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**Chemotherapy for advanced hepatocellular carcinoma in the sorafenib age**

Miyahara K *et al.* Chemotherapy for advanced hepatocellular carcinoma

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**Abstract**

The kinase inhibitor sorafenibis the only systemic therapy proven to have a positive effect on survival of patients with advanced hepatocellular carcinoma (HCC). After development of sorafenib and its introduction as a therapeutic agent used in the clinic, several critical questions have been raised. Clinical parameters and biomarkers predicting sorafenib efficacy are the most important issues that need to be elucidated. Although it is difficult to know the responders in advance using conventional characteristics of patients, there are specific serum cytokines and/or gene amplification in tumor tissues that have been reported to predict efficacy of sorafenib. Risk and benefits of continuation of sorafenib beyond radiological progression is another issue to consider because no other standard therapy for advanced HCC as yet exists. In addition, effectiveness of the expanded application of sorafenib is still controversial, although a few studies have shed some light on combinational treatment with sorafenib for intermediate-stage HCC. Recently, over 50 relevant drugs have been developed and are currently under investigation. The efficacy of some of these drugs has been extensively examined, but none have demonstrated any superiority over sorafenib, so far. However, there are several drugs that have shown efficacy for treatment after sorafenib failure, and these are proceeding to further studies. To address these issues and questions, we have done extensive literature review and summarize the most current status of therapeutic application of sorafenib.

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**Key words:** Biomarker; Molecular targeted therapy; Clinical trial; Hepatic arterial infusion chemotherapy; Hepatocellular carcinoma; Sorafenib

**Core tip:** Sorafenib is the only systemic therapy proven to have a positive effect on survival and to be well tolerated in patients with advanced hepatocellular carcinoma (HCC). We summarize the most current status of sorafenib therapy, focusing on (1) safety and efficacy of sorafenib for advanced HCC; (2) biomarkers predicting efficacy of sorafenib; (3) expanded application for the treatment of non-advanced HCC; (4) sorafenib efficacy beyond radiological progression; and (5) novel therapeutics and hepatic arterial infusion chemotherapy.

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**INTRODUCTION**

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide and is associated with the second lowest 5-year survival rate of all tumor types[1]. For patients diagnosed at early stages, potentially curative treatments are available, such as radiofrequency ablation, resection, and liver transplantation; and patients at intermediate stages may be treated with transcatheter arterial chemoembolization (TACE). However, for disease that is diagnosed at an advanced stage or progresses after locoregional therapies, sorafenib is the choice of treatment.

Sorafenib, which is an oral multi-kinase inhibitor, suppresses tumor angiogenesis and proliferation by inhibiting the activity of such targets as vascular endothelial growth factor (VEGF) receptor, platelet-derived growth factor (PDGF) receptor, mast/stem cell growth factor receptor (c-KIT), rearranged during transfection (RET), Fms-like tyrosine kinase 3 (FLT-3), and the proto-oncoprotein, c-RAF[2,3]. In addition, sorafenib also has been shown to induce apoptosis as direct effects on tumor cell[4]. The safety and efficacy of sorafenib in patients with advanced HCC was demonstrated in two phase III randomized, double-blind, placebo-controlled trials, the Sorafenib HCC Assessment Randomized Protocol (SHARP) and Asia-Pacific (AP) trials[5,6], thereby establishing sorafenib as the standard systemic therapy for advanced HCC[7,8].

HCC is often resistant to chemotherapy, and the potential for liver failure accompanying this disease has complicated the therapies that are employed. However, there is currently no systemic therapy other than sorafenib, although many clinical trials are on-going. The aim of the present review is to summarize recent clinical evidence and present a current status of sorafenib in therapeutic treatment of HCC.

**STATUS OF SORAFENIB IN CLINICAL GUIDELINES**

Sorafenib is recommended as a treatment in patients with (1) extrahepatic lesions, (2) macrovascular invasion; or (3) those who do not response to TACE/arterial injection chemotherapy, when the liver function is Child-Pugh (CP) -A, in a consensus-based treatment algorithm for HCC (JSH Consensus 2010)[9]. The recommendation was based on the results demonstrated in SHARP and AP trials (Table 1). Patients recommended for sorafenib in this algorithm overlap with those recommended according to the European Association for the Study of the Liver (EASL), the European Organization for Research and Treatment of Cancer (EORTC)[10], the American Association for the Study of Liver Diseases (AASLD)[8], and the National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline[11]. The EASL-EOTC, AASLD, and NCCN guidelines indicate sorafenib as an option for CP-B patients; whereas, no clear evidence, based on randomized controlled trials, has been presented on safety of sorafenib in CP-B patients.

The recent report in Global investigation of therapeutic decisions in HCC and of its treatment with sorafenib (GIDEON), which is a global, non-interventional, surveillance study, has presented data from sorafenib treatment of patients with liver dysfunction[12]. In the study, CP subgroups showed similar incidence of all grade of adverse events (AEs) [84.0 (CP-A) *vs* 88.6% (CP-B)] and time to progression (TTP) [4.7 (CP-A) *vs* 4.4 mo (CP-B)]. In contrast, serious AEs were more common in CP-B (60.4%) than CP-A (36.0%) patients. The finding that severity of AEs is associated with poor liver function provides a certain warning to the use of sorafenib for the CP-B patient, even if the treatment efficacy is consistent irrespective of liver function.

**CLINICAL CHARACTERISTICS AND EFFICACY OF SORAFENIB**

Clinical characteristics at baseline that might affect responses to therapy have been examined. Subgroup analyses of SHARP and AP trials, in which patients with well-preserved liver function had been enrolled, demonstrated the baseline status related to outcomes during sorafenib treatment[13-15]. In both analyses, the patients with Eastern Cooperative Oncology Group performance status (ECOG PS) 1 or 2, aspartate/alanine transaminase (AST/ALT) elevation, or macroscopic vascular invasion (MVI) had similar hazard ratios with the total population [hazard ratio (HR) of 0.69 in SHARP; 0.68 in AP]. These findings provide an opportunity for patients with these statuses to be treated with sorafenib, but it should be noted that high ECOG PS, AST/ALT elevation, or presence of MVI themselves were associated with short OS. Sorafenib treatment for patients with prior local therapy, prior TACE, or extrahepatic spread (EHS) also resulted in longer median OS than placebo, except for those with prior hepatectomy in the AP trial. However, careful interpretation of these results is needed because the studies did not aim to show the differences between these subgroups, and statistical confirmation had not yet been performed.

