Editorial

A New Era of Systemic Therapy for Hepatocellular Carcinoma with Regorafenib and Lenvatinib

Prof. M. Kudo *Editor Liver Cancer* **Introduction**

The SHARP study in 2007 [1] and the Asia Pacific study in 2008 [2] led to the worldwide approval of sorafenib as the standard therapy for unresectable hepatocellular carcinoma (HCC). However, clinical trials investigating sunitinib [3], brivanib [4], and linifanib [5] as first-line treatments, with sorafenib as a control arm, failed to meet their primary endpoint of improving overall survival (OS). In addition, global phase III studies investigating second-line therapy with brivanib [6], everolimus [7], and ramucirumab [8], and a regional trial investigating S-1 (tegafur/gimeracil/oteracil) in Japan, were unsuccessful (Table 1). Thus, sorafenib was the only systemic therapeutic agent available for HCC, and for some time no options were available for patients with progressive disease or those intolerant to sorafenib. However, between June 2016 and January 2017, promising results of global phase III studies were reported. The results of a trial of regorafenib were reported at a conference [9] and in a journal [10], and results with lenvatinib were reported in a press release [11], indicating the arrival of a new era of liver cancer therapy.

Sorafenib-Regorafenib Sequential Therapy

Sorafenib is the standard treatment for advanced-stage HCC (Barcelona Clinic Liver Cancer [BCLC] stage C) and the only therapeutic agent for advanced-stage HCC with vascular invasion and/or extrahepatic spread. However, in addition to patients with advanced-stage

Table 1. Phase III clinical trials for HCC

Target population	Design	Trial name	Presentation	Publication
<i>Early</i>				
Adjuvant (prevention of recurrence)	1 Peretinoin vs. placebo ^a	NIK-333	ASCO 2010	JG 2014
	2 Sorafenib vs. placebo ^a	STORM	ASCO 2014	Lancet-O 2015
	3 Peretinoin vs. placebo	NIK-333/K-333	Ongoing	
<i>Intermediate</i>				
Improvement of TACE	1 TACE +/- sorafenib ^a	Post-TACE	ASCO-GI 2010	EJC 2011
	2 TACE +/- brivanib ^a	BRISK-TA	ILCA 2013	Hepatol 2014
	3 TACE +/- orantinib ^a	ORIENTAL	EASL 2015	
<i>Advanced</i>				
First line	1 Sorafenib vs. sunitinib ^a	SUN1170	ASCO 2011	JCO 2013
	2 Sorafenib vs. brivanib ^a	BRISK-FL	AASLD 2012	JCO 2013
	3 Sorafenib vs. linifanib ^a	LiGHT	ASCO-GI 2013	JCO 2015
	4 Sorafenib +/- HAIC ^a	SILIUS	EASL 2016	
	5 Sorafenib vs. lenvatinib	REFLECT	TBD	
	6 Sorafenib vs. nivolumab	CheckMate 459	Ongoing	
Second line	1 Brivanib vs. placebo ^a	BRISK-PS	EASL 2012	JCO 2013
	2 Everolimus vs. placebo ^a	EVOLVE-1	ASCO-GI 2014	JAMA 2014
	3 Ramucirumab vs. placebo ^a	REACH	ESMO 2014	Lancet-O 2015
	4 S-1 vs. placebo ^a	S-CUBE	ASCO-GI 2015	
	5 Regorafenib vs. placebo ^b	RESORCE	WCGI 2016	Lancet 2017
	6 Tivantinib vs. placebo	JET-HCC	Ongoing	
	7 Ramucirumab vs. placebo	REACH-2	Ongoing	
	8 Pembrolizumab vs. placebo	KEYNOTE-240	Ongoing	

HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy. ^a Trial halted or with negative results. ^b Trial with positive results.

HCC (BCLC-C), patients with intermediate-stage HCC (BCLC-B) were included in the SHARP study and the Asia Pacific study; therefore, sorafenib is a widely approved agent for systemic therapy not only for advanced-stage HCC but also for unresectable HCC (including intermediate-stage HCC). In fact, sorafenib is often administered to patients with intermediate-stage HCC (BCLC-B) in clinical practice and to 16.4–19.6% of patients in clinical trials worldwide [3–5].

