

## Novel molecular targets in hepatocellular carcinoma

Ariel Ka-Man Chow, Simon Wing-Lung Yau, Lui Ng

**ORCID number:** Ariel Ka-Man Chow 0000-0002-5729-5415; Simon Wing-Lung Yau 0000-0001-9463-4722; Lui Ng 0000-0002-9010-2645.

**Author contributions:** Chow AKM wrote the paper; Yau SWL and Ng L commented and proof read the paper.

**Conflict-of-interest statement:** The authors declare no conflicts of interest related to this article.

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

**Manuscript source:** Invited manuscript

**Received:** February 28, 2020

**Peer-review started:** February 28, 2020

**First decision:** April 25, 2020

**Revised:** June 4, 2020

**Accepted:** June 20, 2020

**Article in press:** June 20, 2020

**Ariel Ka-Man Chow, Simon Wing-Lung Yau,** School of Nursing and Health Studies, The Open University of Hong Kong, Hong Kong, China

**Lui Ng,** Department of Surgery, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China

**Corresponding author:** Lui Ng, PhD, Research Assistant Professor, Department of Surgery, Li Ka Shing Faculty of Medicine, The University of Hong Kong, 21 Sassoon Road, Hong Kong, China. [luing@hku.hk](mailto:luing@hku.hk)

### Abstract

Globally, hepatocellular carcinoma (HCC) is a leading cause of cancer and cancer-related deaths. The therapeutic efficacy of locoregional and systemic treatment in patients with advanced HCC remains low, which results in a poor prognosis. The development of sorafenib for the treatment of HCC has resulted in a new era of molecular targeted therapy for this disease. However, the median overall survival was reported to be barely higher in the sorafenib treatment group than in the control group. Hence, in this review we describe the importance of developing more effective targeted therapies for the management of advanced HCC. Recent investigations of molecular signaling pathways in several cancers have provided some insights into developing molecular therapies that target critical members of these signaling pathways. Proteins involved in the Hedgehog and Notch signaling pathways, Polo-like kinase 1, arginine, histone deacetylases and Glypican-3 can be potential targets in the treatment of HCC. Monotherapy has limited therapeutic efficacy due to the development of inhibitory feedback mechanisms and induction of chemoresistance. Thus, emphasis is now on the development of personalized and combination molecular targeted therapies that can serve as ideal therapeutic strategies for improved management of HCC.

**Key words:** Hepatocellular carcinoma; Prognosis; Arginine deprivation; Cancer stem cells; Glypican-3; Hedgehog signaling pathway; Histone deacetylases; Personalized medicine; Molecular targeted therapy; Notch signaling pathway; Polo-like kinase 1; Tumour-associated antigens

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Hepatocellular carcinoma (HCC) remains a critical concern worldwide due to the severity of disease outcome. The primary cause is the low efficacy of current therapeutic

**Published online:** August 24, 2020**P-Reviewer:** Corrales FJ, Shimizu Y, Tchilikidi KY**S-Editor:** Gong ZM**L-Editor:** Webster JR**P-Editor:** Li JH

regimens available to treat advanced HCC. This review provides details on novel potentially vulnerable targets in the oncogenic signaling pathways associated with HCC development and progression, which should be targeted to develop molecular combination therapies to improve disease management. Moreover, the identification and establishment of novel biomarkers would complement this process in assisting timely management of the disease *via* powerful personalized drug regimens.

**Citation:** Chow AKM, Yau SWL, Ng L. Novel molecular targets in hepatocellular carcinoma. *World J Clin Oncol* 2020; 11(8): 589-605

**URL:** <https://www.wjgnet.com/2218-4333/full/v11/i8/589.htm>

**DOI:** <https://dx.doi.org/10.5306/wjco.v11.i8.589>

## INTRODUCTION

Cancer of the liver is the sixth most commonly diagnosed cancer worldwide, and is responsible for 4.7% of all new cancer cases and 8.2% of all cancer-related deaths<sup>[1]</sup>. Although the five-year survival rate of liver cancer have improved from an abysmal 3% four decades ago to 18%, it is still significantly lower than the survival rates observed in many other solid cancers with a high global incidence, including breast (90%), colorectal (65%), and prostate (98%) cancers<sup>[2]</sup>. Three quarters of liver cancer patients present with hepatocellular carcinoma (HCC); while the other subtypes include cholangiocarcinoma, angiosarcoma, hepatoblastoma, and other non-cancerous liver diseases. The most common cause of HCC is hepatitis B virus (HBV) or hepatitis C virus (HCV) infection which is responsible for more than 90% of HCC cases in developing countries and nearly half the number of cases in developed countries<sup>[3]</sup>. Other risk factors include aflatoxin B<sub>1</sub> consumption, alcoholic liver disease, non-alcoholic fatty liver disease, smoking, autoimmune hepatitis, hemochromatosis, obesity, and diabetes. Importantly, in countries endemic for HBV, the introduction of a new universal vaccination program aided by mass screening has been shown to significantly reduce the rate of HBV-induced HCC in children and young adults<sup>[4,5]</sup>. Nevertheless, patients with early HCC are always asymptomatic or develop nonspecific complaints such as abdominal pain, enlarged abdomen, jaundice, and weight loss which results in HCC being initially undetected. Consequently, the management of high risk groups using routine serum  $\alpha$ -fetoprotein monitoring and abdominal ultrasonography is important for better control over disease progression<sup>[6]</sup>. For the management of early and intermediate HCC, liver resection, orthotopic liver transplantation, thermal ablation including radiofrequency ablation and microwave ablation, transarterial therapies including radioembolization with yttrium-90 and transarterial embolization with chemotherapeutic agents, and selective internal radiotherapy are potentially curative<sup>[6-8]</sup>. Although a 5-year survival rate of 50%-75% can be achieved, these curative therapies are only applicable for HCC patients with a smaller tumour size and adequate liver function<sup>[7,9-13]</sup>. Moreover, for patients presenting with advanced HCC, neoadjuvant and adjuvant systemic therapies are prescribed to reduce the rate of recurrence or the development of extrahepatic metastases; however, systemic chemotherapy has been reported to have a low tumour response rate and is commonly associated with the development of chemoresistance in advanced HCC<sup>[14-17]</sup>.

The most actively used first-line systemic therapeutic agent approved for patients with nonresectable advanced HCC is sorafenib, an oral multikinase inhibitor targeting Raf, epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), FMS-like tyrosine kinase-3 and c-kit<sup>[18,19]</sup>. At least two large-scale, randomized, placebo-controlled drug trials independently confirmed the effectiveness of sorafenib treatment in inhibiting tumour growth and angiogenesis in advanced HCC; although, the median increase in the overall survival period of HCC patients treated with sorafenib was just under 3 mo as compared to the placebo group<sup>[20,21]</sup>. Moreover, prolonged exposure of HCC cells to sorafenib has been shown to induce resistance, caused by activation of the phosphoinositide 3-kinase (PI3K)/AKT pathway, resulting in enhanced tumour growth and the development of distant metastases<sup>[22,23]</sup>. Considering this predicament in managing HCC using sorafenib alone, it is essential to explore alternative options such as investigating potentially druggable molecular targets or the administration of alternative drug regimens, to achieve an improved disease outcome. Recently, the

FDA approved lenvatinib (Lenvima) as an alternate first-line therapeutic agent demonstrated a non-inferior role in improving the overall survival of HCC patients relative to sorafenib<sup>[19,24]</sup>. Furthermore, for HCC patients not benefitting from sorafenib, regorafenib or nivolumab and ipilimumab are the approved second-line therapeutic agents<sup>[25,26]</sup>. Treatment with lenvatinib was found to have improved secondary endpoints including a higher objective response rate, longer progression-free survival and longer time to progression than patients treated with sorafenib alone<sup>[19]</sup>, HCC patients not responding to first-line sorafenib treatment were found to have a better overall survival following the administration of second-line drugs<sup>[25,27,28]</sup>. Due to the limited options available for the systemic treatment of HCC patients, there is an immediate requirement to develop novel therapeutic compounds with high efficacy to improve disease management. In this review, we explore some of the novel molecular targets currently known in HCC. Emphasis will also be paid to the development and clinical application of personalized molecular targeted therapies as powerful therapeutic strategies to improve prognosis in HCC.

## POTENTIAL DRUGGABLE MOLECULAR TARGETS IN HCC

An important aspect of cancer therapeutics is the development of targeted therapy that makes use of chemical compounds designed to regulate the activity of specific molecular targets involved in critical oncogenic signaling pathways that ultimately govern the proliferation, growth, survival and distant metastatic dissemination of cancer cells. Consequently, targeted therapy has the advantage of delivering focussed and powerful suppression of cancer development and progression, albeit with a lower toxicity to non-malignant cells; which is a common pitfall associated with systemic chemotherapy and radiotherapy. With an increase in our understanding of the molecular biology of HCC, many such druggable molecular targets associated with HCC genesis and progression have been identified. Key targets include: (1) Intracellular signaling proteins such as those involved in the PI3K/Akt/mammalian target of rapamycin (mTOR) pathway, ras/raf/mitogen-activated protein kinase (MAPK) pathway, Janus kinase (JAK)/Signal transducer and activator of transcription (STAT) pathway and Wnt/ $\beta$ -catenin pathway; (2) Angiogenic factors such as VEGF, fibroblast growth factor (FGF), angiopoietins, platelet-derived endothelial cell growth factor (PD-ECGF), heparanase, matrix metalloproteinases (MMPs), PDGFR, and COX-2; (3) Peptide growth factors and their receptors such as EGF and its receptor (EGFR), hepatocyte growth factor (HGF) and its receptor (c-Met), insulin-like growth factor (IGF) and its receptor (IGFR) and transforming growth factor-alpha (TGF- $\alpha$ ); (4) Cell cycle regulators such as cyclins and cyclin-dependent kinases (CDKs); and (5) Transcription factors such as nuclear factor-kappa B and activator protein 2. The details of these targets have been comprehensively reviewed elsewhere<sup>[29-36]</sup>. Examples of the therapeutic agents against these molecular targets, currently in phase II/III clinical trials for the treatment of HCC are summarized in [Table 1](#). However, the anti-tumour activity as well as the primary outcome measures, such as time to progression and overall response rate and safety level, exhibited by most of these compounds are either equivalent or significantly less than the effectiveness of sorafenib in HCC<sup>[37-40]</sup>. Consequently, it is important to identify novel molecular targets that are druggable in HCC. [Table 2](#) summarizes potential pipeline compounds targeting novel targets that are a part of oncogenic signaling pathways in several cancers, including HCC. Given the importance of these oncogenic pathways in HCC development, these pipeline compounds hold promise as novel therapeutic strategies in HCC treatment. Hence, the following section specifically focuses on these targets to understand their role in HCC pathogenesis.

