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

- Eric Assenat has served on the advisory board for AstraZeneca, Ipsen, Roche, and Servier.

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 [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.

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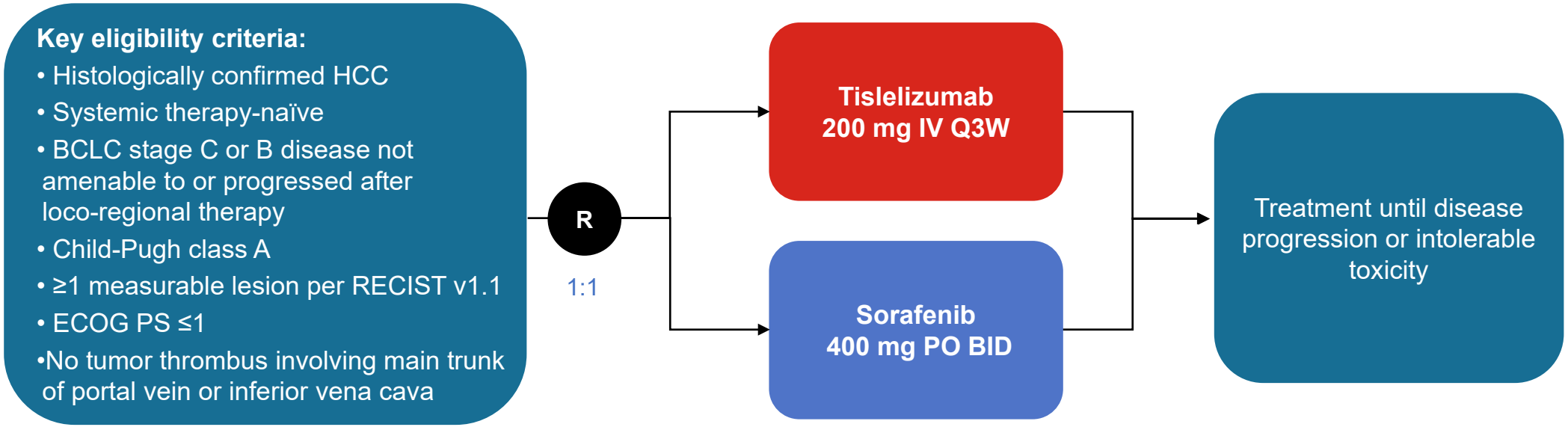
RATIONALE-301: Study Design

- 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 tested with regards to: **(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.

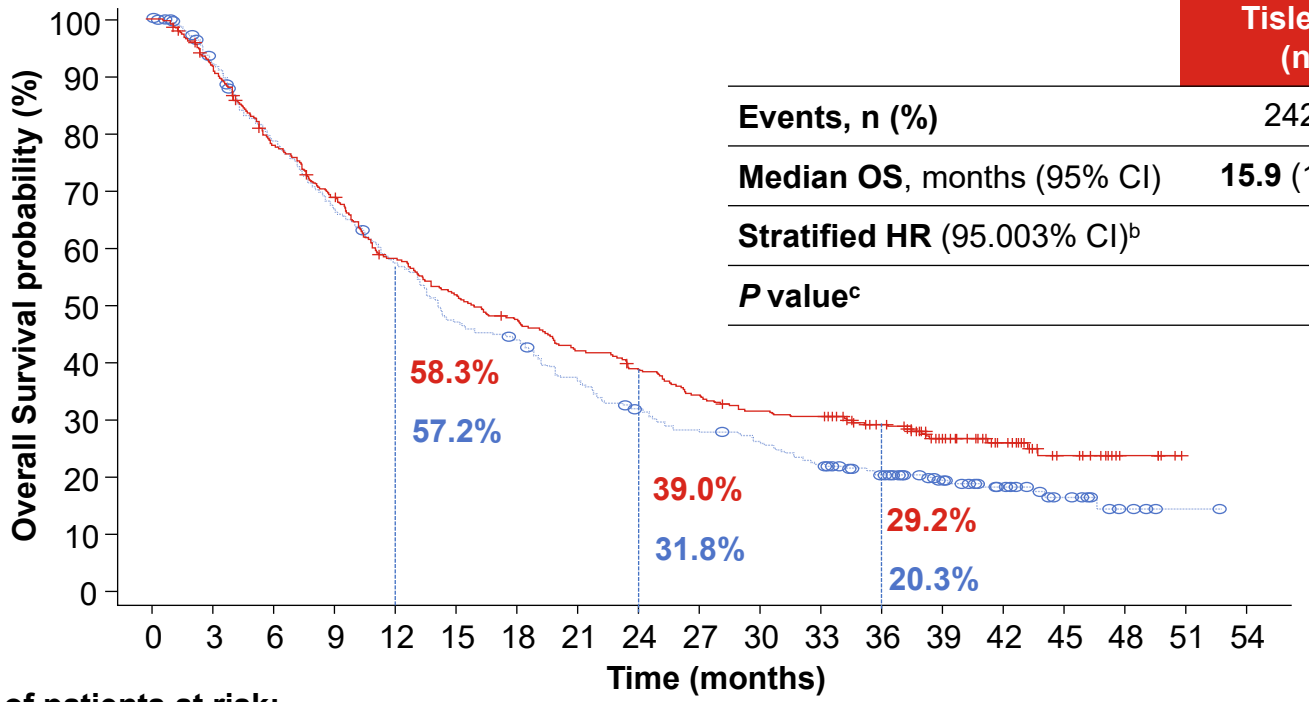
RATIONALE-301: Patient Baseline Characteristics

