World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v18.i6.498

World J Gastroenterol 2012 February 14; 18(6): 498-506
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Targeted systemic therapies for hepatocellular carcinoma: Clinical perspectives, challenges and implications

Catherine Frenette, Robert Gish

Catherine Frenette, Robert Gish, California Pacific Medical Center, San Francisco, CA 94115, United States
Author contributions: Frenette C and Gish R contributed equally to the writing of this manuscript.
Correspondence to: Catherine Frenette, MD, Medical Director of Liver Transplantation, Director of Liver Cancer Program, The Methodist Hospital, Houston, TX 77030, United States. ctfrenette@tmhs.org
Telephone: +1-713-4410179 Fax: +1-731-4415248
Received: February 21, 2011 Revised: June 6, 2011
Accepted: June 13, 2011
Published online: February 14, 2012

Abstract

Hepatocellular carcinoma (HCC) is a lethal disease in most patients, due to its aggressive course and a lack of effective systemic therapies for advanced disease. Surgical resection and liver transplantation remain the only curative options for a small subset of patients. Few patients with HCC are diagnosed early enough to be eligible for curative treatment. Angiogenesis inhibition is a natural therapeutic target for all solid tumors, but particularly for the highly vascularized HCC tumors. With the approval of the targeted agent sorafenib, there are now additional options for patients with HCC. Although sorafenib does produce some improvement in survival in HCC patients, the responses are not durable. In addition, there are significant dermatologic, gastrointestinal, and metabolic toxicities, and, as importantly, there is still limited knowledge of its usefulness in special subpopulations with HCC. Other angiogenesis inhibitors are in development to treat HCC both in the first-line setting and for use following sorafenib failure; the furthest in development is brivanib, a dual fibroblast growth factor pathway and vascular endothelial growth factor receptor inhibitor. Additional agents with antiangiogenic properties also in phase Ⅱ and Ⅲ development for the treatment of patients with HCC include bevacizumab, ramucirumab, ABT-869, everolimus and ARQ 197.

Key words: Hepatocellular carcinoma; Angiogenesis; Vascular endothelial growth factor; Fibroblast growth factor; Sorafenib; Tumor response; Brivanib

Peer reviewer: Jean Paul Galmiche, MD, Professor, Department of Gastroenterology and Hepatology, Hôpital Hôtel Dieu, 44093 Nantes cedex, France

Frenette C, Gish R. Targeted systemic therapies for hepatocellular carcinoma: Clinical perspectives, challenges and implications. *World J Gastroenterol* 2012; 18(6): 498-506 Available from: URL: http://www.wjgnet.com/1007-9327/full/v18/i6/498.htm DOI: http://dx.doi.org/10.3748/wjg.v18.i6.498

INTRODUCTION

Primary liver cancer, including hepatoma and hepatocellular carcinoma (HCC) is diagnosed in more than 560 000 people worldwide each year[1], including more than 24 000 Americans[2]. HCC accounts for up to 90% of all primary liver cancers[3]. HCC can be treated curatively with surgical resection or liver transplantation if diagnosed at an early stage; however, since most HCC patients present with advanced disease, only 15% are eligible for curative treatments[4]. Even for patients undergoing surgical resection, recurrence rates may be as high as 50% after 2 years and 76% by 10 years[5,6]. Patients meeting the Milan criteria who undergo liver transplantation can achieve a 5-year cancer-free survival rate greater than 60%[7].

As most patients with HCC are diagnosed with advanced disease, they generally have a poor prognosis, with median survival times of less than 1 year[3]. This is due, at least in part, to the absence of effective systemic therapies. Systemic therapies examined in the past, including both cytotoxic and hormonal agents, have provided limited or no benefit for these patients[6]. In late 2007, the angiogenesis inhibitor sorafenib was approved for use

in advanced HCC based on an improvement in survival compared with placebo[8,9]. While initial responses are observed, over time a loss of efficacy is apparent that may be due to "resistance" *via* escape/compensatory mechanisms. Like other angiogenesis inhibitors, sorafenib also has known class side effects, including skin-related toxicities, hypertension, proteinuria, diarrhea, and an increased risk for thromboembolism and bleeding events[10-12]. While most are manageable, certain rare events can be life-threatening (i.e., gastrointestinal perforation, fatal hemoptysis, thromboembolic events). Thus, the balance between risk and benefit in every clinical setting is an integral part of the differentiation and evaluation of targeted agents.

RATIONALE FOR ANGIOGENESIS INHIBITION IN HCC

Angiogenesis is a ubiquitous process that is required for tumor growth[13,14]. Angiogenic processes are also indirectly involved in tumor invasion and metastasis through the secretion of matrix-degrading proteinases by vascular endothelial cells[15] and the ability of tumor cells to travel to distant sites *via* the vascular network[16].

Proangiogenic factors are attractive therapeutic targets because they stimulate cancer formation, growth, and proliferation *via* angiogenesis using a number of distinct mechanisms. Established proangiogenic factors and their receptor signaling pathways include vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF)-2, platelet-derived growth factor (PDGF), angiogenin, and angiopoietin-2 (Ang-2)[17]. Other mediators, such as c-MET and mTOR, although not directly related to new vessel formation, affect angiogenesis *via* influences on downstream signaling.

HCC tumors are generally hypervascularized[18], suggesting that they may be especially vulnerable to angiogenesis inhibition. Several endogenous proangiogenic factors are expressed in HCC[19-22], and evidence indicates they play a role in HCC pathogenesis. For instance, serum VEGF levels increase with advancing HCC stages, being highest in patients with metastatic disease[23]. Elevated VEGF levels after locoregional therapy also are associated with poor prognosis and diminished response to therapy[24,25]. Expression of the proangiogenic factor FGF-2, the target of newer agents, is also elevated in patients with HCC[22] and its expression in HCC correlates with tumor microvessel density[26] and postoperative recurrence rate[27]. Tumor angiogenin expression correlates with microvascular density in patients with HCC, and high serum angiogenin levels are associated with decreased survival at 5 years[28]. Finally, mRNA angiopoietin expression level (*via* Ang-2/Ang-1 ratio) is positively correlated with tumor portal vein invasion, diameter, microvascular density, and poor prognosis[29]. Taken together, this evidence provides a strong rationale for targeting angiogenesis and related proangiogenic factors to provide more effective therapies for the treatment of HCC.

