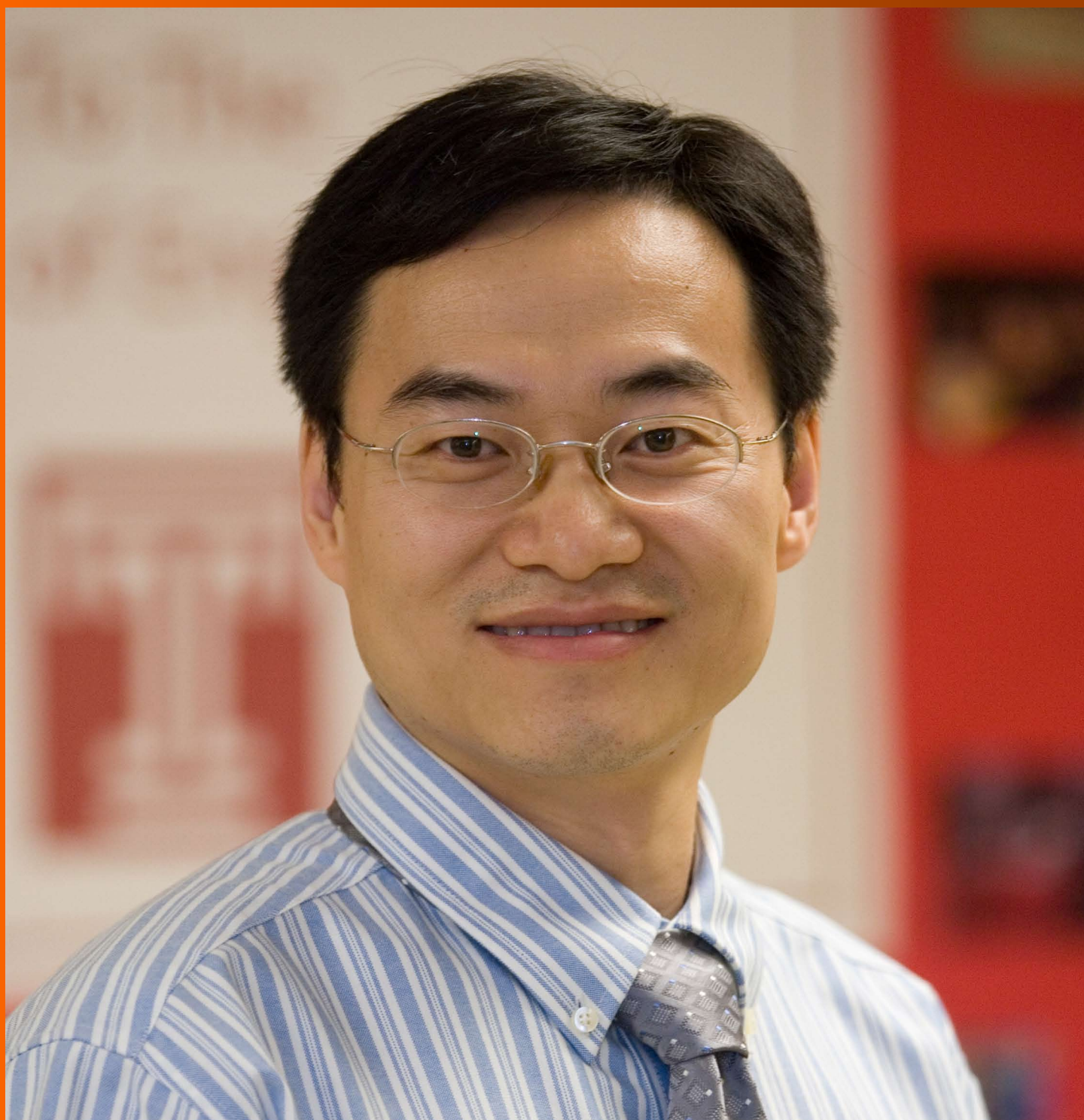


World Journal of *Clinical Oncology*

World J Clin Oncol 2017 June 10; 8(3): 178-304





REVIEW

- 178 Histone deacetylases, microRNA and leptin crosstalk in pancreatic cancer
Tchio Mantho CI, Harbuzariu A, Gonzalez-Perez RR
- 190 Multidisciplinary approach of colorectal cancer liver metastases
Fiorentini G, Sarti D, Aliberti C, Carandina R, Mambrini A, Guadagni S
- 203 Evolving role of Sorafenib in the management of hepatocellular carcinoma
Ziogas IA, Tsoulfas G
- 214 Magnetic resonance imaging for diagnosis and neoadjuvant treatment evaluation in locally advanced rectal cancer: A pictorial review
Engin G, Sharifov R

MINIREVIEWS

- 230 Immunotherapy in pancreatic cancer: Unleash its potential through novel combinations
Guo S, Contratto M, Miller G, Leichman L, Wu J
- 241 Current state and controversies in fertility preservation in women with breast cancer
Taylan E, Oktay KH
- 249 Biological mesh reconstruction of the pelvic floor following abdominoperineal excision for cancer: A review
Schiltz B, Buchs NC, Penna M, Scarpa CR, Liot E, Morel P, Ris F
- 255 Potential prognostic biomarkers in pancreatic juice of resectable pancreatic ductal adenocarcinoma
Agrawal S

ORIGINAL ARTICLE

Case Control Study

- 261 Levels of neutrophil gelatinase-associated lipocalin in patients with head and neck squamous cell carcinoma in Indian population from Haryana state
Verma M, Dahiya K, Soni A, Dhankhar R, Ghalaat VS, Bansal A, Kaushal V

SYSTEMATIC REVIEWS

- 266 Recurrence-free survival as a putative surrogate for overall survival in phase III trials of curative-intent treatment of colorectal liver metastases: Systematic review
Araujo RLC, Herman P, Riechelmann RP

META-ANALYSIS

- 273** Robot-assisted laparoscopic *vs* open gastrectomy for gastric cancer: Systematic review and meta-analysis
Caruso S, Patriti A, Roviello F, De Franco L, Franceschini F, Ceccarelli G, Coratti A

CASE REPORT

- 285** Bilateral diffuse grade 5 radiation pneumonitis after intensity modulated radiation therapy for localized lung cancer
Osborn VW, Leaf A, Lee A, Garay E, Safdieh J, Schwartz D, Schreiber D
- 289** Prostatic adenocarcinoma, oncocytic variant: Case report and literature review
Klaimont MM, Zafar N
- 293** Pancreatic neuroendocrine tumor Grade 1 patients followed up without surgery: Case series
Sugimoto M, Takagi T, Suzuki R, Konno N, Asama H, Watanabe K, Nakamura J, Kikuchi H, Waragai Y, Takasumi M, Kawana S, Hashimoto Y, Hikichi T, Ohira H
- 300** Target migration from re-inflation of adjacent atelectasis during lung stereotactic body radiotherapy
Mao B, Verma V, Zheng D, Zhu X, Bennion NR, Bhurud AR, Poole MA, Zhen W

Contents

World Journal of Clinical Oncology
Volume 8 Number 3 June 10, 2017

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Editorial Board Member of *World Journal of Clinical Oncology*, Bin Wang, PhD, Assistant Professor, Department of Biomedical Engineering, Widener University, Chester, PA 19013, United States

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INDEXING/ABSTRACTING

World Journal of Clinical Oncology is now indexed in PubMed, PubMed Central and Scopus.

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I-III Editorial Board

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NAME OF JOURNAL
World Journal of Clinical Oncology

ISSN
ISSN 2218-4333 (online)

LAUNCH DATE
November 10, 2010

FREQUENCY
Bimonthly

EDITOR-IN-CHIEF
Godefridus J Peters, PhD, Professor, Department of Medical Oncology, Cancer Center Amsterdam, VU University Medical Center, Amsterdam 1081 HV, Netherlands

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World Journal of Clinical Oncology
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
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PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive,
Suite 501, Pleasanton, CA 94588, USA
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PUBLICATION DATE
June 10, 2017

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ONLINE SUBMISSION

<http://www.f6publishing.com>

Evolving role of Sorafenib in the management of hepatocellular carcinoma

Ioannis A Ziogas, Georgios Tsoulfas

Ioannis A Ziogas, Aristotle University of Thessaloniki School of Medicine, 54124 Thessaloniki, Greece

Georgios Tsoulfas, 1st Department of Surgery, Aristotle University of Thessaloniki, 56403 Thessaloniki, Greece

Author contributions: Ziogas IA and Tsoulfas G contributed equally to this work.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

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Manuscript source: Invited manuscript

Correspondence to: Georgios Tsoulfas, MD, PhD, FACS, Assistant Professor of Surgery, 1st Department of Surgery, Aristotle University of Thessaloniki, 66 Tsimiski Street, 56403 Thessaloniki, Greece. tsoulfasg@gmail.com
Telephone: +30-6971-895190
Fax: +30-2310-332022

Received: January 28, 2017

Peer-review started: February 10, 2017

First decision: March 27, 2017

Revised: April 3, 2017

Accepted: April 23, 2017

Article in press: April 25, 2017

Published online: June 10, 2017

Abstract

Hepatocellular carcinoma (HCC) is one of the most common malignant diseases worldwide and comes third

in cancer-related mortality. Although there is a broad spectrum of treatment options to choose from, only a few patients are eligible candidates to receive a curative therapy according to their stage of disease, and thus palliative treatment is implemented in the majority of the patients suffering from liver cancer. Sorafenib, a multikinase inhibitor, is the only currently approved agent for systemic therapy in patients with advanced stage HCC and early stage liver disease. It has been shown to improve the overall survival, but with various side effects, while its cost is not negligible. Sorafenib has been in the market for a decade and has set the stage for personalized targeted therapy. Its role during this time has ranged from monotherapy to neoadjuvant and adjuvant treatment with surgical resection, liver transplantation and chemoembolization or even in combination with other chemotherapeutic agents. In this review our aim is to highlight in depth the current position of Sorafenib in the armamentarium against HCC and how that has evolved over time in its use either as a single agent or in combination with other therapies.

