

MET inhibitors for treatment of advanced hepatocellular carcinoma: A review

Xing-Shun Qi, Xiao-Zhong Guo, Guo-Hong Han, Hong-Yu Li, Jiang Chen

Xing-Shun Qi, Xiao-Zhong Guo, Hong-Yu Li, Jiang Chen, Department of Gastroenterology, General Hospital of Shenyang Military Area, Shenyang 100840, Liaoning Province, China
Xing-Shun Qi, Guo-Hong Han, Xijing Hospital of Digestive Diseases, Fourth Military Medical University, Xi'an 710032, Shaanxi Province, China

Author contributions: Qi XS conceived this work, performed the literature search and selection, and drafted the manuscript; Guo XZ, Han GH, Li HY and Chen J gave critical comments and revised the manuscript; all authors have made an intellectual contribution to the manuscript and approved the submission.

Conflict-of-interest: All authors disclosed no conflicts of interest for this work.

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

Correspondence to: Xiao-Zhong Guo, MD, PhD, Professor, Department of Gastroenterology, General Hospital of Shenyang Military Area, No. 83 Wenhua Road, Shenyang 110840, Liaoning Province, China. guo_xiao_zhong@126.com

Telephone: +86-24-28897603

Fax: +86-24-28851113

Received: December 10, 2014

Peer-review started: December 10, 2014

First decision: December 26, 2014

Revised: January 9, 2015

Accepted: February 11, 2015

Article in press: February 11, 2015

Published online: May 14, 2015

in phase III randomized controlled trials. Recently, the subgroup analysis of a phase II randomized controlled trial has shown that tivantinib, a selective MET inhibitor, can significantly improve the overall survival in patients with MET-positive advanced HCC after the failure or intolerance of a prior systemic therapy. These findings enlighten the role of MET inhibitors in the treatment of advanced HCC. In this paper, we review all ongoing and completed clinical trials regarding this topic. As for the first-line therapy of advanced HCC, INC280 and foretinib are being evaluated in 2 phase II single-arm trials; and MSC2156119J and golvatinib plus sorafenib are being compared with sorafenib alone in 2 phase II randomized controlled trials. As for the second-line therapy of advanced HCC, tivantinib and cabozantinib are being compared with placebo in 2 phase III randomized controlled trials.

Key words: MET; Hepatocyte growth factor; Tivantinib; Cabozantinib; INC280; MSC2156119J; Golvatinib; Foretinib

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

Core tip: MET inhibitors are being tested as the first-line or second-line therapy for advanced hepatocellular carcinoma after the failure of a loco-regional or systemic therapy, especially in patients with high MET expression. Ongoing phase III randomized controlled trials will provide the decisive recommendations regarding the use of MET inhibitors in advanced hepatocellular carcinoma.

Abstract

The current standard treatment option for advanced hepatocellular carcinoma (HCC) is sorafenib, but its clinical benefit is modest. In spite of many attempts, few drugs can provide any significant improvement of survival as the first- or second-line therapy of choice

Qi XS, Guo XZ, Han GH, Li HY, Chen J. MET inhibitors for treatment of advanced hepatocellular carcinoma: A review. *World J Gastroenterol* 2015; 21(18): 5445-5453 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v21/i18/5445.htm> DOI: <http://dx.doi.org/10.3748/wjg.v21.i18.5445>

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common malignancy and the third major cause of tumor-related death in the world^[1]. The incidence of HCC and its mortality are still rising. Currently, the algorithm widely employed for the treatment of HCC is primarily based on the BCLC staging system^[2,3], in which only early stage HCC is eligible for the curative treatments, such as hepatectomy and liver transplantation. Although the rate of diagnosis of early stage HCC is gradually surpassing that of advanced stage HCC during the recent years^[4], the long-term overall survival remains very poor in patients with advanced HCC^[5,6]. The only drug approved by the United States Food and Drug Administration for the treatment of advanced HCC is sorafenib^[7,8], which is a small molecular multi-targeted receptor tyrosine kinase inhibitor that blocks tumor angiogenesis and cell proliferation. Although the exclusive role of sorafenib is being persistently challenged, nearly all phase III randomized controlled trials are negative regardless of the first-line therapy in comparison with sorafenib or the second-line therapy in comparison with placebo^[9-12]. Accordingly, the agents inhibiting other deregulated signaling pathways, such as the hepatocyte growth factor (HGF)-MET axis, are emerging^[13-16].