CHALLENGES AND LIMITATIONS OF SORAFENIB IN TREATING HCC

Sorafenib was the first systemic targeted therapy to be approved by the US Food and Drug Administration for patients with unresectable HCC[30], based on a 2.8-mo survival advantage over best supportive care (BSC) [hazard ratio (HR) 0.69, $P = 0.00058$] in the Sorafenib Hepatocellular carcinoma Assessment Randomized Protocol (SHARP) trial[31]. Sorafenib, which is also approved for advanced renal cell carcinoma (RCC)[30] inhibits the following receptor tyrosine kinases: VEGFR-2, VEGFR-3, PDGFR-β, c-KIT, and Flt-3[32]. It also binds to the serine-threonine kinases Raf, MEK, and ERK[32,33]. The VEGFR and PDGFR pathways and Raf-1 have all been implicated in the pathogenesis of HCC[34,35], providing a rationale for sorafenib activity in HCC.

Although sorafenib represents a much needed treatment option for patients with HCC, it also produces toxicities that may significantly affect patients' quality of life. High rates of dermatologic side effects are commonly reported with sorafenib, the most clinically significant being hand-foot skin reaction (HFSR)[36]. HFSR typically develops in the first few weeks of therapy, with painful hyperkeratotic lesions on the palms and soles that are surrounded by a ring of erythema localized on areas of pressure or flexure[37]. A meta-analysis examining the incidence of HFSR in phase Ⅱ and Ⅲ trials across solid tumors reported an incidence of 33.8% with sorafenib use, 8.9% of which were grade 3[38]. In the SHARP trial, sorafenib-associated HFSR had an overall incidence of 21% and a grade 3 incidence of 8%[9]. Of particular concern, HSFR appears to be more prevalent in Asian patients, the population most affected worldwide by HCC. A phase Ⅲ trial conducted solely in Asian patients with HCC reported a doubling of the overall incidence of HFSR compared with the SHARP trial[8,9]. Similarly, a phase Ⅲ trial of sorafenib monotherapy following transarterial chemoembolization in Asian patients reported an HFSR incidence of 82%[39].

Bleeding events, albeit rare, are also a toxicity of sorafenib and other angiogenesis inhibitors. In a meta-analysis of 2109 patients enrolled in sorafenib clinical trials or expanded-access programs, the relative risk of bleeding events was 1.86 ($P < 0.001$) and the incidence of grade 3 or higher bleeding events was 2.2%[40]. It is notable that patients with HCC have not demonstrated an increased incidence of bleeding events with sorafenib; for example, in the SHARP trial, grade 3/4 bleeding events were 1% in the sorafenib arm.

By design, SHARP was conducted in the Americas, Europe, and Australasia, and thus generated limited data in Asian patients. Patients included in SHARP had preserved liver function and were of mostly Child-Pugh (C-P) A status[9]. In order to gain additional data, a randomized phase Ⅲ trial in Asian patients with advanced HCC was completed, but again C-P B and C patients were excluded[8,39]. The overall trend of response to sorafenib from

this Asian population was similar to those of SHARP, with time to progression (TTP) and overall survival (OS) improved compared with placebo, and similar treatment effects (HRs of 0.68-0.69). However, median OS appeared to be shorter (6.2 mo) *vs* SHARP (10.7 mo), most likely due to more advanced disease based on performance status, number of tumor sites, and presence of lung metastases compared with SHARP[8,9]. A subsequent single-arm, phase Ⅱ trial was conducted in Asian patients with worse prognosis, including C-P B and C status (29%) and portal vein thrombosis (43%)[41]. In this trial, 26% of patients derived clinical benefit from sorafenib. Again, the incidence of toxicities was higher than in SHARP, with grade 3/4 diarrhea occurring in 20% and grade 3/4 HFSR in 16% of patients. As the majority of HCC cases are found in Asia[42], the development of safe and more effective therapies for this population represents a significant unmet need.

Hence, while the sorafenib trials have provided valuable information in patients with preserved liver function[8,9,41], determining efficacy and safety in the substantial portion of patients with advanced HCC remains a challenge. Other recent phase Ⅱ trials are beginning to provide preliminary evidence of sorafenib safety and efficacy in patients with more advanced disease. A trial of sorafenib monotherapy in 59 patients with unresectable HCC, including 39% with C-P B status and 17% of C-P C status, showed promising activity regardless of disease stage and liver function[43]. Responses for patients of C-P B status were similar to those from SHARP. Median OS, however, declined with more advanced C-P status, most likely due to underlying cirrhosis, and because drug toxicities are more prevalent with compromised liver function, causing liver-related or systemic complications that lead to early treatment discontinuations. In a second phase Ⅱ trial, pharmacokinetic profiles of sorafenib were similar in both C-P A and B subgroups, while median TTP and OS appeared shorter and adverse events related to poorer liver function were more frequent in C-P B patients[44]. Finally, another single-arm, phase Ⅱ trial in 51 Asian patients, including 15 (29%) with C-P B/C status, found no significant differences between C-P B/C status patients and C-P A patients in disease control rate, median OS, grade 3/4 hematologic toxicities, or grade 3/4 nonhematologic toxicities[41].

Despite initial responses to sorafenib, and similar to other targeted agents, most HCC patients experience a loss of efficacy. Furthermore, across clinical trials, 20%-38% of patients discontinued sorafenib due to adverse events[8,9,41]. Similar to what has been reported with bevacizumab, some data indicate that patients who discontinue sorafenib therapy may experience "rebound," whereby symptom and tumor progression develops rapidly upon discontinuation[45]. While this accelerated growth effect appears to be temporarily curtailed with re-initiation of therapy, insensitivity to treatment returns quickly. No effective second-line treatment options currently exist outside of clinical trials for patients who are resistant or refractory to and/or intolerant of sorafenib.

THE FAILED PROMISE OF SUNITINIB

Next to sorafenib, sunitinib is the most studied multitargeted tyrosine kinase inhibitor. Like sorafenib, sunitinib is an inhibitor of VEGFR and PDGFR and is currently indicated for the treatment of RCC, as well as for gastrointestinal stromal tumors[46]. While early indications were that sunitinib would have efficacy in HCC, the phase Ⅲ SUN 1170 trial comparing sunitinib with sorafenib in patients with advanced HCC was discontinued due to increased serious sunitinib-related adverse events and the improbability of achieving noninferior efficacy[47]. As a result, sunitinib is no longer in development for the treatment of HCC.