Key words: Sorafenib; Hepatocellular carcinoma; Liver neoplasm; Multikinase inhibitor; Targeted therapy; Tumor angiogenesis; Signaling pathways; Adjuvant therapy; Liver cancer; Liver transplantation; Liver resection

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Core tip: Hepatocellular carcinoma (HCC) is an aggressive and invasive malignancy. Curative options, such as resection and liver transplantation, are limited to only a few patients, who are suitable candidates. Sorafenib is the only approved systemic treatment in HCC, especially for advanced tumor stage and early stage liver disease. Recent findings suggest that it may also be helpful in carefully selected decompensated patients. Its adjuvant role is yet to be proven with more promising results. The combination of Sorafenib with other chemotherapy agents has shown improved efficacy and safety. We aim

to present the evolution of Sorafenib's use over the last decade.

Ziogas IA, Tsoulfas G. Evolving role of Sorafenib in the management of hepatocellular carcinoma. *World J Clin Oncol* 2017; 8(3): 203-213 Available from: URL: <http://www.wjgnet.com/2218-4333/full/v8/i3/203.htm> DOI: <http://dx.doi.org/10.5306/wjco.v8.i3.203>

INTRODUCTION

Hepatocellular carcinoma (HCC), the most common primary malignant neoplasm of the liver (85%-90%)^[1], is the sixth most frequent cancer in the world and the third cause of cancer-related^[2]. Cirrhosis is the stage of chronic liver disease characterized by disrupted architecture of the liver, therefore resulting in its dysfunction over the time. Regardless of the cause leading to cirrhosis, it is a major condition predisposing to a malignant transformation of the liver eventually leading to HCC^[3]. Nowadays, the incidence of HCC is increasing rapidly owing to the large number of people suffering from cirrhosis, mainly caused by hepatitis B and C virus infection, as well as due to longer survival among cirrhotic patients^[1].

Equally important to the presence and stage of cirrhosis, is the stage of the HCC, as any treatment that will follow will be in accordance to that. Specifically, surgical resection, ablation and liver transplantation are the only acceptable potentially curative options, but as it turns out, despite screening and frequent follow-ups, only 40%-60% of cirrhotic patients are diagnosed with very early or early stage HCC, therefore being eligible for curative treatment^[4,5]. Unfortunately, most patients are diagnosed with more advanced stage HCC, *i.e.*, portal vein invasion and/or extrahepatic spread or general symptoms attributed to cancer, unresponsive to such modalities. As a result alternative treatment combinations and algorithms including embolization, chemotherapy, radiotherapy, molecular target therapy or immunotherapy are constantly being generated in order to improve the overall survival (OS) of such patients^[4,6,7].

In particular, an aspect of systemic therapy tends to focus on an important characteristic of HCC, its angiogenesis, by developing antiangiogenic drugs that impede the formation of new blood vessels, thus inhibiting the proliferation and growth of the liver tumor^[8]. Sorafenib, an antiangiogenic drug, is the first and currently the only chemotherapeutic regimen approved as a palliative type of treatment in advanced stage HCC^[9]. This review describes the general characteristics of Sorafenib, its current place in the clinician's therapeutic armamentarium, as well as the clinical results of the evolving role of Sorafenib when combined or compared to other treatment modalities.

GENERAL PRINCIPLES

Molecular mechanisms

As stated above, HCC is a tumor with abundant vasculature and high heterogeneity, especially when it comes to the various signaling pathways involved^[10]. One of the key pathways involved in the growth and proliferation of HCC is the Raf/MEK/ERK mitogen-activated protein (MAP) kinase cascade, which shows particularly increased activity^[11]. This over-activation is mainly achieved by the combined action of hepatitis virus proteomics and growth factors, with platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) playing a critical role and highlighting the linkage between angiogenesis and HCC development^[12-14]. Sorafenib (Nexavar, BAY 43-9006), a biaryl urea, is an oral multikinase inhibitor of the serine/threonine-kinases (c-RAF and BRAF), therefore blocking the Raf/MEK/ERK pathway, and of the vascular endothelial growth factor receptor 2 (VEGFR2), VEGFR3, platelet-derived growth factor receptor (PDGFR), FLT3, Ret, and c-KIT^[15]. Moreover, it has been shown to result in apoptosis in various human tumor cell lines, independently of its involvement in the Raf/MEK/ERK pathway, by: (1) down-regulating an anti-apoptotic protein, the myeloid cell leukemia-1 (Mcl-1), member of the Bcl-2 family; and (2) inhibiting the phosphorylation of eukaryotic translation initiation factor 4E (eIF4E), which normally, when phosphorylated, promotes the expression of oncogenic genes^[16]. According to this rationale, Sorafenib is an effective drug against not only the tumor compartment, but also the formation of new vessels^[17,18]. Its mechanism of action is illustrated in Figure 1.

Sorafenib's history

This therapeutic action was firstly assessed in an uncontrolled phase 2 clinical trial of 137 patients with advanced and unresectable HCC, not having received any prior systemic therapy and with Child Pugh (CP) A or B cirrhosis^[19]. The dosage administered was 400 mg orally twice a day in 4-wk cycles with a partial response of 2.2%, a minor response of 5.8% and a 33.6% of the patients reporting non progressive disease for at least 16 wk. Some other major data reported were the 4.2-mo median time to progression (TTP) and the 9.2-mo OS, while CP A and B patients showed only negligible differences regarding the pharmacokinetics^[19].

Such positive results could not but be followed by the international phase 3, randomized, double-blind, placebo-controlled "Sorafenib HCC Assessment Randomized Protocol" (SHARP) clinical trial^[9]. For this purpose, 602 patients with advanced stage HCC, Eastern Cooperative Oncology Group (ECOG) performance status from 0 to 2, CP A liver disease and without any preceding systemic treatment, were randomized either for Sorafenib, same dosage as in phase 2, or for placebo. According to the data reported, Sorafenib resulted in a median OS of 10.7 mo vs the 7.9 mo of the placebo, as well as in a median

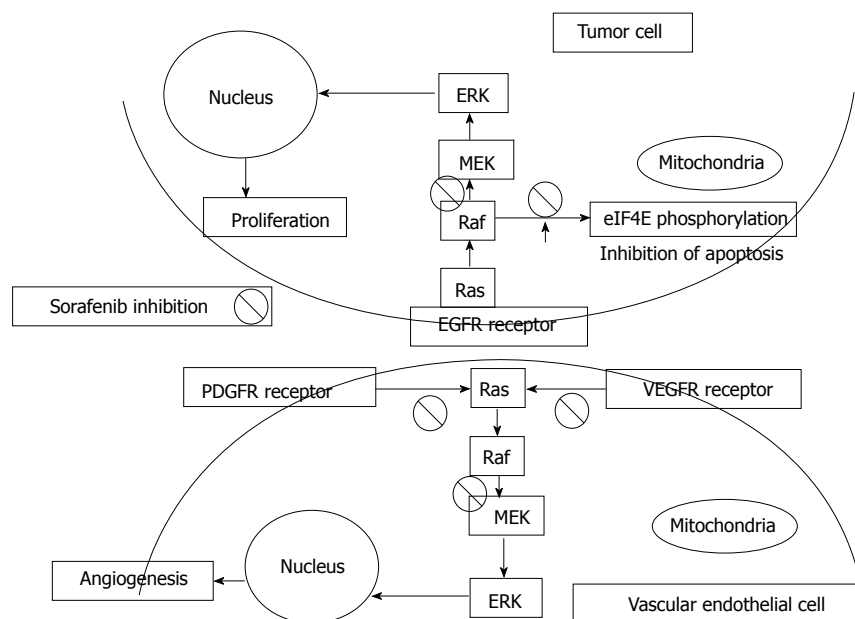


Figure 1 Sorafenib's mechanism of action. In tumor cells sorafenib blocks the Raf/MEK/ERK cascade and can lead to apoptosis through various mechanisms, such as inhibition of eukaryotic translation initiation factor 4E phosphorylation. In vascular endothelial cells, it inhibits receptor tyrosine kinases, such as VEGFR and PDGFR. PDGFR: Platelet-derived growth factor receptor; VEGFR: Vascular endothelial growth factor receptor.

TTP of 24 wk compared to 12 wk of the placebo. Also, although the median TTP based on radiologic findings was 5.5 mo in the Sorafenib arm compared to 2.8 mo in the placebo arm, there was again no complete response, while the partial response was limited^[9]. In spite of the positive clinical effects and the improvement in OS, Sorafenib was assessed within the frontiers of advanced stage HCC, but very early stage liver disease. This leads to many questions regarding its potential place in the treatment of patients with both advanced HCC and liver disease.

Adverse effects

On the other hand, nobody claimed that Sorafenib was harmless. The SHARP trial, as a phase 3 study, except for the effectiveness, also reported details about some possible adverse effects, which were more frequent in the Sorafenib group compared to the placebo one (80% vs 52%, respectively). The most commonly described toxicities were grade 1 and 2 regarding the severity, *i.e.*, weight loss, anorexia, diarrhea, changes in voice, hand-foot skin reaction, rash or desquamation and hair loss^[9]. Some of these toxicities led to drug discontinuation (Sorafenib 11% vs placebo 5%)^[9]. Another important study, the Sorafenib Italian Assessment (SOFIA) trial, showed that intervening by down-dosing at the appropriate time might be beneficial regarding an improved toxicity-tolerance rate and an increased OS^[20].

Moreover, significant findings from the routine clinical practice were presented by Sacco *et al.*^[21], who stated that when Sorafenib is administered early at a low dose, especially in patients characterized as high-risk, it may be easier to render the patients compliant to the continuation of the therapy and for the drug to be well-tolerated. As a

result, Sorafenib may induce some harmful events, mostly minor, which can be better tolerated by adjusting the dosage.

