Tislelizumab Versus Sorafenib in First-Line Treatment of Unresectable Hepatocellular Carcinoma (HCC): RATIONALE-301 Japanese Subpopulation Analysis

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Declaration of Conflict of Interests

- Prof Masatoshi Kudo reports:
  - Lecture fees from Eli Lilly, Bayer, Eisai, Chugai, Takeda, and MSD
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Background

HCC is the predominant subtype of liver cancer, accounting for approximately 80% of cases and occurring most commonly in Africa and Asia.[1,2]

Tislelizumab, a monoclonal antibody with high binding affinity for PD-1, was specifically engineered to minimize Fc-γ receptor binding on macrophages.[3,4]

The phase 3 RATIONALE-301 trial (NCT03412773) met its primary endpoint in the overall study population of OS noninferiority of tislelizumab vs sorafenib (HR: 0.85; 95% CI: 0.71, 1.02) as a first-line treatment of patients with unresectable HCC; OS superiority vs sorafenib was not met.[5] Tislelizumab was also associated with greater and more durable antitumor responses and a favorable safety profile compared with sorafenib.[5]

Here, we present the efficacy and safety results of the Japanese subgroup analysis from RATIONALE-301.

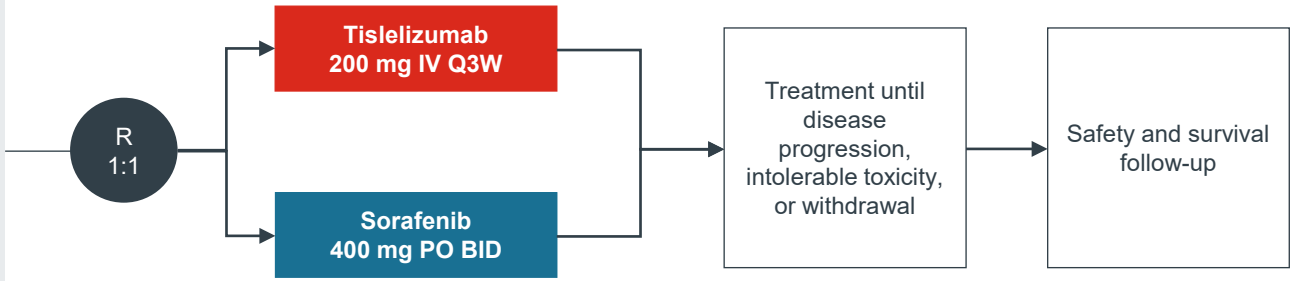
1. Golabi P, et al. *Medicine*. 2017;96(9):e5904; 2. Vogel A, et al. *Ann Oncol*. 2018;29(suppl 4):iv238-iv255; 3. Zhang T, et al. *Cancer Immunol Immunother*. 2018;67(7):1079-1090;
4. Hong Y, et al. *FEBS Open Bio*. 2021;11(3):782-792; 5. Qin S, et al. *JAMA Oncol*. 2023. doi: 10.1001/jamaoncol.2023.4003 (Epub ahead of print).
Abbreviations: CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; OS, overall survival; PD-1, programmed cell death protein 1.

RATIONALE-301 Study Design

- Randomized, open-label, multiregional phase 3 study

Key eligibility criteria

- Histologically confirmed HCC
- Systemic therapy-naïve
- BCLC stage C or B disease not amenable to or progressed after loco-regional therapy
- Child-Pugh class A
- ≥1 measurable lesion per RECIST v1.1
- ECOG PS ≤1
- No tumor thrombus involving main trunk of portal vein or inferior vena cava



Endpoints

- **Primary endpoint**: OS in the ITT analysis set
- **Key secondary endpoints**: ORR, PFS, and DoR assessed by blinded independent review committee per RECIST v1.1, and safety

Stratification factors

- Macrovascular invasion (present vs absent)
- Extrahepatic spread (present vs absent)
- ECOG PS (0 vs 1)
- Etiology (HCV vs other[a])
- Geography (Asia [excluding Japan] vs Japan vs rest of world [EU/US])

[a]Includes HBV.
Abbreviations: BCLC, Barcelona Clinic Liver Cancer; BID, twice daily; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EU, Europe; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ITT, intent-to-treat; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; Q3W, once every 3 weeks; R, randomized; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; US, United States.
Qin S, et al. *JAMA Oncol*. 2023. doi: 10.1001/jamaoncol.2023.4003 (Epub ahead of print).

