

# World Journal of *Gastroenterology*

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Editorial board member of *World Journal of Gastroenterology*, Yong-Song Guan, MD, PhD, Professor, Department of Oncology, West China Hospital of Sichuan University, Chengdu 610041, Sichuan Province, China

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## Targeted and immune therapies for hepatocellular carcinoma: Predictions for 2019 and beyond

Masatoshi Kudo

**ORCID number:** Masatoshi Kudo (0000-0002-4102-3474).

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**Masatoshi Kudo**, Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Osaka 589-8511, Japan

**Corresponding author:** Masatoshi Kudo, MD, PhD, Director, Full Professor, Professor and Chairman, Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, 377-2, Ohno-Higashi, Osaka 589-8511, Japan. [m-kudo@med.kindai.ac.jp](mailto:m-kudo@med.kindai.ac.jp)

**Telephone:** +81-723660221-3149

**Fax:** +81-723672880

### Abstract

Systemic therapy for hepatocellular carcinoma (HCC) has markedly advanced since the survival benefit of a molecular targeted agent, sorafenib, were demonstrated in the SHARP and Asia Pacific trials in 2007. Treatment options for patients with advanced HCC increased by sorafenib, and long-term survival for patients with advanced stage HCC has become possible to some extent. However, development of a more potent first-line novel molecular targeted agent replacing sorafenib and a potent second-line agent after disease progression on or intolerant to sorafenib has been warranted because sorafenib lacks tumor shrinking/necrotizing effects and induces relatively severe adverse events such as hand foot skin reaction. Many agents in the 1st line and 2nd line setting were attempted to develop between 2007 and 2016, but all of these clinical trials failed. On the other hand, clinical trials of 4 agents (regorafenib, lenvatinib, cabozantinib, and ramucirumab) succeeded in succession in 2017 and 2018, and their use in clinical practice is possible (regorafenib and lenvatinib) or underway (cabozantinib and ramucirumab). Furthermore, all of 5 clinical trials of combination therapy with transcatheter chemoembolization (TACE) plus a molecular targeted agent failed to date, however, the combination of TACE and sorafenib (TACTICS trials) was reported to be successful and presented at ASCO in 2018. Phase 3 clinical trials of immune checkpoint inhibitors and a combination therapy of immune checkpoint inhibitors and molecular targeted agents are also ongoing, which suggests treatment paradigm of HCC in all stages from early, intermediate and advanced stage, is expected to be changed drastically in the very near future.

**Key words:** Hepatocellular carcinoma; Molecular targeted agent; Immune checkpoint inhibitor; Sorafenib; Lenvatinib

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**Core tip:** Systemic therapy for hepatocellular carcinoma (HCC) has markedly advanced since sorafenib was approved in 2007. Since then, there was no active drug for 10 years that prolong overall survival, however, in 2017 and 2018, clinical trials of 4 more molecular targeted agents including lenvatinib as first line agent, regorafenib, cabozantinib and ramucirumab as second line agent have shown their survival benefit. In addition, immune check point inhibitors, nivolumab and pembrolizumab, were approved by Food and Drug Administration. Combination cancer immunotherapy, that combines immune checkpoint inhibitors and molecular targeted agents show great promise in the treatment of HCC.

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is treated by surgical resection, local ablation, transarterial chemoembolization (TACE), or intra-arterial infusion chemotherapy. Most practice guidelines relevant to HCC were revised in 2017 and 2018<sup>[1-5]</sup>. In this article, the current status and future perspective of systemic therapy for HCC, which has advanced markedly will be reviewed.

Since first appearance of the molecular targeted agent, sorafenib, in 2007, systemic therapy for HCC has changed markedly. Treatment options for extrahepatic spread and vascular invasion have increased, and relatively long-term survival has been achieved, even for patients with Barcelona Clinic Liver Cancer (BCLC) stage C advanced HCC. However, sorafenib does not shrink or induce necrosis in tumors and has relatively severe adverse events (AEs), including hand foot skin reaction. Thus, development of a novel molecular targeted agent that can replace sorafenib, along with a second-line agent that can prevent/slow disease progression while a patient is undergoing treatment with sorafenib is desirable. Between 2007 and 2016, many comparative trials of new agents with sorafenib have been conducted; however, eight clinical trials of first-line agents and eight of second-line agents failed (Table 1)<sup>[6-20]</sup>. In 2017 and 2018, clinical trials of three agents (regorafenib, lenvatinib, cabozantinib, and ramucirumab) reported successful outcomes; indeed, some of these drugs are now used in clinical practice (Table 1). All of three trials in adjuvant setting after curative treatments failed (Table 2)<sup>[21-24]</sup>. In addition, five trials of combination therapy with transcatheter chemoembolization (TACE) plus a molecular targeted agent have been conducted to date, but all of them failed to show its benefit<sup>[25-29]</sup> (Table 2). In 2018, the combination of TACE and sorafenib, the TCTICS trial, reported improved progression-free survival (PFS); the results were presented at the 2018 ASCO-GI and ASCO meetings in 2018<sup>[30]</sup>. Herein, recent advances and future prospects for molecular targeted therapy for HCC will be discussed.

## MOLECULAR TARGETED AGENTS: FIRST-LINE AGENTS

### Sorafenib

Sorafenib is an oral drug that suppresses tumor growth by inhibiting the serine-threonine kinases C-Raf, wild-type B-Raf, and mutant (V600E) B-Raf, all of which are components of the Raf/MEK/ERK pathway (mitogen-activated proteins kinase pathway). This pathway acts downstream of the vascular endothelial growth factor receptor (VEGFR), the platelet-derived growth factor receptor (PDGFR), and the epidermal growth factor receptor. It also exerts anti-tumor effects by suppressing neovascularization. It achieves tumor neovascularization by inhibiting the tyrosine kinases VEGFR1, VEGFR2, VEGFR3, PDGFR $\beta$ , RET, and fms-related tyrosine kinase 3 (FLT-3). Two large-scale pivotal trials (the SHARP and Asia-Pacific trials) of sorafenib reported significant prolongation of overall survival (OS) compared with placebo<sup>[31,32]</sup>; indeed, sorafenib is now the standard therapeutic agent for advanced HCC. However, its ability to shrink tumors is weak and its systemic toxicity is relatively high. Therefore, novel molecular targeted agents with more potency or similar effects, but

