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TOPIC HIGHLIGHT

2016 Hepatocellular Carcinoma: Global view

Hepatocellular carcinoma: Will novel targeted drugs really impact the next future?

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Abstract

Cancer treatment has been revolutionized by the advent of new molecular targeted and immunotherapeutic agents. Identification of the role of tumor angiogenesis changed the understanding of many tumors. After the unsuccessful results with chemotherapy, sorafenib, by interfering with angiogenic pathways, has become pivotal in the treatment of hepatocellular carcinoma. Sorafenib is the only systemic treatment to show a modest but statistically significant survival benefit. All novel drugs and strategies for treatment of advanced hepatocellular carcinoma must be compared with the results obtained with sorafenib, but no new drug or drug combination has yet achieved better results. In our opinion, the efforts to impact the natural history of the disease will be directed not only to drug development but also to understanding the underlying liver disease (usually hepatitis B virus- or hepatitis C virus-related) and to interrupting the progression of cirrhosis. It will be important to define the role and amount of mutations in the complex pathogenesis of hepatocellular carcinoma and to better integrate locoregional and systemic therapies. It will be important also to optimize the therapeutic strategies with existing chemotherapeutic drugs and new targeted agents.

Key words: Hepatocellular carcinoma; Targeted therapy; Pathway; Angiogenesis; Sorafenib

Core tip: Hepatocellular carcinoma (HCC) is a tumor with increasing incidence and epidemiologic relevance. Advanced hepatocellular carcinoma that is not amenable to radical treatments (*i.e.*, transplantation or surgical resection) has a dismal prognosis (1-2 mo). Sorafenib, a tyrosine kinase inhibitor which targets multiple pro-angiogenic factors, is a cornerstone in the history of HCC treatments. Since the introduction of sorafenib, novel biological drugs have been investigated in hepatocellular carcinoma patients, but no monotherapy or combination therapy has significantly improved

outcomes in clinical trials. Insights into tumor gene profile are critical in recognizing various classes of hepatocellular carcinoma in order to help determine which therapeutic approaches will be beneficial. Well-designed clinical trials may disclose differences in efficacy end-points, thus leading the way to clinical use.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world and the second most common cause of cancer-related death[1]. Without specific treatment, HCC has a very poor prognosis: the median survival for patients with early and advanced tumors is 6-9 mo and 1-2 mo, respectively. The occurrence of HCC is associated mainly with endemic hepatitis B virus (HBV) infection and aflatoxin B1 exposure in Africa and Asia, with hepatitis C virus (HCV) infection and non-alcoholic steatohepatitis, in Western countries and Japan. Increasing attention is being given to the mechanisms underlying the development of HCC. In fact HCV, HBV and non-alcoholic steatohepatitis are the primary determinants of hepatocarcinogenesis, and any pharmacologic intervention, from prevention to antiviral therapies, may significantly impact HCC development and growth and, thereafter, response to anti-cancer treatments[2]. In addition to tumor progression, functional liver impairment due to cirrhosis influences drug metabolism and, ultimately, the patients' outcome. Regardless of the underlying causes of HCC, most of the morbidity and mortality results from the cirrhosis-related complications: ascites, hepatic encephalopathy, variceal hemorrhage, and hepatorenal syndrome. The unsuccessful medical treatment of HCC is, at least in part, due to complex molecular alterations present in HCC tissue and to the activation of multiple signal transduction pathways that control cell proliferation and tumor progression[3]. Immune-mediated chronic inflammation in hepatitis promotes progressive fibrosis and development of liver cirrhosis, which themselves are early factors responsible for carcinogenesis[2,4]. Integration of HBV DNA into the host genome not only induces chromosomal instability but, depending on the site of DNA integration, may activate oncogenes or inactivate tumor-suppressor genes[4].

The critical signaling pathways for HCC are the Wnt/β-catenin pathway, chromatin remodeling, oxidative stress and signaling involving vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), epidermal growth factor (EGF), fibroblast derived growth factor (FGF), and insulin growth factor (IGF), and intracellular mediators such as RAS/RAF/MAPK and PI3K/AKT[5]. In Figure 1, a comprehensive representation of pathways involved in HCC and targeted drugs are shown. HCC is considered a relatively chemorefractory tumor. Moreover, underlying cirrhosis and impaired liver function can affect the schedule of administration and activity of chemotherapeutic agents. Response rates achieved with single agents and combination chemotherapies do not exceed 10%-20% in most studies, and encouraging survival benefit has thus far not been shown.

The concept of targeted therapies has emerged as a promising approach for the medical treatment of various cancers, including HCC[1,3]. Until now, sorafenib (multi-kinase inhibitor) has been the only systemic therapy with a demonstrated survival benefit in HCC. In the SHARP trial[6], median overall survival was 10.7 mo in the sorafenib group and 7.9 mo in the placebo group (hazard ratio in the sorafenib group, 0.69; 95%CI: 0.55-0.87, $P < 0.001$). Subsequently, several phase Ⅲ trials, which included patients with intermediate-stage or advanced-stage HCC, investigated first-line and second-line treatments but failed to detect any significant survival benefits.

In this report, we have searched Medline/PubMed through February 5, 2016 for published studies and clinical trials of HCC treatment, including the main drugs involved in advanced study or under investigation. In particular, we selected drugs with published results and those studied in phase Ⅱ and Ⅲ trials. Search for clinical trials was performed on https://clinicaltrials.gov/ct2/search/advanced, using the search terms hepatocellular carcinoma and "experimental drug", "open studies", "interventional study", with selection of phase 2 and 3 trials. Finally, we have tried to imagine the future areas of clinical investigation most promising in HCC.

DRUGS TARGETING ANGIOGENESIS

Angiogenesis is one of the prominent features of liver cancer and is also one of the targets of sorafenib, the first approved drug in HCC treatment. Tumor angiogenesis is predominantly promoted by VEGF and PDGF. This latter is also linked to increased metastatic potential of HCC[7].

