Systemic Therapy for Hepatocellular Carcinoma: 2017 Update

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Keywords

Systemic therapy · Hepatic arterial infusion chemotherapy · Molecular targeted therapy · Immune checkpoint inhibitor

Abstract

Systemic therapy for hepatocellular carcinoma (HCC) changed drastically after the introduction of the molecular targeted agent sorafenib in 2007. Sorafenib provides an additional therapeutic option for patients with extrahepatic spread or vascular invasion, resulting in improved survival even among patients with advanced HCC; however, the toxicity of sorafenib and its unsatisfactory antitumor effects remain unsolved issues. The development of novel molecular targeted agents as alternatives to sorafenib has been limited by difficulties unique to HCC. Recent studies have demonstrated the efficacy of two molecular targeted agents, the second-line agent regorafenib, which is used after sorafenib failure, and the first-line agent lenvatinib, which has been shown to be noninferior to sorafenib. Another category of agents that are attracting considerable interest are immune checkpoint inhibitors such as anti-PD-1/PD-L1 or CTLA-4 antibodies, which kill cancer cells via a unique mechanism. The therapeutic effects of some of these agents are currently under investigation in phase III studies. The most recent topics

of interest are the combination of anti-PD-1/PD-L1 therapies with other immune checkpoint inhibitors, such as anti-CTLA-4 antibodies, or with a tyrosine kinase inhibitor, or with locoregional therapies such as resection, ablation, or trans-arterial chemoembolization.

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Introduction

Systemic therapy against hepatocellular carcinoma (HCC) changed drastically following the introduction of the molecular targeted agent sorafenib in 2007. The introduction of sorafenib provided an additional therapeutic option for HCC patients with extrahepatic spread or vascular invasion, and survival improved to some extent even among patients with advanced HCC. Although novel molecular targeted agents have been tested to overcome the poor antitumor effect and toxicity associated with sorafenib, none of them showed satisfactory results for various reasons.

Another category of agents that attracted considerable attention in recent years is that of immune checkpoint inhibitors [1]. These include anti-programmed cell death protein 1 (PD-1)/anti-programmed cell death protein

ligand 1 (PD-L1) or cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibodies, which kill cancer cells via a unique mechanism involving immune responses. Phase III studies of some of these agents are currently ongoing, and expectations are high regarding their therapeutic effects. However, the high cost of these agents has become an important social issue, and there is an increasing need to establish appropriate biomarkers. This article describes the current status, problems, and future perspectives of recent clinical trials of new anti-HCC agents [1–4].

Molecular Targeted Agents

Sorafenib is an oral kinase inhibitor that exerts antitumor effects through the following mechanisms: (1) tumor growth suppression mediated by targeting serine/threonine kinases that are components of the Raf/MEK/ERK pathway (e.g., C-Raf, wild-type B-Raf, and mutant V600E B-Raf), a common downstream pathway of signals transduced via VEGFR, PDGFR, and EGFR; and (2) angiogenesis suppression by targeting tyrosine kinases (e.g., VEGFR1, VEGFR2, VEGFR3, PDGFR- α/β , RET, and Fms-related tyrosine kinase 3 [FLT3]) [5, 6]. Sorafenib became the standard of care for advanced HCC following confirmation of its effect by significantly improving overall survival (OS) over placebo in two large-scale trials, the SHARP trial [7, 8] and the Asia-Pacific trial [4].

Current Status of the Development of Molecular Targeted Agents for HCC

Several clinical trials have investigated the efficacy of novel molecular targeted agents, mainly as adjuvant therapy after curative treatment, in combination with transarterial chemoembolization (TACE), as first-line therapy for advanced HCC, or as second-line therapy. To date, 20 phase III trials of molecular targeted agents for HCC failed to show a benefit in OS or time to tumor progression (TTP)/progression-free survival (PFS) (Table 1). The results of the phase III trials are outlined in the next paragraphs.

Prevention of Recurrence after Curative Treatment (Adjuvant Therapy)

Sorafenib. A phase III trial comparing adjuvant sorafenib to placebo after radiofrequency ablation [9–11] or hepatectomy [12–15] (STORM trial) found no difference in the primary endpoint of recurrence-free survival (RFS) [16]. A possible explanation for the failure of sorafenib to suppress secondary HCC occurrence

and metastatic recurrence is the weak involvement of angiogenesis in the development of microcarcinoma, even in cases of multicentric tumors or intrahepatic metastasis.

