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Editorial

Lenvatinib May Drastically Change the Treatment Landscape of Hepatocellular Carcinoma

Masatoshi Kudo

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

Prof. M. Kudo

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Introduction

Sorafenib, which was shown to improve survival in the SHARP [1] and Asia-Pacific [2] trials, has been the standard therapy for unresectable hepatocellular carcinoma (HCC) since 2007.

Since then, several first-line clinical trials have been conducted with the aim of developing molecular targeted agents showing better efficacy or safety than sorafenib [3] (Table 1). A superiority trial comparing sorafenib with sunitinib (SUN1170 trial) showed that sunitinib is not superior but rather significantly inferior to sorafenib regarding the primary endpoint of overall survival (OS) [4]. The BRISK-FL and LiGHT trials showed that brivanib and linifanib are not superior and, moreover, not noninferior, despite the fact that the trial designs allowed for assessment of noninferiority [5, 6]. A superiority trial of sorafenib plus erlotinib (SEARCH trial) [7], a superiority trial of sorafenib plus doxorubicin (CALGB808028 trial), and a trial investigating sorafenib plus hepatic arterial infusion chemotherapy (HAIC) (SILIUS trial) [8] all failed. The results of two superiority trials comparing sorafenib with radioembolization called SARAH (SorAfenib versus Radioembolization in Advanced Hepatocellular carcinoma) [9] and SIRveNIB (Study to Compare Selective Internal Radiation Therapy [SIRT] Versus Sorafenib in Locally Advanced Hepatocellular Carcinoma [HCC]) were also reported at EASL 2017 and ASCO 2017, although these trials failed as well [10]. These results highlight the diffi-

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

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Table 1. Phase III clinical trials of advanced-stage HCC

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

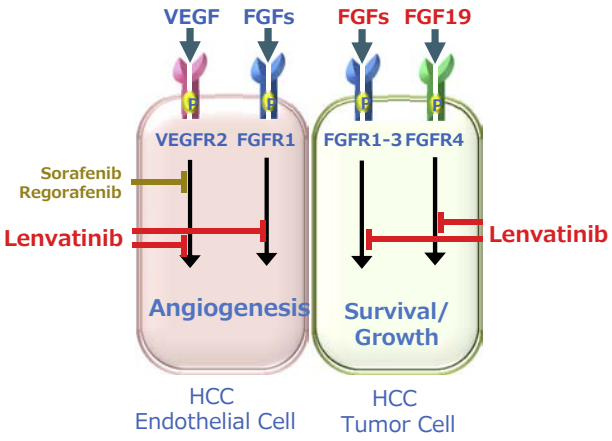
Red, positive trials; Blue, ongoing trials; Black, negative trials. [a] HAIC, hepatic arterial infusion chemotherapy. [b] DT; doxorubicin-loaded nanoparticles.

Table 2. Randomized phase II and phase III clinical trials of early/intermediate-stage HCC

Target population		Design	Trial name	Result	Presentation	Publication	1st author
Early	Adjuvant (prevention of recurrence)	1. Vitamin K_2 vs. placebo		Negative		Hepatology 2011	Yoshida H.
		2. Peretinoin vs. placebo	NIK-333	Negative	ASCO 2010	J Gastroenterol 2014	Okita K.
		3. Sorafenib vs. placebo	STORM	Negative	ASCO 2014	Lancet Oncol 2015	Bruix J.
		4. Peretinoin vs. placebo	NIK-333/K-333	Ongoing			
	Improvement of RFA	1. RFA ± LTLD[a]	HEAT	Negative	ILCA 2013	Clin Cancer Res 2017	Tak W.Y.
		2. RFA ± LTLD[a]	OPTIMA				
Intermediate	Improvement of TACE	1. TACE ± sorafenib	Post-TACE	Negative	ASCO-GI 2010	Eur J Cancer 2011	Kudo M.
		2. TACE ± sorafenib	SPACE (Ph II)	Negative	ASCO-GI 2012	J Hepatol 2016	Lencioni R.
		3. TACE ± brivanib	BRISK-TA	Negative	ILCA 2013	Hepatology 2014	Kudo M.
		4. TACE ± orantinib	ORIENTAL	Negative	EASL 2015	Lancet Gastroenterol Hepatol 2017	Kudo M.
		5. TACE ± sorafenib	TACE-2	Negative	ASCO 2016	Lancet Gastroenterol Hepatol 2017	Meyer T.
		6. TACE ± sorafenib	TACTICS (Ph II)	Positive	ASCO-GI 2018		Kudo M.

Red, positive trial; Blue, ongoing trial, Black, negative trials. [a] LTLD, lyso-thermosensitive liposomal doxorubicin.

TKR	IC_{50} (nmol/L)	
	Sorafenib	Lenvatinib
VEGFR-1	21	4.7
VEGFR-2	21	3
VEGFR-3	16	2.3
FGFR1	340	61
FGFR2	150	27
FGFR3	340	52
FGFR4	3400	43
PDGFRα	1.6	29
PDGFRβ	27	160
c-KIT	140	85
RET	15	6.4



c-KIT, receptor for stem cell factor; c-MET, proto-oncogene for hepatocyte growth factor receptor; IC_{50}, 50% inhibitory concentration; PDGFR, platelet-derived growth factor receptor; PTC, papillary thyroid cancer; RET, rearranged during transfection; TKI, tyrosine kinase inhibitor; TKR, tyrosine kinase receptor; VEGFR, vascular endothelial growth factor receptor.

Fig. 1. Dual inhibition of VEGF and FGF pathways by lenvatinib (cited from Tohyama et al. [13]).

culties associated with conducting clinical trials of first-line HCC drugs using OS as the endpoint, and demonstrate the superiority of sorafenib for improving survival compared with other drugs.

Amid these failed trials, the results of a phase III trial of lenvatinib and sorafenib were presented at ASCO 2017. The trial met the primary endpoint of noninferiority, a shocking result that produced the greatest breakthrough in 10 years, suggesting a new option for first-line molecular targeted therapy [11]. Another recent development was the improvement in progression-free survival (PFS) achieved with sorafenib plus transcatheter arterial chemoembolization (TACE), as this approach was extremely challenging to develop (Table 2) [12].

Development History of Lenvatinib

Lenvatinib was discovered at Tsukuba Research Laboratory in Japan as a result of exploratory research on angiogenesis inhibitors. It primarily inhibits vascular endothelial growth factor (VEGF) receptors (VEGFR1–3), fibroblast growth factor (FGF) receptors (FGFR1–4), KIT, and RET [13]. Lenvatinib simultaneously suppresses the activity of factors involved in tumor angiogenesis while also suppressing proliferation signals from VEGFR and FGFR, which are strongly expressed in cancer cells. Because of these properties, lenvatinib is an extremely effective inhibitor of angiogenesis (Fig. 1) [14]. Inhibition of FGFR4 in particular is considered a critical and important factor in the antitumor effects of lenvatinib [15–19].