Table 1 Phase III clinical trials of advanced stage hepatocellular carcinoma

Target population		Design	Trial name	Result	Presentation	Publication	1 <sup>st</sup> author
Advanced	First line	1 Sorafenib <i>vs</i> Sunitinib	SUN1170	Negative	ASCO 2011	JCO 2013 <sup>[6]</sup>	Cheng AL
		2 Sorafenib +/- Erlotinib	SEARCH	Negative	ESMO 2012	JCO 2015 <sup>[7]</sup>	Zhu AX
		3 Sorafenib <i>vs</i> Brivanib	BRISK-FL	Negative	AASLD 2012	JCO 2013 <sup>[8]</sup>	Johnson PJ
		4 Sorafenib <i>vs</i> Linifanib	LiGHT	Negative	ASCO-GI 2013	JCO 2015 <sup>[9]</sup>	Cainap C
		5 Sorafenib +/- Doxorubicin	CALGB 80802	Negative	ASCO-GI 2016		
		6 Sorafenib +/- HAIC	SILIUS	Negative	EASL 2016	Lancet GH 2018 <sup>[10]</sup>	Kudo M
		7 Sorafenib +/- Y90	SARAH	Negative	EASL 2017	Lancet-O 2017 <sup>[11]</sup>	Vilgrain V
		8 Sorafenib +/- Y90	SIRveNIB	Negative	ASCO 2017	JCO 2018 <sup>[12]</sup>	Chow P
		9 Sorafenib <i>vs</i> Lenvatinib	REFLECT	Positive	ASCO 2017	Lancet 2018 <sup>[34]</sup>	Kudo M
		10 Sorafenib <i>vs</i> Nivolumab	CheckMate-459	Ongoing			
		11 Sorafenib <i>vs</i> Durvalumab + Tremelimumab <i>vs</i> Durva	HIMALAYA	Ongoing			
		12 Sorafenib <i>vs</i> Atezolizumab + Bevacizumab	Imbrave 150	Ongoing			
		13 Sorafenib <i>vs</i> Tislelizumab		Ongoing			
	Second line	1 Brivanib <i>vs</i> Placebo	BRISK-PS	Negative	EASL 2012	JCO 2013 <sup>[13]</sup>	Llovet JM
		2 Everolimus <i>vs</i> Placebo	EVOLVE-1	Negative	ASCO-GI 2014	JAMA 2014 <sup>[14]</sup>	Zhu AX
		3 Ramucirumab <i>vs</i> Placebo	REACH	Negative	ESMO 2014	Lancet-O 2015 <sup>[15]</sup>	Zhu AX
		4 S-1 <i>vs</i> Placebo	S-CUBE	Negative	ASCO 2015	Lancet GH 2017 <sup>[16]</sup>	Kudo M
		5 ADI-PEG 20 <i>vs</i> Placebo	NA	Negative	ASCO 2016	Ann Oncol 2018 <sup>[17]</sup>	Abou-Alfa G
		6 Regorafenib <i>vs</i> Placebo	RESORCE	Positive	WCGC 2016	Lancet 2017 <sup>[41]</sup>	Bruix J
		7 Tivantinib <i>vs</i> Placebo	METIV-HCC	Negative	ASCO 2017	Lancet-O 2018 <sup>[18]</sup>	Rimassa L
		8 Tivantinib <i>vs</i> Placebo	JET-HCC	Negative	ESMO 2017		
		9 DT <i>vs</i> Placebo	ReLive	Negative	ILCA 2017		
		10 Cabozantinib <i>vs</i> Placebo	CELESTIAL	Positive	ASCO-GI 2018	NEJM 2018 <sup>[45]</sup>	Abou-Alfa G
		11 Ramucirumab <i>vs</i> Placebo	REACH-2	Positive	ASCO 2018	Lancet-O 2019 <sup>[30]</sup>	Zhu AX
		12 Pembrolizumab <i>vs</i> Placebo	KEYNOTE-240	Negative			

HAIC: Hepatic arterial infusion chemotherapy; Doxorubicin-loaded nanoparticles.

less toxicity, have been unmet need.

### ***Lenvatinib: Overview of the results of the REFLECT trial***

Although eight clinical trials with various agents/modalities comparing with sorafenib conducted in the last decade has shown negative outcomes, the results of the REFLECT trial with use of lenvatinib met its primary endpoint of non-inferiority

**Table 2 Randomized phase II, phase III clinical trials of early / intermediate stage hepatocellular carcinoma**

Target population		Design	Trial name	Result	Presentation	Publication	1 <sup>st</sup> author
Early	Adjuvant (prevention of recurrence)	1 Vitamin K2 <i>vs</i> Placebo		Negative		Hepatology 2011 <sup>[21]</sup>	Yoshida H
		2 Peretinoin <i>vs</i> Placebo	NIK-333	Negative	ASCO 2010	JG 2014 <sup>[22]</sup>	Okita K
		3 Sorafenib <i>vs</i> Placebo	STORM	Negative	ASCO 2014	Lancet-O 2015 <sup>[23]</sup>	Bruix J
		4 Peretinoin <i>vs</i> Placebo	NIK-333/K-333	Ongoing			
Intermediate	Improvement of RFA	1 RFA +/- LTLD	HEAT	Negative	ILCA 2013	CCR 2017 <sup>[24]</sup>	Tak WY
		2 RFA +/- LTLD	OPTIMA				
	Improvement of TACE	1 TACE +/- Sorafenib	Post-TACE	Negative	ASCO-GI 2010	EJC 2011 <sup>[25]</sup>	Kudo M
		2 TACE +/- Sorafenib	SPACE (Ph II)	Negative	ASCO-GI 2012	J Hepatol 2016 <sup>[26]</sup>	Lencioni R
		3 TACE +/- Brivanib	BRISK-TA	Negative	ILCA 2013	Hepatol 2014 <sup>[27]</sup>	Kudo M
		4 TACE +/- Orantinib	ORIENTAL	Negative	EASL 2015	Lancet GH 2017 <sup>[28]</sup>	Kudo M
		5 TACE +/- Sorafenib	TACE-2	Negative	ASCO 2016	Lancet GH 2017 <sup>[29]</sup>	Meyer T
		6 TACE +/- Sorafenib	TACTICS (Ph II)	Positive	ASCO-GI 2018 <sup>[30]</sup>		Kudo M

LTLD: Lyso-thermosensitive liposomal doxorubicin.

of prolonging OS compared with sorafenib. Lenvatinib is an oral kinase inhibitor that selectively inhibits receptor tyrosine kinases involved in neovascularization and progression to high malignancy grade tumors and a poor prognosis; targeted kinases include VEGFR1, VEGFR2, VEGFR3, fibroblast growth factor receptor (FGFR) 1, FGFR2, FGFR3, FGFR4, PDGFR $\alpha$ , KIT, and RET. In particular, strong inhibition of FGFR4 is considered important for preventing aggressive growth or progression to a higher malignancy grade of HCC. The drug also suppresses invasion and metastasis. A single-arm phase II study of lenvatinib as a treatment for advanced HCC reported a time to progression (TTP) of 7.4 mo and an OS of 18.7 mo, which are very favorable<sup>[33]</sup>. Subsequently, a phase III study comparing sorafenib with lenvatinib, the REFLECT trial, was conducted<sup>[34]</sup>.

The REFLECT trial was a global phase III study to show the non-inferiority of lenvatinib to sorafenib, in which patients with unresectable HCC, not previously treated with systemic chemotherapy, were allocated randomly to the lenvatinib or sorafenib arms at a 1:1 ratio. Stratification factors were Asian/non-Asian, vascular invasion and/or extrahepatic spread (presence or absence), Eastern Cooperative Oncology Group performance status 0 or 1, and body weight < 60 kg or  $\geq$  60 kg. Administration was continued until disease progression or development of a non-tolerable adverse event. The primary endpoint was verification of non-inferiority in terms of OS; the non-inferiority margin of OS was set at 1.08, which is very strict. PFS, TTP, objective response rate (ORR), and safety were evaluated as secondary endpoints.

