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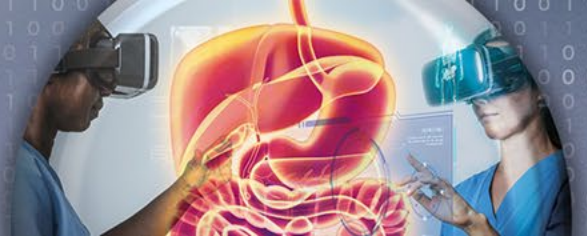

Results from a global Phase 2 study of tislelizumab, an investigational PD-1 antibody, in patients with unresectable hepatocellular carcinoma

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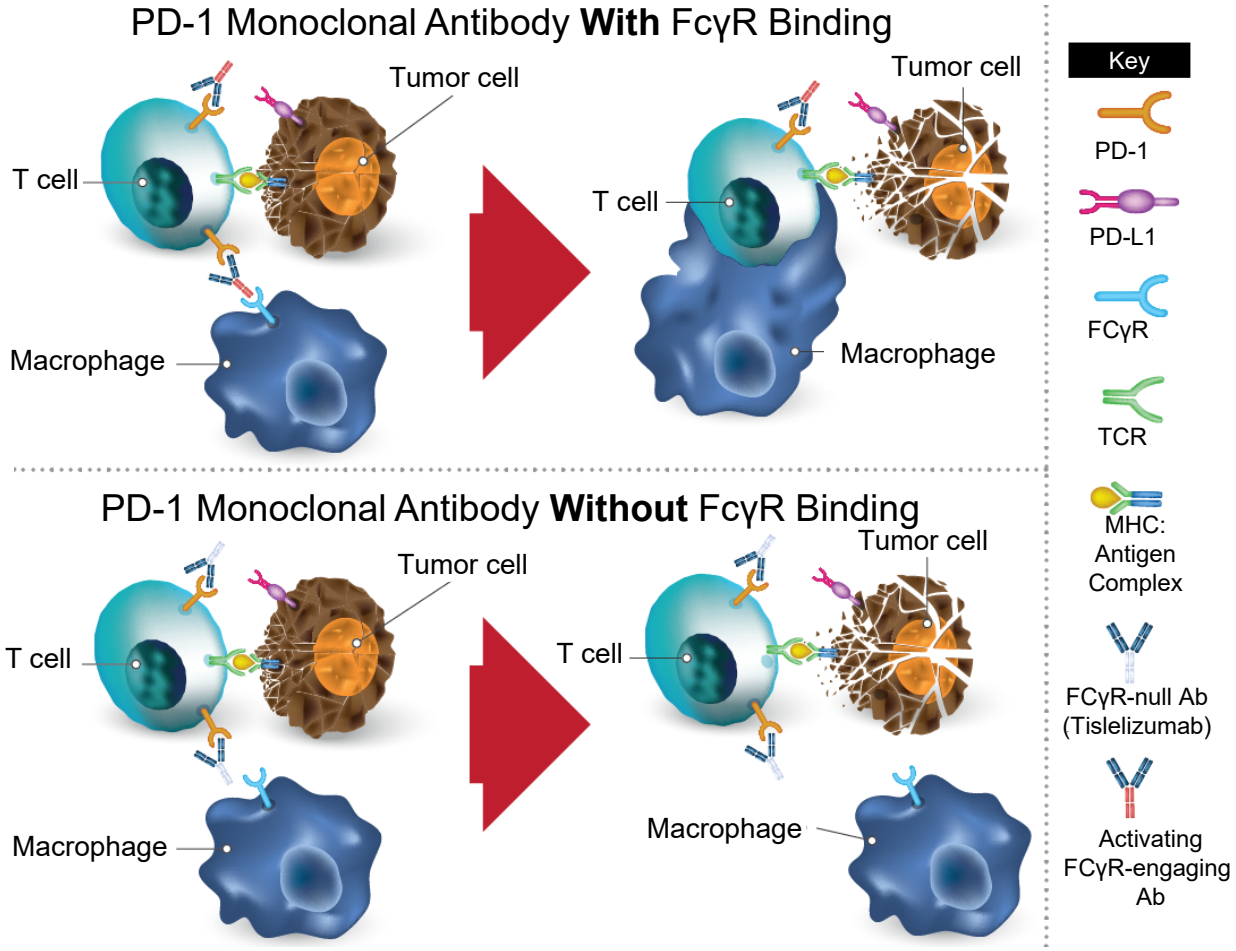
Tislelizumab: A Novel Monoclonal Anti-PD-1 Antibody

