New agents on the horizon in hepatocellular carcinoma

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Ther Adv Med Oncol
(2013) 5(1) 41–50
DOI: 10.1177/1758834012458480

Abstract: Despite the successful approval and extensive application of sorafenib, the prognosis for patients with advanced hepatocellular carcinoma (HCC) remains poor. Fortunately, there have been renewed and continued interests and active research in developing other molecularly targeted agents in HCC during the past few years. While there is early evidence of antitumor activity of several agents in phase I/II studies, phase III efforts with a few targeted agents have failed, highlighting the challenges of new drug development in HCC. This review summarizes the current status of other molecularly targeted agents under development in advanced HCC.

Keywords: bevacizumab, brivanib, EGFR inhibitors, everolimus, hepatocellular carcinoma, linifanib, Met inhibitors, sorafenib, sunitinib, targeted agents

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Introduction

Hepatocellular carcinoma (HCC) continues to present many challenges. First, it is the sixth most common cancer and the third most common cause of cancer-related mortality worldwide [Parkin *et al.* 2005]. Second, most patients will present with the advanced stage of disease, defined as the presence of extrahepatic disease, vascular invasion, or the presence of disease-related symptoms. These patients will not benefit from curative treatment options including surgical resection, liver transplantation, or radiofrequency ablation. Third, despite the approval of sorafenib, based on phase III trials demonstrating overall survival benefits, and its extensive application in clinical practice during the past few years, it is increasingly clear that the benefits of sorafenib remain modest. More importantly, the mechanisms mediating the sorafenib-related benefits, toxicity and resistance remain elusive. Fourth, most patients with HCC have underlying cirrhosis, which would have an adverse impact on the overall survival of these patients and limit the number of patients who are potentially eligible for clinical trials. Nevertheless, we have witnessed an unparalleled time period of active drug development in HCC. Many molecularly targeted agents that inhibit different pathways of hepatocarcinogenesis are under various phases of clinical development and novel targets are being assessed in HCC. This review will attempt to summarize briefly the current status of other molecularly targeted agents under investigation in HCC.

Antiangiogenic agents

HCCs are vascular tumors and increased levels of vascular endothelial growth factor (VEGF) and microvessel density (MVD) have been observed [Messerini *et al.* 2004; Miura *et al.* 1997; Yamaguchi *et al.* 1998, 2000]. In contrast to the normal architecture of hepatic parenchyma, HCCs display marked vascular abnormalities. In addition, liver tumor vessels have an abnormal blood flow, deficient leukocyte rolling, and are excessively leaky. In turn, this leads to hypovascular areas and severe hypoxia and/or necrosis: all hallmarks of liver tumors [Zhu *et al.* 2011b]. VEGF is one of the main inducers of liver tumor angiogenesis. High VEGF expression has been associated with inferior survival [Chao *et al.* 2003; Jeng *et al.* 2004; Poon *et al.* 2004]. Inhibition of angiogenesis represents a potential therapeutic strategy in HCC and many antiangiogenic agents have entered clinical studies in HCC.

Sunitinib

Sunitinib is an oral multikinase inhibitor that targets receptor tyrosine kinases (RTKs) including

Table 1. Phase II studies of sunitinib in advanced hepatocellular carcinoma.

Dose schedule and sample size	37.5 mg 4 weeks on / 2 weeks off (*N* = 34) [Zhu *et al.* 2009]	50 mg 4 weeks on / 2 weeks off (*N* = 37) [Faivre *et al.* 2009]	37.5 mg 4 weeks on / 2 weeks off (*N* = 17) [Hoda *et al.* 2008]	37.5 mg continuous (*N* = 45) [Koeberle *et al.* 2009]
Objective response rate, *n* (%)	1 (2.9)	1 (2.7)	1 (5.9)	1 (2.2)
Disease control rate*	52%	38%	53%	42%
Overall survival (months)	9.8	8.0	–	9.3
Time to progression (months)	4.1		–	1.5
Progression-free survival (months)	3.9	3.7	–	1.5

