Randomized, Phase 3 Study of Tislelizumab Versus Sorafenib as First-Line Treatment for Unresectable Hepatocellular Carcinoma (HCC): RATIONALE-301 Age ≥65 Years Subgroup

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Conclusions

In the subgroup of patients aged ≥65 years in the RATIONALE-301 trial, tislelizumab demonstrated numerically longer median overall survival (OS) and a higher objective response rate (ORR) vs sorafenib.

The longer median OS observed with tislelizumab in patients aged ≥65 years vs the overall population could be attributed to regional imbalances and more favorable baseline characteristics observed in this subgroup.

Tislelizumab showed a favorable safety profile vs sorafenib in the ≥65 years subgroup, consistent with the overall population.

Background

HCC is one of the most commonly diagnosed cancers globally, and the proportion of patients affected in the ≥65 years age group is increasing each year.[1,2] Tislelizumab, a monoclonal antibody with high affinity and binding specificity for programmed cell death protein 1, was specifically engineered to minimize Fc-γ receptor binding on macrophages.[3,4]

The phase 3, open-label RATIONALE-301 trial (NCT03412773) met its primary endpoint. Tislelizumab showed noninferior OS vs sorafenib (15.9 months vs 14.1 months [hazard ratio (HR)=0.85, 95% confidence interval (CI): 0.71, 1.02]) and a favorable safety profile in the first-line treatment of patients with unresectable HCC.[5] Here, we present post-hoc results from the subgroup of patients aged ≥65 years in RATIONALE-301.

Methods

- Eligible patients were aged ≥18 years with systemic therapy-naïve, histologically confirmed HCC (Barcelona Clinic Liver Cancer [BCLC] Stage C or Stage B that was not amenable to/progressed after loco-regional therapy, Child-Pugh A), ≥1 measurable lesion (per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1) and an Eastern Cooperative Oncology Group performance status (ECOG PS) ≤1[5]
- Patients were randomized (1:1) to open-label:
  - **Arm A**: Tislelizumab 200 mg intravenously every 3 weeks; or
  - **Arm B**: Sorafenib 400 mg orally twice daily[5]
- Patients received treatment until disease progression, intolerable toxicity, or withdrawal[5]
- **Primary endpoint:** OS in the intent-to-treat (ITT) analysis set[5]
- **Secondary endpoints included:** ORR and progression-free survival (PFS) assessed by blinded independent review committee per Response Evaluation Criteria In Solid Tumors v1.1, and safety[5]
- Scan the QR code for full methodology from the previously presented final analysis

Results

Patient Disposition and Baseline Characteristics

- At data cutoff (July 11, 2022), median survival follow-up in the ≥65 years subgroup was 38.9 months in the tislelizumab arm vs 39.9 months in the sorafenib arm
- In total, 255 (37.8%) of the 674 randomized patients were in the ≥65 years subgroup (tislelizumab: n=134, sorafenib: n=121), with median age of 71.0 years (range: 65-86)
- Baseline demographics and disease characteristics in patients aged ≥65 years are shown in **Table 1**
- Compared with the overall population, the majority of patients in the ≥65 years subgroup were enrolled in Europe/USA and Japan (36.9% vs 66.3%), had less advanced disease (BCLC Stage B: 22.3% vs 33.3%; Stage C: 77.7% vs 66.7%; extrahepatic spread: 61.9% vs 51.4%; distant metastases: 58.5% vs 49.0%), more satisfactory performance status (ECOG PS 0: 54.0% vs 61.2%), and fewer viral infections (uninfected: 24.0% vs 41.6%), respectively

