ESMO WORLD CONGRESS ON Gastrointestinal Cancer

Results from a global Phase 2 study of tislelizumab, an investigational PD-1 antibody, in patients with previously treated advanced hepatocellular carcinoma

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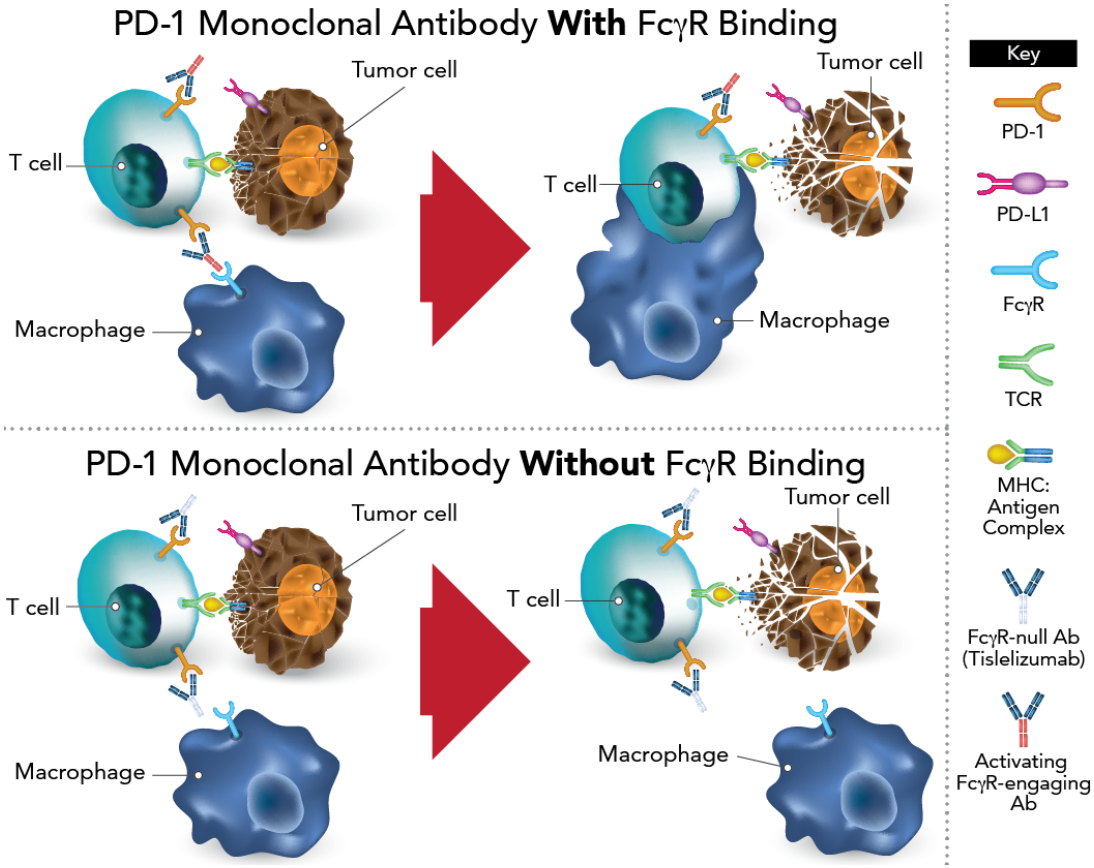
Disclosure of Conflict of Interest

- Personal fees from BeiGene, Berry Genomics, Celgene, CytomX, Eisai, Eli Lilly, Exelixis, Flatiron, Genentech/Roche, Genoscience, Helio, Incyte, Ipsen, Legend Biotech, Loxo, Merck, MINA, QED, Redhill, Rafael, Silenseed, Sillajen, Sobi, Surface Oncology, Therabionics, Twoxar, Vector and Yiviva
- Grants from Arcus, Agios, Astra Zeneca, Bayer, BioNtech, BMS, Celgene, Flatiron, Genentech/Roche, Genoscience, Incyte, Polaris, Puma, QED, Sillajen and Yiviva
- Patent in ‘articles and methods for preventing and treating dermatologic adverse events’, identified by International Patent Application No. PCT/US2014/031545 filed on March 24, 2014, and priority application Serial No.: 61/804,907; Filed: March 25, 2013

