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Final Analysis of RATIONALE-301: Randomized, Phase 3 Study of Tislelizumab Versus Sorafenib as First-Line Treatment for Unresectable Hepatocellular Carcinoma

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DECLARATION OF INTERESTS

Masatoshi Kudo reports relevant financial relationship(s) with Eli Lilly, Bayer, Eisai, Chugai, Takeda (all invited speaker), and Gilead Sciences, Taiho, Sumitomo Dainippon Pharma, Takeda, Otsuka, EA Pharma, AbbVie, Eisai (all research grant).

RATIONALE-301: Background

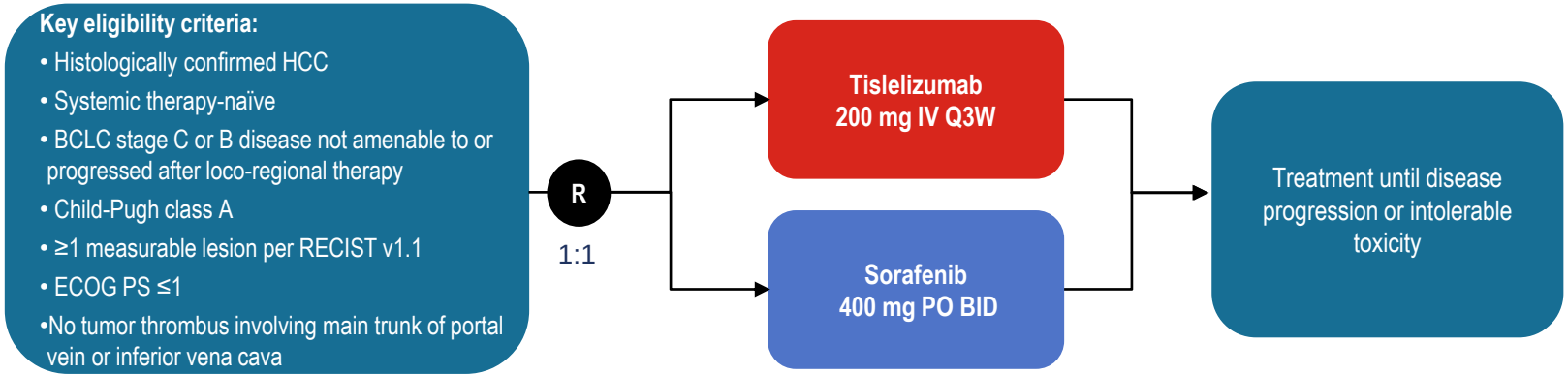
- Liver cancer is the sixth most common cancer globally and the third leading cause of cancer death[1]
- HCC is the predominant subtype of liver cancer, accounting for approximately 80% of cases and occurring most commonly in Asia[2,3]
- Currently atezolizumab plus bevacizumab is the standard treatment for 1L HCC; no single-agent checkpoint inhibitor has been approved in this setting[3,4]
- Tislelizumab, a monoclonal antibody with high binding affinity for PD-1, was specifically engineered to minimize Fcγ receptor binding on macrophages[5,6]
- In the phase 2 RATIONALE-208 study (NCT03419897), tislelizumab monotherapy demonstrated durable responses and was generally well tolerated in patients with previously treated advanced HCC[7]
- Here, we report the final analysis results of RATIONALE-301, which compared the efficacy and safety of tislelizumab with sorafenib as a single-agent, 1L treatment in patients with unresectable HCC

Abbreviations: 1L, first-line; HCC, hepatocellular carcinoma; PD-1, programmed cell death protein 1.

1. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available at: https://gco.iarc.fr/today/data/factsheets/cancers/11-Liver-fact-sheet.pdf. Accessed August 2022. 2. Golabi P, et al. *Medicine.* 2017;96(9):e5904. 3. Vogel A, et al. *Ann Oncol.* 2021;32(6):801-805. 4. Gordan JD, et al. *J Clin Oncol.* 2020;38(36):4317-4345. 5. Zhang T, et al. *Cancer Immunol Immunother*. 2018;67(7):1079-1090. 6. Hong Y, et al. *FEBS Open Bio.* 2021;11(3):782-792. 7. Ducreux M, et al. *Ann Oncol*. 2021; 32 (Abs O-1) [presented at WCGI 2021].