*Partial response plus stable disease

VEGFR1, VEGFR2, PDGFR-alpha/beta, c-KIT, FLT3, and RET kinases [Arora and Scholar, 2005; Mendel *et al.* 2003; Pawson, 2002]. The currently available data with sunitinib in HCC come from four single-arm phase II studies that used three different dose schedules [Faivre *et al.* 2009; Hoda *et al.* 2008; Koeberle *et al.* 2009; Zhu *et al.* 2009] (Table 1). Zhu and colleagues performed a study in patients with advanced HCC using sunitinib at 37.5 mg orally once daily on a standard 4-weeks-on, 2-weeks-off regimen (6 weeks per cycle) [Zhu *et al.* 2009]. The primary endpoint of the study was progression-free survival (PFS). Of the 34 patients enrolled, one patient had a partial response (PR) of 20 months duration and an additional 10 patients (38.5%) had stable disease (SD) of at least 12 weeks duration. The median PFS was 3.9 months and overall survival (OS) was 9.8 months. In another European/Asian phase II study, sunitinib was administered at 50 mg daily for 4 weeks every 6 weeks to patients with unresectable HCC [Faivre *et al.* 2009]. The primary endpoint of the study was overall response rate per RECIST criteria. Of the 37 patients enrolled, one patient (2.7%) had a PR and 13 patients (35%) of patients had SD as best response. The median OS was 8.0 months and PFS 3.7 months. Koeberle and colleagues reported their experience with sunitinib using the 37.5 mg daily dosing schedule. Of the 45 patients enrolled, median PFS and OS were 1.5 and 9.3 months, respectively [Koeberle *et al.* 2010].

The most common adverse events included hematologic toxicities, fatigue, and transaminase elevation [Hoda *et al.* 2008; Koeberle *et al.* 2009; Zhu *et al.* 2009]. At the higher dose of 50 mg daily, sunitinib treatment led to more pronounced grade 3–4 toxicities and a higher death rate of 10% in this patient population [Faivre *et al.* 2009].

A randomized phase III study comparing sunitinib at 37.5 mg continuous daily dosing versus sorafenib at 400 mg twice daily in advanced HCC was conducted and timely completed. Unfortunately, in this large study of 1073 patients, sunitinib failed to demonstrate either superiority or noninferiority in OS when compared with sorafenib (Table 2) [Cheng *et al.* 2011]. Significant toxicities including thrombocytopenia and neutropenia were seen with sunitinib leading to discontinuation.

Brivanib

Brivanib alaninate is a dual inhibitor of VEGFR and fibroblast growth factor receptor (FGFR) signaling pathways that can induce tumor growth inhibition in mouse HCC xenograft models [Huynh *et al.* 2008]. A phase II study was conducted to assess the efficacy and safety of brivanib in patients with unresectable, locally advanced or metastatic HCC who had received either no prior systemic therapy (Cohort A, $n = 55$) or one prior regimen of angiogenesis inhibitor (Cohort B, $n = 46$) (Table 3). The treatment schedule consisted of continuous daily dosing of brivanib at 800 mg. Both schedules reported preliminary evidence of antitumor activity. Median PFS and OS were 2.7 (95% confidence interval [CI] 1.4–3.0) and 10 months

Table 2. Phase III study of sunitinib in comparison with sorafenib in advanced hepatocellular carcinoma.

Treatment and dose schedule	Sunitinib 37.5 mg daily (n = 529)	Sorafenib 400 mg bid (n = 544)	Hazard ratio (95% confidence interval)
Overall survival (months)	8.1	10.0	1.31 (1.13–1.52) p = 0.0019
Progression-free survival (months)	3.6	2.9	1.12 (0.98–1.29) p = 0.1386
Time to progression (months)	4.1	4.0	1.13 (0.97–1.31) p = 0.1785

Table 3. Phase II study of brivanib in advanced hepatocellular carcinoma.