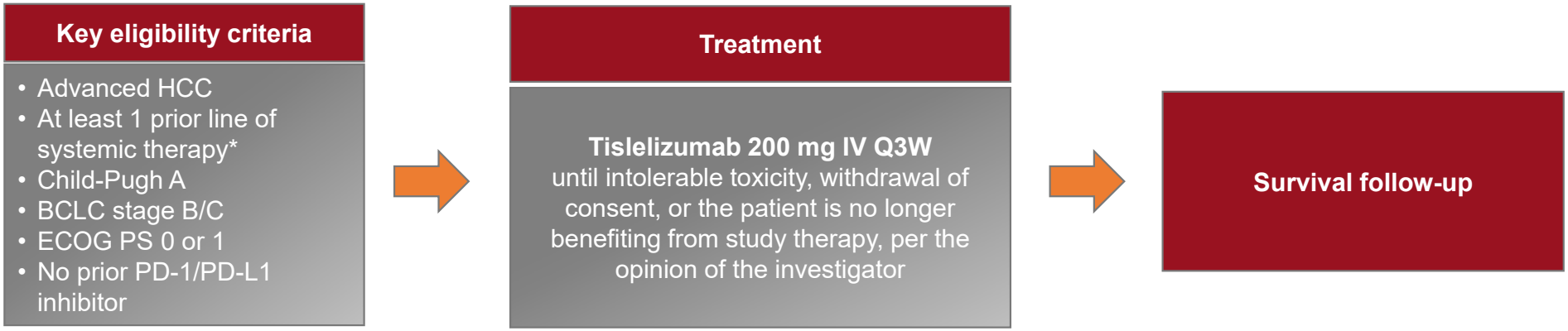
Tislelizumab: A Novel Monoclonal Anti-PD-1 Antibody

- Tislelizumab is an anti-PD-1 monoclonal antibody with high affinity and specificity for PD-1, engineered to minimize binding to FcγR on macrophages to limit antibody-dependent phagocytosis, a mechanism of T-cell clearance and a potential mechanism of resistance to anti-PD-1 therapy[1]
- Single-agent tislelizumab (200 mg) Q3W has been found to be well tolerated, and has shown antitumor activity in patients with advanced solid tumors, including HCC[2,3]



1. Zhang T, et al. *Cancer Immunol Immunother.* 2018;67(7):1079-1090; 2. Desai J, et al. *J Immunother Cancer* 2020;8:e000453; 3. Shen L, et al. *J Immunother Cancer* 2020;8:e000437
Ab, antibody; FcγR, Fc gamma receptor; HCC, hepatocellular carcinoma; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; Q3W, every 3 weeks; TCR, T-cell receptor

RATIONALE 208: A Global Single-Arm Phase 2 Study of Tislelizumab for HCC



Radiological assessments were performed every 6 weeks for the first 18 weeks and then every 9 weeks thereafter

***At least 100 patients were to be enrolled who had 1 line of prior systemic therapy; at least 100 patients were to be enrolled who had ≥2 lines of prior therapy**

- Primary endpoint was ORR by IRC per RECIST v1.1
- Secondary endpoints included:
  - DOR, PFS, DCR, and CBR assessed by IRC, and OS
  - ORR, DOR, PFS, DCR and CBR assessed by investigators
  - The safety/tolerability profile of tislelizumab

BCLC, Barcelona Clinic Liver Cancer; CBR, clinical benefit rate; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance score; HCC, hepatocellular carcinoma; IRC, independent review committee; IV, intravenous; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors

Demographics and Baseline Disease Characteristics

		Overall (N=249)	1 prior line (n=138)	≥2 prior lines (n=111)
Median Age, years (range)		62 (28, 90)	63.5 (28, 90)	60 (28, 82)
Male, n (%)		217 (87.1)	121 (87.7)	96 (86.5)
Region, n (%)	Mainland China & Taiwan	122 (49.0)	72 (52.2)	50 (45.0)
	Europe	127 (51.0)	66 (47.8)	61 (55.0)
ECOG PS, n (%)	0	129 (51.8)	70 (50.7)	59 (53.2)
	1	120 (48.2)	68 (49.3)	52 (46.8)
BCLC Staging, n (%)	B	24 (9.6)	14 (10.1)	10 (9.0)
	C	225 (90.4)	124 (89.9)	101 (91.0)
Child-Pugh, n (%)	A	248 (99.6)[a]	138 (100)	110 (99.1)[a]
Extrahepatic Spread, n (%)		200 (80.3)	113 (81.9)	87 (78.4)
Macrovascular Invasion, n (%)		45 (18.1)	22 (15.9)	23 (20.7)
PD-L1 Expression, n (%)[b]	Positive (TC ≥1%)	15 (6.0)	10 (7.2)	5 (4.5)
	Negative (TC 0%)	143 (57.4)	84 (60.9)	59 (53.2)
	Unknown	91 (36.5)	44 (31.9)	47 (42.3)
Baseline α-fetoprotein, μg/L, n (%)	>400	112 (45.0)[c]	53 (38.4)[c]	59 (53.2)
HCC Etiology, n (%)	Hepatitis B	128 (51.4)[d]	72 (52.2)	56 (50.5)
	Hepatitis C	36 (14.5)	21 (15.2)	15 (13.5)
	Non-viral	90 (36.1)	46 (33.3)	44 (39.6)
Median Duration of Study Follow-up, months (range)		12.4 (0.1, 21.4)	13.3 (0.1, 21.4)	11.9 (0.7, 20.2)

Data cut-off date is 27 Feb 2020. [a]One patient had Child-Pugh classification B at study entry; [b]PD-L1 expression centrally assessed by immunohistochemistry with the Ventana SP263 assay; [c]α-fetoprotein at baseline missing in one patient; [d]Five patients had hepatitis B/hepatitis C co-infection (n=1, 1 prior line; n=4, ≥2 prior lines)
BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance score; HCC, hepatocellular carcinoma; PD-L1, programmed death ligand 1; TC, tumor cells

Antitumor Activity of Tislelizumab (IRC)

	Overall (N=249)	1 prior line (n=138)	≥2 prior lines (n=111)
ORR (CR+PR), % (95% CI)	**13.3 (9.3, 18.1)**	**13.8 (8.5, 20.7)**	**12.6 (7.1, 20.3)**
CR, n (%)	3 (1.2)	2 (1.4)	1 (0.9)
PR, n (%)	30 (12.0)	17 (12.3)	13 (11.7)
SD, n (%)	97 (39.0)	52 (37.7)	45 (40.5)
PD, n (%)	107 (43.0)	60 (43.5)	47 (42.3)
Not assessable, n (%)[a]	10 (4.0)	5 (3.6)	5 (4.5)
DCR (CR+PR+SD), % (95% CI)	**53.0 (46.6, 59.3)**	**52.9 (44.2, 61.5)**	**53.2 (43.5, 62.7)**
CBR (CR+PR+SD ≥24 weeks), % (95% CI)	**24.1 (18.9, 29.9)**	**26.1 (19.0, 34.2)**	**21.6 (14.4, 30.4)**
Response duration ≥12 months, % (95% CI)[b]	**79.2 (59.3, 90.2)**	**82.6 (55.2, 94.1)**	**73.0 (35.3, 90.9)**