The population of patients with intermediate-stage HCC is extremely heterogeneous, comprising 3 main subpopulations: (1) patients with a good prognosis who can be treated with curative therapy, (2) those for whom transarterial chemoembolization (TACE) is indicated, and (3) those for whom TACE is not recommended. This subclassification of intermediate-stage HCC recently became a well-discussed issue, and the Kinki criteria are used to subclassify patients with intermediate-stage HCC [12, 13]. The OS of patients with B1, B2, and B3 HCC according to the Kinki criteria corresponds to that of patients with HCC of BCLC stages A, B, and C. In addition, patients with BCLC substage B2 HCC, especially those with multiple HCC tumors in both lobes, are not good candidates for TACE. For patients with intermediate-stage HCC (BCLC-B) who do not respond to TACE, an early switch to sorafenib therapy (rather than repeat ineffective TACE) results in a better survival benefit; therefore, early identification of patients that are refractory to TACE is crucial [14–17]. These data underscore the importance of establishing globally recognized, common criteria for identifying TACE failure/refractory patients in order to improve the survival of HCC patients [18].

Table 2. Results of the RESORCE trial

	Regorafenib	Placebo	HR (95% CI); <i>p</i> value
Subjects, <i>n</i>	379	194	
BCLC stage C, %	86	89	
Treatment duration, months	3.6 (1.6–7.6)	1.9 (1.4–3.9)	
OS, months	10.6 (9.1–12.1)	7.8 (6.3–8.8)	0.63 (0.50–0.79); <i>p</i> < 0.0001
PFS (mRECIST), months	3.1 (2.8–4.2)	1.5 (1.4–1.6)	0.46 (0.37–0.56); <i>p</i> < 0.0001
TTP (mRECIST), months	3.2 (2.9–4.2)	1.5 (1.4–1.6)	0.44 (0.36–0.55); <i>p</i> < 0.0001
DCR, %	65	36	<i>p</i> < 0.0001
ORR, %	11	4	<i>p</i> = 0.0047
Adverse events (grade ≥3), %	79.7	58.5	

Values are presented as median (range) unless specified otherwise. BCLC, Barcelona Clinic Liver Cancer; OS, overall survival; PFS, progression-free survival; TTP, time to progression; DCR, disease control rate; ORR, objective response rate.

The results of the RESORCE study were published recently [10]. The success of the study is attributed to the following 3 points: (1) patients for whom sorafenib therapy was terminated because of adverse events were excluded from the trial, and second-line therapy with regorafenib was provided to HCC patients who had significant disease progression during sorafenib therapy; (2) vascular invasion and extrahepatic spread were considered as separate stratification factors to avoid imbalance in the 2 arms (test agent vs. placebo); and (3) patients showing tolerance to sorafenib (patients who tolerated 400 mg sorafenib daily for a minimum of 20 days within the last 28 days before radiological progression) were enrolled. This trial design prevented the risk of dropouts due to adverse events associated with regorafenib (since the toxicity of regorafenib is similar to that of sorafenib) and minimized the effect of post-trial treatment after disease progression [18]. According to the results of the RESORCE trial, the median OS (mOS) of patients treated with regorafenib was 10.6 months (7.8 for placebo; HR 0.63; *p* < 0.0001) (Table 2). Subgroup analysis revealed that the HR of OS in patients with a Child-Pugh score of 5 was significantly better than that in patients with a Child-Pugh score of 6 (0.60 [0.40–0.79] vs. 0.80 [0.57–1.13]). This also supports the following approach to improving prognosis in the future: an early switch to sorafenib when patients become refractory to TACE and still have good liver function, such as with a Child-Pugh score of 5, with a subsequent switch to regorafenib as soon as possible after patients have shown progressive disease on sorafenib.

An exploratory analysis of the RESORCE trial showed a favorable OS of 26 months from the start of sorafenib therapy among patients who received sorafenib-regorafenib sequential therapy (19.2 months in the placebo group) [19]. These are extremely important data, because the 26-month prognosis is comparable with the conventional figure after TACE for patients with intermediate-stage HCC [20]. To date, 3 prospective phase III trials evaluating combination therapy with sorafenib and TACE have been performed (Table 1). The results of 2 of these trials have been published: the Japan-Korea TACE study (*n* = 450) [21] and the brivanib-TACE (BRISK-TA) study, which evaluated adjuvant brivanib therapy in combination with TACE (*n* = 502) [20]. Because the mOS was not reached in the placebo arm in the post-TACE study, the BRISK-TA study is currently the only prospective phase III study that investigated the OS with TACE and provided a valid mOS for the placebo arm. Since this was a randomized controlled trial (RCT) of TACE (with the largest number of patients included in any trial worldwide) and the placebo arm was free from selection bias, it provides standard outcomes for TACE worldwide. Additionally, most (82%) of the patients in the BRISK-TA study had