Table 1. Baseline Characteristics

	≥65 Years Subgroup			Overall Population[5]
	Tislelizumab (n=134)	Sorafenib (n=121)	Total (N=255)	Total (N=674)
Median age, years (range)	71.0 (65.0-86.0)	71.0 (65.0-86.0)	71.0 (65.0-86.0)	61.0 (23.0-86.0)
Male sex, n (%)	107 (79.9)	103 (85.1)	210 (82.4)	570 (84.6)
Geographic region, n (%)				
Asia (excluding Japan)	46 (34.3)	40 (33.1)	86 (33.7)	425 (63.1)
Japan	33 (24.6)	28 (23.1)	61 (23.9)	77 (11.4)
EU/US	55 (41.0)	53 (43.8)	108 (42.4)	172 (25.5)
Child-Pugh class A/B, n (%)	133 (99.3)/1 (0.7)	121 (100.0)/0 (0.0)	254 (99.6)/1 (0.4)	672 (99.7)/1 (0.1)[a]
BCLC Stage B/C, n (%)	43 (32.1)/91 (67.9)	42 (34.7)/79 (65.3)	85 (33.3)/170 (66.7)	150 (22.3)/524 (77.7)
ECOG PS 0/1, n (%)	83 (61.9)/51 (38.1)	73 (60.3)/48 (39.7)	156 (61.2)/99 (38.8)	364 (54.0)/310 (46.0)
EHS present, n (%)	73 (54.5)	58 (47.9)	131 (51.4)	417 (61.9)
MVI present, n (%)	19 (14.2)	18 (14.9)	37 (14.5)	100 (14.8)
Hepatitis etiology, n (%)				
HBV	46 (34.3)	41 (33.9)	87 (34.1)	409 (60.7)
HCV	29 (21.6)	23 (19.0)	52 (20.4)	85 (12.6)
Uninfected	53 (39.6)	53 (43.8)	106 (41.6)	162 (24.0)
Distant metastasis, n (%)	70 (52.2)	55 (45.5)	125 (49.0)	394 (58.5)
Loco-regional therapy, n (%)	95 (70.9)	86 (71.1)	181 (71.0)	515 (76.4)

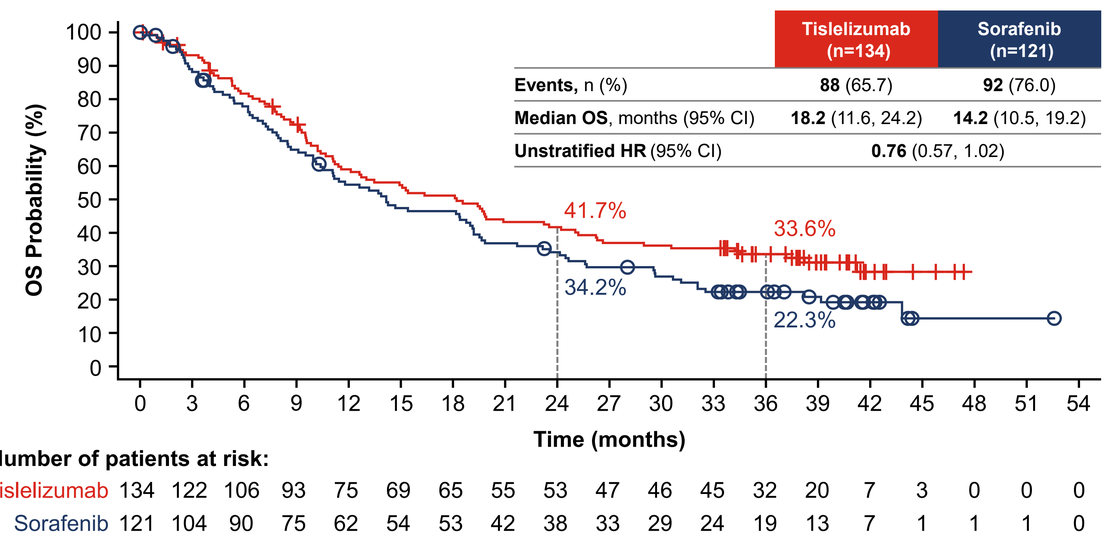
[a]Data for one patient were missing. **Abbreviations:** BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; EHS, extrahepatic spread; EU, Europe; HBV/HCV, hepatitis B/C virus; MVI, macrovascular invasion; US, United States.

Efficacy

OS (≥65 Years Subgroup):

- Patients in the ≥65 years subgroup had a numerically longer median OS (18.2 months [95% CI: 11.6, 24.2] vs 14.2 months [95% CI: 10.5, 19.2]) in the tislelizumab vs sorafenib arm, respectively (**Figure 1**)
- Median OS in the tislelizumab arm was longer in the ≥65 years subgroup than in the overall population (18.2 months [95% CI: 11.6, 24.2] vs 15.9 months [95% CI: 13.2, 19.7], respectively), but similar in the sorafenib arm (14.2 months and 14.1 months, respectively)[5]

Figure 1. Primary Endpoint: OS (ITT Analysis Set)



Data cutoff: 11 July, 2022. **Abbreviations:** CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival.