- Antitumor activity assessed by investigator was similar to IRC

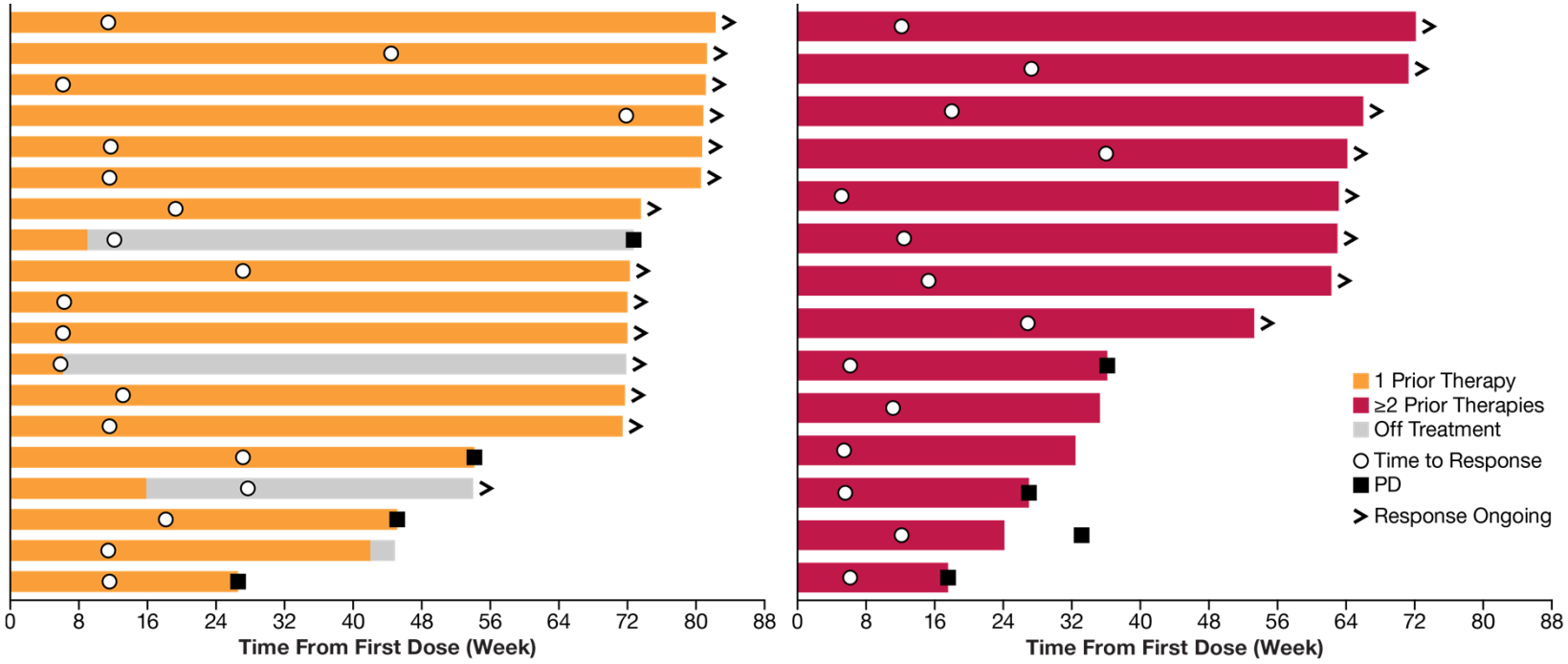
Data cut-off date is 27 Feb 2020

[a]No post-baseline assessment or an unevaluable post-baseline assessment

[b]Based on Kaplan-Meier estimation assessed in patients that achieved a CR or PR

CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DCR, disease control rate; IRC, independent review committee; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease

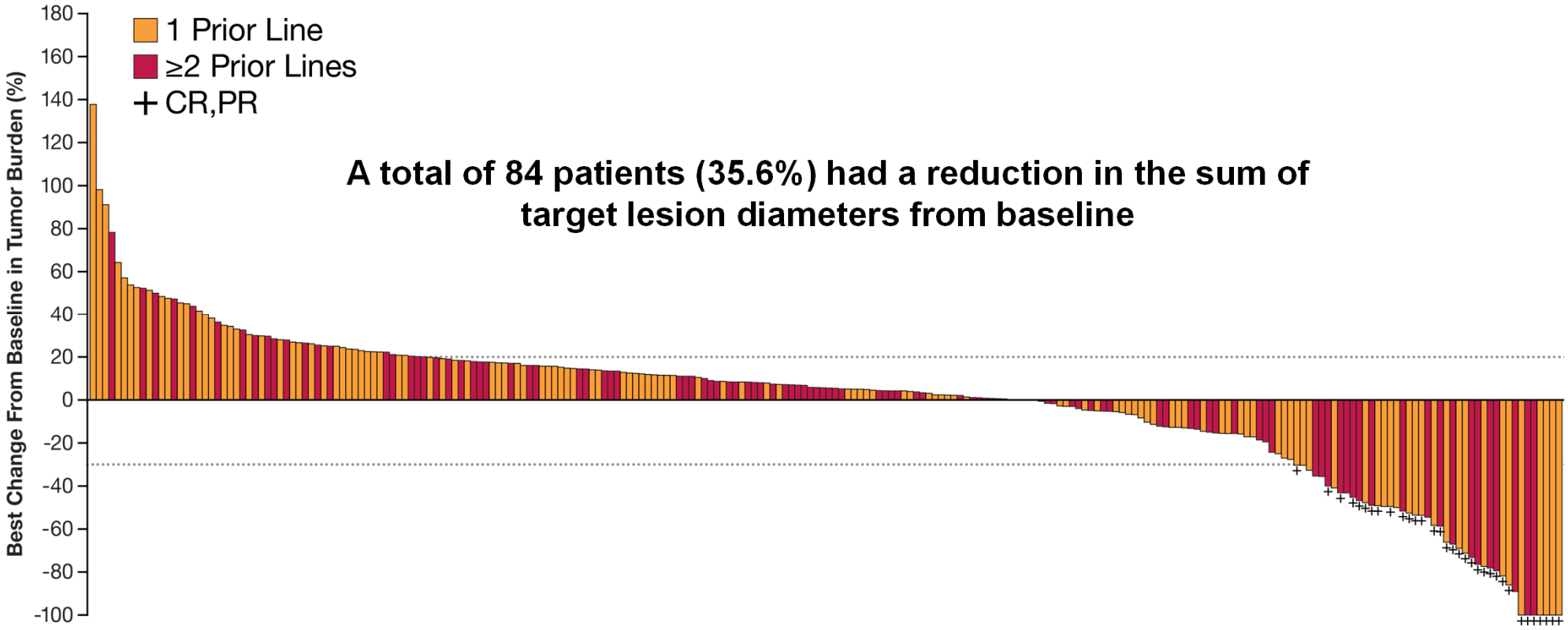
Duration of Response (IRC)