MET gene (also called MET proto-oncogene) was first discovered in human osteosarcoma, and it is also called the N-methyl-N'-nitroso-guanidine human osteosarcoma (MNNG HOS) transforming gene^[15,16]. In humans, *MET* gene is firstly transcribed into a 6641 base pair mature mRNA, and then translated into a 1390 amino-acid MET protein. MET receptor tyrosine kinase binds its sole ligand HGF (also called scatter factor), which activates the RAS - mitogen activated protein kinase (MAPK) pathway, phosphatidylinositol-3 kinase (PI3K) - protein kinase B (PKB or AKT) pathway, mammalian target of rapamycin pathway, signal transducer and activator of transcription (STAT) pathway, beta-catenin pathway, and Notch pathway^[14-16]. They can lead to tumor cell growth, proliferation, invasion, and metastasis^[17]. MET overexpression or activation can be observed in 20%-48% of HCC patients and predicts a worse survival^[18-21]. Experimental evidence also demonstrates that MET inhibition can be negatively associated with the growth of MET-positive HCC cells^[22]. In this paper, we perform a comprehensive review of clinical trials regarding MET inhibitors in the treatment of advanced HCC, with special emphasis on ongoing or completed phase II and III trials.

OVERVIEW OF MET INHIBITORS

MET inhibitors are often classified as selective and non-selective MET tyrosine kinase inhibitors. The former includes AMG-208, ASLAN002 (BMS

777607), Amgen, INC280, JNJ38877605, MK-2461, MK-8033, MSC2156119J (EMD 1214063), PF4217903, PHA665752, SGX126, tivantinib (ARQ 197), and volitinib (HMPL-504). The latter includes ANG-797, cabozantinib (XL184), crizotinib (Xalkori, PF-02341066), foretinib (GSK1363089 or XL880), golvatinib (E7050), MGCD265, and MP470. Among them, tivantinib, cabozantinib, INC280, MSC2156119J, golvatinib, and foretinib are being evaluated in HCC patients (Table 1).

TIVANTINIB (ARQ 197)

Phase I studies - monotherapy

Tivantinib, which is produced by ArQule, Inc. and Daiichi Sankyo Co., is a selective, non-adenosine triphosphate competitive inhibitor of MET. At least 3 phase I dose-escalation trials have evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of tivantinib monotherapy in adult patients with advanced solid tumors^[23-25]. In the first study by Rosen *et al.*^[23], a total of 79 patients with metastatic, solid tumors refractory to the available therapy were enrolled between January 2006 and August 2009 at three institutes in the United States. In the second study by Yap *et al.*^[24], 51 patients with advanced solid tumors for which the effective treatment was unavailable were enrolled between April 2007 and July 2009 at one center in the United Kingdom. In the third study by Yamamoto *et al.*^[25], 47 patients with cytologically or histologically confirmed solid malignancy for which no standard therapy was available were enrolled between February 2008 and August 2010 at 8 institutes in Japan. Both of the Western studies suggested that the recommended phase II dose should be 360 mg twice per day^[23,24]. Given that tivantinib could be rapidly metabolized by CYP2C19^[24], the Japanese study further recommended that 360 mg twice per day should be appropriate for extensive metabolizers, but 240 mg twice per day should be given to poor metabolizers^[25].

Based on the findings regarding the recommended dose of tivantinib in Western patients^[23,24], Santoro *et al.*^[26] conducted a phase Ib multi-center trial to confirm the safety of a fixed dose of tivantinib (360 mg twice per day) in previously treated HCC with Child-Pugh A or B liver cirrhosis. A total of 21 HCC patients were enrolled between March 2009 and November 2010, of whom 8 and 13 were at BCLC stage B and C, respectively. Sixteen patients were evaluable for the tumor response. None of them achieved any objective responses, and 9 patients achieved the best response of stable diseases. The median time-to-progression was 3.3 mo (range: 1.7-5.3) in these patients.

