Chemotherapy and target therapy for hepatocellular carcinoma: New advances and challenges

Gan-Lu Deng, Shan Zeng, Hong Shen

Gan-Lu Deng, Shan Zeng, Hong Shen, Institute of Medical Sciences, Xiangya Hospital, Central South University, Changsha 410008, Hunan Province, China
Hong Shen, Department of Oncology, Central South University, Changsha 410008, Hunan Province, China

Author contributions: Deng GL performed the research and wrote the draft paper; Zeng S collected the clinical information and analyzed the data; Shen H designed the research and revised the final version.

Supported by The grants from the National Nature Science Foundation of China, Nos. 30770971, 30800518, 81070362, 81172470 and 81372629; and two key projects from the Nature Science Foundation of Hunan Province, Nos. 11JJ2049 and 12JJ3118.

Conflict-of-interest: None.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Correspondence to: Hong Shen, Professor, Institute of Medical Sciences, Xiangya Hospital, Central South University, No 87, Xiangya Road, Changsha 410008, Hunan Province, China. hongshen2000@yahoo.com

Telephone: +86-731-84327628
Fax: +86-731-84327633
Received: August 25, 2014
Peer-review started: August 26, 2014
First decision: September 28, 2014
Revised: October 26, 2014
Accepted: January 18, 2015
Article in press: January 20, 2015
Published online: April 18, 2015

Abstract
Primary liver cancer is one of the commonest causes of death. Hepatocellular carcinoma (HCC) accounts for 90% of primary liver cancers. For patients with unresectable or metastatic HCC, conventional chemotherapy is of limited or no benefit. Sorafenib is the only systemic treatment to demonstrate a statistically significant but modest overall survival benefit, leading to an era of targeted agents. Many clinical trials of targeted drugs have been carried out with many more in progress. Some drugs like PTK787 showed potential benefits in the treatment of HCC. Despite these promising breakthroughs, patients with HCC still have a dismal prognosis. Recently, both a phase III trial of everolimus and a phase II clinical trial of trebananib failed to demonstrate effective antitumor activity in advanced HCC. Sorafenib still plays a pivotal role in advanced HCC, leading to further explorations to exert its maximum efficacy. Combinations targeted with chemotherapy or transarterial chemoembolization is now being tested and might bring about advances. New targeted agents such as mammalian target of rapamycin inhibitors are under investigation, as well as further exploration of the mechanism of hepatocarcinogenesis.

Key words: Hepatocellular carcinoma; Ramucirumab; Regorafenib; Tivantinib; Molecular targeted therapy; Sorafenib; Linifanib; Erlotinib; Everolimus; Sunitinib; Brivanib

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Sorafenib is the first drug and now the only systemic treatment to prolong overall survival benefit in patients with hepatocellular carcinoma. In recent years, many molecular targeted agents have been developed and tested. This review article aims to summarize the efforts of systemic therapeutic options and explore the potential new systemic options for this disease.

Deng GL, Zeng S, Shen H. Chemotherapy and target therapy for hepatocellular carcinoma: New advances and challenges. World J Hepatol 2015; 7(5): 787-798 Available from: URL: http://www.wjgnet.com/1948-5182/full/v7/i5/787.htm DOI: http://dx.doi.org/10.4254/wjh.v7.i5.787
INTRODUCTION
Liver cancer is a dominant health problem around the world. It was estimated as the sixth most common cancer in 2012 (782000 new cancer cases worldwide, 5.6% of the total) and the second major cause of cancer death in 2012 (746000 deaths, 9.1% of the total), in accordance with the World Health Organization GLOBOCAN database. Hepatocellular carcinoma (HCC) accounts for 90% of primary liver cancer. The incidence is geographically related, as is the mortality, with Eastern and South-Eastern Asia and Western Africa having a high incidence.

HCC can be treated curatively with surgical resection or liver transplantation if diagnosed early; however, since the majority of HCC patients are diagnosed at an advanced stage, their median survival times are generally less than 1 year, leading to a poor prognosis. Only 15% are eligible for curative treatment. The 2 year recurrence rate can reach up to 50%, even for patients undergoing surgery, with a 10 year rate of 76%. One of the primary reasons for the poor prognosis in HCC patients is the absence of potent therapies, particularly in the advanced stage. Cytotoxic and hormonal agents, parts of systemic treatment, have been studied previously and benefited these patients rarely. Not until the recognition of sorafenib have unresectable or advanced patients of HCC had a global standard treatment. With the advent of sorafenib, systemic therapy for these patients has entered a new era of molecular targeted therapy. While initial responses have been observed, a loss of efficacy is apparent over time, which may be due to "resistance" via escape/compensatory mechanisms. The prognosis of HCC is still poor. Thus, new treatments and agents are eagerly needed. In this review article, we will take a journey through the history of systemic therapeutic options for HCC, passing through the current standard options and exploring the potential new systemic options for this disease.

CHEMOTHERAPY
In terminal stage HCC, chemotherapy treatment is not routinely used as it is chemorefractory and because of adverse events (AEs). Numerous research has reported 10%-20% response rates for chemotherapeutic agents in HCC. However, chemotherapeutic agents have shown their limited usage because of toxicities. Poor hepatic reserves make it more difficult to endure. Anthracyclines, such as doxorubicin, demonstrated response rates ranging from 0% to 79% but the elevated toxicity restricts its use.

Lacking advantage as a monotherapy, several combination regimens have been studied. The combination PIAF (cisplatin, interferon, doxorubicin and 5-fluorouracil (5-FU)) regimen received, a combination of cisplatin, interferon, doxorubicin and 5-FU, received positive results with a median overall survival (OS) of 8.9 mo. However, results of a subsequent study comparing PIAF with doxorubicin alone were disappointing. This study failed to meet its primary endpoint (OS: 8.6 mo vs 6.8 mo, \( P = 0.83 \)), displaying meaningless survival benefit. In a retrospective multicenter study of combination gemcitabine with oxaliplatin (GEMOX) in advanced HCC, GEMOX demonstrated effective antitumor effects by obtaining 8 mo OS with manageable toxicity. An overall response rate (ORR) of 22% and disease control rate (DCR) of 66% were observed. Another phase III study was conducted to evaluate the role of FOLFOX4 (infusional fluorouracil, leucovorin and oxaliplatin) in terminal HCC patients. This palliative chemotherapy was disappointing and failed to meet its primary endpoint. FOLFOX4, compared with doxorubicin alone, displayed no survival benefit (OS: 6.40 mo vs 4.97 mo, \( P = 0.07 \)).

To date, chemotherapy (single agents or combination) has been tested in abundant clinical studies in advanced HCC, but no conspicuous persuasive efficacy in prolonging survival, usually a few months, has been shown. This abominable prognosis and the weak tolerance make new medical therapies an urgent need. Various studies have been conducted to test targeted agents, single or in combination, to improve the outcome of patients with HCC. In a randomized phase III trial in patients with advanced HCC (Child-Pugh A) treated with doxorubicin plus sorafenib or doxorubicin alone, the combination chemotherapy resulted in a greater median time to progression (TTP) (6.4 mo vs 2.8 mo; \( P = 0.02 \)), OS (13.7 mo vs 6.5 mo; \( P = 0.006 \)) and PFS (6.0 mo vs 2.7 mo; \( P = 0.006 \)) when compared to doxorubicin monotherapy.