Table 3. Comparison of mOS between TACE and sorafenib-regorafenib sequential therapy

	TACE (placebo arm of brivanib-TACE trial) [20]	Sorafenib-regorafenib sequential therapy (RESORCE trial) [10, 19]
Subjects, <i>n</i>	253	379
Child-Pugh class, <i>n</i> (%)		
A	231 (91)	373 (98)
B	20 (8)	5 (1)
C	2 (1)	0 (0)
BCLC stage, <i>n</i> (%)		
A	57 (23)	1 (0 < 1)
B	150 (59)	53 (14)
C	44 (17)	325 (86)
D	2 (1)	0 (0)
mOS, months	26.1	26

mOS, median overall survival; TACE, transarterial chemoembolization; BCLC, Barcelona Clinic Liver Cancer.

early- or intermediate-stage HCC (BCLC-B, 59%; BCLC-A, 23%) and only 17% had advanced-stage HCC. Conversely, 86% of the patients in the RESORCE trial had advanced-stage HCC (BCLC-C), even though the detailed status of BCLC stage at the start of sorafenib therapy is not disclosed. A simple comparison of OS between the 2 cohorts in different RCTs shows similar outcomes: 26.1 months for the control arm of BRISK-TA versus 26 months for sorafenib-regorafenib sequential therapy (Table 3). Although comparing one arm from an RCT with an arm from exploratory analysis of a different RCT may not be appropriate, both were well-designed prospective randomized clinical trials that minimized the effect of selection bias. Considering that the patients in the sorafenib-regorafenib sequential therapy trial overwhelmingly had advanced-stage HCC, the OS in the study, which is comparable to that in BRISK-TA, is extremely impressive. There is no doubt that the group of subjects with advanced-stage HCC were superselected; nevertheless, the effect of sorafenib-regorafenib sequential therapy in patients with advanced-stage HCC is comparable to that of TACE in those for whom TACE is indicated.

Since the prognosis after sorafenib-regorafenib sequential therapy is promising, the appropriate time to start sorafenib therapy may need to be reconsidered. Conventionally, patients are switched from TACE to systemic therapy when they become refractory to TACE; however, a more proactive approach, such as the earlier introduction of systemic therapy to subgroups of patients who are likely to become refractory to TACE when their liver function is still preserved (Child-Pugh A), may be beneficial (Fig. 1).

Another unaddressed question is the proportion of patients who can be treated by sorafenib-regorafenib sequential therapy. In other words, even after the approval of regorafenib, further studies are needed to obtain real-world data on the percentage of patients undergoing sorafenib therapy who can complete the therapy and also complete regorafenib therapy after failure of sorafenib treatment and disease progression. However, the optimal time point to determine TACE refractoriness should not be missed, since the prognosis after sorafenib-regorafenib sequential therapy is good (26 months from the initiation of sorafenib therapy). Early identification of subgroups likely to become refractory to TACE is also important (Fig. 2). The selection of patients who are likely to respond to systemic therapy is a valid and important line of inquiry regarding therapy with other agents, including lenvatinib (discussed below) and sorafenib.

Fig. 1. Treatment strategy for systemic therapy for hepatocellular carcinoma. Identification of the subgroup that easily develops to transarterial chemoembolization (TACE) failure/refractoriness may be important. For that subgroup, systemic therapy with a lenvatinib/sorafenib-regorafenib sequence may be a more adequate treatment strategy than repeating ineffective TACE for improving patient survival/benefit. BSC, best supportive care; OS, overall survival.

A New First-Line Therapy Option: Lenvatinib

Lenvatinib is an oral multi-tyrosine kinase receptor inhibitor that targets VEGF receptors 1–3, FGFR 1–4, PDGFR α , and the KIT and RET proto-oncogenes. It is approved worldwide for the treatment of radioactive iodine-refractory differentiated thyroid cancer. A phase II study evaluating lenvatinib for HCC treatment showed good outcomes, with an mOS of 18.7 months, a time to progression (TTP) of 7.4 months, an objective response rate (ORR) of 37%, and a disease control rate of 78% (according to the modified Response Evaluation Criteria in Solid Tumors [RECIST]) [22]. Considering that the ORR in the control arm of the BRISK-TA study was 42%, the ORR of 37% among those treated with lenvatinib may indicate that the levels of tumor necrosis induced by lenvatinib are similar to those induced by TACE (Table 4).