RATIONALE-301: Study Design

Randomized, open-label, multicenter, multiregional phase 3 study



Primary endpoint: OS in the ITT population

Key secondary endpoints: ORR, PFS, and DoR by BIRC 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)

[a]Includes HBV. Abbreviations: BCLC, Barcelona Clinic Liver Cancer; BID, twice daily; BIRC, blinded independent review committee; DoR, duration of response; ECOG PS, European Cooperative Oncology Group performance status; 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, oral; Q3W, once every 3 weeks; RECIST, Response Evaluation Criteria In Solid Tumors.

RATIONALE-301: Statistical Design

- The statistical design included an interim analysis of OS when 403 events were observed
- The final analysis of OS took place when 497 OS events were observed
- The upper (efficacy) boundary is based on the O'Brien-Fleming boundary, approximated by the Hwang-Shih-DeCani spending function
- Endpoints were sequentially tested in the following order: (1) noninferiority of OS, (2) superiority of OS, (3) ORR, and (4) PFS
- HR was based on a Cox proportional hazard model including treatment as a covariate, and geography (Asia [including Japan] vs rest of world [EU/US]), macrovascular invasion and/or extrahepatic spread (present vs absent), etiology (HCV vs other[a]), and ECOG PS (0 vs 1) as stratification factors
- Non-inferiority of OS between treatment arms was claimed if the upper limit of the hazard ratio 95.003% confidence interval was <1.08
- Superiority of OS between treatment arms was claimed if the one-sided *P*-value was <0.0223

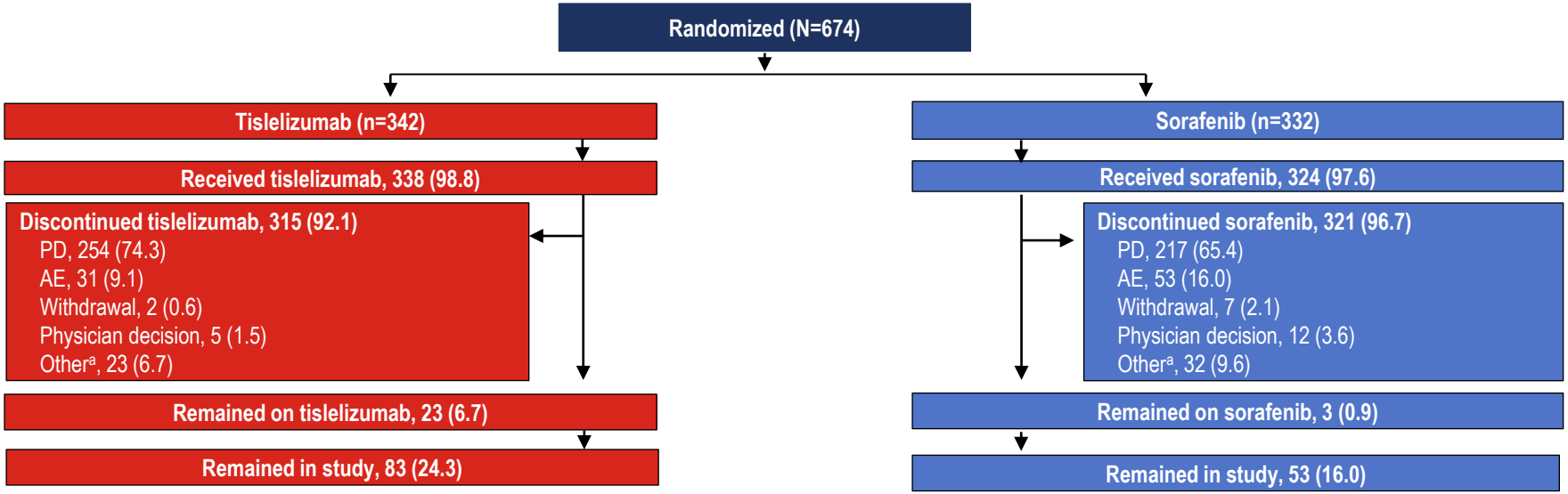
[a]Includes HBV. Abbreviations: ECOG PS, European Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