Dose schedule and sample size	First line 800 mg daily (n = 55) [Park *et al.* 2011]	Second line 800 mg daily (n = 46) [Finn *et al.* 2012]
Objective response rate, n (%)	4 (7.2)	2 (4.3)
Overall survival (95% confidence interval) (months)	10.0 (6.8–15.2)	9.8 (5.5–13.2)
Time to progression (months)	2.8 (1.4–3.5)	1.8 (1.4–4.0)
Progression-free survival (months)	2.7 (1.4–3.0)	2.0 (1.4–3.9)

(95% CI 6.8–15.2) in the first-line study [Park *et al.* 2011]. Median OS and time to progression (TTP) as assessed by study investigators following second-line treatment with brivanib were 9.79 and 2.7 months, respectively [Finn *et al.* 2012]. Interestingly, greater than 50% decrease in serum alpha-fetoprotein (AFP) from baseline was seen in more than 40% of patients in both Cohorts A and B. the most common adverse events included fatigue, hypertension, nausea, and diarrhea. Most frequently observed grade 3–4 adverse events included fatigue (16%), aspartate transaminase (AST) elevation (19%), and hyponatremia (41%) in Cohort A and hypertension (7.3%), diarrhea (4.9%), and headache (4.9%) in Cohort B. Despite the ambitious phase III development program with brivanib in HCC, the recent press release reported that brivanib failed to demonstrate improved OS when compared with placebo in patients with advanced HCC who failed sorafenib (see http://www.businesswire.com/news/home/20111222005831/en/BRISK-PS-Study-Investigational-Compound-Brivanib-Hepatocellular-Carcinoma). Currently, the first-line study comparing brivanib with sorafenib in patients with newly diagnosed advanced HCC and underlying Child A cirrhosis is ongoing.

Linifanib (ABT-869)

Linifanib (ABT-869) is an orally active, potent, and selective inhibitor of VEGFR and PDGFR. Preliminary results from an open-label, multicenter phase II study of linifanib in advanced HCC were reported [Toh *et al.* 2009]. Linifanib was given at 0.25 mg/kg daily in Child-Pugh A or once every other day in Child-Pugh B patients until progressive disease or intolerable toxicity. The primary endpoint was the progression free rate at 16 weeks. Of the 44 patients enrolled, 34 were available for analyses (28 with Child A and 6 with Child B cirrhosis). The estimated response rate was 8.7% (95% CI 1.1–28) for the 23 patients with Child A cirrhosis. For all 34 patients, median TTP was 112 days (95% CI 110 to not available), median PFS was 112 days (95% CI 61–168), and median OS was 295 days (95% CI 182–333). The most common adverse events for all patients were hypertension (41%), fatigue

(47%), diarrhea (38%), rash (35%), proteinuria (24%), vomiting (24%), cough (24%), and peripheral edema (24%). The most common grade 3–4 adverse events were hypertension (20.6%) and fatigue (11.8%). A phase III study comparing linifanib *versus* sorafenib in advanced HCC should be completed in the near future.

Ramucirumab (IMC-1121B)

Ramucirumab (IMC-1121B), a recombinant human monoclonal antibody against VEGFR-2, has been examined in a phase II study. Of the 43 patients enrolled, 42 received ramucirumab at 8 mg/kg IV every 2 weeks until disease progression or intolerable toxicity. This study demonstrated a relapse rate (RR) of 10%, PFS of 4.0 months, and OS of 12.0 months in patients who have not received prior systemic therapy [Zhu *et al.* 2010]. The most frequent adverse events were fatigue (62%), headache (38%), and hypertension (38%). Grade 3–4 adverse events included fatigue (10% grade 3), gastrointestinal bleeding (7% grade 3), hypertension (12% grade 3; 2% grade 4), infusion-related reactions (5% grade 3), and headache (2% grade 3). Ramucirumab is undergoing phase III development in the second-line setting against placebo in patients who failed sorafenib.