FOOD AND DRUG ADMINISTRATION APPROVAL

According to the European Association for the Study of the Liver (EASL) - European Organisation for Research and Treatment of Cancer (EORTC) guidelines (2012), Sorafenib is currently the only standard systemic treatment for HCC^[6]. Its use is approved since 2007 upon the publication of the results of two studies: (1) the SHARP trial^[9], conducted in the United States of America and Europe; and (2) the Sorafenib Asia-Pacific (Sorafenib-AP) trial^[22], conducted in South Korea, China and Taiwan, which both showed an increased OS and a reduced risk of mortality in patients treated with Sorafenib. However, the aforementioned guidelines^[6] highlight that Sorafenib is recommended only in patients with early stage liver disease - Child-Pugh A - and advanced stage HCC - Barcelona - Clinic Liver Cancer (BCLC) stage C - or as an adjuvant therapy combined with loco-regional treatment options. Sorafenib's current place in the treatment algorithm, in accordance with the BCLC staging system for HCC, is presented in Figure 2^[4,23].

MONOTHERAPY

As mentioned above, the results of systemic monotherapy with Sorafenib were encouraging according to a phase 2 trial^[19] and two phase 3 trials (SHARP^[9] and Sorafenib-AP^[22]). There was general agreement that Sorafenib has a great impact in increasing the OS, even though in the

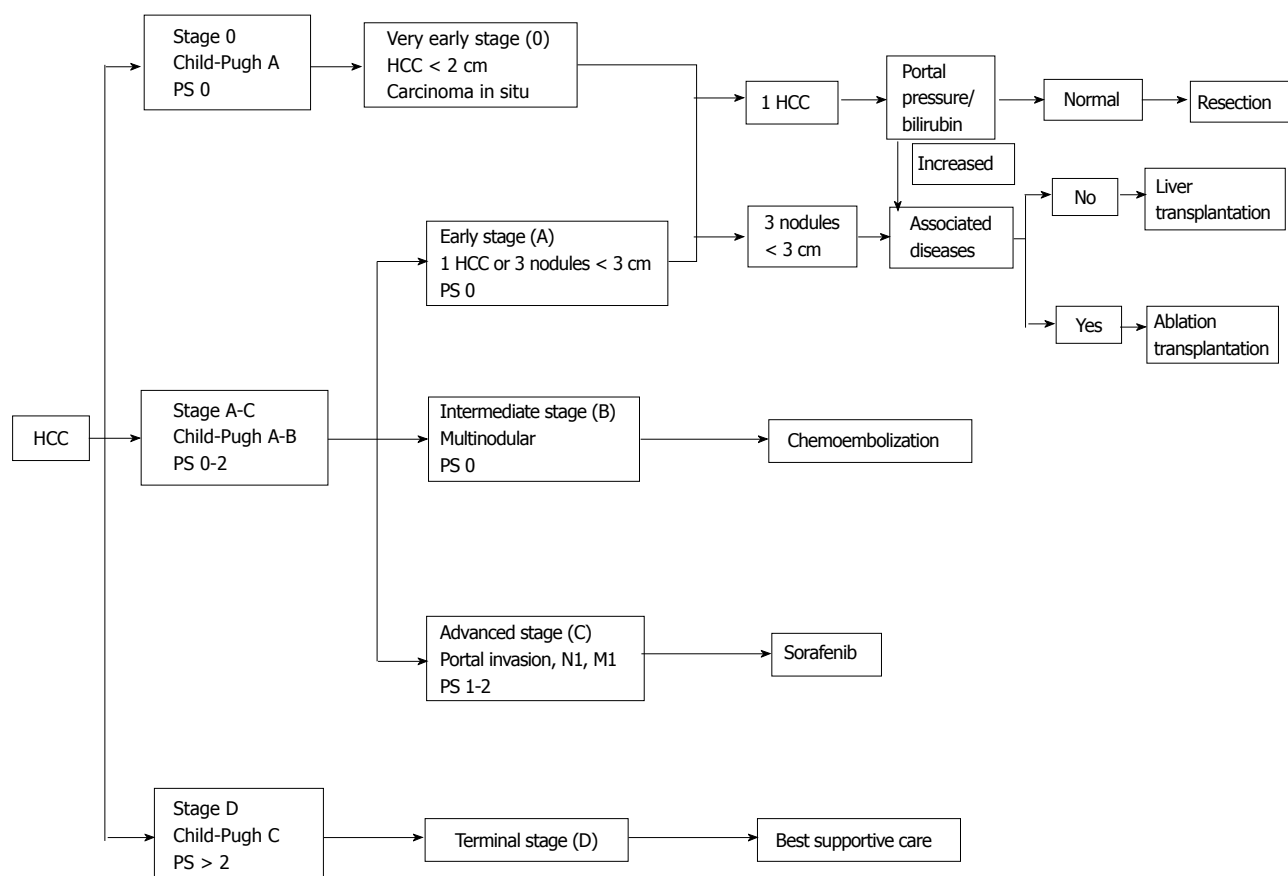


Figure 2 Barcelona clinic liver cancer staging system and treatment algorithm. PS: Performance status; N: Nodules; M: Metastases; HCC: Hepatocellular carcinoma.

phase 2 study 28% of the patients, who had CP B cirrhosis, showed a shorter median OS of 3.2 mo and could tolerate the treatment for only 1.8 mo. Also the incidence of ascites, encephalopathy and advanced hyperbilirubinemia is higher in advanced liver disease^[24]. Interestingly, a phase 1 study, assessing the use of Sorafenib in patients with higher Child-Pugh class, underlined its link with the dose-limiting rises in serum bilirubin concentration^[25]. Therefore, treatment guidelines^[7] recommend taking bilirubin into consideration when adjusting the dose of Sorafenib. In addition, a post-marketing trial (GIDEON)^[26] has shown equivalent results regarding safety and dosing strategy regardless of the Child-Pugh score. On the other hand, several studies evaluating the role of Sorafenib among the different stages of liver function reserve, reported a decreased response in advanced CP class, while liver-specific toxicities were independent of the liver cirrhosis stage^[27-29].

On the whole, a systematic review has shown that in a male elderly population with advanced HCC and CP A cirrhosis, Sorafenib monotherapy can yield a statistically significant, yet clinically insignificant, increase in OS, time to tumor progression and disease control rate^[30]. Besides, the cumulative data underline the decrease response of HBV-infected patients when compared to HCV, while patients with worse level of cirrhosis tend to display a more prominent Sorafenib-driven toxicity^[30].

A study published in 2017 analysing the SEER-

Medicare database, reported that elderly patients with advanced stage HCC may survive longer if treated with Sorafenib vs placebo (150.5 d vs 62 d, respectively), while the most remarkable factor associated with increased mortality was treatment taking place in an urban setting, although this survival effect was found to be neither prolonged, nor cost-effective in decompensated patients^[31]. Currently, a randomized controlled phase 3 study - the B Child Patient-Optimization of Sorafenib Treatment (BOOST) study - is ongoing so as to evaluate the safety and efficacy of Sorafenib in CP B patients and is going to provide helpful information regarding the treatment of patients with decompensated disease^[32]. However, reality is that for most patients Sorafenib is only one of the treatments that they receive, thus rendering it essential to review the adjuvant role of Sorafenib within the spectrum of other therapies.

SORAFENIB AND SURGICAL RESECTION

Currently, surgical resection remains the treatment of choice for HCC, when it is associated with solitary masses and the hepatic remnant can maintain liver function^[6]. Recently, there has been great interest concerning the down-staging of advanced HCC in order to make surgical resection even more efficient. One way to accomplish that is by taking advantage of Sorafenib's use as a

neoadjuvant treatment. In fact, a study has reported the incidence of Sorafenib-driven tumor necrosis, when used pre-operatively, therefore making resection an applicable treatment modality for a previously unresectable HCC tumor^[33]. Moreover, the use of Sorafenib before surgery was not found to lead to any intra- or post-operative side-effects^[34].

However, it is unclear whether Sorafenib could also be efficacious as an adjuvant therapy post-operatively. Specifically, a phase 3 study (STORM) evaluating its use after resection or ablation showed that Sorafenib is not superior to placebo when it comes to OS, recurrence-free survival or time to recurrence^[35]. Unfortunately, many patients enrolled in this study could not tolerate the standard dose used^[35]. These results are against incorporating Sorafenib in the guidelines as an appropriate adjuvant treatment option after resection^[6].

SORAFENIB AND LIVER TRANSPLANTATION

Another curative treatment, especially for patients within the Milan criteria is orthotopic liver transplantation^[36]. The challenges involved in liver transplantation, such as graft availability, have led to the increased use of grafts, including split grafts or those from living donors or from marginal donors. However, sometimes the delay between joining the waiting list and actually having a liver transplant may be quite significant, leading to patients dropping off the list^[37]. Consequently, those patients with HCC waiting for a liver donor for at least six months are recommended to receive the so called "bridging therapy", which mainly consists of locoregional treatment approaches, such as radiofrequency ablation (RFA) or transarterial chemoembolization (TACE)^[6]. The rationale of "bridging" is entirely understandable when trying to prevent tumor progression in cirrhotic patients with HCC, who patiently wait a suitable donor organ to become available. An alternative strategy is down-staging of HCC patients outside the Milan criteria, in an effort to make them eligible for transplantation. A legitimate question is whether Sorafenib has an adjuvant role in this endeavor.

This neoadjuvant use of Sorafenib for down-staging comes with little evidence not demonstrating any significant advantages, even though some cases seem to accomplish reduction in the tumor boarder, down-staging and therefore allowing the patient to be added to the waiting list^[38,39]. All-in-all, Sorafenib has shown a safe profile, when used before transplantation, with insignificant post-operative negative events^[40,41]. Besides, the Sorafenib-driven hypoxia, because of its antiangiogenic effects, is thought to result in alterations in molecular mechanisms and growth factors, thus allowing the tumor to develop resistance and become more invasive or even metastatic^[42]. Until more convincing data is reported from large clinical trials, the use of Sorafenib in this setting should be limited to investigational protocols.