**BIOMARKERS FOR PREDICTING OUTCOMES OF SORAFENIB TREATMENT**

Predictive biomarkers are expected to advance the potential of personalized medicine in cancer treatment. Biomarker research for predicting the efficacy of sorafenib is a growing field, and a few candidate markers in plasma, serum, and tissue have been reported (Table 2). Llovet *et* *al*[16] reported results of sub-analysis in the SHARP trial, examining expression of 10 molecules in plasma of HCC patients. Plasma c-KIT and hepatocyte growth factor (HGF) were suggested as possible predictors of response to sorafenib, although the association was not statistically significant. In other preliminary studies, angiogenesis-related cytokines in serum, including angiopoietin-2, were reported to correlate with treatment response[17]. Several candidates for tissue markers, such as FGF3/FGF4[18], αB-crystallin[19], JNK[20], and pERK[21], have been proposed. Amplification of FGF3/FGF4 was observed only in objective responders, but not in patients with stable or progressive disease. Frequency of FGF3/FGF4 amplification remains below a few percent in HCC[22-24]; however, FGF3/FGF4 amplification might represent a promising therapeutic target, and it provides a novel insight for molecular-based therapy in HCC. Various molecules thought to have potential to be novel markers or therapeutic targets have been identified on the basis of basic research observations[4,25-28] (Table 2), but none of them has been verified in clinical studies. Candidate biomarkers should be validated in prospective clinical trials, in order to assess their potential to lead to personalized therapy.

**CONVENTIONAL TUMOR MARKERS DURING TREATMENT WITH SORAFENIB**

Conventional tumor markers for the diagnosis of HCC, *i.e.*, α-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP), have been reported to show contrasting behavior after administration of sorafenib. Early AFP decrease correlates with beneficial efficacy of sorafenib in patients with HCC[29-31], as observed in other therapies. However, DCP increases with sorafenib administration, regardless of the treatment response[29]. Interestingly, a few reports have shown that elevation of DCP[32,33] and NX-DCP, which is a vitamin K-specific phenotype of DCP[34], is associated with a highly therapeutic effect of sorafenib. These markers are expected to be used for monitoring HCC patients undergoing treatment, rather than as predictive biomarkers.

**ADVERSE EVENTS AND EFFICACY OF SORAFENIB**

Various adverse events were frequently observed during sorafenib therapy (Table 3). Adverse events of molecular-targeted agents sometimes associate with a favorable effect on prognosis[35-46]. Regarding sorafenib therapy, development of skin toxicities[47,48] and arterial hypertension[49] in some trials correlated with longer time to disease progression or longer survival in patients with HCC, and similar correlations were seen in those with renal cell carcinoma[50,51]. However, this correlation has not been identified in randomized controlled trials, and validation might be difficult if there are agents for preventive care being administrated, such as preventive and therapeutic skin care, systemic analgesics for pain, vitamin B6, *etc*., for hand-foot skin reaction[52]. Furthermore, haphazard continuation of chemotherapies with side effects requires careful management, as these may sometimes lead to dangerous conditions.

**EFFICACY OF SORAFENIB IN NON-ADVANCED HCC**

Sorafenib is recommended for treatment of advanced HCC in clinical algorithms, as described above, but the utility for early or intermediate stages of HCC remain unclear. Intermediate-stage HCC with multiple nodules and without major vascular invasion or extrahepatic spread is commonly treated by TACE. Ischemic injury after TACE induces up-regulation of VEGF[53], which is associated with poor prognosis[54,55]. However, combination with sorafenib, which inhibits angiogenic factors, including VEGF receptor, could theoretically reinforce the efficacy of TACE.

Several clinical trials evaluating effects of TACE with sorafenib in treatment of intermediate-stage HCC are being conducted (Table 4). Two single-arm phase II trials have shown promising efficacy[56,57]. A randomized placebo-controlled study of sorafenib or placebo in combination with TACE for intermediate-stage HCC (SPACE) successfully demonstrated that sorafenib prolongs TTP after TACE, although improvement of OS or time to untreatable progression (TTUP) was not observed[58]. In a randomized phase III trial in patients who responded to TACE (post TACE study), sorafenib did not significantly prolong TTP after TACE, compared to placebo[59]. In this study, a long lag time of > 9 wk prior to administration of sorafenib may also have contributed to the absence of a positive effect of sorafenib. In response, a trial titled Transcatheter Arterial Chemoembolization Therapy in Combination with Sorafenib (TACTICS, NCT01217034) is currently being conducted, with a stipulated lag time (3−21 d).

Furthermore, sorafenib is under evaluation as an adjuvant therapy for the prevention of recurrence following surgery or local ablation. The trial is a phase III, randomized, double-blind, and placebo-controlled study, titled Sorafenib as Adjuvant Treatment in the Prevention of Recurrence of HCC (STORM trial; NCT00692770). The results from this study will provide more information about whether sorafenib has efficacy for HCC at early stages and reduces the risk of recurrence.

**CONTINUATION OF SORAFENIB AFTER RADIOLOGICAL PROGRESSION**

In general, tumor progression implies resistance to the therapy being employed, and it is thus a motivation to change therapy regimen. However, in contrast to typical cytotoxic agents, sorafenib seldom induces an objective response (2%−3%)[5,6]; this modest response would make it difficult for physicians to decide whether to continue or discontinue sorafenib treatment. Several reports speculate about sorafenib efficacy beyond radiological progression. Sorafenib administration beyond first radiological progression was seen to continuously suppress tumor growth[60], and long-term treatment was associated with prolonged survival regardless of therapeutic effect[61]. Interestingly, the SHARP trial was designed to continue sorafenib after radiological progression, if symptomatic progression was absent[5]. Hence, it is reasonable to consider continuing sorafenib at the time of radiological progression when patients will tolerate the therapy and have no symptomatic disease progression or liver dysfunction in the present status, with no other effective therapy.

**HEPATIC ARTERIAL INFUSION CHEMOTHERAPY**

Before the development of molecular targeted therapies based on evidence from randomized controlled trials, hepatic arterial infusion chemotherapy (HAIC) had been used to treat advanced HCC with vascular invasion and/or multiple intrahepatic lesions. The protocol of HAIC is not standardized. The most frequently used regimens in Japan are (1) continuous infusion of 5-fluorouracil plus low-dose cisplatin combination therapy (termed low-dose FP, for fluorouracil and platinum); (2) continuous intra-arterial infusion of 5-fluorouracil plus systemic interferon therapy (5-FU plus IFN), or one-shot infusion of cisplatin (one-shot CDDP). The response rates of HAIC were reported to be 24.5%−38.5% in low-dose FP[62-68]; 21.5%−63% in 5-FU plus IFN[69-77]; 3.6%−33.8% in one-shot CDDP[78-81], which were higher than that of sorafenib; but the survival benefit of these therapies are controversial. The lack of evidence based on randomized controlled trials in most of the regimens is a serious criticism of the importance of HAIC in HCC treatment. Trials evaluating the efficacy of HAIC in combination with sorafenib are currently on-going: Comparing Efficacy of Sorafenib *vs* Sorafenib in Combination with Low-dose FP in Patients with Advanced HCC (SILIUS Phase III trial; NCT01214343); and Randomized Phase II Study of Sorafenib and Hepatic Arterial Infusion Chemotherapy with Cisplatin *vs* Sorafenib for Advanced HCC (UMIN000005703).