Peretinoin. This agent acts by removing precancerous lesions and thereby suppresses cancer development by inhibiting the phosphorylation of retinoid nuclear receptors to induce differentiation and apoptosis [17, 18]. A placebo-controlled phase II/III study examining adjuvant peretinoin after hepatectomy or radiofrequency ablation showed significant benefits in the primary endpoint of RFS in the 600 mg peretinoin group, but not in the 300 mg peretinoin group, over placebo [19]. The primary comparison showed no significant differences between the overall peretinoin group and the placebo group. A second phase III trial comparing 600 mg peretinoin with placebo in HCV-positive Child-Pugh class A patients is currently underway (NIK-333 trial). Another trial comparing RFS associated with peretinoin to placebo in HBV-positive patients in Japan, South Korea, and Taiwan is also ongoing (K-333 trial).

Combination Therapy with TACE

Sorafenib. A phase III post-TACE trial comparing sorafenib and placebo after TACE [9, 14, 20, 21] was conducted in patients who responded to TACE in Japan and South Korea. However, the primary endpoint of prolonged TTP was not achieved, mainly because of the short treatment duration (17 weeks) and the long period (9 weeks) between TACE and the start of sorafenib or placebo. A phase II study comparing sorafenib and placebo in combination therapy with scheduled TACE using doxorubicin-eluting beads (SPACE trial) was successful [22]. The primary endpoint of prolonged TTP was positive, albeit without clinical meaningfulness. There was no significant difference in the secondary outcome of OS. The time to untreatable progression was shorter in the sorafenib group than in the placebo group. In the TACE 2 trial, which was conducted in the UK, the primary endpoint of prolonged PFS was not achieved [23]. This failure could be attributed to the short sorafenib/placebo treatment duration (17.1 weeks) after TACE, as the definition of progression was determined based on RECIST 1.1: one single new lesion in the liver is determined as “progression” per RECIST 1.1, which is not a good definition for a TACE combination trial [24].

Orantinib. This oral kinase inhibitor targets VEGFR2, PDGFR, and FGFR to suppress angiogenesis [25]. A phase III trial comparing orantinib and placebo in combination therapy with TACE (ORIENTAL study) was ter-

Table 1. Phase III clinical trials for HCC

	Trial setting	Design	Trial name	Presentation	Publication
Early	Adjuvant (prevention of recurrence)	1 Peretinoin vs. placebo*	NIK-333	ASCO 2010	JG 2014
		2 Sorafenib vs. placebo*	STORM	ASCO 2014	Lancet-O 2015
		3 <i>Peretinoin vs. placebo</i>	<i>NIK-333/K-333</i>		
Intermediate	Improvement of TACE	1 TACE +/- sorafenib*	Post-TACE	ASCO-GI 2010	EJC 2011
		2 TACE +/- brivanib*	BRISK-TA	ILCA 2013	Hepatol 2014
		3 TACE +/- orantinib*	ORIENTAL	EASL 2015	Lancet GH 2017
		4 TACE +/- sorafenib	TACE 2	ASCO 2016	Lancet GH 2017
Advanced	First line	1 Sorafenib vs. sunitinib*	SUN1170	ASCO 2011	JCO 2013
		2 Sorafenib vs. brivanib*	BRISK-FL	AASLD 2012	JCO 2013
		3 Sorafenib vs. linifanib*	LiGHT	ASCO-GI 2013	JCO 2015
		4 Sorafenib +/- HAIC*	SILIUS	EASL 2016	
		5 Sorafenib +/- erlotinib*	SEARCH	ESMO 2012	JCO 2013
		6 Sorafenib +/- doxorubicin*	CALGB808028	ASCO 2016	
		7 Sorafenib vs. SIRT*	SARAH	EASL 2017	
		8 Sorafenib vs. SIRT*	SIRveNIB	ASCO 2017	
		9 Sorafenib vs. lenvatinib	REFLECT	ASCO 2017	
		10 <i>Sorafenib vs. nivolumab</i>	<i>CheckMate-459</i>		
	Second line	1 Brivanib vs. placebo*	BRISK-PS	EASL 2012	JCO 2013
		2 Everolimus vs. placebo*	EVOLVE-1	ASCO-GI 2014	JAMA 2014
		3 Ramucirumab vs. placebo*	REACH	ESMO 2014	Lancet-O 2015
		4 S-1 vs. placebo*	S-CUBE	ASCO-GI 2015	Lancet GH 2017
		5 Regorafenib vs. placebo	RESORCE	WCGC 2016	Lancet 2017
		6 Tivantinib vs. placebo*	METIV-HCC	ASCO 2017	
		7 Tivantinib vs. placebo*	JET-HCC	ESMO 2017	
		8 Cabozantinib vs. placebo	CELESTIAL	(Press release)	
		9 <i>Ramucirumab vs. placebo</i>	<i>REACH-2</i>		
		10 <i>Pembrolizumab vs. placebo</i>	<i>KEYNOTE-240</i>		