A worldwide press release by Eisai Co., Ltd. (January 25, 2017) revealed the results of the phase III REFLECT trial involving 954 patients with unresectable HCC [11]. Achievement of the primary endpoint (OS) in the lenvatinib trial was not inferior to that with sorafenib. The secondary endpoints (progression-free survival, TTP, and ORR) also showed that lenvatinib is statistically superior to sorafenib, with clinical significance. Details will be reported at relevant conferences and in journals. The approval of lenvatinib as a novel agent for unresectable HCC in Asia, Japan, Europe, and the USA is anticipated. The improvement of OS with lenvatinib, which is similar to that reported for sorafenib, will likely lead to the approval of lenvatinib as a first-line agent, in addition to sorafenib, for unresectable HCC.

Once lenvatinib will be approved and will become available for treating HCC patients, criteria for the differential use of lenvatinib and sorafenib in the clinical setting will need to be established. The benefits of sorafenib-regorafenib sequential therapy were demonstrated

Fig. 2. Heterogeneity and treatment strategy for intermediate-stage hepatocellular carcinoma. Substage B2 (bilobar multiple nodules) may be a candidate for clinical trials of transarterial chemoembolization (TACE) combination therapy with tyrosine kinase inhibitors or immunotherapy. This subgroup may easily become refractory to TACE. CP, Child-Pugh; RFA, radiofrequency ablation; cTACE, conventional subsegmental Lipiodol TACE; DEB, drug-eluting beads; HAIC, hepatic arterial infusion chemotherapy. Modified with permission by Kudo et al. [12].

Table 4. Comparison of ORR and DCR between TACE and lenvatinib

	TACE (placebo arm of brivanib-TACE trial) [20]	Lenvatinib (phase II trial) [22]
Subjects, <i>n</i>	253	46
Child-Pugh class, <i>n</i> (%)		
A	231 (91)	45 (97.8)
B	20 (8)	1 (2.2)
C	2 (1)	
BCLC stage, <i>n</i> (%)		
A	57 (23)	0 (0)
B	150 (59)	19 (41.3)
C	44 (17)	27 (58.7)
D	2 (1)	0 (0)
ORR, <i>n</i> (%)	106 (42)	17 (37)
DCR, <i>n</i> (%)	199 (79)	36 (78)

ORR, objective response rate; DCR, disease control rate; TACE, transarterial chemoembolization; BCLC, Barcelona Clinic Liver Cancer

in a solid reliable prospective study [10, 19]. Second-line therapy with regorafenib resulted in significant improvement in patients who had suffered disease progression while on first-line sorafenib, with an mOS of 26 months from the start of sorafenib therapy, even in a group with predominantly advanced-stage HCC (BCLC-C) [19]. However, it is pertinent to note that the subject population was carefully selected.

On the other hand, lenvatinib showed clinically significant antitumor effects (progression-free survival, TTP, and ORR) superior to sorafenib, as disclosed by a press release [11] and phase II trial results [22]. This therapeutic agent is expected to be as effective as TACE in terms of reducing tumor size and inducing tumor necrosis. In some cases, it is expected to permit conversion from systemic therapy to TACE or curative options such as resection or ablation [23–26]. This is a potential advantage of lenvatinib.

For all intents and purposes, the arrival of regorafenib and lenvatinib provides the possibility of systemic therapy as an option for a subgroup of patients with intermediate-stage HCC who easily become or are refractory to TACE, in addition to those with advanced-stage HCC. Patients with intermediate-stage HCC who are likely to become refractory to TACE need to be identified to allow proactive intervention with systemic therapy (Fig. 1).

Conclusion

The results of phase III studies investigating 2 new therapeutic agents for HCC – namely, regorafenib and lenvatinib – were recently disclosed. The former was presented at a conference in June 2016, and results were published in a journal in January 2017; the latter was announced in a press release in January 2017. Sorafenib-regorafenib sequential therapy is of particular interest. The performance of lenvatinib will remain unclear until relevant congresses or publications; however, based on the contents of the press release, it is very likely to be indicated for the first-line treatment of unresectable HCCs. This suggests that additional therapeutic options will become available for patients with intermediate-stage (BCLC-B) as well as advanced-stage (BCLC-C) HCC.