Bevacizumab

Bevacizumab is a recombinant, humanized monoclonal antibody that targets VEGF and is one of the earlier agents entering HCC clinical trials. Siegel and colleagues reported their experience using single-agent bevacizumab in HCC in a phase II study [Siegel *et al.* 2008]. Two dosages of bevacizumab, 5 mg/kg and 10 mg/kg administered intravenously once every 2 weeks, were tested in patients with HCC with no overt extrahepatic metastases or invasion of major blood vessels. Of the 46 patients evaluable for efficacy, 6 (13%) had objective responses (95% CI 3–23%), and 65% were progression free at 6 months. Median PFS was 6.9 months (95% CI 6.5–9.1 months) and median OS was 12.4 months (95% CI 9.4–19.9 months). Grade 3–4 adverse events included hypertension (15%) and thrombosis (6%, including 4% with arterial thrombosis). Grade 3 or higher hemorrhage occurred in 11% of patients, including one fatal variceal bleed. Despite the initial encouraging results, there is no phase III development plan for bevacizumab.

Cediranib (AZD2171)

Cediranib (AZD2171) is a potent oral, pan-VEGF RTK inhibitor with activity against PDGF receptors and c-Kit. Cediranib is a potent inhibitor of both KDR (IC_{50} <0.002 μM) and Flt-1 (IC_{50} = 0.005 μM) and shows activity against c-kit, PDGF receptor β, and Flt-4 at nanomolar concentrations [Wedge *et al.* 2005]. Alberts and colleagues reported their early experiences of toxicity and efficacy of cediranib from a NCCTG phase II study in patients with advanced HCC [Alberts *et al.* 2011]. Cediranib was given at 45 mg orally once daily using a 28-day treatment cycle. Twenty-eight patients were enrolled and evaluable for efficacy. The median OS was 5.8 months (95% CI 3.4–7.3 months) and TTP 2.8 months (95% CI 2.3–4.4 months). Twenty-six patients (93%) experienced a grade 3+ adverse event including fatigue (46%), anorexia (25%), hypertension (21%), and elevated alanine aminotransferase (18%). Another phase II trial evaluating cediranib at a lower dose of 30 mg daily in HCC is ongoing.

Pazopanib (GW786034)

Pazopanib (GW786034) is an oral angiogenesis inhibitor targeting VEGFR, PDGFR, and c-Kit. Yau and colleagues reported a phase I study to determine the maximum tolerated dose (MTD), safety, pharmacokinetics, pharmacodynamics and efficacy of pazopanib in patients with locally unresectable and/or advanced HCC [Yau *et al.* 2011]. Doses of pazopanib were escalated from 200 to 800 mg once daily using a modified 3 + 3 design. Of the 28 Asian patients enrolled, MTD was determined to be 600 mg once daily. Diarrhea, skin hypopigmentation, and AST elevation were the most commonly reported adverse events at the MTD. A total of 19 patients (73%) had either partial response (PR) or SD. Changes in tumor DCE-MRI parameters were seen following pazopanib administration.

TSU-68

TSU-68 is an oral tyrosine kinase inhibitor of VEGFR-2, PDGFR and FGFR-2. A phase I/II study was conducted with TSU-68 in advanced HCC [Kanai *et al.* 2011]. After the phase I study, 200 mg twice daily was determined to be the phase II dose. Two patients (5.7%) had PR. TTP was 2.1 months and OS 13.1 months. Common adverse events included hypoalbuminemia,

Table 4. Phase II trials of epidermal growth factor receptor inhibitors in hepatocellular carcinoma.