Bold type: positive trials; italics: ongoing trials. HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; SIRT, selective internal radiation therapy. * RCT halted or negative results.

minated after the interim analysis because the criteria for trial continuation regarding the primary endpoint of OS were not met [26]. The failure of this trial could be attributed to the considerable toxicity of orantinib.

Brivanib. This oral kinase inhibitor targets VEGFR and FGFR. A phase III trial comparing brivanib and placebo in combination with TACE (BRISK-TA study) [27] was terminated during the recruitment phase because of the failure of parallel trials of brivanib as first-line or second-line therapy. Although the agent did not show superiority in OS over placebo, significant improvements in PFS and TTP were reported. In addition, the time to vascular invasion and time to extrahepatic spread were significantly longer in the brivanib arm, suggesting a positive antitumor effect of brivanib.

First-Line Therapy for Advanced HCC

Sunitinib. This oral kinase inhibitor targets VEGFR, PDGFR, KIT, FLT3, and RET [28]. A phase III study comparing sunitinib and sorafenib as first-line therapy (SUN1170) showed that the primary endpoint of OS was significantly worse in patients receiving sunitinib [29]. There were no differences in the secondary endpoints of PFS and TTP between the two treatment groups. These results were attributed to the high dose reduction and interruption rates due to severe hematological toxicities in the sunitinib group.

Brivanib. A phase III study comparing brivanib and sorafenib as first-line therapy (BRISK-FL study) did not prove the noninferiority of brivanib to sorafenib in the primary outcome of OS [30].

Table 2. SIRT with ^{90}Y versus sorafenib in patients with locally advanced hepatocellular carcinoma

	SIRT (<i>n</i> = 237)	Sorafenib (<i>n</i> = 222)	HR	<i>p</i> value
Primary endpoint (ITT)				
Median OS, months	8.0	9.9	1.15 (0.94–1.41)	0.18
Secondary endpoint				
Median PFS (ITT), months	4.1	3.7	1.03 (0.85–1.25)	0.76
ORR (RECIST 1.1)	19%	11.6%		0.042
Safety (TEAE, $\geq$ grade 3)				
Fatigue	20%	41%		
Diarrhea	3%	30%		
Abdominal pain	6%	14%		
Hand-foot skin reaction	1%	12%		

Vilgrain et al. [39]. SIRT, selective internal radiation therapy; ITT, intention to treat; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; TEAE, treatment-emergent adverse event.

Table 3. The SARAH trial: SIRT with ^{90}Y versus sorafenib in patients with locally advanced hepatocellular carcinoma

	SIRT (<i>n</i> = 237)	Sorafenib (<i>n</i> = 222)	HR	<i>p</i> value
Primary endpoint (ITT)				
Median OS, months	8.0	9.9	1.15 (0.94–1.41)	0.18
Forest plot (ITT)				
Macroscopic vascular invasion (yes)			1.19 (0.92–1.54)	
Main portal vein (yes)			1.39 (0.88–2.19)	

Vilgrain et al. [39]. SARAH Clinical Study Results Investor Presentation, April 24, 2017. SIRT, selective internal radiation therapy; ITT, intention to treat; OS, overall survival

Table 4. Phase III multicenter open-label randomized controlled trial of SIRT versus sorafenib in locally advanced hepatocellular carcinoma: the SIRveNIB study