New trials have been designed with the aim of improving the results obtained with sorafenib single agent[8].

Phase Ⅲ trials are evaluating sorafenib in combination with transarterial chemoembolization (TACE) (Table 1). Sorafenib in combination with chemotherapeutic regimens known to be active in HCC (doxorubicin, FOLFOX or XELOX regimen, 5-fluorouracil/mitomycin) is under evaluation in phase Ⅱ studies (Table 2). Patients with advanced stages of cirrhosis are usually excluded from clinical studies, so whether and

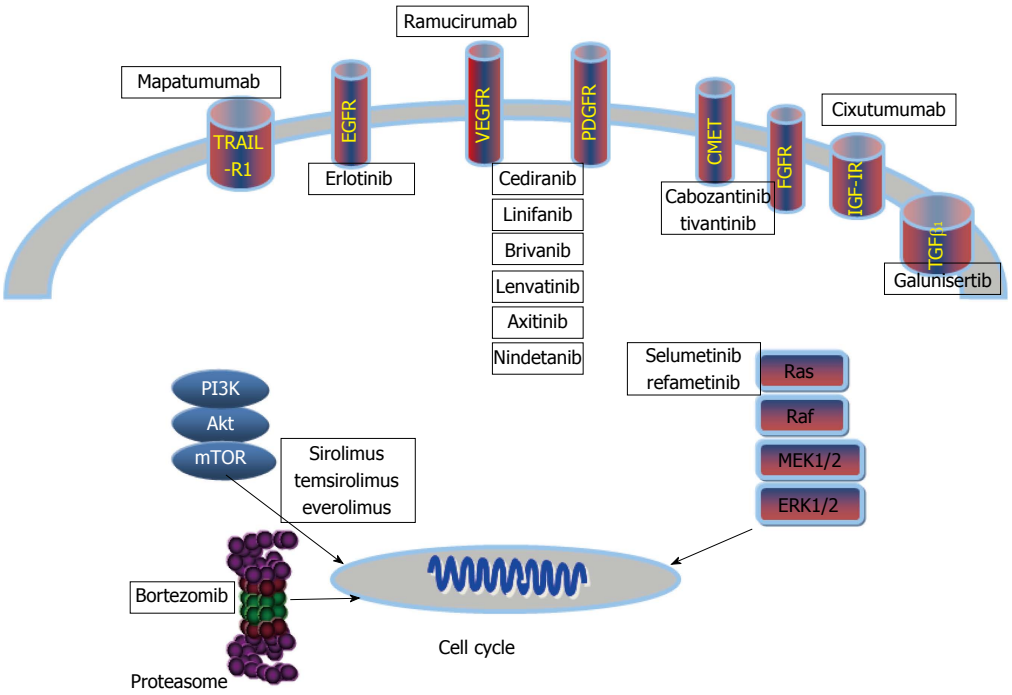

Figure 1 Targeted therapies and signaling pathways in hepatocellular carcinoma.

how to treat these patients is challenging. A Chinese study found similar clinical and progression-free survival benefit among Child-Pugh A and B patients treated with sorafenib[9]. A retrospective Italian study highlighted the safety of sorafenib across the various Child-Pugh classes[10]. The Prodige 21 study is investigating sorafenib in HCC patients with Child B cirrhosis (NCT01357486, Table 2). In that study, two drugs, sorafenib at full doses (400 mg twice a day) and pravastatin, are used in the experimental arms. However, low doses of sorafenib might have clinical activity[11], as shown preliminarily *in vitro*[12], and may permit treatment of HCC in patients with advanced Child-Pugh classes who are at increased risk of toxicity. Sorafenib is also under evaluation in combination with stereotactic radiosurgery (RTOG-1112) in early HCC.

Regorafenib is another multi-kinase inhibitor that has growth inhibitory action against a variety of tumors *in vitro*. A phase Ⅲ trial is testing regorafenib in HCC patients whose disease progressed during sorafenib therapy (NCT01774344; Table 1).

Cediranib (AZD2171) is a potent inhibitor of VEGF receptor tyrosine kinases. Competing with adenosine triphosphate, cediranib binds to and inhibits all three VEGF receptor (VEGF-1,-2,-3) tyrosine kinases, thereby blocking VEGF-signaling, angiogenesis, and tumor-cell growth. Cediranib, 30-mg orally once daily (4 wk/cycle), was tested in a Phase Ⅱ study, where it resulted in stable disease in 5 of 17 patients (29%), an estimated 3-mo progression-free survival (PFS) rate of 77%, median PFS of 5.3 mo, and a median overall survival of 11.7 mo. In that study, Grade 3 toxicities included hypertension (29%), hyponatremia (29%) and hyperbilirubinemia (18%)[13]. Despite the authors' claim of some anti-tumor activity, no further studies are ongoing.

Linifanib (ABT-869) is a novel oral ATP-competitive inhibitor of all VEGF and PDGF receptor tyrosine kinases. Forty-four patients with advanced HCC were treated with 0.25 mg/kg daily. The estimated progression-free rate at 16 wk was 31.8%, the estimated objective response rate (ORR) 9.1%, the median time to progression (TTP) 3.7 mo, and the median overall survival 9.7 mo. The most common adverse events were diarrhea (55%) and fatigue (52%). The most common grade 3/4 adverse events were hypertension (25%) and fatigue (14%)[14]. A Phase Ⅲ trial comparing linifanib (17.5 mg daily) and sorafenib in advanced HCC found similar overall survival for the two agents[15].

