Subgroup analysis of the number of prior lines of systemic therapy and clinical outcomes associated with tislelizumab in patients with previously treated advanced hepatocellular carcinoma

Philippe Merle*,[1] Julien Edeline,[2] Weijia Fang,[3] Eric Assenat,[4] Hongming Pan,[5] Lorenza Rimassa,[6,7] Zhiwei Li,[8] Jean-Frédéric Blanc,[9] Chia-Jui Yen,[10] Paul Ross,[11] Sheng Hu,[12] Tao Zhang,[13] Albert Tran,[14] Guoliang Shao,[15] Mohamed Bouattour,[16] Yajin Chen,[17] John Wu,[18] Bai Li,[19] Sandra Chica-Duque,[20] Zhenggang Ren[21]

[1]Hepatology Unit, Croix-Rousse Hospital, Lyon, France; [2]Department of Medical Oncology, Eugene Marquis Center, Rennes, France; [3]Department of Medical Oncology, The First Affiliated Hospital, Zhejiang University, Hangzhou, China; [4]Department of Oncology, St-Eloi University Hospital, Montpellier, France; [5]Department of Medical Oncology, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Zhejiang, China; [6]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy; [7]Medical Oncology and Hematology Unit, IRCCS Humanitas Research Hospital, Humanitas Cancer Center, Rozzano, Milan, Italy; [8]Division of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital, Zhejiang University, Hangzhou, China; [9]Service Hépato-Gastroentérologie et Oncologie Digestive, Hôpital Haut-Lévêque, CHU de Bordeaux, Bordeaux, France; [10]Clinical Medicine Research Center, National Cheng Kung University Hospital, Tainan, Taiwan; [11]Department of Gastroenterology, Guy's and St. Thomas' NHS Foundation Trust and King's College London, London, UK; [12]Department of Internal Medicine Oncology, Hubei Cancer Hospital, Wuhan, China; [13]Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Cancer Center, Wuhan, China; [14]Département Digestif, CHU de Nice-Hôpital Archet, Nice, France; [15]Department of Radiology, Zhejiang Cancer Hospital, Hangzhou, China; [16]Department of Medical Oncology, Beaujon University Hospital, Paris, France; [17]Department of Hepatobiliary Surgery, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China; [18]BeiGene (Ridgefield Park) Co., Ltd., Ridgefield Park, NJ, USA; [19]BeiGene (Beijing) Co., Ltd., Beijing, China; [20]BeiGene (San Mateo) Co., Ltd., San Mateo, CA, USA; [21]Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China. *Presenting author

Conclusions

- Tislelizumab demonstrated durable antitumor activity regardless of the number of PL of systemic therapy in this study of patients with previously treated advanced HCC.

- IRC-assessed ORR was 13.0% and 12.6% in the 1 PL and ≥ 2 PL subgroups, respectively, and median DoR was not reached in either subgroup.

- Tislelizumab was generally well tolerated regardless of the number of PL of therapy; the safety profile was consistent with the established profile of PD-1/PD-L1 inhibitors.[1,2]

- 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.[3]

Background

Tislelizumab, a monoclonal antibody with high binding affinity to the PD-1 receptor, was specifically engineered to minimize Fcγ receptor binding on macrophages.[4,5]

The global, single-arm Phase 2 RATIONALE-208 study (NCT03419897) investigated the efficacy, safety and tolerability of tislelizumab monotherapy in patients who had received at least one prior line of systemic therapy for advanced hepatocellular carcinoma (HCC).[6]

In the primary analysis, tislelizumab demonstrated encouraging and durable clinical activity and was well tolerated in the overall study population (N=249; data cutoff: Feb 27, 2020).[6]

This analysis explored whether the clinical activity of tislelizumab in the RATIONALE-208 study varied based on the number of prior lines (PL) of systemic therapy, using updated data (cutoff: Jun 30, 2021).

Methods

- The study design for the RATIONALE-208 study has been reported previously[6] (scan QR code to read full study methods):

Results

Patient disposition

- Among the 249 patients enrolled in the study (all of whom received tislelizumab), 138 had received 1 PL of systemic therapy and 111 had received ≥ 2 PL of systemic therapy (**Table 1**)

- At the data cutoff date (Jun 30, 2021) the median follow-up was 13.3 and 11.9 months in the 1 PL and ≥ 2 PL subgroups, respectively

Efficacy

- Objective response rate assessed by independent review committee was similar in the 1 PL and ≥ 2 PL subgroups (13.0% [95% CI: 7.9, 19.8] and 12.6% [95% CI: 7.1, 20.3], respectively) (**Table 2**)

- Among responders, responses were ongoing in 6/18 patients (33.3%) and 2/14 patients (14.3%) in the 1 PL and ≥ 2 PL subgroups, respectively (**Figure 1**)

- Overall survival and progression-free survival rates were similar in the 1 PL and ≥ 2 PL subgroups (**Figures 2 and 3**)

Safety and tolerability

- Median duration of exposures were 4.2 (range: 0.5–36.6) months and 4.1 (range: 0.7–34.1) months for the 1 PL and ≥ 2 PL subgroups, respectively

- Tislelizumab was generally well tolerated in patients with previously treated advanced HCC (**Table 3**)