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



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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:
Global Single Arm Open-Label Phase 2 Study of Tislelizumab for Advanced HCC

Key eligibility criteria

- Advanced HCC
- ≥1 prior line of systemic therapy*
- Child-Pugh A
- BCLC stage B/C
- ECOG PS 0 or 1
- No prior PD-1/PD-L1 inhibitor

Treatment

Tislelizumab 200 mg IV Q3W
until intolerable toxicity, withdrawal of consent, or the patient is no longer benefiting from study therapy, per the opinion of the investigator

Survival follow-up

*** 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**

Radiological assessments: every 6 weeks for first 18 weeks, then every 9 weeks thereafter

- Primary endpoint: ORR by IRC per RECIST v1.1
- Secondary endpoints:
  - DOR, PFS, DCR, and CBR assessed by IRC, and OS
  - ORR, DOR, PFS, DCR and CBR assessed by investigators
  - Safety/tolerability

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.

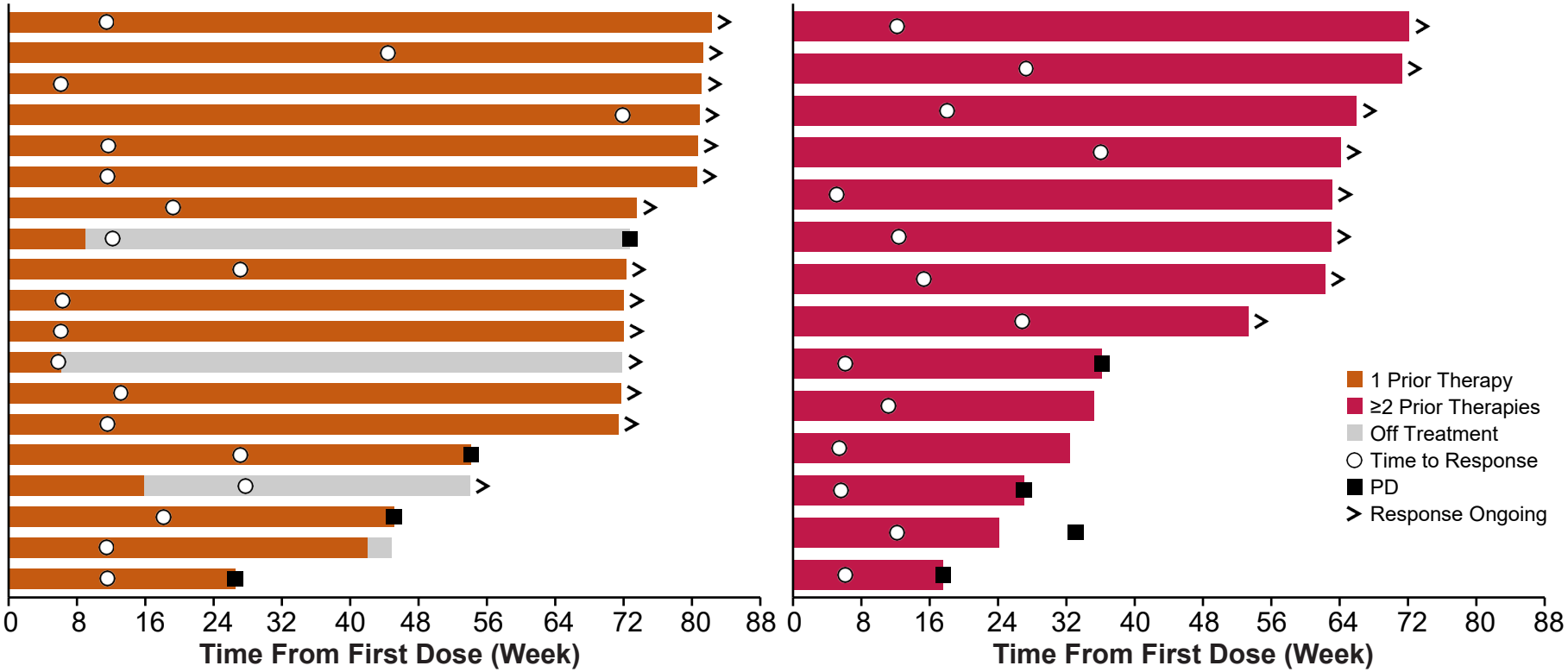
Antitumor Activity of Tislelizumab (IRC)

