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Tislelizumab Versus Sorafenib in First-Line Treatment of Unresectable Hepatocellular Carcinoma: The RATIONALE-301 Chinese Subpopulation Analysis

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Declaration Of Interests

Dr Shukui Qin declares no conflicts of interest

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Introduction

Liver cancer is the sixth most common cancer globally and the third leading cause of cancer death.[1]

HCC is the predominant subtype of liver cancer, accounting for approximately 80% of cases and occurring most commonly in Africa and Asia.[2,3]

1L treatment options for advanced HCC include anti-PD-(L)1 + anti-VEGF combinations or monotherapy with a TKI;[4,5] no single-agent checkpoint inhibitor has been approved in this setting.

Tislelizumab, a monoclonal antibody with high binding affinity for PD-1, was specifically engineered to minimize Fcγ receptor binding on macrophages.[6,7]

1L

In the overall population of the phase 3 RATIONALE-301 trial (NCT03412773), tislelizumab demonstrated OS non-inferiority vs sorafenib (HR: 0.85, 95% CI: 0.71, 1.02) as a 1L treatment of patients with unresectable HCC; OS superiority vs sorafenib was not met.[8] Tislelizumab was also associated with a favorable safety profile.[8]

This analysis compared the efficacy and safety of tislelizumab in the Chinese subgroup with the overall population of RATIONALE-301.

Abbreviations: 1L, first-line; CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; OS, overall survival, PD-1, programmed cell death protein 1; PD-L1, programmed death- ligand 1; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

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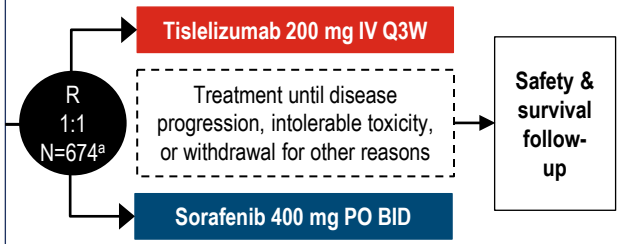
RATIONALE-301 Study Design and Baseline Characteristics

Randomized, open-label, multiregional phase 3 study[1]

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

Secondary endpoints:
- ORR, PFS, DoR, TTP, DCR, and CBR by BIRC
- Safety

Baseline Characteristics

	Chinese Subgroup (n=425)		Overall Population (N=674)	
	Tislelizumab (n=215)	Sorafenib (n=210)	Tislelizumab (n=342)	Sorafenib (n=332)
Median age, years (range)	55 (25-85)	54 (23-85)	62 (25-86)	60 (23-86)
Male, n (%)	182 (84.7)	180 (85.7)	289 (84.5)	281 (84.6)
Child-Pugh score, n (%)				
5	158 (73.5)	163 (77.6)	263 (76.9)	248 (74.7)
6	57 (26.5)	47 (22.4)	77 (22.5)	84 (25.3)
BCLC staging[b], n (%)				
Stage B	25 (11.6)	29 (13.8)	70 (20.5)	80 (24.1)
Stage C	190 (88.4)	181 (86.2)	272 (79.5)	252 (75.9)
ECOG PS, n (%)				
0	92 (42.8)	91 (43.3)	183 (53.5)	181 (54.5)
1	123 (57.2)	119 (56.7)	159 (46.5)	151 (45.5)
Extrahepatic spread, n (%)				
Absent	62 (28.8)	64 (30.5)	123 (36.0)	134 (40.4)
Present	153 (71.2)	146 (69.5)	219 (64.0)	198 (59.6)
Macrovascular invasion, n (%)				
Absent	183 (85.1)	177 (84.3)	291 (85.1)	283 (85.2)
Present	32 (14.9)	33 (15.7)	51 (14.9)	49 (14.8)
Median follow-up[c], months (range)	13.8 (0.1-50.8)	13.1 (0.1-49.4)	15.0 (0.1-50.8)	13.5 (0.0-54.5)
Min study follow-up[d], months	34	33	33	33