RATIONALE-301: Patient Baseline Characteristics

		Tislelizumab (n=342)	Sorafenib (n=332)
Median age, years (range)		62.0 (25.0-86.0)	60.0 (23.0-86.0)
Male sex, n (%)		289 (84.5)	281 (84.6)
Geographic region, n (%)	Asia (excluding Japan)	215 (62.9)	210 (63.3)
	Japan	38 (11.1)	39 (11.7)
	Rest of world[a]	89 (26.0)	83 (25.0)
ECOG PS, n (%)	0	183 (53.5)	181 (54.5)
	1	159 (46.5)	151 (45.5)
BCLC staging at study entry, n (%)	B	70 (20.5)	80 (24.1)
	C	272 (79.5)	252 (75.9)
HCC etiology, n (%)	HBV	203 (59.4)	206 (62.0)
	HCV	46 (13.5)	39 (11.7)
	HBV and HCV co-infection	11 (3.2)	7 (2.1)
	Non-viral	82 (24.0)	80 (24.1)
Extrahepatic spread, n (%)		219 (64.0)	198 (59.6)
Macrovascular invasion, n (%)		51 (14.9)	49 (14.8)
Local regional therapy, n (%)		265 (77.5)	250 (75.3)
AFP ≥400 ng/ml, n (%)		135 (39.5)	116 (34.9)
Child-Pugh score, n (%)	5	263 (76.9)	248 (74.7)
	6	77 (22.5)	84 (25.3)

[a]Rest of world includes EU and US. Abbreviations: AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, European Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus.

RATIONALE-301: Patient Disposition

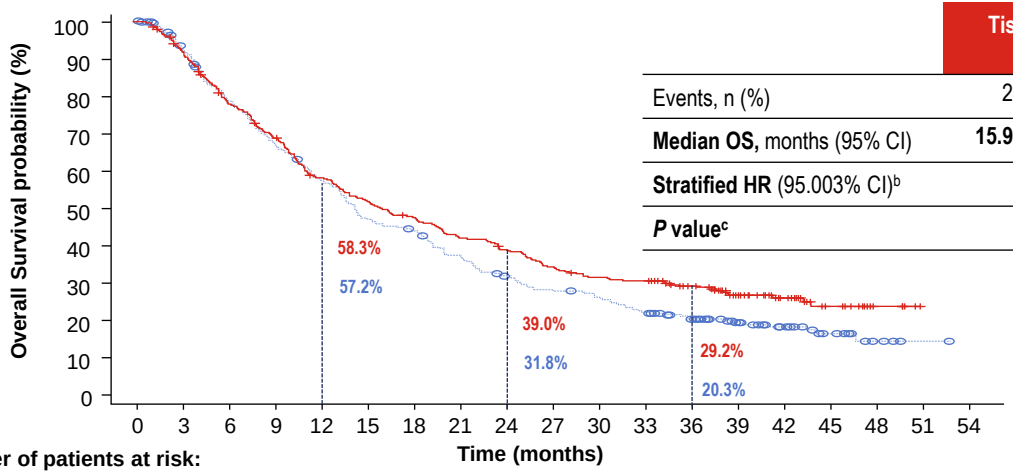


- Minimum study follow-up time[b] was 33.0 months in both treatment arms

Data cutoff: July 11, 2022. Values are n (%), unless stated otherwise. [a]'Other' includes noncompliance with study drug, related to COVID-19, and patients who withdrew from study treatment and remained on survival follow-up. [b]Minimum study follow-up time is defined as the difference between the date of cutoff and the date of last patient randomized. Abbreviations: AE, adverse event; PD, progressive disease.