	Year	Patients *N*	RR (%)	Median PFS (Months)	Median OS (Months)
Erlotinib [Philip *et al.* 2005]	2005	38	9	3.2	13
Erlotinib [Thomas *et al.* 2007]	2007	40	0	3.1	6.3
Lapatinib [Ramanathan *et al.* 2009]	2009	40	5	2.3	6.2
Lapatinib [Bekaii-Saab *et al.* 2009]	2009	26	0	1.9	12.6
Cetuximab [Gruenwald *et al.* 2007]	2007	32	0	2	–
Cetuximab [Zhu *et al.* 2007]	2007	30	0	1.4	9.6

Abbreviations: OS, overall survival; PFS, progression-free survival; RR, response rate

diarrhea, anorexia, abdominal pain, malaise, edema, and AST/alanine transaminase (ALT) elevation.

Lenvatinib (E7080)

Lenvatinib is an oral tyrosine kinase inhibitor targeting VEGFR1-3, FGFR1-4, RET, KIT and PDGFRβ. The preliminary data from a phase I/II study in HCC was presented at GI ASCO in 2012 [Okita *et al.* 2012]. Of the 46 patients enrolled, 33% of patients had PR based on the investigator assessment using modified RECIST criteria. However, grade 3 hypertension was encountered in 48% of the patients.

Epidermal growth factor receptor inhibitors

Increasing evidence has highlighted the importance of epidermal growth factor receptor (EGFR)/HER1 and its ligands epidermal growth factor (EGF) and transforming growth factor-alpha (TGF-alpha) in hepatocarcinogenesis. The expression of several EGF family members, specifically EGF, TGF-alpha, and heparin binding EGF, as well as EGFR, has been described in several HCC cell lines and tissues [Carlin *et al.* 1988; Harada *et al.* 1999; Ito *et al.* 2001; Kira *et al.* 1997; Kiss *et al.* 1997; Yeh *et al.* 1987]. Multiple strategies to target EGFR signaling pathways have been developed and two classes of anti-EGFR agents have established clinical activity in cancer: monoclonal antibodies that competitively inhibit extracellular endogenous ligand binding and small molecules that inhibit the intracellular tyrosine kinase (TK) domain. Table 4 summarizes phase II studies with EGFR inhibitors. Other than the modest activity with erlotinib, the rest of the EGFR inhibitors failed to show any activity as single agents in advanced HCC.

EGFR tyrosine kinase inhibitors

Two phase II clinical studies have evaluated the safety and efficacy of erlotinib (Tarceva) given at 150 mg daily, in patients with advanced HCC [Philip *et al.* 2005; Thomas *et al.* 2007]. In the study by Philip and colleagues, 3 out of 38 patients (9%) had PR and 12 patients (32%) were progression free at 6 months [Philip *et al.* 2005]. Median OS was 13 months. In another report by Thomas and colleagues, 17 out of 40 patients (43%) achieved PFS at 16 weeks and the PFS rate at 24 weeks was 28% [Thomas *et al.* 2007]. No PR or CR was observed in this study. The median time to failure, defined as either disease progression or death, was 13.3 weeks. The median time of OS was 25.0 weeks (95% CI 17.9–42.3 weeks) from the date of erlotinib therapy initiation. In an Eastern Cooperative Oncology Group's Study E1203, gefitinib given at 250 mg daily was examined in a single-arm phase II study [O'Dwyer *et al.* 2006]. A two-stage design was used and 31 patients were accrued to the first stage. One patient had PR and seven patients had SD. The median PFS was 2.8 months (95% CI 1.5–3.9 months) and median OS was 6.5 months (95% CI 4.4–8.9 months).

The criterion for second-stage accrual was not met and the authors concluded that gefitinib as a single agent was not active in advanced HCC. Lapatinib, a selective dual inhibitor of both EGFR and HER-2/NEU tyrosine kinases, also demonstrated modest activity in HCC [Ramanathan *et al.* 2009]. Among the 40 patients with advanced HCC, the response rate was 5%, PFS 2.3 (95% CI 1.7–5.6) months, and OS of 6.2 (95% CI 5.1 to infinity) months. In another phase II study of 26 advanced HCC patients treated with lapatinib at 1500 mg daily, no responses were seen and median PFS of 1.9 months and OS of 12.6 months were observed [Bekaii-Saab *et al.* 2009].