CHALLENGES IN ASSESSING TUMOR RESPONSE

The 2 traditional imaging criteria widely used for measuring tumor responses to treatment are Response Evaluation Criteria In Solid Tumors (RECIST)[48], which are used primarily in the United States, and the World Health Organization (WHO) criteria[49], which are used internationally. With the advent of targeted therapies that are cytostatic, and in particular regarding HCC tumors, these traditional criteria are limited in their usefulness to assess treatment response because (1) cirrhotic livers may not remodel around a necrotic tumor; (2) HCC tumors are occasionally diffuse and infiltrative in cirrhotic livers; (3) arterial phase enhancement of premalignant dysplastic nodules can be mistaken for progression; and (4) cytostatic targeted agents alter tumor vascularity without affecting tumor size[50]. Both criteria have been updated in the past decade to account for HCC tumor viability in order to appropriately evaluate the extent of tumor necrosis and/or viability to quantify treatment response. The European Association for the Study of the Liver updated the WHO criteria in 2000[51], and in 2008 the American Association for the Study of Liver Diseases updated RECIST[52] and then further clarified the modified criteria in 2010[53]. Specific differences between these current criteria-modified WHO (mWHO) and modified RECIST (mRECIST)-for treatment response in HCC are listed in Table 1.

As an example of the variability in response assessment that can arise according to which of the 2 criteria is used, Finn *et al*[54] retrospectively compared response assessment by the necrosis-adjusted mRECIST (mRECIST has not yet been validated) for HCC with the prospective use of mWHO criteria in 101 patients with HCC who received brivanib, an antiangiogenic targeted agent. They found that mWHO criteria underreported treatment benefit compared with mRECIST for HCC, with 31 patients classified as having progressive disease under the mWHO criteria but stable disease or partial response under mRECIST. This suggests that these patients may have been prematurely discontinued from treatment while still deriving benefit. These discrepancies can be explained by differences in the methodologies of mRECIST and

Table 1 Response assessment by modified World Health Organization criteria and modified Response Evaluation Criteria in Solid Tumors

Parameter	Modified WHO	Modified RECIST
Type of assessment	Spiral CT	Spiral CT or dynamic MRI
Frequency of assessment	⩾ 4 wk	6-8 wk
Measurement of tumor volume	Bidimensional measurement	Unidimensional measurement
Tumor necrosis measurement	Reduction in viable tumor area using contrast-enhanced radiological imaging	Reduction in viable tumor area using contrast-enhanced radiological imaging
Viable tumor definition	Enhanced areas inside treatment lesions	Uptake of contrast agent in the arterial phase
Complete response	Complete disappearance of tumor enhancement determined by 2 observations ⩾ 4 wk apart	Disappearance of any intratumoral arterial enhancement in all target lesions
Partial response	> 50% reduction in total area of tumor enhancement determined by 2 observations ⩾ 4 wk apart	⩾ 30% decrease in the sum of diameters of viable target lesions, taking as reference the baseline sum of the diameters of target lesions
Stable disease	Insufficient shrinkage to qualify for partial response and insufficient increase to qualify for progressive disease	Any cases that do not qualify for either partial response or progressive disease
Progressive disease	> 25% increase in total area of tumor enhancement or the appearance of new lesions	⩾ 20% increase in the sum of the diameters of viable target lesions, taking as reference the smallest sum of the diameters of viable target lesions recorded since the treatment started or the appearance of 1 or more new lesions

CT: Computed tomography; MRI: Magnetic resonance imaging; RECIST: Response Evaluation Criteria in Solid Tumors; WHO: World Health Organization.

Table 2 Agents with antiangiogenic properties in development for the treatment of hepatocellular carcinoma

Agent	Therapeutic target	Phase of study
Brivanib	VEGFR, FGFR	Ⅲ
Bevacizumab	VEGF	Ⅱ
Ramucirumab	VEGFR-2	Ⅲ
ABT-869	VEGFR-1, VEGFR-2, PDGFR-β, c-KIT, Flt-3	Ⅲ
Everolimus	mTOR	Ⅲ
ARQ 197	c-MET	Ⅱ

PDGFR: Platelet-derived growth factor receptor; VEGFR: Vascular endothelial growth factor receptor.

mWHO, which employ different measurements and calculations of tumor size, thereby producing distinct interpretations of treatment response. In addition, there are differences in how progression is defined, with cytologic confirmation of ascites required with mRECIST and small new lesions (< 1 cm) unlikely representing progression with the mRECIST. While not conclusive, these results suggest that treatment response based on assessment criteria vary widely and indicate the need for further clinical validation.

LOSS OF EFFICACY TO ANTIANGIOGENIC THERAPY: ESCAPE AND RESISTANCE

Clinical trials of antiangiogenic agents have shown that most patients with advanced tumors eventually experience progression, including those who initially respond to treatment[8,9,55-57]. Recent evidence suggests that relapse during treatment with antiangiogenic agents occurs due to VEGF inhibition-driven hypoxia, which induces upregulation of alternate proangiogenic signals such as FGF, which overrides the VEGFR inhibition[58]. This was demonstrated preclinically in murine tumors that initially responded to treatment with an anti-VEGFR-2 antibody, but relapsed after 2 wk, showing higher levels of other proangiogenic signals, including FGF-1 and FGF-2, than untreated tumors[59]. Moreover, blockage of FGF signaling in this model slowed tumor growth and attenuated its revascularization during the relapse phase. Clinically, this has been observed in patients with HCC[26,27,60] and, more recently, in glioblastoma patients treated with the pan-VEGFR inhibitor AZD2171, in whom increased plasma levels of FGF were detected upon relapse[61]. Another study showed that approximately half of patients with metastatic colorectal cancer who received bevacizumab plus chemotherapy had more than a 5-fold increase in either placental growth factor or FGF prior to progression[62]. Patients with late-stage breast cancer have been reported to express a large number of proangiogenic factors, including FGF-2, in contrast to earlier stage lesions, which primarily express VEGF[58,63]. Taken together, these data support the hypothesis that tumor progression during inhibition of angiogenesis may be facilitated *via* activation of compensatory proangiogenic and tumorigenic mechanisms.

COMPOUNDS IN DEVELOPMENT FOR TREATMENT OF HCC

Several compounds in development stand to address the challenges and limitations of targeted therapy in the treatment of HCC. These are discussed in the following sections and summarized in Table 2.