RATIONALE-301: Overall Survival

Tislelizumab demonstrated OS noninferiority[a] vs sorafenib; OS superiority vs sorafenib was not met



	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:

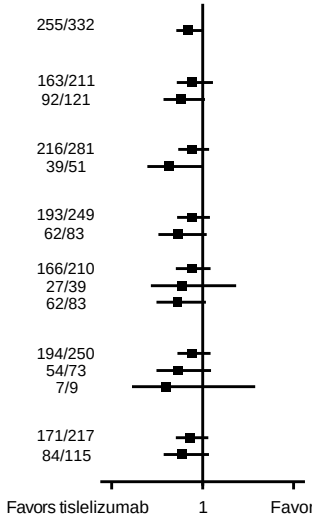
Tislelizumab	342	307	259	228	191	170	155	137	126	111	101	98	77	53	33	18	4	0	0
Sorafenib	332	291	247	208	179	147	136	113	96	84	77	66	52	39	29	13	4	1	0

Data cutoff: July 11, 2022. OS was assessed in the ITT population. [a]Prespecified boundary of NI: 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 [EU/US]), 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, European Cooperative Oncology Group performance status; HCV, hepatitis C virus; HR, hazard ratio; ITT, intent-to-treat; NI, non-inferiority; OS, overall survival.

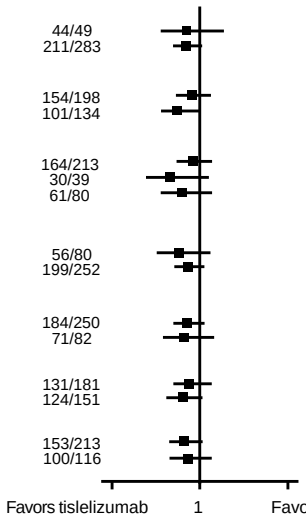
RATIONALE-301: Overall Survival by Subgroups[a]

The OS results observed in the overall population were consistently observed across all subgroups

Subgroup	Event/Total: Tislelizumab	Event/Total: Sorafenib	HR for death (95% CI)
Overall	242/342	255/332	0.84 (0.70, 1.00)
Age			
Age <65 years	154/208	163/211	0.89 (0.71, 1.11)
Age ≥65 years	88/134	92/121	0.76 (0.57, 1.02)
Gender			
Male	208/289	216/281	0.88 (0.73, 1.07)
Female	34/53	39/51	0.62 (0.39, 0.99)
Geographical region			
Asia (including Japan)	185/253	193/249	0.88 (0.72, 1.07)
EU/US	57/89	62/83	0.73 (0.51, 1.04)
Asia (excluding Japan)	163/215	166/210	0.88 (0.71, 1.10)
Japan	22/38	27/39	0.78 (0.44, 1.38)
EU/US	57/89	62/83	0.73 (0.51, 1.04)
Race			
Asian	187/255	194/250	0.88 (0.72, 1.08)
White	45/71	54/73	0.73 (0.49, 1.09)
Other	10/16	7/9	0.60 (0.23, 1.57)
MVI and/or EHS			
Present	174/240	171/217	0.86 (0.70, 1.06)
Absent	68/102	84/115	0.78 (0.56, 1.07)



Subgroup	Event/Total: Tislelizumab	Event/Total: Sorafenib	HR for death (95% CI)
Macrovascular invasion			
Present	42/51	44/49	0.83 (0.54, 1.27)
Absent	200/291	211/283	0.84 (0.69, 1.02)
Extrahepatic spread			
Present	160/219	154/198	0.90 (0.72, 1.12)
Absent	82/123	101/134	0.73 (0.55, 0.98)
Hepatitis virus infection			
HBV	158/214	164/213	0.91 (0.73, 1.14)
HCV	26/46	30/39	0.64 (0.38, 1.08)
Non-viral	58/82	61/80	0.78 (0.55, 1.12)
BCLC stage			
B	44/70	56/80	0.75 (0.50, 1.11)
C	198/272	199/252	0.85 (0.70, 1.04)
Previous local regional therapy			
Yes	185/265	184/250	0.86 (0.70, 1.05)
No	57/77	71/82	0.82 (0.58, 1.16)
ECOG performance score			
0	124/183	131/181	0.87 (0.68, 1.12)
1	118/159	124/151	0.79 (0.61, 1.01)
Alpha-fetoprotein			
<400 ng/ml	139/206	153/213	0.81 (0.64, 1.02)
≥400 ng/ml	102/135	100/116	0.86 (0.65, 1.13)