On the other hand, the post-operative adjuvant

use of Sorafenib has proven to be inefficient (STORM trial)^[35], but when it comes to post-transplantation, results may be different. Specifically, a lot of studies agree with the fact that the use of Sorafenib, either concomitantly with mammalian target of rapamycin (mTOR) inhibitors or without them, can improve the survival when used for recurrent disease after liver transplantation, with the disadvantage of some drug-induced toxicity leading to a decrease in the dosage or even cessation of treatment^[43-50]. As a matter of fact, Sorafenib has also resulted in complete remission of recurrent HCC after liver transplantation^[51]. In general its use in this setting is thought to be safe^[52].

Alltogether, current evidence is not favorable regarding the adjuvant use of sorafenib either pre- or post-transplantation and more research on this particular topic needs to take place, especially in the form of randomized controlled trials^[53].

SORAFENIB AND LOCOREGIONAL THERAPIES

Current guidelines suggest the implementation of transarterial TACE in patients with intermediate stage HCC, consisting of multiple nodules, presenting without symptoms, invasion of the vessels or metastases and without advanced liver disease^[6]. Although TACE can be helpful and efficient in this particular group of patients by improving survival^[4], it is classified as a palliative option because it cannot achieve complete necrosis of the tumor and is associated with increased recurrent disease and tumor proliferation^[54]. This tumor growth is also promoted by the ischemic area appearing after treatment with TACE, and owes its existence to the overexpression of certain growth factors, with VEGF playing a major role^[55,56]. VEGF's place in this equation lies on the side of tumor progression and metastasis and thus Sorafenib can be the ideal agent to deal with this process and impede angiogenesis, while simultaneously supplementing the promising action of TACE by eliminating the possibilities of future proliferation or recurrence^[57].

Some phase 2 studies^[58,59] evaluating the concurrent use of TACE and Sorafenib in patients with HCC not amenable to resection have shown a fairly safe profile for this combination with encouraging results regarding the efficacy and toxicity. When this duet was compared to TACE plus placebo in intermediate stage HCC on the background of HCV infection, it greatly improved time to tumor progression, without any unforeseen adverse events^[60]. The comparison mentioned above was also assessed in a meta-analysis of six studies (1254 patients) reassuring that TACE plus sorafenib in either intermediate or advanced stage HCC patients can increase OS, time to tumor progression, as well as objective response rate, while the risk of side effects is also high^[61]. Other recent meta-analyses, however, evaluating the marriage of Sorafenib and TACE for unresectable HCC showed an improvement in time to tumor progression, but not in

OS^[62,63].

It should also be mentioned that Sorafenib has been assessed in combination with drug-eluting beads (DEB)-TACE, an alternative method of delivering regional chemotherapy with minimal systemic exposure, for the management of both intermediate and advanced stage HCC. The results proved the increased efficacy and safety of this strategy^[57].

Another important issue is that of the time of TACE and Sorafenib administration, for which three different options have been suggested: (1) TACE is followed by antiangiogenic therapy; (2) continuous antiangiogenic treatment interrupted only for the moment of TACE administration; and (3) continuous antiangiogenic therapy with no interruption at the moment of TACE administration^[64]. Although the first two options are superior regarding the risk of bleeding, which is reduced, the third eliminates the possibilities of VEGF increase after TACE.

In general, it appears that Sorafenib plus TACE can lead to improved clinical results, especially regarding the intermediate stage HCC, mainly consisting of a highly heterogeneous group of patients for whom the overall approach is still to be defined based on several ongoing studies^[57,65].

SORAFENIB AND OTHER CHEMOTHERAPEUTIC DRUGS

Sorafenib and hypoxia-inducible factor-1 α inhibitors

Locoregional treatment modalities can be efficient when it comes to HCC, but up to a point. Radiofrequency and microwave ablation trigger hypoxia and consequently hypoxia-induced angiogenesis, thus increasing the possibility of HCC recurrence. This process is primarily mediated by the hypoxia-inducible factor (HIF)-1 α /vascular endothelial growth factor-A (VEGF-A) pathway, which can be impeded by Sorafenib^[66]. Therefore, Sorafenib has been shown to limit the tumor's invasive nature *in vitro*, a result of the cobalt chloride's increase of the expression of HIF-1 α , and to reduce proliferation and promote apoptosis in HCC cells^[66].

2-Methoxyestradiol (2ME2), an inactive end product of estrogen metabolism, has recently been proven to have an antitumor effect by inhibiting proliferation and angiogenesis and by promoting apoptosis in many cancer types and especially in HCC^[67]. The most important mechanism 2ME2 acts is through the inhibition of HIF-1 and the down-regulation of the HIF-driven VEGF expression^[68]. It has been shown that 2ME2 comes up with synergistic effects in combination with Sorafenib in accordance to HCC suppression and antiangiogenesis, effects mostly driven by HIF-1 and -2 deregulation^[69].

Sorafenib and mTOR inhibitors

mTOR, a protein kinase, plays a key role in cell growth, proliferation, angiogenesis and metabolism in several cancers, including HCC^[70]. It represents the target of rapamycin and its analogues, as well as Everolimus

and Sirolimus, which present with an antitumor profile through the down-regulation of hypoxia-inducible factor, thus resulting in low VEGF and PDGF expression.

Everolimus has been evaluated in a phase 1/2 study in patients with advanced stage HCC, who were previously treated with systemic therapy, and has shown encouraging results in terms of tolerability and efficacy^[71]. However, when Everolimus was combined with Sorafenib, again in a phase 1 trial, so that its maximum tolerated dose (MTD) could be determined, the results were disappointing regarding its efficacy in the MTD^[72]. In addition, a randomized clinical trial (EVOLVE-1)^[73] assessing the use of Everolimus in patients with advanced HCC, who presented with tumor progression during or after taking Sorafenib or who showed limited tolerability towards Sorafenib, reported no increase in OS.

On the other hand, the significant immunosuppressive role of mTOR inhibitors has been used in combination with Sorafenib vs Sorafenib alone in cases of post-transplantation late recurrent HCC, thus highlighting the broadening of the horizons in the treatment options against HCC towards the direction of personalized molecular targeted therapy^[74]. Besides, cohort studies^[46,49] assessing the combination of Sorafenib and mTOR inhibitors in the same disease context showed improved survival, but with some serious adverse events.

As a result, it is suggested that further studies are carried out, so as to evaluate the combination of mTOR inhibitors with Sorafenib in terms of achieving the maximum possible synergy and the minimum possible toxicity overlap.

Sorafenib and PI3K/AKT inhibitors

Despite the blockade of the Raf/MEK/ERK cascade by Sorafenib, HCC has remarkable compensation through the over-expression of several other pro-survival pathways. The phosphoinositide 3-kinase (PI3K)/AKT pathway comes into play here as one of those and data state that it can render the tumor less susceptible to Sorafenib^[75]. Thus, synergy may result from the combination of Sorafenib with a PI3K/AKT inhibitor, such as PKI-587 which simultaneously blocks the mTOR pathway, and this significant additive inhibitory effect has been proven in liver cancer stem cell patterns^[76].

Sorafenib and WNT/ β -catenin inhibitors

The complexity of the molecular mechanisms involved in the multistep process of tumor growth in HCC has been shown to incorporate mutations in the Wnt/ β -catenin pathway as well^[77]. Therefore, it is possible that the Wnt/ β -catenin pathway represents a novel target for systemic treatment in HCC and as such it may also show an additive effect when used concurrently with Sorafenib. Indeed, not only has Sorafenib been able to down-regulate this pathway in different models^[78], but also FH535, a Wnt/ β -catenin inhibitor, was found to impede tumor growth of HCC and hepatoblastoma^[79,80]. Moreover, when Sorafenib was combined with FH535, their synergistic

effect on inhibiting the proliferation of HCC was more significant^[81,82].

Sorafenib and MEK inhibitors

The MAPK/ERK kinases (MEK) 1 and 2 can be consequently activated if a Ras mutation shows up, as they are found downstream in the RAS cascade, the activation of which can therefore provide proliferative and anti-apoptotic capabilities to the tumor. This “vertical” type of inhibition totally differs from the “parallel” blockade previously described in the mTOR inhibition, in which two unconnected cascades are concurrently inhibited^[83]. Interestingly, MEK inhibitors, such as Refametinib (BAY 869766) which is an allosteric MEK 1/2 inhibitor, have proven their efficacy in preclinical HCC models^[84]. When combined with Sorafenib in a phase 2 trial, Refametinib was found efficacious, especially in case of Ras mutations, and was well-tolerated^[85].

Sorafenib and JAK/STAT inhibitors

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway plays an important part as a signal transduction cascade, with several proteins of the STAT family participating in cell growth, immunity and survival^[86]. The one with the most significant role in oncogenesis is STAT3^[87]. This STAT3 protein is key in modulating sensitization of HCC in recombinant tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), an antitumor drug with encouraging efficacy^[88]. When Sorafenib was combined with TRAIL, it decreased the expression of STAT3 and proteins involved in its actions, thus rendering, the previously resistant to TRAIL, HCC susceptible to TRAIL-induced apoptosis^[88]. Besides, Sorafenib targets STAT3 in a kinase-independent manner in patients with HCC^[88,89].