- At data cut-off, 22 (66.7%) of the 33 responses were ongoing
- Median duration of response was not reached despite a median response follow-up of 11.7 months
- The event-free rate at 12 months was 79.2% (95% CI: 59.3%, 90.2%)

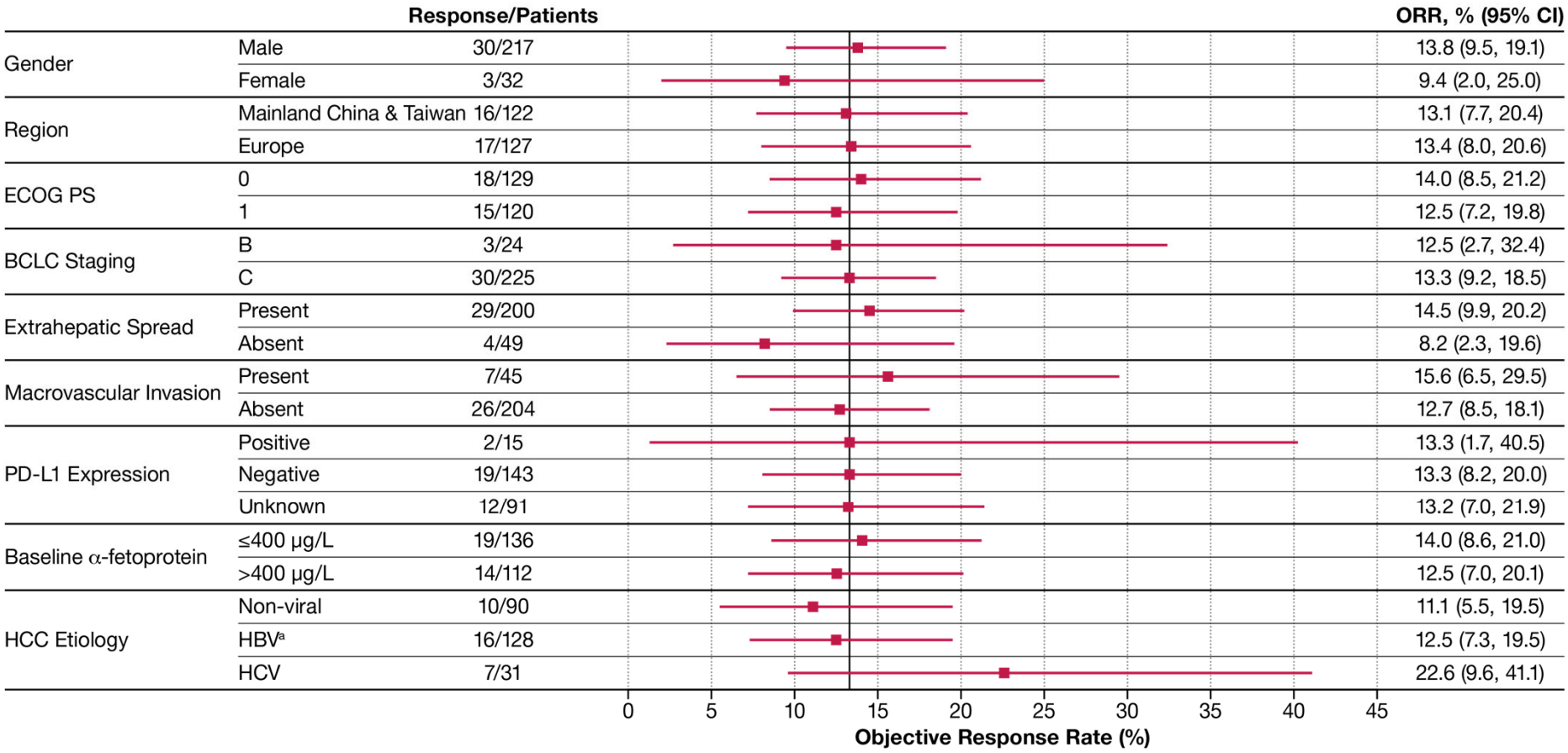
Data cut-off date is 27 Feb 2020
Each bar represents an individual patient
CI, confidence interval; IRC, independent review committee; PD, progressive disease