The recommended dose is 24 mg/day based on the results of phase I trials in solid cancers and subsequent trials in other cancers. However, a recommended dose had to be established specifically for patients with HCC, because lenvatinib is primarily metabolized by cytochrome P450 3A in the liver, and could potentially have a different adverse event (AE) profile in patients with HCC associated with liver cirrhosis than in patients with other solid cancers. A phase I trial in patients with Child-Pugh A and B HCC was conducted for that purpose. Based

Table 3. REFLECT: investigator assessment according to mRECIST

	Lenvatinib (n = 478)	Sorafenib (n = 476)	HR/OR	p value
OS, months	13.6 (12.1–14.9)	12.3 (10.4–13.9)	HR 0.92 (0.79–1.06)	–
PFS, months	7.4 (6.9–8.8)	3.7 (3.6–4.6)	HR 0.66 (0.57–0.77)	<0.0001
TTP, months	8.9 (7.4–9.2)	3.7 (3.6–5.4)	HR 0.63 (0.53–0.73)	<0.0001
ORR, %	24.1 (20.2–27.9)	9.2 (6.6–11.8)	OR 3.13 (2.15–4.56)	<0.0001

Values in parentheses are 95% CI. OS, overall survival; PFS, progression-free survival; TTP, time to progression; ORR, objective response rate; HR, hazard ratio; OR, odds ratio. Cited and modified from Kudo et al. [11].

on the results, the recommended dose was set at 12 mg/day for Child-Pugh A patients and 8 mg/day for Child-Pugh B patients [20].

A phase II trial in patients with HCC conducted in Japan and South Korea confirmed the potent antitumor effect of lenvatinib and the feasibility of managing AEs in patients with HCC [21]. A later detailed analysis of the pharmacokinetics of lenvatinib in patients with HCC determined that the optimal dose was 8 mg/day for patients weighing less than 60 kg and 12 mg/day for patients weighing 60 kg or more. These findings sparked the planning of a phase III trial comparing lenvatinib with sorafenib (REFLECT trial).

Overview of the REFLECT Trial Results

The REFLECT trial was a global, randomized, open-label, phase III noninferiority trial. The trial enrolled patients with unresectable HCC with no history of systemic chemotherapy, and they were randomized 1:1 to lenvatinib and sorafenib arms. Patients were stratified by region (Asia or non-Asia), macroscopic portal vein involvement and/or extrahepatic spread, ECOG performance status (0 or 1), and body weight (<60 kg or ≥60 kg). Treatment was continued until disease progression or onset of an intolerable AE. Noninferiority of OS was set as the primary endpoint, and the noninferiority margin was set at 1.08. Time to progression (TTP), PFS, objective response rate (ORR), and safety were evaluated as secondary endpoints.

Of the 954 patients enrolled, 478 were assigned to the lenvatinib arm and 476 to the sorafenib arm. In the lenvatinib arm, 67% of enrolled patients were from the Asia-Pacific region and 33% were from Western countries. Body weight was <60 kg in 32% and ≥60 kg in 68% of patients. Macroscopic vein involvement and/or extrahepatic spread was detected in 69% of patients, and 78% were Barcelona clinic liver cancer stage C. The proportion of patients with HCC caused by hepatitis C was favorably imbalanced toward sorafenib (26 vs. 19% in the lenvatinib arm) [11]. Conversely, the proportion of patients with HCC caused by hepatitis B was 53% in the lenvatinib arm and 48% in the sorafenib arm. The proportion of patients with an α-fetoprotein (AFP) level of ≥200 ng/mL was also favorably imbalanced toward sorafenib (39 vs. 46% in the lenvatinib arm).

The primary endpoint of OS was 13.6 months in the lenvatinib arm and 12.3 months in the sorafenib arm. The upper limit of the 95% confidence interval (CI) of the hazard ratio (HR), which was 0.92 (0.79–1.06), was below the predetermined noninferiority margin of 1.08, which demonstrated the statistically significant noninferiority of lenvatinib with respect to OS [11]. PFS, TTP, and ORR (lenvatinib arm/sorafenib arm) per investigator assessment using the modified RECIST criteria (mRECIST) were 7.4/3.7 months, 8.9/3.7 months, and 24.1/9.2%, respectively. These results demonstrate that lenvatinib had a statistically signifi-

Table 4. REFLECT: masked independent imaging review according to mRECIST

	Lenvatinib (*n* = 478)	Sorafenib (*n* = 476)	HR/OR	*p* value
PFS, months	7.3 (5.6–7.5)	3.7 (3.6–3.7)	HR 0.64 (0.55–0.75)	<0.0001
TTP, months	7.4 (7.2–9.1)	3.7 (3.6–3.9)	HR 0.60 (0.51–0.71)	<0.0001
ORR, %	40.6 (36.2-45.0)	12.4 (9.4-15.4)	OR 5.01 (3.59–7.01)	<0.0001

Values in parentheses are 95% CI. PFS, progression-free survival; TTP, time to progression; ORR, objective response rate; HR, hazard ratio; OR, odds ratio. Cited and modified from Kudo et al. [11].

Table 5. REFLECT: masked independent imaging review according to RECIST1.1

	Lenvatinib (*n* = 478)	Sorafenib (*n* = 476)	HR/OR	*p* value
PFS, months	7.3 (5.6–7.5)	3.6 (3.6–3.9)	HR 0.65 (0.56–0.77)	<0.0001
TTP, months	7.4 (7.3–9.1)	3.7 (3.6–5.4)	HR 0.61 (0.51–0.72)	<0.0001
ORR, %	18.8 (15.3–22.3)	6.5 (4.3–8.7)	OR 3.34 (2.17–5.14)	<0.0001

Values in parentheses are 95% CI. PFS, progression-free survival; TTP, time to progression; ORR, objective response rate; HR, hazard ratio; OR, odds ratio. Cited and modified from Kudo et al. [11].

cantly better antitumor effect than sorafenib (Table 3) [11]. Another surprising finding was that tumor shrinkage according to the masked independent imaging review using mRECIST was considerably greater in the lenvatinib arm than in the sorafenib arm (ORR: 40.6 vs. 12.4%) (Table 4) [11]. This favorable antitumor effect indicated by the PFS, TTP, and ORR rates was reproduced exactly in a masked independent imaging review using RECIST 1.1 (Table 5) [11].

Since patients were not stratified by AFP in this trial, the lenvatinib arm had a higher proportion of patients with AFP of ≥200 ng/mL. When this AFP imbalance was corrected by analysis of covariance in the OS analysis, lenvatinib demonstrated a statistically significant superior effect over sorafenib with respect to OS (HR = 0.856, 95% CI = 0.736–0.995, nominal $p = 0.0342$) (Fig. 2) [11]. This result indicates that the trial may have demonstrated superiority if patients had been stratified by AFP.