In addition, the SH2 domain-containing tyrosine phosphatases family (SHP-1 and SHP-2), which are included in the family of protein tyrosine phosphatases (PTP), consist of two Src Homology (SH) 2 domains just as their name indicates^[90]. These phosphatases dephosphorylate STAT3, leading to a significant decrease in its activation^[91] and as a result they represent a potential target for systemic treatment of HCC. In fact, SHP-1 is a target of Sorafenib and through conformational modifications and signaling pathways, in which STAT3 is also involved, Sorafenib can also exhibit its anti-HCC effect^[92]. However, we have already experienced the evolution of Sorafenib through its derivatives, such as SC-43 and SC-40, which are potent SHP-1 agonists and have proven to be superior to Sorafenib for the management of HCC^[92]. Another novel derivative of Sorafenib, SC-59, when combined with radiotherapy has also shown to be superior to Sorafenib for treating HCC and its actions are mediated through STAT3 inhibition^[93]. Last but not least, the synergistic combination of Sorafenib with SC-43, through their SHP-1 agonist effects, has been found efficacious, as it decreased tumor size and improved survival in preclinical models^[94].

Sorafenib and phytochemicals

Data from preclinical models indicate that dietary phytochemicals with anti-inflammatory, antioxidant and anti-neoplastic characteristics may reduce the risk of HCC.

Curcumin is a yellow polyphenol derived from turmeric and has been shown to be protective against HCC caused by aflatoxins in mice^[95]. Due to its solubility issues, polymeric nanoparticle formations of curcumin (NFC) have been developed and it is reported that the use of NFC alone or in combination with Sorafenib presents with remarkable findings regarding the suppression of tumor proliferation and invasiveness of HCC, as well as that of lung metastases^[96].

Resveratrol is also a dietary polyphenol, mostly present in grapes, berries, peanuts and red wine, and has appeared as a promising chemopreventive agent against liver cancer^[97]. The combination of Resveratrol and Sorafenib can lead to apoptosis and reduced tumor growth in HCC mice by fighting the diverted metabolic phenotype of aerobic glycolysis^[98].

Indole-3-carbinol (I3C), found in cruciferous vegetables, is also one of the phytochemicals that have recently emerged with antineoplastic and antiangiogenic properties^[99]. Specifically, its combined use with sorafenib has shown synergy by increasing the latter's cytotoxicity and antiangiogenic properties, by promoting cell cycle arrest and apoptosis, as well as by reducing the expression of p-Akt, HIF-1 α , VEGF and EGFR in HCC cells^[99].

Regorafenib: A new era

Several antiangiogenic drugs with the same antiangiogenic capabilities as Sorafenib have been developed over time for the management of HCC, mostly as second-line systemic therapy agents.

In case of failure to respond to Sorafenib, patients with HCC can be treated with another multikinase inhibitor, Regorafenib^[100]. The addition of a fluorine atom in the central phenyl ring of Sorafenib transforms Regorafenib into an agent with increased potency^[101]. A phase 2 study evaluating Regorafenib for intermediate or advanced HCC in patients that had previously received Sorafenib reported encouraging results, such as an OS of 13.8 mo, a safety profile similar to Sorafenib and no deaths attributed to Regorafenib^[102]. Recently, in July 2016, at the ESMO World Congress on Gastrointestinal Cancer in Barcelona findings from a phase 3 trial (RESORCE, NCT01774344) assessing Regorafenib in HCC patients, who received prior therapy with Sorafenib, exhibited a remarkable increase in median OS for those treated with Regorafenib vs those receiving placebo as a second-line agent after radiologic progression under Sorafenib (10.6 vs 7.8)^[103].

Almost a decade has passed with numerous clinicians and scientists getting negative results in trials for systemic therapy in HCC patients, while the RESORCE trial is the only one after the SHARP trial to come forward with positive findings. The most important causes of those negative results are: (1) the heterogeneity among the

HCC patients recruited and the lack of selection criteria based on molecular patterns; and (2) the imbalance between adverse events and tolerable dosage vs anticancer efficiency and drug potency of the tested agents. Current advances in medicine and biology will improve our knowledge regarding the different and complex molecular mechanisms and driving mutations involved in this vast heterogeneity of this unique and multidimensional type of cancer and will guide us towards the right direction of conducting successful trials in the near future^[104].

CONCLUSION

Sorafenib represents a type of medicinal revolution, therefore making antiangiogenesis drugs a feasible choice when it comes to dealing with cancer and opening the road for personalized targeted therapy. Currently, Sorafenib is the only accepted treatment for systemic therapy, as it has shown to increase the OS in patients suffering from advanced HCC, but with liver disease of early stage with tolerable adverse effects. Recently, studies show that Sorafenib is also safe in patients with advanced liver disease as well, but neither adequately efficient, nor cost-effective. Thus, ongoing studies (*i.e.*, BOOST trial) are going to define its role in decompensated population in the future and up until then, patient selection in patients treated with Sorafenib is critical.

All-in-all, Sorafenib has evolved through time by being evaluated in several treatment protocols either as a neoadjuvant or as an adjuvant agent. Its use prior to or after liver transplantation has demonstrated a range of some minor advantages to even complete remission of recurrence, while preserving an acceptable safety profile. Still, a lot of research is needed in this field, as Sorafenib's role post-resection was not that much promising, while its combination with TACE showed encouraging results. Overall, understanding the molecular mechanisms of HCC and Sorafenib, as well as those resulting from the implementation of other treatment methods, will guide us to the future development of combinations involving Sorafenib, agents with higher efficacy that derive from Sorafenib or even second-line agents that will complement the therapeutic role that Sorafenib could not accomplish by itself.

REFERENCES

- 1 **El-Serag HB**, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology* 2007; **132**: 2557-2576 [PMID: 17570226 DOI: 10.1053/j.gastro.2007.04.061]
- 2 **Ursino S**, Greco C, Cartei F, Colosimo C, Stefanelli A, Cacopardo B, Berretta M, Fiorica F. Radiotherapy and hepatocellular carcinoma: update and review of the literature. *Eur Rev Med Pharmacol Sci* 2012; **16**: 1599-1604 [PMID: 23111978]
- 3 **Fattovich G**, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology* 2004; **127**: S35-S50 [PMID: 15508101 DOI: 10.1053/j.gastro.2004.09.014]
- 4 **Forner A**, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet* 2012; **379**: 1245-1255 [PMID: 22353262 DOI: 10.1016/S0140-6736(11)61347-0]
- 5 **Llovet JM**, Bruix J. Novel advancements in the management of hepatocellular carcinoma in 2008. *J Hepatol* 2008; **48** Suppl 1: S20-S37 [PMID: 18304676 DOI: 10.1016/j.jhep.2008.01.022]
- 6 **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]
- 7 **Kudo M**, Trevisani F, Abou-Alfa GK, Rimassa L. Hepatocellular Carcinoma: Therapeutic Guidelines and Medical Treatment. *Liver Cancer* 2016; **6**: 16-26 [PMID: 27995084 DOI: 10.1159/000449343]
- 8 **Taketomi A**. Clinical trials of antiangiogenic therapy for hepatocellular carcinoma. *Int J Clin Oncol* 2016; **21**: 213-218 [PMID: 26899258 DOI: 10.1007/s10147-016-0966-0]
- 9 **Llovet JM**, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378-390 [PMID: 18650514 DOI: 10.1056/NEJMoa0708857]
- 10 **Thorgeirsson SS**, Grisham JW. Molecular pathogenesis of human hepatocellular carcinoma. *Nat Genet* 2002; **31**: 339-346 [PMID: 12149612 DOI: 10.1038/ng0802-339]
- 11 **Calvisi DF**, Ladu S, Gorden A, Farina M, Conner EA, Lee JS, Factor VM, Thorgeirsson SS. Ubiquitous activation of Ras and Jak/Stat pathways in human HCC. *Gastroenterology* 2006; **130**: 1117-1128 [PMID: 16618406 DOI: 10.1053/j.gastro.2006.01.006]
- 12 **Stöckl L**, Berting A, Malkowski B, Foerster R, Hofschneider PH, Hildt E. Integrity of c-Raf-1/MEK signal transduction cascade is essential for hepatitis B virus gene expression. *Oncogene* 2003; **22**: 2604-2610 [PMID: 12730674 DOI: 10.1038/sj.onc.1206320]
- 13 **Giambartolomei S**, Covone F, Levrero M, Balsano C. Sustained activation of the Raf/MEK/Erk pathway in response to EGF in stable cell lines expressing the Hepatitis C Virus (HCV) core protein. *Oncogene* 2001; **20**: 2606-2610 [PMID: 11420671 DOI: 10.1038/sj.onc.1204372]
- 14 **Gjollb JA**, Wilhelm S, Carter C, Kelley SL. Role of Raf kinase in cancer: therapeutic potential of targeting the Raf/MEK/ERK signal transduction pathway. *Semin Oncol* 2006; **33**: 392-406 [PMID: 16890795 DOI: 10.1053/j.seminoncol.2006.04.002]
- 15 **Wilhelm SM**, Carter C, Tang L, Winkie 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 DOI: 10.1158/0008-5472.CAN-04-1443]
- 16 **Rahmani M**, Davis EM, Bauer C, Dent P, Grant S. Apoptosis induced by the kinase inhibitor BAY 43-9006 in human leukemia cells involves down-regulation of Mcl-1 through inhibition of translation. *J Biol Chem* 2005; **280**: 35217-35227 [PMID: 16109713 DOI: 10.1074/jbc.M506551200]
- 17 **Liu L**, Cao Y, Chen C, Zhang X, McNabola A, Winkie 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 DOI: 10.1158/0008-5472.CAN-06-1377]
- 18 **Villanueva A**, Newell P, Chiang DY, Friedman SL, Llovet JM. Genomics and signaling pathways in hepatocellular carcinoma. *Semin Liver Dis* 2007; **27**: 55-76 [PMID: 17295177 DOI: 10.1055/s-2006-960171]
- 19 **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 DOI: 10.1200/JCO.2005.01.3441]
- 20 **Iavarone M**, Cabibbo G, Piscaglia F, Zavaglia C, Grieco A, Villa E, Cammà C, Colombo M. Field-practice study of sorafenib therapy for