**NOVEL THERAPEUTICS FOR ADVANCED HCC**

After the successful result of sorafenib in the SHARP and AP trials, more than 50 reagents are currently under evaluation in phase I to IV trials (www.clinicaltrials.gov.). Recently, phase III studies have been reported to evaluate the survival benefit of sunitinib, brivanib, linifanib, and the combination of sorafenib plus erlotinib over sorafenib monotherapy; however, there have so far been no agents showing survival improvement or alleviation of AEs[5,6,82-86]. Linifanib shows longer TTP and similar OS compared to sorafenib, but linifanib is inferior to sorafenib in safety[86]. Brivanib, as a second-line therapy after failure by, or intolerance to, sorafenib, shows longer TTP but similar OS relative to placebo[85]. The failures in these trials point to the difficulty of both improving the OS and alleviation of the AEs concurrently in advanced HCC.

For effective use of molecular-targeted agents, clinical trials to investigate new agents in combination with predictive markers are on-going. These include c-MET inhibitor (tivantinib; ARQ 197) and monoclonal antibody against glypican-3 (GC33). For patients with c-MET-high tumors, TTP was found to be longer with tivantinib than for those with placebo in a randomized phase II trial (2.7 *vs* 1.4 mo, *p* = 0.03)[87]. For patients treated with GC33, TTP was longer in patients with GPC3-high tumors than in those with GPC3-low tumors in a phase I trial (26.0 *vs* 7.1 wk, *p* = 0.033)[88]. The efficacy of these surrogate markers are being evaluated in randomized, placebo-controlled phase III (NCT01755767) and II (NCT01507168) trials.

**CONCLUSION**

We have reviewed current status of chemotherapy for advanced HCC. Sorafenib has been established as a standard therapy prolonging survival in patients with advanced HCC, but it only provides a small treatment response. To compensate for the modest effect on tumor regression, new molecular-targeted drugs and their biomarkers for prediction of treatment efficacy are being investigated. In addition, several novel therapeutics in combination with HAIC are being evaluated in clinical trials. The development of these markers and therapeutics in the near future will improve prognosis of advanced HCC and provide novel insights into molecular-based therapy for HCC.

**REFERENCES**

1 **Jemal A**, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin* 2010; **60**: 277-300 [PMID: 20610543 DOI: 10.3322/caac.20073]

2 **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 [PMID: 15466206]

3 **Wilhelm SM**, Adnane L, Newell P, Villanueva A, Llovet JM, Lynch M. Preclinical overview of sorafenib, a multikinase inhibitor that targets both Raf and VEGF and PDGF receptor tyrosine kinase signaling. *Mol Cancer Ther* 2008; **7**: 3129-3140 [PMID: 18852116 DOI: 10.1158/1535-7163.MCT-08-0013]

4 **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 [PMID: 17178882]

5 **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; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378-390 [PMID: 18650514 DOI: 10.1056/NEJMoa0708857]

6 **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 [PMID: 19095497 DOI: 10.1016/S1470-2045(08)70285-7]

7 **Llovet JM**, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, Sherman M, Schwartz M, Lotze M, Talwalkar J, Gores G; Panel of Experts in HCC-Design Clinical Trials. Design and endpoints of clinical trials in hepatocellular carcinoma. *J Natl Cancer Inst* 2008; **100**: 698-711 [PMID: 18477802 DOI: 10.1093/jnci/djn134]

8 **Bruix J**, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology* 2011; **53**: 1020-1022 [PMID: 21374666 DOI: 10.1002/hep.24199]

9 **Arii S**, Sata M, Sakamoto M, Shimada M, Kumada T, Shiina S, Yamashita T, Kokudo N, Tanaka M, Takayama T, Kudo M. Management of hepatocellular carcinoma: Report of Consensus Meeting in the 45th Annual Meeting of the Japan Society of Hepatology (2009). *Hepatol Res* 2010; **40**: 667-685 [PMID: 20633193 DOI: 10.1111/j.1872-034X.2010.00673.x]

10 **European Association For The Study Of The Liver; European Organisation For Research And Treatment Of Cancer.** EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012; **56**: 908-943 [PMID: 22424438 DOI: 10.1016/j.jhep.2011.12.001]

11 **Benson AB**, Abrams TA, Ben-Josef E, Bloomston PM, Botha JF, Clary BM, Covey A, Curley SA, D'Angelica MI, Davila R, Ensminger WD, Gibbs JF, Laheru D, Malafa MP, Marrero J, Meranze SG, Mulvihill SJ, Park JO, Posey JA, Sachdev J, Salem R, Sigurdson ER, Sofocleous C, Vauthey JN, Venook AP, Goff LW, Yen Y, Zhu AX. NCCN clinical practice guidelines in oncology: hepatobiliary cancers. *J Natl Compr Canc Netw* 2009; **7**: 350-391 [PMID: 19406039]

12 **Marrero JA**, Lencioni R, Ye SL, Kudo M, Bronowicki JP, Chen XP, Dagher L, Furuse J, Geschwind JF, de Guevara LL, Papandreou C, Sanyal AJ, Takayama T, Yoon SK, Nakajima K, Venook AP. Final analysis of GIDEON (Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma [HCC] and of Its Treatment with Sorafenib [Sor]) in >3000 Sor-treated patients (pts): Clinical findings in pts with liver dysfunction. *J Clin Oncol* 2013; Suppl: abstr 4126

13 **Raoul JL**, Bruix J, Greten TF, Sherman M, Mazzaferro V, Hilgard P, Scherubl H, Scheulen ME, Germanidis G, Dominguez S, Ricci S, Nadel A, Moscovici M, Voliotis D, Llovet JM. Relationship between baseline hepatic status and outcome, and effect of sorafenib on liver function: SHARP trial subanalyses. *J Hepatol* 2012; **56**: 1080-1088 [PMID: 22245896 DOI: 10.1016/j.jhep.2011.12.009]

14 **Bruix J**, Raoul JL, Sherman M, Mazzaferro V, Bolondi L, Craxi A, Galle PR, Santoro A, Beaugrand M, Sangiovanni A, Porta C, Gerken G, Marrero JA, Nadel A, Shan M, Moscovici M, Voliotis D, Llovet JM. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. *J Hepatol* 2012; **57**: 821-829 [PMID: 22727733 DOI: 10.1016/j.jhep.2012.06.014]

15 **Cheng AL**, Guan Z, Chen Z, Tsao CJ, Qin S, Kim JS, Yang TS, Tak WY, Pan H, Yu S, Xu J, Fang F, Zou J, Lentini G, Voliotis D, Kang YK. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma according to baseline status: subset analyses of the phase III Sorafenib Asia-Pacific trial. *Eur J Cancer* 2012; **48**: 1452-1465 [PMID: 22240282 DOI: 10.1016/j.ejca.2011.12.006]

16 **Llovet JM**, Peña CE, Lathia CD, Shan M, Meinhardt G, Bruix J; SHARP Investigators Study Group. Plasma biomarkers as predictors of outcome in patients with advanced hepatocellular carcinoma. *Clin Cancer Res* 2012; **18**: 2290-2300 [PMID: 22374331 DOI: 10.1158/1078-0432.CCR-11-2175]