Of the 954 patients registered, 478 and 476 were allocated to the lenvatinib and sorafenib groups, respectively. Overall, 67% of patients in the lenvatinib group were from the Asia-Pacific region and 33% were from western countries. Of these, 32% weighed less than 60 kg and 68% weighed 60 kg or more in lenvatinib arm. Vascular invasion and/or extrahepatic spread were noted in 69%, and BCLC stage C HCCs accounted for 78% in the lenvatinib arm. Regarding the cause of disease, HCC due to hepatitis C accounted for 19% in the lenvatinib arm and 27% in the sorafenib arm, suggesting an advantageous imbalance toward sorafenib<sup>[34]</sup>. In contrast, HCC due to hepatitis B accounted for 53% of cases in the lenvatinib arm and for 48% of cases in the sorafenib arm. In the lenvatinib arm, 46% of patients had an alpha fetoprotein (AFP) level exceeding 200 ng/mL *vs* 39% in the sorafenib group, also indicating an advantageous imbalance toward sorafenib.

The primary endpoint OS in the lenvatinib and sorafenib arms was 13.6 and 12.3 mo, respectively, and the hazard ratio (HR) was 0.92 (0.79-1.06); this was lower than the non-inferiority margin with a specified upper limit of a 95% confidence interval

(CI) of 1.08. These data suggest that lenvatinib was not inferior to sorafenib in terms of OS<sup>[34]</sup>. In addition, the PFS reported by institutional investigators according to the modified Response Evaluation Criteria in Solid Tumors (modified RECIST) criteria was 7.3 and 3.6 mo for the lenvatinib and sorafenib arms, respectively. TTP was 7.4 and 3.7 mo, respectively, and the ORR was 40.6% and 12.6% according to the results of Masked Independent Review Committee, respectively. Thus, lenvatinib had significantly more favorable anti-tumor effects than sorafenib (Table 3)<sup>[34]</sup>. Evaluation by Masked Independent Review Committee based on RECIST1.1 also confirmed that lenvatinib had favorable anti-tumor effects with regard to PFS, TTP, and ORR as well. Furthermore, when analysis was confined to intermediate stage HCC, the PFS in the lenvatinib arm was 9.1 mo, which is fairly long, and the ORR of BCLC B-stage HCC in the lenvatinib arm for the Japanese population was 61.3%, which is extremely high<sup>[35]</sup>.

Because AFP was not included as a stratification factor, more patients with an AFP level exceeding 200 ng/mL were enrolled in the lenvatinib group. When this was corrected by analysis of covariance, the lenvatinib arm showed a superior OS (HR = 0.856; 95%CI = 0.736-0.995; nominal *P*-value = 0.0342)<sup>[34]</sup>. Based on these findings, if AFP was included as a stratified factor, the study would likely have confirmed the superiority of lenvatinib over sorafenib<sup>[36,37]</sup>. The probability that lenvatinib was superior to sorafenib after adjustment for AFP is as high as 0.743<sup>[38]</sup>.

Sub-analysis of OS revealed that the OS-prolonging effects of lenvatinib were superior to those of sorafenib in almost all subsets. It should be noted that specifically that in the group with body weight < 60 kg, the OS benefits of lenvatinib were superior to those of sorafenib at a dose of 8 mg, and the HR was more favorable than that in the group weighing ≥ 60 kg or higher at a dose of 12 mg (HR, 0.85 *vs* 0.95, respectively). This suggests that weight-based dosing is successful<sup>[37,39]</sup>. In addition, the HR in the group with a baseline AFP of ≥ 200 ng/mL was 0.78 (95%CI, 0.63-0.98), confirming that lenvatinib has favorable OS benefits even in a group with a high AFP level and a poor prognosis. The treatment durations for the lenvatinib and sorafenib arms were 5.7 and 3.7 mo, respectively; therefore, lenvatinib can be given orally for a longer duration and the frequency of subjective AEs such as hand foot skin reaction and diarrhea is lower, indicating superior tolerability.

Based on the above findings, lenvatinib is not inferior to sorafenib in terms of OS; indeed, lenvatinib showed statistically significant and clinically meaningful improvement in all secondary endpoints (PFS, TTP, and ORR), confirming its efficacy as a first-line agent for patients with unresectable HCC. Regarding the AEs, hypertension, proteinuria and hypothyroidism were more frequently observed in lenvatinib arm although hand-foot skin reaction, diarrhea and alopecia were less frequently observed in lenvatinib arm as compared with sorafenib arm<sup>[34]</sup>. This AE profile suggests that AEs in lenvatinib arm are more favorable and tolerable than sorafenib since most of AEs observed in lenvatinib arm are asymptomatic and can be manageable by medication (hypertension, hypothyroidism) or by dose reduction (proteinuria). Based on these results, lenvatinib has been approved to treat HCC on March 23, 2018 in Japan. It was also approved in HCC by the Food and Drug Administration on August 16, 2018, in Europe on August 23, 2018, in South Korea on September 4, 2018, in China on August 29, 2018 and in Taiwan on November 28, 2018.

## MOLECULAR TARGETED AGENTS: SECOND-LINE AGENTS

### *Regorafenib: Overview of the RESORCE trial*

Regorafenib is an oral kinase inhibitor. It targets protein kinases such as VEGFR1, VEGFR2, VEGFR3, TIE2, PDGFRβ, FGFR, KIT, RET, RAF-1, and BRAF<sup>[40]</sup>. Because it is synthesized simply by binding fluorine to sorafenib, it has almost the same molecular structure as sorafenib and a similar, but stronger toxicity profile. Therefore, unlike other drugs, a placebo-controlled phase III study (RESORCE trial) was performed that included only patients who progressed under sorafenib treatment and those intolerant to sorafenib patients were excluded. The primary endpoint, OS, in the regorafenib arm was 10.6 mo and that in the placebo arm was 7.8 mo, which is a significant improvement<sup>[41]</sup>. PFS and TTP were also significantly more favorable (Table 4). This is the first drug for which efficacy was proved as a second-line systemic agent who progressed on sorafenib.

Regarding the AE profiles of regorafenib is as follows; grade 3/4 drug-related treatment-emergent AEs include hand-foot skin reaction in 13%, fatigue in 6%, hypertension in 13% and diarrhea in 2%<sup>[41]</sup>. However, most these AEs were manageable by medication or dose reduction/interruption. Based on these results, its use as a second-line agent for HCC in Japan was approved in May 2017. However, the drug is unsuitable for patients with sorafenib intolerance; this means that there is an

**Table 3 Results of the REFLECT trial<sup>[34]</sup>**

	Lenvatinib (n = 478)	Sorafenib (n = 476)	HR, P-value
OS (M, 95% CI)	13.6 (12.1-14.9)	12.3 (10.4-13.9)	HR 0.92 (0.79-1.06)
PFS (M, 95% CI)	7.3 (5.6-7.5)	3.6 (3.6-3.7)	HR 0.64 (0.55-0.75) <i>P</i> < 0.0001
TTP (M, 95% CI)	7.4 (7.2-9.1)	3.7 (3.6-3.9)	HR 0.60 (0.51-0.71) <i>P</i> < 0.0001
Objective response (independent review, mRECIST)			
CR	10 (2%)	4 (1%)	
PR	184 (38%)	55 (12%)	
SD	159 (33%)	219 (46%)	
PD	79 (17%)	152 (32%)	
ORR	194 (40.6%)	59 (12.4%)	<i>P</i> < 0.0001
DCR	353 (73.8%)	278 (58.4%)	<i>P</i> < 0.0001

OS: Overall survival; PFS: Progression-free survival; TTP: Time to progression; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; ORR: Objective response rate; DCR: Disease control rate.

unmet need for a second-line treatment in this group. However, this was soon solved by successful trials of cabozantinib and ramucirumab in 2018 as mentioned later.