	SIRT (<i>n</i> = 182)	Sorafenib (<i>n</i> = 178)	HR	<i>p</i> value
Primary endpoint (ITT)				
Median OS, months	8.54	10.58	1.17	0.203
Secondary endpoint				
Median TTP (overall), months	5.88	5.36	0.93	
Median TTP (liver specific), months	6.08	5.39	0.91	
Tumor response rate	16.5%	1.7%		<0.001
Safety				
Severe AEs	27.7%	50.6%		

Chow et al. [40]. SIRT, selective internal radiation therapy; ITT, intention to treat; OS, overall survival; TTP, time to tumor progression; AE, adverse event.

Linifanib. This oral kinase inhibitor targets VEGFR and PDGFR. A phase III study comparing linifanib to sorafenib as first-line therapy (LiGHT trial) did not prove the noninferiority of linifanib to sorafenib in the primary endpoint of OS [31].

Sorafenib plus Erlotinib. Erlotinib is an oral kinase inhibitor targeting the EGFR tyrosine kinase. A phase III study assessing the addition of erlotinib to first-line sorafenib therapy (SEARCH study) showed that the primary endpoint of OS was comparable between the sorafenib plus placebo group and the sorafenib plus erlotinib group, confirming no additional effect of erlotinib [32].

Lenvatinib. This oral kinase inhibitor targets the receptor tyrosine kinases involved in tumor angiogenesis and malignant transformation (e.g., VEGFR1, VEGFR2, VEGFR3, FGFR1, FGFR2, FGFR3, FGFR4, PDGFR- α/β , KIT, and RET) [33]. Following favorable outcomes of a phase II single-arm study on patients with advanced HCC (TTP, 7.4 months; OS, 18.7 months) [34], a phase III study comparing lenvatinib and sorafenib (REFLECT trial) demonstrated that lenvatinib was statistically non-inferior in OS (primary endpoint) and resulted in statistically significant and clinically meaningful improvements in PFS, TTP, and ORR (secondary endpoints) [35]. Lenvatinib is currently approved for the treatment of thyroid cancer, and an indication expansion (application submitted in June 2017) is expected to be approved by 2018.

Intra-Arterial Radioembolization with ^{90}Y . ^{90}Y radioembolization is reported to be effective for the treatment of HCC [36–38]. However, the results of two prospective randomized trials, the SARAH (Sorafenib versus Radioembolization in Advanced Hepatocellular Carcinoma) and SIRveNIB (Study to Compare Selective Internal Radiation Therapy versus Sorafenib in Locally Advanced Hepatocellular Carcinoma) trials were negative, as reported at the 2017 annual meetings of the European Association for the Study of the Liver and the American Society of Clinical Oncology (ASCO) [39, 40] (Tables 2–4). In both trials, the ORR was significantly better in the ^{90}Y groups; however, there was no statistically significant difference in the primary endpoint of OS. In addition, there was no significant difference in survival benefit in patients with vascular invasion. These negative trials indirectly demonstrate the difficulty in achieving the predefined primary endpoint of improving OS among HCC patients in the first-line setting and the better-than-expected superiority of sorafenib in improving survival among such patients.

Hepatic Arterial Infusion Chemotherapy. Hepatic arterial infusion chemotherapy (HAIC) has been reported to be useful in patients with advanced HCC, especially with vascular invasion [41–43]. However, the SILIUS trial, which compared HAIC plus sorafenib with sorafenib alone, could not show any additive effect compared to sorafenib alone in patients with advanced HCC.

Second-Line Therapy for Advanced HCC

Sorafenib is the standard of care for advanced HCC. Several agents versus placebo were evaluated as second-line therapy in patients who progressed on sorafenib or those who were intolerant to sorafenib.

Brivanib. Brivanib was compared with sorafenib in combination therapy with TACE and as a first-line therapy. It was also evaluated as a second-line therapy in a placebo-controlled study (BRISK-PS trial), in which brivanib showed significantly improved TTP and ORR (secondary endpoint) but not OS (primary endpoint) [44]. The failure of this trial was partly attributed to the higher frequency of vascular invasion in the brivanib arm than in the placebo arm, as the stratification factor was set as “vascular invasion and/or extrahepatic spread.” After this negative trial, vascular invasion thereafter tended to be included as an independent stratification factor in the following second-line trials (Table 5).