		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: 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:

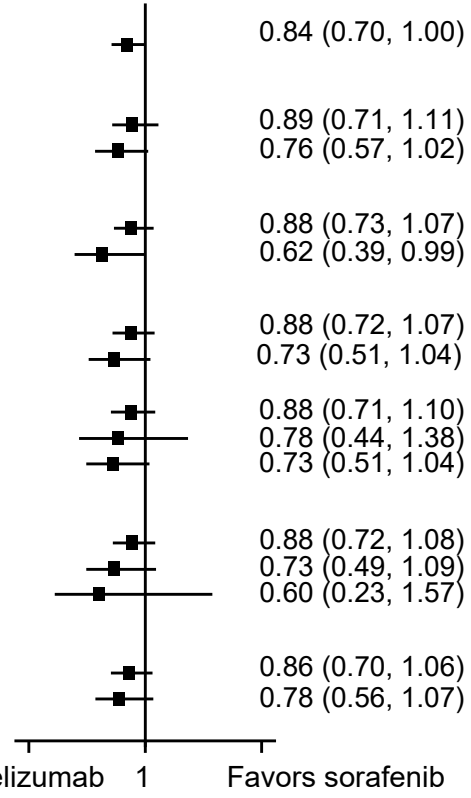
Tislelizumab	342	307	259	228	191	170	155	137	126	111	101	98	77	53	33	18	4	0	0
Sorafenib	332	291	247	208	179	147	136	113	96	84	77	66	52	39	29	13	4	1	0

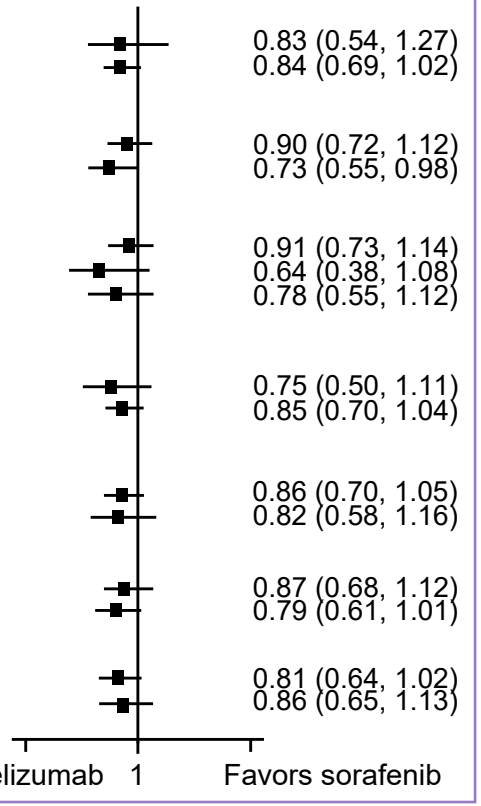
Data cutoff: July 11, 2022. OS was assessed in the ITT population. [a]Prespecified boundary of NI: upper bound of 95.003% CI of stratified HR <1.08; pre-specified boundary of superiority: one-sided *P* value <0.0223 (approximate HR <0.8352). [b]HR was based on a Cox proportional hazard model including 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 (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)
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 PS			
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)