Brivanib

Brivanib is currently in phase Ⅲ trials in HCC. It is distinct from both sorafenib and sunitinib in that it is an oral, selective, dual inhibitor of the FGF and VEGF signalling pathways[64,65]. Since FGF signaling may contribute to acquired "resistance," or compensatory signaling,

during anti-VEGFR therapy[58], the simultaneous inhibition of these[64,65] 2 pathways by brivanib may both delay initial progression in response to antiangiogenic therapy (as first-line treatment) and successfully treat tumors that have already progressed during anti-VEGFR therapy (as second-line treatment). With respect to its potential as first-line therapy, brivanib has delayed initial progression compared with sorafenib in preclinical studies[66]. It has also shown specific inhibitory activity in patient-derived HCC xenografts implanted in mice[67]. Clinically, brivanib has demonstrated a disease control rate of 51%, a median TTP of 2.8 mo, and an OS of 10 mo as first-line monotherapy in a phase Ⅱ trial of predominantly Asian patients with HCC[68]. A retrospective analysis using mRECIST for HCC criteria also demonstrated an objective response rate of 25%, with 9% complete responses[68]. Brivanib was also associated with a low incidence of grade 3/4 adverse events, including hypertension (10.9%), diarrhea (3.6%), and HFSR (1.8%)[68]. Due to its unique mechanism of action and favorable safety profile, brivanib is currently under phase Ⅲ investigation as first-line therapy *vs* sorafenib in patients with advanced HCC (BRISK-FL). As a potential second-line agent following antiangiogenic therapy, brivanib has demonstrated activity against xenograft tumors that were nonresponsive to bevacizumab[69]. Allen *et al*[66] also used a mouse model of pancreatic neuroendocrine cancer to show that brivanib administered after sorafenib failure could delay tumor growth modestly, despite showing evidence of revascularization. In a phase Ⅱ trial of brivanib in patients with HCC who had been treated with sorafenib, brivanib produced a median TTP of 2.7 mo and an OS of 9.8 mo[70]; in a retrospective analysis of paired TTP, at least 40% of patients had longer TTP with brivanib than with prior sorafenib[71]. Brivanib is currently under investigation in 2 second-line phase Ⅲ trials-1 in Asian patients following sorafenib failure (progression or intolerance; BRISK-APS), and another similar trial that is enrolling an ethnically unselected patient population (BRISK-PS).

Bevacizumab

The anti-VEGF monoclonal antibody bevacizumab was the first angiogenesis inhibitor to be approved as an antineoplastic agent[72]. Bevacizumab has shown activity in phase Ⅱ HCC testing in combination with chemotherapy[72-75], with the epidermal growth factor receptor inhibitor erlotinib[76], and as monotherapy[77]. Despite initial safety concerns, particularly gastrointestinal bleeding and thrombosis, phase Ⅱ trials in HCC have shown toxicities to be manageable[78]. New bevacizumab combinations are under investigation in ongoing phase Ⅱ HCC trials, including combination with sorafenib, everolimus, temsirolimus, chemoembolization, and hepatic arterial infusion of floxuridine and dexamethasone.

Ramucirumab

The monoclonal antibody ramucirumab is a specific inhibitor of VEGFR-2[79]. A phase Ⅱ study of 42 patients with advanced HCC and primarily well-preserved liver function (75% C-P A status) showed that first-line ramucirumab monotherapy produced a disease control rate of 50% and a median progression-free survival (PFS) of 4.3 mo[80]. This positive study prompted the initiation of the phase Ⅲ REACH trial in HCC, which is comparing ramucirumab/supportive care with placebo/supportive care for second-line treatment after sorafenib.

ABT-869

ABT-869 is a multitargeted tyrosine kinase inhibitor that inhibits multiple members of the VEGFR and PDGFR families[81]. In a xenograft model of HCC, ABT-869 significantly reduced tumor burden, either alone or in combination with rapamycin[82]. Interim phase Ⅱ results in patients with advanced HCC showed a median TTP of 3.7 mo with ABT-869 treatment and a safety profile consistent with angiogenesis inhibition[83]. ABT-869 is in phase Ⅲ testing as a first-line treatment for advanced HCC versus sorafenib.

INHIBITION OF OTHER ANGIOGENIC AND TUMORIGENIC PATHWAYS

mTOR inhibitors: Everolimus and sirolimus

mTOR inhibitors are not traditionally considered direct angiogenesis inhibitors; rather, they have well-known immunosuppressive properties. In fact, 2 of these agents, sirolimus and everolimus, are used to prevent rejection in organ transplant recipients[84]. mTOR inhibitors also have antineoplastic properties, *via* mTOR regulation of tumor proliferation and metabolism[85]. MTOR indirectly modulates angiogenesis through regulation of VEGF expression and translation of proteins involved in angiogenesis[86]. Clinically, there is growing evidence to suggest that mTOR inhibitors may reduce *de novo* malignant growth[87] and recurrence in the liver post-transplant[88]. In patients with advanced HCC, everolimus produced a median PFS of 3.8 mo and a disease control rate of 44% in phase Ⅰ/Ⅱ testing[81]. Consequently, the ongoing phase Ⅲ EVOLVE-1 trial has been initiated to compare everolimus with BSC in patients with HCC who progressed on or after sorafenib or who were intolerant to sorafenib.

ARQ 197

Similar to everolimus, ARQ 197 has antiangiogenic properties, but is not considered an angiogenesis inhibitor. ARQ 197 is an inhibitor of the oncogene c-MET, which stimulates tumor growth, invasion, metastasis, and angiogenesis *via* binding of its ligand, hepatocyte growth factor[89]. In phase I testing in cirrhotic patients with HCC, ARQ 197 demonstrated some activity and was well tolerated, with serious adverse events that were primarily hematologic[90]. ARQ 197 is currently in phase Ⅱ testing in second-line advanced HCC.

CONCLUSION

Unmet needs for HCC remain, despite the availability of

sorafenib. Indeed, sorafenib has some significant limitations, including modest, transient benefits, and toxicity challenges; and its use in patients with more advanced liver disease and in Asian patients has not yet been fully defined. The development of newer targeted therapies that inhibit angiogenesis simultaneously with inhibition of other key proangiogenic factors in HCC, such as FGFR or c-MET signaling, is providing further insights into the underlying pathogenesis of HCC tumors. Compounds that directly block angiogenesis and tumorigenesis *via* dual inhibition of FGFR and VEGFR, such as brivanib, and other compounds that indirectly modulate angiogenesis, such as mTOR inhibitors, are providing novel mechanisms that exploit critical pathways in HCC tumor progression and may have the potential to improve clinical outcomes both as monotherapy and in the case of escape from sorafenib. In the coming years, a number of phase Ⅲ clinical trials examining these angiogenesis inhibitors will be mature, providing a better picture of the clinical utility and treatment options for patients with HCC.