The RESORCE trial was successful for the following reasons: (1) For second-line treatment with regorafenib, patients that discontinued sorafenib due to AEs were excluded, in other words, only patients with progressive disease (PD) under sorafenib treatment were included; (2) vascular invasion and extrahepatic spread were set as independent stratification factors to prevent imbalanced distribution between the two arms (active drug and placebo arms); (3) AFP, a strong poor prognostic factor, was also included as a stratification factor; and (4) only patients with sufficient sorafenib tolerance were selected (limited to patients who were able to tolerate sorafenib doses of 400 mg or higher for 20 d or longer during the 28-d period before PD). This study design prevented dropout due to AEs caused by regorafenib since molecular structure of regorafenib is very similar to sorafenib, and minimized the influence of post-treatment effects following PD after regorafenib treatment<sup>[41]</sup>. According to the RESORCE trial, the median survival time for patients treated with regorafenib was 10.6 mo (placebo: 7.8 mo; HR = 0.63; *P* < 0.0001). Sub-analysis of OS revealed that it was significantly more favorable for patients when sorafenib was first used at a Child-Pugh score of 5 than for patients introduced to sorafenib at a score of 6; this suggests that early switching from TACE to sorafenib for patients who become refractory to TACE at a Child-Pugh score of 5, and early switching to regorafenib for patients who become refractory to sorafenib, are important for extending survival. Furthermore, the median duration of pre-treatment with sorafenib before the RESORCE trial was 7.8 mo, which is relatively long. Many patients with long SD that responded to sorafenib well were enrolled in this trial. Thus, the effects on patients with rapid PD have been unclear. However, a recent report of sub-analysis of the RESORCE trial showed that the HR for OS in patients with rapid PD on sorafenib (TTP: 2.3 mo) was 0.66, thereby clarifying that regorafenib has OS benefit, even in patients showing rapid PD on sorafenib<sup>[42]</sup>.

### **Sequential therapy with sorafenib and regorafenib**

Based on the results of the RESORCE trial, sorafenib-regorafenib sequential therapy extended OS from the time of sorafenib treatment initiation to 26 mo (placebo group: 19.2 mo), thereby providing a favorable outcome<sup>[42,43]</sup>. This is a very important message to clinical practice. This outcome (OS = 26 mo) is almost comparable with that for intermediate stage HCC patients treated with conventional TACE<sup>[27]</sup>. At present, the BRISK-TA trial, a prospective phase III study involving the largest number of patients in the world, is the world largest TACE combination trial. Therefore, the outcome of the placebo arm of this trial is considered to be the world standard outcome of TACE treatment with no selection bias. In addition, the target groups of this trial comprised patients with BCLC B, BCLC A, and BCLC C (59%, 23%, and 17% of patients, respectively). Thus, 82% of all patients had early/intermediate stage disease and only 17% had advanced stage disease. In contrast, patients with advanced stage BCLC C accounted for 86% of patients enrolled in the RESORCE trial. When these two cohorts were compared, the OS of TACE-treated patients were 26.1 mo and that of patients who received sorafenib-regorafenib sequential therapy was 26 mo. Although it may be inappropriate to compare the results of the different

**Table 4 Results of the RESORCE trial<sup>[41]</sup>**

	Regorafenib (n = 379)	Placebo (n = 194)	HR, P-value
OS (M, 95%CI)	10.6 (9.1-12.1)	7.8 (6.3-8.8)	HR 0.63 (95%CI 0.50-0.79) <i>P</i> < 0.0001
PFS (M, 95%CI)	3.1 (2.8-4.1)	10.6 (1.4-1.6)	HR 0.46 (95%CI 0.37-0.56) <i>P</i> < 0.0001
TTP (M, 95%CI)	3.2 (2.9-4.2)	10.6 (1.4-1.6)	HR 0.44 (95%CI 0.36-0.55) <i>P</i> < 0.0001
Objective response (investigator assessed, mRECIST)			
CR	2 (1%)	0	
PR	38 (10%)	8 (4%)	
SD	206 (54%)	62 (32%)	
PD	86 (23%)	108 (56%)	
ORR	40 (11%)	8 (4%)	<i>P</i> = 0.0047
DCR	247 (65%)	70 (36%)	<i>P</i> < 0.0001

OS: Overall survival; PFS: Progression-free survival; TTP: Time to progression; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; ORR: Objective response rate; DCR: Disease control rate.

randomized controlled trials (RCTs), it should be justified because there was no selection bias in the placebo group from the well-designed RCT. Considering that sorafenib-regorafenib sequential therapy targets far more advanced cases of HCC, the finding of a comparable OS result for TACE- and sorafenib-regorafenib-treated patients implicates very important issue. Although it was a highly selected patient population, the survival benefit of sorafenib-regorafenib sequential therapy for advanced stage HCC were comparable with those of TACE for intermediate stage HCC<sup>[27,42-44]</sup>. Therefore, sorafenib-regorafenib sequential therapy is expected to achieve a favorable outcome in the real-world clinical practice as well, suggesting that the timing of sorafenib introduction should be re-considered. Previously, a patient was switched from TACE to systemic therapy when they became refractory to TACE. However, it may be more important to identify a subgroup likely to become refractory to TACE and then introduce systemic therapy at an earlier time when the liver function reserve is maintained at a Child-Pugh score of 5 before becoming refractory to TACE<sup>[43,44]</sup>.

#### **Cabozantinib: Overview of the CELESTIAL trial**

Cabozantinib is an oral multi-kinase inhibitor that inhibits the activity of VEGF, c-MET, RET, AXL, TIE2, and FLT3. The survival-prolonging effects of cabozantinib as a second-line agent for patients with HCC refractory/intolerant to sorafenib treatment compared with placebo control were presented at the American Society of Clinical Oncology Gastrointestinal Cancer Symposium (ASCO-GI), held in January 2018. In total, 707 patients with unresectable HCC were allocated to the cabozantinib and placebo groups (2:1 ratio). The median OS for the cabozantinib group (*n* = 470) was 10.2 mo (95%CI, 9.1-12.0), demonstrating significant survival benefit when compared with the placebo group [8.0 mo (95%CI, 6.8-9.4)] (Table 5)<sup>[45,46]</sup>. Systemic chemotherapy with a drug other than sorafenib was allowed during this trial, with the drug positioned as the second- or third-line therapy.