Ramucirumab (IMC-1121B) is a fully humanized monoclonal antibody that binds to the extracellular domain of VEGFR-2. The REACH study was a second-line, randomized, placebo-controlled, phase 3 study in patients with advanced HCC after first-line treatment with sorafenib. Median overall survival for the ramucirumab group was 9.2 mo compared with 7.6 mo for the placebo group (HR = 0.87, 95%CI: 0.72-1.05, P = 0.14)[16]. Grade 3 or greater adverse events, occurring in 5% or more of patients in either treatment group, were ascites, hypertension, asthenia, progression of malignant neoplasm, increased aspartate aminotransferase concentration, thrombocytopenia, and increased blood bilirubin values. The authors' conclusion was that second-line treatment with ramucirumab did not significantly improve survival compared with placebo in patients with advanced HCC. A subgroup analysis, conducted to evaluate the relationship between alpha-fetoprotein

Table 1 On-going National Cancer Institute-sponsored phase Ⅲ trials

Target molecule	Molecule	trial	Phase	Details	Locoregional treatment	Primary outcome	Estimated enrollment	Start date	Estimated study completion date	Ref.
VEGFR	Ramucirumab	Ramucirumab (LY3009806) *vs* placebo in participants with hepatocellular carcinoma and elevated baseline alpha-fetoprotein (REACH-2)	Ⅲ	CPA, BCLC Stage C disease or BCLC Stage B disease not amenable to locoregional therapy or refractory to locoregional therapy, Prior sorafenib treatment		OS	399 pts	July 2015	April 2018	NCT02435433
VEGF	Sorafenib	TACE with or without Sorafenib	Ⅲ	CPA or B7, first line treatment, branch not main PVI	Y	PFS	400 pts	October 2009	February 2018	NCT01004978
	Sorafenib	A randomized, controlled phase Ⅲ trial of sorafenib with or without conventional TACE in patients with advanced HCC (STAH Study)	Ⅲ	CPA or B7		OS	338 pts	February 2013	October 2017	NCT01829035
	Regorafenib	Study of regorafenib after sorafenib in patients with hepatocellular carcinoma (RESORCE)	Ⅲ	CPA		OS	573 pts	May 2013	October 2016	NCT01774344
VEGF, FGF, PDGF, RET,KIT	Lenvatinib	A multicenter, open-label, phase 3 trial to compare the efficacy and safety of lenvatinib (E7080) *vs* sorafenib in first-line treatment of subjects with unresectable hepatocellular carcinoma	Ⅲ	CPA, BCLC Stage B or C		OS	954 pts	March 2013	April 2016	NCT01761266
MET, RET, VEGF	Cabozantinib (XL 184)	Randomized controlled trial of XL184 *vs* placebo after sorafenib (CELESTIAL)	Ⅲ	CPA		OS	760 pts	August 2013	October 2016	NCT01908426
MET	Tivantinib (ARQ197)	Study of tivantinib in subjects with inoperable hepatocellular carcinoma who have been treated with one prior therapy (METIV-HCC)	Ⅲ	MET Diagnostic-High tissue		OS	368 pts	December 2012	June 2017	NCT01755767
	Tivantinib (ARQ197)	A randomized double-blind, placebo-controlled Japanese phase Ⅲ trial of ARQ 197 in hepatocellular carcinoma (HCC) (JET-HCC)	Ⅲ	c-Met high in tumor sample, CPA		PFS	160 pts	January 2014	December 2016	NCT02029157
PD-1	Nivolumab	First line treatment with nivolumab *vs* sorafenib (CheckMate 459: CHECKpoint pathway and nivoluMAb clinical trial evaluation 459)	Ⅲ	CPA		TTP, OS	726 pts	November 2015	June 2019	NCT02576509
PD-1	Pembrolizumab	Study of pembrolizumab (MK-3475) *vs* best supportive care in participants with previously Systemically treated advanced hepatocellular carcinoma (MK-3475-240/KEYNOTE-240)	Ⅲ	CPA, BCLC Stage C disease or BCLC Stage B disease not amenable to locoregional therapy		PFS, OS	408 pts	April 2016	April 2018	NCT02702401

PFS: Progression free survival; TTP: Time to progression; ORR: Overall response rate; OS: Overall survival; VEGF: Vascular endothelial growth factor; PDGF: Platelet derived growth factor; FGF: Fibroblast derived growth factor; PD-1: Programmed death-1; CP: Child-Pugh class; BCLC: Barcelona Clinic Liver Cancer; PVI: Portal vein invasion; TACE: Transarterial chemoembolization.

(AFP) levels and ramucirumab treatment response, found significantly improved median overall survival in patients who had elevated baseline AFP levels ($\geqslant$ 400 ng/mL) (P = 0.0059)[17]. Based on this preliminary result, the REACH-2 study has been designed to focus on patients with elevated baseline AFP (NCT02435433, Table 2).

Brivanib (BMS-582664) is a selective dual inhibitor of VEGF and FGF signaling pathways, which has inhibited angiogenesis and tumor growth in xenograft models of HCC[18]. Brivanib has also shown clinical activity and good tolerability in patients with unresectable HCC. A multicenter, double-blind, randomized, placebo-controlled