References

- 1 Llovet JM, Ricci S, Mazzaferro V, et al: Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;359:378–390.
- 2 Cheng AL, Kang YK, Chen Z, 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.
- 3 Cheng AL, Kang YK, Lin DY, et al: Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. *J Clin Oncol* 2013;31:4067–4075.
- 4 Johnson PJ, Qin S, Park JW, et al: Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. *J Clin Oncol* 2013;31:3517–3524.
- 5 Cainap C, Qin S, Huang WT, et al: Linifanib versus sorafenib in patients with advanced hepatocellular carcinoma: results of a randomized phase III trial. *J Clin Oncol* 2015;33:172–179.
- 6 Llovet JM, Decaens T, Raoul JL, 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.
- 7 Zhu AX, Kudo M, Assenat E, 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.
- 8 Zhu AX, Park JO, Ryoo BY, 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.

- 9 Bruix J, Merle P, Granito A, et al: Efficacy and safety of regorafenib versus placebo in patients with hepatocellular carcinoma (HCC) progressing on sorafenib: results of the international, randomized phase 3 RESORCE trial (abstract LBA-03). *Ann Oncol* 2016;27(suppl 2):ii140–ii141.
- 10 Bruix J, Qin S, Merle P, 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.
- 11 Eisai Co., Ltd.: Phase III trial of anticancer agent Lenvima® as first-line treatment for unresectable hepatocellular carcinoma meets primary endpoint. News Release No. 17-06, January 25, 2017.
- 12 Kudo M, Arizumi T, Ueshima K, et al: Subclassification of BCLC B stage hepatocellular carcinoma and treatment strategies: proposal of modified Bolondi's subclassification (Kinki criteria). *Dig Dis* 2015;33:751–758.
- 13 Arizumi T, Ueshima K, Iwanishi M, et al: Validation of Kinki criteria, a modified substaging system, in patients with intermediate stage hepatocellular carcinoma. *Dig Dis* 2016;34:671–678.
- 14 Ogasawara S, Chiba T, Ooka Y, et al: Efficacy of sorafenib in intermediate-stage hepatocellular carcinoma patients refractory to transarterial chemoembolization. *Oncology* 2014;87:330–341.
- 15 Arizumi T, Ueshima K, Chishina H, et al: Validation of the criteria of transcatheter arterial chemoembolization failure or refractoriness in patients with advanced hepatocellular carcinoma proposed by the LCSGJ. *Oncology* 2014;87(suppl 1):32–36.
- 16 Kudo M, Matsui O, Izumi N, et al: Transarterial chemoembolization failure/refractoriness: JSH-LCSGJ criteria 2014 update. *Oncology* 2014;87(suppl 1):22–31.
- 17 Arizumi T, Ueshima K, Minami T, et al: Effectiveness of sorafenib in patients with transcatheter arterial chemoembolization (TACE) refractory and intermediate-stage hepatocellular carcinoma. *Liver Cancer* 2015;4:253–262.
- 18 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.
- 19 Finn RS, Merle P, Granito A, et al: Outcomes with sorafenib (SOR) followed by regorafenib (REG) or placebo (PBO) for hepatocellular carcinoma (HCC): results of the international, randomized phase 3 RESORCE trial. *J Clin Oncol* 2017;35(suppl 4S):abstract 344.
- 20 Kudo M, Han G, Finn RS, et al: Brivanib as adjuvant therapy to transarterial chemoembolization in patients with hepatocellular carcinoma: a randomized phase III trial. *Hepatology* 2014;60:1697–1707.
- 21 Kudo M, Imanaka K, Chida N, et al: Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. *Eur J Cancer* 2011;47:2117–2127.
- 22 Ikeda K, Kudo M, Kawazoe S, et al: Phase 2 study of lenvatinib in patients with advanced hepatocellular carcinoma. *J Gastroenterol* 2016, Epub ahead of print.
- 23 Kudo M, Izumi N, Sakamoto M, et al: Survival analysis over 28 years of 173,378 patients with hepatocellular carcinoma in Japan. *Liver Cancer* 2016;5:190–197.
- 24 Kudo M: Surveillance, diagnosis, treatment, and outcome of liver cancer in Japan. *Liver Cancer* 2015;4:39–50.
- 25 Kudo M: Locoregional therapy for hepatocellular carcinoma. *Liver Cancer* 2015;4:163–164.
- 26 Tsurusaki M, Murakami T: Surgical and locoregional therapy of HCC: TACE. *Liver Cancer* 2015;4:165–175.