Results from another combination therapy (phase II, bevacizumab, capecitabine and oxaliplatin) also revealed an encouraging efficacy, with 6.8 mo PFS and 9.8 mo OS. This improvement implied that target agents and chemotherapy probably act synergistically but we need further investigations to be clear about the effectiveness of these treatments.

MOLECULAR TARGETS IN HCC
Without standard treatment, evaluating novel therapeutic options for patients with advanced HCC has become an interesting area for further investigation due to a high unmet medical need. Basic science researchers have made efforts to delineate a better profile of the oncogenic processes and signaling pathways that regulate tumor cell proliferation, differentiation, angiogenesis, invasion and metastasis, which has resulted in the promotion of molecular targeted therapies progress. Within the past several years, many new targeted agents have been researched in clinical studies, some available for medical treatment. However, sunitinib, brivanib, linifanib and...
eluting bead (DEB)-TACE is an improvement of cTACE at 1 year, 47% at 2 years and 26% at 3 years.

Conventional transarterial chemoembolization (cTACE) was still dismal, with less than 1 year of survival. Despite initial responses to sorafenib and similar to other targeted agents, most HCC patients experience loss of efficacy and the situation of advanced HCC treatment has not changed. Despite multiple clinical trials, the potential of sorafenib shows modest survival benefit when compared with placebo. The Nexavar-Tarceva combination therapy, a phase II/III study of combination sorafenib with erlotinib (SEARCH) (NCT00901901), had no survival benefit (OS: 9.5 mo vs 8.5 mo, P = 0.204), according to the study report at the European Society for Medical Oncology (ESMO) Congress in 2012 in Vienna.

Sorafenib combined with chemotherapy or targeted agents
In studies of sorafenib compared with placebo, sorafenib decreased tumor size less obviously. However, chemotherapy shrinks the true volume of tumor, in spite of the lack of compelling evidence in benefiting survival for advanced patients. This implies the benefit of the combination regimen of sorafenib with a chemo-therapeutic agent. Accordingly, many phase II/III clinical trials have been launched globally to compare “sorafenib plus” combination to sorafenib monotherapy.[7]. Unfortunately, the “sorafenib plus” combination has failed to show superiority in clinical trials. The Nexavar-Tarceva combination therapy, a phase III study of combination sorafenib with erlotinib (SEARCH) (NCT00901901), had no survival benefit (OS: 9.5 mo vs 8.5 mo, P = 0.204), according to the study report at the European Society for Medical Oncology (ESMO) Congress in 2012 in Vienna.

Other antiangiogenic therapies
Beyond sorafenib, sunitinib is a fresh multi-targeted tyrosine-kinase inhibitor showing efficacy in gastrointestinal stromal tumors (GIST)[21], advanced renal cell carcinoma[22] and advanced pancreatic neuroendocrine tumors[23]. Sunitinib shows evidence of modest antitumor activity with manageable AEs in several clinical trials in patients with advanced HCC[24-26]. The futility and safety reasons of sunitinib forced a phase III trial...
| Trial | Dosage | OS (mo) | PFS/TTP (mo) | AEs | Ref. |
|-------|--------|---------|--------------|-----|------|
| VEGF/VEGFR | | | | | |
| Sorafenib | Phase III (SHARP) vs placebo | 400 mg bid | 10.7 vs 7.9 | 5.5 vs 2.8 | HFSR, hypophosphatemia, diarrhea | [10] |
| | Phase III (Asian) vs placebo | 400 mg bid | 65 vs 4.2 | 2.8 vs 1.4 | HFSR, diarrhea, hypertension | [11] |
| | + TACE vs TACE alone | 400 mg bid | 75 vs 5.1 | 6.3 vs 4.3 | HFSR, alopecia, diarrhea | [19] |
| | + TACE | 400 mg bid | 12 vs 8 | 8.5 vs 2.8 | HFSR, diarrhea, rash | [20] |
| Sunitinib | Phase II | 375 mg/d | 9.8 vs 7.9 | TTP 4.1 | Leukopenia/neutropenia, thrombocytopenia, AST elevation | [24] |
| | Phase II | 50 mg/d | 8.0 vs 5.3 | 5.5 vs 2.8 | HFSR, neutropenia, asthma, thrombocytopenia, fatigue | [25] |
| | Phase III vs sorafenib | 375 mg/d | 7.9 vs 10.2 | 4.1 vs 3.8 | HFSR, thrombocytopenia and neutropenia | [27] |
| Brivanib | Phase II | 800 mg/d | 10 | 2.8 | Fatigue, hypertension, and diarrhea | [30] |
| | First-line | 800 mg/d | 9.9 | 2.7 | Fatigue, hypertension, nausea and diarrhea | [31] |
| | Second-line | 800 mg/d | 9.4 vs 8.2 | 4.2 vs 2.7 | Fatigue, asthenia, hypertension | [32] |
| Vatalanib (PTK787) | Phase II (BRISK-PS) vs placebo | 800 mg/d | 95 vs 9.9 | 4.2 vs 4.1 | Hypoaesthesia, AST elevation, fatigue | [33] |
| | Phase I / II (+ doxorubicin) | 800 mg/d | 7.3 | PFS 5.4 mo | Mucositis, alopecia, neutropenia and neutropenic sepsis | [38] |
| Linifanib | Phase II | 0.25 mg/kg | 9.7 | 3.7 | Diarrhea, hypertension and fatigue | [35] |
| TSU-68 | Phase II | 400 mg bid | 13.1 | 2.1 | Hypoaesthesia, diarrhea, anorexia | [40] |
| EGF/EGFR | Cediranib | Phase II | 45 mg /d | 5.8 | 2.8 | Fatigue, anorexia and hypertension | [42] |
| | Phase II | 30 mg /d | 11.7 | PFS 5.3 mo | Hypertension hypoaesthesia and hyperbilirubinemia | [43] |
| | Erlotinib | Phase II | 1500 mg/d | 13 | Skin rash, diarrhea, fatigue | [51] |
| | Phase II | 1500 mg/d | 10.75 | Diarrhea, folliculitis, fatigue | [52] |
| | Cetuximab | Phase II | 250 mg/m² | 9.6 | PFS 1.4 mo | Elevated AST, fever, hypomagnesemia | [48] |
| | Phase II (+ gemcitabine + oxaliplatin) | 250 mg/m² + 1000 mg/m² + 100 mg/m² | 9.5 | PFS 4.7 mo | Thrombocytopenia, neutropenia, and anemia | [49] |
| | Lapatinib | Phase II | 1500 mg/d | 6.2 | PFS 2.3 mo | Diarrhea, fatigue, and elevations of AST / ALT | [54] |
| | Phase II | 1500 mg/d | 12.6 | PFS 1.9 mo | Diarrhea, nausea and rash | [55] |
| IGF/IGFR | Cixutumumab | Phase II | 6 mg/kg weekly | 80 | 4-mo-PFS 30% | Diabetes, elevated of AST / ALT, hypoaesthesia | [59] |
| PI3K/Akt/mTOR | Everolimus | Phase I / II | 5 mg/d or 10 mg/d | 8.4 | PFS 3.8 mo | Lymphopenia, hypoaesthesia aspartate transaminase, | [70] |
| | Phase III vs placebo | 75 mg/d | 7.56 vs 7.33 | 2.96 vs 2.6 | | |
| | Sirolimus | Phase II | 20 mg/wk | 26.4 wk | 15.3 wk | Fatigue, ascites, acne, mucositis | [72] |
| | Met | Phase II | 360 mg bid | cMet-high | 66 vs 6.2 | 1.6 vs 1.4 | Neutropenia, anemia, asthenia | [87] |

