Editorial

Cabozantinib as a Second-Line Agent in Advanced Hepatocellular Carcinoma

Masatoshi Kudo

Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine,
Osaka-Sayama, Japan

Prof. M. Kudo

Editor *Liver Cancer* **Introduction**

The results of the phase III CELESTIAL trial of cabozantinib were presented by Prof. Ghassan Abou-Alfa at the ASCO Gastrointestinal Cancer Symposium held in San Francisco from January 18 to 20, 2018 [1]. Although most of the previous clinical trials of second-line agents, except regorafenib [2], failed [3–8], the CELESTIAL trial yielded positive results in line with most expectations and produced a fourth molecular-targeted drug option for hepatocellular carcinoma (HCC). Based on this trial, cabozantinib can be added as a second-line option to the first-line drugs sorafenib [9, 10] and lenvatinib [11] and the second-line drug regorafenib [2] (Table 1).

Phase II Trial of Cabozantinib

The structural formula of cabozantinib is relatively similar to that of regorafenib [12, 13] (Fig. 1), although the kinase inhibitory activity (IC_{50}) of cabozantinib is different. Cabozantinib was originally identified as a dual inhibitor of VEGFR-2 and c-MET [14, 15], whereas current data suggest that it is a more potent inhibitor of MET, AXL, RET, FLT3, and TIE-2 than regorafenib (Tables 2, 3). VEGF, MET, and AXL are involved in tumor proliferation and angiogenesis, and MET and AXL are involved in the acquisition of resistance to antiangiogenic drugs [14–18]. VEGF, MET, or AXL expression is considered a poor prognostic factor [14–18].

Masatoshi Kudo
Department of Gastroenterology and Hepatology
Kindai University Faculty of Medicine
377-2 Ohno-Higashi, Osaka-Sayama 589-8511 (Japan)
m-kudo@med.kindai.ac.jp

Table 1. Phase III clinical trials of advanced stage HCC

	Design	Trial name	Result	Presentation	Publication	First author
First line	1 Sorafenib vs. sunitinib	SUN1170	Negative	ASCO 2011	J Clin Oncol 2013	Cheng
	2 Sorafenib ± erlotinib	SEARCH	Negative	ESMO 2012	J Clin Oncol 2015	Zhu
	3 Sorafenib vs. brivanib	BRISK-FL	Negative	AASLD 2012	J Clin Oncol 2013	Johnson
	4 Sorafenib vs. linifanib	LiGHT	Negative	ASCO-GI 2013	J Clin Oncol 2015	Cainap
	5 Sorafenib ± doxorubicin	CALGB 80802	Negative	ASCO-GI 2016		
	6 Sorafenib ± HAIC	SILIUS	Negative	EASL 2016	Lancet Gastroenterol Hepatol 2018	Kudo
	7 Sorafenib ± Y90	SARAH	Negative	EASL 2017	Lancet Oncol 2017	Vilgrain
	8 Sorafenib ± Y90	SIRveNIB	Negative	ASCO 2017	J Clin Oncol 2018	Chow
	9 Sorafenib vs. lenvatinib	REFLECT	Positive	ASCO 2017	Lancet 2018	Kudo
	10 Sorafenib vs. nivolumab	CheckMate-459	Ongoing			
	11 Sorafenib vs. durvalumab + tremelimumab vs. durvalumab	HIMALAYA	Ongoing			
Second line	1 Brivanib vs. placebo	BRISK-PS	Negative	EASL 2012	J Clin Oncol 2013	Llovet
	2 Everolimus vs. placebo	EVOLVE-1	Negative	ASCO-GI 2014	JAMA 2014	Zhu
	3 Ramucirumab vs. placebo	REACH	Negative	ESMO 2014	Lancet Oncol 2015	Zhu
	4 S-1 vs. placebo	S-CUBE	Negative	ASCO 2015	Lancet Gastroenterol Hepatol 2017	Kudo
	5 ADI-PEG 20 vs. placebo	NA	Negative	ASCO 2016		
	6 Regorafenib vs. placebo	RESORCE	Positive	WCGC 2016	Lancet 2017	Bruix
	7 Tivantinib vs. placebo	METIV-HCC	Negative	ASCO 2017		
	8 Tivantinib vs. placebo	JET-HCC	Negative	ESMO 2017		
	9 DT vs. placebo	ReLive	Negative	ILCA 2017		
	10 Cabozantinib vs. placebo	CELESTIAL	Positive	ASCO-GI 2018		Ghassan
	11 Ramucirumab vs. placebo	REACH-2	Ongoing			
	12 Pembrolizumab vs. placebo	KEYNOTE-240	Ongoing			