	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
- Confirmed ORR was consistent for patients who received one prior line of therapy and two or more prior lines of therapy

Data cut-off date is 27 Feb 2020. Two-sided Cis of ORR were calculated using a binomial exact method.
[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.

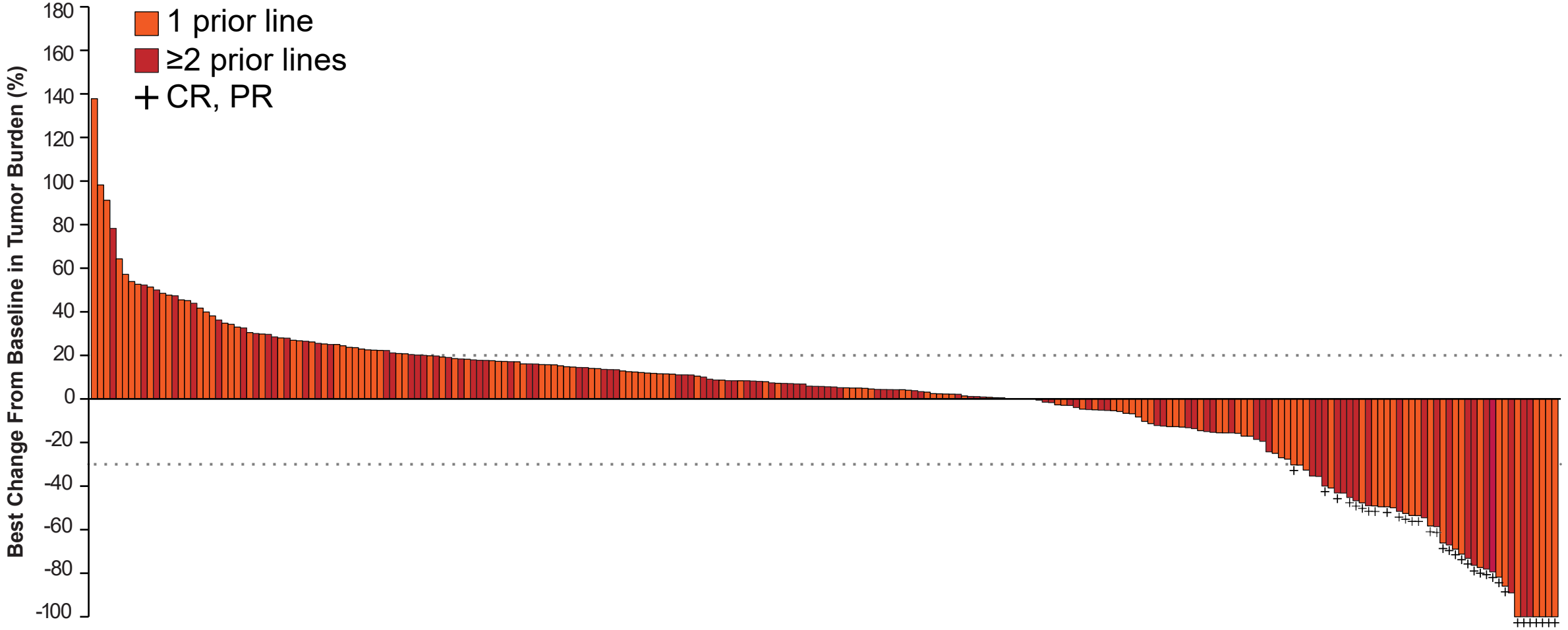
Duration of Response (IRC)