17 **Miyahara K**, Nouso K, Tomoda T, Kobayashi S, Hagihara H, Kuwaki K, Toshimori J, Onishi H, Ikeda F, Miyake Y, Nakamura S, Shiraha H, Takaki A, Yamamoto K. Predicting the treatment effect of sorafenib using serum angiogenesis markers in patients with hepatocellular carcinoma. *J Gastroenterol Hepatol* 2011; **26**: 1604-1611 [PMID: 22011296 DOI: 10.1111/j.1440-1746.2011.06887.x]

18 **Arao T**, Ueshima K, Matsumoto K, Nagai T, Kimura H, Hagiwara S, Sakurai T, Haji S, Kanazawa A, Hidaka H, Iso Y, Kubota K, Shimada M, Utsunomiya T, Hirooka M, Hiasa Y, Toyoki Y, Hakamada K, Yasui K, Kumada T, Toyoda H, Sato S, Hisai H, Kuzuya T, Tsuchiya K, Izumi N, Arii S, Nishio K, Kudo M. FGF3/FGF4 amplification and multiple lung metastases in responders to sorafenib in hepatocellular carcinoma. *Hepatology* 2013; **57**: 1407-1415 [PMID: 22890726 DOI: 10.1002/hep.25956]

19 **Huang XY**, Ke AW, Shi GM, Zhang X, Zhang C, Shi YH, Wang XY, Ding ZB, Xiao YS, Yan J, Qiu SJ, Fan J, Zhou J. αB-crystallin complexes with 14-3-3ζ to induce epithelial-mesenchymal transition and resistance to sorafenib in hepatocellular carcinoma. *Hepatology* 2013; **57**: 2235-2247 [PMID: 23316005 DOI: 10.1002/hep.26255]

20 **Hagiwara S**, Kudo M, Nagai T, Inoue T, Ueshima K, Nishida N, Watanabe T, Sakurai T. Activation of JNK and high expression level of CD133 predict a poor response to sorafenib in hepatocellular carcinoma. *Br J Cancer* 2012; **106**: 1997-2003 [PMID: 22596232 DOI: 10.1038/bjc.2012.145]

21 **Abou-Alfa GK**, Schwartz L, Ricci S, Amadori D, Santoro A, Figer A, De Greve J, Douillard JY, Lathia C, Schwartz B, Taylor I, Moscovici M, Saltz LB. Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. *J Clin Oncol* 2006; **24**: 4293-4300 [PMID: 16908937]

22 **Takeo S**, Arai H, Kusano N, Harada T, Furuya T, Kawauchi S, Oga A, Hirano T, Yoshida T, Okita K, Sasaki K. Examination of oncogene amplification by genomic DNA microarray in hepatocellular carcinomas: comparison with comparative genomic hybridization analysis. *Cancer Genet Cytogenet* 2001; **130**: 127-132 [PMID: 11675133]

23 **Nishida N**, Fukuda Y, Komeda T, Kita R, Sando T, Furukawa M, Amenomori M, Shibagaki I, Nakao K, Ikenaga M. Amplification and overexpression of the cyclin D1 gene in aggressive human hepatocellular carcinoma. *Cancer Res* 1994; **54**: 3107-3110 [PMID: 8205525]

24 **Chochi Y**, Kawauchi S, Nakao M, Furuya T, Hashimoto K, Oga A, Oka M, Sasaki K. A copy number gain of the 6p arm is linked with advanced hepatocellular carcinoma: an array-based comparative genomic hybridization study. *J Pathol* 2009; **217**: 677-684 [PMID: 19097070 DOI: 10.1002/path.2491]

25 **Shan J**, Shen J, Liu L, Xia F, Xu C, Duan G, Xu Y, Ma Q, Yang Z, Zhang Q, Ma L, Liu J, Xu S, Yan X, Bie P, Cui Y, Bian XW, Qian C. Nanog regulates self-renewal of cancer stem cells through the insulin-like growth factor pathway in human hepatocellular carcinoma. *Hepatology* 2012; **56**: 1004-1014 [PMID: 22473773 DOI: 10.1002/hep.25745]

26 **Blivet-Van Eggelpoël MJ**, Chettouh H, Fartoux L, Aoudjehane L, Barbu V, Rey C, Priam S, Housset C, Rosmorduc O, Desbois-Mouthon C. Epidermal growth factor receptor and HER-3 restrict cell response to sorafenib in hepatocellular carcinoma cells. *J Hepatol* 2012; **57**: 108-115 [PMID: 22414764 DOI: 10.1016/j.jhep.2012.02.019]

27 **Chen HC**, Jeng YM, Yuan RH, Hsu HC, Chen YL. SIRT1 promotes tumorigenesis and resistance to chemotherapy in hepatocellular carcinoma and its expression predicts poor prognosis. *Ann Surg Oncol* 2012; **19**: 2011-2019 [PMID: 22146883 DOI: 10.1245/s10434-011-2159-4]

28 **Tai WT**, Cheng AL, Shiau CW, Huang HP, Huang JW, Chen PJ, Chen KF. Signal transducer and activator of transcription 3 is a major kinase-independent target of sorafenib in hepatocellular carcinoma. *J Hepatol* 2011; **55**: 1041-1048 [PMID: 21354226 DOI: 10.1016/j.jhep.2011.01.047]

29 **Kuzuya T**, Asahina Y, Tsuchiya K, Tanaka K, Suzuki Y, Hoshioka T, Tamaki S, Kato T, Yasui Y, Hosokawa T, Ueda K, Nakanishi H, Itakura J, Takahashi Y, Kurosaki M, Izumi N. Early decrease in α-fetoprotein, but not des-γ-carboxy prothrombin, predicts sorafenib efficacy in patients with advanced hepatocellular carcinoma. *Oncology* 2011; **81**: 251-258 [PMID: 22116493 DOI: 10.1159/000334454]

30 **Shao YY**, Lin ZZ, Hsu C, Shen YC, Hsu CH, Cheng AL. Early alpha-fetoprotein response predicts treatment efficacy of antiangiogenic systemic therapy in patients with advanced hepatocellular carcinoma. *Cancer* 2010; **116**: 4590-4596 [PMID: 20572033 DOI: 10.1002/cncr.25257]

31 **Yau T**, Yao TJ, Chan P, Wong H, Pang R, Fan ST, Poon RT. The significance of early alpha-fetoprotein level changes in predicting clinical and survival benefits in advanced hepatocellular carcinoma patients receiving sorafenib. *Oncologist* 2011; **16**: 1270-1279 [PMID: 21885876 DOI: 10.1634/theoncologist.2011-0105]

32 **Nakazawa T**, Hidaka H, Shibuya A, Koizumi W. Rapid regression of advanced hepatocellular carcinoma associated with elevation of des-gamma-carboxy prothrombin after short-term treatment with sorafenib - a report of two cases. *Case Rep Oncol* 2010; **3**: 298-303 [PMID: 21347197 DOI: 10.1159/000319831]