Red, positive trials; blue, ongoing trials; black, negative trials. HCC, hepatocellular carcinoma; HAIC, hepatic arterial infusion chemotherapy; DT, doxorubicin-loaded nanoparticles.

Fig. 1. Chemical structure of cabozantinib and regorafenib.

A waterfall plot from the phase II trial showed tumor shrinkage in a large proportion of patients. Progression-free survival (PFS) was 4.2 months in sorafenib-naïve patients and 5.5 months in sorafenib-pretreated patients, and overall survival (OS) was 11.5 months [15] (Table 4). The overall response rate (ORR) was 5%, the disease control rate was 81%, and PFS was 5.2 months (Table 4). Considering that some patients in the cabozantinib trial received first-line therapy, the results were not very good compared with the results of the phase II trial of regorafenib [19] (Table 4). Cabozantinib was also associated with a higher incidence of adverse events (AEs) than regorafenib (Table 5).

Table 2. Cabozantinib targets VEGFR-2, c-MET, RET, AXL, TIE2, and FLT3

Biochemical activity	IC ₅₀ , nmol/L
VEGFR-2	14
c-MET	2
c-KIT	752
RET	8
AXL	8
TIE2	13
FLT3	21
PDGFR-β	575

Table 3. Mode of action: cabozantinib and regorafenib

Biochemical activity	Cabozantinib IC ₅₀ , nM	Regorafenib IC ₅₀ ± SD, nM
MET	2	NA
AXL	8	NA
VEGFR-2	14	4.2±1.6
VEGFR-1	NA	13±0.4
VEGFR-3	NA	46±10
BRAF	NA	28±10
TIE-2	13	311±46
PDGFR-β	575	22±3
FGFR1	NA	202±18
c-Kit	752	7±2
RET	8	1.5±0.7
Flt-3	21	NA

Modified from [12, 13].

Table 4. Comparison of efficacy (phase II): cabozantinib and regorafenib

	Cabozantinib (n = 41)	Regorafenib (n = 36)
ORR, %	5	3
DCR, %	81	72
PFS/TTP, months	5.2 (5.5)	4.3
OS, months	11.5	13.8

ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; TTP, time to progression; OS, overall survival.

Phase III CELESTIAL Trial

In light of these results, a phase III trial of cabozantinib was conducted (Fig. 2). The trial design was not as sophisticated as that of the RESORCE trial [2, 20]. For example, vascular invasion and/or extrahepatic spread was included as a stratification factor, which may result in an unfavorable imbalance regarding patients with vascular invasion. In fact, this unfavorable imbalance was present in the BRISK-PS trial and resulted in negative results [3]. The BRISK-PS trial did not include alpha-fetoprotein as a stratification factor, which caused an unfavorable balance against the trial drug similar to that seen in the REFLECT trial [11]. The RESORCE trial led to the inclusion of vascular invasion as an independent stratification factor

Table 5. Cabozantinib vs. regorafenib: comparison of adverse events (phase II)

	Cabozantinib (n = 41)		Regorafenib (n = 36)	
	all grades	grade 3–4	all grades	grade 3–4
Hand foot skin reaction	56	15	53	14
Fatigue	56	2	53	17
Hypertension	24	10	36	3
Appetite loss	29	0	36	0
Nausea	37	2	33	0
Vomiting	37	2	14	0
Diarrhea	63	20	53	6
Body weight loss	22	2	19	0
Constipation	22	0	25	0

Values are shown as percentages. Modified from [15, 19].