[a]Stratified by macrovascular invasion (present vs absent), extrahepatic spread (present vs absent), ECOG PS (0 vs 1), etiology (HCV vs HBV), and geography (Asia vs Japan vs ROW). [b]At study entry. [c]Follow-up time is defined as the time from the randomization date to the study discontinuation date (death, consent withdrawal, lost to follow up) or to cutoff date if a patient is still undergoing treatment. [d]Minimum study follow-up time is defined as the difference between the date of cutoff and the date of last patient randomized. Abbreviations: BCLC; Barcelona Clinic Liver Cancer; BID, twice daily; BIRC, blinded independent review committee; CBR, clinical benefit rate; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IV, intravenously; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; Q3W, every three weeks; R, randomized; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; ROW; rest of world; TTP, time to progression. 1. Qin S, et al. ESMO Congress 2022. Presentation LBA36.

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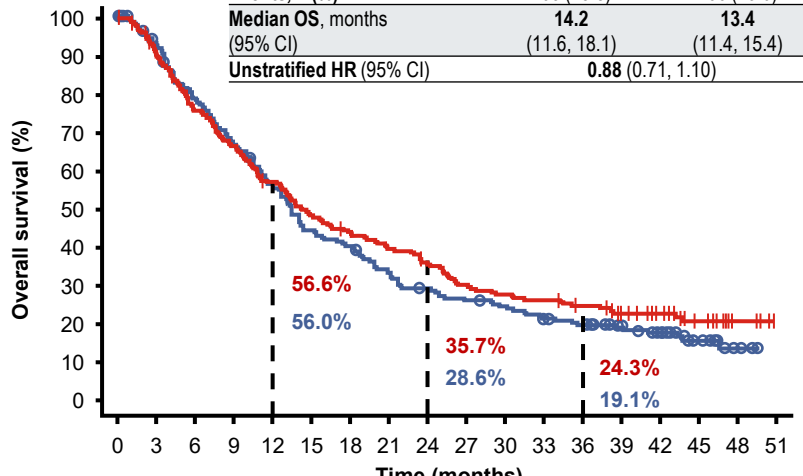
Efficacy: Overall Survival

Tislelizumab demonstrated comparable OS vs sorafenib in the Chinese subgroup, similar to the overall population[a]

OS: Chinese Subgroup

	Tislelizumab (n=215)	Sorafenib (n=210)
Events, n (%)	163 (75.8)	166 (79.0)
Median OS, months (95% CI)	**14.2** (11.6, 18.1)	**13.4** (11.4, 15.4)
Unstratified HR (95% CI)	**0.88** (0.71, 1.10)	

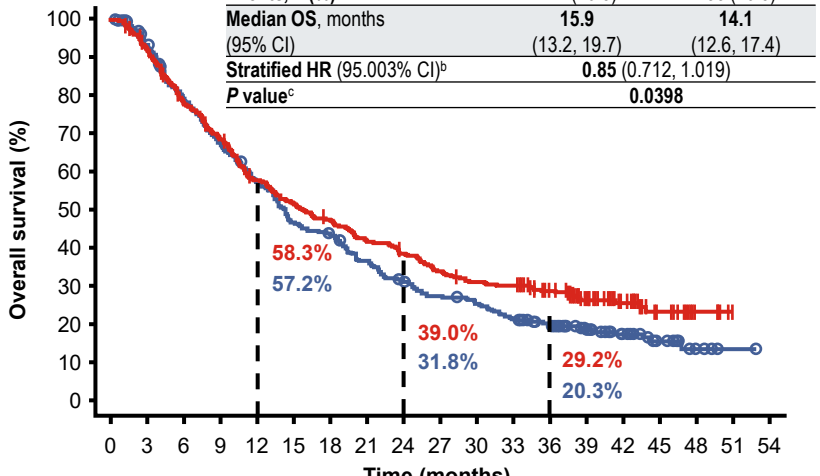


Number of patients at risk:

Tislelizumab	215	190	157	138	117	99	89	80	72	60	55	52	47	37	30	18	4	0
Sorafenib	210	186	157	131	111	87	79	64	55	49	45	40	34	27	22	12	3	0

OS: Overall Population

	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)[b]	**0.85** (0.712, 1.019)	
***P* value**[c]	**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

Data presented for the ITT analysis set. Data cutoff: July 11, 2022.[a]Tislelizumab demonstrated OS non-inferiority vs sorafenib and OS superiority vs sorafenib was not met in the overall population. Prespecified boundary of non-inferiority: upper bound of 95.003% CI of stratified HR <1.08; pre-specified boundary of superiority: one-sided *P* value <0.0223 (approximate HR <0.8352). [b]HR was based on a Cox proportional hazard model including treatment as a covariate, geography (Asia [including Japan] vs rest of world [*Europe/United States*]), macrovascular invasion and/or extrahepatic spread (present vs absent), etiology (HCV vs other), and ECOG PS (0 vs 1) as stratification factors. [c]One-sided stratified log-rank test.
Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HCV, hepatitis C virus; HR, hazard ratio; ITT, intent-to-treat; NI, non-inferiority; OS, overall survival.

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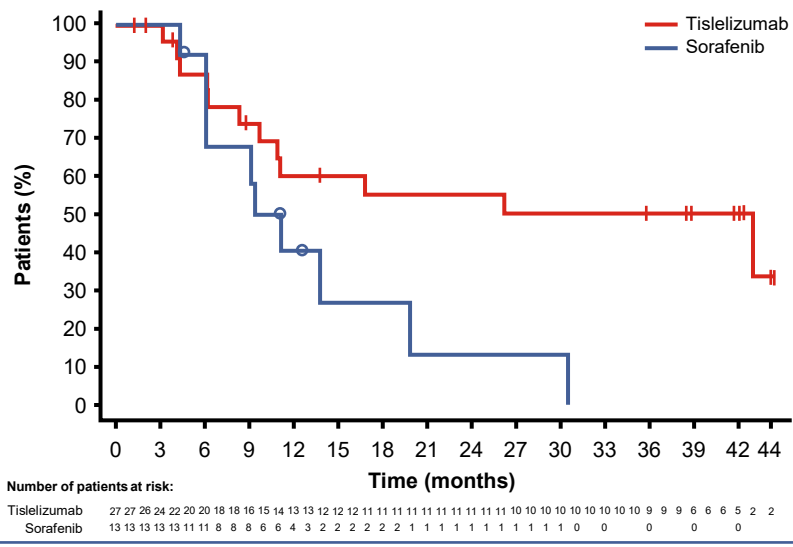
Efficacy: Tumor Response

Higher ORR and longer DoR were observed for tislelizumab vs sorafenib in the Chinese subgroup, similar to the overall population

	Chinese Subgroup (n=425)		Overall Population (N=674)	
	Tislelizumab (n=215)	Sorafenib (n=210)	Tislelizumab (n=342)	Sorafenib (n=332)
Confirmed ORR, n (%)	27 (12.6)	13 (6.2)	49 (14.3)	18 (5.4)
95% CI	(8.4, 17.7)	(3.3, 10.4)	(10.8, 18.5)	(3.2, 8.4)
ORR difference, % (95% CI)[a]	5.0 (-0.4, 10.4)		8.3 (3.9, 12.7)	
Confirmed best overall response, n (%)				
CR	6 (2.8)	1 (0.5)	10 (2.9)	1 (0.3)
PR	21 (9.8)	12 (5.7)	39 (11.4)	17 (5.1)
SD	47 (21.9)	81 (38.6)	94 (27.5)	139 (41.9)
Non-CR/Non-PD	7 (3.3)	5 (2.4)	8 (2.3)	10 (3.0)
PD	118 (54.9)	83 (39.5)	169 (49.4)	121 (36.4)
Could not be determined	16 (7.4)	28 (13.3)	22 (6.4)	44 (13.3)
DCR, n (%)	81 (37.7)	99 (47.1)	151 (44.2)	167 (50.3)
CBR, n (%)	48 (22.3)	49 (23.3)	87 (25.4)	81 (24.4)
Median DoR, months	42.9	11.0	36.1	11.0
(95% CI)	(9.7, NE)	(6.2, 19.6)	(16.8, NE)	(6.2, 14.7)
Median PFS, months	2.1	2.4	2.1	3.4
(95% CI)	(2.1, 2.1)	(2.1, 4.1)	(2.1, 3.5)	(2.2, 4.1)