In the OS subanalysis, lenvatinib was superior to sorafenib for improving OS in almost all groups. One particularly noteworthy finding was that lenvatinib was more effective than sorafenib for improving OS even in patients weighing <60 kg who received a dose of only 8 mg, and the HR was even better than that in patients weighing ≥60 kg who received 12 mg (< 60 kg: HR = 0.85 vs. ≥60 kg: HR = 0.95). This indicated that weight-based dosing is successful. Lenvatinib also yielded a good improvement in OS in patients with high AFP, a poor prognostic factor, as indicated by the HR of 0.78 (95% CI = 0.63–0.98) (Fig. 2). The only subgroup in which the numerical values indicated that sorafenib yielded better OS was that of patients enrolled in Western countries. This can be attributed to the fact that patients in the sorafenib arm in those countries frequently received post-study systemic anticancer treatment (38.9 vs. 26.1% in the lenvatinib arm), and patients in the sorafenib arm more frequently underwent anticancer procedures such as TACE (11.5 vs. 7.0% in the lenvatinib arm) (Table 6) [11]. In the Asia-Pacific region, the percentage of patients who received post-study therapy was well balanced; however, in the Western region, 45.2% of patients in the sorafenib arm received

Table 6. Post-study anticancer therapy during survival follow-up

	Lenvatinib			Sorafenib		
	Asia-Pacific subgroup (*n* = 321)	Western subgroup (*n* = 157)	total (*n* = 478)	Asia-Pacific subgroup (*n* = 319)	Western subgroup (*n* = 157)	total (*n* = 476)
Received any anticancer therapy during survival follow-up, *n* (%)	162 (50.5)	44 (28.0)	206 (43.1)	172 (53.9)	71 (45.2)	243 (51.1)
Received any anticancer medication (not given for any procedure) during survival follow-up, *n* (%)	115 (35.8)	41 (26.1)	156 (32.6)	123 (38.6)	61 (38.9)	184 (38.7)
Underwent any anticancer procedure during survival follow-up, *n* (%)	111 (34.6)	11 (7.0)	122 (25.5)	112 (35.1)	18 (11.5)	130 (27.3)

Anticancer therapy includes anticancer medication and anticancer procedure. Cited from Kudo et al. [11].

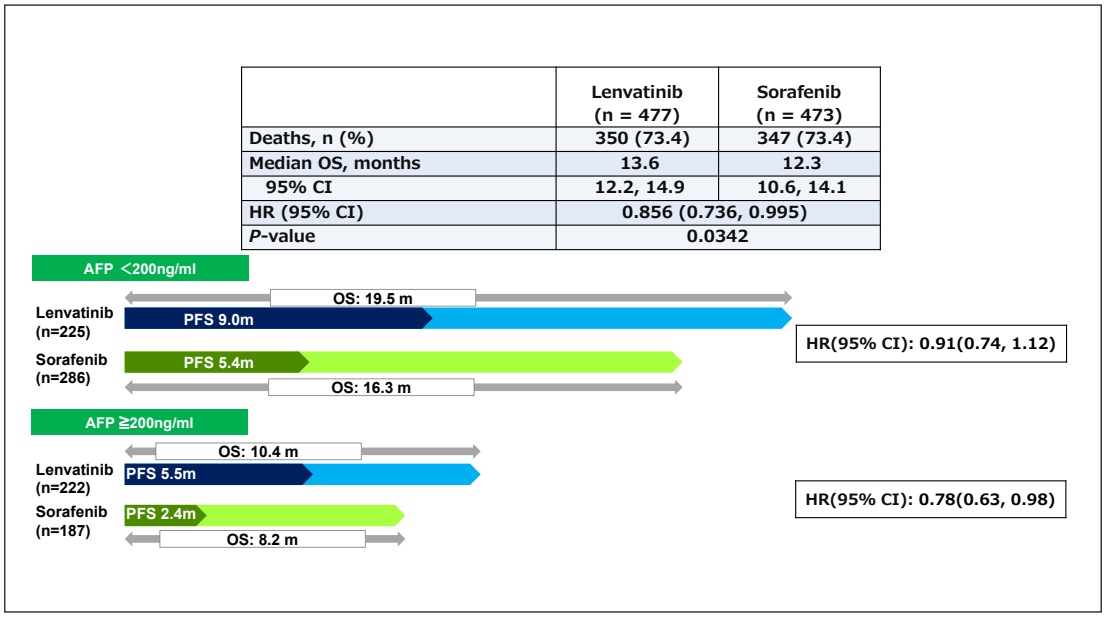


Fig. 2. Overall survival adjusted by baseline AFP (<200 ng/mL and ≥200 ng/mL). AFP, α-fetoprotein; HR, hazard ratio.

post-study treatment versus 28.0% in the lenvatinib arm. An imbalance between the treatment arms was observed in the proportion of patients who received post-anticancer therapy during the survival follow-up, which was higher in the sorafenib than in the lenvatinib arm: 51.1% (243/476) versus 43.1% (206/478), respectively. In post-study treatment, new agents were used in 17.0% of patients in the sorafenib arm compared with 5.9% in the lenvatinib arm. In the lenvatinib arm, 25.3% of patients received sorafenib after progression, and 11.8% of patients in the sorafenib arm were rechallenged with sorafenib (Table 7) [22].

Table 7. Subsequent anticancer therapy during survival follow-up

	Lenvatinib (*n* = 478), *n* (%)	Sorafenib (*n* = 476), *n* (%)
Subjects with any anticancer medication[a]	156 (32.6)	184 (38.7)
Post-study treatment with new agents	28 (5.9)	81 (17.0)
Investigational drugs[b]	20 (4.2)	73 (15.3)
Checkpoint inhibitors	9 (1.9)	9 (1.9)
Cytotoxic chemotherapy	44 (9.2)	77 (16.2)
Sorafenib	121 (25.3)	56 (11.8)
Other	25 (5.2)	31 (6.5)

[a] Anticancer medication: not given for any procedure. [b] Investigational drugs including drugs coded as investigational drugs, tivantinib, regorafenib, cabozantinib, and the other VEGF inhibitors.

Treatment duration was 5.7 months in the lenvatinib arm and 3.7 months in the sorafenib arm, indicating that treatment with lenvatinib was better tolerated. Dose intensity of the planned starting dose was also slightly better in the lenvatinib arm than in the sorafenib arm (88 vs. 83%).

The above results demonstrate the statistically significant noninferiority of lenvatinib over sorafenib with respect to OS, and statistically and clinically meaningful improvements were also observed in the secondary endpoints (PFS, TTP, and ORR). These findings indicate that lenvatinib is an effective first-line drug for unresectable HCC.

Factors Contributing to the Success of the REFLECT Trial

Several critical factors contributed to the first successful demonstration of noninferiority of a first-line drug in 10 years. The REFLECT trial was the first noninferiority trial of a molecular targeted agent with dose selection by body weight (12 vs. 8 mg). In the GIDEON observational study, only 45.5% of Japanese patients started sorafenib at 800 mg, and there was no clear evidence to support reducing doses based on patients' body weight [23]. In the lenvatinib arm, the same level of efficacy was obtained across weight groups (<60 kg and ≥60 kg), and toxicity was within an acceptable range. The incidence of hand-foot skin reaction and diarrhea was lower, enabling longer treatment duration in the lenvatinib than in the sorafenib arm. The antitumor effect was surprisingly better (ORR: 40.6%), and no other molecular targeted drug has yielded such good response rates (Fig. 3, 4) [24–27]. PFS and TTP were also better for lenvatinib than for sorafenib, supporting that its antitumor effect is more potent than that of sorafenib. Another factor contributing to the success of the trial was that patients could receive an additional 2 months of treatment with lenvatinib because of its acceptable AE profile and slightly greater tolerability than sorafenib in some respects.