Table 2 On-going National Cancer Institute-sponsored phase Ⅱ trials

Target molecule	Molecule	Trial	Phase	Details	Primary outcome	Estimated enrollment	Start date	Estimated study completion date	Ref.
VEGFR	Ramucirumab	A study of LY2875358 in combination with ramucirumab (LY3009806) in participants with advanced cancer	Ⅰ / Ⅱ	Part A: Escalating doses of LY2875358 will be given in combination with a fixed dose of ramucirumab to evaluate the safety of the combination Part B: evaluation of safety and activity	Dose-limiting toxicities in part A ORR in part B	70 pts	March 2014	April 2017	NCT02082210
VEGF	Sorafenib	Sorafenib with Capecitabine and Oxaliplatin (SECOX)	Ⅱ		PFS	52 pts	September 2007	December 2008 (status unknown)	NCT00752063
	Sorafenib	Sorafenib + mFOLFOX for hepatocellular carcinoma (HCC)	Ⅱ	CPA, BCLC C or B not suitable for TACE	TTP	40 pts	January 2013	December 2017	NCT01775501
	Sorafenib	Sorafenib plus doxorubicin in patients with advanced HCC with disease progression on sorafenib	Ⅱ	CPA	OS	30 pts	April 2013	April 2016	NCT01840592
	Sorafenib	Comparison study of sorafenib and 5-fluorouracil/ mitomycin for metastatic HCC	Ⅱ	Eligible patients have pulmonary metastasis and intrahepatic tumors controlled with locoregional therapies	PFS	40 pts	November 2010	July 2016	NCT01171482
	Sorafenib	Palliative treatment of HCC in patient with CHILD B cirrhosis (PRODIGE 21)	Ⅱ	Sorafenib *vs* pravastatin *vs* sorafenib + pravastatin BCLC B or C	Time to radiologic progression	160 pts	November 2011	February 2016	NCT01357486
	Sorafenib	A study of LY2157299 in participants with advanced HCC	Ⅱ	LY2157299 *vs* sorafenib *vs* placebo CPA	OS	120 pts	August 2014	December 2016	NCT02178358
	Axitinib	Axitinib as second-line treatment for advanced HCC	Ⅱ	CPA	disease stabilization	45 pts	April 2011	December 2016	NCT01273662
TβRI	Galunisertib (LY2157299)	Galunisertib with nivolumab	Ⅰ / Ⅱ	A study of galunisertib (LY2157299) in combination with nivolumab in advanced refractory solid tumors and in recurrent or refractory NSCLC, HCC, or glioblastoma CPA	Phase 1b: MTD of Galunisertib in combination with nivolumab	100 pts	October 2015	March 2019	NCT02423343
	Galunisertib (LY2157299)	A study of LY2157299 in participants with advanced HCC	Ⅱ	A Randomized phase 2 study of LY2157299 *vs* LY2157299 - sorafenib combination *vs* sorafenib in patients with advanced HCC CPA	OS	120 pts	August 2014	October 2016	NCT02178358
	Galunisertib (LY2157299)	A study of LY2157299 in participants with HCC	Ⅱ	The study consists of three parts: Part A: HCC participants with an increased alpha feto protein (AFP) level are treated with either 160 mg LY2157299 or 300 mg LY2157299; Part B: HCC participants with a normal AFP level are treated with 300 mg LY2157299; Part C: treatment-naïve HCC participants are treated with 160 mg LY2157299 + sorafenib or 300 mg LY2157299 + Sorafenib	TTP Relation-ship of change in response biomarker to clinical benefit	190 pts	March 2011	October 2016	NCT01246986
mTOR	Temsirolimus plus sorafenib	Phase Ⅱ combination of temsirolimus and sorafenib in advanced hepatocellular carcinoma	Ⅱ	TEM 10 mg iv weekly + SOR 200 mg bid CPA, CPB ⩽ 7	TTP	27 pts	September 2012	September 2017	NCT01687673

VEGF, PDGF, FGF	Nindetanib	Phase Ⅰ/Ⅱ comparison of efficacy and safety of BIBF 1120 and sorafenib in patients with advanced hepatocellular carcinoma	Ⅰ/Ⅱ	Nindetanib 200 mg bid or sorafenib 400 mg bid CPA	MTD in phase Ⅰ TTP in phase Ⅱ	125 pts	October 2009	January 2016	NCT01004003
PD-1	Pembrolizumab	Pembrolizumab (Keytruda) in advanced hepatocellular carcinoma	Ⅱ	CP < 7, at sorafenib progression	Disease control rate	28 pts	March 2016	March 2019	NCT02658019
	Pembrolizumab	Study of Pembrolizumab (MK-3475) as monotherapy in adults with previously systemically treated advanced hepatocellular carcinoma (MK-3475-224/KEYNOTE-224)	Ⅱ	CPA	ORR	100 pts	April 2016	November 2017	NCT02702414
	Pembrolizumab	Study of pembrolizumab (MK-3475) in participants with advanced solid tumors (MK-3475-158/KEYNOTE-158)	Ⅱ	Multiple types of advanced (unresectable and/or metastatic) solid tumors that have progressed on standard of care therapy may be enrolled	ORR	1100 pts	December 2015	April 2018	NCT02628067
S100A9	Tasquinimob	A study with tasquinimod treating patients in four independent cohorts of hepatocellular, ovarian, renal cell and gastric cancers	Ⅱ	BCLC C or B not amenable to locoregional therapy, CPA, previous treatment with sorafenib	PFS	201 pts	December 2012	February 2016	NCT01743469
PD-1	Nivolumab, nivolumab plus ipilimumab	Study to evaluate the effectiveness, safety and tolerability of nivolumab and the combination nivolumab plus ipilimumab in subjects with advanced liver cancer	Ⅰ/Ⅱ		Safety, ORR	600 pts	September 2012	July 2018	NCT01658878
PD-L1	MEDI4736	Biological/vaccine: MEDI4736 + tremelimumab Biological/vaccine: MEDI4736 Biological/vaccine: Tremelimumab	Ⅱ		Safety	120 pts	October 2015	April 2018	NCT02519348

PFS: Progression free survival; TTP: Time to progression; ORR: Overall response rate; MTD: Maximum tolerated dose; OS: Overall survival; VEGF: Vascular endothelial growth factor; PDGF: Platelet derived growth factor; FGF: Fibroblast derived growth factor; PD-1: Programmed death-1; PD-L1: Programmed death ligand 1; CP: Child-Pugh class; BCLC: Barcelona Clinic Liver Cancer.

trial assessed brivanib in patients with HCC who had been treated with sorafenib[19]. Median overall survival was 9.4 mo for brivanib and 8.2 mo for placebo (HR = 0.89, 95.8%CI: 0.69-1.15, $P = 0.3307$). Exploratory analyses showed a median TTP of 4.2 mo for brivanib and 2.7 mo for placebo (HR = 0.56, 95%CI: 0.42-0.76, $P < 0.001$), and an ORR by modified response evaluation criteria in solid tumors (RECIST) of 10% for brivanib and 2% for placebo (OR = 5.72). The most frequent treatment-related grade 3-to-4 adverse events for brivanib were hypertension (17%), fatigue (13%), hyponatremia (11%), and decreased appetite (10%). Brivanib was also compared to sorafenib in first-line treatment[20]: median overall survival was 9.9 mo for sorafenib and 9.5 mo for brivanib; TTP, ORR, and Disease Control Rate also were similar between the study arms.