Monoclonal antibodies against EGFR

Cetuximab, a chimeric monoclonal antibody against EGFR, was tested in two phase II studies in patients with advanced HCC. In our study, 30 patients with advanced HCC were enrolled [Zhu *et al.* 2007]. The initial dose of cetuximab was 400 mg/m^2 given intravenously followed by weekly intravenous infusions at 250 mg/m^2. No responses were seen. Five patients had SD (median time, 4.2 months; range, 2.8–4.2 months). The median overall survival was 9.6 months (95% CI 4.3–12.1 months) and the median PFS was 1.4 months (95% CI 1.2–2.6 months). Cetuximab trough concentrations were not notably altered in patients with Child A and Child B cirrhosis. Gruenwald and colleagues reported their preliminary experience of cetuximab in a similarly designed study in HCC [Gruenwald *et al.* 2007]. Of the 32 patients enrolled, 27 patients were evaluable for efficacy. No responses were seen and the median TTP for all patients was 8.0 weeks.

Taken together, with the exception of erlotinib showing modest activity in single-arm studies, the other EGFR inhibitors have not demonstrated convincing antitumor activity as single agents. Only erlotinib is being examined in ongoing phase III study to assess its relative contribution when added to sorafenib in comparison to sorafenib alone in patients with advanced HCC.

mTOR inhibitors

Mammalian target of rapamycin (mTOR) functions to regulate protein translation, angiogenesis, and cell cycle progression in many cancers including HCC. Preclinical data have demonstrated that mTOR inhibitors were effective in inhibiting cell growth and tumor vascularity in HCC cell lines and HCC tumor models. The importance of the mTOR pathway in HCC was examined in a comprehensive study with 314 HCC and 37 non-tumoral tissues using a series of molecular techniques to assess the mutation, DNA copy number changes, messenger RNA and gene expression, and protein activation [Villanueva *et al.* 2008]. Aberrant mTOR signaling (p-RPS6) was present in half of the cases and chromosomal gains in RICTOR (25% of patients) and positive p-RPS6 staining correlated with HCC recurrence following resection.

A number of mTOR inhibitors (sirolimus, temsirolimus and everolimus) are available clinically. Chen and colleagues reported their early experience of a randomized, phase I, and pharmacokinetic study of everolimus in advanced HCC [Chen *et al.* 2009]. Two different schedules were tested in this randomized phase I study: continuous daily dosing and once-weekly dosing. A total of 36 patients were enrolled. Dose-limiting toxicities observed included hyperbilirubinemia, ALT elevation, thrombocytopenia, infection, diarrhea, and cardiac ischemia. The MTD for weekly and daily dosing schedules was determined to be 70 and 7.5 mg, respectively. Interestingly, reactivation of HBV and flaring of HCV was observed in four and one patients, respectively. The disease control rate of 31 evaluable patients was 61% (10/16) and 46.7% (7/15, including one partial response) of patients receiving daily and weekly treatment, respectively. Another phase I/II study evaluating everolimus using continuous daily dosing schedule in advanced HCC was reported. Twenty-eight patients were enrolled and evaluable for efficacy and toxicity. Everolimus was well tolerated in patients with advanced HCC at either 5 or 10 mg daily dosing, and 25 patients, most of whom had prior systemic treatment, were treated at 10 mg/day in the phase II study. One patient (4%) had PR (95% CI 0.9–19.6%). The median PFS and OS were 3.8 months (95% CI 2.1–4.6) and 8.4 months (95% CI 3.9–21.1), respectively [Zhu *et al.* 2011a].