### **Hedgehog signaling pathway**

The Hedgehog (Hh) pathway is an evolutionarily conserved signaling cascade that plays a critical role in early embryonic development and adult tissue homeostasis. Under normal circumstances, the adult liver does not manufacture the Hh protein unless the organ is undergoing regeneration after a partial hepatectomy<sup>[41]</sup>. However, recent evidence suggests that dysregulation of Hh signaling contributes to the development of HCC<sup>[42-44]</sup>. In its oncogenic role, the Hh protein impairs the inhibitory activity of patched homolog-1 (Ptch), resulting in the release of the proto-oncoprotein smoothed (Smo) from Ptch<sup>[42]</sup>. The released Smo subsequently induces the nuclear translocation of glioma-associated oncogene homolog (GLI) transcription factor, resulting in increased transcription of regulatory genes such as, cyclins and  $\beta$ -catenin

**Table 1 Summary of current molecular targeted compounds under phase II/III clinical studies for the treatment of hepatocellular carcinoma**

Drug	Targets	Descriptions	Ref./ClinicalTrials.gov identifier
<i>Phase II</i>			
Bevacizumab	VEGF	Monoclonal antibody  Inhibits tumour growth of HCC cell line or patient-derived HCC xenografts  Shows significant antitumour activity in patients with non-metastatic HCC, but serious bleeding complications occurs in 11% of patients.	[116-118]
Cediranib	VEGFR	Tyrosine kinase inhibitor  Shows high toxicity and ineffective for patients with unresectable or metastatic HCC	[119]
Cetuximab	EGFR	Human-mouse chimeric monoclonal antibody  Shows no obvious response in patients with advanced HCC	[120]
Dovitinib	c-KIT, Flt-3, FGFR, VEGFR	Multikinase inhibitor  Significantly prolongs survival and inhibits primary tumour growth and lung metastasis in HCC xenograft models  Shows less antitumour activity than sorafenib as a frontline systemic therapy for HCC	[98,121]
Erlotinib	EGFR	Tyrosine kinase inhibitor  Shows modest prolonged progression-free survival and overall survival in patients with unresectable HCC	[122,123]
Gefitinib	EGFR	Tyrosine kinase inhibitor  Inhibits tumour growth of HCC xenografts in mouse model	NCT00071994, [124]
Selumetinib	MEK1	Tyrosine kinase inhibitor  Suppresses tumour growth of HCC xenografts in mouse model  Shows inadequate antitumour activity with no radiographic response and short progression-free survival in patients with locally advanced or metastatic HCC	[125,126]
<i>Phase III</i>			
Brivanib	FGFR, VEGFR	Tyrosine kinase inhibitor  Inhibits tumour growth of patient-derived HCC xenografts by increasing apoptosis, reducing microvessel density and decreasing VEGFR phosphorylation  Shows promising antitumour activity in patients with advanced HCC	[127-129]
Linifanib	PDGFR, VEGFR	Receptor tyrosine kinase inhibitor  Inhibits tumour growth of HCC xenografts in mouse model  Shows similar overall survival in patients with advanced HCC as compared with sorafenib	[99,130,131]
Sunitinib	c-Kit, Flt-3, PDGFR, VEGFR	Multi-targeted receptor tyrosine kinase inhibitor  Inhibits tumour growth of patient-derived HCC xenografts by increasing apoptosis and reducing microvessel density  Shows significantly poorer overall survival than sorafenib in patients with advanced HCC, and shows more frequent and severe toxicity in treated patients	[132-134]
TSU-68 (Orantinib)	FGFR, PDGFR, VEGFR	Tyrosine kinase inhibitor  Suppresses the tumour growth of subcutaneously co-injected HCC cell lines (Huh7/WI-38) xenografts	[135-137]

Orantinib combined with TACE shows no improvement in overall survival in patients with unresectable HCC

EGFR: Epidermal growth factor receptor; FGFR: Fibroblast growth factor receptor; Flt-3: FMS-like tyrosine kinase-3; HCC: Hepatocellular carcinoma; MEK1: Mitogen-activated protein kinase (MAPK) kinase; PDGFR: Platelet-derived growth factor receptor; TACE: Transcatheter arterial chemoembolization; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor.

which promote cell cycle progression, a higher rate of cell proliferation and an associated tumour growth in HCC. Moreover, activation of the Hh signaling pathway also enhances the metastatic potential of HCC cells through focal adhesion kinase (FAK)/AKT and ERK-mediated production and activation of MMP-2 and MMP-9<sup>[45,46]</sup>. In addition to the Hh protein, mRNA levels of Ptch and GLI were found to be over-expressed in HCC and have been reported to serve as potential biomarkers to determine disease recurrence and overall survival following curative surgery<sup>[47]</sup>. In addition, blocking of the Hh signaling pathway by a Smo inhibitor (Vismodegib) has been found to exert anti-proliferative effects in HCC cells<sup>[42,48]</sup>, suggesting that targeting the Hh signaling pathway is a potential therapeutic option for HCC patients.

### Notch pathway

The Notch cell-cell signaling cascade is highly conserved and regulates cell fate, cell proliferation and cell death in several developmental and physiological processes<sup>[49]</sup>. Four Notch proteins are found in mammals and they are transmembrane proteins composed of a large extracellular domain for ligand binding and a cytoplasmic Notch intracellular domain (Nidc) for signal transduction. Mammalian Notch ligands include Delta-like ligand (DLL)1, DLL3, DLL4, Jagged1 and Jagged2 which are also membrane-bound. Therefore, activation of the Notch signaling pathway is mediated by ligand-receptor interaction between adjacent cells which leads to a conformational change in Notch receptors. After  $\gamma$ -secretase-induced cleavage of the Notch receptor, cytoplasmic Nidc is released and then translocated to the nucleus. Nuclear Nidc functions as a transcription factor to cause the transcription of its target genes including, HES-family members p21 and c-Myc<sup>[50]</sup>.

Dysregulation of the Notch signaling pathway is observed in several types of cancers, including HCC. Aberrant expression of Notch receptors and its ligand Jagged1 has been detected in HCC tissues when compared with the adjacent non-malignant mucosae<sup>[51-54]</sup>. Activation of Notch signaling has also been reported to induce HCC tumour formation in mice<sup>[55]</sup>. Moreover, Notch signaling also contributes to enhancement of the oncogenic effects of HBV and HCV in HCC pathogenesis<sup>[56-58]</sup>. Several studies have verified that targeting critical members of the Notch signaling pathway represents a potential therapeutic avenue for HCC treatment. Giovannini *et al.*<sup>[59]</sup> demonstrated that selective ablation of the Notch protein in combination with chemotherapeutics such as doxorubicin results in increased DNA damage, cellular apoptosis, and a concurrent decrease in cell cycle progression in HCC cells. Treatment with  $\gamma$ -secretase inhibitors (GSI) was found to inhibit growth of HCC cells *in vitro*<sup>[60,61]</sup>. Zhou and colleagues inhibited the Notch signaling pathway using DAPT which suppressed the invasion of HCC cells by impacting signaling of the extracellular signal-regulated kinases 1 and 2 (ERK1/2), thereby repressing the activity of MMP2, MMP9 and VEGF<sup>[62]</sup>. Active clinical studies on the use of GSIs such as MK-0752 and RO4929097 demonstrated a significant anti-tumour effect in different cancer models<sup>[63-66]</sup>, which suggests its therapeutic potential in treating HCC.

### Polo-like kinase 1

Polo-like kinase 1 (Plk1) is a serine/threonine kinase with peak expression during the mitotic phase of the cell cycle<sup>[67]</sup>. Plk1 functions as a cell cycle regulator promoting mitosis by modulating the activities of cell division cycle 25 homolog C (Cdc25C) and CDK1/Cyclin B<sup>[68,69]</sup>. Overexpression of Plk1 overrides the mitotic checkpoint which results in immature cell division and genetic instability leading to aneuploidies and tumour development<sup>[70]</sup>. In HCC, activation of Plk1 by HBx, a hepatitis B viral protein, was found to impair the DNA damage checkpoint and DNA repair pathways causing increased genetic instability and malignant transformation<sup>[71]</sup>. Consequently, Plk1 has been reported to be upregulated in numerous cancers, including HCC. In addition, a higher expression of Plk1 was found to predict poor prognosis in HCC<sup>[72-74]</sup>. Silencing Plk1 inhibited proliferation of HCC cells *in vitro* and *in vivo* by inducing G2/M arrest and enhanced apoptosis<sup>[75-77]</sup>, suggesting that targeting Plk1 with small molecule inhibitors is a potential strategy for the treatment of HCC. Gilmartin *et al.*<sup>[78]</sup> described a

**Table 2 Summary of potential pipeline compounds targeting novel molecular targets in several cancers**

Drug	Descriptions	Phase	Type of tumour	Ref./ClinicalTrials.gov identifier
<i>Hh signaling pathway</i>				
Erismodegib, (LDE-225)	Smo antagonist	0	Pancreatic cancer	NCT01694589
	<i>In vitro</i> and <i>in vivo</i> test results on HCC cells are not available	I	Advanced solid tumours	NCT00880308
		I	SCLC	NCT01579929
		II	Advanced or metastatic basal cell carcinoma	NCT01327053
		I/II	Medulloblastoma	NCT01125800
Vismodegib	Smo antagonist	I	HCC and lymphoma	NCT01546519
	Promotes regression of liver fibrosis and HCC tumour growth in a murine model of primary liver cancer <sup>[138]</sup>	I	Advanced or metastatic basal cell carcinoma	
	Shows no obvious response in patients with hepatic impairment <sup>[139]</sup>	II	Ovarian cancer	NCT00739661
<i>Notch signaling pathway</i>				
MK-0752	γ-secretase inhibitor	I	Advanced solid tumour	[63]
	<i>In vitro</i> and <i>in vivo</i> test results on HCC cells are not available	I	Brain and central nervous system tumours	[64]
RO4929097	γ-secretase inhibitor	I	Refractory metastatic or locally advanced solid tumours	[65]
	Prevents tumour development and decreases liver fibrosis in mouse model <sup>[141]</sup>	II	Metastatic colorectal cancer	[66]
<i>Plk1</i>				
HMN-214	Stilbene derivative interferes with the subcellular spatial distribution of Plk1 at centrosomes	I	Advanced solid tumours	[79]
	<i>In vitro</i> and <i>in vivo</i> test results on HCC cells are not available			
GSK461364	Reversible ATP-competitive Plk1 inhibitor	I	Advanced solid tumours and non-Hodgkin's lymphoma	[81]
	<i>In vitro</i> and <i>in vivo</i> test results on HCC cells are not available			
<i>Arginine deprivation</i>				
ADI-PEG-20	Arginine deiminase	I	Pediatric ASS-deficient tumour	NCT01528384
	Shows its safe and efficacious in stabilizing the progression of advanced HCC in an Asian population	II	SCLC	[142], NCT01266018
		II	Advanced melanoma	[143]
	Shows no overall survival benefit in second line setting for patients with advanced HCC	II	Malignant pleural mesothelioma	NCT01279967
		II/III	Advanced HCC	[87,144]
BCT100/ Peg-rhArg1	Recombinant human arginase I	I	Leukemia and lymphoma	NCT01551628
	Inhibits tumour growth of HCC xenografts in mouse model <sup>[85]</sup>	I/II	Advanced HCC	[90], NCT01092091
<i>HDACs</i>				
Resminostat	HDACs (1, 3 & 6) inhibitor <sup>[145]</sup>	I/II	Advanced HCC	[146]
	Combined with sorafenib shows no significant efficacy advantage over sorafenib monotherapy in patients with advanced HCC in East Asian populations	II	Hodgkin's lymphoma	NCT01037478
		I/II	Advanced colorectal carcinoma	NCT01277406
Chidamide	HDACs inhibitor (1, 2, 3 & 10) <sup>[147]</sup>	I	Advanced solid tumours and lymphomas	[148]
	Inhibits proliferation of HCC cells <i>in vitro</i> <sup>[95]</sup>			

Panobinostat,(LBH-589)	Pan-HDAC inhibitor Inhibits tumour growth and lung metastasis of HCC xenografts in mouse model <sup>[149]</sup>	I	Prostate carcinoma	[150]	
		I	Advanced solid tumours	[151]	
		II	Refractory metastatic renal cell carcinoma	[152]	
<i>Glypican-3</i>					
Codrituzumab (GC33)	Anti-GPC3 monoclonal antibody	I	Advanced or metastatic HCC	[153]	
					Inhibits tumour growth of HCC xenografts in mouse model <sup>[102]</sup>
					Shows no clinical benefit in advanced HCC patients who has failed prior systemic therapy

HCC: Hepatocellular carcinoma; HDAC: Histone deacetylase; Plk1: Polo-like kinase-1; SCLC: Small cell lung cancer; Smo: Proto-oncoprotein smoothened.

reversible ATP-competitive Plk1 inhibitor with a very high selectivity for Plk1 relative to other Plk subtypes or a panel of 48 other kinases that included CDK2/Cyclin A, MEK and serine/threonine kinase NEK2. Moreover, the authors demonstrate that the inhibition of Plk1 resulted in a dose-dependent arrest of cell cycle progression, leading to cell culture growth inhibition and tumour regression in xenograft models; while the toxicity of the drug in slow dividing non-cancerous cells was minimal. Therefore, GSK461364 offers the feasibility to overcome the limitation of traditional chemotherapy. Other phase I/II clinical studies of Plk1 inhibitors also demonstrated an anti-tumour effect by causing tumour regression and inhibition of tumour growth<sup>[79-82]</sup>. These studies suggest that Plk1 may be a potential therapeutic target in the treatment of HCC.