Lenvatinib (E7080) is an oral multi-targeted tyrosine kinase inhibitor of VEGFR1-3, FGFR1-4, PDGFRβ, RET and KIT. A phase 1/2 open-label study evaluated the safety and efficacy of lenvatinib in 46 patients with advanced disease and Child Pugh A liver function status. Patients were treated with a starting dose of lenvatinib 2 mg daily (28-d cycles) until disease progression or development of unmanageable toxicities occurred. Median TTP was 12.8 mo (95%CI: 7.23-14.7), and median overall survival 18.7 mo (95%CI: 12.8-25.1). The most common adverse events were hypertension 76% (Gr 3, 54%), palmar-plantar erythrodysesthesia syndrome 61% (Gr 3, 7%), proteinuria 59% (Gr 3, 20%), anorexia 57% (Gr 3, 2%), thrombocytopenia 50% (Gr 3, 33%), and fatigue 48% (Gr 3, 0%). ORR was 37%, and 45.7% of patients had stable disease. Based on these phase 2 data, a global, randomized, open-label phase 3 trial is ongoing to determine if lenvatinib is non-inferior or superior compared with sorafenib in advanced HCC (NCT01761266; Table 1)[21].

Axitinib, a potent, selective inhibitor of VEGF receptors, has been efficacious in phase 2 and 3 trials in previously treated patients with metastatic renal cell carcinoma. In preclinical studies, axitinib had antiangiogenic and anti-tumor activity in human tumor models. Phase Ⅱ or phase Ⅲ studies have found that axitinib has single-agent clinical activity in a range of tumor types, including renal cell carcinoma[22], thyroid cancer[23], non small-cell lung cancer[24], and melanoma[25]. Results of a phase Ⅱ trial using 5 mg bid in second-line therapy of HCC have recently been published[26]: median overall survival was not significantly improved in the axitinib/best

Supportive care (BSC) arm (12.7 mo) *vs* placebo/BSC (9.7 mo) (HR = 0.907, 95%CI: 0.646-1.274; one-sided stratified *P* = 0.287). Despite the absence of overall survival benefit, improvements in PFS, TTP, and clinical benefit rate with axitinib/BSC compared with placebo/BSC were shown. Most common adverse events with axitinib/BSC were diarrhea (54%), hypertension (54%), and decreased appetite (47%). Axitinib in second-line treatment is still being evaluated in a phase Ⅱ ongoing trial (NCT 01273662; Table 2).

AGENTS TARGETING SIGNAL TRANSDUCTION

Agents developed to target signal transduction may act at the level of growth factor receptor or within the cell at the level of intracellular signaling. A number of strategies, including monoclonal antibodies and tyrosine kinase inhibitors, have been developed and tested in various phases of clinical trials.

A key signal transduction pathway implicated in HCC is the EGFR-RAS-MAPKK pathway. EGFR is frequently expressed in human HCC cell cultures and tumor tissues. The ligands EGF, hepatocyte growth factor (HGF), PDGF, and VEGF, among others, activate the RAS/MAPK signaling pathway and induce transcription of genes, such as *c-fos* and *c-jun*, which are key elements for cell proliferation[27]. HCV core protein can directly activate the Raf/MEK/ERK cascade[28].

Mutations of Raf and Ras are rare findings in HCC. Potent drugs blocking Ras/MAPK signaling are still at the exploratory phase, except for sorafenib, which can inhibit B-Raf at nanomolar concentrations.

Although phase Ⅱ studies reported that erlotinib monotherapy had activity in patients with advanced HCC[29,30], combining erlotinib with sorafenib did not enhance efficacy compared with sorafenib alone[31]. Median overall survival was similar in the sorafenib plus erlotinib and sorafenib plus placebo groups (9.5 mo *vs* 8.5 mo, respectively, HR = 0.929, *P* = 0.408), as was median TTP (3.2 mo *vs* 4.0 mo, respectively; HR = 1.135, *P* = 0.18). In the sorafenib/erlotinib arm the ORR was higher (6.6% *vs* 3.9%, respectively, *P* = 0.102) than in the sorafenib/placebo arm, whereas the DCR was significantly lower (43.9% *vs* 52.5%, respectively, *P* = 0.021). Drug-related serious adverse events were similar in the two arms.

AZD6244 (selumetinib, ARRY-142886) targets the MAPK pathway by inhibiting MEK. AZD6244 is well tolerated but appears to have minimal activity in advanced HCC[32].

Refametinib, an oral allosteric MEK inhibitor, has had anti-tumor activity in combination with sorafenib *in vitro* and *in vivo*. A phase Ⅱ study evaluated efficacy and safety of refametinib plus sorafenib in Asian patients with HCC[33] (NCT01204177). Anti-tumor activity was found in patients, however, dose modifications were required due to adverse events, which occurred in almost all patients.

IGFR signaling has a major role in the regulation of fetal development, proliferation, differentiation, cell growth, and apoptosis. The IGF family consists of two ligands (IGF-Ⅰ, IGF-Ⅱ), two receptors, and six binding proteins. Ligand binding leads to the activation of the PI3K/Akt/mTor and MAPK pathways, among others. Dysregulation of IGFR signaling in HCC predominantly occurs at the level of IGF-Ⅱ and the IGF-I receptor (IGF-1R)[34,35]. Somatostatin reduces release of growth factors, such as IGF-1 or EGF[36,37] and inhibits angiogenesis. The somatostatin analog octreotide, can be considered the first "biological" agent used in HCC. Several IGF-1R inhibitors are under investigation. The most advanced clinical antibody against IGF-1R is cixutumumab (IMC-A12), but cixutumumab monotherapy did not have clinically meaningful activity in an unselected HCC population[38].