**OS:** Overall survival; **PFS:** Progression-free survival; **TTP:** Time to progression; **VEGF:** Vascular endothelial growth factor; **VEGFR:** Vascular endothelial growth factor receptor; **mTOR:** Mammalian target of rapamycin; **PI3K:** Phosphatidylinositol-3-kinase; **Met:** Met proto-oncogene; **EGFR:** Epidermal growth factor receptor; **HFSR:** Hand-foot skin reaction; **IEGF:** Epidermal growth factor; **TACE:** Transarteri al chemoembolization; **AEs:** Adverse events; **BRISK-PS:** Brivanib study in patients at risk-post sorafenib; **AST:** Aspartate transaminase; **ALT:** Alanine transaminas; **IGF:** Insulin-like growth factor; **IGFR:** Insulin-like growth factor receptor.
c-kit and c-fms receptor tyrosine kinases, such as PDGFR-inhibits both FLT-1 and Flk-1/KDR and other class that binds directly to the ATP-binding sites of VEGFR, linifanib (5.4 mo) for linifanib showing a similar OS in linifanib and sorafenib (9.1 mo). Secondary endpoints of TTP, ORR and DCR were similar in both study arms for brivanib vs sorafenib (9.9 mo, brivanib vs sorafenib, showing non-inferiority brivanib as first-line agent in advanced HCC patients who had no prior systemic therapy. This research was also disappointing. It failed to meet the primary endpoint in improving OS (9.5 mo). A subsequent randomized phase III study of combining TACE with either TSU-68 or placebo conducted in Japan, South Korea and Taiwan is currently recruiting patients with unresectable HCC.

Cediranib (AZD2171) is another multitargeted inhibitor of VEGFR, c-kit, PDGFR-β and FLT-4. In a phase II clinical trial of cediranib (45 mg/d) in advanced HCC patients, cediranib was not effective at this dose and schedule due to the high incidence of toxicity reactions. A 5.8 mo OS and 2.8 mo TTP were observed. Another trial combining TSU-68 with TACE in patients with advanced HCC showed a trend towards prolonged PFS; however, this observation was not statistically significant. A subsequent randomized phase III trial showed that the coactions of PTK/ZK and interferon/5-FU markedly controlled tumor growth both in cell lines and a xenograft HCC model. Attempting to combine vatalanib with another agent may be a potent agent in HCC management.

TSU-68, a tyrosine kinase inhibitor of PDGFR, FGFR and VEGFR, has revealed promising preliminary efficacy in a phase I/II trial of heavily pretreated advanced HCC patients, with a 13.1 mo OS and 2.1 mo TTP. Another trial combining TSU-68 with TACE in patients with advanced HCC showed a trend towards prolonged PFS; however, this observation was not statistically significant. A subsequent randomized phase III study of combining TACE with either TSU-68 or placebo conducted in Japan, South Korea and Taiwan is currently recruiting patients with unresectable HCC.

Bevacizumab, an anti-VEGF monoclonal antibody, was the first angiogenesis inhibitor to be approved as an antineoplastic agent. Bevacizumab has shown encouraging effects both as a single agent and in combination with cytotoxic drugs (gemcitabine, oxaliplatin and capcitabine) or erlotinib in several phase II trials in patients with advanced HCC with a different tolerability profile. Results of the 5.3 mo PFS and 11.7 mo OS in this group were compared favorably to data reported with 45 mg/d dosing of cediranib in advanced HCC (2.8 mo TTP and 5.8 mo OS). Longer duration of treatment at 30 mg/d dosing and patient selection bias might have contributed to different results.

Bevacizumab, an anti-VEGF monoclonal antibody, was the first angiogenesis inhibitor to be approved as an antineoplastic agent. Bevacizumab has shown encouraging effects both as a single agent and in combination with cytotoxic drugs (gemcitabine, oxaliplatin and capcitabine) or erlotinib in several phase II trials in patients with advanced HCC. A 5.8 mo OS and 2.8 mo TTP were observed. Another trial combining TSU-68 with TACE in patients with advanced HCC showed a trend towards prolonged PFS; however, this observation was not statistically significant. A subsequent randomized phase III study of combining TACE with either TSU-68 or placebo conducted in Japan, South Korea and Taiwan is currently recruiting patients with unresectable HCC.

Linifanib (ABT-869), a multitargeted tyrosine kinase inhibitor, inhibits the members of the VEGFR and PDGFR families. Linifanib as single agent showed clinical antitumor activity in OS (9.7 mo) and TTP (3.7 mo). ABT-869 appeared to benefit HCC patients, with an acceptable safety profile. Accordingly, a randomized phase III trial to evaluate the efficacy and tolerability of linifanib as first-line therapy vs sorafenib (NCT01009593) was conducted and is ongoing in 1035 advanced HCC patients who had no prior systemic therapy. This trial failed to meet its primary endpoint, showing a similar OS in linifanib and sorafenib (9.1 mo for linifanib vs 9.8 mo for sorafenib). Longer TTP favored linifanib (5.4 mo vs 4.0 mo).

Vatalanib (PTK787), a tyrosine kinase inhibitor that binds directly to the ATP-binding sites of VEGFR, inhibits both FLT-1 and Flk-1/KDR and other class III receptor tyrosine kinases, such as PDGFR-β, FLT-4, c-kit and c-fms. A phase I/II research of vatalanib combined with intravenous doxorubicin in advanced HCC was conducted, resulting in a 7.3 mo OS and 5.4 mo PFS. This was the first coactions trial of protein tyrosine kinase (PTK) and intravenous doxorubicin that demonstrated potent efficacy in advanced HCC patients and provided the basis for further clinical trials combining antiangiogenic agents together with chemotherapy to augment the efficacy. A preclinical trial showed that the coactions of PTK/IZ and interferon/5-FU markedly controlled tumor growth both in cell lines and a xenograft HCC model. Attempting to combine vatalanib with another agent may be a potent agent in HCC management.

Deng GL et al. Therapy for hepatocellular carcinoma.
its encouraging anticancer effect, demonstrating a 69% DCR, 4.0 mo median PFS and 12.0 mo OS in 42 patients with advanced or metastatic liver cancer. The majority of patients enrolled in this trial have well-preserved liver function. An interesting aspect in this trial is the observed OS stratified by liver function difference, showing longer OS favoring ramucirumab Child-Pugh B group than Child-Pugh A group (18.0 mo vs 4.4 mo, both are barcelona clinic liver cancer-C)\(^\text{(47)}\). This positive study spurred the initiation of REACH (NCT01140347). REACH is a large, second-line, randomized phase III trial testing ramucirumab in pretreated patients with advanced stage HCC. Five hundred and forty-four hepatocellular carcinoma patients whose disease progressed during or following first-line therapy with sorafenib who were randomized to either ramucirumab or placebo. However, according to the preliminary results released at the ESMO Congress in 2014, ramucirumab was disappointing as it failed to show superiority in terms of OS when compared with placebo (9.2 mo vs 7.6 mo, ramucirumab vs placebo).

**EPIDERMAL GROWTH FACTOR RECEPTOR, INSULIN-LIKE GROWTH FACTOR RECEPTOR AND HEPATOCYTE GROWTH FACTOR/CAR C以外のMESENCHYMAL TO EPITHELIAL TRANSITION FACTOR SIGNALING**

Epidermal growth factor receptor (EGFR) is frequently overexpressed in HCC, confirmed by many preclinical trials. Drugs targeting EGFR consist of anti-EGFR antibodies (like cetuximab) and inhibitors of EGFR tyrosine kinases (like erlotinib, lapatinib).

