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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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Disclosures

- ***AV**: AstraZeneca, Amgen, BeiGene, Ltd., Böhringer Mannheim, BMS, BTG, Daiichi-Sankyo, Eisai, GSK, Imaging Equipment Ltd (AAA), Incyte, Ipsen, Jiangsu Hengrui, MSD, Pierre-Fabre, Roche, Servier, Sirtex, Taiho, and Terumo*
- ***MK**: AbbVie, Bayer, Chugai, EA Pharma, Eisai, Eli Lilly, GE Healthcare, Gilead Sciences, MSD, Otsuka, Sumitomo Dainippon Pharma, Taiho, and Takeda*
- ***SQ**: no conflicts of interest*
- ***YC**, **SL,** and **FB** are employees of BeiGene, Ltd.*
- ***RA** is an employee of BeiGene, Ltd., and holds stock in AstraZeneca, BeiGene, Ltd., Syndax, and Takeda*
- ***RSF**: AstraZeneca, BMS, Bayer, CStone, Jiangsu Hengrui, Eisai, Eli Lilly, Exelixis, Merck, Pfizer, and Roche*
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Background

- HCC is one of the most commonly diagnosed cancers globally and the proportion of patients affected aged ≥65 is increasing each year[1,2]
- Tislelizumab, a monoclonal antibody with high affinity and binding specificity for PD-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 [HR=0.85, 95% CI: 0.71, 1.02]) and a favorable safety profile in the first-line treatment of patients with unresectable HCC[5]

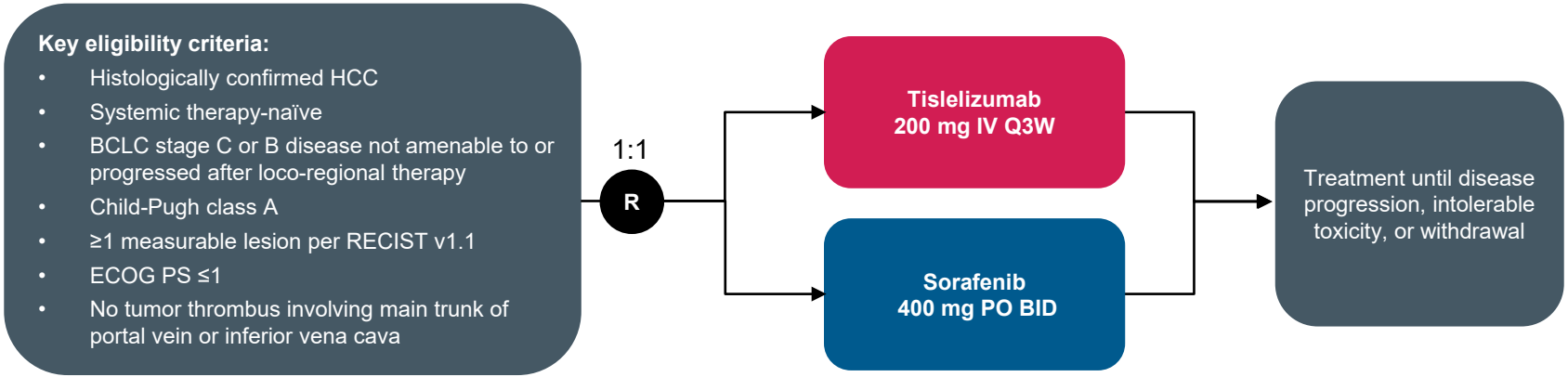
Here, we present post-hoc analysis results from the subgroup of patients aged ≥65 years in RATIONALE-301

Abbreviations: CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; OS, overall survival; PD-1, programmed cell death protein 1.

1. Brunot A, et al. *J Hepatocell Carcinoma.* 2016;3:9-18; 2. Zhang Q-Q, et al. *Front Oncol.* 2020;10:479; 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. *Ann Oncol.* 2022;33(suppl 7):S808-S869.

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 [EU/US])

[a]Includes HBV. Abbreviations: BCLC, Barcelona Clinic Liver Cancer; BID, twice daily; BIRC, blinded independent review committee; 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, Response Evaluation Criteria In Solid Tumors; US, United States, v, version.