### **Arginine deprivation in arginine-driven HCC**

Arginine is a semi-essential amino acid biosynthesized from citrulline in the urea cycle through the action of argininosuccinate synthetase (ASS-1), argininosuccinate lyase (ASL) and ornithine transcarbamylase (OTC)<sup>[83]</sup>. HCC is auxotrophic for arginine as it lacks the expression of ASS-1, ASL and/or OTC<sup>[84,85]</sup>. Therefore, enzymes capable of removing arginine can function as potential therapeutic agents in HCC. ADI-PEG-20 is an arginine deiminase (ADI) which has been shown to induce HCC regression through arginine depletion in ASS-deficient tumours<sup>[86,87]</sup>. For ASS-positive but OTC-deficient HCC, a recombinant human arginase I (rhArg1) has been shown to be potent in inhibiting HCC tumour growth<sup>[84,88-90]</sup>. A recent study by our group demonstrated that treatment with a pegylated rhArg1, BCT100, inhibits proliferation of HCC cells through an enhanced caspase-dependent apoptosis and induction of S-phase cell cycle arrest<sup>[85]</sup>. Moreover, the drug also inhibited xenograft tumour growth in a dose-dependent manner. At the molecular level, arginine deprivation was observed to inhibit the Wnt/ $\beta$ -catenin and Akt/mTOR signaling pathways with a concurrent downregulation of survivin and X-linked inhibitor of apoptosis (XIAP) expression<sup>[85]</sup>. Therefore, human recombinant arginase may be a potential agent in arginine-driven tumours such as HCC.

### **Histone deacetylases**

One of the key regulatory mechanisms of gene expression is *via* epigenetic post-translational modifications of histone proteins. Among other covalent modifications, acetylation of the histones is a critical physiological process that is regulated by a balance between the activities of histone acetyltransferases and histone deacetylases (HDACs). Contrary to the acetyltransferases, HDACs work by removing acetyl groups from the lysine amino acid on the histone protein to increase the net positive charge on the histone tails, resulting in high-affinity binding between the histones and the DNA backbone. High HDAC activity results in a condensed and a transcriptionally inactive chromatin<sup>[91]</sup>. Moreover, aberrant expression of HDAC family members has been observed in multiple steps of cancer development including, cell proliferation, autophagy and cell cycle progression (HDAC 1, 2, 3 and 8), apoptosis (HDAC 1 and 2), differentiation (HDAC 3, 4, 5, and 8), angiogenesis (HDAC 4, 6, 7 and 10), migration (HDAC 6), and chemosensitivity (HDAC 1). The functional roles played by each family member of HDACs have been reviewed elsewhere in greater detail<sup>[92]</sup>. Dysregulated expression of HDACs has been found to correlate with a poor disease outcome in several cancers including HCC<sup>[92-94]</sup>. Specifically, upregulation of HDAC 3

and 5 mRNA expression was observed to be associated with DNA copy number gains in HCC<sup>[93]</sup>. Several HDAC inhibitors (HDACi) have been shown to have an anti-proliferative effect on HCC cells *in vitro* and *in vivo*. Panobinostat, a pan-HDAC inhibitor, has been found to enhance apoptosis and inhibit tumour growth in HCC cells through down-regulation of the anti-apoptotic protein survivin<sup>[93]</sup>. Chidamide, a benzamide type inhibitor of HDAC 1, 2, 3 and 10 subtypes, inhibits HCC cell growth by inducing cell cycle arrest at G0/1 phase by the up-regulation of p21<sup>[95]</sup>. Although most of the studies of HDACi in HCC are still at the pre-clinical stage, HDACi in HCC therapy has great potential.

### **Glypican-3**

The glypican (GPC) family represents a group of cell-surface heparan sulphate proteoglycans which interact with growth factors, act as a co-receptor and modulate growth factor activity. Glypican-3 (GPC3), a carcinoembryonic antigen, promotes cell proliferation by modulating fibroblast growth factor 2 (FGF2) activity<sup>[96]</sup> and canonical Wnt signaling<sup>[97]</sup>. Interestingly, GPC3 is a transcriptional target of c-Myc, while the expression of c-Myc is under the regulation of GPC3<sup>[98]</sup>. This positive feedback loop between GPC3 and c-Myc also determines the oncogenic behaviour of GPC3. GPC3 is a diagnostic marker for HCC which is over-expressed in 70% of cases, while its expression is correlated with a poor outcome<sup>[99,100]</sup>. Silencing GPC3 in HCC cells induced apoptosis *via* the Bax/Bcl-2/cytochrome c/caspase-3 signaling pathway<sup>[101]</sup>. An antibody against GPC3 has also been developed, and it has been shown to cause antibody-dependent cell-mediated cytotoxicity in HCC cells<sup>[102]</sup>. In addition, due to its highly specific expression in HCC tumours, but not in the normal hepatocytes or benign hepatocellular mass lesions<sup>[103]</sup>, GPC3 serves as a tumour-associated antigen which is an ideal target for immunotherapy. Tumour immunotherapy is the use of the host tumour-specific immune response to selectively target the tumour-associated antigens present on tumour cells. A phase I trial of a GPC3-derived peptide vaccine demonstrated measurable immune response and antitumor efficacy which correlated with overall survival in advanced stage HCC patients<sup>[104]</sup>.

---

## **CANCER STEM CELLS AS THERAPEUTIC TARGETS FOR HCC TREATMENT**

---

Cancer stem cells (CSCs) are a subpopulation of cancer cells possessing stem cell-like properties. Briefly, CSCs are tumour-initiating cells in the bulk of tumours that are capable of self-renewal and can divide and differentiate into multiple cell lineages. Markers of CSCs in HCC include ALDH, CD13, CD44, CD90, CD133, CD326 (EpCAM), and OV6, and a side population (SP) determined through an adenosine triphosphate (ATP)-binding cassette (ABC) membrane transporter<sup>[105,106]</sup>. CSCs also play a crucial role in tumour recurrence, metastasis and chemoresistance. A recent study reported that circulating CD45<sup>+</sup>CD90<sup>+</sup>CD44<sup>+</sup> CSCs can predict post-hepatectomy HCC recurrence<sup>[107]</sup>. Importantly, while systemic chemotherapy is effective in killing differentiated, fast-growing cancer cells, it induces chemoresistance and enriches the population of CSCs which significantly increases the risk of disease recurrence and metastasis. Ma *et al.*<sup>[108]</sup> reported a CSC population in HCC characterized by their CD133 phenotype which were shown to survive chemotherapy of doxorubicin and fluorouracil with preferential expression of survival proteins involved in the AKT and Bcl-2 pathway. The authors further demonstrated that treatment with an AKT1 inhibitor significantly reduced the expression of these survival proteins, thereby enhancing the chemosensitivity of CD133<sup>+</sup> CSCs. In a different study, CD133<sup>+</sup> cells were also observed to contribute to radio-resistance in HCC in a mouse xenograft model<sup>[109]</sup>. Other molecular pathways including TGF- $\beta$ , Wnt, Notch and Hh, that are deregulated in HCC were also found in CSCs<sup>[105,110,111]</sup>. Therefore, molecular therapy that is targeted towards CSCs can assist in preventing tumour-initiation, recurrence, metastasis or even chemoresistance in HCC.

---

## **PERSONALIZED AND COMBINED MOLECULAR TARGETED THERAPIES IN HCC**

---

Development of HCC is a multi-step process and the mechanisms involved in the initiation, progression and metastasis are not completely understood. Recent studies



have demonstrated the role of multiple signaling pathways that contribute to the pathogenesis of HCC. Although no single pathway is deemed dominant, the inhibition of a single pathway may induce a feedback mechanism within an alternate pathway resulting in a low response rate to monotherapy. For example, rapamycin up-regulates the expression and phosphorylation of PDGFR $\beta$  and the subsequent activation of the AKT and MAPK pathway through the PDGFR $\beta$ -dependent feedback loop results in rapamycin resistance<sup>[112]</sup>. Therefore, emphasis is focussed on a personalized and combined molecular targeted therapy as an ideal therapeutic strategy for HCC.

An *in vitro* study demonstrated that the level of EGFR expression predicts the cell line response to sorafenib treatment and the addition of gefitinib or erlotinib (EGFR inhibitors) or cetuximab (a monoclonal antibody against EGFR) significantly enhances the efficacy of sorafenib and a synergistic anti-proliferative effect is also demonstrated<sup>[113]</sup>. Therefore, by screening the EGFR status, we can predict the tumour's response to sorafenib treatment, and the addition of an EGFR inhibitor may help sensitize the tumour's response to sorafenib. However, an *in vivo* orthotopic model failed to demonstrate a synergistic anti-tumour effect of combination treatment with erlotinib and sorafenib<sup>[114]</sup>. A recent press release also reported that a large scale phase III clinical trial on the efficacy of combining erlotinib with sorafenib treatment in HCC (SEARCH trial, NCT00901901) failed to demonstrate any additional benefit on the overall survival of patients with unresectable HCC over sorafenib treatment alone<sup>[115]</sup>. Although these studies failed to show a clinical impact of one combined treatment in HCC, presently several clinical studies are evaluating alternate combination based molecular targeted therapies, examples of which are summarized in Table 3. Importantly, the success of personalized therapies in HCC heavily depends on the identification of novel biomarkers that provide critical information pertaining to the progress of the disease. As small tissue biopsy or fine-needle aspiration biopsy specimens are easily obtained, evaluation of biomarkers associated with crucial signaling pathways within these specimens can provide indications for treatment of these patients with drug combinations with/without locoregional therapies to maximize tumour response and survival rates.

---

## CONCLUSION

---

HCC has been a cause of concern for a long time owing to a high rate of mortality and an overall poor outcome associated with the disease. Molecular investigations have indicated the dysregulation of several critical signaling pathways that contribute to the genesis and progression of HCC. Hence, the role of molecular therapy targeting pivotal members within these signaling pathways is undisputed. While monotherapy is frequently associated with a low tumor response rate and chemoresistance events, there is a need to explore and develop personalized and combined molecular targeted therapies as a powerful therapeutic strategy in HCC. Additionally, an increase in the discovery and clinical application of novel biomarkers that can speak volumes about the developing tumor would provide important information for guiding the clinician on the usage of appropriate personalized therapies in HCC.

**Table 3 Clinical study of combined molecular targeted therapy based on sorafenib treatment for hepatocellular carcinoma**

Drug + Sorafenib	Phase	Ref./ClinicalTrials.gov identifier
<i>VEGF inhibitors</i>		
Bevacizumab	I/II	NCT00867321
Lenvatinib	I/II (HCC)	NCT01271504
<i>mTOR inhibitor</i>		
Everolimus (RAD001)	II	NCT01005199
	I/II	[154]
Temsirolimus	I/II	NCT01335074, NCT01687673, NCT01008917
<i>HDAC inhibitors</i>		
Resminostat	II (Advanced HCC)	NCT00943449
Panobinostat	I (HCC)	NCT00823290
<i>Anti-GPC3 antibody</i>		
GC33	I	NCT00976170
<i>MEK1 inhibitor</i>		
Selumetinib (AZD6244)	I/II	NCT01029418
<i>HGFR inhibitor</i>		
Tivantinib (ARQ197)	I	NCT00827177
<i>TNF-<math>\alpha</math> secretion inhibitor</i>		
Lenalidomide	I	NCT01348503
<i>TRAIL receptor 1 antibody</i>		
Mapatumumab	I/II	NCT00712855, NCT01258608

HGFR: Hepatocyte growth factor receptor; TNF- $\alpha$ : Tumour necrosis factor- $\alpha$ ; TRAIL: Anti-TNF-related apoptosis-inducing ligand; HCC: Hepatocellular carcinoma; VEGF: Vascular endothelial growth factor; mTOR: Mammalian target of rapamycin.

## ACKNOWLEDGEMENTS

We would like to thank Dr. Deepak Iyer for editing this manuscript.