Best Percent Change From Baseline in Tumor Burden (IRC)



Data cut-off date is 27 Feb 2020
CR, complete response; IRC, independent review committee; PR, partial response

Subgroup Analysis of ORR per RECIST v1.1

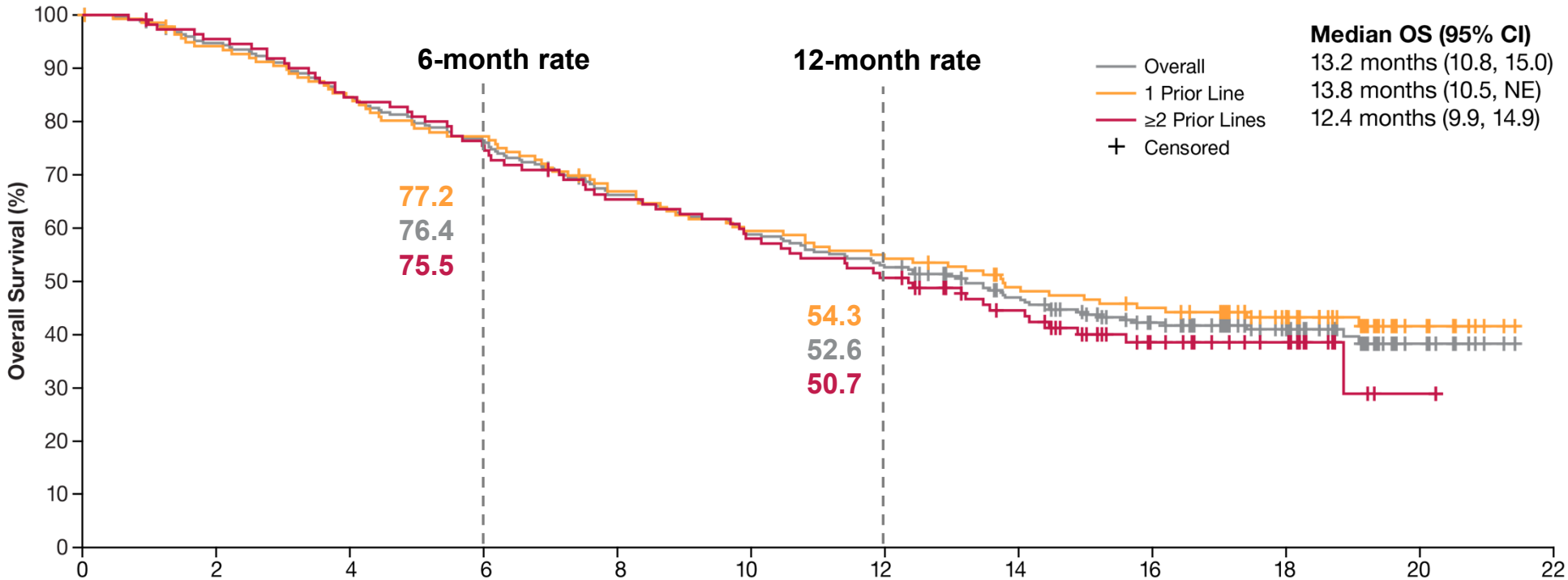


Data cut-off date is 27 Feb 2020

[a]Five patients had hepatitis B/hepatitis C co-infection

BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B; HCC, hepatocellular carcinoma; HCV, hepatitis C; PD-L1, programmed death ligand 1; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumours

Overall Survival



Patients at Risk (n)

Overall	249	233	208	188	161	143	128	104	79	55	12	0
1 Prior Line	138	128	115	105	90	80	73	63	57	41	11	0
≥2 Prior Lines	111	105	93	83	71	63	55	41	22	14	1	0

Data cut-off date is 27 Feb 2020
CI, confidence interval; OS, overall survival; NE, not estimable

Progression-Free Survival (IRC)

	Overall (N=249)	1 prior line (n=138)	≥2 prior lines (n=111)
Events, n (%)	**198 (79.5)**	**111 (80.4)**	**87 (78.4)**
Progressive disease	187 (75.1)	103 (74.6)	84 (75.7)
Death	11 (4.4)	8 (5.8)	3 (2.7)
Patients censored, n (%)	**51 (20.5)**	**27 (19.6)**	**24 (21.6)**
Median PFS (95% CI), months[a]	**2.7 (1.4, 2.8)**	**2.6 (1.4, 2.8)**	**2.7 (1.4, 2.8)**
Median follow-up (95% CI), months[b]	**16.4 (14.3, 16.6)**	**16.6 (16.4, 18.5)**	**12.3 (7.5, 14.5)**

- PFS assessed by investigator was similar to IRC

Data cut-off date is 27 Feb 2020
[a]Medians were estimated by Kaplan-Meier method with their 95% CIs estimated using the method of Brookmeyer and Crowley; [b]Follow-up was calculated by reverse Kaplan-Meier method
CI, confidence interval; IRC, independent review committee; PFS, progression-free survival

Summary of Adverse Events

	Overall (N=249)	1 prior line (n=138)	≥2 prior lines (n=111)
Treatment-emergent adverse events, n (%)	**236 (94.8)**	**130 (94.2)**	**106 (95.5)**
Grade ≥3	121 (48.6)	69 (50.0)	52 (46.8)
Serious	90 (36.1)	52 (37.7)	38 (34.2)
Led to discontinuation	26 (10.4)	16 (11.6)	10 (9.0)
Led to death[a]	2 (0.8)	0 (0.0)	2 (1.8)
Led to dose delay	77 (30.9)	44 (31.9)	33 (29.7)
Treatment-related adverse events, n (%)	**158 (63.5)**	**91 (65.9)**	**67 (60.4)**
Grade ≥3	36 (14.5)	24 (17.4)	12 (10.8)
Serious	17 (6.8)	13 (9.4)	4 (3.6)
Led to discontinuation	12 (4.8)	9 (6.5)	3 (2.7)
Led to death[a]	0 (0.0)	0 (0.0)	0 (0.0)
Led to dose delay	43 (17.3)	25 (18.1)	18 (16.2)

Data cut-off date is 27 Feb 2020
[a]Death events due to disease progression were excluded
AE, adverse event