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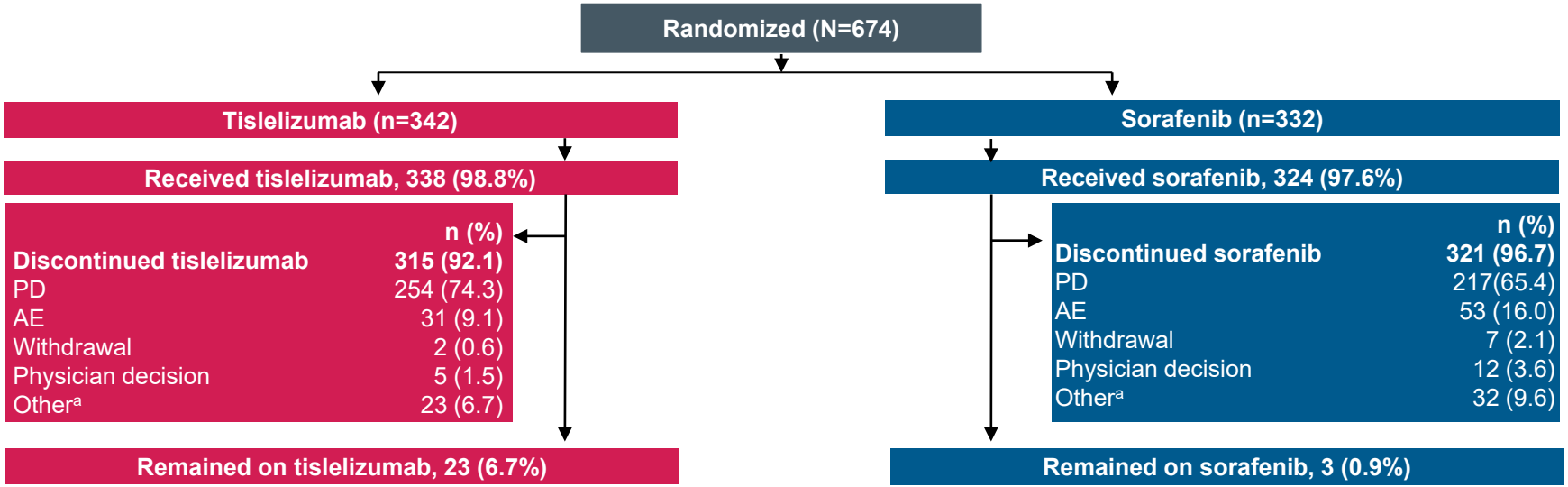
Patient Disposition



- Minimum study follow-up time[b] was 38.9 months (tislelizumab arm) vs 39.9 months (sorafenib arm)
- 255 (37.8%) of the 674 randomized patients were in the ≥65 years subgroup (tislelizumab: n=134, sorafenib: n=121)

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 cut-off and the date of last patient randomized. Abbreviations: AE, adverse event; PD, progressive disease.

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Baseline Characteristics

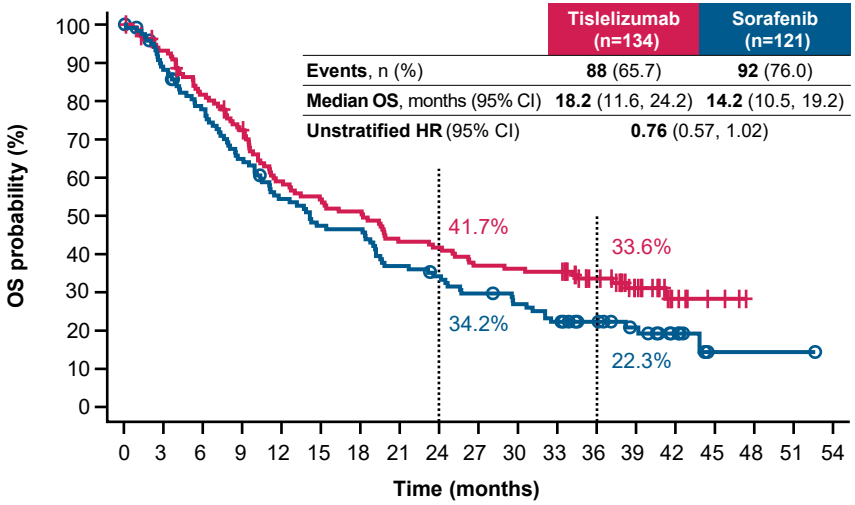
	≥65 Years Subgroup			Overall Population[1]
	Tislelizumab (n=134)	Sorafenib (n=121)	Total (N=255)	Total (N=674)
Median age, years (range)	71.0 (65.0, 86.0)	71.0 (65.0, 86.0)	71.0 (65.0, 86.0)	61.0 (23.0, 86.0)
Male sex, n (%)	107 (79.9)	103 (85.1)	210 (82.4)	570 (84.6)
Geographic region, n (%)				
Asia (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, n (%)				
A	133 (99.3)	121 (100.0)	254 (99.6)	672 (99.7)
B	1 (0.7)	0 (0.0)	1 (0.4)	1 (0.1)[a]
BCLC Stage, n (%)				
B	43 (32.1)	42 (34.7)	85 (33.3)	150 (22.3)
C	91 (67.9)	79 (65.3)	170 (66.7)	524 (77.7)
ECOG PS, n (%)				
0	83 (61.9)	73 (60.3)	156 (61.2)	364 (54.0)
1	51 (38.1)	48 (39.7)	99 (38.8)	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 were missing for one patient. 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.