Everolimus. This selective mTOR inhibitor suppresses angiogenesis and tumor growth. A placebo-controlled phase III study (EVOLVE-1) did not show a significant improvement in the primary outcome of OS [45].

Tivantinib. This agent selectively inhibits the hepatocyte growth factor receptor c-MET; strong expression of c-MET in liver cancer tissues is associated with poor prognosis. Following a phase II study that showed significant improvements in OS and TTP among patients with c-MET overexpression who received tivantinib [46, 47], a placebo-controlled phase III study was conducted on patients overexpressing c-MET in liver cancer tissues; this was the first biomarker-selected clinical trial for HCC. To reflect ethnic differences in metabolizing enzyme activities, studies with fundamentally the same design were separately carried out globally (METIV-HCC) and in Japan (JET-HCC) (Table 1). The primary endpoint of METIV-HCC was OS and that of JET-HCC was PFS. However, the primary endpoint of OS or PFS was not met in either trial; the results of the former were reported at ASCO 2017 [48]. According to the results presented at ASCO, OS in the placebo arm was too good (OS, 9.1 months). The reason for this negative trial remains unknown. In addition, c-MET expression was not a prog-

Table 5. Phase III clinical trials: advanced stage, second line versus placebo

Study arm vs. placebo arm	BRISK-PS (brivanib) [44]	EVOLVE-1 (everolimus) [45]	REACH (ramucirumab) [50]	S-CUBE (S-1) [52]	RESORCE (regorafenib) [54]	METIV-HCC (tivantinib) [48]	KEYNOTE-240 (pembrolizumab) [69]
Intolerance to sorafenib	12–13%	18.5–20%	13–15%	30.6–33.8%	0%	17–21%	–
Stratification factor	Reason for sorafenib discontinuation ECOG PS score Extrahepatic spread and/or vascular invasion	Region Macrovascular invasion	Region Cause of liver disease	Medical institutions Extrahepatic metastasis and/or vascular invasion	Region ECOG PS score Extrahepatic spread Vascular invasion AFP	Extrahepatic spread Vascular invasion AFP	Region Vascular invasion AFP

After the BRISK-PS trial, where AFP and MVI imbalance was observed in the testing arm, AFP and MVI started to be included as independent stratification factors in the recent trials, although they are known to be prognostic factors. ECOG PS, Eastern Cooperative Oncology Group performance status; AFP, α -fetoprotein; MVI, macroscopic vascular invasion.

Table 6. Comparison of phase II–III studies [46–48] on tivantinib: second line, MET-high hepatocellular carcinoma

	Phase II				Phase III			
	tivantinib (n = 22)	placebo (n = 15)	HR	p value	tivantinib (n = 226)	placebo (n = 114)	HR	p value
MET-high, overall	48%		–	–	100%		–	–
Sample before SOR	40%		–	–	33% (197)		–	–
Sample after SOR	82%		–	–	67% (394)		–	–
Median OS (95% CI), months	7.2 (3.9–14.6)	3.8 (2.1–6.8)	0.38 (0.18–0.81)	0.01	8.4 (6.8–10.0)	9.1 (7.3–10.4)	0.97 (0.75–1.25)	0.81
Median PFS (95% CI), months	2.2 (1.4–4.6)	1.4 (1.4–1.4)	0.45 (0.21–0.95)	0.02	2.1 (1.9–3.0)	2.0 (1.9–3.6)	0.96 (0.75–1.22)	0.72

SOR, sorafenib; OS, overall survival; PFS, progression-free survival.

nostic factor in this phase III trial (Table 6). The JET-HCC trial was also reported as a negative study without any detailed disclosure of the results. This was presented at ESMO 2017.

Ramucirumab. This humanized IgG₁ monoclonal antibody selectively inhibits VEGFR2 [49]. A placebo-controlled phase III study (REACH) showed no significant improvement in the primary endpoint of OS; however, a stratified analysis showed a significant improvement in OS among patients with α -fetoprotein (AFP) levels ≥ 400 ng/mL [50, 51]. In the Japanese cohort, both the overall cohort and the patients with AFP levels ≥ 400 ng/mL showed significantly better survival than the placebo arm [50, 51]. A second placebo-controlled phase III study including only patients with AFP levels ≥ 400 ng/mL is currently underway (REACH-2).