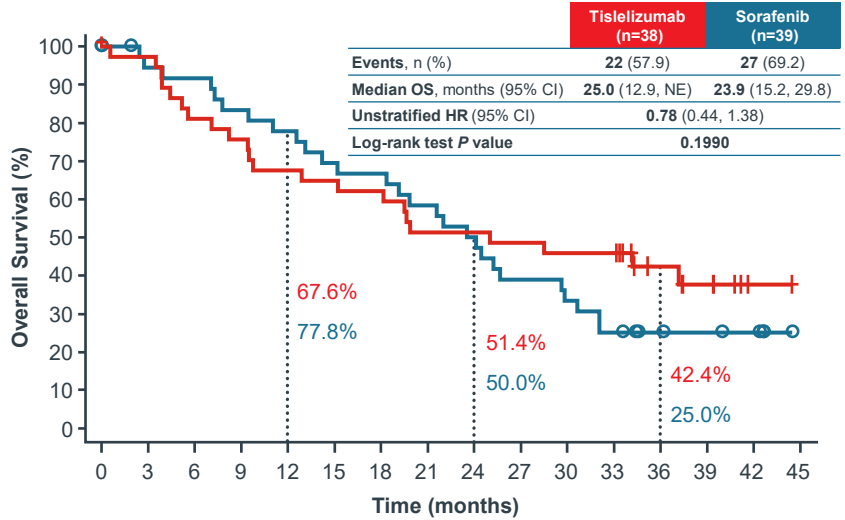
Patient Disposition and Baseline Characteristics

	Japanese Subgroup			Overall Population
	Tislelizumab (n=38)	Sorafenib (n=39)	Total (n=77)	Total (N=674)
Median age, years (range)	75.5 (59.0-86.0)	70.0 (48.0-84.0)	74.0 (48.0-86.0)	61.0 (23.0-86.0)
Male, n (%)	32 (84.2)	34 (87.2)	66 (85.7)	570 (84.6)
Child-Pugh Class A, n (%)	38 (100.0)	39 (100.0)	77 (100.0)	672 (99.7)
BCLC Stage,[a] n (%)				
B	20 (52.6)	24 (61.5)	44 (57.1)	150 (22.3)
C	18 (47.4)	15 (38.5)	33 (42.9)	524 (77.7)
ECOG PS, n (%)				
0	35 (92.1)	37 (94.9)	72 (93.5)	364 (54.0)
1	3 (7.9)	2 (5.1)	5 (6.5)	310 (46.0)
Extrahepatic spread present, n (%)	17 (44.7)	13 (33.3)	30 (39.0)	417 (61.9)
Macrovascular invasion present, n (%)	3 (7.9)	2 (5.1)	5 (6.5)	100 (14.8)
Alpha-fetoprotein, n (%)				
≥200 ng/mL	12 (31.6)	10 (25.6)	22 (28.6)	281 (41.7)
≥400 ng/mL	10 (26.3)	9 (23.1)	19 (24.7)	251 (37.2)

Data presented for ITT analysis set. [a]At study entry.
Abbreviations: BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status.

Overall Survival

Japanese Subgroup

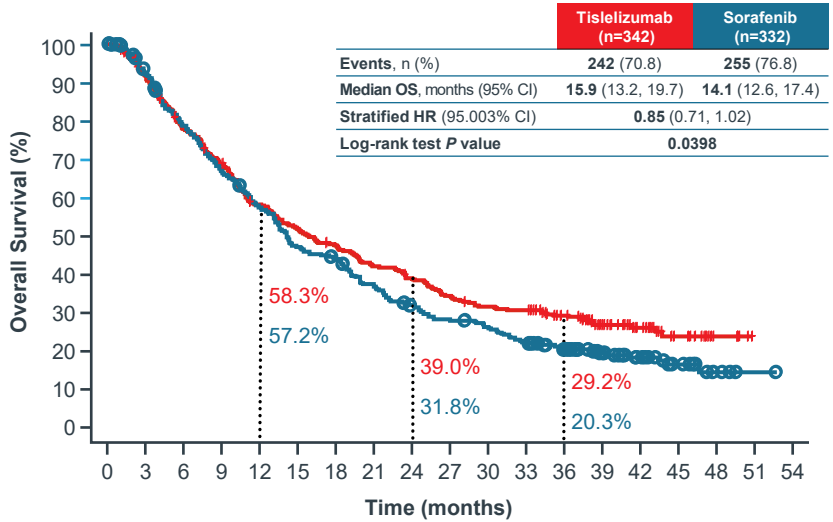


	Tislelizumab (n=38)	Sorafenib (n=39)
Events, n (%)	**22** (57.9)	**27** (69.2)
Median OS, months (95% CI)	**25.0** (12.9, NE)	**23.9** (15.2, 29.8)
Unstratified HR (95% CI)	**0.78** (0.44, 1.38)	
Log-rank test *P* value	**0.1990**	

Number of patients at risk:

Tislelizumab	38	36	30	28	25	24	23	19	19	18	17	17	9	6	1	0
Sorafenib	39	34	33	30	28	25	24	21	18	14	12	9	6	5	4	0

Overall Population[1]



	Tislelizumab (n=342)	Sorafenib (n=332)
Events, n (%)	**242** (70.8)	**255** (76.8)
Median OS, months (95% CI)	**15.9** (13.2, 19.7)	**14.1** (12.6, 17.4)
Stratified HR (95.003% CI)	**0.85** (0.71, 1.02)	
Log-rank test *P* value	**0.0398**	

Number of patients at risk:

Tislelizumab	342	307	259	228	191	170	155	137	126	111	101	98	77	53	33	18	4	0	0
Sorafenib	332	291	247	208	179	147	136	113	96	84	77	66	52	39	29	13	4	1	0

- Median survival follow-up in the Japanese subgroup was 37.4 months (range: 34.1-40.8) in the tislelizumab arm vs 39.9 months (range: 33.5-42.6) in the sorafenib arm.