Cetuximab (IMC-C225, ERBITUX) is a recombinant chimeric immunoglobulin G1 monoclonal antibody targeting the extracellular domain of EGFR. A phase II clinical trial of cetuximab was conducted to test its safety and efficacy in patients with advanced stage liver cancer. This study failed to show satisfactory results, with no patients obtaining a complete or partial response. Despite its safe toxicity profiles, this trial was also not sufficiently powered to demonstrate a significant benefit given its premature termination due to poor accrual (OS: 9.6 mo, PFS: 1.4 mo). Patients showed good tolerance\(^\text{(48)}\). The results of another research comparing GEMOX in combination with cetuximab are awaited\(^\text{(49)}\).

Erlotinib (Tarceva, OSI-774) specifically inhibits the EGFR/human epidermal-growth-factor receptor 1 (HER1) which proved to have an important role both in cell lines and animal models of hepatocellular carcinoma\(^\text{(50)}\). Results of a phase II clinical trial testing erlotinib monotherapy in patients with advanced stage liver cancer suggested a benefit with erlotinib manifested by 59% disease control. A 13 mo OS was observed, supporting its anticancer activity\(^\text{(51)}\). The other clinical study of erlotinib alone showed modest efficacy with 43% DCR in HCC, as well as a weak prolonged OS (10.75 mo\(^\text{(52)}\). In contrast to previous positive results with erlotinib, the SEARCH trial, a randomized trial protocol that combined sorafenib with erlotinib for HCC patients, failed to exhibit positive results, revealing that erlotinib when added to sorafenib did not prolong OS in advanced HCC, according to the report of the ESMO Congress in 2012.

Lapatinib, inhibitor of EGFR and HER2/NEU by docking into the ATP binding site of the two receptors, showed no or little efficacy in advanced HCC patients in clinical trials\(^\text{(53)}\). In one study, lapatinib did not meet the predefined efficacy rate, with the response rate of 5%, and likely did not have significant activity in HCC, with a 2.3 mo PFS and 6.2 mo OS\(^\text{(54)}\). Results from the other study revealed modest activity of lapatinib based on the lack of objective responses (primary endpoint of this study), short median PFS (1.9 mo) and relatively modest proportion of patients with stable disease (40%). A 12.6 mo OS was observed\(^\text{(55)}\).

Insulin-like growth factor (IGF) signaling has been widely studied in preclinical trials and its dysregulation in liver cancer by up-regulating IGF-2 and down-regulating IGF-2 receptor has been witnessed\(^\text{(56)}\). Strategies to target this signaling consisting of monoclonal antibodies and small molecule inhibitors against IGF-1R are still being researched. To date, unfortunately all IGF-R antibodies demonstrate no benefit in advanced HCC. Equally disappointing results were also reported from a phase II clinical trial of cixutumumab (IMC-A12), a fully human IgG1 monoclonal antibody that binds specifically to IGF-R1\(^\text{(57)}\). It inhibits tumor cells growth and apoptosis in a human tumor xenograft model by effectively blocking ligand-induced phosphorylation\(^\text{(58)}\). However, results from the phase II study indicated that IMC-A12 monotherapy is ineffective, with a 8.0 mo OS and a 4 mo PFS rate of 30%\(^\text{(59)}\). BIIB022 is a non-glycosylated monoclonal antibody for IGF-1R\(^\text{(60)}\). A phase I/II research was halted early because of a business decision by the sponsor company.

**Mitogen-activated protein kinase pathway (retrovirus-associated DNA sequences/rapidly accelerated fibrosarcoma/mitogen-activated protein kinase kinase/extracellular signal-regulated kinase)**

The rapidly accelerated fibrosarcoma (RAF)/mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway primarily participates in cell growth, survival and differentiation and is up-regulated in HCC\(^\text{(61,62)}\). Targeting RAF kinase is one of the most promising targetted approaches for the medical management of HCC. Sorafenib is also a strong inhibitor against the Raf serine/threonine kinases, the pro-angiogenic receptor tyrosine kinases VEGFR, PDGFR and FGFR1, and tyrosine kinases\(^\text{(63)}\). Selumetinib (AZD6244) is a non-ATP competitive small molecular inhibitor of the MAPK mitogen-activated protein kinase kinase (MEK) 1/2\(^\text{(64)}\). A phase II trial of selumetinib, the first study of
an inhibitor of MEK in HCC, conducted in patients with advanced or metastatic liver cancer pretreated with systemic therapy showed depressor results due to a lack of response in radiography and short PFS (8 wk). There was no difference in TTP and a 4.2 mo OS was observed. This research was discontinued prematurely when a planned interim analysis was conducted[65].

**PI3K/Akt/mammalian target of rapamycin pathway**

The PI3K/AKT/mammalian target of rapamycin target protein (mTOR) signal pathway is especially active in HCC and indirectly modulates angiogenesis through regulation of VEGF expression and translation of proteins involved in angiogenesis[66, 67], mTOR exists widely in various biological cells and is considered to regulate tumor proliferation and metabolism directly or indirectly[67]. mTOR inhibitors (such as everolimus and sirolimus) are not traditionally considered as direct angiogenesis inhibitors; rather, they have well-known immunosuppressive properties and are applied to prevent rejection in organ transplant recipients[68].

Everolimus (Certican, RAD 001), an oral specific mTOR, showed antineoplastic properties in both cell lines and patient tissues derived HCC tumors in murine xenograft models via mTOR regulation of tumor proliferation and metabolism[69]. In phase I / II testing, everolimus resulted in a 3.8 mo PFS and 8.4 mo OS in advanced HCC patients, showing preliminary antitumor activity. This study had a 44% DCR[70]. Everolimus has different antitumor activities and signaling pathway compared to sorafenib and it should be effective in patients who do not respond to sorafenib. However, the latest results from a phase III trial combining everolimus with placebo (EVOLVE-1 study) declared the failure of everolimus with non-improvement of OS in advanced HCC patients failed with or intolerant to sorafenib. In this study, the median OS in the everolimus arm was 7.56 mo vs 7.33 mo in the placebo arm (P = 0.675). The median TTP was 2.96 mo vs 2.6 mo (everolimus vs placebo). There was no benefit in the median TTP in the overall population or in any of the pre-stratified subgroups[71]. A phase I / II research comparing the combination of everolimus and sorafenib with sorafenib alone was conducted to test the efficacy of the everolimus combination regimen and the results of this trial are awaited (NCT01035229).

Sirolimus exhibited some antitumor activity in a phase II study in patients with advanced liver cancer, showing an OS of 26.4 wk. The median time to radiological progression was 15.3 wk[72]. Further trials are needed to assess the value of sirolimus in HCC.

**COMPOUNDS IN DEVELOPMENT FOR TREATMENT OF HCC**

Nintedanib (BIBF 1120) is an orally available, small, multiple receptor tyrosine kinase inhibitor of VEGFR 1-3, FGFR and PDGFR. BIBF 1120 clearly inhibited tumor growth and angiogenesis in a xenograft model and exhibited relatively mild effects on HCC cell lines in vivo[73-75]. Results from a phase III study in patients with advanced recurrent non-small cell lung cancer who had failed with first-line chemotherapy showed that nintedanib notably benefited patients with adenocarcinoma in median PFS and OS, including those with a poor prognosis (NCT00805194)[76]. Combination regimen of nintedanib with carboplatin and paclitaxel for medical management of advanced ovarian cancer is ongoing (NCT01015118). As for hepatocellular carcinoma, nintedanib is still being researched to compare the safety and efficacy with sorafenib (NCT00987935 and NCT01004003).