The REFLECT trial did not demonstrate superiority over sorafenib likely because of the unfavorably high proportion of high-AFP patients in the lenvatinib arm, which was due to the lack of stratification by AFP and macroscopic vein involvement, as well as the higher proportion of patients with hepatitis C (a favorable prognostic factor for sorafenib) in the sorafenib arm [28]. Another possible reason was that both arms consisted of patients with favorable prognosis who were good candidates for post-study treatment because of the exclusion of patients with tumor thrombus at the main portal vein (VP4) and ≥50% tumor occupancy in the liver [29, 30]. The longer post-progression survival associated with post-study treatment in both arms may have diluted the OS benefit, as observed in previous failed trials [31–33]. In fact,

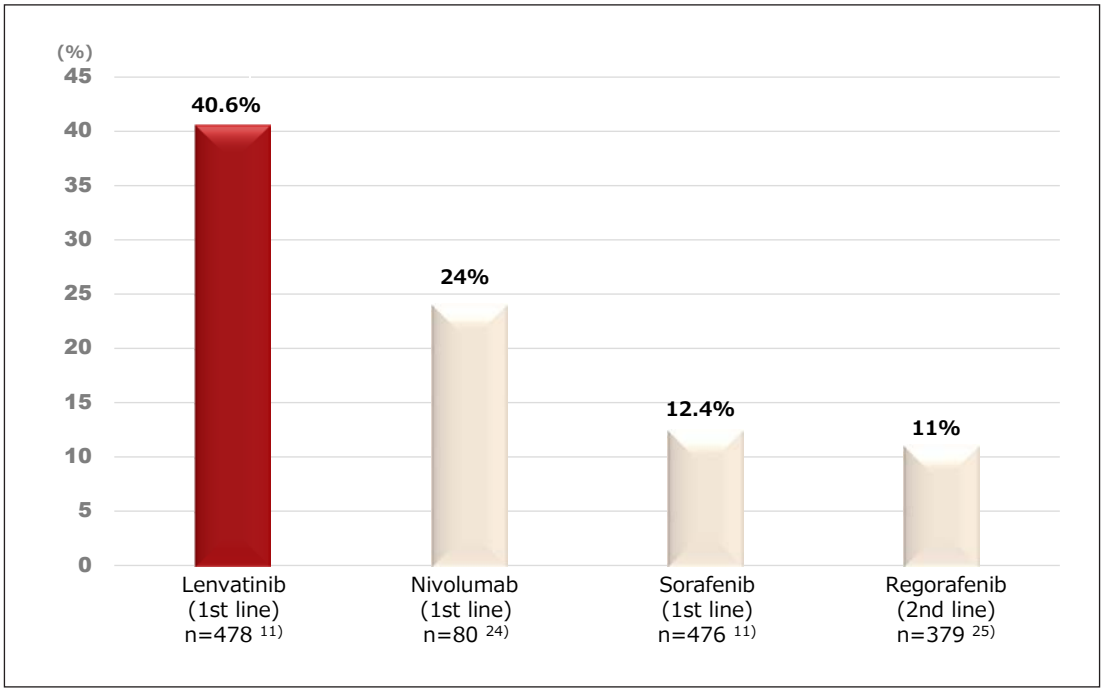


Fig. 3. Objective response rate by mRECIST in systemic therapy [11, 24, 25].

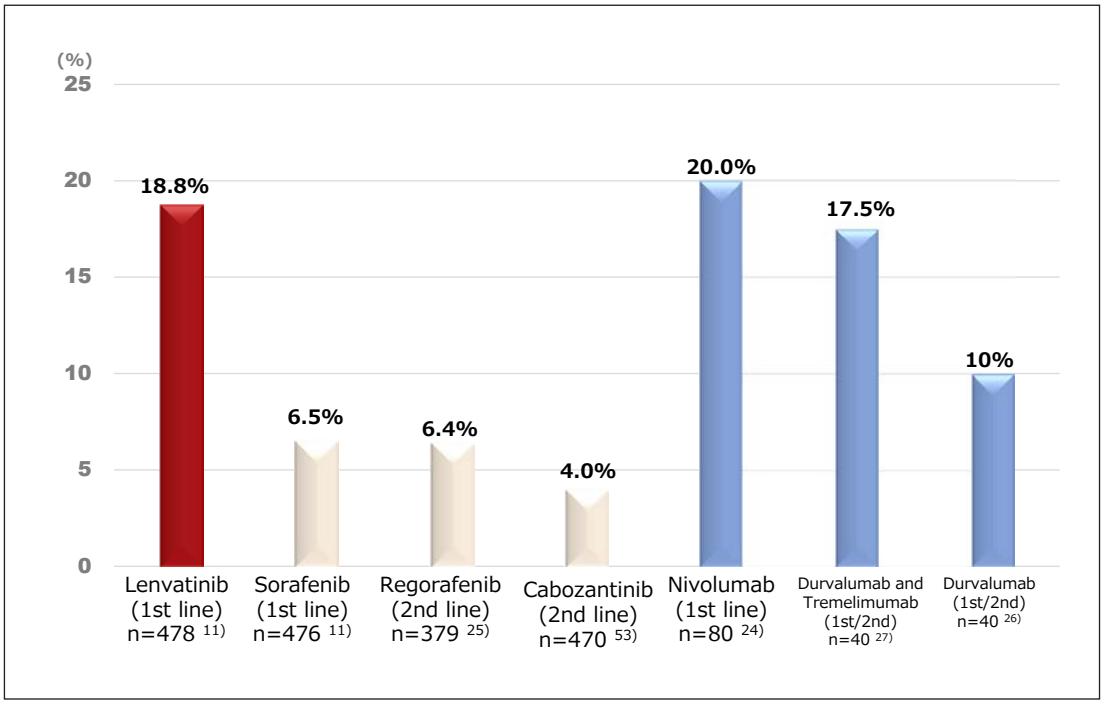


Fig. 4. Objective response rate by RECIST1.1 in systemic therapy [11, 24–27, 53].

Table 8. Stratification factors in phase III clinical trials in first-line agents for HCC

Study arm vs. sorafenib arm	SUN1170 (sunitinib)	BRISK-FL (brivanib)	LiGHT (linifanib)	SEARCH (+ erlotinib)	CheckMate-459 (nivolumab)	REFLECT (lenvatinib)
Stratification factor	Region Vascular invasion and/or extrahepatic spread Prior TACE	Region ECOG-PS score Extrahepatic spread and/or vascular invasion	Region ECOG-PS score Vascular invasion and/or extrahepatic spread Hepatitis B virus infection	Region ECOG-PS score Vascular invasion and/or extrahepatic spread Smoking status	Region Vascular invasion and/or extrahepatic spread Etiology	Region ECOG-PS score Vascular invasion and/or extrahepatic spread Body weight

Cited and modified from previously published studies [4–7, 11, 56].

patients in both the lenvatinib and sorafenib arms of the REFLECT trial received a significant amount of post-study treatment (Tables 6, 7), which resulted in extremely long OS in the sorafenib arm (12.3 months), the longest ever observed in clinical trials of first-line agents (SHARP: 10.7 months, Asia-Pacific: 6.5 months, SUN1170: 10.2 months, Brisk-FL: 9.9 months, LiGHT: 9.8 months) [1, 2, 4–6].

The imbalance in AFP was a critical issue. This was an accidental imbalance resulting from the lack of inclusion of AFP as a stratification factor. However, AFP was not commonly used as a stratification factor when the REFLECT trial was started, and it was not included in any past or current first-line trials [4–7, 11] (Table 8). In their review, Llovet et al. [34] do not recommend using AFP as a stratification factor in first-line trials. Nevertheless, as noted above, lenvatinib demonstrated statistically significant superiority over sorafenib with respect to OS when the AFP imbalance was corrected by analysis of covariance, indicating that AFP should be used as a stratification factor in future first-line trials.