1. Qin S, et al. *Ann Oncol.* 2022;33(suppl 7):S808-S869.

Overall Survival (ITT Analysis Set)

≥65 Years Subgroup

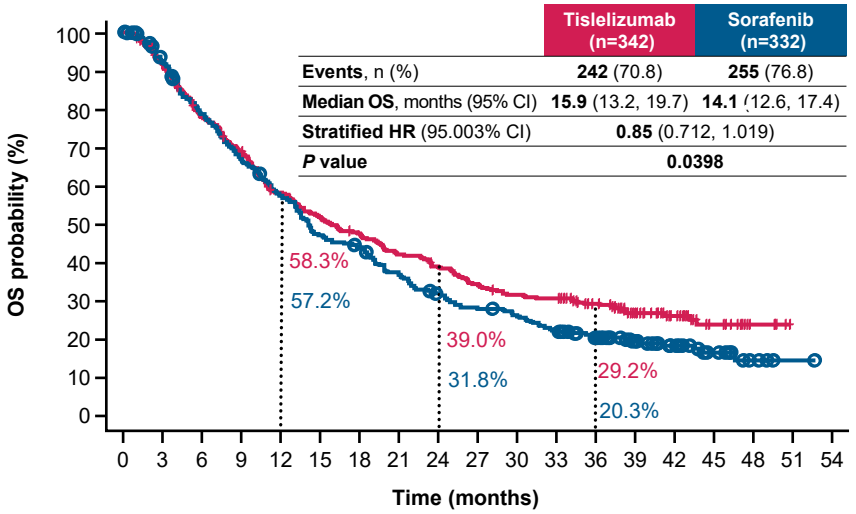


	Tislelizumab (n=134)	Sorafenib (n=121)
Events, n (%)	**88** (65.7)	**92** (76.0)
Median OS, months (95% CI)	**18.2** (11.6, 24.2)	**14.2** (10.5, 19.2)
Unstratified HR (95% CI)	**0.76** (0.57, 1.02)	

Number of patients at risk:

Tislelizumab	134	122	106	93	75	69	65	55	53	47	46	45	32	20	7	3	0	0	0
Sorafenib	121	104	90	75	62	54	53	42	38	33	29	24	19	13	7	1	1	1	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** (0.712, 1.019)	
***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

- **Patients in the ≥65 years subgroup had a numerically longer median OS with tislelizumab vs sorafenib**
- **Median OS in the tislelizumab arm was longer in the ≥65 years subgroup (18.2 months) than in the overall population (15.9 months), but similar in the sorafenib group (14.2 months and 14.1 months, respectively)[1]**

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

1. Qin S, et al. *Ann Oncol.* 2022;33(suppl 7):S808-S869.

Secondary Efficacy Endpoints (ITT Analysis Set)

	≥65 Years Subgroup		Overall Population[1]	
Outcomes	**Tislelizumab (n=134)**	**Sorafenib (n=121)**	**Tislelizumab (n=342)**	**Sorafenib (n=332)**
Median PFS,[a] months (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 DoR,[a] months (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; DoR, duration of response; ITT, intent to treat; NE, not evaluable; ORR, objective response rate; PFS, progression-free survival.