Regarding the AE profiles, grade 3/4 AEs include diarrhea (10%), decreased appetite (6%), hand-foot skin reaction (17%), fatigue (10%) and hypertension (16%)<sup>[45]</sup>. However, most of AEs were manageable by medication or dose reduction/interruption. As this trial was not performed in Japan, a bridging phase 2 study is now underway; therefore, its approval as a second-line agent is expected in the near future in Japan as well.

#### **Ramucirumab: Overview of the REACH-2 trial**

Ramucirumab is a recombinant monoclonal human immunoglobulin IgG1 antibody specific for VEGFR-2. It is injected intravenously and inhibits VEGFR-2 activity by blocking its binding to VEGF-A, VEGF-C, and VEGF-D. Thus, it exerts anti-tumor effects by inhibiting endothelial cell proliferation, migration, and survival, thereby preventing tumor neovascularization.

The previous phase of the REACH trial examined the survival benefit of ramucirumab compared with placebo in patients with unresectable advanced HCC that was refractory/intolerant to sorafenib treatment. No survival benefit was proven in this trial<sup>[15]</sup>. However, sub-analysis limited to patients with an AFP level ≥ 400 ng/mL revealed improved survival; this result was reproducible regardless of the

**Table 5 Results of the CERESTIAL trial<sup>[45]</sup>**

	Cabozantinib (n = 470)	Placebo (n = 237)	HR, P-value
OS (M, 95%CI)	10.2 (9.1-12.0)	8.0 (6.8-9.4)	HR 0.76 (95%CI 0.63-0.92) <i>P</i> = 0.0049
PFS (M, 95%CI)	5.2 (4.0-5.5)	1.9 (1.9-1.9)	HR 0.44 (95%CI 0.36-0.52) <i>P</i> < 0.0001
Objective response (investigator assessed, RECIST 1.1)			
CR (%)	0	0	
PR (%)	4	0.4	
SD (%)	60	33	
PD (%)	21	55	
NE (%)	15	11	
ORR (% , 95CI)	4 (2.3-6.0)	0.4 (0.0-2.3)	<i>P</i> = 0.0086
DCR (%)	64	33.4	

OS: Overall survival; PFS: Progression-free survival; TTP: Time to progression; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; NE: Not evaluable; ORR: Objective response rate; DCR: Disease control rate.

geographic region<sup>[47,48]</sup>. Thus, the REACH-2 trial was planned and conducted. The study design was not markedly different from that of the original REACH trial except that the subjects were limited to patients with an AFP level of  $\geq 400$  ng/mL, and macroscopic vascular invasion was included as a stratification factor. The results were presented at ASCO in June 2018. The study results were positive in terms of the primary endpoint: improvement of OS<sup>[49,50]</sup>. The median OS in the ramucirumab group was 8.5 mo and that in the placebo group was 7.3 mo, confirming a significant survival benefit over placebo (HR = 0.710; *P* = 0.0199) (Table 6).

Regarding the AE profiles, grade 3/4 AEs include hypertension (12%), thrombocytopenia (5%), hepatic encephalopathy (3%) and neutropenia (3%). These AEs were manageable by medication and/or dose reduction/interruption. Most importantly, relative dose intensity was as high as 98.5%, which suggests tolerability of this drug is fairly high<sup>[49]</sup>. Based on these results, ramucirumab is expected to be approved for patients refractory or intolerant to sorafenib treatment and with an AFP level  $\geq 400$  ng/mL.

## TACE COMBINATION TRIAL: RESULTS OF THE TACTICS TRIAL

The TACTICS trial was a multicenter prospective RCT comparing TACE plus sorafenib with TACE alone that was conducted at 33 sites in Japan<sup>[30,51]</sup>. A total of 156 patients with unresectable HCC were assigned to receive sorafenib plus TACE (*n* = 80) or TACE alone (*n* = 76) at a 1: 1 ratio. The inclusion criteria were Child-Pugh score  $\leq 7$ , a maximum of two previous TACE sessions, and  $\leq 10$  HCCs with none exceeding 10 cm in size. The exclusion criteria were extrahepatic spread and vascular invasion. Patients in the TACE plus sorafenib arm started sorafenib 2-3 wk before TACE at a dose of 400 mg once daily. The purpose of this sequential pretreatment with sorafenib was to assess tolerability to sorafenib, normalize the tumor vasculature to improve TACE effectiveness, and attenuate VEGF upregulation after the TACE procedure. Sorafenib was temporarily suspended 2 d before and after TACE. In patients showing sorafenib tolerance, the dose was increased to 800 mg daily when possible. TACE was performed on demand, and repeated TACE was generally performed in cases with viable lesions that grew by  $\geq 50\%$  over baseline. Response was assessed using computed tomography, magnetic resonance imaging, or other related modalities every 8 wk. The study had two co-primary endpoints, namely, PFS and OS, and adopted a gatekeeping strategy. The secondary endpoints were the time until TACE was no longer feasible or no longer showed any benefit (time to un-TACEable progression: TTUP), TTP, response rate, and safety. As further explained below, the development of new intrahepatic lesions was not defined as tumor progression. This criterion was introduced to maximize the duration of sorafenib administration and to keep the progression criteria for TACE as consistent as possible with those currently used in clinical practice. Use of the RECIST criteria as response evaluation criteria/a stopping rule is inappropriate because repeated TACE is generally performed after detecting a new intrahepatic lesion, which does not qualify as treatment failure

**Table 6 Results of the REACH-2 trial<sup>[49]</sup>**

	Ramucirumab (n = 197)	Placebo (n = 95)	HR, P-value
OS (M, 95%CI)	8.5	7.3	HR 0.710 (95%CI 0.531-0.949) <i>P</i> = 0.0199
PFS (M, 95%CI)	2.8	1.6	HR 0.452 (95%CI 0.339-0.603) <i>P</i> < 0.0001
Objective response (RECIST 1.1)			
CR (n, %)	0 (0.0)	0 (0.0)	
PR (n, %)	9 (4.6)	1 (1.1)	
SD (n, %)	109 (55.3)	36 (37.9)	
PD (n, %)	66 (33.5)	48 (50.5)	
NE (n, %)	13 (6.6)	10 (10.5)	
ORR (%; 95CI)	9 (4.6)	1 (1.1)	<i>P</i> = 0.1697
DCR (%)	118 (59.9)	37 (38.9)	<i>P</i> = 0.0006

OS: Overall survival; PFS: Progression-free survival; TTP: Time to progression; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; NE: Not evaluable; ORR: Objective response rate; DCR: Disease control rate.

requiring a switch to a next line of treatment. Therefore, the TACE progression criteria were created specifically for the TACTICS trial and were consistent with those used in clinical practice.

The criteria for progression with TACE (unTACEable progression) were: (1)  $\geq 25\%$  increase in intrahepatic viable lesions; (2) decline in hepatic functional reserve to Child-Pugh class C; (3) appearance of extrahepatic lesions; (4) appearance of vascular invasion; or (5) meeting the Japan Society of Hepatology criteria for TACE-refractory disease<sup>[52]</sup>. Therefore, PFS was defined as the time to either unTACEable progression or death. The most important feature of the TACTICS trial design is that the RECIST criteria were not used, and consequently the development of new intrahepatic lesions was not considered progression. This enabled long-term administration of sorafenib.