AE Profile

Certain AEs were slightly more frequent in the lenvatinib arm than in the sorafenib arm, including hypertension, proteinuria, dysphonia, and hypothyroidism. Hand-foot skin reaction, diarrhea, and hair loss were slightly more frequent in the sorafenib arm than in the lenvatinib arm. The low incidence of hand-foot skin reaction, diarrhea, and other events that directly impact compliance is one reason that patients continued lenvatinib for a longer period than sorafenib. However, treatment-emergent AEs (TEAEs) of all grades were more frequent in the lenvatinib arm; the incidence of TEAEs of grade 3 or higher in particular was higher in the lenvatinib arm than in the sorafenib arm (57 vs. 49%), and the incidence of serious TEAEs was also slightly higher in the lenvatinib arm than in the sorafenib arm (18 vs. 10%) [11]. However, this can be attributed to the longer duration of treatment with lenvatinib (+2 months). The incidence of AEs of all grades, grade 3 or higher, as well as SAEs was either comparable between the two arms or lower in the lenvatinib arm after correction by actual treatment duration (Table 9) [35].

Significance of Body Weight-Based Dosing

In the phase II trial, a uniform daily dose of 12 mg irrespective of body weight and surface area led to dose reduction in a large proportion of patients: dose adjustment occurred in 34 of 46 patients (74%) because of treatment-related AEs, and withdrawal occurred in 10 patients (22%) because of toxicity. Close examination of the patients' background suggested

Table 9. Treatment-emergent adverse events (TEAEs) adjusted by treatment duration

	Lenvatinib (n = 476), AE rate	Sorafenib (n = 475), AE rate
TEAEs		
TEAE episodes	18.89%	19.73%
Related TEAE episodes	10.94%	11.98%
TEAE episodes of grade ≥3	3.16%	3.33%
Related TEAE episodes of grade ≥3	1.59%	1.80%
Serious TEAE episodes	1.26%	0.97%
Serious related TEAE episodes	0.41%	0.28%
Related episodes of TEAE leading to study drug:		
Dose reduction	0.84%	0.97%
Reductions or interruption	1.59%	1.77%
Withdrawal	0.15%	0.18%

Lenvatinib, total duration 324.2 years; sorafenib, total duration 239.1 years.

that body weight and serum lenvatinib levels were associated with dose reduction or early treatment withdrawal. More precisely, patients who had dose reduction or early withdrawal within 30 days of lenvatinib treatment were significantly lighter (median weight, 54.1 vs. 67.6 kg) and had a significantly higher minimum plasma concentration of lenvatinib (trough concentration [$C1D15C_{trough}$], 62.4 vs. 33.9 ng/mL) [36, 37].

Relationship between Body Weight and Plasma Level of Lenvatinib in HCC Patients

Following the phase I and II trials, population pharmacokinetics were analyzed in 65 HCC patients enrolled in those trials, and in 155 patients with solid cancer and 232 healthy individuals enrolled in other clinical trials [36]. A relationship was observed between body weight and plasma lenvatinib level (represented by the area under the blood concentration time curve [AUC]), indicating that exposure to lenvatinib increased as body weight decreased [36, 37]. This trend was more prominent in HCC patients than in patients with other types of solid cancers, suggesting that the relationship has an especially strong impact in HCC patients.

Relationship between Pharmacokinetics of Lenvatinib and Dose Reduction or Withdrawal in HCC Patients

Forty-five patients who participated in trials for HCC treatment were divided into a low AUC group (<2,051.1 ng•h/mL), an intermediate AUC group (>2,051.1 to ≤2,747.1 ng•h/mL), and a high AUC group (>2,747.1 ng•h/mL) to examine the relationship between AUC and time to dose reduction or withdrawal of lenvatinib. Kaplan-Meier plots showed a reduction in the time to dose reduction or withdrawal with increasing AUC [36, 37]. A similar relationship was observed between body weight and time to dose reduction or withdrawal; time to dose reduction or withdrawal became shorter as body weight decreased, demonstrating that dose reduction or withdrawal may be required earlier in lighter patients than in heavier patients [36, 37].

Optimal Cutoff Values for Body Weight and AUC in HCC Patients Treated with Lenvatinib

Strong correlations between lenvatinib withdrawal, blood concentration (AUC), and body weight indicated that dose adjustment by body weight and AUC may improve the safety of lenvatinib for the treatment of patients with HCC. The sensitivity and specificity of different

body weight cutoff values for predicting the early occurrence (within 30 days after the start of therapy) of dose reduction and withdrawal were calculated to draw receiver operating characteristic (ROC) curves [36, 37]. The optimal body weight cutoff (the point at which the distance between the top left corner of the graph and the ROC is smallest) that most effectively distinguished the high-risk group for early withdrawal or dose reduction of lenvatinib was 57.8 kg, showing a sensitivity of 0.77 and specificity of 0.67 (false-positive rate, 0.33). Similarly, the optimal AUC cutoff was 2,430 ng•h/mL, with a sensitivity of 0.71 and specificity of 0.71 (false-positive rate, 0.29) [36, 37].

Significance of Maintaining the AUC within a Certain Range and Lenvatinib Dose Adjustment in HCC

Regarding the prediction of early withdrawal or dose reduction of lenvatinib, the AUC was more effective than other factors such as sex, body weight, age, liver function, platelet count, ECOG performance status, Child-Pugh class, hepatitis viral status, portal vein tumor thrombus, prior chemotherapy, prior antihypertensive therapy, and prior surgery. An AUC probability curve [36, 37] can predict early withdrawal or dose reduction of lenvatinib. Consequently, the AUC needs to be maintained below a certain level to reduce the occurrence of early withdrawal or dose reduction; for example, lenvatinib dosing may be adjusted to obtain an AUC value that is below the optimal cutoff (2,430 ng•h/mL).

Based on the findings that the optimal body weight cutoff for a similar prediction was 57.8 kg, the predicted AUC values for weight-based dosing (daily dose of 12 or 8 mg in patients with body weight ≥60 kg or <60 kg, respectively) were calculated and plotted against body weight [36, 37]. The predicted AUC values were in the range of 1,540–2,050 ng•h/mL in patients with body weight <60 kg, and 1,410–2,310 ng•h/mL in those with body weight ≥60 kg. These AUC ranges were similar and lower than 2,430 ng•h/mL in both body weight categories, indicating that the weight-based dose adjustment might efficiently reduce early withdrawal and dose reduction of lenvatinib.

Relationship between the AUC and the Efficacy of Lenvatinib in the Treatment of HCC

A major concern is that lenvatinib dose adjustment to reduce the AUC could impair efficacy. To test this, patients enrolled in the phase II trial that tested an initial daily dose of 12 mg were divided into the low AUC group (<2,051.1 ng•h/mL), the intermediate AUC group (>2,051.1 to ≤2,747.1 ng•h/mL), and the high AUC group (>2,747.1 ng•h/mL) to examine the relationship between AUC and efficacy. There was no trend in TTP in the three groups [36, 37], suggesting that a certain level of efficacy can be maintained even when the AUC is small.