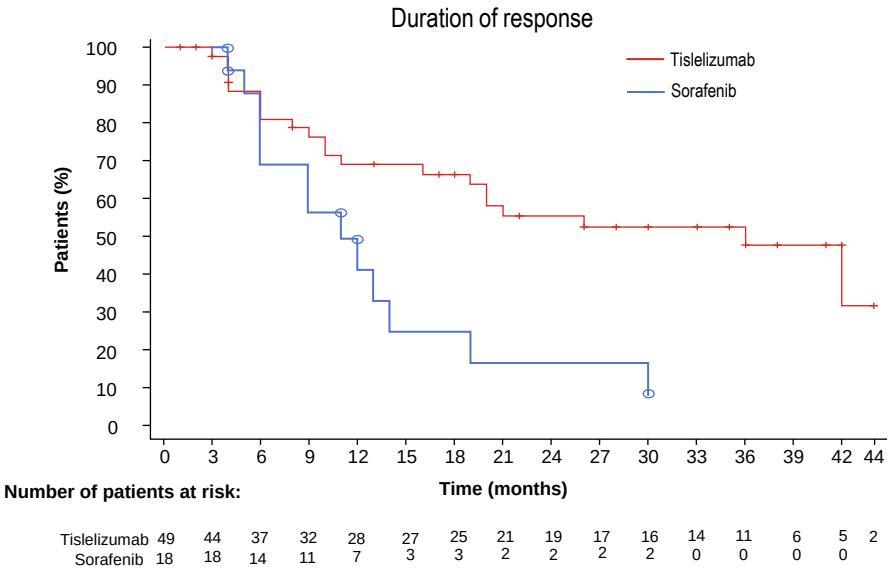


Data cutoff: July 11, 2022. [a]All subgroups were predefined. Abbreviations: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; ECOG PS, European Cooperative Oncology Group performance status; EHS, extrahepatic spread; HR, hazard ratio; MVI, macrovascular invasion; OS, overall survival.

RATIONALE-301: Overall Response Rate by IRC

Tislelizumab was associated with a higher ORR and more durable responses vs sorafenib

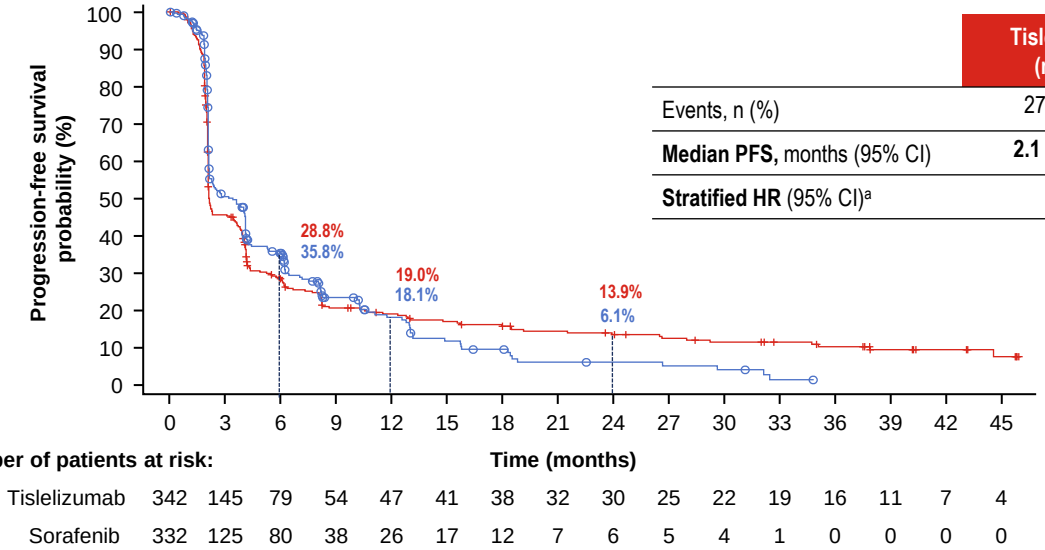
	Tislelizumab (n=342)	Sorafenib (n=332)
ORR, n (%) [95% CI][a]	49 (14.3) [10.8, 18.5]	18 (5.4) [3.2, 8.4]
Best overall response, n (%)[a]		
CR	10 (2.9)	1 (0.3)
PR	39 (11.4)	17 (5.1)
SD	94 (27.5)	139 (41.9)
PD	169 (49.4)	121 (36.4)
Undetermined[b]	22 (6.4)	44 (13.3)
Non-CR/non-PD[c]	8 (2.3)	10 (3.0)
Responders	**Tislelizumab (n=49)**	**Sorafenib (n=18)**
Median DoR, months (95% CI)	36.1 (16.8, NE)	11.0 (6.2, 14.7)
Patients with ongoing response, n (%)[d]	20/28 (71.4)	2/5 (40.0)