1. Qin S, et al. *Ann Oncol.* 2022;33(suppl 7):S808-S869.

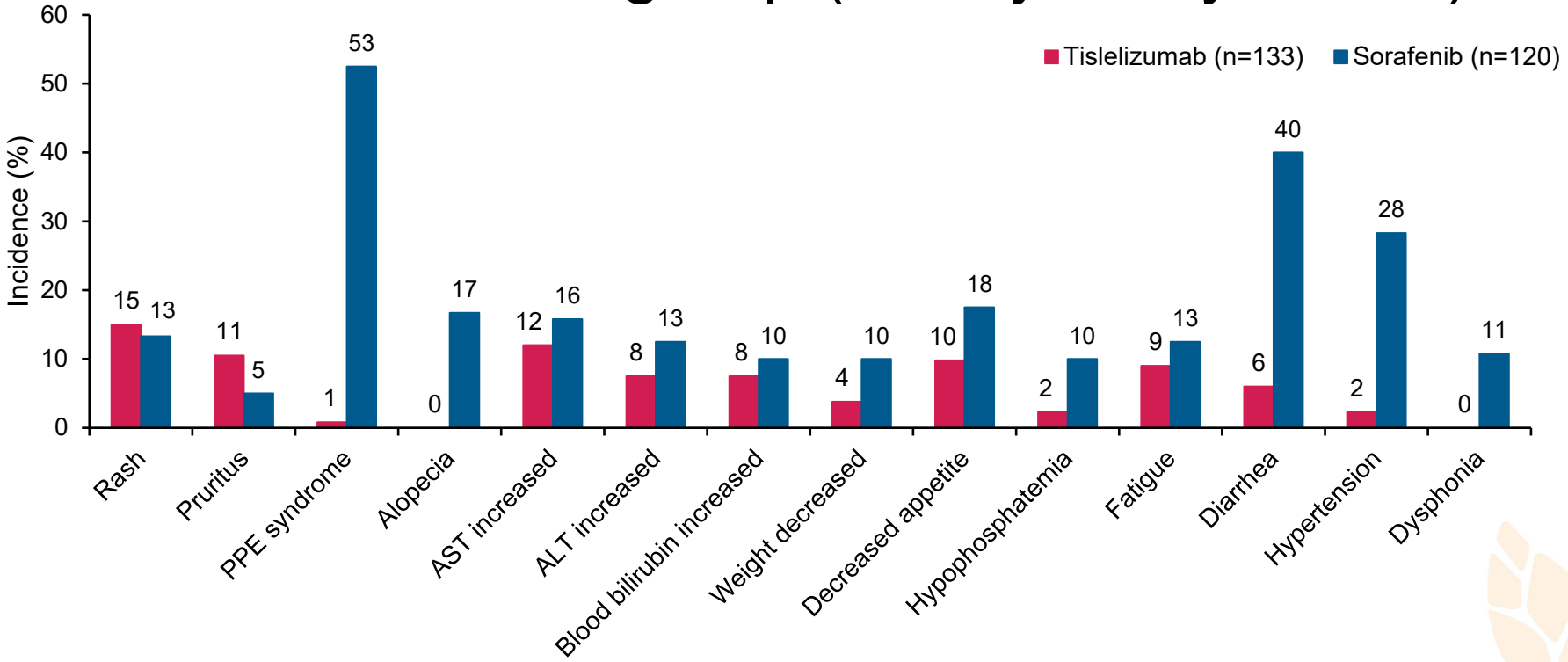
Safety Summary (Safety Analysis Set)

Patients, n (%)	≥65 Years Subgroup		Overall Population[1]	
	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 study drug modification	45 (33.8)	83 (69.2)	105 (31.1)	210 (64.8)
Leading to dose held/interrupted	45 (33.8)	70 (58.3)	105 (31.1)	177 (54.6)
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

1. Qin S, et al. *Ann Oncol.* 2022;33(suppl 7):S808-S869.

Most Common TRAEs in ≥10% of Patients in ≥65 Years Subgroup (Safety Analysis Set)



Data cutoff: July 11, 2022. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; PPE, palmar-plantar erythrodysesthesia; TRAE, treatment-related treatment-emergent adverse event.

Conclusions

Compared with the overall population, patients aged ≥65 years had less advanced disease (lower percentage of patients with BCLC Stage C, extrahepatic spread, and distant metastases); more satisfactory performance status, and fewer viral infections.

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

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

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; ORR, objective response rate; OS, overall survival.

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Thank you

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