## REFERENCES

- 1 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]
- 2 **American Cancer Society**. Cancer facts figures 2019. Atlanta: American Cancer Society. 2019
- 3 **Parkin DM**. The global health burden of infection-associated cancers in the year 2002. *Int J Cancer* 2006; **118**: 3030-3044 [PMID: 16404738 DOI: 10.1002/ijc.21731]
- 4 **Chang MH**, You SL, Chen CJ, Liu CJ, Lee CM, Lin SM, Chu HC, Wu TC, Yang SS, Kuo HS, Chen DS; Taiwan Hepatoma Study Group. Decreased incidence of hepatocellular carcinoma in hepatitis B vaccinees: a 20-year follow-up study. *J Natl Cancer Inst* 2009; **101**: 1348-1355 [PMID: 19759364 DOI: 10.1093/jnci/djp288]
- 5 **McMahon BJ**, Bulkow LR, Singleton RJ, Williams J, Snowball M, Homan C, Parkinson AJ. Elimination of hepatocellular carcinoma and acute hepatitis B in children 25 years after a hepatitis B newborn and catch-up immunization program. *Hepatology* 2011; **54**: 801-807 [PMID: 21618565 DOI: 10.1002/hep.24442]
- 6 **El-Serag HB**. Hepatocellular carcinoma. *N Engl J Med* 2011; **365**: 1118-1127 [PMID: 21992124 DOI: 10.1056/NEJMra1001683]
- 7 **Signoriello S**, Annunziata A, Lama N, Signoriello G, Chiodini P, De Sio I, Daniele B, Di Costanzo GG, Calise F, Olivieri G, Castaldo V, Lanzetta R, Piai G, Marone G, Visconti M, Fusco M, Di Maio M, Perrone F, Gallo C, Gaeta GB. Survival after locoregional treatments for hepatocellular carcinoma: a cohort study in real-world patients. *ScientificWorldJournal* 2012; **2012**: 564706 [PMID: 22654628 DOI: 10.1100/2012/564706]
- 8 **Vogel A**, Cervantes A, Chau I, Daniele B, Llovet JM, Meyer T, Nault JC, Neumann U, Ricke J, Sangro B, Schirmacher P, Verslype C, Zech CJ, Arnold D, Martinelli E; ESMO Guidelines Committee. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2018; **29**:

- iv238-iv255 [PMID: 30285213 DOI: 10.1093/annonc/mdy308]
- 9 **Colombo M.** Treatment of hepatocellular carcinoma. *Antiviral Res* 2001; **52**: 209-215 [PMID: 11672831 DOI: 10.1016/s0166-3542(01)00186-3]
  - 10 **Lee JG, Kang CM, Park JS, Kim KS, Yoon DS, Choi JS, Lee WJ, Kim BR.** The actual five-year survival rate of hepatocellular carcinoma patients after curative resection. *Yonsei Med J* 2006; **47**: 105-112 [PMID: 16502491 DOI: 10.3349/ymj.2006.47.1.105]
  - 11 **Heckman JT, Devera MB, Marsh JW, Fontes P, Amesur NB, Holloway SE, Nalesnik M, Geller DA, Steel JL, Gamblin TC.** Bridging locoregional therapy for hepatocellular carcinoma prior to liver transplantation. *Ann Surg Oncol* 2008; **15**: 3169-3177 [PMID: 18696158 DOI: 10.1245/s10434-008-0071-3]
  - 12 **Fan ST, Poon RT, Yeung C, Lam CM, Lo CM, Yuen WK, Ng KK, Liu CL, Chan SC.** Outcome after partial hepatectomy for hepatocellular cancer within the Milan criteria. *Br J Surg* 2011; **98**: 1292-1300 [PMID: 21656513 DOI: 10.1002/bjs.7583]
  - 13 **Andreou A, Vauthey JN, Cherqui D, Zimmitti G, Ribero D, Truty MJ, Wei SH, Curley SA, Laurent A, Poon RT, Belghiti J, Nagorney DM, Aloia TA; International Cooperative Study Group on Hepatocellular Carcinoma.** Improved long-term survival after major resection for hepatocellular carcinoma: a multicenter analysis based on a new definition of major hepatectomy. *J Gastrointest Surg* 2013; **17**: 66-77; discussion p.77 [PMID: 22948836 DOI: 10.1007/s11605-012-2005-4]
  - 14 **Fuchs CS, Clark JW, Ryan DP, Kulke MH, Kim H, Earle CC, Vincitore M, Mayer RJ, Stuart KE.** A phase II trial of gemcitabine in patients with advanced hepatocellular carcinoma. *Cancer* 2002; **94**: 3186-3191 [PMID: 12115351 DOI: 10.1002/cncr.10607]
  - 15 **Yeo W, Mok TS, Zee B, Leung TW, Lai PB, Lau WY, Koh J, Mo FK, Yu SC, Chan AT, Hui P, Ma B, Lam KC, Ho WM, Wong HT, Tang A, Johnson PJ.** A randomized phase III study of doxorubicin versus cisplatin/interferon alpha-2b/doxorubicin/fluorouracil (PIAF) combination chemotherapy for unresectable hepatocellular carcinoma. *J Natl Cancer Inst* 2005; **97**: 1532-1538 [PMID: 16234567 DOI: 10.1093/jnci/dji315]
  - 16 **Lopez PM, Villanueva A, Llovet JM.** Systematic review: evidence-based management of hepatocellular carcinoma--an updated analysis of randomized controlled trials. *Aliment Pharmacol Ther* 2006; **23**: 1535-1547 [PMID: 16696801 DOI: 10.1111/j.1365-2036.2006.02932.x]
  - 17 **Gish RG, Porta C, Lazar L, Ruff P, Feld R, Croitoru A, Feun L, Jeziorski K, Leighton J, Gallo J, Kennealey GT.** Phase III randomized controlled trial comparing the survival of patients with unresectable hepatocellular carcinoma treated with nilotexed or doxorubicin. *J Clin Oncol* 2007; **25**: 3069-3075 [PMID: 17634485 DOI: 10.1200/JCO.2006.08.4046]
  - 18 **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 DOI: 10.1158/0008-5472.CAN-06-1377]
  - 19 **Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, Baron A, Park JW, Han G, Jassem J, Blanc JF, Vogel A, Komov D, Evans TRJ, Lopez C, Dutcus C, Guo M, Saito K, Kraljevic S, Tamai T, Ren M, Cheng AL.** Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018; **391**: 1163-1173 [PMID: 29433850 DOI: 10.1016/S0140-6736(18)30207-1]
  - 20 **Llovet JM, Ricci S, Mazzaferro V, Hilgert 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]
  - 21 **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]
  - 22 **Chow AK, Ng L, Lam CS, Wong SK, Wan TM, Cheng NS, Yau TC, Poon RT, Pang RW.** The Enhanced metastatic potential of hepatocellular carcinoma (HCC) cells with sorafenib resistance. *PLoS One* 2013; **8**: e78675 [PMID: 24244338 DOI: 10.1371/journal.pone.0078675]
  - 23 **Chen KF, Chen HL, Tai WT, Feng WC, Hsu CH, Chen PJ, Cheng AL.** Activation of phosphatidylinositol 3-kinase/Akt signaling pathway mediates acquired resistance to sorafenib in hepatocellular carcinoma cells. *J Pharmacol Exp Ther* 2011; **337**: 155-161 [PMID: 21205925 DOI: 10.1124/jpet.110.175786]
  - 24 **Spallanzani A, Orsi G, Andrikou K, Gelsomino F, Rimini M, Riggi L, Cascinu S.** Lenvatinib as a therapy for unresectable hepatocellular carcinoma. *Expert Rev Anticancer Ther* 2018; **18**: 1069-1076 [PMID: 30220234 DOI: 10.1080/14737140.2018.1524297]
  - 25 **Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, Pracht M, Yokosuka O, Rosmorduc O, Breder V, Gerolami R, Masi G, Ross PJ, Song T, Bronowicki JP, Ollivier-Hourmand I, Kudo M, Cheng AL, Llovet JM, Finn RS, LeBerre MA, Baumhauer A, Meinhardt G, Han G; RESORCE Investigators.** Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017; **389**: 56-66 [PMID: 27932229 DOI: 10.1016/S0140-6736(16)32453-9]
  - 26 **Kudo M, Matilla A, Santoro A, Melero I, Gracian AC, Acosta-Rivera M, Choo SP, El-Khoueiry AB, Kuromatsu R, El-Rayes BF, Numata K, Itoh Y, Costanzo FD, Crysler OV, Reig M, Shen Y, Neely J, Cruz CMD, Baccan C, Sangro B.** Checkmate-040: Nivolumab (nivo) in patients (pts) with advanced hepatocellular carcinoma (ahcc) and child-pugh b (cpb) status. *J Clin Oncol* 2019; **37**: 327-327 [DOI: 10.1200/JCO.2019.37.4\_suppl.327]
  - 27 **Abou-Alfa GK, Meyer T, Cheng AL, El-Khoueiry AB, Rimassa L, Ryoo BY, Cicin I, Merle P, Chen Y, Park JW, Blanc JF, Bolondi L, Klumpfen HJ, Chan SL, Zagonel V, Pressiani T, Ryu MH, Venook AP, Hessel C, Borgman-Hagey AE, Schwab G, Kelley RK.** Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. *N Engl J Med* 2018; **379**: 54-63 [PMID: 29972759 DOI: 10.1056/NEJMoa1713030]