Fig. 2. CELESTIAL trial: study design.

and alpha-fetoprotein as a stratification factor in the design of trials of second-line drugs [21]. However, the CELESTIAL trial had a conventional design with few strategic elements (Table 6) and did not even exclude sorafenib-intolerant patients as in the RESORCE trial [2, 20, 21]. The only inclusion criteria regarding prior treatment were (a) prior sorafenib treatment, (b) progression following at least 1 prior systemic treatment for HCC, and (c) up to 2 prior systemic regimens for advanced HCC; the exact number of sorafenib-intolerant patients enrolled remains unclear.

Between September 2013 and September 2017, the trial enrolled 773 patients with unresectable HCC showing disease progression after at least 1 prior systemic chemotherapy regimen containing sorafenib. The second interim analysis performed in January 2016 demonstrated the superiority of cabozantinib in terms of the primary endpoint of OS. There was an imbalance in baseline patient characteristics between the cabozantinib and placebo groups caused by the failure to include vascular invasion and extrahepatic spread as independent stratification factors; namely, the rate of vascular invasion was only 27% in the cabozantinib group compared with 34% in the placebo group, which favored the cabozantinib

Table 6. Phase III clinical trials: advanced stage second line versus placebo

	BRISK-PS Brivanib	EVOLVE-1 Everolimus	REACH Ramucirumab	S-CUBE S1	RESORCE Regorafenib	METIV-HVV Tivantinib	KEYNOTE-240 Pembrolizumab	CELESTIAL Cabozantinib
Intolerance of sorafenib, %	12–13	18.5–20	13–15	30.6–33.8	0	17–21	–	N/A
Stratification factor	Reason for sorafenib discontinuation ECOG-PS score Extrahepatic spread, and/or vascular invasion	Region MVI	Region Cause of liver disease (HBV, HCV, other)	Medical institutions Extrahepatic metastasis and/or vascular invasion	Region ECOG-PS score Extrahepatic spread Vascular invasion AFP	Extrahepatic spread Vascular invasion AFP	Region Vascular invasion AFP	Region Disease etiology (HBV, HCV, other) Extrahepatic metastasis and/or vascular invasion

After the BRISK-PS trial, where there was an imbalance of AFP and MVI in the testing arm, AFP and MVI started to be included as independent stratification factors in most trials, but not in the CELESTIAL trial. Modified from [1–6]. AFP, alpha-fetoprotein; MVI, macrovascular invasion.

Table 7. Baseline characteristics

	Cabozantinib (n = 470)	Placebo (n=237)
Median (range) age, years	64 (22–86)	64 (24–86)
Male, %	81	85
ECOG performance status 0/1, %	52/48	55/45
AFP ≥400 ng/mL, %	41	43
Enrollment region, %		
Asia/Europe/North America/Pacific	25/49/23/3	25/46/25/5
Etiology of HCC, %		
HBV	38	38
HCV	22	22
Other	40	41
Extrahepatic spread of disease, %	79	77
Macrovascular invasion, %	27	34
Extrahepatic spread and/or macrovascular invasion, %	85	84

Asia: Hong Kong, South Korea, Singapore, Taiwan; Pacific: Australia and New Zealand. Cited from [1]. AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma.

group (Table 7). This resulted in significantly better OS in the cabozantinib group (10.2 months, 95% CI: 9.1–12.0) than in the placebo group (8.2 months, 95% CI: 9.1–12.0) and consequently in a positive result for the clinical trial. PFS, the secondary endpoint, was also better in the cabozantinib group (5.2 months, 95% CI: 4.0–5.5) than in the placebo group (1.9 months, 95% CI: 1.9–1.9) (Table 8). PFS of 1.9 months in the placebo arm in the CELESTIAL trial was similar to that of 1.5 months in the placebo arm in the RESORCE trial (Fig. 3). Moreover, ORR was superior in the cabozantinib group (4 vs. 0.4%; $p = 0.0086$) (Table 9). Post-trial treatment was performed in a comparably low proportion of patients in the cabozantinib and placebo groups (25 vs. 30%), demonstrating the poor condition of the patient population. In summary, although the relative number of sorafenib-intolerant patients in the trial was not reported, it can be inferred from the trial results that the proportion was relatively low (Table 10).