Most Common Treatment-Related Adverse Events

TRAEs occurring in ≥5% of overall population

	Overall (N=249)		1 prior line (n=138)		≥2 prior lines (n=111)	
	All grades	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Increased AST	32 (12.9)	7 (2.8)	18 (13.0)	5 (3.6)	14 (12.6)	2 (1.8)
Increased ALT	23 (9.2)	3 (1.2)	13 (9.4)	2 (1.4)	10 (9.0)	1 (0.9)
Asthenia	19 (7.6)	0 (0.0)	9 (6.5)	0 (0.0)	10 (9.0)	0 (0.0)
Hypothyroidism	19 (7.6)	0 (0.0)	9 (6.5)	0 (0.0)	10 (9.0)	0 (0.0)
Increased blood bilirubin	17 (6.8)	1 (0.4)	12 (8.7)	1 (0.7)	5 (4.5)	0 (0.0)
Pruritus	17 (6.8)	0 (0.0)	10 (7.2)	0 (0.0)	7 (6.3)	0 (0.0)
Rash[a]	15 (6.0)	1 (0.4)	8 (5.8)	0 (0.0)	7 (6.3)	1 (0.9)
Diarrhea	14 (5.6)	1 (0.4)	6 (4.3)	1 (0.7)	8 (7.2)	0 (0.0)
Pyrexia	14 (5.6)	0 (0.0)	7 (5.1)	0 (0.0)	7 (6.3)	0 (0.0)
Increased blood creatine phosphokinase MB	13 (5.2)	0 (0.0)	7 (5.1)	0 (0.0)	6 (5.4)	0 (0.0)
Fatigue	13 (5.2)	2 (0.8)	7 (5.1)	1 (0.7)	6 (5.4)	1 (0.9)

Data cut-off date is 27 Feb 2020
Data presented as n (%)
[a]Includes papular rash
ALT, alanine aminotransferase; AST, aspartate aminotransferase; MB, myocardial band; TRAE, treatment-related adverse event

Conclusions

- Tislelizumab demonstrated encouraging and durable clinical activity in patients with HCC who had received at least one prior systemic therapy
  - Objective response rate per IRC was 13.3%
  - While median DOR was not reached (response follow-up of 11.7 months), 66.7% of patients had ongoing responses at data cut-off, and the 12-month event-free rate was 79.2%
- Median OS was 13.2 months
- Tislelizumab demonstrated consistent response and survival estimates regardless of the number of prior treatment lines, HCC etiology, and region
- Tislelizumab monotherapy was generally well tolerated and no new safety signals were identified
  - Adverse events were consistent with the overall safety profile of tislelizumab observed in previous studies and were generally of low severity
- These results show clinical activity and efficacy of tislelizumab in patients with HCC with a high unmet medical need. This is despite the lack of randomization against a standard of care. A large, global, randomized Phase 3 study comparing tislelizumab with sorafenib as a first-line treatment in adult patients with advanced HCC (NCT03412773) is currently ongoing

DOR, duration of response; HCC, hepatocellular carcinoma; IRC, independent review committee; OS, overall survival

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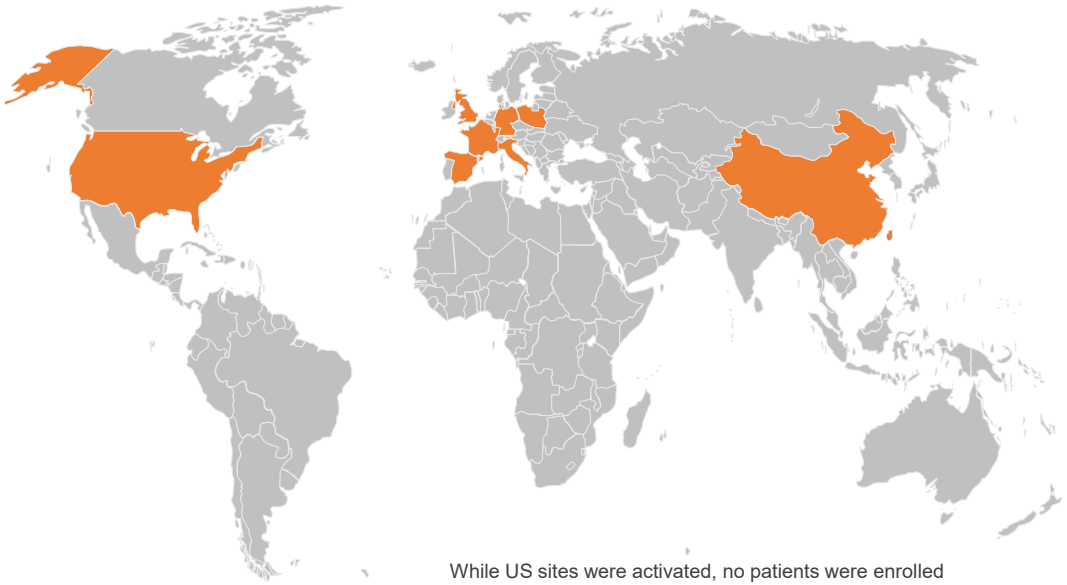

While US sites were activated, no patients were enrolled

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