- 10.1056/NEJMoa1717002]
- 28 **El-Khoueiry AB**, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, Kim TY, Choo SP, Trojan J, Welling TH Rd, Meyer T, Kang YK, Yeo W, Chopra A, Anderson J, Dela Cruz C, Lang L, Neely J, Tang H, Dastani HB, Melero I. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet* 2017; **389**: 2492-2502 [PMID: 28434648 DOI: 10.1016/S0140-6736(17)31046-2]
  - 29 **Roberts LR**, Gores GJ. Hepatocellular carcinoma: molecular pathways and new therapeutic targets. *Semin Liver Dis* 2005; **25**: 212-225 [PMID: 15918149 DOI: 10.1055/s-2005-871200]
  - 30 **Pang R**, Tse E, Poon RT. Molecular pathways in hepatocellular carcinoma. *Cancer Lett* 2006; **240**: 157-169 [PMID: 16239065 DOI: 10.1016/j.canlet.2005.08.031]
  - 31 **Pang RW**, Poon RT. From molecular biology to targeted therapies for hepatocellular carcinoma: the future is now. *Oncology* 2007; **72** Suppl 1: 30-44 [PMID: 18087180 DOI: 10.1159/000111705]
  - 32 **Finn RS**. Development of molecularly targeted therapies in hepatocellular carcinoma: where do we go now? *Clin Cancer Res* 2010; **16**: 390-397 [PMID: 20068087 DOI: 10.1158/1078-0432.CCR-09-2084]
  - 33 **Ierardi E**, Rosania R, Zotti M, Giorgio F, Prencipe S, Valle ND, Francesco VD, Panella C. From chronic liver disorders to hepatocellular carcinoma: Molecular and genetic pathways. *World J Gastrointest Oncol* 2010; **2**: 259-264 [PMID: 21160638 DOI: 10.4251/wjgo.v2.i6.259]
  - 34 **Huynh H**. Molecularly targeted therapy in hepatocellular carcinoma. *Biochem Pharmacol* 2010; **80**: 550-560 [PMID: 20371362 DOI: 10.1016/j.bcp.2010.03.034]
  - 35 **Zhu AX**. Molecularly targeted therapy for advanced hepatocellular carcinoma in 2012: current status and future perspectives. *Semin Oncol* 2012; **39**: 493-502 [PMID: 22846866 DOI: 10.1053/j.seminoncol.2012.05.014]
  - 36 **Chan SL**, Yeo W. Targeted therapy of hepatocellular carcinoma: present and future. *J Gastroenterol Hepatol* 2012; **27**: 862-872 [PMID: 22369685 DOI: 10.1111/j.1440-1746.2012.07096.x]
  - 37 **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]
  - 38 **Cheng AL**, Thongprasert S, Lim HY, Sukeepaisarnjaroen W, Yang TS, Wu CC, Chao Y, Chan SL, Kudo M, Ikeda M, Kang YK, Pan H, Numata K, Han G, Balsara B, Zhang Y, Rodriguez AM, Zhang Y, Wang Y, Poon RT. Randomized, open-label phase 2 study comparing frontline dovitinib versus sorafenib in patients with advanced hepatocellular carcinoma. *Hepatology* 2016; **64**: 774-784 [PMID: 27082062 DOI: 10.1002/hep.28600]
  - 39 **Cainap C**, Qin S, Huang WT, Chung IJ, Pan H, Cheng Y, Kudo M, Kang YK, Chen PJ, Toh HC, Gorbunova V, Eskens FA, Qian J, McKee MD, Ricker JL, Carlson DM, El-Nowiem S. Linifanib versus Sorafenib in patients with advanced hepatocellular carcinoma: results of a randomized phase III trial. *J Clin Oncol* 2015; **33**: 172-179 [PMID: 25488963 DOI: 10.1200/JCO.2013.54.3298]
  - 40 **Xu Q**, Huang Y, Shi H, Song Q, Xu Y. Sunitinib versus sorafenib plus transarterial chemoembolization for inoperable hepatocellular carcinoma patients. *J BUON* 2018; **23**: 193-199 [PMID: 29552783]
  - 41 **Cai Y**, Zheng H, Gong W, Che Y, Jiang B. The role of hedgehog signaling pathway in liver regeneration. *Hepatogastroenterology* 2011; **58**: 2071-2076 [PMID: 22024090 DOI: 10.5754/hge11155]
  - 42 **Huang S**, He J, Zhang X, Bian Y, Yang L, Xie G, Zhang K, Tang W, Stelter AA, Wang Q, Zhang H, Xie J. Activation of the hedgehog pathway in human hepatocellular carcinomas. *Carcinogenesis* 2006; **27**: 1334-1340 [PMID: 16501253 DOI: 10.1093/carcin/bgi378]
  - 43 **Patil MA**, Zhang J, Ho C, Cheung ST, Fan ST, Chen X. Hedgehog signaling in human hepatocellular carcinoma. *Cancer Biol Ther* 2006; **5**: 111-117 [PMID: 16397407 DOI: 10.4161/cbt.5.1.2379]
  - 44 **Cheng WT**, Xu K, Tian DY, Zhang ZG, Liu LJ, Chen Y. Role of Hedgehog signaling pathway in proliferation and invasiveness of hepatocellular carcinoma cells. *Int J Oncol* 2009; **34**: 829-836 [PMID: 19212688 DOI: 10.3892/ijo\_00000209]
  - 45 **Chen JS**, Huang XH, Wang Q, Huang JQ, Zhang LJ, Chen XL, Lei J, Cheng ZX. Sonic hedgehog signaling pathway induces cell migration and invasion through focal adhesion kinase/AKT signaling-mediated activation of matrix metalloproteinase (MMP)-2 and MMP-9 in liver cancer. *Carcinogenesis* 2013; **34**: 10-19 [PMID: 22948179 DOI: 10.1093/carcin/bgs274]
  - 46 **Lu JT**, Zhao WD, He W, Wei W. Hedgehog signaling pathway mediates invasion and metastasis of hepatocellular carcinoma via ERK pathway. *Acta Pharmacol Sin* 2012; **33**: 691-700 [PMID: 22543708 DOI: 10.1038/aps.2012.24]
  - 47 **Jeng KS**, Sheen IS, Jeng WJ, Lin CC, Lin CK, Su JC, Yu MC, Fang HY. High expression of patched homolog-1 messenger RNA and glioma-associated oncogene-1 messenger RNA of sonic hedgehog signaling pathway indicates a risk of postresection recurrence of hepatocellular carcinoma. *Ann Surg Oncol* 2013; **20**: 464-473 [PMID: 22911366 DOI: 10.1245/s10434-012-2593-y]
  - 48 **Tada M**, Kanai F, Tanaka Y, Tateishi K, Ohta M, Asaoka Y, Seto M, Muroyama R, Fukai K, Imazeki F, Kawabe T, Yokosuka O, Omata M. Down-regulation of hedgehog-interacting protein through genetic and epigenetic alterations in human hepatocellular carcinoma. *Clin Cancer Res* 2008; **14**: 3768-3776 [PMID: 18559595 DOI: 10.1158/1078-0432.CCR-07-1181]
  - 49 **Bray SJ**. Notch signalling: a simple pathway becomes complex. *Nat Rev Mol Cell Biol* 2006; **7**: 678-689 [PMID: 16921404 DOI: 10.1038/nrm2009]
  - 50 **Bolós V**, Grego-Bessa J, de la Pompa JL. Notch signaling in development and cancer. *Endocr Rev* 2007; **28**: 339-363 [PMID: 17409286 DOI: 10.1210/er.2006-0046]
  - 51 **Gao J**, Chen C, Hong L, Wang J, Du Y, Song J, Shao X, Zhang J, Han H, Liu J, Fan D. Expression of Jagged1 and its association with hepatitis B virus X protein in hepatocellular carcinoma. *Biochem Biophys Res Commun* 2007; **356**: 341-347 [PMID: 17359939 DOI: 10.1016/j.bbrc.2007.02.130]
  - 52 **Gramantieri L**, Giovannini C, Lanzi A, Chicco P, Ravaoli M, Venturi A, Grazi GL, Bolondi L. Aberrant

- Notch3 and Notch4 expression in human hepatocellular carcinoma. *Liver Int* 2007; **27**: 997-1007 [PMID: 17696940 DOI: 10.1111/j.1478-3231.2007.01544.x]
- 53 **Gao J**, Song Z, Chen Y, Xia L, Wang J, Fan R, Du R, Zhang F, Hong L, Song J, Zou X, Xu H, Zheng G, Liu J, Fan D. Deregulated expression of Notch receptors in human hepatocellular carcinoma. *Dig Liver Dis* 2008; **40**: 114-121 [PMID: 17920003 DOI: 10.1016/j.dld.2007.08.001]
- 54 **Wang M**, Xue L, Cao Q, Lin Y, Ding Y, Yang P, Che L. Expression of Notch1, Jagged1 and beta-catenin and their clinicopathological significance in hepatocellular carcinoma. *Neoplasma* 2009; **56**: 533-541 [PMID: 19728763 DOI: 10.4149/neo\_2009\_06\_533]
- 55 **Villanueva A**, Alsinet C, Yanger K, Hoshida Y, Zong Y, Toffanin S, Rodriguez-Carunchio L, Solé M, Thung S, Stanger BZ, Llovet JM. Notch signaling is activated in human hepatocellular carcinoma and induces tumor formation in mice. *Gastroenterology* 2012; **143**: 1660-1669.e7 [PMID: 22974708 DOI: 10.1053/j.gastro.2012.09.002]
- 56 **Wang F**, Zhou H, Yang Y, Xia X, Sun Q, Luo J, Cheng B. Hepatitis B virus X protein promotes the growth of hepatocellular carcinoma by modulation of the Notch signaling pathway. *Oncol Rep* 2012; **27**: 1170-1176 [PMID: 22218807 DOI: 10.3892/or.2012.1620]
- 57 **Iwai A**, Takegami T, Shiozaki T, Miyazaki T. Hepatitis C virus NS3 protein can activate the Notch-signaling pathway through binding to a transcription factor, SRCAP. *PLoS One* 2011; **6**: e20718 [PMID: 21673954 DOI: 10.1371/journal.pone.0020718]
- 58 **Wang F**, Zhou H, Xia X, Sun Q, Wang Y, Cheng B. Activated Notch signaling is required for hepatitis B virus X protein to promote proliferation and survival of human hepatic cells. *Cancer Lett* 2010; **298**: 64-73 [PMID: 20638778 DOI: 10.1016/j.canlet.2010.06.003]
- 59 **Giovannini C**, Gramantieri L, Chieco P, Minguzzi M, Lago F, Pianetti S, Ramazzotti E, Marcu KB, Bolondi L. Selective ablation of Notch3 in HCC enhances doxorubicin's death promoting effect by a p53 dependent mechanism. *J Hepatol* 2009; **50**: 969-979 [PMID: 19304334 DOI: 10.1016/j.jhep.2008.12.032]
- 60 **Shen Y**, Lv D, Wang J, Yin Y, Miao F, Dou F, Zhang J. GSI-I has a better effect in inhibiting hepatocellular carcinoma cell growth than GSI-IX, GSI-X, or GSI-XXI. *Anticancer Drugs* 2012; **23**: 683-690 [PMID: 22569108 DOI: 10.1097/CAD.0b013e3283549a22]
- 61 **Suwanjune S**, Wongchana W, Palaga T. Inhibition of gamma-secretase affects proliferation of leukemia and hepatoma cell lines through Notch signaling. *Anticancer Drugs* 2008; **19**: 477-486 [PMID: 18418214 DOI: 10.1097/CAD.0b013e3282fc6cdd]
- 62 **Zhou L**, Wang DS, Li QJ, Sun W, Zhang Y, Dou KF. Downregulation of the Notch signaling pathway inhibits hepatocellular carcinoma cell invasion by inactivation of matrix metalloproteinase-2 and -9 and vascular endothelial growth factor. *Oncol Rep* 2012; **28**: 874-882 [PMID: 22736202 DOI: 10.3892/or.2012.1880]
- 63 **Krop I**, Demuth T, Guthrie T, Wen PY, Mason WP, Chinnaiyan P, Butowski N, Groves MD, Kesari S, Freedman SJ, Blackman S, Watters J, Loboda A, Podtelezhnikov A, Lunceford J, Chen C, Giannotti M, Hing J, Beckman R, Lorusso P. Phase I pharmacologic and pharmacodynamic study of the gamma secretase (Notch) inhibitor MK-0752 in adult patients with advanced solid tumors. *J Clin Oncol* 2012; **30**: 2307-2313 [PMID: 22547604 DOI: 10.1200/JCO.2011.39.1540]
- 64 **Fouladi M**, Stewart CF, Olson J, Wagner LM, Onar-Thomas A, Kocak M, Packer RJ, Goldman S, Gururangan S, Gajjar A, Demuth T, Kun LE, Boyett JM, Gilbertson RJ. Phase I trial of MK-0752 in children with refractory CNS malignancies: a pediatric brain tumor consortium study. *J Clin Oncol* 2011; **29**: 3529-3534 [PMID: 21825264 DOI: 10.1200/JCO.2011.35.7806]
- 65 **Tolcher AW**, Messersmith WA, Mikulski SM, Papadopoulos KP, Kwak EL, Gibbon DG, Patnaik A, Falchook GS, Dasari A, Shapiro GI, Boylan JF, Xu ZX, Wang K, Koehler A, Song J, Middleton SA, Deutsch J, Demario M, Kurzrock R, Wheler JJ. Phase I study of RO4929097, a gamma secretase inhibitor of Notch signaling, in patients with refractory metastatic or locally advanced solid tumors. *J Clin Oncol* 2012; **30**: 2348-2353 [PMID: 22529266 DOI: 10.1200/JCO.2011.36.8282]
- 66 **Strosberg JR**, Yeatman T, Weber J, Coppola D, Schell MJ, Han G, Almhanna K, Kim R, Valone T, Jump H, Sullivan D. A phase II study of RO4929097 in metastatic colorectal cancer. *Eur J Cancer* 2012; **48**: 997-1003 [PMID: 22445247 DOI: 10.1016/j.ejca.2012.02.056]
- 67 **Anger M**, Kues WA, Klima J, Mielenz M, Kubelka M, Motlik J, Esner M, Dvorak P, Carnwath JW, Niemann H. Cell cycle dependent expression of Plk1 in synchronized porcine fetal fibroblasts. *Mol Reprod Dev* 2003; **65**: 245-253 [PMID: 12784245 DOI: 10.1002/mrd.10289]
- 68 **Roshak AK**, Capper EA, Imburgia C, Fornwald J, Scott G, Marshall LA. The human polo-like kinase, PLK, regulates cdc2/cyclin B through phosphorylation and activation of the cdc25C phosphatase. *Cell Signal* 2000; **12**: 405-411 [PMID: 11202906 DOI: 10.1016/s0898-6568(00)00080-2]
- 69 **Toyoshima-Morimoto F**, Taniguchi E, Nishida E. Plk1 promotes nuclear translocation of human Cdc25C during prophase. *EMBO Rep* 2002; **3**: 341-348 [PMID: 11897663 DOI: 10.1093/embo-reports/kvf069]
- 70 **Lu LY**, Yu X. The balance of Polo-like kinase 1 in tumorigenesis. *Cell Div* 2009; **4**: 4 [PMID: 19161615 DOI: 10.1186/1747-1028-4-4]
- 71 **Studach L**, Wang WH, Weber G, Tang J, Hullinger RL, Malbrue R, Liu X, Andrisani O. Polo-like kinase 1 activated by the hepatitis B virus X protein attenuates both the DNA damage checkpoint and DNA repair resulting in partial polyploidy. *J Biol Chem* 2010; **285**: 30282-30293 [PMID: 20624918 DOI: 10.1074/jbc.M109.093963]
- 72 **He ZL**, Zheng H, Lin H, Miao XY, Zhong DW. Overexpression of polo-like kinase1 predicts a poor prognosis in hepatocellular carcinoma patients. *World J Gastroenterol* 2009; **15**: 4177-4182 [PMID: 19725153 DOI: 10.3748/wjg.15.4177]
- 73 **Pellegrino R**, Calvisi DF, Ladu S, Ehemann V, Staniscia T, Evert M, Dombrowski F, Schirmacher P, Longrich T. Oncogenic and tumor suppressive roles of polo-like kinases in human hepatocellular carcinoma. *Hepatology* 2010; **51**: 857-868 [PMID: 20112253 DOI: 10.1002/hep.23467]
- 74 **Wang XQ**, Zhu YQ, Lui KS, Cai Q, Lu P, Poon RT. Aberrant Polo-like kinase 1-Cdc25A pathway in metastatic hepatocellular carcinoma. *Clin Cancer Res* 2008; **14**: 6813-6820 [PMID: 18980975 DOI: 10.1158/1078-0432.CCR-08-0626]