The RAS/MAPK pathway is activated in 50% of patients who have early stage HCCs and almost all of those with advanced-stage HCCs[39,40]. Several compounds have been developed that target the c-MET/HGF signaling pathway, including antibodies against HGF or c-MET, or selective small-molecule inhibitors of c-MET[41].

Cabozantinib (XL184) is a small-molecule inhibitor of the tyrosine kinases c-Met and VEGFR2, and has been shown to reduce tumor growth, metastasis, and angiogenesis. A phase Ⅲ trial is underway in HCC patients who have received prior sorafenib[42] (NCT01908426; Table 1).

Tivantinib (ARQ 197), a selective oral inhibitor of MET, has shown promising anti-tumor activity in HCC as monotherapy and in combination with sorafenib. Seventy-one patients were randomly assigned to receive tivantinib (38 at 360 mg twice-daily and 33 at 240 mg twice-daily); 36 patients were randomly assigned to receive placebo. TTP was longer for patients treated with tivantinib (1.6 mo, 95%CI: 1.4-2.8) than with placebo [1.4 mo (1.4-1.5); HR = 0.64, 90%CI: 0.43-0.94; *P* = 0.04]. For patients with MET-high tumors, median TTP was longer with tivantinib than with placebo [2.7 mo, 95%CI: 1.4-8.5 for 22 MET-high patients on tivantinib *vs* 1.4 mo (1.4-1.6) for 15 MET-high patients on placebo; HR = 0.43, 95%CI: 0.19-0.97, *P* = 0.03]. The most common grade 3 or worse adverse events in the tivantinib-treated group were neutropenia and anemia. Tivantinib at higher doses was associated with increased rate of grade 3 or worse neutropenia (21% *vs* 6%, respectively). Four patients treated with tivantinib died due to severe neutropenia[43]. Results of two phase Ⅲ trials of tivantinib in pre-treated MET-high HCC are awaited (Table 1).

LY2875358 is a novel humanized bivalent anti-MET antibody that has high neutralization and internalization activities, which can inhibit activation

of both HGF-dependent and HGF-independent MET pathways and tumor growth[44] . A phase Ⅰ/Ⅱ trial with LY2875358 and ramucirumab is ongoing in patients with advanced cancer, including HCC patients (NCT02082210; Table 1).

AGENTS TARGETING THE PI3K/AKT/MTOR PATHWAY

The PI3K/Akt/mTOR pathway is a pivotal signaling cascade in cancer, particularly in HCC, and interferes with cell growth, proliferation, angiogenesis, and apoptosis [45]. The pathway is activated through several receptor tyrosine kinases (RTKs) (*e.g.*, EGFR or IGFR). PI3K activity is additionally controlled by the tumor suppressor gene phosphatase and tensin homolog, which is mutated in a subgroup of HCCs. PI3K activates the serine/threonine kinase Akt, which phosphorylates and inactivates several pro-apoptotic proteins. The most relevant target downstream of Akt is mTOR, a central regulator of cell proliferation and angiogenesis[45]. Phosphorylation of mTOR and its downstream targets were detected in human HCC. The PI3K/Akt/mTOR pathway is activated in 15%-41% of HCCs, and mTOR inhibitors had antineoplastic activity in experimental models of HCC[46,47].

Several compounds which inhibit mTOR [sirolimus (rapamycin) and its analogues temsirolimus (CCI-779) and everolimus (RAD001)] are already used as immunosuppressants after liver transplantation, or for the treatment of renal cell carcinoma. Retrospective studies in patients who have had liver transplantation for HCC and concomitant immunosuppression with mTOR inhibitors have been reported[48], with an outcome that suggests a prolonged overall survival and reduced tumor recurrence. Rapamycin is undergoing several trials intended to establish its role in this setting.

EVOLVE-1 was a randomized, double-blind, phase 3 study conducted with 546 adults with Barcelona Clinic Liver Cancer stage B or C HCC and Child-Pugh A liver function after treatment with sorafenib. Study subjects received everolimus, 7.5 mg/d, or matching placebo, both given together with best supportive care[49]. No significant difference in overall survival was seen between treatment groups, with 303 deaths (83.7%) in the everolimus group and 151 deaths (82.1%) in the placebo group (HR = 1.05, 95%CI: 0.86-1.27, P = 0.68; median OS, 7.6 mo with everolimus, 7.3 mo with placebo). Median TTP with everolimus and placebo was 3.0 mo and 2.6 mo, respectively (HR = 0.93, 95%CI: 0.75-1.15), and disease control rate (DCR) was 56.1% and 45.1%, respectively (P = 0.01). The most common grade 3/4 adverse events for everolimus *vs* placebo were anemia, asthenia, and decreased appetite. No benefit was found for the combination of everolimus and pasireotide, a long-acting somatostatin multi-receptor ligand, in HCC[50]. Also, no evidence was found that everolimus plus sorafenib is more efficacious than sorafenib alone[51]. Median PFS (6.6 mo *vs* 5.7 mo), TTP (7.6 mo *vs* 6.3 mo), duration of disease stabilization (6.7 mo *vs* 6.7 mo), and overall survival (10 mo 12 mo) were similar in the sorafenib and sorafenib plus everolimus arms. Grade 3/4 adverse events were more common with the combination therapy. Everolimus has been tested also in association with TACE[52].

There are no published data on phase Ⅱ trials regarding temsirolimus alone in HCC; however, the combination of temsirolimus and bevacizumab was evaluated in 28 patients, with a favorable ORR of 19% and overall survival of 14 mo[52].A phase Ⅱ study evaluating temsirolimus plus sorafenib is ongoing (NCT01687673; Table 2).