33 **Ueshima K**, Kudo M, Takita M, Nagai T, Tatsumi C, Ueda T, Kitai S, Ishikawa E, Yada N, Inoue T, Hagiwara S, Minami Y, Chung H, Sakurai T. Des-γ-carboxyprothrombin may be a promising biomarker to determine the therapeutic efficacy of sorafenib for hepatocellular carcinoma. *Dig Dis* 2011; **29**: 321-325 [PMID: 21829024 DOI: 10.1159/000327570]

34 **Miyahara K**, Nouso K, Morimoto Y, Tomoda T, Kobayashi S, Takeuchi Y, Hagihara H, Kuwaki K, Ohnishi H, Ikeda F, Miyake Y, Nakamura S, Shiraha H, Takaki A, Yamamoto K. Evaluation of the effect of sorafenib using serum NX-des-γ-carboxyprothrombin in patients with hepatocellular carcinoma. *Hepatol Res* 2013; **43**: 1064-1070 [PMID: 23347420 DOI: 10.1111/hepr.12055]

35 **Cunningham D**, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, Bets D, Mueser M, Harstrick A, Verslype C, Chau I, Van Cutsem E. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004; **351**: 337-345 [PMID: 15269313]

36 **Van Cutsem E**, Köhne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, D'Haens G, Pintér T, Lim R, Bodoky G, Roh JK, Folprecht G, Ruff P, Stroh C, Tejpar S, Schlichting M, Nippgen J, Rougier P. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009; **360**: 1408-1417 [PMID: 19339720 DOI: 10.1056/NEJMoa0805019]

37 **Pérez-Soler R**, Chachoua A, Hammond LA, Rowinsky EK, Huberman M, Karp D, Rigas J, Clark GM, Santabárbara P, Bonomi P. Determinants of tumor response and survival with erlotinib in patients with non--small-cell lung cancer. *J Clin Oncol* 2004; **22**: 3238-3247 [PMID: 15310767]

38 **Soulieres D**, Senzer NN, Vokes EE, Hidalgo M, Agarwala SS, Siu LL. Multicenter phase II study of erlotinib, an oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with recurrent or metastatic squamous cell cancer of the head and neck. *J Clin Oncol* 2004; **22**: 77-85 [PMID: 14701768]

39 **Herbst RS**, Arquette M, Shin DM, Dicke K, Vokes EE, Azarnia N, Hong WK, Kies MS. Phase II multicenter study of the epidermal growth factor receptor antibody cetuximab and cisplatin for recurrent and refractory squamous cell carcinoma of the head and neck. *J Clin Oncol* 2005; **23**: 5578-5587 [PMID: 16009949]

40 **Gordon AN**, Finkler N, Edwards RP, Garcia AA, Crozier M, Irwin DH, Barrett E. Efficacy and safety of erlotinib HCl, an epidermal growth factor receptor (HER1/EGFR) tyrosine kinase inhibitor, in patients with advanced ovarian carcinoma: results from a phase II multicenter study. *Int J Gynecol Cancer* 2005; **15**: 785-792 [PMID: 16174225]

41 **Xiong HQ**, Rosenberg A, LoBuglio A, Schmidt W, Wolff RA, Deutsch J, Needle M, Abbruzzese JL. Cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor, in combination with gemcitabine for advanced pancreatic cancer: a multicenter phase II Trial. *J Clin Oncol* 2004; **22**: 2610-2616 [PMID: 15226328]

42 **Moore MJ**, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, Au HJ, Murawa P, Walde D, Wolff RA, Campos D, Lim R, Ding K, Clark G, Voskoglou-Nomikos T, Ptasynski M, Parulekar W. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 2007; **25**: 1960-1966 [PMID: 17452677]

43 **Scartozzi M**, Galizia E, Chiorrini S, Giampieri R, Berardi R, Pierantoni C, Cascinu S. Arterial hypertension correlates with clinical outcome in colorectal cancer patients treated with first-line bevacizumab. *Ann Oncol* 2009; **20**: 227-230 [PMID: 18842611 DOI: 10.1093/annonc/mdn637]

44 **Österlund P**, Soveri LM, Isoniemi H, Poussa T, Alanko T, Bono P. Hypertension and overall survival in metastatic colorectal cancer patients treated with bevacizumab-containing chemotherapy. *Br J Cancer* 2011; **104**: 599-604 [PMID: 21304526 DOI: 10.1038/bjc.2011.2]

45 **Spano JP**, Chodkiewicz C, Maurel J, Wong R, Wasan H, Barone C, Létourneau R, Bajetta E, Pithavala Y, Bycott P, Trask P, Liau K, Ricart AD, Kim S, Rixe O. Efficacy of gemcitabine plus axitinib compared with gemcitabine alone in patients with advanced pancreatic cancer: an open-label randomised phase II study. *Lancet* 2008; **371**: 2101-2108 [PMID: 18514303 DOI: 10.1016/S0140-6736(08)60661-3]

46 **Bono P**, Elfving H, Utriainen T, Osterlund P, Saarto T, Alanko T, Joensuu H. Hypertension and clinical benefit of bevacizumab in the treatment of advanced renal cell carcinoma. *Ann Oncol* 2009; **20**: 393-394 [PMID: 19211503 DOI: 10.1093/annonc/mdn729]

47 **Vincenzi B**, Santini D, Russo A, Addeo R, Giuliani F, Montella L, Rizzo S, Venditti O, Frezza AM, Caraglia M, Colucci G, Del Prete S, Tonini G. Early skin toxicity as a predictive factor for tumor control in hepatocellular carcinoma patients treated with sorafenib. *Oncologist* 2010; **15**: 85-92 [PMID: 20051477 DOI: 10.1634/theoncologist.2009-0143]

48 **Otsuka T**, Eguchi Y, Kawazoe S, Yanagita K, Ario K, Kitahara K, Kawasoe H, Kato H, Mizuta T; the Saga Liver Cancer Study Group. Skin toxicities and survival in advanced hepatocellular carcinoma patients treated with sorafenib. *Hepatol Res* 2012; **42**: 879-886 [PMID: 22469363 DOI: 10.1111/j.1872-034X.2012.00991.x]

49 **Estfan B**, Byrne M, Kim R. Sorafenib in advanced hepatocellular carcinoma: hypertension as a potential surrogate marker for efficacy. *Am J Clin Oncol* 2013; **36**: 319-324 [PMID: 22547010 DOI: 10.1097/COC.0b013e3182468039]

50 **Di Fiore F**, Rigal O, Ménager C, Michel P, Pfister C. Severe clinical toxicities are correlated with survival in patients with advanced renal cell carcinoma treated with sunitinib and sorafenib. *Br J Cancer* 2011; **105**: 1811-1813 [PMID: 22095228 DOI: 10.1038/bjc.2011.507]

51 **Ravaud A**, Sire M. Arterial hypertension and clinical benefit of sunitinib, sorafenib and bevacizumab in first and second-line treatment of metastatic renal cell cancer. *Ann Oncol* 2009; **20**: 966-97; author reply 967 [PMID: 19403939 DOI: 10.1093/annonc/mdp201]