- 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.

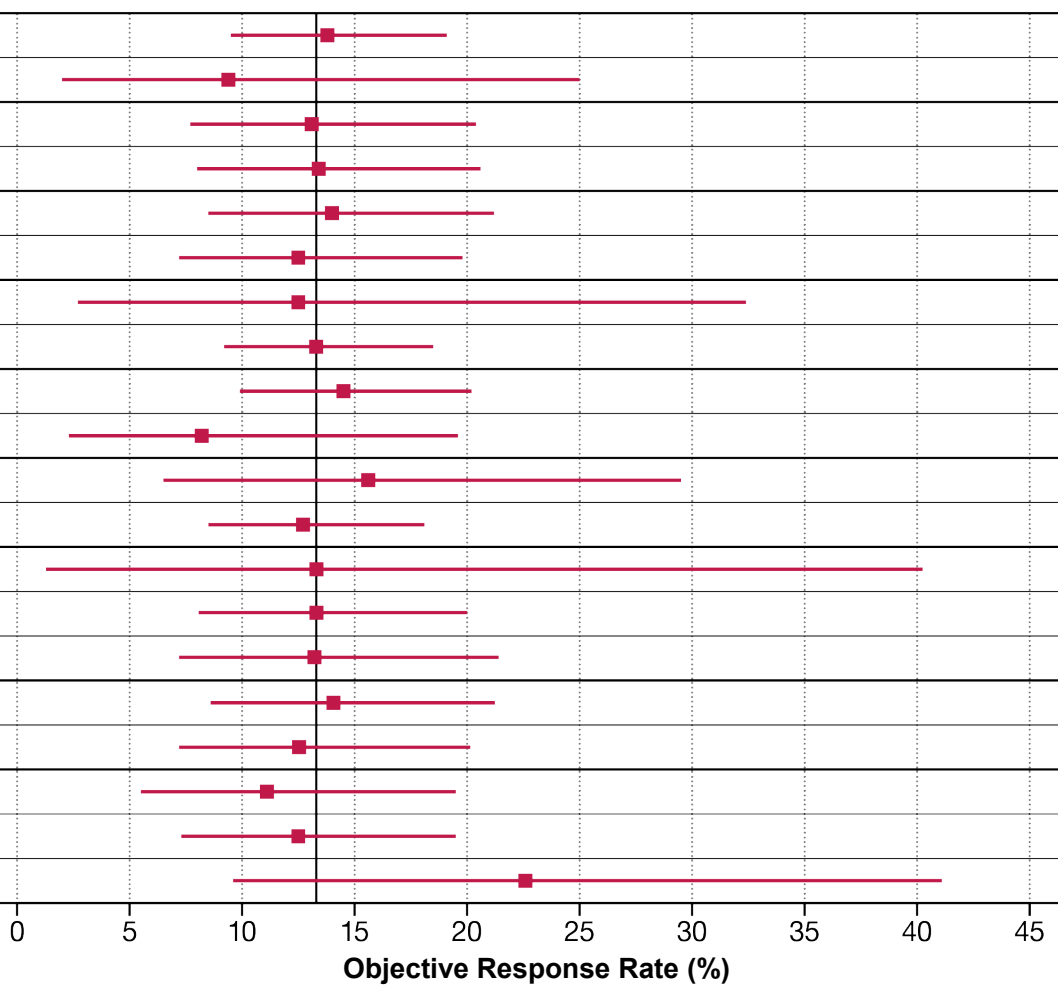
Best Percent Change From Baseline in Tumor Burden (IRC)