S-1. A cytotoxic agent of S-1 also failed to show survival benefit in patients who progressed or intolerant to sorafenib. This trial was conducted only in Japan [52].

Regorafenib. This oral kinase inhibitor targets multiple protein kinases, including VEGFR1, VEGFR2, VEGFR3,

TIE2, PDGFR- α/β , FGFR, KIT, RET, RAF-1, and BRAF [53]. Because regorafenib and sorafenib have remarkably similar toxicity profiles due to a similar molecular structure, a placebo-controlled phase III study (RESORCE) was conducted using different inclusion criteria, namely, HCC nonresponsive but tolerant to sorafenib. The results indicated a significant improvement in the primary endpoint of OS (10.6 months with regorafenib vs. 7.8 months with placebo), as well as in PFS and TTP [54]. Regorafenib thus became the first second-line agent with proven improved efficacy when compared to placebo. Following this positive study, an indication expansion for regorafenib was approved in April 2017 in the USA and in May 2017 in Japan, allowing its use in second-line therapy for HCC. Regorafenib is not suitable for the treatment of patients intolerant to sorafenib, and a second-line treatment for this subgroup of patients remains an unmet need (Fig. 1). The success of this trial is attributed to the following four points: (1) only sorafenib progressors were included in the trial (i.e., intolerant patients were excluded); (2) vascular invasion and extrahepatic spread were

set as independent stratification factors; (3) AFP ≥ 400 ng/mL was included as a stratification factor; and (4) tolerability was strictly defined as receiving sorafenib ≥ 400 mg daily for at least 20 of the last 28 days of treatment (Table 7). Compared with previous negative phase III second-line trials, the only difference in the patient characteristics in the RESORCE trial was the absence of patients intolerant to sorafenib (Table 8). This superb trial design led to the positive results of the RESORCE study [3].

Cabozantinib. Cabozantinib is a dual inhibitor of MET/VEGFR2 in tumors. On October 16, 2017, the results of phase 3 CELESTIAL trial of cabozantinib were released by press to be positive by meeting its primary endpoint of prolonging its overall survival in patients with advanced HCC. The details will be presented in the future congress and journal. In the near future, we will have another second-line agent for HCC.

Major Difficulties Associated with Clinical Trials of Molecular Targeted Agents in HCC

Many clinical trials of molecular targeted agents did not meet their primary endpoints of prolonging OS, possibly because of the uniqueness of the treatment strategies and modalities with regard to HCC.

Molecular and Biological Heterogeneity of HCC

HCCs are very heterogeneous, as is reflected in the tumorigenesis of HCC. The inclusion criteria of clinical trials are mainly based on liver function and tumor stage (e.g., Child-Pugh class A and the presence of extrahepatic spread and/or vascular invasion). However, the recruited patients do not show uniformity in the biological characteristics of the tumors. Therefore, refined patient selection by biomarkers (e.g., genetic abnormalities and expressed proteins) was recently proposed [55]. For example, c-MET overexpression was used as a biomarker in trials of tivantinib [46–48], and RAS was used as a biomarker in a trial of an MEK inhibitor [56]. A trial of an FGFR inhibitor using FGF19 as a biomarker is currently ongoing. However, following the negative outcomes of a phase III study of tivantinib [48] and this phase II study of an MEK inhibitor, development of the two agents was halted. A biomarker selection-based trial design alone may not be sufficient to overcome the difficulties associated with HCC trials; other trial designs may be more important and should be refined.

Liver Cancer with Cirrhosis

HCC is frequently associated with liver cirrhosis. Liver cirrhosis poses a considerable problem unique to HCC.

Table 7. Reasons for the success of the RESORCE trial (regorafenib)

Good anticancer activity of the agent (compared to placebo)
Acceptable toxicity and tolerability (only patients tolerant to sorafenib)
Superb trial design
Decreasing the imbalance of strong prognostic factors (AFP and vascular invasion were independent stratification factors)
Decreasing post-trial treatment because of the short post-progression survival

Fig. 1. Regorafenib use in practice. SD, stable disease.