The results for the primary endpoint of PFS were very favorable, with a median of 25.2 mo in the TACE plus sorafenib arm and 13.5 mo in the TACE alone arm (HR, 0.59; *P* = 0.006; Table 7)<sup>[30,51]</sup>. TTUP results were also favorable, with a median of 26.7 mo in the TACE plus sorafenib arm and 20.6 mo in the TACE alone arm (HR, 0.57; *P* = 0.02; Table 7). Similarly, TTP results were favorable, with a median of 26.7 mo in the TACE plus sorafenib arm and 16.4 mo in the TACE alone arm (HR, 0.54; *P* = 0.005). PFS results were also better for the TACE plus sorafenib arm in all subgroup analyses<sup>[30]</sup>. The response rates after the first TACE session did not differ significantly between the arms. There were no unexpected AEs. The median duration of sorafenib administration was long at 38.7 mo, and the median daily dose was somewhat low at 355.2 mg. The interval between TACE sessions was 21.1 wk in the TACE plus sorafenib arm, which was significantly longer than the interval of 16.9 wk in the TACE alone arm (*P* = 0.018). Other parameters that were significantly longer in the TACE plus sorafenib arm than in the TACE alone arm were time to detection of vascular invasion (31.3 mo *vs* 4.0 mo), time to detection of extrahepatic spread (15.7 mo *vs* 6.9 mo), and time to stage progression (22.5 mo *vs* 6.3 mo) (Table 7)<sup>[30,51]</sup>.

## SELECTION OF THE USE OF MOLECULAR TARGETED AGENTS FOR HCC PATIENTS

In 2018, sorafenib and lenvatinib became first-line molecular targeted agents for HCC available worldwide. Regorafenib is also available as a second-line agent worldwide, but the following strict conditions are applicable: (1) Disease progression under sorafenib treatment; (2) exclusion of patients intolerant to sorafenib; (3) confirmation of sufficient tolerance to sorafenib (patients must tolerate  $\geq 400$  mg of sorafenib for 20 d or longer during the 28-d period before PD); and (4) Child-Pugh A liver function.

A successful outcome for the cabozantinib bridging study in Japan will result in an application for approval. Also, ramucirumab for use in patients with an AFP  $\geq 400$  ng/mL will be expected to be approved. This will open up an era in which we have access to two first-line drugs and three second-line drugs (Figure 1)<sup>[53]</sup>. The HCC practice guideline published by the European Association of Study of the Liver revised in 2018<sup>[3]</sup> described regorafenib, cabozantinib, and ramucirumab as second-line agents to be used when a patient becomes refractory to sorafenib; however, no data are available regarding their use as second-line agents after lenvatinib treatment,

**Table 7 Results of TACTICS trial<sup>[30]</sup>**

	TACE with sorafenib median (M)	TACE alone median (M)	HR (95% CI)	P value
PFS	25.2	13.5	0.59 (0.41-0.87)	0.006
TTUP	26.7	20.6	0.57 (0.36-0.92)	0.02
TTP	26.7	16.4	0.54 (0.35-0.83)	0.005
TTVI	31.3	4.0	0.26 (0.09-0.75)	0.005
TTEHS	15.7	6.9	0.21 (0.06-0.70)	0.006
TTSP	22.5	6.3	0.31 (0.15-0.63)	0.001

TACE: Transcatheter arterial chemoembolization; HR: Hazard ratio; PFS: Progression free survival; TTUP: Time to untreatable or unTACEable progression; TTP: Time to progression; TTVI: Time to vascular invasion; TTEHS: Time to extrahepatic spread; TTSP: Time to stage progression.

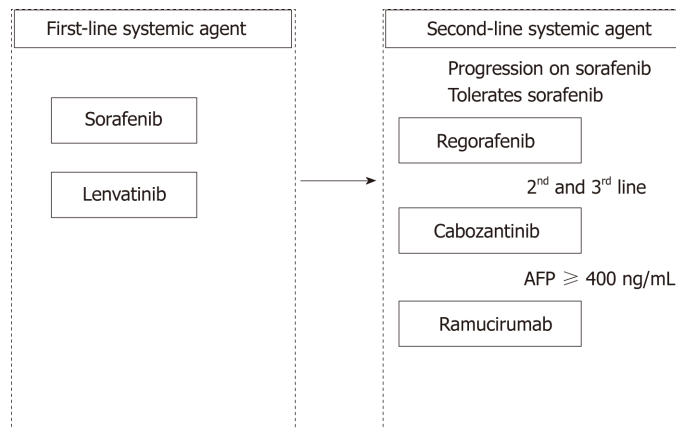
which is an unmet need. In contrast, the guidelines published by the American Association for the Study of Liver Diseases revised in August 2018 state that although there is no clear evidence for their use as second-line agents after patients become refractory to lenvatinib, use of multi-kinase inhibitors, such as sorafenib-regorafenib, cabozantinib or ramucirumab may be considered<sup>[4]</sup>.

Indeed, after its approval for use in HCC patients in Japan, lenvatinib was administered to more than 8000 patients over 11 mo. Based on recent reports of early experiences, lenvatinib was administered patients not only as a first-line agent, but also as a second-line agent after sorafenib, and as a third-line agent after sorafenib-regorafenib sequential therapy in approximately half of patients (Figure 2). In addition, when the drug is used in this manner the response rate is as high as 40%-50% when assessed by mRECIST, a percentage similar to that reported in the REFLECT trial, in a real world clinical practice. Thus, lenvatinib is expected to have positive effects in the real world clinical practice setting even after treatment with sorafenib and even regorafenib. In addition, it is possible that sorafenib, regorafenib, ramucirumab, and cabozantinib are effective even after PD on lenvatinib. However, regorafenib should be administered only when tolerance to sorafenib is confirmed (Figure 2).

One important issue is whether sorafenib or lenvatinib should be used as the first option among 2 first-line agents. From an oncological and scientific viewpoint, the drug with the higher response rate should be selected for patients with advanced cancer who do not have much time left. In the oncology field, it is common sense that a survival benefit is obtained when the patient responds to the agent. However, there used to be some confusion between survival benefit in “responders” in individual patients, and a correlation between “response rate” and the result in the clinical trial. Even if the response rate of a testing drug is high, this does not always mean that the trial meets the primary endpoint of OS benefit. However, OS in responders were always better than non-responders even primary endpoint was negative as shown in previous trials<sup>[10,26,29]</sup>. The response rate for sorafenib is not high, but the drug reliably provides a survival benefit by stabilizing disease progression, the SD effect. However, even sorafenib shows a clear survival benefit in responders compared with non-responders according to mRECIST used to evaluate a database from prospective clinical trials with no selection bias<sup>[10,26,29]</sup>, indicating that lenvatinib with its higher response rate than sorafenib increases the percentage of patients who benefit from survival-prolonging effects. Thus, oncologically speaking, agent with higher response rate may be used as the first choice of treatment among the first-line agents.