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

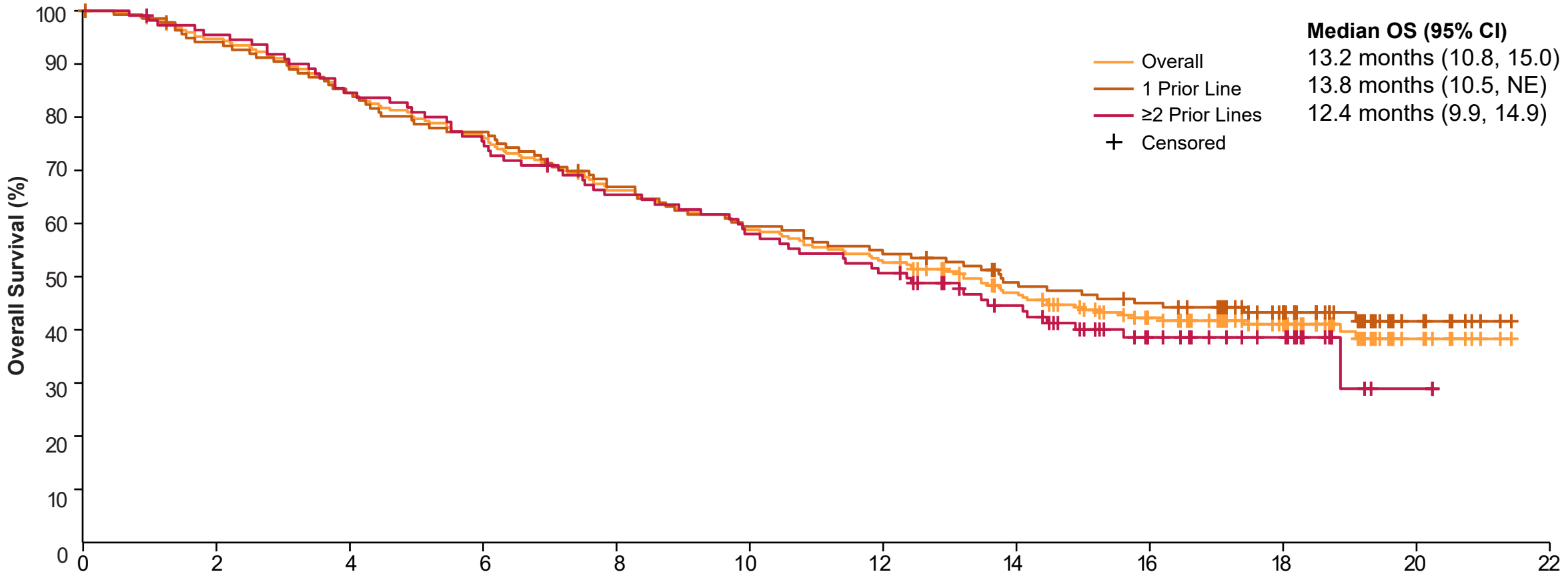
Subgroup Analysis of ORR per RECIST v1.1