Data presented for ITT analysis set. Data cutoff: July 11, 2022.

1. Qin S, et al. *JAMA Oncol*. 2023. doi: 10.1001/jamaoncol.2023.4003 (Epub ahead of print).

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; NE, not evaluable; OS, overall survival.

Secondary Efficacy Endpoints

	Japanese Subgroup (n=77)		Overall Population[1] (N=674)	
	Tislelizumab (n=38)	Sorafenib (n=39)	Tislelizumab (n=342)	Sorafenib (n=332)
Confirmed objective response rate,[a,b] n (%) [95% CI][c]	5 (13.2) [4.4, 28.1]	3 (7.7) [1.6, 20.9]	49 (14.3) [10.8, 18.5]	18 (5.4) [3.2, 8.4]
Median progression-free survival,[a] month (95% CI)	4.0 (2.1, 5.6)	4.2 (2.1, 8.2)	2.1 (2.1, 3.5)	3.4 (2.2, 4.1)
Best overall response,[a,b,d] n (%)				
Complete response	1 (2.6)	0 (0.0)	10 (2.9)	1 (0.3)
Partial response	4 (10.5)	3 (7.7)	39 (11.4)	17 (5.1)
Stable disease	16 (42.1)	16 (41.0)	94 (27.5)	139 (41.9)
Progressive disease	14 (36.8)	13 (33.3)	169 (49.4)	121 (36.4)
Median duration of response,[a] months (95% CI)	NE (19.7, NE)	NE (14.7, NE)	36.1 (16.8, NE)	11.0 (6.2, 14.7)
Disease control rate, n (%)	22 (57.9)	21 (53.8)	151 (44.2)	167 (50.3)

Data presented for ITT analysis set. 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.
1. Qin S, et al. *JAMA Oncol*. 2023. doi: 10.1001/jamaoncol.2023.4003 (Epub ahead of print).
Abbreviations: CI, confidence interval; ITT, intent-to-treat; NE, not evaluable.

Safety Summary

	Japanese Subgroup (n=74)		Overall Population[1] (N=662)	
	Tislelizumab (n=37)	Sorafenib (n=37)	Tislelizumab (n=338)	Sorafenib (n=324)
TRAE of any grade	22 (59.5)	36 (97.3)	259 (76.6)	311 (96.0)
TRAE of grade ≥3	7 (18.9)	20 (54.1)	75 (22.2)	173 (53.4)
Serious TRAE	4 (10.8)	4 (10.8)	40 (11.8)	33 (10.2)
TRAE leading to study drug discontinuation	4 (10.8)	6 (16.2)	21 (6.2)	33 (10.2)
TRAE leading to study drug modification	10 (27.0)	30 (81.1)	68 (20.1)	187 (57.7)
TRAE leading to death	0 (0.0)	0 (0.0)	3 (0.9)	2 (0.6)

- The most common TRAEs reported by patients in the tislelizumab arm (≥10%) were:

Rash
n=8 (21.6%)

AST increased
n=4 (10.8%)

ALT increased
n=4 (10.8%)

Fatigue
n=4 (10.8%)

Data presented for safety analysis set. Data cutoff: July 11, 2022.
1. Qin S, et al. *JAMA Oncol*. 2023. doi: 10.1001/jamaoncol.2023.4003 (Epub ahead of print).
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TRAE, treatment-related treatment-emergent adverse event.

Conclusions

In the Japanese subgroup of RATIONALE-301, tislelizumab demonstrated overall survival noninferiority, with greater and more durable antitumor responses compared with sorafenib as first-line treatment in patients with unresectable hepatocellular carcinoma.

Tislelizumab had a favorable safety profile compared with sorafenib in Japanese patients with unresectable hepatocellular carcinoma, characterized by a much lower rate of TRAE of any grade, TRAE of grade ≥3, and TRAE leading to study drug discontinuation and study drug modification.

The efficacy and safety results obtained in the Japanese subgroup were consistent with the published results from the overall study population.[1]

1. Qin S, et al. *JAMA Oncol*. 2023. doi: 10.1001/jamaoncol.2023.4003 (Epub ahead of print).
Abbreviation: TRAE, treatment-related treatment-emergent adverse event.

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