Because liver function can be impaired in patients with cirrhosis, drugs tend to exert profound toxic effects, sometimes at an irrecoverable level. In such cases, the expected drug effect may not be exerted because dose reductions and interruptions are often inevitable. The balance between the potency and the toxicity of an agent is important for the development of new agents for the treatment of HCC.

Importance of the Stratification Factor

The design of a clinical study strongly influences the study outcomes. For example, the stratification factor “vascular invasion and/or extrahepatic spread versus neither of them” has typically been used [29–31]; however, the effect of vascular invasion on prognosis is considerably stronger than the effect of extrahepatic spread. In fact, an imbalance in the presence of vascular invasion favoring placebo may explain the lack of differences in OS between brivanib and placebo as second-line therapy [3, 44]. Different results may be obtained if patients with

Table 8. Phase III trials: second line

	RESORCE regorafenib arm [52] (n = 379)	BRISK-PS brivanib arm [44] (n = 263)	EVOLVE-1 everolimus arm [45] (n = 362)	REACH ramucirumab arm [50] (n = 283)
Male	88%	82%	84%	83%
Median age (range), years	64 (19–85)	64 (19–89)	67 (21–86)	64 (28–87)
Asian	41%	48%	38%	46%
ECOG PS 0/1	65/35%	57/39%	59/36%	56/44%
Child-Pugh class A	98%	92%	98%	98%
BCLC stage B/C	14/86%	9/87%	13.5/86.5%	12/88%
MVI	29%	31%	33%	29%
EHS	70%	65%	74%	73%
MVI and/or EHS	80%	–	83%	–
Etiology				
Alcohol	24%	23%	18%	–
HBV	38%	39%	25%	35%
HCV	21%	28%	26%	27%
NASH	7%	–	4%	–
Intolerance to sorafenib	0%	13%	19%	13%

ECOG PS, Eastern Cooperative Oncology Group performance status; BCLC, Barcelona Clinic Liver Cancer; MVI, macroscopic vascular invasion; EHS, extrahepatic spread; NASH, nonalcoholic steatohepatitis.

high AFP values are assigned equally to each group, as observed in the REFLECT trial (lenvatinib), which achieved noninferiority but could not achieve superiority to sorafenib [35].

Post-Trial Treatment

In the treatment of HCC, locoregional approaches are generally used, often proactively, even in patients with Child-Pugh class B or C cancer [57–61]. The patients were repeatedly treated locoregionally after the trial, using TACE, ablation, or HAIC, which resulted in improved post-progression survival, and this likely explains the lack of a difference in OS despite a significant difference in PFS. Post-trial treatment is therefore a major factor distinguishing HCC from other solid cancers.

Another issue unique to HCC is that trials of second-line therapies involve patients that have progressed on and those intolerant to sorafenib. Those who have progressed on sorafenib will have a poor prognosis because they have already experienced ineffective sorafenib treatment. However, those who are intolerant to sorafenib will often have considerably better liver function and tumor status because they may have discontinued sorafenib early and therefore can undergo several post-trial treatments, resulting in improved post-progression survival without any difference in OS (Fig. 2) [62].

Immune Checkpoint Inhibitors

Immune Checkpoint Inhibitors

PD-1 was discovered by Tasuku Honjo in 1992 in a search for molecules inducing T-cell apoptosis [63]. It was later identified as a receptor that negatively regulates immune responses. After the discovery of the PD-1 ligands PD-L1 and PD-L2 in 2000 [64], blockade of the PD-1/PD-L1 pathway was shown to cancel tumor-induced immune suppression to restore intrinsic immune activities, thereby killing tumors. Treatment strategies based on anti-PD-1/PD-L1 agents that inhibit this pathway were subsequently developed. Blockade of CTLA-4, discovered by James Allison in 1995 [65], was also reported to induce rejection of tumors in mice [66]. Such molecules regulating T-cell activities and their inhibitors are referred to as immune checkpoint molecules and immune checkpoint inhibitors, respectively. In relation to HCC treatment, trials of anti-PD-1 antibodies (nivolumab and pembrolizumab), anti-PD-L1 antibodies (avelumab, durvalumab, and atezolizumab), and anti-CTLA-4 antibodies (ipilimumab and tremelimumab) are currently underway.