- 75 **Liu X**, Erikson RL. Polo-like kinase (Plk)1 depletion induces apoptosis in cancer cells. *Proc Natl Acad Sci USA* 2003; **100**: 5789-5794 [PMID: [12732729](#) DOI: [10.1073/pnas.1031523100](#)]
- 76 **He Z**, Wu J, Dang H, Lin H, Zheng H, Zhong D. Polo-like kinase 1 contributes to the tumorigenicity of BEL-7402 hepatoma cells via regulation of Survivin expression. *Cancer Lett* 2011; **303**: 92-98 [PMID: [21330050](#) DOI: [10.1016/j.canlet.2011.01.007](#)]
- 77 **Mok WC**, Wasser S, Tan T, Lim SG. Polo-like kinase 1, a new therapeutic target in hepatocellular carcinoma. *World J Gastroenterol* 2012; **18**: 3527-3536 [PMID: [22826617](#) DOI: [10.3748/wjg.v18.i27.3527](#)]
- 78 **Gilmartin AG**, Bleam MR, Richter MC, Erskine SG, Kruger RG, Madden L, Hassler DF, Smith GK, Gontarek RR, Courtney MP, Sutton D, Diamond MA, Jackson JR, Laquerre SG. Distinct concentration-dependent effects of the polo-like kinase 1-specific inhibitor GSK461364A, including differential effect on apoptosis. *Cancer Res* 2009; **69**: 6969-6977 [PMID: [19690138](#) DOI: [10.1158/0008-5472.CAN-09-0945](#)]
- 79 **Garland LL**, Taylor C, Pilkington DL, Cohen JL, Von Hoff DD. A phase I pharmacokinetic study of HMN-214, a novel oral stilbene derivative with polo-like kinase-1-interacting properties, in patients with advanced solid tumors. *Clin Cancer Res* 2006; **12**: 5182-5189 [PMID: [16951237](#) DOI: [10.1158/1078-0432.CCR-06-0214](#)]
- 80 **Rudolph D**, Steegmaier M, Hoffmann M, Grauert M, Baum A, Quant J, Haslinger C, Garin-Chesa P, Adolf GR. BI 6727, a Polo-like kinase inhibitor with improved pharmacokinetic profile and broad antitumor activity. *Clin Cancer Res* 2009; **15**: 3094-3102 [PMID: [19383823](#) DOI: [10.1158/1078-0432.CCR-08-2445](#)]
- 81 **Olmos D**, Barker D, Sharma R, Brunetto AT, Yap TA, Taegtmeier AB, Barriuso J, Medani H, Degenhardt YY, Allred AJ, Smith DA, Murray SC, Lampkin TA, Dar MM, Wilson R, de Bono JS, Blagden SP. Phase I study of GSK461364, a specific and competitive Polo-like kinase 1 inhibitor, in patients with advanced solid malignancies. *Clin Cancer Res* 2011; **17**: 3420-3430 [PMID: [21459796](#) DOI: [10.1158/1078-0432.CCR-10-2946](#)]
- 82 **Schöffski P**, Awada A, Dumez H, Gil T, Bartholomeus S, Wolter P, Taton M, Fritsch H, Glomb P, Munzert G. A phase I, dose-escalation study of the novel Polo-like kinase inhibitor volasertib (BI 6727) in patients with advanced solid tumours. *Eur J Cancer* 2012; **48**: 179-186 [PMID: [22119200](#) DOI: [10.1016/j.ejca.2011.11.001](#)]
- 83 **Morris SM Jr**. Recent advances in arginine metabolism: roles and regulation of the arginases. *Br J Pharmacol* 2009; **157**: 922-930 [PMID: [19508396](#) DOI: [10.1111/j.1476-5381.2009.00278.x](#)]
- 84 **Lam TL**, Wong GK, Chong HC, Cheng PN, Choi SC, Chow TL, Kwok SY, Poon RT, Wheatley DN, Lo WH, Leung YC. Recombinant human arginase inhibits proliferation of human hepatocellular carcinoma by inducing cell cycle arrest. *Cancer Lett* 2009; **277**: 91-100 [PMID: [19138817](#) DOI: [10.1016/j.canlet.2008.11.031](#)]
- 85 **Chow AK**, Ng L, Sing Li H, Cheng CW, Lam CS, Yau TC, Cheng PN, Fan ST, Poon RT, Pang RW. Antitumor efficacy of a recombinant human arginase in human hepatocellular carcinoma. *Curr Cancer Drug Targets* 2012; **12**: 1233-1243 [PMID: [22873218](#) DOI: [10.2174/156800912803988002](#)]
- 86 **Izzo F**, Marra P, Beneduce G, Castello G, Vallone P, De Rosa V, Cremona F, Ensor CM, Holtsberg FW, Bomalaski JS, Clark MA, Ng C, Curley SA. Pegylated arginine deiminase treatment of patients with unresectable hepatocellular carcinoma: results from phase I/II studies. *J Clin Oncol* 2004; **22**: 1815-1822 [PMID: [15143074](#) DOI: [10.1200/JCO.2004.11.120](#)]
- 87 **Yang TS**, Lu SN, Chao Y, Sheen IS, Lin CC, Wang TE, Chen SC, Wang JH, Liao LY, Thomson JA, Wang-Peng J, Chen PJ, Chen LT. A randomised phase II study of pegylated arginine deiminase (ADI-PEG 20) in Asian advanced hepatocellular carcinoma patients. *Br J Cancer* 2010; **103**: 954-960 [PMID: [20808309](#) DOI: [10.1038/sj.bjc.6605856](#)]
- 88 **Cheng PN**, Lam TL, Lam WM, Tsui SM, Cheng AW, Lo WH, Leung YC. Pegylated recombinant human arginase (rhArg-peg5,000mw) inhibits the in vitro and in vivo proliferation of human hepatocellular carcinoma through arginine depletion. *Cancer Res* 2007; **67**: 309-317 [PMID: [17210712](#) DOI: [10.1158/0008-5472.CAN-06-1945](#)]
- 89 **Tsui SM**, Lam WM, Lam TL, Chong HC, So PK, Kwok SY, Arnold S, Cheng PN, Wheatley DN, Lo WH, Leung YC. Pegylated derivatives of recombinant human arginase (rhArg1) for sustained in vivo activity in cancer therapy: preparation, characterization and analysis of their pharmacodynamics in vivo and in vitro and action upon hepatocellular carcinoma cell (HCC). *Cancer Cell Int* 2009; **9**: 9 [PMID: [19374748](#) DOI: [10.1186/1475-2867-9-9](#)]
- 90 **Yau T**, Cheng PN, Chan P, Chan W, Chen L, Yuen J, Pang R, Fan ST, Poon RT. A phase I dose-escalating study of pegylated recombinant human arginase 1 (Peg-rhArg1) in patients with advanced hepatocellular carcinoma. *Invest New Drugs* 2013; **31**: 99-107 [PMID: [22426640](#) DOI: [10.1007/s10637-012-9807-9](#)]
- 91 **de Ruijter AJ**, van Gennip AH, Caron HN, Kemp S, van Kuilenburg AB. Histone deacetylases (HDACs): characterization of the classical HDAC family. *Biochem J* 2003; **370**: 737-749 [PMID: [12429021](#) DOI: [10.1042/BJ20021321](#)]
- 92 **Witt O**, Deubzer HE, Milde T, Oehme I. HDAC family: What are the cancer relevant targets? *Cancer Lett* 2009; **277**: 8-21 [PMID: [18824292](#) DOI: [10.1016/j.canlet.2008.08.016](#)]
- 93 **Lachenmayer A**, Toffanin S, Cabellos L, Alsinet C, Hoshida Y, Villanueva A, Minguez B, Tsai HW, Ward SC, Thung S, Friedman SL, Llovet JM. Combination therapy for hepatocellular carcinoma: additive preclinical efficacy of the HDAC inhibitor panobinostat with sorafenib. *J Hepatol* 2012; **56**: 1343-1350 [PMID: [22322234](#) DOI: [10.1016/j.jhep.2012.01.009](#)]
- 94 **Quint K**, Agaimy A, Di Fazio P, Montalbano R, Steindorf C, Jung R, Hellerbrand C, Hartmann A, Sitter H, Neureiter D, Ocker M. Clinical significance of histone deacetylases 1, 2, 3, and 7: HDAC2 is an independent predictor of survival in HCC. *Virchows Arch* 2011; **459**: 129-139 [PMID: [21713366](#) DOI: [10.1007/s00428-011-1103-0](#)]
- 95 **Wang H**, Guo Y, Fu M, Liang X, Zhang X, Wang R, Lin C, Qian H. Antitumor activity of Chidamide in hepatocellular carcinoma cell lines. *Mol Med Rep* 2012; **5**: 1503-1508 [PMID: [22484326](#) DOI: [10.3892/mmr.2012.858](#)]
- 96 **Midorikawa Y**, Ishikawa S, Iwanari H, Imamura T, Sakamoto H, Miyazono K, Kodama T, Makuuchi M, Aburatani H. Glypican-3, overexpressed in hepatocellular carcinoma, modulates FGF2 and BMP-7