High response rates on imaging lead to both physicians and patients to be motivated to continue treatment. This high tumor response obtained in many patients will increase patient compliance and possibly increase the conversion rate to more curative modalities such as resection, ablation, and curative TACE<sup>[35]</sup>. Furthermore, the recently published response rate for Japanese BCLC B patients was 61.3%, which is fairly high and is superior to the world standard response rate of TACE (42%)<sup>[27,54,55]</sup> and initial TACE (52%) in the Japanese subgroup<sup>[56]</sup> as reported in the OPTIMIS trial. The response rate was particularly high when compared with that for the 2nd and later TACE session in the OPTIMIS trial, and for Japanese patients whose disease became refractory to TACE, in which ORR was just 13.9%<sup>[57]</sup>.

Therefore, drugs with a high response rate may be used as the first choice for BCLC B patients unsuitable for TACE, *i.e.*, patients likely to become refractory. This statement does not entirely rule out the usefulness of TACE; indeed, as reported by the TACTICS trial<sup>[30]</sup>, when a tumor enlarges during targeted therapy then treatment of the enlarged tumor with super-selective TACE to control growth while preserving



**Figure 1 Systemic therapy in hepatocellular carcinoma: 2018 and beyond<sup>[53]</sup>.** Two first-line systemic agents, sorafenib and lenvatinib, are approved and can be used in the clinical practice. Second-line agent, regorafenib is approved for clinical use for progressors on sorafenib. Cabozantinib and ramucirumab will be approved in 2019. AFP: Alpha fetal protein.

liver function may be a good strategy in a real world clinical practice.

## IMMUNE CHECKPOINT INHIBITORS

### ***Nivolumab***

Nivolumab is the first recombinant monoclonal human immunoglobulin IgG4 antibody specific for human PD-1. A phase I/II study of advanced HCC, the Checkmate-040 trial, reported a response rate of 20%, which included three complete responders. The disease control rate was 64%, which is very promising. The drug also showed a durable and long-lasting response effect in responders<sup>[58]</sup>. AE profiles are fairly mild; grade 3 AE was only observed in 1 % (fatigue). Grade 1/2 AEs include rash (19%), pruritus (10%), diarrhea (10%), decreased appetite (10%) and fatigue (8%)<sup>[58]</sup>. Subsequently, a trial involving an increased number of patients was performed and the updated results were reported at ASCO in 2017. The median survival of patients treated with nivolumab as a first-line therapy was 28.6 mo whereas that of patients treated with nivolumab as a second-line was 15 mo; again, very promising. Based on the results of the phase I/II study described above, the United States marked nivolumab for priority review as a second-line agent after sorafenib; it was approved by the Food and Drug Administration in September 2017. The head-to-head phase III study (CheckMate-459) of nivolumab vs sorafenib as a first-line agent is now ongoing and the results are eagerly awaited. If this study is positive, 1<sup>st</sup> option among 1<sup>st</sup> line agents will undoubtedly become nivolumab because of its durable long-lasting response in responders.

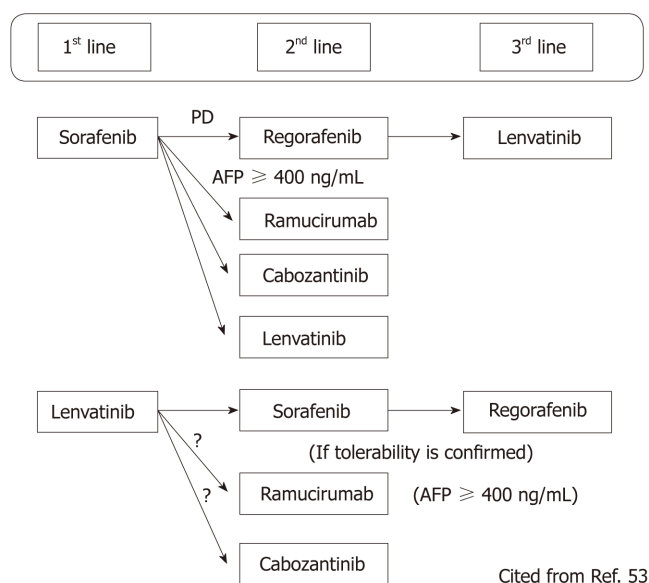
### ***Pembrolizumab***

Similar to nivolumab pembrolizumab is a recombinant monoclonal human immunoglobulin IgG4 antibody specific for human PD-1. A phase II study of HCC patients reported a response rate of 17%, indicating that the effects are comparable with those of nivolumab<sup>[59]</sup>. AE profiles are also mild and comparable with those of nivolumab: grade 3 AEs were observed only in 4% (fatigue) and 1% (decreased appetite). Grade 1/2 AEs include fatigue (17%), pruritus (12%), diarrhea (11%) and rash (10%)<sup>[59]</sup>. A placebo-controlled phase III study of pembrolizumab as a second-line treatment for patients refractory/intolerant to sorafenib was conducted<sup>[60]</sup>, however, the information was press released on Feb 19, 2019 that this trial did not meet its primary endpoints of prolonging PFS nor OS.

### ***Combination therapy with immune checkpoint inhibitor/molecular targeted agents***

The results of a phase 1b study of combination therapy with an anti-PD-L1 antibody, atezolizumab, and another antibody to VEGF, bevacizumab, were reported at ASCO in 2018. Although there were only 23 patients, the response rate according to a RECIST 1.1-based blind review reached 65%, with combination therapy showing a synergistic effect<sup>[61]</sup>. Based on this result, FDA designated this combination trial as a breakthrough therapy in July 2018. However, updated results presented at ESMO 2018 on October 21, 2018 revealed ORR according to modified RECIST- based

Real world practice: Possible sequential therapies



**Figure 2 Possible sequential therapies of molecular targeted agents for hepatocellular carcinoma in the real-world practice<sup>[53]</sup>.** There are solid evidence for use of regorafenib, ramucirumab, cabozantinib after sorafenib as confirmed by RESORCE, REACH-2 and CERESTIAL trials. However, lenvatinib has been proven to be effective after sorafenib or regorafenib in the real world practice as a second-line or third-line agent. Effectiveness of second-line agents after lenvatinib failure should be explored in the real-world practice setting. AFP: Alphafeto protein.

independent review assessment dropped to 34% as a result of increased numbers of patients to 73 (Table 8)<sup>[62]</sup>. Therefore, we have to be cautious on the results derived from small numbers of patients in phase 1/2 trial. A randomized controlled phase III study of combination therapy versus sorafenib is underway (the IMbrave150 trial) (Table 1)<sup>[60,63]</sup>. Other combination cancer immunotherapies in HCC are also ongoing (Table 8)<sup>[64,65]</sup>.

VEGF released by cancer cells suppresses anti-tumor immune responses (Figure 3). VEGF activates the main players in an immunosuppressive tumor microenvironment; these include regulatory T cells (Tregs), tumor-associated macrophages, and myeloid-derived suppressor cells. Cytokines released by these cells inhibit dendritic cell maturation and activation and proliferation of NK cells and CD8-positive cells, thereby driving an immunosuppressive microenvironment (Figure 3)<sup>[66]</sup>. Accordingly, combination treatment with a molecular targeted drug plus an anti-VEGF agent, bevacizumab, is appropriate to induce synergistic effects.