Data cutoff: July 11, 2022. ORR was assessed in the ITT population. [a]Confirmed responses; [b]Patients with no postbaseline tumor assessment (not assessable) or a nonevaluable tumor assessment. [c]Patients were assessed as non-CR/non-PD if the IRC was not able to identify the target lesions at screening. Patients with no target lesions were evaluated based on the assessment of nontarget lesions or the presence of new lesions. [d]Patients who had PD or died were excluded from this analysis. Abbreviations: CI, confidence interval; CR, complete response; DoR, duration of response; IRC, independent review committee; ITT, intent-to-treat; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

RATIONALE-301: Progression-Free Survival by IRC

The median PFS was longer with sorafenib versus tislelizumab



	Tislelizumab (n=342)	Sorafenib (n=332)
Events, n (%)	276 (80.7)	224 (67.5)
Median PFS, months (95% CI)	**2.1** (2.1, 3.5)	**3.4** (2.2, 4.1)
Stratified HR (95% CI)[a]	**1.11** (0.92, 1.33)	

Data cutoff: July 11, 2022. PFS was assessed in the ITT population. [a]HR was based on a Cox proportional hazard model including treatment as a covariate, geography (Asia [including Japan] vs rest of world [EU/US]), macrovascular invasion and/or extrahepatic spread (present vs absent), etiology (HCV vs other), and ECOG PS (0 vs 1) as stratification factors. Abbreviations: CI, confidence interval; ECOG PS, European Cooperative Oncology Group performance status; HCV, hepatitis C virus; HR, hazard ratio; IRC, independent review committee; ITT, intent-to-treat; PFS, progression-free survival.

RATIONALE-301: Safety Summary

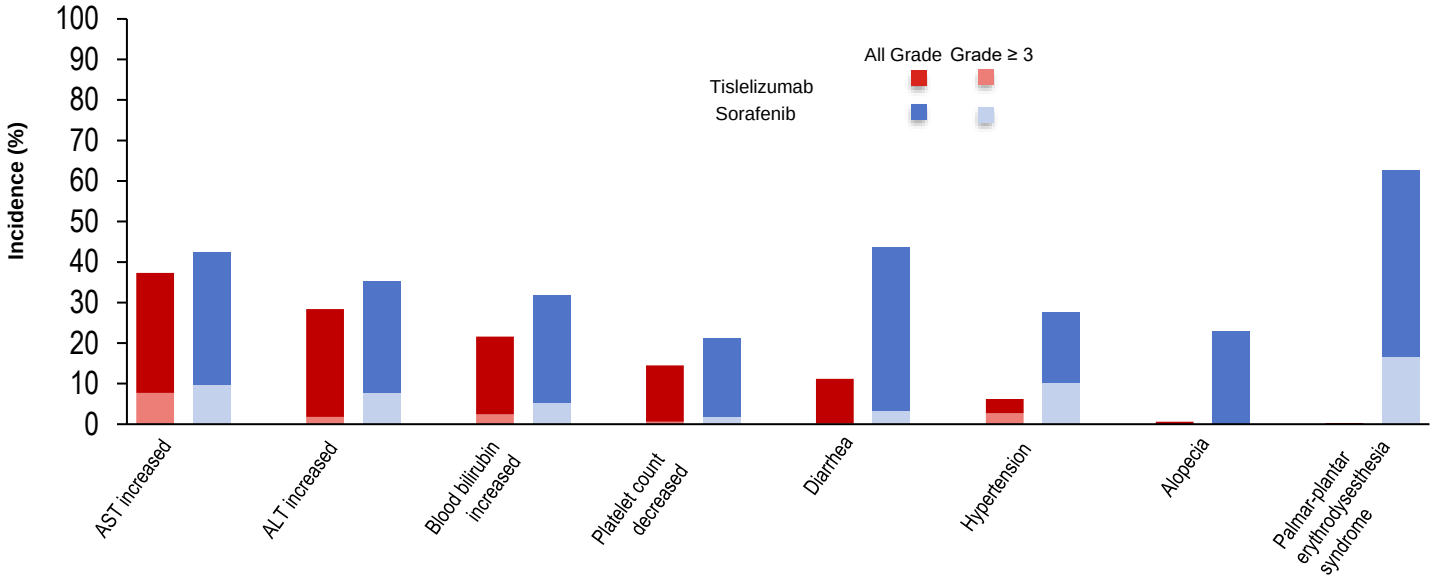
TEAEs and treatment-related TEAEs at grade ≥3 were less frequent with tislelizumab and treatment with tislelizumab led to fewer discontinuations/dose modifications vs sorafenib