DoR: Chinese Subgroup



Data presented for the ITT analysis set. Data cutoff: July 11, 2022. [a]Objective response rate differences between arms in the overall population were calculated using the exact Cochran-Mantel-Haenszel method stratified by geography (Asia [including Japan] vs EU/US), macrovascular invasion and/or extrahepatic spread (present vs absent), etiology (HCV vs other) and ECOG PS (0 vs 1). Objective response rate difference arms in the Chinese subgroup were calculated using the exact Cochran-Mantel-Haenszel method stratified by macrovascular invasion and/or extrahepatic spread (present vs absent), etiology (HCV vs other) and ECOG PS (0 vs 1).

Abbreviations: CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HCV, hepatitis C virus; ITT, intent-to-treat; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

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Safety: Overall Safety Profiles

The safety profile of tislelizumab was favourable vs sorafenib in the Chinese subgroup, and comparable with the overall population

	Chinese Subgroup (n=418)		Overall Population (N=662)	
	Tislelizumab (n=213)	Sorafenib (n=205)	Tislelizumab (n=338)	Sorafenib (n=324)
Median duration of treatment, months (range)	4.1 (2.1, 8.3)	2.5 (2.0, 6.4)	4.1 (0.6, 50.4)	2.7 (0.0, 49.0)
Safety, n (%)				
Any TEAE	205 (96.2)	205 (100.0)	325 (96.2)	324 (100.0)
Treatment-related	166 (77.9)	199 (97.1)	259 (76.6)	311 (96.0)
TEAE at ≥grade 3	110 (51.6)	135 (65.9)	163 (48.2)	212 (65.4)
Treatment-related	53 (24.9)	112 (54.6)	75 (22.2)	173 (53.4)
Serious TEAE	59 (27.7)	52 (25.4)	101 (29.9)	91 (28.1)
Treatment-related	25 (11.7)	21 (10.2)	40 (11.8)	33 (10.2)
TEAE leading to discontinuation	18 (8.5)	28 (13.7)	37 (10.9)	60 (18.5)
Treatment-related	9 (4.2)	15 (7.3)	21 (6.2)	33 (10.2)
TEAE leading to drug modification	53 (24.9)	118 (57.6)	105 (31.1)	210 (64.8)
Treatment-related	41 (19.2)	109 (53.2)	68 (20.1)	187 (57.7)
TEAE leading to death	11 (5.2)	7 (3.4)	15 (4.4)	17 (5.2)
Treatment-related	2 (0.9)	1 (0.5)	3 (0.9)	2 (0.6)

Safety analysis set. Data cutoff: July 11, 2022.
Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event.

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Safety: Most Common TEAEs

The proportion of patients with TEAEs with incidence ≥10% was higher in the sorafenib arm vs tislelizumab arm in both populations