Nivolumab

Nivolumab (recombinant) is the world's first humanized monoclonal IgG₄ antibody to human PD-1. Promis-

Fig. 2. Relationship between progression-free survival (PFS) and overall survival (OS). The HR comes close to 1.0 if post-progression survival (PPS) becomes long due to effective post-trial treatment.

ing outcomes were reported in a phase I/II trial of nivolumab for the treatment of HCC (Checkmate-040), including an ORR of 20% (including 2 cases of complete response) and a disease control rate of 67%; a long-lasting durable response in patients showing an objective response was also characteristic of nivolumab therapy [67]. A trial examining a larger number of cases is currently underway, and the update presented at ASCO 2017 was again promising: OS with nivolumab was 28.6 months among sorafenib-naïve patients and 15 months among sorafenib-experienced patients [68]. A head-to-head phase III trial comparing nivolumab and sorafenib is also ongoing. Following the outcomes of the above-mentioned phase I/II trial [35], the FDA approved nivolumab as second-line treatment for HCC in September 2017 in the USA.

Pembrolizumab

Pembrolizumab (recombinant) is another humanized monoclonal IgG₄ antibody to human PD-1. Following a phase II study on HCC, a phase III placebo-controlled study examining second-line pembrolizumab in patients who have progressed on or are intolerant to sorafenib is currently underway [69].

Other Immune Checkpoint Inhibitors

All anti-PD-L1 antibodies, avelumab as a monotherapy, atezolizumab in combination with the anti-glypican-3 antibody codrituzumab, and durvalumab in combination with the anti-CTLA-4 antibody tremelimumab, are currently being evaluated in phase I or phase II studies. Inhibitory antibodies against other suppressive immune checkpoint molecules such as TIM3 and Lag3 and agonistic antibodies to OX40 are being investigated in early-stage studies.

Combination Therapy Using an Immune Checkpoint Inhibitor with a Molecular Targeted Agent

The results of an open-label phase Ib trial assessing the efficacy and safety of lenvatinib plus pembrolizumab were reported at ESMO 2016. Among 13 cases of solid tumors, a partial response was achieved in 9 cases and stable disease was achieved in 4 cases; this amazing anti-tumor effect had an ORR of 69.2% and a disease control rate of 100% [70]. The efficacy of an immune checkpoint inhibitor in combination with a molecular targeted agent has attracted much interest in recent years. A clinical trial investigating the efficacy of such combination treatment for HCC has already started in Japan and the USA (NCT03006926). The approach is extremely promising because of the additive therapeutic effect of the two agents and the synergistic effect by improving the tumor-induced immunosuppressive microenvironment.

Need for Biomarkers

The indications for ipilimumab (anti-CTLA-4 antibody) and nivolumab (anti-PD-1 antibody), which were first approved for use in the treatment of malignant melanoma, are gradually expanding. These agents, which exert favorable therapeutic effects mediated by unique anti-tumor mechanisms, benefit many patients; however, the high cost of treatment is a social problem and a healthcare financial burden. Consequently, there is an increasing need to establish appropriate biomarkers to identify patients who will respond to specific agents or will have adverse events. Given that pembrolizumab is available to patients with PD-L1-positive non-small cell lung cancer, establishing biomarkers will help reduce medical costs. Possible current biomarkers predictive of a response to immune checkpoint inhibitors are PD-L1 expression, tumor-infiltrating lymphocytes, or the mutation burden of each patient.

In May 2017, the FDA approved pembrolizumab for the treatment of any solid tumor confirmed to have high microsatellite instability or deficient mismatch repair [71, 72]. This marks the first approval of a cancer treatment based on specific genetic abnormalities rather than the organ where the tumor originated and points to a future of biomarker-based treatment selection.

Conclusion

This article outlined most of the current systemic therapies and ongoing clinical trials for HCC. Among the molecular targeted agents, regorafenib was approved for

the treatment of HCC as a second-line agent, and lenvatinib will become clinically available as a first-line agent in 2018. Although increased options for treatment combining molecular targeted agents and immune checkpoint inhibitors will benefit HCC patients, adequate selection of a treatment strategy may become a more important issue.

Disclosure Statement

The author has no conflicts of interest to declare.

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