Patients	Tislelizumab (n=338)	Sorafenib (n=324)
Safety, n (%)		
Any TEAE	325 (96.2)	324 (100.0)
Treatment-related	259 (76.6)	311 (96.0)
TEAE at ≥grade 3	163 (48.2)	212 (65.4)
Treatment-related	75 (22.2)	173 (53.4)
Serious TEAE	101 (29.9)	91 (28.1)
Treatment-related	40 (11.8)	33 (10.2)
TEAE leading to discontinuation	37 (10.9)	60 (18.5)
Treatment-related	21 (6.2)	33 (10.2)
TEAE leading to drug modification[a]	105 (31.1)	210 (64.8)
Treatment-related	68 (20.1)	187 (57.7)
TEAE leading to death	15 (4.4)	17 (5.2)
Treatment-related	3 (0.9)	2 (0.6)
Immune-mediated AEs	58 (17.2)	10 (3.1)
Immune-mediated AEs treated with systemic corticosteroids	43 (12.7)	10 (3.1)
Immune-mediated AEs in ≥5% of patients		
Hepatitis	18 (5.3)	1 (0.3)
Hypothyroidism	18 (5.3)	0 (0)
Treatment		
Median duration of treatment, months	4.1	2.7

Safety was assessed in the safety population. Data cutoff: July 11, 2022. [a]Drug modification included an interrupted/held or reduced dose. Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event.

RATIONALE-301: TEAEs Reported in ≥20% of Patients

The incidence of TEAEs at any grade and at ≥grade 3 were lower with tislelizumab vs sorafenib; grade ≥3 hypertension and palmar-plantar erythrodysesthesia syndrome were more common with sorafenib



Data cutoff: July 11, 2022. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

Conclusions

RATIONALE-301 met its primary endpoint of OS noninferiority with tislelizumab vs sorafenib in 1L HCC

- Tislelizumab monotherapy demonstrated clinically meaningful OS benefit that was noninferior to sorafenib (mOS: 15.9 months vs 14.1 months, respectively; stratified HR 0.85 [95% CI 0.712, 1.019; *P*=0.0398) in patients with unresectable HCC
- Tislelizumab was also associated with a higher ORR (14.3% vs 5.4%) and more durable responses (mDoR: 36.1 vs 11.0 months) vs sorafenib; mPFS was 2.1 vs 3.4 months with tislelizumab vs sorafenib, respectively
- Fewer patients experienced treatment-related TEAEs, ≥grade 3 TEAEs, treatment-related ≥grade 3 TEAEs, and TEAEs leading to discontinuation or dose modification with tislelizumab vs sorafenib
- The most commonly reported TEAEs were driven by the known toxicities of tislelizumab and sorafenib, and the safety profile of tislelizumab was consistent with that observed in other tumor types
- Single-agent tislelizumab demonstrated a clinically meaningful antitumor benefit vs sorafenib with a favorable and manageable safety profile as a 1L treatment option for patients with unresectable HCC

Abbreviations: 1L, first-line; CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; mDoR, median duration of response; mPFS, median progression-free survival; ORR, objective response rate; OS, overall survival; TEAEs, treatment-emergent adverse events.

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