ACKNOWLEDGMENTS

We thank Lena Prisco, PhD, and Mark English, PhD, of PAREXEL and Bristol-Myers Squibb for their editorial assistance with this paper.

REFERENCES

1 **Stewart BW,** Kleihues P. World cancer report. Lyon: IARC Press, 2003
2 **Jemal A**, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin* 2010; **60**: 277-300
3 **Nordenstedt H,** White DL, El-Serag HB. The changing pattern of epidemiology in hepatocellular carcinoma. *Dig Liver Dis* 2010; **42**: S206-S214
4 **Finn RS.** Development of molecularly targeted therapies in hepatocellular carcinoma: where do we go now? *Clin Cancer Res* 2010; **16**: 390-397
5 **Poon RT**, Fan ST, Lo CM, Liu CL, Wong J. Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. *Ann Surg* 2002; **235**: 373-382
6 **Zhu AX.** Systemic therapy of advanced hepatocellular carcinoma: how hopeful should we be? *Oncologist* 2006; 11: 790-800
7 **Pelletier SJ**, Fu S, Thyagarajan V, Romero-Marrero C, Batheja MJ, Punch JD, Magee JC, Lok AS, Fontana RJ, Marrero JA. An intention-to-treat analysis of liver transplantation for hepatocellular carcinoma using organ procurement transplant network data. *Liver Transpl* 2009; **15**: 859-868
8 **Cheng AL,** Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, Liu J, Wang J, Tak WY, Pan H, Burock K, Zou J, Voliotis D, Guan Z. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; **10**: 25-34
9 **Llovet JM**, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378-390
10 Nexavar [prescribing information]. Wayne, NJ: Bayer HealthCare Pharmaceuticals Inc., 2009
11 **Launay-Vacher V,** Deray G. Hypertension and proteinuria: a class-effect of antiangiogenic therapies. *Anticancer Drugs* 2009; **20**: 81-82
12 **Roodhart JM**, Langenberg MH, Witteveen E, Voest EE. The molecular basis of class side effects due to treatment with inhibitors of the VEGF/VEGFR pathway. *Curr Clin Pharmacol* 2008; **3**: 132-143
13 **Carmeliet P,** Jain RK. Angiogenesis in cancer and other diseases. *Nature* 2000; **407**: 249-257
14 **Ribatti D,** Vacca A, Dammacco F. The role of the vascular phase in solid tumor growth: a historical review. *Neoplasia* 1999; **1**: 293-302
15 **Mignatti P**, Rifkin DB. Biology and biochemistry of proteinases in tumor invasion. *Physiol Rev* 1993; **73**: 161-195
16 **Aznavoorian S**, Murphy AN, Stetler-Stevenson WG, Liotta LA. Molecular aspects of tumor cell invasion and metastasis. *Cancer* 1993; **71**: 1368-1383
17 **Maruotti N**, Cantatore FP, Crivellato E, Vacca A, Ribatti D. Angiogenesis in rheumatoid arthritis. *Histol Histopathol* 2006; **21**: 557-566
18 **Ribatti D**, Vacca A, Nico B, Sansonno D, Dammacco F. Angiogenesis and anti-angiogenesis in hepatocellular carcinoma. *Cancer Treat Rev* 2006; **32**: 437-444
19 **Ferrara N,** Davis-Smyth T. The biology of vascular endothelial growth factor. *Endocr Rev* 1997; **18**: 4-25
20 **Mochida S**, Ishikawa K, Toshima K, Inao M, Ikeda H, Matsui A, Shibuya M, Fujiwara K. The mechanisms of hepatic sinusoidal endothelial cell regeneration: a possible communication system associated with vascular endothelial growth factor in liver cells. *J Gastroenterol Hepatol* 1998; **13** Suppl: S1-S5
21 **Tanaka S**, Mori M, Sakamoto Y, Makuuchi M, Sugimachi K, Wands JR. Biologic significance of angiopoietin-2 expression in human hepatocellular carcinoma. *J Clin Invest* 1999; **103**: 341-345
22 **Uematsu S**, Higashi T, Nouso K, Kariyama K, Nakamura S, Suzuki M, Nakatsukasa H, Kobayashi Y, Hanafusa T, Tsuji T, Shiratori Y. Altered expression of vascular endothelial growth factor, fibroblast growth factor-2 and endostatin in patients with hepatocellular carcinoma. *J Gastroenterol Hepatol* 2005; **20**: 583-588
23 **Jinno K**, Tanimizu M, Hyodo I, Nishikawa Y, Hosokawa Y, Doi T, Endo H, Yamashita T, Okada Y. Circulating vascular endothelial growth factor (VEGF) is a possible tumor marker for metastasis in human hepatocellular carcinoma. *J Gastroenterol* 1998; **33**: 376-382
24 **Montella L**, Addeo R, Caraglia M, Faiola V, Guarrasi R, Vincenzi B, Palmeri A, Capasso E, Nocera V, Tarantino L, Ariete M, Martorelli A, Del Prete S. Vascular endothelial growth factor monitoring in advanced hepatocellular carcinoma patients treated with radiofrequency ablation plus octreotide: a single center experience. *Oncol Rep* 2008; **20**: 385-390
25 **Tamesa T**, Iizuka N, Mori N, Okada T, Takemoto N, Tangoku A, Oka M. High serum levels of vascular endothelial growth factor after hepatectomy are associated with poor prognosis in hepatocellular carcinoma. *Hepatogastroenterology* 2009; **56**: 1122-1126
26 **El-Assal ON**, Yamanoi A, Ono T, Kohno H, Nagasue N. The clinicopathological significance of heparanase and basic fibroblast growth factor expressions in hepatocellular carcinoma. *Clin Cancer Res* 2001; **7**: 1299-1305
27 **Poon RT**, Ng IO, Lau C, Yu WC, Fan ST, Wong J. Correlation of serum basic fibroblast growth factor levels with clinicopathologic features and postoperative recurrence in hepatocellular carcinoma. *Am J Surg* 2001; **182**: 298-304
28 **Hisai H**, Kato J, Kobune M, Murakami T, Miyanishi K, Takahashi M, Yoshizaki N, Takimoto R, Terui T, Niitsu Y. Increased expression of angiogenin in hepatocellular carcinoma in