Table 8. Time to event: CELESTIAL (second and third line) versus RESORCE

	CELESTIAL trial (second and third line)		RESORCE trial (SOR → REG)	
	cabozantinib (n = 470)	placebo (n = 237)	regorafenib (n=379)	placebo (n = 194)
TTP, months	N/A	N/A	3.2	1.5
HR				0.44
p value				<0.0001
PFS, months	5.2	1.9	3.1	1.5
HR		0.44		0.46
p value		<0.0001		<0.0001
OS, months	10.2	8.2	10.6	7.8
HR		0.76		0.63
p value		0.0049		<0.0001

TTP, time to progression; PFS, progression-free survival; OS, overall survival. Modified from [1, 2].

Fig. 3. Phase III trial: second line. Time to progression (TTP) was shorter in the placebo arm in the CELESTIAL trial, similar to placebo arm in the RESORCE trial, suggesting that there were fewer sorafenib-intolerant patients in the CELESTIAL trial. Anticancer activity may be higher than that of other agents, as indicated by the longer TTP. MKI, multikinase inhibitor.

Comparison between Regorafenib and Cabozantinib: Efficacy and Safety

Cabozantinib and regorafenib had comparable efficacy in terms of OS, ORR, and PFS (Tables 8, 9). Patients who received prior treatment with sorafenib alone showed slightly better outcomes (Table 10), which were comparable to those of regorafenib.

The duration of treatment with cabozantinib was 3.8 months, which was comparable to the 3.6 months for regorafenib and indicates acceptable tolerability, similar to that of regorafenib.

Table 9. Tumor response: CELESTIAL vs. RESORCE

	CELESTIAL trial		RESORCE trial	
	cabozantinib (n = 470)	placebo (n = 237)	regorafenib (n = 379)	placebo (n = 194)
Response criteria	RECIST 1.1		RECIST 1.1	
ORR, %	4	0.4	6.6	2.6
p value		0.0086		0.02
DCR, %	64	33.4	65.7	34.5
p value		N/A		<0.0001

ORR, objective response rate; DCR, disease control rate. Modified from [1, 2].

Table 10. Time to event: CELESTIAL (SOR → CAB) vs. RESORCE

	CELESTIAL trial (SOR→CAB)		RESORCE trial (SOR → REG)	
	cabozantinib (n = 331)	placebo (n = 164)	regorafenib (n = 379)	placebo (n = 194)
TTP, months	N/A	N/A	3.2	1.5
HR		N/A		0.44
p value				<0.0001
PFS, months	5.5	1.9	3.1	1.5
HR				0.46
p value		0.40		<0.0001
OS, months	11.3	7.2	10.6	7.8
HR		0.70		0.63
p value				<0.0001

TTP, time to progression; PFS, progression-free survival; OS, overall survival. Modified from [1, 2].

Dose reduction or discontinuation because of treatment-related AEs was more common with cabozantinib than with regorafenib. Specific AEs such as palmar-plantar erythrodysesthesia, diarrhea, and asthenia were more common with cabozantinib than with regorafenib, indicating that cabozantinib may have a slightly higher toxicity than regorafenib (Table 11).

Key Factors Contributing to the Success of the CELESTIAL Trial

The following 5 factors may have contributed to the success of the CELESTIAL trial of cabozantinib despite the unsophisticated trial design compared with that of the RESORCE trial and the drug's slightly higher toxicity (Table 12).

1. Cabozantinib has a sufficiently potent antitumor activity.
2. Toxicity and tolerability were clinically acceptable.
3. An imbalance in vascular invasion favored cabozantinib.

Table 11. Safety analysis: CELESTIAL vs. RESORCE

	Cabozantinib (n = 467)	Regorafenib (n = 374)
Treatment duration, months	3.8	3.6
Dose reduction due to adverse event, %	62	48
Discontinuation due to TRAE, %	16	10
<i>Grade 3/4</i>		
Any grade 3 or 4 adverse event, %	68	66
Palmar-plantar erythrodysesthesia, %	17	13
Fatigue, %	10	9
Hypertension, %	16	15
Diarrhea, %	10	3
Asthenia, %	7	NA
Bilirubin increased, %	NA	10
AST increased, %	12	11
Ascites, %	NA	4
Anemia, %	4	5
Hypophosphatemia, %	NA	9

AST, aspartate aminotransferase; NA, not applicable. TRAE, treatment-related adverse event. NCI-CTCAE v4.03.