		Response/Patients	ORR, % (95% CI)
Gender	Male	30/217	13.8 (9.5, 19.1)
	Female	3/32	9.4 (2.0, 25.0)
Region	Mainland China & Taiwan	16/122	13.1 (7.7, 20.4)
	Europe	17/127	13.4 (8.0, 20.6)
ECOG PS	0	18/129	14.0 (8.5, 21.2)
	1	15/120	12.5 (7.2, 19.8)
BCLC Staging	B	3/24	12.5 (2.7, 32.4)
	C	30/225	13.3 (9.2, 18.5)
Extrahepatic Spread	Present	29/200	14.5 (9.9, 20.2)
	Absent	4/49	8.2 (2.3, 19.6)
Macrovascular Invasion	Present	7/45	15.6 (6.5, 29.5)
	Absent	26/204	12.7 (8.5, 18.1)
PD-L1 Expression	Positive	2/15	13.3 (1.7, 40.5)
	Negative	19/143	13.3 (8.2, 20.0)
	Unknown	12/91	13.2 (7.0, 21.9)
Baseline α-fetoprotein	≤400 μg/L	19/136	14.0 (8.6, 21.0)
	≥400 μg/L	14/112	12.5 (7.0, 20.1)
HCC Etiology	Non-viral	10/90	11.1 (5.5, 19.5)
	HBV[a]	16/128	12.5 (7.3, 19.5)
	HCV	7/31	22.6 (9.6, 41.1)



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 advanced HCC who had received at least one prior systemic therapy
  - Objective response rate per IRC: 13.3%
  - Median DOR was not reached (response follow-up of 11.7 months), but 66.7% of patients had ongoing responses at data cut-off; 12-month event-free rate was 79.2%
  - Median OS: 13.2 months
- Tislelizumab demonstrated consistent, durable objective response and overall 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, 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

Acknowledgements

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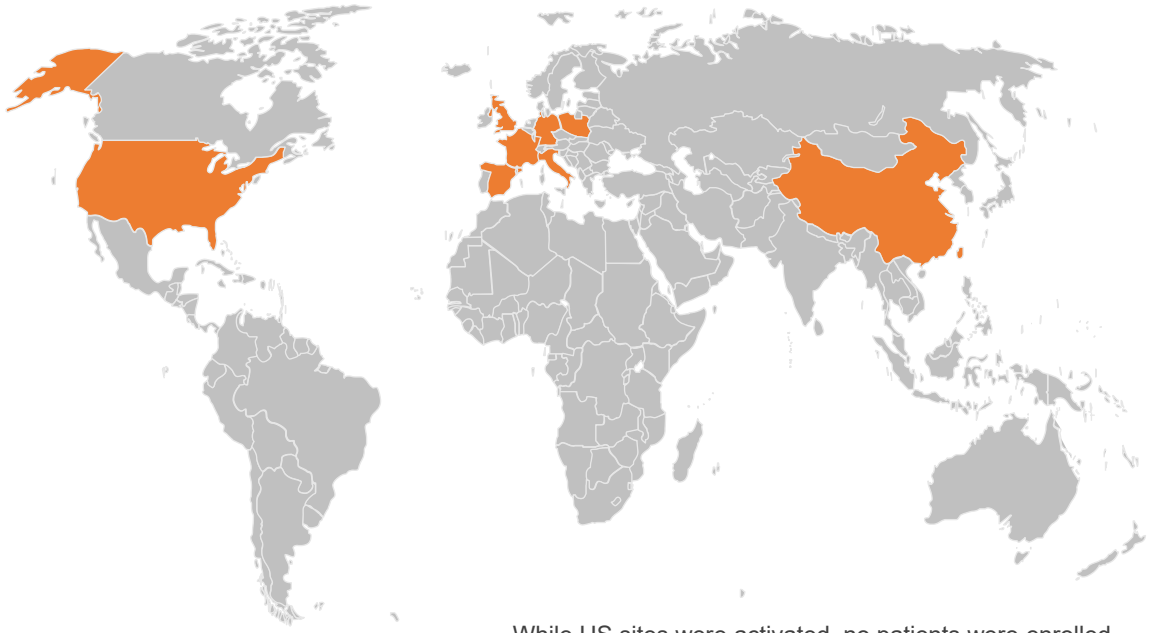

While US sites were activated, no patients were enrolled

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