The results of a phase 1b study of combination treatment with lenvatinib plus pembrolizumab were reported at the same ASCO meeting in 2018. The results of this study were also promising. The effects were evaluated in 26 patients; although the mean duration of follow-up was less than 3 mo, the response rate was 42.3%, with no PD patients (Table 8)<sup>[67]</sup>. However, again we have to be cautious on the results derived from small numbers of patients in phase 1/2 trial similar to atezolizumab/bevacizumab combination trial. The synergistic effects of lenvatinib plus an anti-PD-1 antibody were also suggested in a mouse model (Figure 4)<sup>[68,69]</sup>. Thus, combination therapy with immune checkpoint inhibitor/molecular targeted drugs may play an important role in the HCC treatment paradigm in the very near future (Figure 5)<sup>[70,71]</sup>. Biomarker that predicts response to immunotherapy or combination immunotherapy is still an unmet need in immunotherapy of HCC and extensive effort to identify such biomarkers is warranted.

## CONCLUSION

Here, the latest results of trials of systemic therapy for HCC are reviewed. With respect to molecular targeted agents, lenvatinib and regorafenib have been approved for treatment of HCC in addition to sorafenib. Cabozantinib and ramucirumab may also be approved in 2019. Many HCC patients will benefit from increased treatment options and their sequential use for HCC; however, selection of therapeutic drugs may become more complex. When the immune checkpoint inhibitors nivolumab and

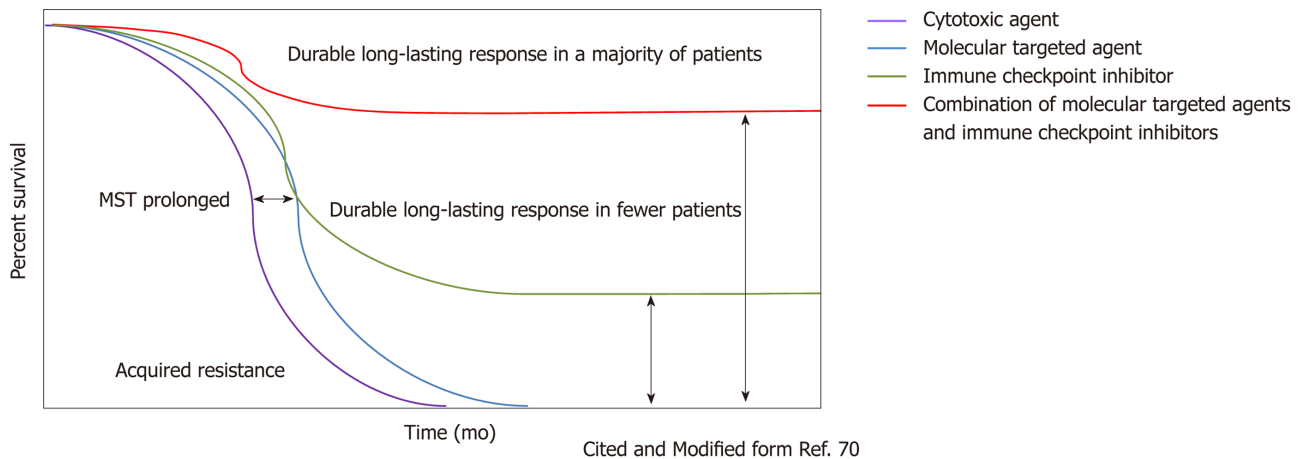
**Table 8 Results of immune checkpoint inhibitors and combination therapy**

	Nivolumab <sup>[68]</sup>	Pembrolizumab <sup>[69]</sup>	Pembrolizumab plus Lenvatinib <sup>[67]</sup>	Atezolizumab plus Bevacizumab <sup>1[62]</sup>	SHR-1210 plus Apatinib <sup>[64]</sup>	Durvalumab plus Tremelimumab <sup>[65]</sup>
	(n = 214)	(n = 104)	(n = 26)	(n = 73)	(n = 18)	(n = 40)
ORR (% , 95%CI)	20 (15-26) <sup>2</sup>	17 (11-26) <sup>2</sup>	42.3 (23.4-63.1) <sup>3</sup>	34 <sup>3</sup>	38.9 <sup>3</sup>	25 <sup>2</sup>
DCR (% , 95%CI)	64 (58-71)	62 (52-71)	100	75	83.3	57.5 (> 16 wk)
PFS (M, 95%CI)	4.0 (2.9-5.4)	4.9 (3.4-7.2)	9.7 (5.6-NE)	7.5 (0.4-23.9)	7.2 (2.6-NE)	NA
OS (M, 95%CI)	NR (9M, 74%)	12.9 (9.7-15.5)	NR	NR	NR	NA
DOR (M)	9.9 (8.3-NE)	≤ 9 (77%)	NE	NR	NE	NA

<sup>1</sup>Independent Review Facility assessment;<sup>2</sup>RECIST 1.1; <sup>3</sup>modified RECIST; ORR: Objective response rate; DCR: Disease control rate; PFS: Progression free survival; OS: Overall survival; DOR: Duration of response; NR: Not reached; NE: Not estimable; NA: Not available.

pembrolizumab become available, the benefits of combination therapy with a molecular targeted agent can also be expected. Indeed, studies of combination therapy with several molecular targeted agents and immune checkpoint inhibitors are ongoing (Table 1, 2, 8) and the results are eagerly awaited. These novel treatment strategies will benefit patients with HCC at all stages from early, intermediate and advanced stage HCCs.

**Figure 4 Mechanism underlying the synergistic effect of combination therapy on hepatocellular carcinoma with lenvatinib and anti-PD-1/PD-L1 antibodies<sup>[68]</sup>.** Lenvatinib inhibits tumor angiogenesis and growth through VEGFR1-R3 and FGFR1-R4 inhibition. Lenvatinib also inhibits VEGF-mediated tumor suppressive microenvironment, such as immunosuppressive cells (tumor associated macrophage, regulatory T cells and myeloid-derived suppressor T cells) or tumor suppressive cytokines (IL10 or TGF- $\beta$ ). Lenvatinib also suppress the co-inhibitory checkpoint inhibitor, TIM 3 and increase the co-stimulatory molecules, CD137, OX40 or ICOS. Finally, PD-1/PD-L1 Ab restores the exhausted T cell activity to kill the cancer cell. Therefore, synergistic effect is obtained by this combination.



**Figure 5 Improved Overall Survival after combination therapy with molecular targeted agents and immune checkpoint inhibitors<sup>[70]</sup>.** Molecular targeted agents improve survival compared with chemotherapy by cytotoxic agents, but will become resistant sooner or later. Durable long-lasting response is obtained by immune checkpoint inhibitors, but only small portion of patients (15%-20%). Durable long-lasting response will be expected by a combination therapy with molecular targeted agents and immune checkpoint inhibitors in the majority of the patients (50%-70%) with advanced hepatocellular carcinoma.

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