Table 1. Baseline demographics and disease characteristics

|		1 prior line of therapy (n=138)*	≥ 2 prior lines of therapy (n=111)
Median age, years (range)		63.5 (28–90)	60.0 (28–82)
Sex, n (%)	Male	121 (87.7)	96 (86.5)
Region, n (%)	Mainland/Taiwan China	72 (52.2)	50 (45.0)
	Europe	66 (47.8)	61 (55.0)
ECOG PS, n (%)	0	70 (50.7)	59 (53.2)
	1	68 (49.3)	52 (46.8)
BCLC staging at study entry, n (%)	B	14 (10.1)	10 (9.0)
	C	124 (89.9)	101 (91.0)
Child-Pugh score, n (%)	A	138 (100.0)	110 (99.1)†
Extrahepatic spread, n (%)		113 (81.9)	87 (78.4)
Macrovascular invasion, n (%)		23 (16.7)	23 (20.7)
HCC etiology, n (%)	Hepatitis B only	71 (51.4)	52 (46.8)
	Hepatitis C only	20 (14.5)	11 (9.9)
	Hepatitis B and C	1 (0.7)	4 (3.6)
	Non-viral	46 (33.3)	44 (39.6)
Prior anti-cancer systemic therapy, n (%)	SOR and LEN naïve‡	12 (8.7)	2 (1.8)
	SOR and/or LEN treated	126 (91.3)	109 (98.2)

*One patient received prior sorafenib treatment as adjuvant therapy and no subsequent systemic therapies; †One patient had Child-Pugh score B at study entry; ‡All patients received oxaliplatin-based therapy as first-line therapy. Prior treatment with immune checkpoint inhibitors was not permitted. BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; LEN, lenvatinib; SOR, sorafenib. Data cutoff: Jun 30, 2021

Table 2. Summary of antitumor activity by IRC

	1 prior line of therapy (n=138)	≥ 2 prior lines of therapy (n=111)
ORR (CR + PR), % (95% CI)	13.0 (7.9, 19.8)	12.6 (7.1, 20.3)
Best overall response, n (%)		
CR	4 (2.9)	1 (0.9)
PR	14 (10.1)	13 (11.7)
SD*	55 (39.9)	45 (40.5)
PD	60 (43.5)	47 (42.3)
Not assessable†	5 (3.6)	5 (4.5)
DCR (CR + PR + SD), % (95% CI)	52.9 (44.2, 61.5)	53.2 (43.5, 62.7)
Median DoR, months (95% CI)	NR (19.3, NE)	NR (6.1, NE)

*Includes two patients assessed as non-CR/non-PD due to a lack of measurable disease per IRC; †No post-baseline assessment or an unevaluable post-baseline assessment. CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; IRC, independent review committee; NE, not estimable; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease. Data cutoff: Jun 30, 2021


Figure 1. Duration of response by IRC
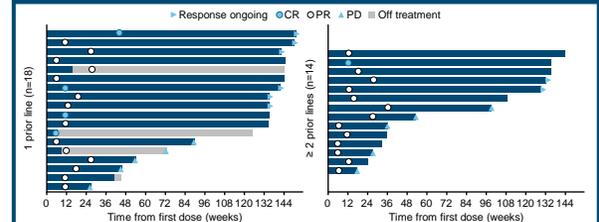
All responders included; each bar represents an individual patient (n=32). Treatment period is plotted only up to the time of the last tumor assessment for patients who were still on treatment. IRC, independent review committee; CR, complete response; PD, progressive disease; PR, partial response. Data cutoff: Jun 30, 2021

Figure 2. Kaplan-Meier plot of OS
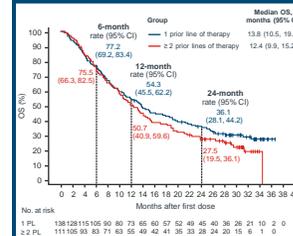
Figure 3. Kaplan-Meier plot of PFS by IRC
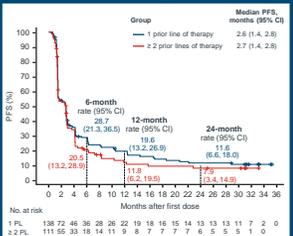
CI, confidence interval; OS, overall survival; PL, prior line. Data cutoff: Jun 30, 2021

CI, confidence interval; IRC, independent review committee; PFS, progression-free survival; PL, prior line. Data cutoff: Jun 30, 2021

Table 3. Summary of adverse event incidence

Patients, n (%)	1 prior line of therapy (n=138)		≥ 2 prior lines of therapy (n=111)	
	Treatment-emergent	Treatment-related	Treatment-emergent	Treatment-related
Any	130 (94.2)	91 (65.9)	106 (95.5)	67 (60.4)
Grade ≥ 3	69 (50.0)	24 (17.4)	54 (48.6)	14 (12.6)
Serious	53 (38.4)	13 (9.4)	40 (36.0)	5 (4.5)
Leading to death	16 (11.6)*	0 (0)	10 (9.0)*	0 (0)
Leading to dose delay†	45 (32.6)	27 (19.6)	34 (30.6)	19 (17.1)
Leading to treatment discontinuation	18 (13.0)	10 (7.2)	10 (9.0)	3 (2.7)
Immune-mediated	28 (20.3)	28 (20.3)	27 (24.3)	27 (24.3)
Grade ≥ 3	7 (5.1)	7 (5.1)	4 (3.6)	4 (3.6)

*In total, 23 patients in the 1 PL and ≥ 2 PL subgroups had disease progression reported as the primary cause of death; †Included patients who were held for dosing after last dose administration, and eventually leading to decision of dose discontinuation. Data cutoff: Jun 30, 2021

References

1. Zhu AX, et al. Lancet Oncol 2018;19:940–52
2. El-Khoueiry AB, et al. Lancet 2017;389:2492–502
3. Qin S, et al. Future Oncol 2019;15:1811–22
4. Zhang T, et al. Cancer Immunol Immunother 2018;67:1079–90
5. Hong Y, et al. FEBS Open Bio 2021;11:782–92
6. Ducreux M, et al. Abstract and oral presentation at ESMO World Congress on Gastrointestinal Cancer 2021 (O-1)

*Author contact details: philippe.merle@inserm.fr (Philippe Merle)