Phase I studies - combination therapy

Camacho *et al.*^[27,28] conducted a phase I b, multi-center, 3 + 3 dose-escalation trial to explore the safety

Table 1 Overview of important clinical trials

First author, Journal (Year)	Study design	Enrollment period	Drugs	Patients	No. Pts
Santoro, BJC (2013)	Phase I, open-label, single-arm study (full-text), NCT00802555	2009.3- 2010.11 completed	Tivantinib	Advanced HCC, Child-Pugh A cirrhosis, previously treated with sorafenib or other therapy	21
Santoro, Lancet Oncol (2013)	Phase II double-blind, placebo-controlled, RCT (full-text), NCT00988741	2009.10.8- 2011.8.25 completed	Tivantinib vs placebo	Advanced HCC with or without MET-high tumors, who had progressed on or were unable to tolerate first-line systemic therapy	107
Verslype/Cohn, JCO (2012, May/Feb)	Phase II randomized discontinuation trial (abstract), NCT00940225	Completed	PR: Continued open-label cabozantinib; SD: Cabozantinib vs placebo; PD: Discontinued	Advanced HCC, ≤ 1 prior systemic regimen, Child-Pugh A	41
Novartis Pharmaceuticals	Phase II, open label, single-arm study (registration), NCT01737827	Ongoing	INC280	Advanced HCC which could not be suitable for treatment with locoregional therapies or has progressed following locoregional therapy, c-MET pathway dysregulation	56
Novartis Pharmaceuticals	Phase II, double-blind, placebo-controlled RCT (registration), NCT01964235	Suspended	INC280 vs placebo	Adult patients with advanced HCC after progression or intolerance to sorafenib treatment, c-MET pathway dysregulation	69
Merck KGaA	Phase I b/ II, single-arm, trial (registration), NCT02115373	Ongoing	MSC2156119J	Advanced HCC, MET+, Child-Pugh A, who have failed sorafenib treatment	48
Qin, JCO (2014)	Phase I b/ II RCT (abstract), NCT01988493	Ongoing	Phase II: MSC2156119J vs sorafenib	Asian patients, MET-positive, advanced HCC, Child-Pugh A	158
O'Neil, JCO (2013)	Phase I b/ II, open-label, study (abstract), NCT01271504	Ongoing	Phase I b: Golvatinib plus sorafenib; Phase II: Golvatinib plus sorafenib vs sorafenib alone	Advanced HCC	13
Yau, JCO (2012)	Phase I / II trial (abstract), NCT00920192	Ongoing	Foretinib	Advanced HCC	13
Santoro, JCO (2013)	Phase III, double-blind, RCT (abstract), NCT01755767	Ongoing	Tivantinib vs placebo	MET diagnostic-high inoperable HCC treated with one prior systemic therapy	303
Abou-Alfa, JCO (2014)	Phase III, double-blind, RCT (abstract), NCT01908426	Ongoing	Cabozantinib vs placebo	Advanced HCC who have received prior sorafenib	760

SD: Stable disease; HCC: Hepatocellular carcinoma; PD: Progressive disease; PR: Partial response; RCT: Randomized controlled trial.

and preliminary efficacy of tivantinib in combination with gemcitabine in patients with advanced solid tumors. This combination therapy is generally well tolerated without clinically apparent drug-drug interaction^[27,28]. In an early report, 25 metastatic patients were enrolled^[27]. According to the RECIST criteria, 4 and 9 of 16 evaluable patients obtained a partial response and a stable disease, respectively. Subsequently, in an extended report, 32 patients were enrolled^[28]. Five of 27 evaluable patients attained a partial response.

In another phase I dose-escalation trial, Goldman *et al*^[29] evaluated the safety, pharmacokinetics, and preliminary efficacy of tivantinib combined with erlotinib in 32 patients with advanced solid malignancy.

The combination therapy was well tolerated. According to the RECIST criteria, 15 patients had a partial response ($n = 1$) or stable disease ($n = 14$).

The safety and antitumor activity of tivantinib plus sorafenib have been assessed in patients with advanced solid tumors. The type of tumors includes renal cell carcinoma^[30], melanoma^[31], HCC^[32], breast cancer, and non-small cell lung cancer^[33]. A total of 20 HCC patients received tivantinib plus sorafenib^[32]. This combination therapy was well tolerated. More importantly, the rates of response and disease control were 10% and 70%, respectively. Best responses included 1 complete response, 1 partial response, and 12 stable diseases. The median progression-free survival time was 3.5 mo. Notably, 8 patients were

previously treated with sorafenib and/or sunitinib, of whom 5 achieved a complete response ($n = 1$), a partial response ($n = 1$), or a stable disease ($n = 3$). This finding suggested the potential rationality of tivantinib as the second-line treatment option for advanced HCC after the failure of sorafenib.