Because of the lack of data on reduced-dose sorafenib, the recommended dose remains at 400 mg twice daily even in patients with lower body weight. However, a dose of 200 mg twice daily yields a satisfactory effect in patients with lower body weight, as in Japanese patients. The REFLECT trial showed that the 8 mg dose used in patients weighing 60 kg or less was comparable or better regarding safety and efficacy than the full 12 mg dose. These results are valuable data supporting the feasibility of determining proper dosing by weight.

Quality of Life Assessment

In the REFLECT trial, quality of life (QOL) was evaluated using two health questionnaires, the EORTC QLQ-C30 and the EORTC QLQ-HCC18 (Table 10). Baseline scores were comparable between the lenvatinib and sorafenib arms, although the scores in both arms decreased after the start of treatment [11].

Table 10. QOL Questionnaire

EORTC QLQ-C30	
Role functioning	Were you limited in doing either your work or other daily activities?
	Were you limited in pursuing hobbies or other leisure activities?
Pain	Did pain interfere with your daily activities?
	Have you had pain?
Diarrhea	Have you had diarrhea?
EORTC QLQ-HCC18	
Nutrition	Have you had problems with sense of taste?
	Have you felt full up to quickly after beginning to eat?
	Have you worried about getting enough nourishment?
	Have you worried about your weight being too low?
Body image	Have you lost muscle from your arms or legs?
	Have you been concerned by the appearance of your abdomen?

However, analysis of time to clinically meaningful deterioration showed that role functioning (nominal $p = 0.0193$), pain (nominal $p = 0.0105$), and diarrhea (nominal $p < 0.0001$) in the EORTC QLQ-C30, and nutrition (nominal $p = 0.0113$) and body image (nominal $p = 0.0051$) deterioration in the EORTC QLQ-HCC18, occurred earlier in patients treated with sorafenib than in those treated with lenvatinib. QLQ-C30 summary scores were also better for lenvatinib than sorafenib (HR = 0.87).

Maintaining good QOL in patients taking medications is critically important to improve compliance. Therefore, the detection of clinically meaningful differences between lenvatinib and sorafenib in these five critical items explains why treatment with lenvatinib could continue for longer and produce such a potent antitumor effect. These high QOL measures should be reproduced in clinical practice, and will most certainly make lenvatinib a highly tolerable and effective first-line drug for patients with HCC.

Results of Exploratory Research on Blood Biomarkers

The results of blood biomarker testing were presented at the Congress of the European Society of Medical Oncology in 2017 [38]. Blood VEGF, FGF19, and FGF23 were elevated in the lenvatinib arm but not in the sorafenib arm. Angiopoietin 2 (Ang2) was decreased in the lenvatinib arm but not in the sorafenib arm. The increase in VEGF indicates that lenvatinib is a more potent inhibitor of VEGFR1–3 activity than sorafenib. The increase in FGF19 indicates that lenvatinib is a potent inhibitor of the activity of the FGF19 receptor, FGFR4. FGF23 is secreted by osteocytes and plays a key role in phosphorus homeostasis and vitamin D metabolism [39]. Increased FGF23 is a surrogate marker of FGFR1 inhibition [40], and is part of the FGF pathway escape mechanism in response to VEGF-targeted antiangiogenic therapies [41]. Therefore, increase of FGF 23 suggests that lenvatinib is a potent inhibiter of FGFR1.

Ang2 and its receptor Tie2 are regulators of angiogenesis [42], and the role of Ang2 in adaptive tumor resistance to anti-VEGF therapy was recently identified [43], suggesting that lenvatinib is a potent agent in the adaptive tumor resistance to anti-VEGF therapy. The blood concentration of PIVKA-II was lower in the lenvatinib arm than in the sorafenib arm, which reflects the potent antitumor effect of lenvatinib.

These results provide important data to explain how the effects of lenvatinib at and above the IC50 calculated from in vitro studies, particularly its suppression of VEGF and FGF receptor activity, can be reproduced in vivo (Fig. 1).

Table 11. Objective response rate of TACE and lenvatinib (mRECIST)

Placebo arm of BRISK-TA trial [49] (*n* = 253) (cTACE)	Placebo arm of SPACE trial [50] (*n* = 153) (DEB-TACE)	Placebo arm of TACE-2 trial [51] (*n* = 156) (DEB-TACE)	Lenvatinib arm of REFLECT trial [11] (*n* = 478) (systemic)
42%	28.1%	52%	40.6%

cTACE, conventional lipiodol transcatheter arterial chemoembolization. DEB-TACE, drug-eluting beads TACE.

Clinical Significance of High Response Rates

Sorafenib is a molecular targeted agent that does not yield a very high response rate, although it improves survival by maintaining stable disease for a long duration. Several drugs show significantly higher response rates than sorafenib in clinical trials; however, these trials all failed because the high response rates never led to an OS benefit (linifanib: 10.1% per RECIST 1.1; sorafenib plus HAIC: 36.3% vs. sorafenib: 17.5% per mRECIST). In a clinical trial of second-line brivanib, the drug yielded a significantly higher ORR per mRECIST than the placebo (10 vs. 2%), although it did not show OS benefit. The same outcomes were obtained with ramucirumab, which yielded a higher response rate per RECIST 1.1 than the placebo (7 vs. <1%), but could not show OS benefit. However, it would be premature to conclude from these findings that the ORR has absolutely no positive impact on survival. Measures such as disease control rate, PFS, TTP, and ORR are inherently critical factors in the antitumor effect of a drug. However, in clinical trials in HCC, other sources of "noise" overwhelm these signals, and a complex web of various factors determines whether the trial will succeed or fail. In fact, even in the RESORCE trial, which succeeded because of its excellent study design, regorafenib had a greater antitumor effect (TTP or PFS) than the placebo and a significantly greater ORR per mRECIST (11 vs. 4%) [25]. Not only the response rate but also a clinical trial design is an important factor for the success to the OS endpoint trial of systemic therapy. However, when it comes to clinical practice, once approved a better response rate is an extremely favorable feature. Indeed, necrotic effect assessed by mRECIST in systemic therapy correlates well with OS [44–47].

A high response rate is extremely important for drugs that have moved from successful clinical trials into clinical use as mentioned above. Drugs with good response rates are not only highly effective, but also increase the motivation of physicians and patients to continue the treatment, as well as increasing compliance; in addition, they have the potential for curative conversion (e.g., surgical resection or ablation or TACE) through downstaging.

For example, TACE, the standard therapy for intermediate-stage HCC, generally has an excellent necrotic effect on tumors and is associated with a good prognosis in responders [48]. Indeed, TACE has made treatment effectiveness feasible for both physicians and patients, increasing their motivation to continue treatment. To describe TACE as the global standard for response rate, the most trustworthy source of data would be the control arms of well-designed prospective randomized trials investigating combination therapy with TACE.