- hepatocellular carcinoma: a prospective multicenter study in Italy. *Hepatology* 2011; **54**: 2055-2063 [PMID: 21898496 DOI: 10.1002/hep.24644]
- 21 **Sacco R**, Bargellini I, Ginanni B, Bertini M, Faggioni L, Federici G, Romano A, Bertoni M, Metrangola S, Altomare E, Parisi G, Tumino E, Scaramuzzino A, Bresci G, Bartolozzi C. Long-term results of sorafenib in advanced-stage hepatocellular carcinoma: what can we learn from routine clinical practice? *Expert Rev Anticancer Ther* 2012; **12**: 869-875 [PMID: 22845401 DOI: 10.1586/era.12.58]
 - 22 **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]
 - 23 **Bruix J**, Gores GJ, Mazzaferro V. Hepatocellular carcinoma: clinical frontiers and perspectives. *Gut* 2014; **63**: 844-855 [PMID: 24531850 DOI: 10.1136/gutjnl-2013-306627]
 - 24 **Abou-Alfa GK**, Amadori D, Santoro A, Figer A, De Greve J, Lathia C, Voliotis D, Anderson S, Moscovici M, Ricci S. Safety and Efficacy of Sorafenib in Patients with Hepatocellular Carcinoma (HCC) and Child-Pugh A versus B Cirrhosis. *Gastrointest Cancer Res* 2011; **4**: 40-44 [PMID: 21673874]
 - 25 **Miller AA**, Murry DJ, Owzar K, Hollis DR, Kennedy EB, Abou-Alfa G, Desai A, Hwang J, Villalona-Calero MA, Dees EC, Lewis LD, Fakih MG, Edelman MJ, Millard F, Frank RC, Hohl RJ, Ratain MJ. Phase I and pharmacokinetic study of sorafenib in patients with hepatic or renal dysfunction: CALGB 60301. *J Clin Oncol* 2009; **27**: 1800-1805 [PMID: 19255312 DOI: 10.1200/JCO.2008.20.0931]
 - 26 **Lencioni R**, Kudo M, Ye SL, Bronowicki JP, Chen XP, Dagher L, Furuse J, Geschwind JF, de Guevara LL, 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* 2014; **68**: 609-617 [PMID: 24283303 DOI: 10.1111/ijcp.12352]
 - 27 **Pressiani T**, Boni C, Rimassa L, Labianca R, Fagioli S, Salvagni S, Ferrari D, Cortesi E, Porta C, Mucciarini C, Latini L, Camaghi C, Banzi M, Fanello S, De Giorgio M, Lutman FR, Torzilli G, Tommasini MA, Ceriani R, Covini G, Tronconi MC, Giordano L, Locupo N, Naimo S, Santoro A. Sorafenib in patients with Child-Pugh class A and B advanced hepatocellular carcinoma: a prospective feasibility analysis. *Ann Oncol* 2013; **24**: 406-411 [PMID: 23041587 DOI: 10.1093/annonc/mds343]
 - 28 **Hollebecque A**, Cattan S, Romano O, Sergent G, Mourad A, Louvet A, Dharancy S, Boleslawski E, Truant S, Pruvot FR, Hebbat M, Ernst O, Mathurin P. Safety and efficacy of sorafenib in hepatocellular carcinoma: the impact of the Child-Pugh score. *Aliment Pharmacol Ther* 2011; **34**: 1193-1201 [PMID: 21958438 DOI: 10.1111/j.1365-2036.2011.04860.x]
 - 29 **Pinter M**, Sieghart W, Graziadei I, Vogel W, Maieron A, Königsberg R, Weissmann A, Kornek G, Plank C, Peck-Radosavljevic M. Sorafenib in unresectable hepatocellular carcinoma from mild to advanced stage liver cirrhosis. *Oncologist* 2009; **14**: 70-76 [PMID: 19144684 DOI: 10.1634/theoncologist.2008-0191]
 - 30 **Xie B**, Wang DH, Spechler SJ. Sorafenib for treatment of hepatocellular carcinoma: a systematic review. *Dig Dis Sci* 2012; **57**: 1122-1129 [PMID: 22451120 DOI: 10.1007/s10620-012-2136-1]
 - 31 **Parikh ND**, Marshall VD, Singal AG, Nathan H, Lok AS, Balkrishnan R, Shahinian V. Survival and cost-effectiveness of sorafenib therapy in advanced hepatocellular carcinoma: An analysis of the SEER-Medicare database. *Hepatology* 2017; **65**: 122-133 [PMID: 27770556 DOI: 10.1002/hep.28881]
 - 32 **National Cancer Institute, Naples**. Sorafenib in First-line Treatment of Advanced B Child Hepatocellular Carcinoma (BOOST). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: <https://clinicaltrials.gov/ct2/show/NCT01405573>
 - 33 **Irtan S**, Chopin-Laly X, Ronot M, Faivre S, Paradis V, Belghiti J. Complete regression of locally advanced hepatocellular carcinoma induced by sorafenib allowing curative resection. *Liver Int* 2011; **31**: 740-743 [PMID: 21457447 DOI: 10.1111/j.1478-3231.2010.02441.x]
 - 34 **Barbier L**, Fuks D, Pessaux P, Muscarel F, Le Treut YP, Faivre S, Belghiti J. Safety of liver resection for hepatocellular carcinoma after sorafenib therapy: a multicenter case-matched study. *Ann Surg Oncol* 2013; **20**: 3603-3609 [PMID: 23715965 DOI: 10.1245/s10434-013-3029-z]
 - 35 **Bruix J**, Takayama T, Mazzaferro V, Chau GY, Yang J, Kudo M, Cai J, Poon RT, Han KH, Tak WY, Lee HC, Song T, Roayaie S, Bolondi L, Lee KS, Makuuchi M, Souza F, Berre MA, Meinhardt G, Llovet JM. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2015; **16**: 1344-1354 [PMID: 26361969 DOI: 10.1016/S1470-2045(15)00198-9]
 - 36 **Mazzaferro V**, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693-699 [PMID: 8594428 DOI: 10.1056/NEJM199603143341104]
 - 37 **Freeman RB**, Edwards EB, Harper AM. Waiting list removal rates among patients with chronic and malignant liver diseases. *Am J Transplant* 2006; **6**: 1416-1421 [PMID: 16686765 DOI: 10.1111/j.1600-6143.2006.01321.x]
 - 38 **Vagefi PA**, Hirose R. Downstaging of hepatocellular carcinoma prior to liver transplant: is there a role for adjuvant sorafenib in locoregional therapy? *J Gastrointest Cancer* 2010; **41**: 217-220 [PMID: 20443078 DOI: 10.1007/s12029-010-9163-y]
 - 39 **Golse N**, Radenne S, Rode A, Ducerf C, Mabrut JY, Merle P. Liver Transplantation After Neoadjuvant Sorafenib Therapy: Preliminary Experience and Literature Review. *Exp Clin Transplant* 2016 May 17; Epub ahead of print [PMID: 27212671 DOI: 10.6002/ect.2015.0299]
 - 40 **Frenette CT**, Boktour M, Burroughs SG, Kaseb A, Aloia TA, Galati J, Gaber AO, Monsour H, Ghobrial RM. Pre-transplant utilization of sorafenib is not associated with increased complications after liver transplantation. *Transpl Int* 2013; **26**: 734-739 [PMID: 23701126 DOI: 10.1111/tri.12117]
 - 41 **Saidi RF**, Shah SA, Rawson AP, Grossman S, Piperdi B, Bozorgzadeh A. Treating hepatocellular carcinoma with sorafenib in liver transplant patients: an initial experience. *Transplant Proc* 2010; **42**: 4582-4584 [PMID: 21168742 DOI: 10.1016/j.transproceed.2010.09.147]
 - 42 **Bergers G**, Hanahan D. Modes of resistance to anti-angiogenic therapy. *Nat Rev Cancer* 2008; **8**: 592-603 [PMID: 18650835 DOI: 10.1038/nrc2442]
 - 43 **Sposito C**, Mariani L, Germini A, Flores Reyes M, Bongini M, Grossi G, Bhoori S, Mazzaferro V. Comparative efficacy of sorafenib versus best supportive care in recurrent hepatocellular carcinoma after liver transplantation: a case-control study. *J Hepatol* 2013; **59**: 59-66 [PMID: 23500153 DOI: 10.1016/j.jhep.2013.02.026]
 - 44 **Waghray A**, Balci B, El-Gazzaz G, Kim R, Pelley R, Narayanan Menon KV, Estfan B, Romero-Marrero C, Aucejo F. Safety and efficacy of sorafenib for the treatment of recurrent hepatocellular carcinoma after liver transplantation. *Clin Transplant* 2013; **27**: 555-561 [PMID: 23758296 DOI: 10.1111/ctr.12150]
 - 45 **Zavaglia C**, Airola A, Mancuso A, Vangeli M, Viganò R, Cordone G, Gentiluomo M, Belli LS. Adverse events affect sorafenib efficacy in patients with recurrent hepatocellular carcinoma after liver transplantation: experience at a single center and review of the literature. *Eur J Gastroenterol Hepatol* 2013; **25**: 180-186 [PMID: 23044808 DOI: 10.1097/MEG.0b013e328359e550]
 - 46 **Gomez-Martin C**, Bustamante J, Castroagudin JF, Salcedo M, Garralda E, Testillano M, Herrero I, Matilla A, Sangro B. Efficacy and safety of sorafenib in combination with mammalian target of rapamycin inhibitors for recurrent hepatocellular carcinoma after liver transplantation. *Liver Transpl* 2012; **18**: 45-52 [PMID: 21932373 DOI: 10.1002/lt.22434]
 - 47 **Kim R**, El-Gazzaz G, Tan A, Elson P, Byrne M, Chang YD, Aucejo F. Safety and feasibility of using sorafenib in recurrent hepatocellular carcinoma after orthotopic liver transplantation. *Oncology* 2010; **79**: 62-66 [PMID: 21071991 DOI: 10.1159/000319548]
 - 48 **Yoon DH**, Ryoo BY, Ryu MH, Lee SG, Hwang S, Suh DJ, Lee HC, Kim TW, Ahn CS, Kim KH, Moon DB, Kang YK. Sorafenib for