Regorafenib (BAY 73-4506) is a structurally unique inhibitor targeting multiple cancer-associated kinases, including angiogenic (VEGFR1-3, TIE2), stromal (PDGFR-β, FGFR) and oncogenic receptor tyrosine kinases (KIT, RET and RAF)[77, 78]. Regorafenib improved the management of metastatic colorectal cancer patients who failed with standard treatments[79], thus leading to the FDA approval of regorafenib. Regorafenib treatment demonstrated a notable benefit in PFS when compared to placebo in metastatic GIST that failed with standard management[80].

A phase II clinical trial testing the efficacy of regorafenib as a second-line drug in patients with liver cancer who progress after prior sorafenib treatment showed positive results in terms of TTP (4.3 mo) and OS (13.8 mo)[81]. A phase III study is currently ongoing (NCT01774344).

The hepatocyte growth factor (HGF)/mesenchymal to epithelial transition factor (Met) pathway is well known to involve in tumor growth, angiogenesis and invasion in various types of cancer. Cellular-Met is a tyrosine kinase receptor for the HGF ligand. HGF inducing activation of c-Met ultimately results in the activation of downstream effector molecules, including phospholipase C, PI3K and ERK. In early gene array studies, elevated expression of c-Met was demonstrated to be related to the poor accrual and short OS in patients with liver cancer[82-84].

A current focus of interest for HCC drug development is the c-Met inhibitor tivantinib (ARQ197). Tivantinib, a selective MET receptor, inhibits MET activation and demonstrated antitumor activity in human HCC and other tumor cell lines, as well as in human tumor xenograft models[85, 86]. A highly publicized phase II trial has provided hope for tivantinib as a potential second line candidate after sorafenib failure, particularly in high c-Met HCC. Results from this study demonstrated nearly doubling the median PFS in high c-Met patients (2.7 mo vs 1.4 mo tivantinib vs placebo; P = 0.03) and the median OS (7.2 mo for high c-Met patients on tivantinib vs 3.8 mo for high c-Met patients on placebo; P = 0.01). Longer TTP was observed in the tivantinib arm than placebo (1.6 mo vs 1.4 mo; P = 0.04). There was no difference in median OS (6.6 mo vs 6.2 mo, tivantinib vs placebo, P = 0.63). Initially a high incidence of neutropenia in this study led to a dose reduction from 360 mg bid to 240 mg bid[87]. This study provides a proof of concept that personalized targeted therapy is paving its way in the field of HCC research. In the
two currently ongoing phase III trials (NCT01755767 for the European/United States trial, NCT02029157 for the Japanese trial), tivantinib is being tested in patients with sorafenib failure against best supportive care and placebo. Despite initial problems with severe neutropenia in the European/United States trial due to a change in the drug formulation used in the phase III trial compared to the phase II trial, this study is currently ongoing and is actively recruiting patients.

Besides tivantinib, there are other c-Met inhibitors undergoing clinical testing, such as cabozantinib, Inc-280 and refametinib. Cabozantinib (XL184), a dual blockade of VEGFR2 and MET, inhibited tumor growth in HCC by decreasing angiogenesis, inhibiting proliferation and promoting apoptosis, but it exhibited more profound efficacy in phosphorylated-MET positive HCC xenografts[80]. A phase III study of cabozantinib vs placebo in HCC patients who have received prior sorafenib (NCT01908426) is ongoing. A similar targeted approach is being taken with the MEK-inhibitor refametinib (BAY 86-9766) in Ras-mutated HCC. Refametinib, a highly selective and potent small molecule allosteric (non-ATP-competitive) inhibitor of MEK 1 and MEK 2, showed potent single agent antitumor activity and acted synergistically in combination with sorafenib in preclinical HCC models, albeit with potential application for only a small subgroup of HCC patients[89-91]. Refametinib in two single-arm phase II trials (first line combined with sorafenib: NCT01915602 and second line vs placebo: NCT01915589) and another c-Met inhibitor Inc-280 in a first-line phase II trial are under investigation (NCT01737827).

**FUTURE PERSPECTIVES**

HCC is a complex causal disease and the prognosis of HCC patients remains poor, especially for advanced HCC. Researchers have shown the contribution of signaling pathway abnormalities to tumor progression and growth. In the coming years, the development of molecular targeted therapy that specifically inhibits angiogenesis factors will be a domain direction in the treatment of HCC with the advent of sorafenib. Targeted agents that inhibit angiogenesis factors simultaneously with inhibition of other key proangiogenic factors in HCC, such as FGFR or c-MET signaling, has provided further insights into the underlying pathogenesis of HCC tumors. Compounds of dual inhibition that block angiogenesis and tumorigenesis directly and other compounds that indirectly modulate angiogenesis 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.

To date, sorafenib is the sole systemic medical management option demonstrating a significant antitumor effect for advanced HCC. Several new promising multi-targeted molecules have been found and are currently under research for the improvement of liver cancer. Unfortunately, HCC are refractory to many targeted therapies. For this reason, resistance to molecular targeted agents is a major challenge for now and in the future. Combination therapy, including various drugs or a single inhibitor of cellular pathways, may provide improvement to overcome this resistance challenge. Targeted agents, combined with either multiple targeted agents or conventional chemotherapeutic agents, may be more effective and require to be further explored. Combination regimens of sorafenib with other targeted drugs are being researched. Sorafenib was a major breakthrough and is still effective, ignoring the drug resistance. To move beyond sorafenib monotherapy, a potential role for this agent in the adjuvant setting following surgical resection, radiofrequency ablation, TACE or in combination with other targeted agents or chemotherapy is under investigation.

Novel pathways and molecular targets undergoing clinical trials are required to define its efficacy in the adjuvant, neoadjuvant and metastatic setting. Exploring the mechanism of hepatocarcinogenesis is also needed to expound its molecular pathogenesis and to confirm other key targets for intervention. Future development of genomic analysis of HCC for the identification of both specific predictive and prognostic biomarkers will be a leap, increasing promise for HCC patients.

**REFERENCES**

1. **Finn RS.** Development of molecularly targeted therapies in hepatocellular carcinoma: where do we go now? *Clin Cancer Res* 2010; 16: 390-397 [PMID: 20068087 DOI: 10.1158/1078-0432.CCR-09-2084]

2. **Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet* 2012; 379: 1245-1255 [PMID: 22353262 DOI: 10.1016/ S0140-6736(11)61347-0]

3. **Yeo W, Mok TS, Zee B, Leung TW, Lai PB, Lau WY, Koh J, Mo FK, Yu SC, Chan AT, Hui P, Ma B, Lam KC, Ho WM, Wong HT, Tang A, Johnson PJ.** A randomized phase III study of doxorubicin versus cisplatin/interferon-alpha-2b/doxorubicin/fluorouracil (PIAF) combination chemotherapy for unresectable hepatocellular carcinoma. *J Natl Cancer Inst* 2005; 97: 1532-1538 [PMID: 16234567 DOI: 10.1093/jnci/dji315]

4. **Leung TW, Yip YZ, Lau WY, So SK, Yu SC, Chan AT, Mok TS, Yeo W, Liew CT, Leung NW, Tang AM, Johnson PJ.** Complete pathological remission is possible with systemic combination chemotherapy for inoperable hepatocellular carcinoma. *Clin Cancer Res* 1999; 5: 1676-1681 [PMID: 10430068]

