. OS in EU/NA Subgroup (Intent-to-Treat Analysis Set)



Data cutoff: July 11, 2022. [a]HR was based on an unstratified Cox regression model including only treatment as a covariate. **Abbreviations**: CI, confidence interval; EU/NA, European/North American; HR, hazard ratio; OS, overall survival.

Figure 4. PFS[a] in EU/NA Subgroup (Intent-to-Treat Analysis Set)



Data cutoff: July 11, 2022. [a]PFS assessed by investigator per Response Evaluation Criteria in Solid Tumors version 1.1. [b]HR was based on an unstratified Cox regression model including only treatment as a covariate. **Abbreviations:** CI, confidence interval; EU/NA, European/North American; HR, hazard ratio; PFS, progression-free survival.

Table 2. Summary of Antitumor Activity (Intent-to-Treat Analysis Set)

	EU/NA Subgroup		Overall Population[6]	
	TIS (n=89)	SOR (n=83)	TIS (n=342)	SOR (n=332)
ORR, n	17	2	49	18
% (95% CI)[a]	19.1 (11.5, 28.8)	2.4 (0.3, 8.4)	14.3 (10.8, 18.5)	5.4 (3.2, 8.4)
ORR difference, % (95% CI)[b]	16.6 (7.7, 25.6)		8.3 (3.9, 12.7)	
BOR, n (%)				
CR	3 (3.4)	0 (0.0)	10 (2.9)	1 (0.3)
PR	14 (15.7)	2 (2.4)	39 (11.4)	17 (5.1)
SD	31 (34.8)	42 (50.6)	94 (27.5)	137 (41.3)
Non-CR/Non-PD	0 (0.0)	3 (3.6)	7 (2.0)	10 (3.0)
PD	37 (41.6)	25 (30.1)	166 (48.5)	117 (35.2)
Nonevaluable[c]	4 (4.5)	11 (13.3)	26 (7.6)	50 (15.1)
mDoR, mo (95% CI)	36.1 (10.1, NE)	9.1 (5.5, NE)	36.1 (16.8, NE)	11.0 (6.2, 14.7)
mOS, mo (95% CI)	18.3 (11.0, 26.6)	13.7 (8.5, 19.0)	15.9 (13.2, 19.7)	14.1 (12.6, 17.4)
mPFS, mo (95% CI)	3.7 (2.2, 4.3)	3.9 (2.2, 6.1)	2.2 (2.1, 3.5)	3.6 (2.2, 4.1)

Data cutoff: July 11, 2022. [a]95% CI was calculated using Clopper-Pearson method. [b]Captures patients who had ≥1 postbaseline tumor assessment, none of which were evaluable for response determination. [c]Patients with no postbaseline tumor assessment or a nonevaluable tumor assessment. **Abbreviations**: CI, confidence interval; CR, complete response; DoR, duration of response; EU/NA, European/North American; m, median; mo, months; NE, not estimable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; SOR, sorafenib; TIS, tislelizumab.

Safety

- A summary of the safety findings is shown in **Table 3**
- Incidence of adverse events were generally lower in the tislelizumab versus sorafenib arm for the EU/NA subgroup and the overall population
- For the EU/NA subgroup, the most common treatment-related adverse events occurring in ≥10% of patients in the tislelizumab versus sorafenib arms were asthenia (15.9% vs 17.1%) and fatigue (13.6% vs 20.7%); and in the overall population were aspartate aminotransferase increased (23.1% vs 28.7%) and alanine aminotransferase increased (16.6% vs 25.0%)

Table 3. Safety Summary (Safety Analysis Set)

n (%)	EU/NA Subgroup		Overall Population[6]	
	TIS (n=88)	SOR (n=82)	TIS (n=338)	SOR (n=324)
Patients with ≥1 TEAE	87 (98.9)	82 (100)	325 (96.2)	324 (100.0)
TRAE	71 (80.7)	76 (92.7)	259 (76.6)	311 (96.0)
Serious TEAE	32 (36.4)	30 (36.6)	101 (29.9)	91 (28.1)
TRAE	11 (12.5)	8 (9.8)	40 (11.8)	33 (10.2)
TEAE leading to death	4 (4.5)	9 (11.0)	15 (4.4)	17 (5.2)
TRAE	1 (1.1)	1 (1.2)	3 (0.9)	2 (0.6)
TEAE leading to any treatment discontinuation	14 (15.9)	24 (29.3)	37 (10.9)	60 (18.5)
TRAE	8 (9.1)	12 (14.6)	21 (6.2)	33 (10.2)
TEAE leading to study drug modification	34 (38.6)	60 (73.2)	105 (31.1)	210 (64.8)
TRAE	17 (19.3)	48 (58.5)	68 (20.1)	187 (57.7)
Patients with ≥1 immune-mediated TEAE	20 (22.7)	1 (1.2)	62 (18.3)	10 (3.1)

Data cutoff: July 11, 2022. **Abbreviations:** EU/NA, European/North American; SOR, sorafenib; TEAE, treatment-emergent adverse event; TIS, tislelizumab; TRAE, treatment-related adverse event.

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Disclosures

Disclosure information is available online with the abstract details.

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