- recurrent hepatocellular carcinoma after liver transplantation. *Jpn J Clin Oncol* 2010; **40**: 768-773 [PMID: 20494947 DOI: 10.1093/jcco/hyq055]
- 49 **Stauffer K**, Fischer L, Seegers B, Vettorazzi E, Nashan B, Sterneck M. High toxicity of sorafenib for recurrent hepatocellular carcinoma after liver transplantation. *Transpl Int* 2012; **25**: 1158-1164 [PMID: 22882364 DOI: 10.1111/j.1432-2277.2012.01540.x]
- 50 **de'Angelis N**, Landi F, Nencioni M, Palen A, Lahat E, Salloum C, Compagnon P, Lim C, Costentin C, Calderaro J, Luciani A, Feray C, Azoulay D. Role of Sorafenib in Patients With Recurrent Hepatocellular Carcinoma After Liver Transplantation. *Prog Transplant* 2016 [PMID: 27555074 DOI: 10.1177/1526924816664083]
- 51 **Lee HY**, Yang KH, Choi BH, Park YM, Yoon KT, Ryu JH, Chu CW. Complete Regression of Recurrent Advanced Hepatocellular Carcinoma After Liver Transplantation in Response to Sorafenib Treatment: A Case Report. *Transplant Proc* 2016; **48**: 247-250 [PMID: 26915876 DOI: 10.1016/j.transproceed.2015.11.012]
- 52 **Vitale A**, Boccagni P, Kertusha X, Zanusi G, D'Amico F, Lodo E, Pastorelli D, Ramirez Morales R, Lombardi G, Senzolo M, Burra P, Cillo U. Sorafenib for the treatment of recurrent hepatocellular carcinoma after liver transplantation? *Transplant Proc* 2012; **44**: 1989-1991 [PMID: 22974889 DOI: 10.1016/j.transproceed.2012.06.046]
- 53 **Castelli G**, Burra P, Giacomini A, Vitale A, Senzolo M, Cillo U, Farinati F. Sorafenib use in the transplant setting. *Liver Transpl* 2014; **20**: 1021-1028 [PMID: 24809799 DOI: 10.1002/lt.23911]
- 54 **Alba E**, Valls C, Dominguez J, Martinez L, Escalante E, Lladó L, Serrano T. Transcatheter arterial chemoembolization in patients with hepatocellular carcinoma on the waiting list for orthotopic liver transplantation. *AJR Am J Roentgenol* 2008; **190**: 1341-1348 [PMID: 18430853 DOI: 10.2214/AJR.07.2972]
- 55 **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 DOI: 10.3748/wjg.v10.i19.2878]
- 56 **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]
- 57 **Cabibbo G**, Tremosini S, Galati G, Mazza G, Gadaleta-Caldarola G, Lombardi G, Antonucci M, Sacco R. Transarterial chemoembolization and sorafenib in hepatocellular carcinoma. *Expert Rev Anticancer Ther* 2014; **14**: 831-845 [PMID: 24850249 DOI: 10.1586/14737140.2014.920694]
- 58 **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]
- 59 **Chung YH**, Han G, Yoon JH, Yang J, Wang J, Shao GL, Kim BI, Lee TY, Chao Y. Interim analysis of START: Study in Asia of the combination of TACE (transcatheter arterial chemoembolization) with sorafenib in patients with hepatocellular carcinoma trial. *Int J Cancer* 2013; **132**: 2448-2458 [PMID: 23129123 DOI: 10.1002/ijc.27925]
- 60 **Sansonno D**, Lauletta G, Russi S, Contedduca V, Sansonno L, Dammacco F. Transarterial chemoembolization plus sorafenib: a sequential therapeutic scheme for HCV-related intermediate-stage hepatocellular carcinoma: a randomized clinical trial. *Oncologist* 2012; **17**: 359-366 [PMID: 22334456 DOI: 10.1634/theoncologist.2011-0313]
- 61 **Zhang L**, Hu P, Chen X, Bie P. Transarterial chemoembolization (TACE) plus sorafenib versus TACE for intermediate or advanced stage hepatocellular carcinoma: a meta-analysis. *PLoS One* 2014; **9**: e100305 [PMID: 24945380 DOI: 10.1371/journal.pone.0100305]
- 62 **Liu L**, Chen H, Wang M, Zhao Y, Cai G, Qi X, Han G. Combination therapy of sorafenib and TACE for unresectable HCC: a systematic review and meta-analysis. *PLoS One* 2014; **9**: e91124 [PMID: 24651044 DOI: 10.1371/journal.pone.0091124]
- 63 **Wang G**, Liu Y, Zhou SF, Qiu P, Xu L, Wen P, Wen J, Xiao X. Sorafenib combined with transarterial chemoembolization in patients with hepatocellular carcinoma: a meta-analysis and systematic review. *Hepatol Int* 2016; **10**: 501-510 [PMID: 26856326 DOI: 10.1007/s12072-015-9700-7]
- 64 **Strebel BM**, Dufour JF. Combined approach to hepatocellular carcinoma: a new treatment concept for nonresectable disease. *Expert Rev Anticancer Ther* 2008; **8**: 1743-1749 [PMID: 18983234 DOI: 10.1586/14737140.8.11.1743]
- 65 **Montella L**, Palmieri G, Addeo R, Del Prete S. Hepatocellular carcinoma: Will novel targeted drugs really impact the next future? *World J Gastroenterol* 2016; **22**: 6114-6126 [PMID: 27468204 DOI: 10.3748/wjg.v22.i27.6114]
- 66 **Xu M**, Zheng YL, Xie XY, Liang JY, Pan FS, Zheng SG, Lü MD. Sorafenib blocks the HIF-1 α /VEGFA pathway, inhibits tumor invasion, and induces apoptosis in hepatoma cells. *DNA Cell Biol* 2014; **33**: 275-281 [PMID: 24611881 DOI: 10.1089/dna.2013.2184]
- 67 **El Naga RN**, El-Demerdash E, Youssef SS, Abdel-Naim AB, El-Merzabani M. Cytotoxic effects of 2-methoxyestradiol in the hepatocellular carcinoma cell line HepG2. *Pharmacology* 2009; **84**: 9-16 [PMID: 19478548 DOI: 10.1159/000221062]
- 68 **Mabjeesh NJ**, Escuin D, LaVallee TM, Pribluda VS, Swartz GM, Johnson MS, Willard MT, Zhong H, Simons JW, Giannakakou P. 2ME2 inhibits tumor growth and angiogenesis by disrupting microtubules and dysregulating HIF. *Cancer Cell* 2003; **3**: 363-375 [PMID: 12726862 DOI: 10.1016/S1535-6108(03)00077-1]
- 69 **Ma L**, Li G, Zhu H, Dong X, Zhao D, Jiang X, Li J, Qiao H, Ni S, Sun X. 2-Methoxyestradiol synergizes with sorafenib to suppress hepatocellular carcinoma by simultaneously dysregulating hypoxia-inducible factor-1 and -2. *Cancer Lett* 2014; **355**: 96-105 [PMID: 25218350 DOI: 10.1016/j.canlet.2014.09.011]
- 70 **Shaw RJ**, Cantley LC. Ras, PI(3)K and mTOR signalling controls tumour cell growth. *Nature* 2006; **441**: 424-430 [PMID: 16724053 DOI: 10.1038/nature04869]
- 71 **Zhu AX**, Abrams TA, Miksad R, Blaszkowsky LS, Meyerhardt JA, Zheng H, Muzikansky A, Clark JW, Kwak EL, Schrag D, Jors KR, Fuchs CS, Iafrate AJ, Borger DR, Ryan DP. Phase 1/2 study of everolimus in advanced hepatocellular carcinoma. *Cancer* 2011; **117**: 5094-5102 [PMID: 21538343 DOI: 10.1002/cncr.26165]
- 72 **Finn RS**, Poon RT, Yau T, Klumpen HJ, Chen LT, Kang YK, Kim TY, Gomez-Martin C, Rodriguez-Lope C, Kunz T, Paquet T, Brandt U, Sellami D, Bruix J. Phase I study investigating everolimus combined with sorafenib in patients with advanced hepatocellular carcinoma. *J Hepatol* 2013; **59**: 1271-1277 [PMID: 23928403 DOI: 10.1016/j.jhep.2013.07.029]
- 73 **Zhu AX**, Kudo M, Assenat E, Cattani S, Kang YK, Lim HY, Poon RT, Blanc JF, 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]
- 74 **Bhoori S**, Toffanin S, Sposito C, Germini A, Pellegrinelli A, Lampis A, Mazzaferro V. Personalized molecular targeted therapy in advanced, recurrent hepatocellular carcinoma after liver transplantation: a proof of principle. *J Hepatol* 2010; **52**: 771-775 [PMID: 20347502 DOI: 10.1016/j.jhep.2010.01.025]
- 75 **Gedaly R**, Angulo P, Hundley J, Daily MF, Chen C, Koch A, Evers BM. PI-103 and sorafenib inhibit hepatocellular carcinoma cell proliferation by blocking Ras/Raf/MAPK and PI3K/AKT/mTOR pathways. *Anticancer Res* 2010; **30**: 4951-4958 [PMID: 21187475]
- 76 **Gedaly R**, Galuppo R, Musgrave Y, Angulo P, Hundley J, Shah M, Daily MF, Chen C, Cohen DA, Spear BT, Evers BM. PKI-587 and sorafenib alone and in combination on inhibition of liver cancer stem cell proliferation. *J Surg Res* 2013; **185**: 225-230 [PMID: 23769634 DOI: 10.1016/j.jss.2013.05.016]
- 77 **Lee JS**. The mutational landscape of hepatocellular carcinoma. *Clin Mol Hepatol* 2015; **21**: 220-229 [PMID: 26523267 DOI: 10.3350/cmh.2015.21.3.220]
- 78 **Lachenmayer A**, Alsinet C, Savic R, Cabellos L, Toffanin S, Hoshida Y, Villanueva A, Minguez B, Newell P, Tsai HW, Barretina J, Thung