5. **Zaanan A, Williet N, Hebbar M, Dabakuys T, Faroux L, Mansourabkhi T, Dubreuil O, Rosmorduc O, Cattan S, Bonnetain F, Boige V, Taeib J. Gemcitabine plus oxaliplatin in advanced hepatocellular carcinoma: a large multicenter AGEO study. *J Hepatol* 2013; 58: 81-88 [PMID: 22989572 DOI: 10.1016/j.jhep.2012.09.006]

6. **Qin S, Bai Y, Lim HY, Thongprasert S, Chao Y, Fan J, Yang TS, Bhudhisawasdi V, Kang WK, Zhou Y, Lee JH, Sun Y.** Randomized, multicenter, open-label study of oxaliplatin plus fluorouracil/leucovorin versus doxorubicin as palliative chemotherapy in patients with advanced hepatocellular carcinoma from Asia. *J Clin Oncol* 2013; 31: 3501-3508 [PMID: 23980077 DOI: 10.1200/JCO.2012.44.5643]

7. **Abou-Alfa GK, Johnson P, Knox JJ, Capanu M, Davidenko I, Lacava J, Leung T, Gansukh B, Saltz LB.** Doxorubicin plus sorafenib vs doxorubicin alone in patients with advanced hepatocellular carcinoma: a randomized trial. *JAMA* 2010; 304: 2154-2160 [PMID: 21081728 DOI: 10.1001/jama.2010.1672]
Hepatocellular carcinoma.

Reyes DK, Cosgrove D, Kamel IR, Bhagat N, Carter C, Tang L, Wilkie D, McNabola A, Rong XM, Gruenberger T, Pomoni M, Langenberger H, Schuchmann M, Pitton M, Sergent G, Pfammatter T, Terraz S, Benhamou Y, Avajon L, Lammer J. Phase II trial of sorafenib combined with concurrent transarterial chemoembolization for the treatment of advanced hepatocellular carcinoma: a randomised controlled trial. Lancet 2009; 363: 1329-1338 [PMID: 17046465 DOI: 10.1016/S0140-6736(06)69446-4]

Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, Oudard S, Negrier S, Szczylik C, Kim ST, Chen I, Bycott PW, Baum CM, Figlin RA. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007; 356: 115-124 [PMID: 17215529 DOI: 10.1056/NEJMoa065050] DOI: 10.1158/1078-0432.CCR-05-2225

Raymond E, Dahan L, Raoul JL, Bang YJ, 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 [PMID: 15466206 DOI: 10.1158/0008-5472.CAN-04-1443]

Llovet JM, Ribes J, Llovet JM, Bruix J. Chemoembolization of liver cancer. J Hepatol 2003; 39: 767-779 [PMID: 12950605 DOI: 10.1016/S0168-8278(03)00277-4]

Sorafenib in combination with transarterial chemoembolization with drug-eluting beads for treatment of hepatocellular carcinoma: results of the PRECISION randomized study of doxorubicin-eluting-bead embolization in the treatment of patients with unresectable hepatocellular carcinoma: initial safety data. Am J Gastroenterol 2008; 103: 3027-3035 [PMID: 19470923 DOI: 10.1200/JCO.2008.20.9098]

Varela M, Real MJ, Burrell M, Arnaiz A, Soldevila P, Ayuso C, Castells M, Montañá X, Llovet JM, Bruix J. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. J Hepatol 2007; 46: 474-481 [PMID: 17239480 DOI: 10.1016/j.jhep.2006.10.020]

Rayes DK, Vossen JA, Kamel IR, Azad NS, Wahlin TA, Torbenson MS, Choti MA, Gesel Windows DF. Single-center phase II trial of transarterial chemoembolization with drug-eluting beads for patients with unresectable hepatocellular carcinoma: initial experience in the United States. Cancer 2009; 115: 526-532 [PMID: 20010173]

Lamour J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, Pitton M, Sergent G, Pfammatter T, Terrass S, Benhamou Y, Avajon Y, Gruenberger T, Pommorini M, Langenberger H, Schuchmann M, Dumortier J, Mueller C, Chevallier P, Lencioni R. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol 2010; 33: 41-52 [PMID: 19908093 DOI: 10.1007/s00270-009-9711-7]

Pawlik TM, Reyes DK, Cosgrove D, Kamel IR, Bhagat N, Geselin Windows DF. Phase II trial of sorafenib combined with concurrent transarterial chemoembolization with drug-eluting beads for hepatocellular carcinoma. J Clin Oncol 2011; 29: 3960-3967 [PMID: 21911714]

Bai W, Wang YJ, Zhao Y, Qi XS, Yin ZX, He CY, Li RJ, Wu KC, Xia JL, Fan DM, Han GH. Sorafenib in combination with transarterial chemoembolization improves the survival of patients with unresectable hepatocellular carcinoma: a propensity score matching study. J Dig Dis 2013; 14: 181-190 [PMID: 23324079 DOI: 10.1111/1751-2980.12038]

Zhang Y, Wang WJ, Guan S, Li HL, Xu RC, Wu JB, Liu JS, Li HP, Bai W, Yin ZX, Fan DM, Zhang ZL, Han GH. Sorafenib combined with transarterial chemoembolization for the treatment of advanced hepatocellular carcinoma: a large-scale multicenter study of 222 patients. Ann Oncol 2013; 24: 1786-1792 [PMID: 23508822 DOI: 10.1093/annonc/mdt072]

Demetri GD, van Oosterom AT, Garrett CR, Blackstein ME, Shah MH, Verweij J, McArthur G, Judson IR, Heinrich MC, Morgan JA, Desai J, Fletcher CD, George S, Bello CL, Huang X, Baum CM, Casali PG. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 2006; 368: 1329-1338 [PMID: 17046465 DOI: 10.1016/S0140-6736(06)69446-4]
hepatocellular carcinoma. *CANCER* 2011; 17: 1973-1983

Finn RS, Kang YK, Mulcahy M, Polite BN, Lim HY, Walters I, Baadelet C, Manekas D, Park JW. Phase II, open-label study of brivanib as second-line therapy in patients with advanced hepatocellular carcinoma. *CANCER* 2012; 18: 2090-2098

Llovet JM, Decaens T, Raoul JL, Boucher E, Kudo M, Chang C, Kang YK, Assenat E, Lim HY, Boige V, Mathurin P, Fortoux L, Lin DY, Bruijx J, Poon RT, Sherman M, Blanc JF, Finn RS, Tak WY, Chao Y, Ezzedrine R, Liu D, Walters I, Park JW. Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized phase III BRISK-PS study. *J Clin Oncol* 2013; 31: 3509-3516

Johnson PJ, Qin S, Park JW, Poon RT, Raoul JL, Philipp PA, Chia HS, Hu TH, Heo J, Xu J, Lu L, Chao Y, Boucher E, Han KH, Paik SW, Robles-Avila J, Kudo M, Yan L, Sobhansiladsuk A, Komov D, Decaens T, Tak WY, Jeng LB, Liu D, Ezzedrine R, Walters I, Cheng AL. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. *J Clin Oncol* 2013; 31: 3517-3524