- signaling. *Int J Cancer* 2003; **103**: 455-465 [PMID: 12478660 DOI: 10.1002/ijc.10856]
- 97 **Capurro MI**, Xiang YY, Lobe C, Filmus J. Glypican-3 promotes the growth of hepatocellular carcinoma by stimulating canonical Wnt signaling. *Cancer Res* 2005; **65**: 6245-6254 [PMID: 16024626 DOI: 10.1158/0008-5472.CAN-04-4244]
- 98 **Li L**, Jin R, Zhang X, Lv F, Liu L, Liu D, Liu K, Li N, Chen D. Oncogenic activation of glypican-3 by c-Myc in human hepatocellular carcinoma. *Hepatology* 2012; **56**: 1380-1390 [PMID: 22706665 DOI: 10.1002/hep.25891]
- 99 **Yu MC**, Lee YS, Lin SE, Wu HY, Chen TC, Lee WC, Chen MF, Tsai CN. Recurrence and poor prognosis following resection of small hepatitis B-related hepatocellular carcinoma lesions are associated with aberrant tumor expression profiles of glypican 3 and osteopontin. *Ann Surg Oncol* 2012; **19** Suppl 3: S455-S463 [PMID: 21822558 DOI: 10.1245/s10434-011-1946-2]
- 100 **Shirakawa H**, Suzuki H, Shimomura M, Kojima M, Gotohda N, Takahashi S, Nakagohri T, Konishi M, Kobayashi N, Kinoshita T, Nakatsura T. Glypican-3 expression is correlated with poor prognosis in hepatocellular carcinoma. *Cancer Sci* 2009; **100**: 1403-1407 [PMID: 19496787 DOI: 10.1111/j.1349-7006.2009.01206.x]
- 101 **Liu S**, Li Y, Chen W, Zheng P, Liu T, He W, Zhang J, Zeng X. Silencing glypican-3 expression induces apoptosis in human hepatocellular carcinoma cells. *Biochem Biophys Res Commun* 2012; **419**: 656-661 [PMID: 22382024 DOI: 10.1016/j.bbrc.2012.02.069]
- 102 **Nakano K**, Orita T, Nezu J, Yoshino T, Ohizumi I, Sugimoto M, Furugaki K, Kinoshita Y, Ishiguro T, Hamakubo T, Kodama T, Aburatani H, Yamada-Okabe H, Tsuchiya M. Anti-glypican 3 antibodies cause ADCC against human hepatocellular carcinoma cells. *Biochem Biophys Res Commun* 2009; **378**: 279-284 [PMID: 19022220 DOI: 10.1016/j.bbrc.2008.11.033]
- 103 **Wang HL**, Anatelli F, Zhai QJ, Adley B, Chuang ST, Yang XJ. Glypican-3 as a useful diagnostic marker that distinguishes hepatocellular carcinoma from benign hepatocellular mass lesions. *Arch Pathol Lab Med* 2008; **132**: 1723-1728 [PMID: 18976006 DOI: 10.1043/1543-2165-132.11.1723]
- 104 **Sawada Y**, Yoshikawa T, Nobuoka D, Shirakawa H, Kuronuma T, Motomura Y, Mizuno S, Ishii H, Nakachi K, Konishi M, Nakagohri T, Takahashi S, Gotohda N, Takayama T, Yamao K, Uesaka K, Furuse J, Kinoshita T, Nakatsura T. Phase I trial of a glypican-3-derived peptide vaccine for advanced hepatocellular carcinoma: immunologic evidence and potential for improving overall survival. *Clin Cancer Res* 2012; **18**: 3686-3696 [PMID: 22577059 DOI: 10.1158/1078-0432.CCR-11-3044]
- 105 **Pang RW**, Poon RT. Cancer stem cell as a potential therapeutic target in hepatocellular carcinoma. *Curr Cancer Drug Targets* 2012; **12**: 1081-1094 [PMID: 22873219 DOI: 10.2174/156800912803987995]
- 106 **Nagano H**, Ishii H, Marubashi S, Haraguchi N, Eguchi H, Doki Y, Mori M. Novel therapeutic target for cancer stem cells in hepatocellular carcinoma. *J Hepatobiliary Pancreat Sci* 2012; **19**: 600-605 [PMID: 22892595 DOI: 10.1007/s00534-012-0543-5]
- 107 **Fan ST**, Yang ZF, Ho DW, Ng MN, Yu WC, Wong J. Prediction of posthepatectomy recurrence of hepatocellular carcinoma by circulating cancer stem cells: a prospective study. *Ann Surg* 2011; **254**: 569-576 [PMID: 21892074 DOI: 10.1097/SLA.0b013e3182300a1d]
- 108 **Ma S**, Lee TK, Zheng BJ, Chan KW, Guan XY. CD133+ HCC cancer stem cells confer chemoresistance by preferential expression of the Akt/PKB survival pathway. *Oncogene* 2008; **27**: 1749-1758 [PMID: 17891174 DOI: 10.1038/sj.onc.1210811]
- 109 **Piao LS**, Hur W, Kim TK, Hong SW, Kim SW, Choi JE, Sung PS, Song MJ, Lee BC, Hwang D, Yoon SK. CD133+ liver cancer stem cells modulate radioresistance in human hepatocellular carcinoma. *Cancer Lett* 2012; **315**: 129-137 [PMID: 22079466 DOI: 10.1016/j.canlet.2011.10.012]
- 110 **Takebe N**, Harris PJ, Warren RQ, Ivy SP. Targeting cancer stem cells by inhibiting Wnt, Notch, and Hedgehog pathways. *Nat Rev Clin Oncol* 2011; **8**: 97-106 [PMID: 21151206 DOI: 10.1038/nrclinonc.2010.196]
- 111 **Mishra L**, Banker T, Murray J, Byers S, Thenappan A, He AR, Shetty K, Johnson L, Reddy EP. Liver stem cells and hepatocellular carcinoma. *Hepatology* 2009; **49**: 318-329 [PMID: 19111019 DOI: 10.1002/hep.22704]
- 112 **Li QL**, Gu FM, Wang Z, Jiang JH, Yao LQ, Tan CJ, Huang XY, Ke AW, Dai Z, Fan J, Zhou J. Activation of PI3K/AKT and MAPK pathway through a PDGFR $\beta$ -dependent feedback loop is involved in rapamycin resistance in hepatocellular carcinoma. *PLoS One* 2012; **7**: e33379 [PMID: 22428038 DOI: 10.1371/journal.pone.0033379]
- 113 **Ezzoukhry Z**, Louandre C, Trécherel E, Godin C, Chaffert B, Dupont S, Diouf M, Barbare JC, Mazière JC, Galmiche A. EGFR activation is a potential determinant of primary resistance of hepatocellular carcinoma cells to sorafenib. *Int J Cancer* 2012; **131**: 2961-2969 [PMID: 22514082 DOI: 10.1002/ijc.27604]
- 114 **Sieghart W**, Pinter M, Dauser B, Rohr-Udilova N, Piguet AC, Prager G, Hayden H, Dienes HP, Dufour JF, Peck-Radosavljevic M. Erlotinib and sorafenib in an orthotopic rat model of hepatocellular carcinoma. *J Hepatol* 2012; **57**: 592-599 [PMID: 22634341 DOI: 10.1016/j.jhep.2012.04.034]
- 115 **Wayne N**. Addition of tarceva® (erlotinib) to nexavar® (sorafenib) did not provide additional benefit to patients with unresectable liver cancer versus nexavar alone in phase 3 trial. South San Francisco, CA and Tokyo, Japan, 2012
- 116 **Siegel AB**, Cohen EI, Ocean A, Lehrer D, Goldenberg A, Knox JJ, Chen H, Clark-Garvey S, Weinberg A, Mandeli J, Christos P, Mazumdar M, Popa E, Brown RS Jr, Rafii S, Schwartz JD. Phase II trial evaluating the clinical and biologic effects of bevacizumab in unresectable hepatocellular carcinoma. *J Clin Oncol* 2008; **26**: 2992-2998 [PMID: 18565886 DOI: 10.1200/JCO.2007.15.9947]
- 117 **Huynh H**, Chow PK, Palanisamy N, Salto-Tellez M, Goh BC, Lee CK, Somani A, Lee HS, Kalpana R, Yu K, Tan PH, Wu J, Soong R, Lee MH, Hor H, Soo KC, Toh HC, Tan P. Bevacizumab and rapamycin induce growth suppression in mouse models of hepatocellular carcinoma. *J Hepatol* 2008; **49**: 52-60 [PMID: 18490075 DOI: 10.1016/j.jhep.2008.02.022]
- 118 **Kubota M**, Shimizu M, Baba A, Ohno T, Kochi T, Shirakami Y, Moriwaki H. Combination of bevacizumab and acyclic retinoid inhibits the growth of hepatocellular carcinoma xenografts. *J Nutr Sci Vitaminol (Tokyo)* 2014; **60**: 357-362 [PMID: 25744425 DOI: 10.3177/jnsv.60.357]

- 119 **Alberts SR**, Fitch TR, Kim GP, Morlan BW, Dakhil SR, Gross HM, Nair S. Cediranib (AZD2171) in patients with advanced hepatocellular carcinoma: a phase II North Central Cancer Treatment Group Clinical Trial. *Am J Clin Oncol* 2012; **35**: 329-333 [PMID: 21422991 DOI: 10.1097/COC.0b013e3182118cdf]
- 120 **Zhu AX**, Stuart K, Blaszkowsky LS, Muzikansky A, Reitberg DP, Clark JW, Enzinger PC, Bhargava P, Meyerhardt JA, Horgan K, Fuchs CS, Ryan DP. Phase 2 study of cetuximab in patients with advanced hepatocellular carcinoma. *Cancer* 2007; **110**: 581-589 [PMID: 17583545 DOI: 10.1002/encr.22829]
- 121 **Huynh H**, Chow PK, Tai WM, Choo SP, Chung AY, Ong HS, Soo KC, Ong R, Linnartz R, Shi MM. Dovitinib demonstrates antitumor and antimetastatic activities in xenograft models of hepatocellular carcinoma. *J Hepatol* 2012; **56**: 595-601 [PMID: 22027573 DOI: 10.1016/j.jhep.2011.09.017]
- 122 **Philip PA**, Mahoney MR, Allmer C, Thomas J, Pitot HC, Kim G, Donehower RC, Fitch T, Picus J, Erlichman C. Phase II study of Erlotinib (OSI-774) in patients with advanced hepatocellular cancer. *J Clin Oncol* 2005; **23**: 6657-6663 [PMID: 16170173 DOI: 10.1200/JCO.2005.14.696]
- 123 **Thomas MB**, Chadha R, Glover K, Wang X, Morris J, Brown T, Rashid A, Dancey J, Abbruzzese JL. Phase 2 study of erlotinib in patients with unresectable hepatocellular carcinoma. *Cancer* 2007; **110**: 1059-1067 [PMID: 17623837 DOI: 10.1002/encr.22886]
- 124 **Zhu BD**, Yuan SJ, Zhao QC, Li X, Li Y, Lu QY. Antitumor effect of Gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor, combined with cytotoxic agent on murine hepatocellular carcinoma. *World J Gastroenterol* 2005; **11**: 1382-1386 [PMID: 15761981 DOI: 10.3748/wjg.v11.i9.1382]
- 125 **O'Neil BH**, Goff LW, Kauh JS, Strosberg JR, Bekaii-Saab TS, Lee RM, Kazi A, Moore DT, Learoyd M, Lush RM, Sebti SM, Sullivan DM. Phase II study of the mitogen-activated protein kinase 1/2 inhibitor selumetinib in patients with advanced hepatocellular carcinoma. *J Clin Oncol* 2011; **29**: 2350-2356 [PMID: 21519015 DOI: 10.1200/JCO.2010.33.9432]
- 126 **Huynh H**, Soo KC, Chow PK, Tran E. Targeted inhibition of the extracellular signal-regulated kinase kinase pathway with AZD6244 (ARRY-142886) in the treatment of hepatocellular carcinoma. *Mol Cancer Ther* 2007; **6**: 138-146 [PMID: 17237274 DOI: 10.1158/1535-7163.MCT-06-0436]
- 127 **Finn RS**, Kang YK, Mulcahy M, Polite BN, Lim HY, Walters I, Baudalet C, Manekas D, Park JW. Phase II, open-label study of brivanib as second-line therapy in patients with advanced hepatocellular carcinoma. *Clin Cancer Res* 2012; **18**: 2090-2098 [PMID: 22238246 DOI: 10.1158/1078-0432.CCR-11-1991]
- 128 **Garcia JA**, Roberts LR. Phase II, open-label study of brivanib as first-line therapy in patients with advanced hepatocellular carcinoma. *J Hepatol* 2012; **56**: 486-487 [PMID: 21963517 DOI: 10.1016/j.jhep.2011.07.033]
- 129 **Huynh H**, Ngo VC, Fargnoli J, Ayers M, Soo KC, Koong HN, Thng CH, Ong HS, Chung A, Chow P, Pollock P, Byron S, Tran E. Brivanib alaninate, a dual inhibitor of vascular endothelial growth factor receptor and fibroblast growth factor receptor tyrosine kinases, induces growth inhibition in mouse models of human hepatocellular carcinoma. *Clin Cancer Res* 2008; **14**: 6146-6153 [PMID: 18829493 DOI: 10.1158/1078-0432.CCR-08-0509]
- 130 **Toh HC**, Chen PJ, Carr BI, Knox JJ, Gill S, Ansell P, McKeegan EM, Dowell B, Pedersen M, Qin Q, Qian J, Scappaticci FA, Ricker JL, Carlson DM, Yong WP. Phase 2 trial of linifanib (ABT-869) in patients with unresectable or metastatic hepatocellular carcinoma. *Cancer* 2013; **119**: 380-387 [PMID: 22833179 DOI: 10.1002/encr.27758]
- 131 **Jasinghe VJ**, Xie Z, Zhou J, Khng J, Poon LF, Senthilnathan P, Glaser KB, Albert DH, Davidsen SK, Chen CS. ABT-869, a multi-targeted tyrosine kinase inhibitor, in combination with rapamycin is effective for subcutaneous hepatocellular carcinoma xenograft. *J Hepatol* 2008; **49**: 985-997 [PMID: 18930332 DOI: 10.1016/j.jhep.2008.08.010]
- 132 **Zhu AX**, Sahani DV, Duda DG, di Tomaso E, Ancukiewicz M, Catalano OA, Sindhvani V, Blaszkowsky LS, Yoon SS, Lahdenranta J, Bhargava P, Meyerhardt J, Clark JW, Kwak EL, Hezel AF, Miksad R, Abrams TA, Enzinger PC, Fuchs CS, Ryan DP, Jain RK. Efficacy, safety, and potential biomarkers of sunitinib monotherapy in advanced hepatocellular carcinoma: a phase II study. *J Clin Oncol* 2009; **27**: 3027-3035 [PMID: 19470923 DOI: 10.1200/JCO.2008.20.9908]
- 133 **Huynh H**, Ngo VC, Choo SP, Poon D, Koong HN, Thng CH, Toh HC, Zheng L, Ong LC, Jin Y, Song IC, Chang AP, Ong HS, Chung AY, Chow PK, Soo KC. Sunitinib (SUTENT, SU11248) suppresses tumor growth and induces apoptosis in xenograft models of human hepatocellular carcinoma. *Curr Cancer Drug Targets* 2009; **9**: 738-747 [PMID: 19754358 DOI: 10.2174/156800909789271530]
- 134 **Cheng AL**, Kang YK, Lin DY, Park JW, Kudo M, Qin S, Chung HC, Song X, Xu J, Poggi G, Omata M, Pitman Lowenthal S, Lanzalone S, Yang L, Lechuga MJ, Raymond E. Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. *J Clin Oncol* 2013; **31**: 4067-4075 [PMID: 24081937 DOI: 10.1200/JCO.2012.45.8372]
- 135 **Kanai F**, Yoshida H, Tateishi R, Sato S, Kawabe T, Obi S, Kondo Y, Taniguchi M, Tagawa K, Ikeda M, Morizane C, Okusaka T, Arioka H, Shiina S, Omata M. A phase I/II trial of the oral antiangiogenic agent TSU-68 in patients with advanced hepatocellular carcinoma. *Cancer Chemother Pharmacol* 2011; **67**: 315-324 [PMID: 20390419 DOI: 10.1007/s00280-010-1320-2]
- 136 **Hara Y**, Yamashita T, Oishi N, Nio K, Hayashi T, Nomura Y, Yoshida M, Hayashi T, Hashiba T, Asahina Y, Kondo M, Okada H, Sunagozaka H, Honda M, Kaneko S. TSU-68 ameliorates hepatocellular carcinoma growth by inhibiting microenvironmental platelet-derived growth factor signaling. *Anticancer Res* 2015; **35**: 1423-1431 [PMID: 25750293]
- 137 **Kudo M**, Cheng AL, Park JW, Park JH, Liang PC, Hidaka H, Izumi N, Heo J, Lee YJ, Sheen IS, Chiu CF, Arioka H, Morita S, Arai Y. Orantinib versus placebo combined with transcatheter arterial chemoembolisation in patients with unresectable hepatocellular carcinoma (ORIENTAL): a randomised, double-blind, placebo-controlled, multicentre, phase 3 study. *Lancet Gastroenterol Hepatol* 2018; **3**: 37-46 [PMID: 28988687 DOI: 10.1016/S2468-1253(17)30290-X]
- 138 **Philips GM**, Chan IS, Swiderska M, Schroder VT, Guy C, Karaca GF, Moylan C, Venkatraman T, Feuerlein S, Syn WK, Jung Y, Witek RP, Choi S, Michelotti GA, Rangwala F, Merkle E, Lascola C, Diehl AM. Hedgehog signaling antagonist promotes regression of both liver fibrosis and hepatocellular carcinoma in a murine model of primary liver cancer. *PLoS One* 2011; **6**: e23943 [PMID: 21912653 DOI: 10.1371/journal.pone.0023943]