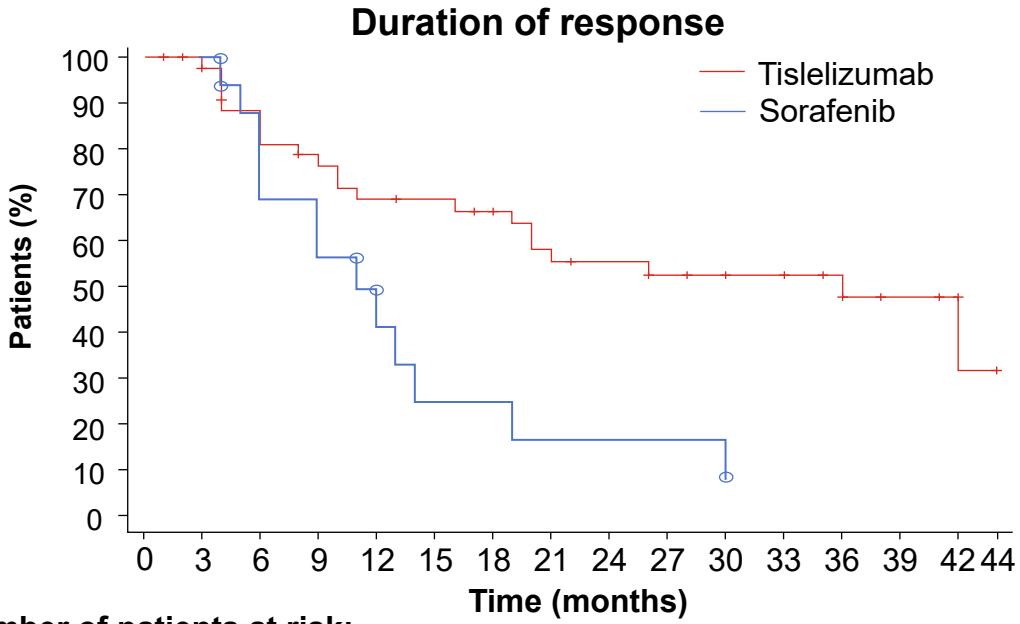


Data cutoff: July 11, 2022. [a]All subgroups were predefined.
Abbreviations: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; ECOG PS, European Cooperative Oncology Group performance status; EHS, extrahepatic spread; HR, hazard ratio; MVI, macrovascular invasion; OS, overall survival.

RATIONALE-301: Objective Response Rate by IRC

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

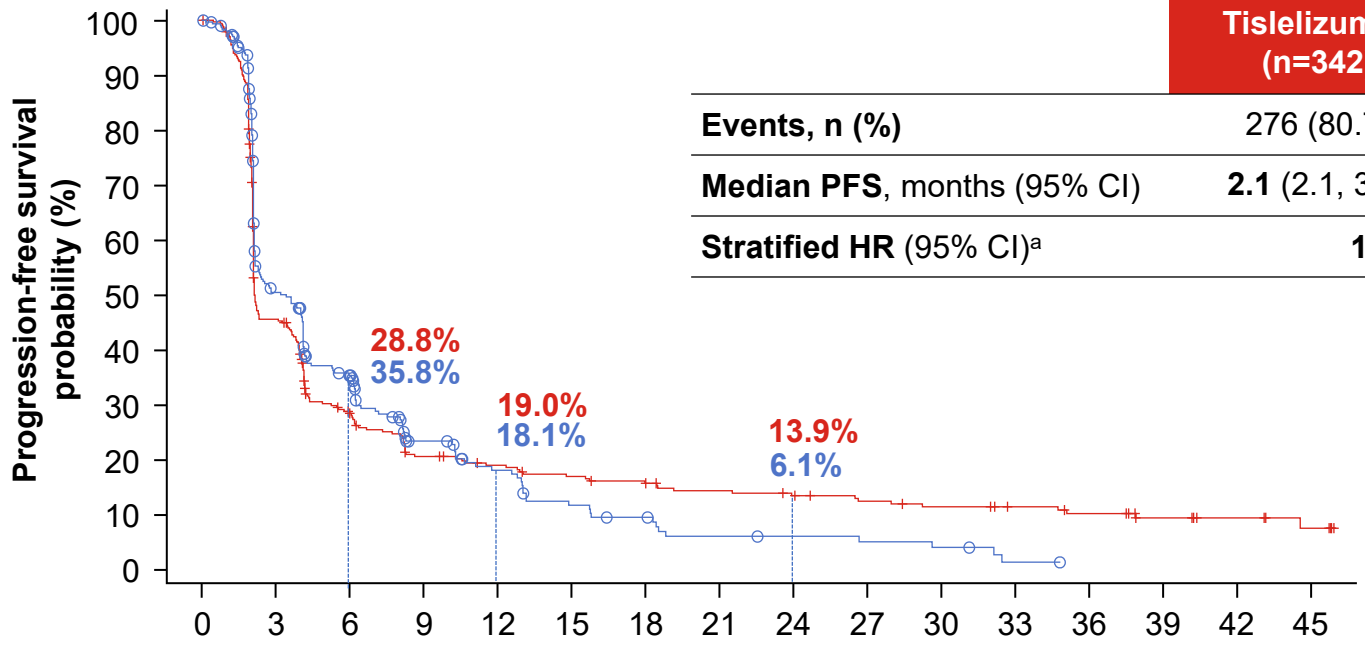
	Tislelizumab (n=342)	Sorafenib (n=332)
ORR, n (%) [95% CI][a]	**49 (14.3) [10.8, 18.5]**	**18 (5.4) [3.2, 8.4]**
Best overall response, n (%)[a]		
CR	10 (2.9)	1 (0.3)
PR	39 (11.4)	17 (5.1)
SD	94 (27.5)	139 (41.9)
PD	169 (49.4)	121 (36.4)
Undetermined[b]	22 (6.4)	44 (13.3)
Non-CR/non-PD[c]	8 (2.3)	10 (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