ORRs in the BRISK-TA [49], SPACE [50], and TACE-2 [51] trials were 42, 28.1, and 52%, respectively (Table 11; Fig. 5), and the BRISK-TA results could be considered the global standard because the study had the largest enrollment and was conducted on a global scale. The ORR for TACE in the control arm of the BRISK-TA trial was 42%, which was comparable to the 40.6% ORR for lenvatinib. This indicates that systemic therapy with lenvatinib can

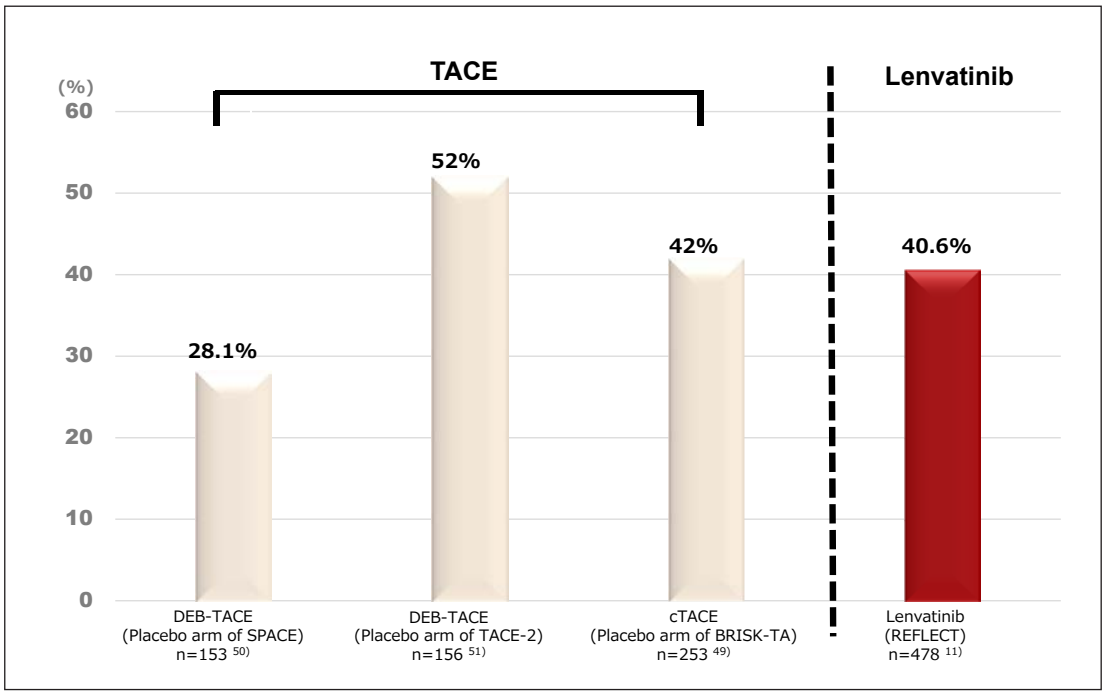


Fig. 5. Objective response rate by mRECIST TACE and lenvatinib [11, 49–51].

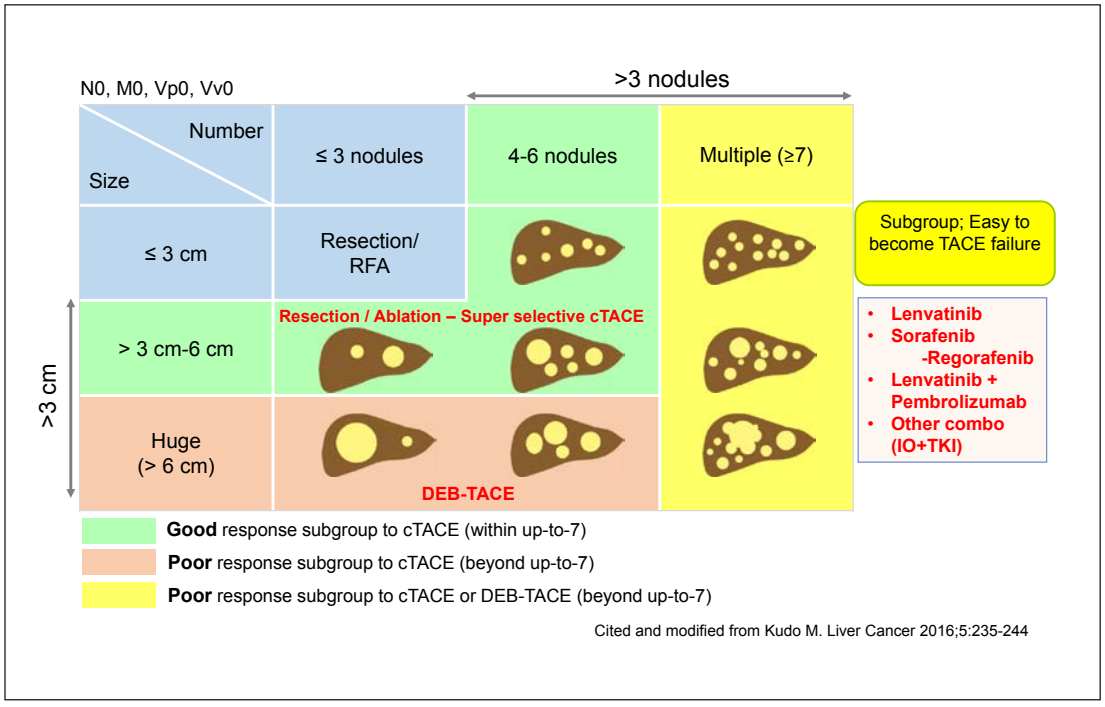


Fig. 6. Heterogeneity and treatment strategy of intermediate-stage HCC [52, 54].

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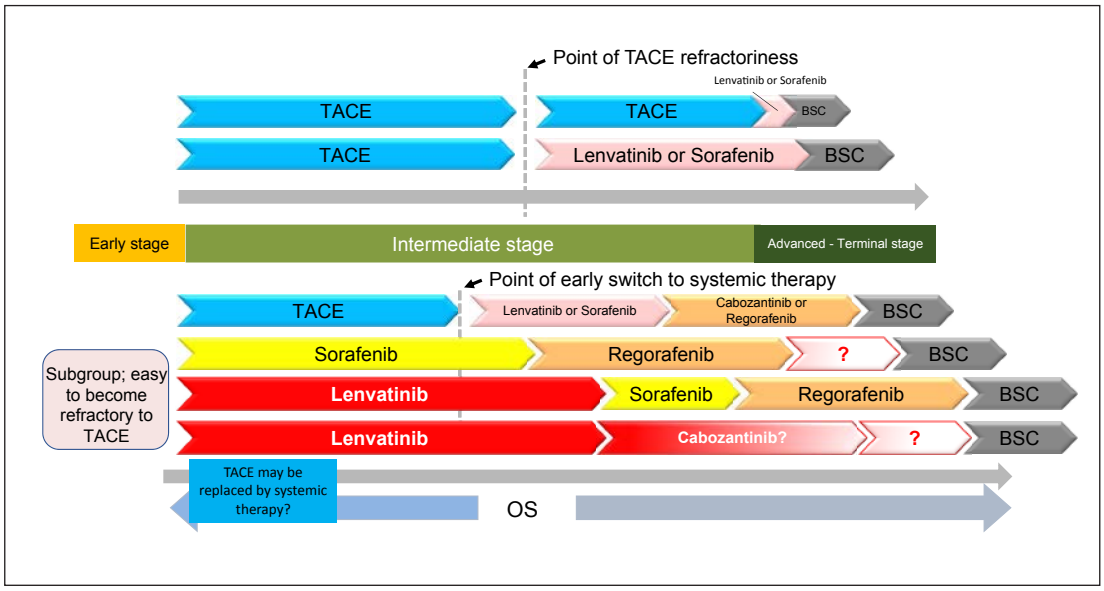

Fig. 7. Treatment strategy for systemic therapy for HCC. Identification of the subgroup that easily develops to TACE failure/refractoriness may be important.