52 **Anderson R**, Jatoi A, Robert C, Wood LS, Keating KN, Lacouture ME. Search for evidence-based approaches for the prevention and palliation of hand-foot skin reaction (HFSR) caused by the multikinase inhibitors (MKIs). *Oncologist* 2009; **14**: 291-302 [PMID: 19276294 DOI: 10.1634/theoncologist.2008-0237]

53 **Li X**, Feng GS, Zheng CS, Zhuo CK, Liu X. Expression of plasma vascular endothelial growth factor in patients with hepatocellular carcinoma and effect of transcatheter arterial chemoembolization therapy on plasma vascular endothelial growth factor level. *World J Gastroenterol* 2004; **10**: 2878-2882 [PMID: 15334691]

54 **Shim JH**, Park JW, Kim JH, An M, Kong SY, Nam BH, Choi JI, Kim HB, Lee WJ, Kim CM. Association between increment of serum VEGF level and prognosis after transcatheter arterial chemoembolization in hepatocellular carcinoma patients. *Cancer Sci* 2008; **99**: 2037-2044 [PMID: 19016764 DOI: 10.1111/j.1349-7006.2008.00909.x]

55 **Sergio A**, Cristofori C, Cardin R, Pivetta G, Ragazzi R, Baldan A, Girardi L, Cillo U, Burra P, Giacomin A, Farinati F. Transcatheter arterial chemoembolization (TACE) in hepatocellular carcinoma (HCC): the role of angiogenesis and invasiveness. *Am J Gastroenterol* 2008; **103**: 914-921 [PMID: 18177453 DOI: 10.1111/j.1572-0241.2007.01712.x]

56 **Pawlik TM**, Reyes DK, Cosgrove D, Kamel IR, Bhagat N, Geschwind JF. 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 DOI: 10.1200/JCO.2011.37.1021]

57 **Park JW**, Koh YH, Kim HB, Kim HY, An S, Choi JI, Woo SM, Nam BH. Phase II study of concurrent transarterial chemoembolization and sorafenib in patients with unresectable hepatocellular carcinoma. *J Hepatol* 2012; **56**: 1336-1342 [PMID: 22314421 DOI: 10.1016/j.jhep.2012.01.006]

58 **Lencioni R**, Llovet JM, Han G, Tak WY, Yang J, Leberre MA, Niu W, Nicholson K, Meinhardt G, Bruix J. Sorafenib or placebo in combination with transarterial chemoembolization (TACE) with doxorubicin-eluting beads (DEBDOX) for intermediate-stage hepatocellular carcinoma (HCC): Phase II, randomized, double-blind SPACE trial. *J Clin Oncol* 2012; suppl 4: abstr LBA154^

59 **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 [PMID: 21664811 DOI: 10.1016/j.ejca.2011.05.007]

60 **Miyahara K**, Nouso K, Morimoto Y, Takeuchi Y, Hagihara H, Kuwaki K, Onishi H, Ikeda F, Miyake Y, Nakamura S, Shiraha H, Takaki A, Iwadou S, Kobayashi Y, Takaguchi K, Takuma Y, Takabatake H, Sakaguchi K, Yamamoto K; the Okayama Liver Cancer Group. Efficacy of sorafenib beyond first progression in patients with metastatic hepatocellular carcinoma. *Hepatol Res* 2013; Epub ahead of print [PMID: 23607549 DOI: 10.1111/hepr.12123]

61 **Nakano M**, Tanaka M, Kuromatsu R, Nagamatsu H, Sakata K, Matsugaki S, Kajiwara M, Fukuizumi K, Tajiri N, Matsukuma N, Sakai T, Ono N, Yano Y, Koga H, Kurogi J, Takata A, Sumie S, Satani M, Yamada S, Niizeki T, Aino H, Iwamoto H, Torimura T, Sata M. Efficacy, safety, and survival factors for sorafenib treatment in Japanese patients with advanced hepatocellular carcinoma. *Oncology* 2013; **84**: 108-114 [PMID: 23147476 DOI: 10.1159/000342650]

62 **Okuda K**, Tanaka M, Shibata J, Ando E, Ogata T, Kinoshita H, Eriguchi N, Aoyagi S, Tanikawa K. Hepatic arterial infusion chemotherapy with continuous low dose administration of cisplatin and 5-fluorouracil for multiple recurrence of hepatocellular carcinoma after surgical treatment. *Oncol Rep* 1999; **6**: 587-591 [PMID: 10203596]

63 **Ando E**, Tanaka M, Yamashita F, Kuromatsu R, Yutani S, Fukumori K, Sumie S, Yano Y, Okuda K, Sata M. Hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis: analysis of 48 cases. *Cancer* 2002; **95**: 588-595 [PMID: 12209752]

64 **Yamasaki T**, Kimura T, Kurokawa F, Aoyama K, Ishikawa T, Tajima K, Yokoyama Y, Takami T, Omori K, Kawaguchi K, Tsuchiya M, Terai S, Sakaida I, Okita K. Prognostic factors in patients with advanced hepatocellular carcinoma receiving hepatic arterial infusion chemotherapy. *J Gastroenterol* 2005; **40**: 70-78 [PMID: 15692792]

65 **Kanayama M**, Nagai H, Sumino Y. Influence of the etiology of liver cirrhosis on the response to combined intra-arterial chemotherapy in patients with advanced hepatocellular carcinoma. *Cancer Chemother Pharmacol* 2009; **64**: 109-114 [PMID: 18979100 DOI: 10.1007/s00280-008-0851-2]

66 **Takaki-Hamabe S**, Yamasaki T, Saeki I, Harima Y, Okita K, Terai S, Sakaida I. Hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma: Is the addition of subcutaneous interferon-alpha-2b beneficial? *Hepatol Res* 2009; **39**: 223-230 [PMID: 19054152 DOI: 10.1111/j.1872-034X.2008.00458.x]

67 **Ueshima K**, Kudo M, Takita M, Nagai T, Tatsumi C, Ueda T, Kitai S, Ishikawa E, Yada N, Inoue T, Hagiwara S, Minami Y, Chung H. Hepatic arterial infusion chemotherapy using low-dose 5-fluorouracil and cisplatin for advanced hepatocellular carcinoma. *Oncology* 2010; **78** Suppl 1: 148-153 [PMID: 20616598 DOI: 10.1159/000315244]

68 **Niizeki T**, Sumie S, Torimura T, Kurogi J, Kuromatsu R, Iwamoto H, Aino H, Nakano M, Kawaguchi A, Kakuma T, Sata M. Serum vascular endothelial growth factor as a predictor of response and survival in patients with advanced hepatocellular carcinoma undergoing hepatic arterial infusion chemotherapy. *J Gastroenterol* 2012; **47**: 686-695 [PMID: 22382631 DOI: 10.1007/s00535-012-0555-6]

69 **Kaneko S**, Urabe T, Kobayashi K. Combination chemotherapy for advanced hepatocellular carcinoma complicated by major portal vein thrombosis. *Oncology* 2002; **62** Suppl 1: 69-73 [PMID: 11868789]