correlation with tumor vascularity. *Clin Cancer Res* 2003; **9**: 4852-4859
29 **Mitsuhashi N**, Shimizu H, Ohtsuka M, Wakabayashi Y, Ito H, Kimura F, Yoshidome H, Kato A, Nukui Y, Miyazaki M. Angiopoietins and Tie-2 expression in angiogenesis and proliferation of human hepatocellular carcinoma. *Hepatology* 2003; **37**: 1105-1113
30 US Food and Drug Administration. FDA approval for sorafenib tosylate. 2010-10-01. Available from: URL: http: //www.cancer.gov/cancertopics/druginfo/fda-sorafenib-tosylate
31 **Kane RC**, Farrell AT, Madabushi R, Booth B, Chattopadhyay S, Sridhara R, Justice R, Pazdur R. Sorafenib for the treatment of unresectable hepatocellular carcinoma. *Oncologist* 2009; **14**: 95-100
32 **Wilhelm SM**, Carter C, Tang L, Wilkie D, McNabola A, Rong H, Chen C, Zhang X, Vincent P, McHugh M, Cao Y, Shujath J, Gawlak S, Eveleigh D, Rowley B, Liu L, Adnane L, Lynch M, Auclair D, Taylor I, Gedrich R, Voznesensky A, Riedl B, Post LE, Bollag G, Trail PA. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res* 2004; **64**: 7099-7109
33 **Liu L**, Cao Y, Chen C, Zhang X, McNabola A, Wilkie D, Wilhelm S, Lynch M, Carter C. Sorafenib blocks the RAF/MEK/ERK pathway, inhibits tumor angiogenesis, and induces tumor cell apoptosis in hepatocellular carcinoma model PLC/PRF/5. *Cancer Res* 2006; **66**: 11851-11858
34 **Mukherjee B**, Das T, Ghosh S, Datta S. Changes in the antioxidant defense and hepatic drug metabolizing enzyme and isoenzyme levels, 8-hydroxydeoxyguanosine formation and expressions of c-raf.1 and insulin-like growth factor II genes during the stages of development of hepatocellular carcinoma in rats. *Eur J Cancer Prev* 2007; **16**: 363-371
35 **Yang ZF,** Poon RT. Vascular changes in hepatocellular carcinoma. *Anat Rec* (Hoboken) 2008; **291**: 721-734
36 **Lacouture ME**, Wu S, Robert C, Atkins MB, Kong HH, Guitart J, Garbe C, Hauschild A, Puzanov I, Alexandrescu DT, Anderson RT, Wood L, Dutcher JP. Evolving strategies for the management of hand-foot skin reaction associated with the multitargeted kinase inhibitors sorafenib and sunitinib. *Oncologist* 2008; **13**: 1001-1011
37 **Robert C**, Soria JC, Spatz A, Le Cesne A, Malka D, Pautier P, Wechsler J, Lhomme C, Escudier B, Boige V, Armand JP, Le Chevalier T. Cutaneous side-effects of kinase inhibitors and blocking antibodies. *Lancet Oncol* 2005; **6**: 491-500
38 **Chu D**, Lacouture ME, Fillos T, Wu S. Risk of hand-foot skin reaction with sorafenib: a systematic review and meta-analysis. *Acta Oncol* 2008; **47**: 176-186
39 **Kudo M**, Imanaka K, Chida N, Nakachi K, Tak WY, Takayama T, Yoon JH, Hori T, Kumada H, Hayashi N, Kaneko S, Tsubouchi H, Suh DJ, Furuse J, Okusaka T, Tanaka K, Matsui O, Wada M, Yamaguchi I, Ohya T, Meinhardt G, Okita K. Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. *Eur J Cancer* 2011; **47**: 2117-2127
40 **Je Y**, Schutz FA, Choueiri TK. Risk of bleeding with vascular endothelial growth factor receptor tyrosine-kinase inhibitors sunitinib and sorafenib: a systematic review and meta-analysis of clinical trials. *Lancet Oncol* 2009; **10**: 967-974
41 **Yau T**, Chan P, Ng KK, Chok SH, Cheung TT, Fan ST, Poon RT. Phase 2 open-label study of single-agent sorafenib in treating advanced hepatocellular carcinoma in a hepatitis B-endemic Asian population: presence of lung metastasis predicts poor response. *Cancer* 2009; **115**: 428-436
42 **Parkin DM**, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: Globocan 2000. *Int J Cancer* 2001; **94**: 153-156
43 **Pinter M**, Sieghart W, Graziadei I, Vogel W, Maieron A, Königsberg R, Weissmann A, Kornek G, Plank C, Peck-Radosavljevic M. Sorafenib in unresectable hepatocellular carcinoma from mild to advanced stage liver cirrhosis. *Oncologist* 2009; **14**: 70-76
44 **Abou-Alfa GK,** Amadori D, Santoro A, Figer A, De Greve J, Lathia C, Voliotis D, Anderson S, Moscovici M, Ricci S. Is sorafenib (S) safe and effective in patients (pts) with hepatocellular carcinoma (HCC) and Child-Pugh B (CPB) cirrhosis? [abstract]. *J Clin Oncol* 2008; **26** (15 suppl): 4518
45 **Desar IM**, Mulder SF, Stillebroer AB, van Spronsen DJ, van der Graaf WT, Mulders PF, van Herpen CM. The reverse side of the victory: flare up of symptoms after discontinuation of sunitinib or sorafenib in renal cell cancer patients. A report of three cases. *Acta Oncol* 2009; **48**: 927-931
46 US Food and Drug Administration. FDA approval for sunitinib malate. 7, 2010-10-07. Available from: URL: http: //www.cancer.gov/cancertopics/druginfo/fda-sunitinib-malate.
47 Pfizer discontinues phase 3 trial of Sutent in advanced hepatocellular carcinoma [press release]. Business Wire Web site. 2010-10-13. Available from: URL: http: //www.businesswire.com/news/home/20100422006892/en/Pfizer-Discontinues-Phase-3-Trial-Sutent-Advanced
48 **Therasse P**, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; **92**: 205-216
49 **Miller AB,** Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981; **47:** 207-214
50 **Thomas MB**, Jaffe D, Choti MM, Belghiti J, Curley S, Fong Y, Gores G, Kerlan R, Merle P, O'Neil B, Poon R, Schwartz L, Tepper J, Yao F, Haller D, Mooney M, Venook A. Hepatocellular carcinoma: consensus recommendations of the National Cancer Institute Clinical Trials Planning Meeting. *J Clin Oncol* 2010; **28**: 3994-4005
51 **Bruix J**, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, Christensen E, Pagliaro L, Colombo M, Rodés J. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* 2001; **35**: 421-430
52 **Llovet JM**, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, Sherman M, Schwartz M, Lotze M, Talwalkar J, Gores GJ. Design and endpoints of clinical trials in hepatocellular carcinoma. *J Natl Cancer Inst* 2008; **100**: 698-711
53 **Lencioni R**, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis* 2010; **30**: 52-60
54 **Finn RS,** Raoul J, Manekas D, Baudelet C, Walters IB. Optimal assessment of treatment benefit with targeted agents for hepatocellular carcinoma (HCC): an analysis of brivanib phase II data [abstract]. *J Clin Oncol* 2010; **28** (15 Suppl): 4096
55 **Hurwitz H**, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R, Kabbinavar F. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; **350**: 2335-2342
56 **Miller K**, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, Shenkier T, Cella D, Davidson NE. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med* 2007; **357**: 2666-2676
57 **Sandler A**, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilenbaum R, Johnson DH. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006; **355**: 2542-2550
58 **Bergers G**, Hanahan D. Modes of resistance to anti-angiogenic therapy. *Nat Rev Cancer* 2008; **8**: 592-603
59 **Casanovas O**, Hicklin DJ, Bergers G, Hanahan D. Drug resistance by evasion of antiangiogenic targeting of VEGF signaling in late-stage pancreatic islet tumors. *Cancer Cell* 2005; **8**:

299-309
60 **Poon RT**, Lau CP, Cheung ST, Yu WC, Fan ST. Quantitative correlation of serum levels and tumor expression of vascular endothelial growth factor in patients with hepatocellular carcinoma. *Cancer Res* 2003; **63**: 3121-3126
61 **Batchelor TT**, Sorensen AG, di Tomaso E, Zhang WT, Duda DG, Cohen KS, Kozak KR, Cahill DP, Chen PJ, Zhu M, Ancukiewicz M, Mrugala MM, Plotkin S, Drappatz J, Louis DN, Ivy P, Scadden DT, Benner T, Loeffler JS, Wen PY, Jain RK. AZD2171, a pan-VEGF receptor tyrosine kinase inhibitor, normalizes tumor vasculature and alleviates edema in glioblastoma patients. *Cancer Cell* 2007; **11**: 83-95
62 **Kopetz S,** Hoff PM, Eng C, Overman MJ, Glover Y, Chang DZ, Wolff RA, Abbruzzee L, Ellis LM, Heymach JV. Levels of angiogenic cytokines prior to disease progression in metastatic colorectal cancer patients treated with bevacizumab. *ASCO-GI* 2009
63 **Relf M**, LeJeune S, Scott PA, Fox S, Smith K, Leek R, Moghaddam A, Whitehouse R, Bicknell R, Harris AL. Expression of the angiogenic factors vascular endothelial cell growth factor, acidic and basic fibroblast growth factor, tumor growth factor beta-1, platelet-derived endothelial cell growth factor, placenta growth factor, and pleiotrophin in human primary breast cancer and its relation to angiogenesis. *Cancer Res* 1997; **57**: 963-969
64 **Bhide RS**, Cai ZW, Zhang YZ, Qian L, Wei D, Barbosa S, Lombardo LJ, Borzilleri RM, Zheng X, Wu LI, Barrish JC, Kim SH, Leavitt K, Mathur A, Leith L, Chao S, Wautlet B, Mortillo S, Jeyaseelan R, Kukral D, Hunt JT, Kamath A, Fura A, Vyas V, Marathe P, D'Arienzo C, Derbin G, Fargnoli J. Discovery and preclinical studies of (R)-1-(4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-5- methylpyrrolo[2,1-f][1,2,4]triazin-6-yloxy)propan-2-ol (BMS-540215), an in vivo active potent VEGFR-2 inhibitor. *J Med Chem* 2006; **49**: 2143-2146
65 **Tille JC**, Wood J, Mandriota SJ, Schnell C, Ferrari S, Mestan J, Zhu Z, Witte L, Pepper MS. Vascular endothelial growth factor (VEGF) receptor-2 antagonists inhibit VEGF- and basic fibroblast growth factor-induced angiogenesis in vivo and in vitro. *J Pharmacol Exp Ther* 2001; **299**: 1073-1085
66 **Allen E,** Walters IB, Rivera IC, Hanahan D. Abstract B16: Anti-angiogenic therapy using brivanib, a combined VEGF and FGF pathway inhibitor, in a mouse model of pancreatic neuroendocrine cancer (PNET), results in sustained vascular blockade, without evidence for evasive/acquired resistance in the form of VEGF-independent revascularization, in contrast to other VEGF inhibitors. *Mol Cancer Ther* 2009; **8** (12 suppl): B16
67 **Huynh H**, Ngo VC, Fargnoli J, Ayers M, Soo KC, Koong HN, Thng CH, Ong HS, Chung A, Chow P, Pollock P, Byron S, Tran E. Brivanib alaninate, a dual inhibitor of vascular endothelial growth factor receptor and fibroblast growth factor receptor tyrosine kinases, induces growth inhibition in mouse models of human hepatocellular carcinoma. *Clin Cancer Res* 2008; **14**: 6146-6153
68 **Park JW**, Finn RS, Kim JS, Karwal M, Li RK, Ismail F, Thomas M, Harris R, Baudelet C, Walters I, Raoul JL. Phase II, open-label study of brivanib as first-line therapy in patients with advanced hepatocellular carcinoma. *Clin Cancer Res* 2011; **17**: 1973-1983
69 **Ayers M,** Dito G, Henley B, Jeyaseelan R, Yoganthan S, Han X, Wu Q, Platero S, Wu S, Feltquate D, Clark E, Fargnoli J.. Comparison of a dual inhibitor of VEGF and FGF signaling, BMS-582664, to the activity of bevacizumab, an inhibitor exclusively of VEGF signaling, in xenograft models of colon carcinoma. *Proc Am Assoc Cancer Res* 2007; **48**: Abstract 1618
70 **Finn RS,** Kang YK, Mulcahy M, Polite BN, Lim HY, Walters I, Baudelet C, Manekas D, Park JW. Phase II, open-label study of brivanib as second-line therapy in patients with advanced hepatocellular carcinoma. *Clin Cancer Res* 2012 [Epub ahead of print]
71 **Finn RS,** Park JW, Kang YK, Baudelet C, Walters I. Time-to-progression sub-analysis of second-line treatment with brivanib after failure of prior antiangiogenic therapy in patients with unresectable, locally advanced, or metastatic hepatocellular carcinoma (Abstract). Boston, MA: The 60th Annual Meeting of the American Association for the Study of Liver Diseases, 2009
72 Avastin [prescribing information]. South San Francisco, CA: Genentech, Inc., 2009
73 **Sun W,** Haller DG, Mykulowycz K, Rosen M, Soulen M, Capparo M, Faust T, Giantonia B, Olthoff K. Combination of capecitabine, oxaliplatin with bevacizumab in treatment of advanced hepatocellular carcinoma (HCC): A phase II study [abstract]. *J Clin Oncol* 2007; **25** (18S): 4574
74 **Hsu CH**, Yang TS, Hsu C, Toh HC, Epstein RJ, Hsiao LT, Chen PJ, Lin ZZ, Chao TY, Cheng AL. Efficacy and tolerability of bevacizumab plus capecitabine as first-line therapy in patients with advanced hepatocellular carcinoma. *Br J Cancer* 2010; **102**: 981-986
75 **Zhu AX**, Blaszkowsky LS, Ryan DP, Clark JW, Muzikansky A, Horgan K, Sheehan S, Hale KE, Enzinger PC, Bhargava P, Stuart K. Phase II study of gemcitabine and oxaliplatin in combination with bevacizumab in patients with advanced hepatocellular carcinoma. *J Clin Oncol* 2006; **24**: 1898-1903
76 **Thomas MB**, Morris JS, Chadha R, Iwasaki M, Kaur H, Lin E, Kaseb A, Glover K, Davila M, Abbruzzese J. Phase II trial of the combination of bevacizumab and erlotinib in patients who have advanced hepatocellular carcinoma. *J Clin Oncol* 2009; **27**: 843-850
77 **Siegel AB**, Cohen EI, Ocean A, Lehrer D, Goldenberg A, Knox JJ, Chen H, Clark-Garvey S, Weinberg A, Mandeli J, Christos P, Mazumdar M, Popa E, Brown RS, Rafii S, Schwartz JD. Phase II trial evaluating the clinical and biologic effects of bevacizumab in unresectable hepatocellular carcinoma. *J Clin Oncol* 2008; **26**: 2992-2998
78 **Finn RS,** Zhu AX. Targeting angiogenesis in hepatocellular carcinoma: focus on VEGF and bevacizumab. *Expert Rev Anticancer Ther* 2009; **9**: 503-509
79 **Spratlin JL**, Cohen RB, Eadens M, Gore L, Camidge DR, Diab S, Leong S, O'Bryant C, Chow LQ, Serkova NJ, Meropol NJ, Lewis NL, Chiorean EG, Fox F, Youssoufian H, Rowinsky EK, Eckhardt SG. Phase I pharmacologic and biologic study of ramucirumab (IMC-1121B), a fully human immunoglobulin G1 monoclonal antibody targeting the vascular endothelial growth factor receptor-2. *J Clin Oncol* 2010; **28**: 780-787
80 **Zhu AX,** Finn RS, Mulcahy MF, Gurtler JS, Sun W, Schwartz JD, Rojas P, Dontabhaktuni A, Youssoufian H, Stuart KE. A phase II study of ramucirumab as first-line monotherapy in patients (pts) with advanced hepatocellular carcinoma (HCC) [abstract]. *J Clin Oncol* 2010; **28** (15s): 4083
81 **Albert DH**, Tapang P, Magoc TJ, Pease LJ, Reuter DR, Wei RQ, Li J, Guo J, Bousquet PF, Ghoreishi-Haack NS, Wang B, Bukofzer GT, Wang YC, Stavropoulos JA, Hartandi K, Niquette AL, Soni N, Johnson EF, McCall JO, Bouska JJ, Luo Y, Donawho CK, Dai Y, Marcotte PA, Glaser KB, Michaelides MR, Davidsen SK. Preclinical activity of ABT-869, a multitargeted receptor tyrosine kinase inhibitor. *Mol Cancer Ther* 2006; **5**: 995-1006
82 **Jasinghe VJ**, Xie Z, Zhou J, Khng J, Poon LF, Senthilnathan P, Glaser KB, Albert DH, Davidsen SK, Chen CS. ABT-869, a multi-targeted tyrosine kinase inhibitor, in combination with rapamycin is effective for subcutaneous hepatocellular carcinoma xenograft. *J Hepatol* 2008; **49**: 985-997
83 **Toh H,** Chen P, Carr BI, Knox JJ, Gill S, Steinberg J, Carlson DM, Qian J, Qin Q, Yong W. A phase II study of ABT-869 in hepatocellular carcinoma (HCC): Interim analysis [abstract]. *J Clin Oncol* 2009; **27** (15s): A4581
84 **Geissler EK,** Schlitt HJ, Thomas G. mTOR, cancer and transplantation. *Am J Transplant* 2008; **8**: 2212-2218