	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)	

Number of patients at risk:

Tislelizumab	342	145	79	54	47	41	38	32	30	25	22	19	16	11	7	4
Sorafenib	332	125	80	38	26	17	12	7	6	5	4	1	0	0	0	0

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

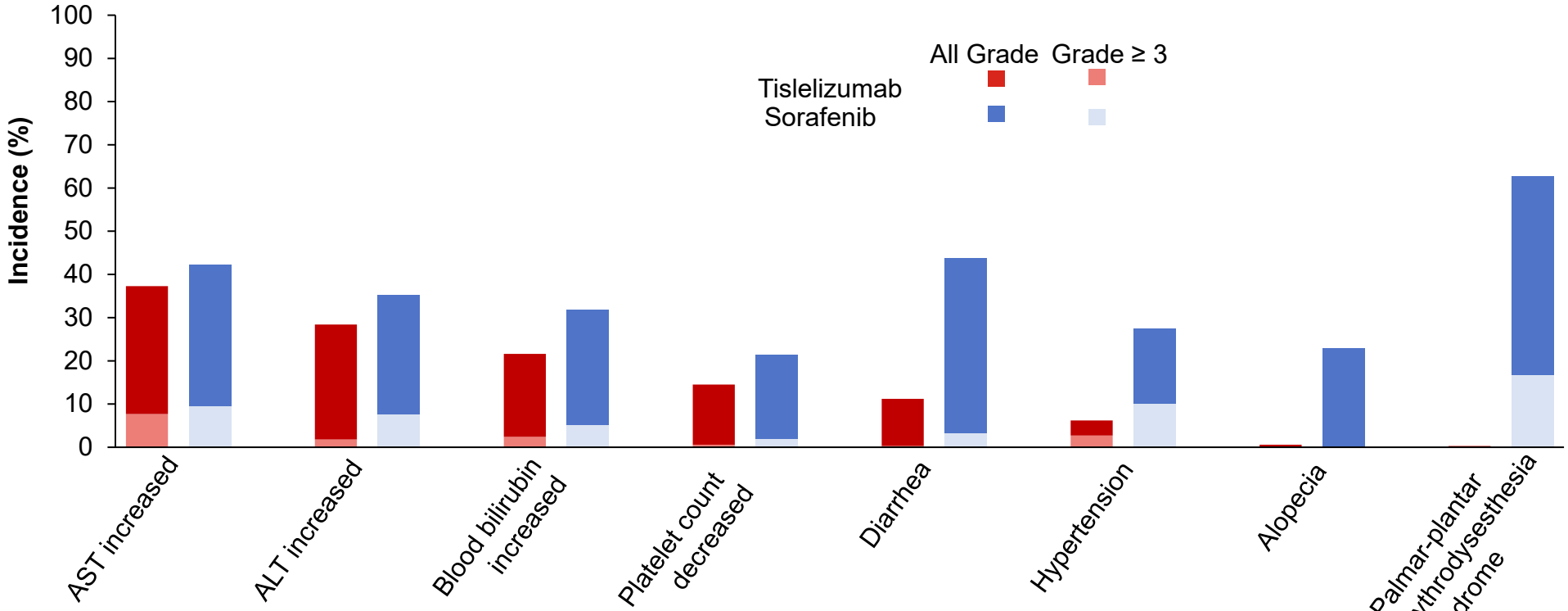
- **TEAEs and treatment-related TEAEs at grade ≥3 were less frequent with tislelizumab and treatment with tislelizumab led to fewer discontinuations/dose modifications vs sorafenib**

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	62 (18.3)	10 (3.1)
Immune-mediated AEs treated with systemic corticosteroids	47 (13.9)	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: 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*=.0398), higher ORR (14.3% vs 5.4%), more durable responses (mDoR: 36.1 vs 11.0 months), and shorter mPFS (2.1 vs 3.4 months) vs sorafenib as 1L treatment in patients with unresectable HCC**

- **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 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**

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