AGENTS TARGETING PROTEIN TURNOVER, CHROMATIN REMODELING, APOPTOSIS, AND CELL CYCLE CONTROL

The ubiquitin-proteasome pathway is the major nonlysosomal proteolytic system, and it triggers degradation of proteins involved in cell cycle progression, apoptosis, angiogenesis, and, particularly, NF-κB activation. The 26S proteasome is a complex molecular machine that induces protein degradation and has become an attractive target for cancer therapy. Bortezomib (PS-341) reversibly and competitively inhibits the 26S proteasome, thus blocking multi-ubiquitinated protein degradation[53]. Bortezomib was tested in a Phase Ⅰ/Ⅱ trial in 18 patients with advanced HCC and achieved stable disease in 46% of patients[54]. In a phase Ⅱ study enrolling 35 patients, no significant activity was shown and grade 3 and 4 adverse events were reported in 68% and 11% of treated patients[55] Moderate or severe liver dysfunction influenced the safety of bortezomib, with required dose adjustment to 0.7 mg/m^2[56]. Further development of the drug was probably restricted by inadequate consideration of this finding, which was particularly significant in HCC. Future research will focus on combination treatment strategies using bortezomib together with other targeted agents such as sorafenib[57]. A phase Ⅱ, open-label, multicenter study examined the efficacy of bortezomib (1.3 mg/m^2 Ⅳ on days 1, 4, 8, and 11) and doxorubicin (15 mg/m^2 Ⅳ on days 1 and 8) in 21-d cycles[58] The combination of the two drugs produced less grade 3 and 4 adverse events than that seen in the previous reported phase Ⅱ study, but failed to demonstrate an ORR of at least 27% and had no encouraging efficacy results.

Evasion of apoptosis is one of the hallmarks of cancer. Several pro-apoptotic receptor agonists targeting the extrinsic apoptosis pathway [including the ligand recombinant human Apo2L/TNF-related apoptosis-inducing ligand (TRAIL)] are in development. Mapatumumab (HGS1012), a fully human agonist

monoclonal antibody targeting TRAIL receptor 1, in combination with sorafenib have been evaluated in a randomized, double-blind, placebo-controlled, phase Ⅱ study[59]. One hundred-one patients were randomized (placebo-sorafenib arm: *n* = 51; mapatumumab-sorafenib arm: *n* = 50). There was no significant difference in median TTP between the two arms [5.6 mo *vs* 4.1 mo, respectively; adjusted hazard ratio one-sided 90%CI: 1.192 (0, 1.737)]. No mapatumumab-related benefit was identified when TTP was evaluated in the stratified subgroups. The addition of mapatumumab to sorafenib did not result in improved secondary efficacy endpoints.

TGF-β SIGNALING

Galunisertib is a selective small-molecule inhibitor of TβRI. A Phase 1b/2 dose escalation and cohort expansion study will evaluate the safety and efficacy of galunisertib in combination with nivolumab in the treatment of advanced refractory solid tumors (Phase 1b) and in recurrent or refractory non-small cell lung cancer, HCC, or glioblastoma (Phase 2). This study is not yet open for participant recruitment (NCT02423343; Table 2). Galunisertib is being evaluated with or without sorafenib in an open label, 3-part, phase 2 study in patients with HCC. The study consists of 4 parts: Part A includes HCC patients with an elevated AFP level treated with galunisertib 160 mg/d (Arm A, *n* = 37) or 300 mg/d (Arm B, *n* = 72); Part B includes HCC patients with a normal AFP level treated with galunisertib 300 mg/d; Part C includes treatment-naïve HCC patients treated with galunisertib 160 or 300 mg/d plus sorafenib 800 mg/d; and Part D includes HCC patients (those intolerant to sorafenib, those whose disease progressed during treatment with sorafenib, or those naïve to treatment with sorafenib) treated with galunisertib 160 or 300 mg/d plus ramucirumab 8 mg/kg on days 1 and 15. Patients will be administered galunisertib daily for 14 d, followed by 14 d off (28-d cycle), with patients in Part C receiving sorafenib daily for 28 d. Adverse events and efficacy data have been presented for Part A[60,61] (NCT01246986; Table 2): median TTP was 12 wk (90%CI: 6.6-12.6) in the overall population, with 12.1 wk in Arm A, 10 wk in Arm B, and 18.3 wk (90%CI: 6.6-42.4) in patients who were sorafenib naïve[60,61]. A Phase 2 study evaluating galunisertib, sorafenib, or galunisertib with sorafenib in patients with advanced HCC is ongoing and recruiting patients (NCT02178358; Table 2).

IMMUNE SYSTEM MODULATORY DRUGS

The immune system plays an important role in the outcome and response to treatment of HCC patients: post-surgical tumor recurrence are reduced when dense lymphocytic tumor infiltration is present and T-cell responses against tumor antigens are associated with patient survival[62]. However, continued exposure to tumor antigens leads to T cell exhaustion, favored by intra-tumor expression of immune check-point inhibitors. In recent years we have witnessed the dawn of a new era in immunotherapy of HCC, with different approaches. While resistance inevitably develops to targeted agents, durable disease control is generally achieved by immunotherapies[63]. Monoclonal antibodies that modulate the activity of immune check-point molecules, which are critical determinants of tumor evasion to immunity, have revolutionized the field of cancer immunotherapy and will probably do so with therapy of HCC also. Cytotoxic T-lymphocyte antigen-4 (CTLA-4) plays a key role in downstaging the activity of T cells. Promising activity has been reported for tremelimumab, a CTLA-4 inhibitor: a phase Ⅱ trial of tremelimumab in HCC patients has recently been reported (NCT01008358)[64]. The study enrolled 21 chronic hepatitis C patients with Child-Pugh A or B cirrhosis and advanced HCC not amenable to percutaneous ablation or transarterial embolization. Partial responses were seen in 17.6% of the patients and 45% had stable disease for more than 6 mo.