70 **Nagano H**. Treatment of advanced hepatocellular carcinoma: intraarterial infusion chemotherapy combined with interferon. *Oncology* 2010; **78** Suppl 1: 142-147 [PMID: 20616597 DOI: 10.1159/000315243]

71 **Enjoji M**, Morizono S, Kotoh K, Kohjima M, Miyagi Y, Yoshimoto T, Nakamuta M. Re-evaluation of antitumor effects of combination chemotherapy with interferon-alpha and 5-fluorouracil for advanced hepatocellular carcinoma. *World J Gastroenterol* 2005; **11**: 5685-5687 [PMID: 16237765]

72 **Obi S**, Yoshida H, Toune R, Unuma T, Kanda M, Sato S, Tateishi R, Teratani T, Shiina S, Omata M. Combination therapy of intraarterial 5-fluorouracil and systemic interferon-alpha for advanced hepatocellular carcinoma with portal venous invasion. *Cancer* 2006; **106**: 1990-1997 [PMID: 16565970]

73 **Uka K**, Aikata H, Takaki S, Kawaoka T, Saneto H, Miki D, Takahashi S, Toyota N, Ito K, Chayama K. Systemic gemcitabine combined with intra-arterial low-dose cisplatin and 5-fluorouracil for advanced hepatocellular carcinoma: seven cases. *World J Gastroenterol* 2008; **14**: 2602-2608 [PMID: 18442216]

74 **Eun JR**, Lee HJ, Moon HJ, Kim TN, Kim JW, Chang JC. Hepatic arterial infusion chemotherapy using high-dose 5-fluorouracil and cisplatin with or without interferon-alpha for the treatment of advanced hepatocellular carcinoma with portal vein tumor thrombosis. *Scand J Gastroenterol* 2009; **44**: 1477-1486 [PMID: 19958061 DOI: 10.3109/00365520903367262]

75 **Nagano H**, Wada H, Kobayashi S, Marubashi S, Eguchi H, Tanemura M, Tomimaru Y, Osuga K, Umeshita K, Doki Y, Mori M. Long-term outcome of combined interferon-α and 5-fluorouracil treatment for advanced hepatocellular carcinoma with major portal vein thrombosis. *Oncology* 2011; **80**: 63-69 [PMID: 21659784 DOI: 10.1159/000328281]

76 **Yamashita T**, Arai K, Sunagozaka H, Ueda T, Terashima T, Yamashita T, Mizukoshi E, Sakai A, Nakamoto Y, Honda M, Kaneko S. Randomized, phase II study comparing interferon combined with hepatic arterial infusion of fluorouracil plus cisplatin and fluorouracil alone in patients with advanced hepatocellular carcinoma. *Oncology* 2011; **81**: 281-290 [PMID: 22133996 DOI: 10.1159/000334439]

77 **Monden M**, Sakon M, Sakata Y, Ueda Y, Hashimura E; FAIT Research Group. 5-fluorouracil arterial infusion + interferon therapy for highly advanced hepatocellular carcinoma: A multicenter, randomized, phase II study. *Hepatol Res* 2012; **42**: 150-165 [PMID: 22044786 DOI: 10.1111/j.1872-034X.2011.00905.x]

78 **Yoshikawa M**, Ono N, Yodono H, Ichida T, Nakamura H. Phase II study of hepatic arterial infusion of a fine-powder formulation of cisplatin for advanced hepatocellular carcinoma. *Hepatol Res* 2008; **38**: 474-483 [PMID: 18430093 DOI: 10.1111/j.1872-034X.2008.00338.x]

79 **Kondo M**, Morimoto M, Numata K, Nozaki A, Tanaka K. Hepatic arterial infusion therapy with a fine powder formulation of cisplatin for advanced hepatocellular carcinoma with portal vein tumor thrombosis. *Jpn J Clin Oncol* 2011; **41**: 69-75 [PMID: 20688778 DOI: 10.1093/jjco/hyq145]

80 **Iwasa S**, Ikeda M, Okusaka T, Ueno H, Morizane C, Nakachi K, Mitsunaga S, Kondo S, Hagihara A, Shimizu S, Satake M, Arai Y. Transcatheter arterial infusion chemotherapy with a fine-powder formulation of cisplatin for advanced hepatocellular carcinoma refractory to transcatheter arterial chemoembolization. *Jpn J Clin Oncol* 2011; **41**: 770-775 [PMID: 21459893 DOI: 10.1093/jjco/hyr037]

81 **Kim BK**, Park JY, Choi HJ, Kim do Y, Ahn SH, Kim JK, Lee do Y, Lee KH, Han KH. Long-term clinical outcomes of hepatic arterial infusion chemotherapy with cisplatin with or without 5-fluorouracil in locally advanced hepatocellular carcinoma. *J Cancer Res Clin Oncol* 2011; **137**: 659-667 [PMID: 20552225 DOI: 10.1007/s00432-010-0917-5]

82 **Cheng A**, Kang Y, Lin D, Park J, Kudo M, Qin S, Omata M, Pitman Lowenthal SW, Lanzalone S, Yang L, Lechuga M, Raymond E, SUN1170 HCC Study Group. Phase III trial of sunitinib (Su) versus sorafenib (So) in advanced hepatocellular carcinoma (HCC). *J Clin Oncol* 2011; suppl; abstr 4000

83 **Zhu AX**, Rosmorduc O, Evans J, Ross P, Santoro A, Carrilho FJ, Leberre MA, Jensen M, Meinhardt G, Kang YK. SEARCH: a phase III, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with hepatocellular carcinoma (HCC). 2012 37th European Society of Medical Oncology Congress; Vienna, Austria. (abstr 917)

84 **Johnson PJ**, Qin S, Park JW, Poon RT, Raoul JL, Philip PA, Hsu CH, Hu TH, Heo J, Xu J, Lu L, Chao Y, Boucher E, Han KH, Paik SW, Robles-Aviña J, Kudo M, Yan L, Sobhonslidsuk A, Komov D, Decaens T, Tak WY, Jeng LB, Liu D, Ezzeddine 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 [PMID: 23980084 DOI: 10.1200/JCO.2012.48.4410]

85 **Llovet JM**, Decaens T, Raoul JL, Boucher E, Kudo M, Chang C, Kang YK, Assenat E, Lim HY, Boige V, Mathurin P, Fartoux L, Lin DY, Bruix J, Poon RT, Sherman M, Blanc JF, Finn RS, Tak WY, Chao Y, Ezzeddine 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 [PMID: 23980090 DOI: 10.1200/JCO.2012.47.3009]

86 **Cainap C**, Qin S, Huang WT, Chung IJ, Pan H, Cheng Y, Kudo M, Kang YK, Chen PJ, Toh HC, Gorbunova V, Eskens F, Qian J, McKee MD, Ricker JL, Carlson DM, El Nowiem S. Phase III trial of linifanib versus sorafenib in patients with advanced hepatocellular carcinoma (HCC). *J Clin Oncol* 2012; suppl 34: abstr 249