Table 12. CELESTIAL trial: key factors of the success

- Cabozantinib has good anticancer activity
- Acceptable toxicity and tolerability
- Imbalance of vascular invasion favoring cabozantinib
- Small number of sorafenib-intolerant patients (short time to progression in placebo)
- Extremely high numbers of enrolled patients (n = 470 vs. 379, 362, 283, 263)
→ Higher power to detect the small difference and eliminate the effect of tiny imbalance

4. The short time to progression in the placebo arm and low proportion of patients having post-trial treatment indicate low enrollment of sorafenib-intolerant patients, which was similar to no enrollment of sorafenib-intolerant patients in the RESORCE trial.
5. The sample size of 470 patients was considerably higher than that of other second-line trials and provided sufficient power to eliminate the effect of the small imbalance and detect small differences as significant (Table 13).

Paradigm Shift in the Treatment Strategy for HCC

Sorafenib was the only HCC drug available between 2007 and 2016. Between 2017 and 2018, 5 drugs, sorafenib, lenvatinib, regorafenib, cabozantinib, and nivolumab, became available. Therefore, it is necessary to establish how these drugs should be used in clinical practice (Fig. 4). Combinations of immune checkpoint inhibitors and molecular-targeted drugs or molecular-targeted drugs and established locoregional therapies [22] are particularly likely to produce a paradigm shift in the treatment of HCC. The treatment landscape for

Table 13. Phase III trials in a second line setting

	CELESTIAL cabozantinib arm (n = 470)	RESORCE regorafenib arm (n = 379)	BRISK-PS brivanib arm (n = 263)	EVOLVE-1 everolimus arm (n = 362)	REACH ramucirumab arm (n = 283)
Male, %	81	88	82	84	83
Median age (range), years	64 (22–86)	64 (19–85)	64 (19–89)	67 (21–86)	64 (28–87)
Asian race, %	25	41	48	38	46
ECOG PS 0/1, %	52/48	65/35	57/39	59/36	56/44
Child Pugh A, %	NA	98	92	98	98
BCLC stage, B/C, %	NA	14/86	9/87	14/87	12/88
AFP ≥400 ng/mL, %	41	43	50 ^a	47 ^a	42
MVI, %	27	29	31	33	29
EHS, %	79	70	65	74	73
Etiology, %					
Alcohol	NA	24	23	18	–
HBV	38	38	39	25	35
HCV	22	21	28	26	27
NASH	NA	7	–	4	–
Intolerance of sorafenib, %	–	0	13	19	13
Median total duration of prior sorafenib, months	5.3	7.8	–	–	–
Median time from disease progression to randomization, months	1.6	0.9	–	–	–

AFP, alpha-fetoprotein; MVI, macrovascular invasion; EHS, extrahepatic spread; NASH, non-alcoholic steatohepatitis.

^a AFP ≥200 ng/mL.

Fig. 4. New treatment landscape in HCC associated with the emergence of multiple molecular-targeted agents. Identification of the subgroup that easily develops to TACE failure/refractoriness may be important. BSC, best supportive care.

HCC will soon undergo major changes as systemic therapy is integrated into the treatment for all stages, from early to intermediate to advanced, which could drastically improve the prognosis of patients with HCC.

Conclusion

The success of the clinical trial of cabozantinib increased the treatment options for HCC, and combination treatment with immunotherapy may soon improve the prognosis of patients with HCC.