Alpert DH, Tapang P, Magoc TJ, Pease LJ, Reuter DR, Wei RQ, Li J, Guo J, Bouquet PF, Ghoreshi-Haak NS, Wang B, Bukofzer GT, Wang YC, Stavropoulos JA, Hartandi K, Niquette AL, Soni N, Johnson EF, McCall JO, Bouska JI, Luo Y, Donawho CK, Dai Y, Marcotte PA, Glaser KB, Michaelides MR, Davidson SK. Preclinical activity of ABT-869, a multitargeted receptor tyrosine kinase inhibitor. *Mol Cancer Ther* 2006; 5: 995-1006

Lin DY, Bruix J, Poon RT, Sherman M, Blanc JF, Finn RS, Tak WY, Chao Y, Ezzedrine R, Liu D, Walters I, Park JW. Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized phase III BRISK-PS study. *CANCER* 2013; 119: 380-387

Cainap C, Qin S, Huang WT, Chung JJ, Pan H, Cheng Y, Kudo M, Kang YK, Chen PJ, Toh HC, Gorbunova V, Supko JG, Blaszkowsky LS. A novel and potent inhibitor of vascular endothelial growth factor receptor tyrosine kinases, impairs vascular endothelial growth factor-induced responses and tumor growth after oral administration. *Cancer Res* 2009; 69: 2180-2189

Yau T, Chan P, Pang R, Ng K, Fan ST, Poon RT. Phase I/II trial of PTK787/ZK222584 combined with intravenous doxorubicin for treatment of patients with advanced hepatocellular carcinoma: implication for antiangiogenic approach to hepatocellular carcinoma. *Cancer* 2010; 116: 5022-5029

Murakami M, Kobayashi S, Marubashi S, Tomimaru Y, Noda T, Wada H, Eguchi H, Takada Y, Tanemura M, Umeshita K, Doki Y, Mori M, Naganoto H. Tyrosine kinase inhibitor PTK/ZK enhances the antitumor effects of interferon-α-5-fluorouracil therapy for hepatocellular carcinoma cells. *Ann Surg Oncol* 2011; 18: 589-596

Kanai F, Yoshida H, Tateishi R, Sato S, Kawabe T, Obi S, Kondo Y, Taniguchi M, Tagawa K, Ikeda M, Morizane C, Okusaka T, Arioka H, Shina H, Shimada S, Hida M. A phase I/II trial of the oral antiangiogenic agent TSU-68 in patients with advanced hepatocellular carcinoma. *Cancer Chemother Pharmacol* 2011; 67: 315-324
Deng GL et al. Therapy for hepatocellular carcinoma

Clin Oncol 2005; 23: 5305-5313 [PMID: 15955900 DOI: 10.1016/j.cjo.2005.16.584]

54 Ramanathan KK, Belani CP, Singh DA, Tanaka M, Lenz HJ, Yen Y, Kindler HL, Iqbal S, Longmate J, Mack PC, Lurje G, Gandour-Edwards R, Daney C, Gandara DR. A phase II study of lapatinib in patients with advanced biliary tree and hepatocellular cancer. Cancer Chemother Pharmacol 2009; 64: 777-783 [PMID: 19169683 DOI: 10.1007/s00280-009-0927-7]

55 Bekaii-Saab T, Markowitz J, Prescott N, Sadee W, Heereema N, Wei L, Dai Z, Papp A, Campbell A, Culler K, Balint C, O’Neil B, Lee RM, Zalupski M, Dansey C, Chen H, Grever M, Eng C, Villalona-Calero M. A multi-institutional phase II study of the efficacy and tolerability of lapatinib in patients with advanced hepatocellular carcinomas. Clin Cancer Res 2009; 15: 5895-5901 [PMID: 19737952 DOI: 10.1186/1078-0432.CCR-09-0465]

56 Tovar V, Alsinet C, Villanueva A, Hoshida Y, Chiang DY, Sole M, Thung S, Moyoano S, Toffanin S, Minguéz B, Cabellos L, Peix J, Schwartz M, Mazafrerro V, Bruix J, Llovet JM. mTOR activation in a molecular subclass of hepatocellular cancer and pre-clinical efficacy of IFG-1R blockade. J Hepatol 2010; 52: 550-559 [PMID: 20026398 DOI: 10.1016/j.jhep.2010.01.015]

57 Burtrum D, Zhu Z, Lu D, Anderson DM, Preswett M, Pereira DS, Bassi R, Abdullah R, Hooper AT, Koo H, Jimenez X, Johnson D, Appblert R, Kussie P, Bohlen P, Witte L, Hicklin DJ, Ludwig DL. A fully human monoclonal antibody to the insulin-like growth factor I receptor blocks ligand-dependent signaling and inhibits human tumor growth in vivo. Cancer Res 2003; 63: 8912-8921 [PMID: 14695208]

58 Wu JD, Olman A, Higgin LS, Haugk K, Vessella R, Ludwig DL, Plymate SR. In vivo effects of the human type I insulin-like growth factor receptor antibody A12 on androgen-dependent and androgen-independent xenograft human prostate tumors. Clin Cancer Res 2005; 11: 3065-3074 [PMID: 15837762 DOI: 10.1186/1078-0432.CCR-04-1586]

59 Abou-Alfa GK, Capanu M, O’Reilly EM, Ma J, Chou JF, Wilhelm SM, Luch M, Gann CN, Barrueco J, Gaschler-Markefski B, Novello S, Ramos A, Martinetti JA, Mazafrerro V, Bruix J, Waxman S, Schwartz M, Meyerzon M, Friedman SL, Llovet JM. Milatopan: role of mTOR signaling in hepatocellular carcinoma. Gastroenterology 2008; 135: 1972-1983, 1983.e1-11 [PMID: 18929564]

60 Zhu AX, Abrams TA, Miksad R, Blaszkowsky LS, Meyerhardt JA, Zheng H, Muzinski A, Clark JW, Kwaal EL, Schrag D, Jors KR, Fuchs CS, Inafre AJ, Borger DR, Ryan DP. Phase I/II study of everolimus in advanced hepatocellular carcinoma. Cancer 2011; 117: 5094-5102 [PMID: 21538343 DOI: 10.1002/ecs2.26165]

61 Zhu AX, Kudo M, Asenat E, Cattan S, Kang YK, Lim HY, Poon RT, Blan JC, Vogel A, Chen CL, Dorval E, Peck-Radosavljevic M, Santoro A, Daniele B, Furuse J, Jappe A, Perraud K, Anak O, Sellami DB, Chen LT. Effect of everolimus on survival in advanced hepatocellular carcinoma after failure of sorafenib: the EVOLVE-1 randomized clinical trial. JAMA 2014; 312: 57-67 [PMID: 25058218 DOI: 10.1001/jama.2014.7189]

62 Decaux T, Luciani A, Iotti E, Hulin A, Roost-Deroual F, Laurent A, Zafrazi ES, Mallat A, Duvoux C. Phase II study of sirolimus in treatment-naive patients with advanced hepatocellular carcinoma. Dig Liver Dis 2012; 44: 610-616 [PMID: 22459565]

63 Hilberg F, Roth G, Krassk M, Kautschtisch S, Sommergruber W, Tontsch-Grunt U, Garin-Chesa P, Bader G, Zoepl B, Quant J, Heckel A, Rettig WJ, BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. Cancer Res 2008; 68: 4713-4782 [PMID: 18559524 DOI: 10.1158/0008-5472.CAN-07-3630]