MEK inhibitor

HCC is characterized by frequent MEK/ERK activation in the absence of RAS or RAF mutation [Huynh *et al.* 2003]. A multicenter, single-arm study with a two-stage design was conducted using selumetinib (AZD6244), a specific inhibitor of MEK, in advanced HCC [O'Neil *et al.*

2011]. The primary endpoint was response rate. Selumetinib was administered orally at a dose of 100 mg bid. Of the 19 patients enrolled, 17 were evaluable for response. Despite the good tolerability of selumetinib, it showed minimal activity in advanced HCC. No response was seen and median TTP was only 8 weeks.

Hepatocyte growth factor/c-Met inhibitors

Dysregulation of c-Met is seen in HCC and silencing the expression of c-Met inhibits HCC growth in HCC cell lines and tumor models. Tivantinib (ARQ197), a selective, non-ATP-competitive inhibitor targeting MET tyrosine kinase, is under early clinical evaluation. In a press release, tivantinib reportedly met the primary endpoint of improving TTP in a randomized phase II study comparing tivantinib with placebo in previously treated patients. Cabozantinib (XL184), a dual c-Met/VEGFR2 inhibitor, also demonstrated early evidence of antitumor activity in a randomized discontinuation phase II study [Cohn *et al.* 2012]. Of the 41 patients enrolled, efficacy and safety data were available for 34 patients. The most common treatment-related grade 3 or higher adverse events were hand–foot syndrome (15%), diarrhea (9%), and thrombocytopenia (9%). Three patients had confirmed PR. The overall disease control rate (DCR = PR+SD) at week 12 was 71%. The median PFS was 4.2 months. Interestingly, the clinical benefits were observed regardless of whether patients received prior sorafenib treatment. Cabozantinib is undergoing additional evaluation in HCC.

Histone deacetylase inhibitor

Belinostat is a novel histone deacetylase inhibitor. A phase I/II multicenter study was conducted in advanced HCC and results were presented [Chan *et al.* 2012]. In phase I portion, 18 patients were accrued with no dose limiting toxicities (DLTs) observed at 1400mg/m^2/day intravenously for 5 days every 3 weeks. Therefore, this dose was selected for phase II development with 42 patients enrolled. With a median follow up of 20.0 months, the PR and SD rate was 2.4% (1/42) and 45.2% (19/42). Median PFS was 2.64 months (95% CI, 1.55-3.17) and OS was 6.60 months (95% CI 4.53–11.60). The most frequent grade 3 or higher toxicities included abdominal pain (9.5%), hyperbilirubinemia (9.5%), elevated ALT (9.5%), anemia (7.1%), and vomiting (7.1%).

Other molecularly targeted agents under development in HCC

Many genetic and epigenetic changes occur during hepatocarcinogenesis. These pathways include the PI3K/Akt/mTOR pathway, insulin growth factor (IGF) and its receptor (IGFR), as well as the Wnt/beta-catenin pathway. Multiple agents targeting these key pathways are under early stage evaluation in HCC. The major challenge for future development of these targeted agents is to assess early evidence of safety profiles and antitumor activity, validate potential target inhibition, and identify likely predictive markers for specific drugs so that the targeted population can be enriched.

Conclusions

Despite the successful development of sorafenib in HCC, there is continued need and opportunity for developing other targeted agents in HCC. Many molecularly targeted agents are at different stages of clinical development in HCC and some have failed in phase III studies. HCC is heterogeneous with various etiology and whether HCC with underlying HBV or HCV will respond differently to various targeted agents should be prospectively evaluated. Future research should continue to unravel the mechanism of hepatocarcinogenesis and to identify key relevant molecular targets for therapeutic intervention. While we are developing other antiangiogenic and targeted agents in HCC, it is imperative that we continue our efforts to identify and validate surrogate and predictive biomarkers that would be helpful to predict clinical efficacy, toxicity, and resistance to these agents. Hopefully we will continue to witness meaningful progress for the development of molecularly targeted agents in HCC in the coming years.

Conflict of interest statement

The author has advisory roles with Sanofi-aventis, Eisai, Bristol-Myers Squibb, Abbott Laboratories and Eisai and has received research support from Bayer, Onyx, Lilly-ImClone and Novartis.

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