References

- 1 Ghassan K, Abou-Alfa GK, Meyer T, Cheng AL, Anthony B, Khoueiry EI, Rimassa L, et al: Cabozantinib (C) versus placebo (P) in patients (pts) with advanced hepatocellular carcinoma (HCC) who have received prior sorafenib: results from the randomized phase III CELESTIAL trial. *J Clin Oncol* 2018;36(suppl 4S):abstr 207.
- 2 Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, Pracht M, et al: Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017;389:56–66.
- 3 Llovet JM, Decaens T, Raoul JL, Boucher E, Kudo M, Chang C, Kang YK, et al: Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized phase III BRISK-PS study. *J Clin Oncol* 2013;31:3509–3516.
- 4 Zhu AX, Kudo M, Assenat E, Cattani S, Kang YK, Lim HY, Poon RT, et al: Effect of everolimus on survival in advanced hepatocellular carcinoma after failure of sorafenib: the EVOLVE-1 randomized clinical trial. *JAMA* 2014;312:57–67.
- 5 Zhu AX, Park JO, Ryoo BY, Yen CJ, Poon R, Pastorelli D, Blanc JF, et al: Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol* 2015;16:859–870.
- 6 Kudo M, Moriguchi M, Numata K, Hidaka H, Tanaka H, Ikeda M, Kawazoe S, et al: S-1 versus placebo in patients with sorafenib-refractory advanced hepatocellular carcinoma (S-CUBE): a randomised, double-blind, multicentre, phase 3 trial. *Lancet Gastroenterol Hepatol* 2017;2:407–417.
- 7 Kudo M: Molecular targeted agents for hepatocellular carcinoma: current status and future perspectives. *Liver Cancer* 2017;6:101–112.
- 8 Cucchetti A, Piscaglia F, Pinna AD, Djulbegovic B, Mazzotti F, Bolondi L: Efficacy and safety of systemic therapies for advanced hepatocellular carcinoma: a network meta-analysis of phase III trials. *Liver Cancer* 2017;6:337–348.
- 9 Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, et al: Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;359:378–390.
- 10 Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, et al: Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009;10:25–34.
- 11 Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, Baron A, et al: Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018:Epub ahead of print.
- 12 Lacy S, Hsu B, Miles D, Aftab D, Wang R, Nguyen L: Metabolism and disposition of cabozantinib in healthy male volunteers and pharmacologic characterization of its major metabolites. *Drug Metab Dispos* 2015;43:1190–1207.
- 13 Strumberg D, Schultheis B: Regorafenib for cancer. *Expert Opin Investig Drugs* 2012;21:879–889.
- 14 Yakes FM, Chen J, Tan J, Yamaguchi K, Shi Y, Yu P, Qian F, et al: Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. *Mol Cancer Ther* 2011;10:2298–2308.
- 15 Kelley RK, Verslype C, Cohn AL, Yang TS, Su WC, Burris H, Braithe F, et al: Cabozantinib in hepatocellular carcinoma: results of a phase 2 placebo-controlled randomized discontinuation study. *Ann Oncol* 2017;28:528–534.
- 16 Gay CM, Balaji K, Byers LA: Giving AXL the axe: targeting AXL in human malignancy. *Br J Cancer* 2017;116:415–423.
- 17 Zhu AX, Duda DG, Sahani DV, Jain RK: HCC and angiogenesis: possible targets and future directions. *Nat Rev Clin Oncol* 2011;8:292–301.

- 18 Ueki T, Fujimoto J, Suzuki T, Yamamoto H, Okamoto E: Expression of hepatocyte growth factor and its receptor, the c-met proto-oncogene, in hepatocellular carcinoma. *Hepatology* 1997;25:619–623.
- 19 Bruix J, Tak WY, Gasbarrini A, Santoro A, Colombo M, Lim HY, Mazzaferro V, et al: Regorafenib as second-line therapy for intermediate or advanced hepatocellular carcinoma: multicentre, open-label, phase II safety study. *Eur J Cancer* 2013;49:3412–3419.
- 20 Kudo M: Regorafenib as second-line systemic therapy may change the treatment strategy and management paradigm for hepatocellular carcinoma. *Liver Cancer* 2016;5:235–244.
- 21 Kudo M: A new era of systemic therapy for hepatocellular carcinoma with regorafenib and lenvatinib. *Liver Cancer* 2017;6:177–184.
- 22 Kudo M, Ueshima K, Torimura T, Tanabe N, Ikeda M, Aikata H, Izumi N, et al: Randomized, open label, multi-center, phase II trial of transcatheter arterial chemoembolization (TACE) therapy in combination with sorafenib as compared with TACE alone in patients with hepatocellular carcinoma: TACTICS trial. ASCO-GI, 2018, Abstract No 206.