64 Kudo K, Aaro T, Tanaka K, Nagoni T, Furuta K, Sakai K, Kandeta H, Matsumoto K, Tamura D, Aomatsu K, De Velasco MA, Fujita Y, Sayo N, Kudo M, Nishio K. Antitumor activity of BIBF 1120, a triple angiokinase inhibitor, and use of VEGFR2+Tyr+ peripheral blood leukocytes as a pharmacodynamic biomarker in vivo. Clin Cancer Res 2011; 17: 1373-1381 [PMID: 21131553 DOI: 10.1186/1078-0432.CCR-09-2755]

65 Tai WT, Shiu CW, Li YS, Chang CW, Huang JW, Hseueh TT, Chen KF. Nintedanib (BIBF-1120) inhibits hepatocellular carcinoma growth independent of angiokinase activity. J Hepatol 2014; 61: 89-97 [PMID: 24653798 DOI: 10.1016/j.jhep.2014.03.017]

66 Deckers M, Han J, Huang J, Beijnen J, Lam A, de Vries J, van der Kuip IA, de Vries EW, van den Heuvel LP, Reck M, Kaiser R, Mellemgaard A, Douillard JY, Orlov S, Krazkowski M, von Pawel J, Gottfried M, Bondarenko I, Liao M, Gann CN, Barucco J, Gaschler-Markfetski B, Novello S. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. Lancet Oncol 2014; 15: 143-155 [PMID: 24411639 DOI: 10.1016/S1470-2045(13)70586-2]

67 D’Alessandro R, Refolo MG, Lippolis C, Giannuzzi G, Carella N, Messa C, Cavallini A, Carr BI. Antagonism of sorafenib and regorafenib actions by platelet factors in hepatocellular carcinoma cell lines. BMC Cancer 2014; 14: 351 [PMID: 24885890 DOI: 10.1186/1471-2407-14-351]
Deng GL et al. Therapy for hepatocellular carcinoma

78 Wilhelm SM, Dumas J, Adnane L, Lynch M, Carter CA, Schütz G, Thierauch KH, Zopf D. Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. Int J Cancer 2011; 129: 245-255 [PMID: 21170960]

79 Grotthey A, Van Cutsen E, Sobrero A, Siena S, Falcone A, Ychou M, Humblet B, Bouche O, Mineur L, Barone C, Adenis A, Tabernero J, Yoshino T, Lenz HJ, Goldberg RM, Sargent DJ, Cihon F, Cupit L, Wagner A, Laurent D. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013; 381: 303-312 [PMID: 23177514 DOI: 10.1016/S0140-6736(12)61900-X]

80 Demetri GD, Reichardt P, Kang YK, Blay JY, Rutkowski P, Gelderblom H, Hohenberger P, Leahy M, von Mehren M, Jornsau H, Badalamenti G, Blackstein M, Le Cesne A, Schöffski P, Maki RG, Bauer S, Nguyen BB, Xu J, Nishida T, Chung J, Kappeler C, Kuss I, Laurent D, Casali PG. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013; 381: 293-302 [PMID: 23177515]

81 Bruix J, Tak WY, Gasbarrini A, Santoro A, Colombo M, Lim HY, Mazzaferro V, Wiest R, Reig M, Wagner A, Bolondi L. Regorafenib as second-line therapy for intermediate or advanced hepatocellular carcinoma: multicentre, open-label, phase II safety study. Eur J Cancer 2013; 49: 3412-3419 [PMID: 23097966 DOI: 10.1016/j.ejca.2013.05.028]

82 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 [PMID: 19123972 DOI: 10.5483/BMBRep.2008.41.12.833]

83 Tavian D, De Petro G, Benetti A, Portolani N, Giulini SM, Barlati S. u-PA and c-MET mRNA expression is co-ordinately enhanced while hepatocyte growth factor mRNA is down-regulated in human hepatocellular carcinoma. Int J Cancer 2000; 87: 644-649 [PMID: 10925356]

84 Ueki T, Fujimoto J, Suzuki T, Yamamoto H, Okamoto E. Expression of hepatocyte growth factor and its receptor, the c-met proto-oncogene, in hepatocellular carcinoma. Hepatology 1997; 25: 619-623 [PMID: 9049208 DOI: 10.1002/hep.510250321]

85 Munshi N, Jeay S, Li Y, Chen CR, France DS, Ashwell MA, Hill J, Moussa MM, Leggott DS, Li CJ. ARQ 197, a novel and selective inhibitor of the human c-Met receptor tyrosine kinase with antitumor activity. Mol Cancer Ther 2010; 9: 1544-1553 [PMID: 20484018]

86 Salvi A, Arici B, Portolani N, Giuliani SM, De Petro G, Barlati S. In vitro c-met inhibition by antisense RNA and plasmid-based RNAi down-modulates migration and invasion of hepatocellular carcinoma cells. Int J Oncol 2007; 31: 451-460 [PMID: 17611703]

87 Santoro A, Rimassa L, Borbath I, Daniele B, Salvagni S, Van Laethem JL, Van Vlierberghe H, Trojan J, Kolligs FT, Weiss A, Miles S, Gasbarrini A, Lencioni M, Cicalaese L, Sherman M, Gridelli C, Buggisch P, Gerken G, Schmid RM, Boni C, Ponsenzi N, Hassanou Z, Abbassida G, Schwartz B, Von Roemeling R, Lamar ME, Chen Y, Porta C. Tivantinib for second-line treatment of advanced hepatocellular carcinoma: a randomised, placebo-controlled phase 2 study. Lancet Oncol 2013; 14: 55-63 [PMID: 23182627 DOI: 10.1016/S1470-2045(12)70490-4]

88 Xiang Q, Chen W, Ren M, Wang J, Zhang H, Deng DY, Zhang L, Shang C, Chen Y. Cabozantinib suppresses tumor growth and metastasis in hepatocellular carcinoma by a dual blockade of VEGFR2 and MET. Clin Cancer Res 2014; 20: 2959-2970 [PMID: 24700742 DOI: 10.1158/1078-0432.CCR-13-2620]

89 Schneider R, Puelpler F, Neuhauß R, Kissel M, Adjei AA, Minner JN, Mumberg D, Ziegelbauer K, Scholz A. Allosteric MEK1/2 inhibitor refametinib (BAY 86-9766) in combination with sorafenib exhibits antitumor activity in preclinical murine and rat models of hepatocellular carcinoma. Neoplasia 2013; 15: 1161-1171 [PMID: 24204195]

90 Weekes CD, Von Hoff DD, Adjei AA, Leffingwell DP, Eckhardt SG, Gore L, Lewis KD, Weiss GI, Ramanathan RK, Dy GK, Ma WW, Sheedy B, Iverson C, Minner JN, Shen Z, Yeh LT, Dubowy RL, Jeffers M, Rajagopalan P, Clendeninn NJ. Multicenter phase I trial of the mitogen-activated protein kinase 1/2 inhibitor BAY 86-9766 in combination with sorafenib exhibits antitumor activity in preclinical murine and rat models of hepatocellular carcinoma. Mol Cancer Ther 2014; 13: 2935-2945 [PMID: 24700742 DOI: 10.1158/1078-0432.CCR-13-2620]

91 Iverson C, Larson G, Lai C, Yeh LT, Dadson C, Weingarten P, Appleby T, Yu T, Maderma A, Vernier JM, Hamatake R, Minner JN, Quist A, Liu SQ. Target B. RDEA119/BAY 869766: a potent, selective, allosteric inhibitor of the human c-Met receptor tyrosine kinase with antitumor activity. Mol Cancer Ther 2010; 9: 1544-1553 [PMID: 20484018]