- S, Ward SC, Bruix J, Mazzaferro V, Schwartz M, Friedman SL, Llovet JM. Wnt-pathway activation in two molecular classes of hepatocellular carcinoma and experimental modulation by sorafenib. *Clin Cancer Res* 2012; **18**: 4997-5007 [PMID: 22811581 DOI: 10.1158/1078-0432.CCR-11-2322]
- 79 **Handeli S**, Simon JA. A small-molecule inhibitor of Tcf/beta-catenin signaling down-regulates PPARGamma and PPARdelta activities. *Mol Cancer Ther* 2008; **7**: 521-529 [PMID: 18347139 DOI: 10.1158/1535-7163.MCT-07-2063]
 - 80 **Liu J**, Li G, Liu D, Liu J. FH535 inhibits the proliferation of HepG2 cells via downregulation of the Wnt/ β -catenin signaling pathway. *Mol Med Rep* 2014; **9**: 1289-1292 [PMID: 24482011 DOI: 10.3892/mmr.2014.1928]
 - 81 **Galuppo R**, Maynard E, Shah M, Daily MF, Chen C, Spear BT, Gedaly R. Synergistic inhibition of HCC and liver cancer stem cell proliferation by targeting RAS/RAF/MAPK and WNT/ β -catenin pathways. *Anticancer Res* 2014; **34**: 1709-1713 [PMID: 24692700]
 - 82 **Vilchez V**, Turcios L, Marti F, Gedaly R. Targeting Wnt/ β -catenin pathway in hepatocellular carcinoma treatment. *World J Gastroenterol* 2016; **22**: 823-832 [PMID: 26811628 DOI: 10.3748/wjg.v22.i2.823]
 - 83 **Rixe O**, Fojo T. Is cell death a critical end point for anticancer therapies or is cytostasis sufficient? *Clin Cancer Res* 2007; **13**: 7280-7287 [PMID: 18094408 DOI: 10.1158/1078-0432.CCR-07-2141]
 - 84 **Schmieder R**, Puehler F, Neuhaus R, Kissel M, Adjei AA, Miner 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 DOI: 10.1593/neo.13812]
 - 85 **Lim HY**, Heo J, Choi HJ, Lin CY, Yoon JH, Hsu C, Rau KM, Poon RT, Yeo W, Park JW, Tay MH, Hsieh WS, Kappeler C, Rajagopalan P, Krissel H, Jeffers M, Yen CJ, Tak WY. A phase II study of the efficacy and safety of the combination therapy of the MEK inhibitor refametinib (BAY 86-9766) plus sorafenib for Asian patients with unresectable hepatocellular carcinoma. *Clin Cancer Res* 2014; **20**: 5976-5985 [PMID: 25294897 DOI: 10.1158/1078-0432.CCR-13-3445]
 - 86 **Kamran MZ**, Patil P, Gude RP. Role of STAT3 in cancer metastasis and translational advances. *Biomed Res Int* 2013; **2013**: 421821 [PMID: 24199193 DOI: 10.1155/2013/421821]
 - 87 **Bowman T**, Garcia R, Turkson J, Jove R. STATs in oncogenesis. *Oncogene* 2000; **19**: 2474-2488 [PMID: 10851046 DOI: 10.1038/sj.onc.1203527]
 - 88 **Chen KF**, Tai WT, Liu TH, Huang HP, Lin YC, Shiau CW, Li PK, Chen PJ, Cheng AL. Sorafenib overcomes TRAIL resistance of hepatocellular carcinoma cells through the inhibition of STAT3. *Clin Cancer Res* 2010; **16**: 5189-5199 [PMID: 20884624 DOI: 10.1158/1078-0432.CCR-09-3389]
 - 89 **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]
 - 90 **Hung MH**, Tai WT, Shiau CW, Chen KF. Downregulation of signal transducer and activator of transcription 3 by sorafenib: a novel mechanism for hepatocellular carcinoma therapy. *World J Gastroenterol* 2014; **20**: 15269-15274 [PMID: 25386075 DOI: 10.3748/wjg.v20.i41.15269]
 - 91 **Wu C**, Guan Q, Wang Y, Zhao ZJ, Zhou GW. SHP-1 suppresses cancer cell growth by promoting degradation of JAK kinases. *J Cell Biochem* 2003; **90**: 1026-1037 [PMID: 14624462 DOI: 10.1002/jcb.10727]
 - 92 **Tai WT**, Shiau CW, Chen PJ, Chu PY, Huang HP, Liu CY, Huang JW, Chen KF. Discovery of novel Src homology region 2 domain-containing phosphatase 1 agonists from sorafenib for the treatment of hepatocellular carcinoma. *Hepatology* 2014; **59**: 190-201 [PMID: 23908138 DOI: 10.1002/hep.26640]
 - 93 **Huang CY**, Tai WT, Hsieh CY, Hsu WM, Lai YJ, Chen LJ, Shiau CW, Chen KF. A sorafenib derivative and novel SHP-1 agonist, SC-59, acts synergistically with radiotherapy in hepatocellular carcinoma cells through inhibition of STAT3. *Cancer Lett* 2014; **349**: 136-143 [PMID: 24735751 DOI: 10.1016/j.canlet.2014.04.006]
 - 94 **Chao TI**, Tai WT, Hung MH, Tsai MH, Chen MH, Chang MJ, Shiau CW, Chen KF. A combination of sorafenib and SC-43 is a synergistic SHP-1 agonist duo to advance hepatocellular carcinoma therapy. *Cancer Lett* 2016; **371**: 205-213 [PMID: 26679051 DOI: 10.1016/j.canlet.2015.11.039]
 - 95 **Soni KB**, Lahiri M, Chackradeo P, Bhide SV, Kuttan R. Protective effect of food additives on aflatoxin-induced mutagenicity and hepatocarcinogenicity. *Cancer Lett* 1997; **115**: 129-133 [PMID: 9149115 DOI: 10.1016/S0304-3835(97)04710-1]
 - 96 **Hu B**, Sun D, Sun C, Sun YF, Sun HX, Zhu QF, Yang XR, Gao YB, Tang WG, Fan J, Maitra A, Anders RA, Xu Y. A polymeric nanoparticle formulation of curcumin in combination with sorafenib synergistically inhibits tumor growth and metastasis in an orthotopic model of human hepatocellular carcinoma. *Biochem Biophys Res Commun* 2015; **468**: 525-532 [PMID: 26482853 DOI: 10.1016/j.bbrc.2015.10.031]
 - 97 **Bishayee A**, Politis T, Darvesh AS. Resveratrol in the chemoprevention and treatment of hepatocellular carcinoma. *Cancer Treat Rev* 2010; **36**: 43-53 [PMID: 19910122 DOI: 10.1016/j.ctrv.2009.10.002]
 - 98 **Dai W**, Wang F, Lu J, Xia Y, He L, Chen K, Li J, Li S, Liu T, Zheng Y, Wang J, Lu W, Zhou Y, Yin Q, Abudumijiti H, Chen R, Zhang R, Zhou L, Zhou Z, Zhu R, Yang J, Wang C, Zhang H, Zhou Y, Xu L, Guo C. By reducing hexokinase 2, resveratrol induces apoptosis in HCC cells addicted to aerobic glycolysis and inhibits tumor growth in mice. *Oncotarget* 2015; **6**: 13703-13717 [PMID: 25938543 DOI: 10.18632/oncotarget.3800]
 - 99 **Abdelmageed MM**, El-Naga RN, El-Demerdash E, Elmazar MM. Indole-3- carbinol enhances sorafenib cytotoxicity in hepatocellular carcinoma cells: A mechanistic study. *Sci Rep* 2016; **6**: 32733 [PMID: 27612096 DOI: 10.1038/srep32733]
 - 100 **Ravi S**, Singal AK. Regorafenib: an evidence-based review of its potential in patients with advanced liver cancer. *Core Evid* 2014; **9**: 81-87 [PMID: 25114628 DOI: 10.2147/CE.S48626]
 - 101 **Trojan J**, Waidmann O. Role of regorafenib as second-line therapy and landscape of investigational treatment options in advanced hepatocellular carcinoma. *J Hepatocell Carcinoma* 2016; **3**: 31-36 [PMID: 27703962 DOI: 10.2147/JHC.S112537]
 - 102 **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: 23809766 DOI: 10.1016/j.ejca.2013.05.028]
 - 103 **Bruix J**, Merle P, Granito A, Huang Y-H, Bodoky G, Yokosuka O, Rosmorduc O, Gerolami R, Masi G, Paul JR. Efficacy and safety of regorafenib versus placebo in patients with hepatocellular carcinoma (HCC) progressing on sorafenib: Results of the international, randomized phase 3 resorcer trial. *Ann Oncol* 2016; **27**: ii1-ii3 [DOI: 10.1093/annonc/mdw237.03]
 - 104 **Brizzi MP**, Pignataro D, Tampellini M, Scagliotti GV, Di Maio M. Systemic treatment of hepatocellular carcinoma: why so many failures in the development of new drugs? *Expert Rev Anticancer Ther* 2016; **16**: 1053-1062 [PMID: 27548441 DOI: 10.1080/14737140.2016.1227706]

P- Reviewer: El-Shemi AG, Ungtrakul T, Vetvicka V, Yamagata M

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