	Chinese Subgroup (n=418)		Overall Population (N=662)	
	Tislelizumab (n=213)	Sorafenib (n=205)	Tislelizumab (N=338)	Sorafenib (N=324)
Patients with at least one TEAE with incidence ≥10%	191 (89.7)	203 (99.0)	290 (85.8)	316 (97.5)
Aspartate aminotransferase increased	100 (46.9)	116 (56.6)	126 (37.3)	137 (42.3)
Alanine aminotransferase increased	76 (35.7)	94 (45.9)	96 (28.4)	114 (35.2)
Blood bilirubin increased	69 (32.4)	93 (45.4)	73 (21.6)	103 (31.8)
Platelet count decreased	48 (22.5)	64 (31.2)	49 (14.5)	69 (21.3)
Gamma-glutamyltransferase increased	39 (18.3)	43 (21.0)	41 (12.1)	43 (13.3)
Blood alkaline phosphatase increased	37 (17.4)	36 (17.6)	40 (11.8)	37 (11.4)
White blood cell count decreased	30 (14.1)	29 (14.1)	31 (9.2)	30 (9.3)
Weight decreased	23 (10.8)	42 (20.5)	33 (9.8)	64 (19.8)
Neutrophil count decreased	26 (12.2)	26 (12.7)	27 (8.0)	29 (9.0)
Bilirubin conjugated increased	20 (9.4)	28 (13.7)	27 (8.0)	33 (10.2)
Hypoalbuminaemia	40 (18.8)	29 (14.1)	44 (13.0)	33 (10.2)
Decreased appetite	25 (11.7)	26 (12.7)	45 (13.3)	57 (17.6)
Hypokalaemia	17 (8.0)	32 (15.6)	22 (6.5)	34 (10.5)
Hyponatraemia	17 (8.0)	25 (12.2)	21 (6.2)	28 (8.6)
Hypophosphataemia	6 (2.8)	28 (13.7)	9 (2.7)	45 (13.9)

	Chinese Subgroup (n=418)		Overall Population (N=662)	
	Tislelizumab (n=213)	Sorafenib (n=205)	Tislelizumab (N=338)	Sorafenib (N=324)
Abdominal pain	27 (12.7)	24 (11.7)	41 (12.1)	43 (13.3)
Diarrhoea	19 (8.9)	87 (42.4)	38 (11.2)	142 (43.8)
Nausea	10 (4.7)	15 (7.3)	26 (7.7)	33 (10.2)
Pruritus	24 (11.3)	11 (5.4)	48 (14.2)	25 (7.7)
Rash	23 (10.8)	39 (19.0)	40 (11.8)	56 (17.3)
Alopecia	1 (0.5)	53 (25.9)	2 (0.6)	74 (22.8)
Palmar-plantar erythrodysaesthesia syndrome	1 (0.5)	147 (71.7)	1 (0.3)	203 (62.7)
Anaemia	34 (16.0)	23 (11.2)	41 (12.1)	32 (9.9)
Thrombocytopenia	13 (6.1)	25 (12.2)	15 (4.4)	31 (9.6)
Pyrexia	36 (16.9)	44 (21.5)	56 (16.6)	60 (18.5)
Fatigue	13 (6.1)	11 (5.4)	37 (10.9)	38 (11.7)
Arthralgia	14 (6.6)	11 (5.4)	40 (11.8)	22 (6.8)
Upper respiratory tract infection	25 (11.7)	13 (6.3)	29 (8.6)	13 (4.0)
Cough	24 (11.3)	18 (8.8)	38 (11.2)	24 (7.4)
Hypertension	17 (8.0)	46 (22.4)	21 (6.2)	89 (27.5)

Safety analysis set. Data cutoff: July 11, 2022.

Abbreviations: TEAE, treatment-emergent adverse event.

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Conclusions

Tislelizumab demonstrated a comparable OS, higher ORR, and more durable responses vs sorafenib in the Chinese subgroup, consistent with the overall population.

Tislelizumab showed a more favorable safety profile and better tolerability than sorafenib with a lower incidence of ≥grade 3 TEAEs, TEAEs leading to drug modification, and TEAEs leading to treatment discontinuation.

The efficacy and safety results from the Chinese subgroup analysis of the RATIONALE-301 study, comparing tislelizumab and sorafenib, demonstrate that tislelizumab is an effective 1L treatment in patients with unresectable HCC.

Abbreviations: 1L, first-line; HCC, hepatocellular carcinoma; ORR, objective response rate; OS, overall survival; TEAE, treatment-emergent adverse event.

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