ORR and PFS (≥65 Years Subgroup):

- Patients in the ≥65 years subgroup had a higher confirmed ORR (18.7% vs 4.1%; odds ratio 5.4 [95% CI: 2.0, 14.7]) and shorter median PFS (3.1 months [95% CI: 2.1, 4.2] vs 3.9 months [95% CI: 2.3, 5.4]) in the tislelizumab vs sorafenib arm, respectively (**Table 2**)

Table 2. Efficacy Endpoints (ITT Analysis Set)

	≥65 Years Subgroup		Overall Population[5]	
Outcomes	Tislelizumab (n=134)	Sorafenib (n=121)	Tislelizumab (n=342)	Sorafenib (n=332)
Median PFS,[a] mo (95% CI)	3.1 (2.1, 4.2)	3.9 (2.3, 5.4)	2.1 (2.1, 3.5)	3.4 (2.2, 4.1)
ORR,[a,b] n (%) [95% CI][c]	25 (18.7) [12.5, 26.3]	5 (4.1) [1.4, 9.4]	49 (14.3) [10.8, 18.5]	18 (5.4) [3.2, 8.4]
Best overall response,[a,b,d] n (%)				
Complete response	6 (4.5)	0 (0.0)	10 (2.9)	1 (0.3)
Partial response	19 (14.2)	5 (4.1)	39 (11.4)	17 (5.1)
Stable disease	40 (29.9)	53 (43.8)	94 (27.5)	139 (41.9)
Progressive disease	59 (44.0)	36 (29.8)	169 (49.4)	121 (36.4)
Median duration of response,[a] mo (95% CI)	NE (19.7, NE)	22.5 (6.2, NE)	36.1 (16.8, NE)	11.0 (6.2, 14.7)
Patients with ongoing response,[a] n (%)	13 (81.3)	1 (50.0)	20 (71.4)	2 (40.0)

Data cutoff: July 11, 2022. [a]Assessed by blinded independent review committee. [b]Confirmed responses. [c]95% CI was calculated using Clopper-Pearson method. [d]These data do not include patients with a non-complete/non-partial, not evaluable, or not assessable response. **Abbreviations:** CI, confidence interval; ITT, intent-to-treat; mo, months; NE, not evaluable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Safety

- In line with the overall population,[5] patients treated with tislelizumab in the ≥65 years subgroup experienced lower incidences of ≥grade 3 treatment-emergent adverse events (TEAEs; 46.6% vs 62.5%) and ≥grade 3 treatment-related TEAEs (TRAEs; 20.3% vs 52.5%) vs patients treated with sorafenib (**Table 3**)
- The most common TRAEs reported by patients in the tislelizumab arm (≥10%) were rash, reported by 20 patients (15.0%), pruritus reported by 14 patients (10.5%), and increased aspartate aminotransferase, reported by 16 patients (12.0%)

Table 3. Safety Summary (Safety Analysis Set)

	≥65 Years Subgroup		Overall Population[5]	
Patients, n (%)	Tislelizumab (n=133)	Sorafenib (n=120)	Tislelizumab (n=338)	Sorafenib (n=324)
TEAE any grade	126 (94.7)	120 (100.0)	325 (96.2)	324 (100.0)
Treatment-related	101 (75.9)	113 (94.2)	259 (76.6)	311 (96.0)
TEAE ≥grade 3	62 (46.6)	75 (62.5)	163 (48.2)	212 (65.4)
Treatment-related	27 (20.3)	63 (52.5)	75 (22.2)	173 (53.4)
Serious TEAE	44 (33.1)	39 (32.5)	101 (29.9)	91 (28.1)
Treatment-related	14 (10.5)	13 (10.8)	40 (11.8)	33 (10.2)
TEAE leading to study drug discontinuation	15 (11.3)	29 (24.2)	37 (10.9)	60 (18.5)
Treatment-related	8 (6.0)	20 (16.7)	21 (6.2)	33 (10.2)
TEAE leading to death	7 (5.3)	6 (5.0)	15 (4.4)	17 (5.2)
Treatment-related	2 (1.5)	1 (0.8)	3 (0.9)	2 (0.6)

Data cutoff: July 11, 2022. **Abbreviation:** TEAE, treatment-emergent adverse event.

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