- 139 **Abou-Alfa GK**, Lewis LD, LoRusso P, Maitland M, Chandra P, Cheeti S, Colburn D, Williams S, Simmons B, Graham RA. Pharmacokinetics and safety of vismodegib in patients with advanced solid malignancies and hepatic impairment. *Cancer Chemother Pharmacol* 2017; **80**: 29-36 [PMID: 28523596 DOI: 10.1007/s00280-017-3315-8]
- 140 **Sekulic A**, Migden MR, Oro AE, Dirix L, Lewis KD, Hainsworth JD, Solomon JA, Yoo S, Arron ST, Friedlander PA, Marmor E, Rudin CM, Chang AL, Low JA, Mackey HM, Yauch RL, Graham RA, Reddy JC, Hauschild A. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. *N Engl J Med* 2012; **366**: 2171-2179 [PMID: 22670903 DOI: 10.1056/NEJMoa1113713]
- 141 **Jung KH**, Zhang J, Zhou C, Shen H, Gagea M, Rodriguez-Aguayo C, Lopez-Berestein G, Sood AK, Beretta L. Differentiation therapy for hepatocellular carcinoma: Multifaceted effects of miR-148a on tumor growth and phenotype and liver fibrosis. *Hepatology* 2016; **63**: 864-879 [PMID: 26599259 DOI: 10.1002/hep.28367]
- 142 **Tran S**, Ready N, Lee MK, Pietanza MC, Jungbluth AA, Pan LS, Venhaus R, Hoffman EW, Peters A, Dukelow K, Bomalaski JS, Wu BW, Old LJ. Phase II study of ADI-PEG 20 in patients with relapsed sensitive or refractory small cell lung cancer. *J Clin Oncol* 2012; **30**: E17558-E17558 [DOI: 10.1200/jco.2012.30.15\_suppl.e17558]
- 143 **Ott PA**, Carvajal RD, Pandit-Taskar N, Jungbluth AA, Hoffman EW, Wu BW, Bomalaski JS, Venhaus R, Pan L, Old LJ, Pavlick AC, Wolchok JD. Phase I/II study of pegylated arginine deiminase (ADI-PEG 20) in patients with advanced melanoma. *Invest New Drugs* 2013; **31**: 425-434 [PMID: 22864522 DOI: 10.1007/s10637-012-9862-2]
- 144 **Abou-Alfa GK**, Qin S, Ryoo BY, Lu SN, Yen CJ, Feng YH, Lim HY, Izzo F, Colombo M, Sarker D, Bolondi L, Vaccaro G, Harris WP, Chen Z, Hubner RA, Meyer T, Sun W, Harding JJ, Hollywood EM, Ma J, Wan PJ, Ly M, Bomalaski J, Johnston A, Lin CC, Chao Y, Chen LT. Phase III randomized study of second line ADI-PEG 20 plus best supportive care versus placebo plus best supportive care in patients with advanced hepatocellular carcinoma. *Ann Oncol* 2018; **29**: 1402-1408 [PMID: 29659672 DOI: 10.1093/annonc/mdy101]
- 145 **Mandl-Weber S**, Meinel FG, Jankowsky R, Odunco F, Schmidmaier R, Baumann P. The novel inhibitor of histone deacetylase resminostat (RAS2410) inhibits proliferation and induces apoptosis in multiple myeloma (MM) cells. *Br J Haematol* 2010; **149**: 518-528 [PMID: 20201941 DOI: 10.1111/j.1365-2141.2010.08124.x]
- 146 **Tak WY**, Ryoo BY, Lim HY, Kim DY, Okusaka T, Ikeda M, Hidaka H, Yeon JE, Mizukoshi E, Morimoto M, Lee MA, Yasui K, Kawaguchi Y, Heo J, Morita S, Kim TY, Furuse J, Katayama K, Aramaki T, Hara R, Kimura T, Nakamura O, Kudo M. Phase I/II study of first-line combination therapy with sorafenib plus resminostat, an oral HDAC inhibitor, versus sorafenib monotherapy for advanced hepatocellular carcinoma in east Asian patients. *Invest New Drugs* 2018; **36**: 1072-1084 [PMID: 30198057 DOI: 10.1007/s10637-018-0658-x]
- 147 **Ning ZQ**, Li ZB, Newman MJ, Shan S, Wang XH, Pan DS, Zhang J, Dong M, Du X, Lu XP. Chidamide (CS055/HBI-8000): a new histone deacetylase inhibitor of the benzamide class with antitumor activity and the ability to enhance immune cell-mediated tumor cell cytotoxicity. *Cancer Chemother Pharmacol* 2012; **69**: 901-909 [PMID: 22080169 DOI: 10.1007/s00280-011-1766-x]
- 148 **Dong M**, Ning ZQ, Xing PY, Xu JL, Cao HX, Dou GF, Meng ZY, Shi YK, Lu XP, Feng FY. Phase I study of chidamide (CS055/HBI-8000), a new histone deacetylase inhibitor, in patients with advanced solid tumors and lymphomas. *Cancer Chemother Pharmacol* 2012; **69**: 1413-1422 [PMID: 22362161 DOI: 10.1007/s00280-012-1847-5]
- 149 **Song X**, Wang J, Zheng T, Song R, Liang Y, Bhatta N, Yin D, Pan S, Liu J, Jiang H, Liu L. LBH589 Inhibits proliferation and metastasis of hepatocellular carcinoma via inhibition of gankyrin/STAT3/Akt pathway. *Mol Cancer* 2013; **12**: 114 [PMID: 24093956 DOI: 10.1186/1476-4598-12-114]
- 150 **Rathkopf D**, Wong BY, Ross RW, Anand A, Tanaka E, Woo MM, Hu J, Dzik-Jurasz A, Yang W, Scher HI. A phase I study of oral panobinostat alone and in combination with docetaxel in patients with castration-resistant prostate cancer. *Cancer Chemother Pharmacol* 2010; **66**: 181-189 [PMID: 20217089 DOI: 10.1007/s00280-010-1289-x]
- 151 **Morita S**, Oizumi S, Minami H, Kitagawa K, Komatsu Y, Fujiwara Y, Inada M, Yuki S, Kiyota N, Mitsuma A, Sawaki M, Tani H, Kimura J, Ando Y. Phase I dose-escalating study of panobinostat (LBH589) administered intravenously to Japanese patients with advanced solid tumors. *Invest New Drugs* 2012; **30**: 1950-1957 [PMID: 21964801 DOI: 10.1007/s10637-011-9751-0]
- 152 **Hainsworth JD**, Infante JR, Spigel DR, Arrowsmith ER, Boccia RV, Burris HA. A phase II trial of panobinostat, a histone deacetylase inhibitor, in the treatment of patients with refractory metastatic renal cell carcinoma. *Cancer Invest* 2011; **29**: 451-455 [PMID: 21696296 DOI: 10.3109/07357907.2011.590568]
- 153 **Abou-Alfa GK**, Puig O, Daniele B, Kudo M, Merle P, Park JW, Ross P, Peron JM, Ebert O, Chan S, Poon TP, Colombo M, Okusaka T, Ryoo BY, Minguez B, Tanaka T, Ohtomo T, Ukrainskyj S, Boissier F, Rutman O, Chen YC, Xu C, Shochat E, Jukofsky L, Reis B, Chen G, Di Laurenzio L, Lee R, Yen CJ. Randomized phase II placebo controlled study of codrituzumab in previously treated patients with advanced hepatocellular carcinoma. *J Hepatol* 2016; **65**: 289-295 [PMID: 27085251 DOI: 10.1016/j.jhep.2016.04.004]
- 154 **Piguet AC**, Saar B, Hlushchuk R, St-Pierre MV, McSheehy PM, Radojevic V, Afthinos M, Terracciano L, Djonov V, Dufour JF. Everolimus augments the effects of sorafenib in a syngeneic orthotopic model of hepatocellular carcinoma. *Mol Cancer Ther* 2011; **10**: 1007-1017 [PMID: 21487053 DOI: 10.1158/1535-7163.MCT-10-0666]



Published by **Baishideng Publishing Group Inc**  
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA  
**Telephone:** +1-925-3991568  
**E-mail:** [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
**Help Desk:** <https://www.f6publishing.com/helpdesk>  
<https://www.wjgnet.com>