Another immune checkpoint molecule, programmed death-1 (PD-1) inhibits effector T-cell responses within tissues. When programmed death-ligand 1 (PD-L1) binds to its receptor, PD-1, delivers a signal that inhibits TCR-mediated activation of IL-2 production and T cell proliferation. This is one of more potent mechanisms of escape of tumor cells to immune system. Clinical trials with two anti-PD-1 monoclonal antibodies, pembrolizumab (humanized IgG4) and nivolumab (fully human IgG4), are underway. A phase 1/2 study evaluating the effectiveness, safety and tolerability of nivolumab and the combination nivolumab plus ipilimumab is ongoing (NCT01658878, Table 2). That study plans to enroll three cohorts of patients stratified by viral etiology (HBV, HCV) and no viral infection. A phase Ⅲ trial is comparing nivolumab to sorafenib in first-line treatment (NCT02576509; Table 1). Pembrolizumab is under investigation in several phase Ⅱ studies (NCT02658019, NCT027024414, NCT02628067). A phase Ⅲ trial (NCT02702401; Table 1) will give information on the efficacy of pembrolizumab in previously treated HCC patients. MEDI4736, another humanized IgG-1κ monoclonal antibody which blocks PD-L1, is a subject of clinical trials. A Study of MEDI4736 with tremelimumab, MEDI4736 or tremelimumab monotherapy in unresectable HCC is recruiting participants (NCT02519348; Table 2).

Tasquinimod is a novel small-molecule inhibitor that targets the tumor microenvironment by controlling immunosuppressive, pro-angiogenic and pro-metastatic functions of regulatory myeloid cells (also called myeloid-derived suppressor cells)[65]. It binds to and inhibits the interactions of S100A9, an immunomodulatory protein that promotes tumor development. Tasquinimod inhibits the growth and metastasis of tumor cells *in vitro* and

in vivo[65]. A phase Ⅱ study is ongoing in treatment of several types of tumors, including HCC (NCT01743469; Table 2).

DISCUSSION

Upon review of medical research in HCC, we find some new molecules disappearing after phase Ⅰ/Ⅱ studies without published results; most drugs in development, with poor results; and only a few new drugs surviving at selection with positive outcomes. HCC is a difficult disease to study because of its clinical and molecular heterogeneity and the presence of underlying liver cirrhosis. Studies conducted during the past decade have defined the main genomic subclasses of HCC: a primary classification of tumors consists of proliferative and non-proliferative genotypes, each comprising approximately 50% of patients[5]. Overall, the proliferative subclass is enriched by activation of classic RAS, mTOR and/or IGF signaling and is associated with a poorer outcome than that of non-proliferative phenotypes. From an epidemiological standpoint, HBV-related HCCs usually cluster within the proliferative subclass, whereas alcohol-related and HCV-related HCCs are enriched in the non-proliferative subclass[5]. Probably each tumor subclass is linked to a specific mutation signature profile and may benefit by an approach different from that for the other subclass. Therefore, it is crucial to select drugs that interfere with oncogenic drivers and not bystander mutations. Similarly to what happened in other tumors, dependency of tumor cells on activated oncogenes or loss of tumor suppressors has been the key to identifying drugs capable of producing favorable clinical results. Thus far, no main driver and pathway has been identified in HCC. However, several studies have provided a broad picture of the mutational profile in HCC and identified an average of 30-40 mutations per tumor, among which 5-8 might be driver mutations[5]. There is a rationale for blocking complementary pathways activated in HCC[66]. Along with the identification of these pathways is the need for tumor tissue to assess markers predictive for response. As in other types of tumors, the identification of biomarkers could predict response to a date therapy. Perhaps a more aggressive tumor phenotype could particularly benefit, if discovered early, from local interventions followed by maintenance medical treatment and, in later stages, by a chemo-targeted approach, either sequential or combined.

Sorafenib has changed the medical approach to advanced HCC; however, data supporting its use are not based on response rate (2% partial response) and improvements in quality of life and cancer symptoms, but only on a modest survival advantage[6]. It is also important to appreciate that there is a difference between criteria of clinical studies and general practice: the majority of trials select Child A and ECOG 0-1 patients, which do not represent the real population of HCC patients. Most studies also lack a stratification taking into account factors like portal invasion and metastases[5]. Specific phase Ⅱ studies exploring potential liver-related toxicities of new agents are required in patients with cirrhosis and HCC before testing in phase Ⅲ randomized controlled trials. We frequently found that increased aspartate aminotransferase concentration, thrombocytopenia, hyperbilirubinemia, and ascites are cited among adverse events, but whether these are due to drug toxicity only or to progression of liver disease is not easy to determine. In clinical practice, usually these events are unchanged or worsen after stopping a drug because they are simply related to the evolution of tumor/cirrhosis. Better supportive liver care in chronic hepatitis/cirrhosis can help tumor treatment; however, thus far, only control of viral infection, through the use of new antiviral agents, might significantly impact on the outcomes of HCC treatment. A recent systematic review concluded that there are few data on the supportive-care needs of patients with advanced liver disease and cirrhosis[67]. Activity of biological therapies at doses different from those registered is another field of investigation[11].

Thus far, efforts at treating HCC have been concentrated on advanced HCC because transplantation, surgery, and local treatments gave the best chance of cure in early HCC. However, attempts to reduce recurrences are ongoing, especially with sorafenib in association with local therapies.

According to American Association for the Study of Liver Diseases and Journal of the National Cancer Institute guidelines[68], new molecules tested in the first-line setting need to be combined with the standard of care, sorafenib, to demonstrate superiority[5]. However, only one randomized controlled trial, which tested sorafenib plus erlotinib *vs* sorafenib alone, was planned according to this recommendation. Furthermore, response criteria must be chosen carefully. Tumor shrinkage is not a valid end point for HCC, especially since tumor activity of targeted therapies is cytostatic rather than cytotoxic[69]. Overall survival is considered as the only valid primary end point, even in the phase Ⅱ setting[5].

CONCLUSION

Thus far, no novel, fully effective drug in the treatment of HCC has been produced. HCC remains a complex disease. The lack of a driver oncogene and the presence of underlying liver cirrhosis are factors which are most responsible for the frequently unsuccessful results with novel drugs. Insights into signaling pathways could help in identifying drugs likely to be effective. We feel that a unique targeted therapy for HCC probably does not exist and a tailored medical approach is the best that can be offered at the moment.

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