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, Cicalese L, Sherman M, Gridelli C, Buggisch P, Gerken G, Schmid RM, Boni C, Personeni N, Hassoun Z, Abbadessa 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 **Zhu AX**, Gold PJ, El-Khoueiry AB, Abrams TA, Morikawa H, Ohishi N, Ohtomo T, Philip PA. First-in-man phase I study of GC33, a novel recombinant humanized antibody against glypican-3, in patients with advanced hepatocellular carcinoma. *Clin Cancer Res* 2013; **19**: 920-928 [PMID: 23362325 DOI: 10.1158/1078-0432.CCR-12-2616]

89 **Lencioni R**, Kudo M, Ye SL, Bronowicki JP, Chen XP, Dagher L, Furuse J, Geschwind JF, Ladrón de Guevara L, Papandreou C, Takayama T, Yoon SK, Nakajima K, Lehr R, Heldner S, Sanyal AJ. GIDEON (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib): second interim analysis. *Int J Clin Pract* 2013; Epub ahead of print [PMID: 24283303 DOI: 10.1111/ijcp.12352]

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**Table 1 Overall survivals in sorafenib treatment**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Clinical trial** | **Sorafenib** | | |  | **Placebo** | | |  | ***P*** |
| ***n*** | **Median OS (mo)** | **95%CI** |  | ***n*** | **Median OS (mo)** | **95%CI** |  |
| SHARP[5] | 299 | 10.7 | 9.4–13.3 |  | 303 | 7.9 | 6.8–9.1 |  | < 0.001 |
| AP[6] | 150 | 6.5 | 5.56–7.56 |  | 76 | 4.2 | 3.75–5.46 |  | 0.014 |

CI: confidence interval; OS: overall survival; AP: Asia-Pacific.

**Table 2** **Biomarkers for predicting outcomes with sorafenib**

|  |  |  |  |
| --- | --- | --- | --- |
| **Ref.** | **Year** | **Obtained from** | **Biomarker** |
| [Llovet *et al*](http://www.ncbi.nlm.nih.gov/pubmed?term=Llovet%20JM%5BAuthor%5D&cauthor=true&cauthor_uid=22374331)[16] | 2012 | Plasma | HGF*,* c-KIT |
| Miyahara *et al*[17] | 2011 | Serum | Angiogenesis-related cytokines1 |
| Arao *et al*[18] | 2013 | Tissue | FGF3/FGF4 |
| Huang *et al*[19] | 2013 | Tissue | αB-Crystallin |
| Hagiwara *et al*[20] | 2012 | Tissue | JNK |
| Abou-Alfa *et al*[21] | 2006 | Tissue | pERK |
| Shan *et al*[25] | 2012 | Cell line | Nanog |
| Blivet-Van Eggelpoël *et al*[26] | 2012 | Cell line | EGFR, HER-3 |
| Chen *et al*[27] | 2012 | Cell line | SIRT1 |
| Tai *et al*[28] | 2011 | Cell line | STAT3 |
| Liu *et al*[4] | 2006 | Cell line | Mcl-1, eIF4E |

1These include angiopoietin-2, follistatin, granulocyte colony-stimulating factor, hepatocyte growth factor, leptin, platelet-derived growth factor-BB, platelet endothelial cell adhesion molecule-1, and vascular endothelial growth factor. HGF: hepatocyte growth factor; c-KIT: also known as SCFR (mast/stem cell growth factor receptor); FGF: fibroblast growth factors; JNK: c-Jun N-terminal kinase; pERK: phosphorylated extracellular signal regulated kinase; EGFR: epidermal growth factor receptor; HER-3: also known as ErbB3; STAT3: signal transducer and activator of transcription 3; Mcl-1: myeloid cell leukemia-1; eIF4E: eukaryotic translation initiation factor 4E.

**Table 3 Incidence of drug-related adverse events of sorafenib treatment**

|  |  |  |  |
| --- | --- | --- | --- |
| **Adverse event, %** | **SHARP[5]** | **AP[6]** | **GIDEON (second interim analysis)[89]** |
|  | **(*n* = 297)** | **(*n* = 149)** | **(*n* = 1571)** |
| Any adverse event | 80 | 82 | 64 |
| Diarrhea | 39 | 26 | 25 |
| Hand-foot skin reaction | 21 | 45 | 24 |
| Fatigue | 22 | 20 | 14 |
| Rash ⁄ desquamation | 16 | 20 | 12 |
| Anorexia | 14 | 13 | 9 |
| Hypertension | 5 | 19 | 7 |
| Alopecia | 14 | 25 | 7 |
| Nausea | 11 | 11 | 6 |
| Weight loss | 9 | NA1 | 5 |

1NA: not available; this adverse event was observed in < 10% of patients in AP trial. Incidence of all grades of adverse events was shown. Adverse events in ≥ 5% of the total population in GIDEON study were listed.

**Table 4** **Clinical trials for evaluating the effect of transcatheter arterial chemoembolization with sorafenib in intermediate stage of hepatocellular carcinoma**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Acronym**  **(NCT number)** | **Reported year** | **Trial phase** | **Study design** | ***n*** | **TACE** | **Outcomes** |
| Pawlik *et* *al*[56] | - | 2011 | II | single-arm (TACE plus sorafenib) | 33 | DEB/scheduled | Disease control rate = 100%, per lesion. Objective response = 58%, per lesion |
| Park *et al*[57] | - | 2012 | II | single-arm (TACE plus sorafenib) | 50 | conventional1/on demand | Median TTP = 7.1 mo  6-mo PFS rate = 52% |
| Kudo *et al*[59] | post TACE study | 2011 | III | TACE plus sorafenib *vs* TACE plus placebo | 458 | conventional1/1 or 2 sessions | Median TTP = 5.4 (Sorafenib)/3.7 (placebo) mo. HR [sorafenib] = 0.87; 95%CI: 0.70−1.09; *p* = 0.252 |
| Lencioni *et al*[58] | SPACE | 2012 | II | TACE plus sorafenib *vs* TACE plus placebo | 307 | DEB/scheduled | Median TTP = 169 (Sorafenib)/166 (placebo) d. HR [sorafenib] = 0.79; 95%CI: 0.588−1.080; *p* = 0.072 |
| Kudo *et al*2 | TACTICS (NCT01217034) | currently recruiting participants | II | TACE plus sorafenib *vs* TACE alone | 2283 | conventional1/on demand | Time To Untreatable Progression4 |
| Meyer *et al*2 | CRUK-TACE-2 (NCT01324076) | currently recruiting participants | III | TACE plus sorafenib *vs* TACE plus placebo | 4123 | DEB/1 session | PFS4 |
| Kauh *et al*2 | (NCT01004978) | currently recruiting participants | III | TACE plus sorafenib *vs* TACE plus placebo | 4003 | conventional1 or DEB/scheduled | PFS4 |

1Conventional TACE indicated transcatheter arterial chemoembolization with gelatin foam and lipiodol; 2The information of the trial can be accessed at ClinicalTrials.gov; 3Estimated Enrollment; 4Primary Outcome Measures. DBE: Drug-eluting beads; NCT: National clinical trial; PFS: Progression-free survival; TACE: Transcatheter arterial chemoembolization; TTP: time to progression.