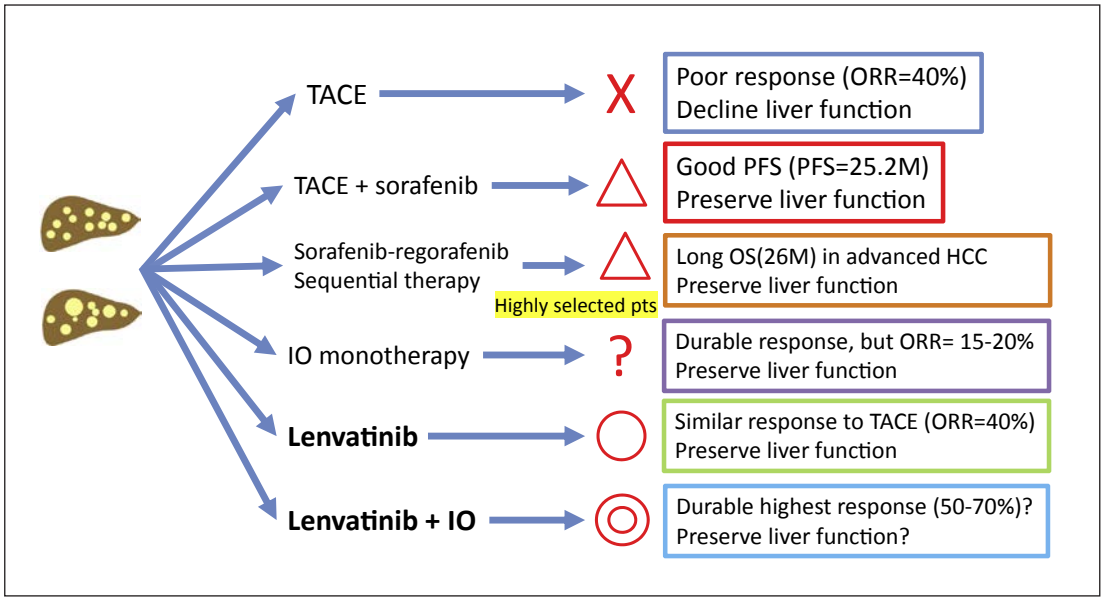

Fig. 8. Future treatment strategy of bilobar multinodular intermediate-stage HCC.

yield a comparable response to that of TACE without impairing hepatic functional reserve in patients with intermediate-stage HCC. Therefore, systemic therapy may be more effective than TACE for improving survival in a subgroup of patients with intermediate-stage HCC (Fig. 6). However, properly designed prospective clinical trials are necessary to confirm this hypothesis. The favorable properties of lenvatinib could result in a paradigm shift in the treatment of not only advanced-stage HCC, but also intermediate-stage HCC.

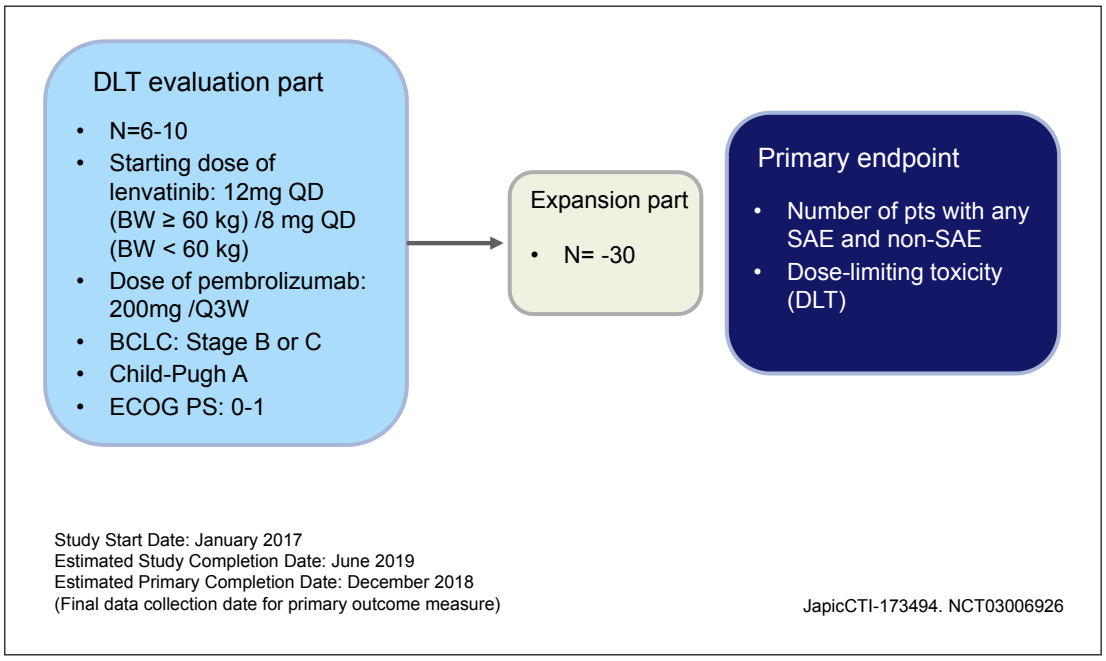

Fig. 9. Phase Ib lenvatinib plus pembrolizumab in unresectable HCC.

Future Perspectives of HCC Treatment with the Introduction of Lenvatinib

The success of the REFLECT trial will drastically change the future treatment landscape of HCC. Approval of lenvatinib would provide physicians with a first-line drug of greater potency than that of current drugs and high tolerability. Questions that remain to be answered include when to use lenvatinib rather than the other first-line drug, sorafenib, and which second-line drug should be used in patients who do not respond to lenvatinib. Regorafenib is currently the only available effective second-line agent [25, 52]; however, cabozantinib will soon become available as well [53]. In this era of multimolecular targeted agents, it may be necessary to rapidly identify the subgroup of intermediate-stage HCC patients who do not respond to TACE besides advanced-stage HCC patients. TACE plus a molecular targeted agent [12] is another optional treatment to improve the clinical outcome; furthermore, systemic therapy is currently a better first choice of treatment for improving survival than TACE for certain subgroups (bilobar multinodular HCC or Kinki criteria B2 substage) of intermediate-stage HCC patients who are conventionally candidates for TACE [54] (Fig. 7, 8).

Conclusion

The emergence of lenvatinib will change the treatment landscape of HCC. Most notably, the ability of lenvatinib to yield response rates as high as those of TACE indicates that systemic therapy may soon replace TACE as the standard therapy in certain subgroups of patients with intermediate-stage HCC (Fig. 6–8). Trials in other cancers show that combination therapy with immune checkpoint inhibitors such as pembrolizumab or nivolumab [55–57] yields extremely high response rates of 50–70%, and it is an ideal treatment with a response that is both long-lasting and durable [58–60]. If this approach is applied as adjuvant or neoadjuvant therapy for curatively treated early-stage HCC or as an addition to or replacement for TACE

in intermediate-stage HCC, a real cure for HCC may cease to be a dream. In fact, clinical trials of combination therapy with lenvatinib and pembrolizumab for HCC have already started (Fig. 9), leaving little doubt that the landscape of HCC treatment will undergo drastic changes in years to come.

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