85 **Wullschleger S,** Loewith R, Hall MN. TOR signaling in growth and metabolism. *Cell* 2006; **124**: 471-484
86 **Huynh H.** Molecularly targeted therapy in hepatocellular carcinoma. *Biochem Pharmacol* 2010; **80**: 550-560
87 **Campistol JM**, Eris J, Oberbauer R, Friend P, Hutchison B, Morales JM, Claesson K, Stallone G, Russ G, Rostaing L, Kreis H, Burke JT, Brault Y, Scarola JA, Neylan JF. Sirolimus therapy after early cyclosporine withdrawal reduces the risk for cancer in adult renal transplantation. *J Am Soc Nephrol* 2006; **17**: 581-589
88 **Chinnakotla S**, Davis GL, Vasani S, Kim P, Tomiyama K, Sanchez E, Onaca N, Goldstein R, Levy M, Klintmalm GB. Impact of sirolimus on the recurrence of hepatocellular carcinoma after liver transplantation. *Liver Transpl* 2009; **15**: 1834-1842
89 **You WK**, McDonald DM. The hepatocyte growth factor/c-Met signaling pathway as a therapeutic target to inhibit angiogenesis. *BMB Rep* 2008; **41**: 833-839
90 **Zucali P,** Santoro A, Rodriguez-Lope C, Simonelli M, Camacho LH, Senzer NN, Bolondi L, Lamar M, Abbadessa G, Schwartz BE. Final results from ARQ 197-114: A phase Ib safety trial evaluating ARQ 197 in cirrhotic patients (pts) with hepatocellular carcinoma (HCC). *J Clin Oncol* 2010; **28** suppl: Abstract 4137

S- Editor Gou SX **L- Editor** O'Neill M **E- Editor** Xiong L