Phase I studies - pooled analyses

Chai *et al.*^[34] summarized the outcomes of 53 patients with HCC or biliary tract cancer receiving tivantinib in phase I trials. They included 23 patients receiving tivantinib monotherapy and 30 patients receiving tivantinib plus sorafenib ($n = 20$), gemcitabine ($n = 8$), and erlotinib ($n = 2$). The overall response rate and disease control rate were 6% and 62%, respectively. The best responses included 1 complete response, 2 partial responses, and 30 stable diseases. On the basis of these findings, phase II trials should be warranted to further explore the efficacy of tivantinib for the treatment of advanced HCC.

Phase II studies

Recently, a phase II, randomized, multi-center, controlled trial has compared the efficacy and safety of tivantinib vs placebo as the second-line therapy for advanced HCC (ClinicalTrials.gov identifier: NCT00988741)^[35]. In this trial, 108 patients with advanced HCC, who had progressed on or were unable to tolerate the first-line systemic therapy, were randomly allocated into the tivantinib ($n = 71$) and placebo groups ($n = 36$).

In the total analysis, the findings were positive for the time to progression, but not for the progression-free survival or overall survival. The median time to progression was significantly longer in the tivantinib group than in the placebo group (1.6 mo vs 1.4 mo; HR = 0.64, $P = 0.04$). However, the statistical significance was marginal, because the absolute difference was only 0.2 mo and the upper limit of hazard ratio was very close to 1. Furthermore, the median progression-free survival and overall survival were similar between the tivantinib and placebo groups (progression-free survival: 1.5 mo vs 1.4 mo; HR = 0.67, $P = 0.06$; overall survival: 6.6 mo vs 6.2 mo; HR = 0.90, $P = 0.63$).

In the subgroup analysis of 37 patients with high MET expression (the staining intensity was scored $\geq 2+$ in more than half of tumor cells), tivantinib can significantly prolong the median time to progression (2.7 mo vs 1.4 mo; HR = 0.43, $P = 0.03$), progression-free survival (2.2 mo vs 1.4 mo; HR = 0.45, $P = 0.02$), and overall survival (7.2 mo vs 3.8 mo; HR = 0.38, $P = 0.01$). By comparison, the statistical significance disappeared in the subgroup analysis of low MET expression. These findings indicated that the survival benefit of tivantinib should be selective in advanced HCC with high MET expression.

Phase III studies

Based on the above-mentioned promising results, a phase III, randomized, double-blind, controlled trial is currently recruiting the patients with MET-high HCC to compare the efficacy and safety of tivantinib vs placebo as the second-line treatment modality (ClinicalTrials.gov identifier: NCT01755767)^[36]. Notably, the dose of tivantinib is 240 mg twice daily. This is probably due to the following facts. First, a phase II trial found a trend toward a longer median overall survival time in patients receiving tivantinib 240 mg twice daily than in those receiving tivantinib 360 mg twice daily (75 mo vs 64 mo, not significant difference)^[35]. Second, a pooled analysis of data from phase I and II trials demonstrated a positive relationship between tivantinib exposure and incidence of grade 2 or 3 neutropenia in HCC patients. If the dose of tivantinib was reduced from 360 to 240 mg twice a day, the incidence of grade 3 neutropenia would be decreased from 28% to 16%^[37].

This trial is being conducted in Europe, Australia, New Zealand, and the Americas. The pre-planned sample size is 303 patients. The target population should be: (1) the patients who have progressed after or not tolerated one prior systemic therapy; (2) those with MET-high tumor; and (3) those with Child-Pugh class A. The primary endpoint is the overall survival and the secondary endpoints include the progression-free survival and safety.

Adverse events

The most common adverse events related to tivantinib include neutropenia, leukocytopenia, anemia, fatigue, and anorexia (Table 2). Notably, 3 studies were performed in a dose-escalation scheme^[23-25], and another 2 studies at a fixed dose of 360 mg twice a day^[26,35]. Therefore, the incidence of grade 3 or 4 adverse events seemed to be relatively higher in the latter 2 studies^[26,35].

CABOZANTINIB (XL184)

Phase I studies

Cabozantinib can inhibit MET, VEGFR2/KDR, KIT, RET, FLT3, and Tie-2, which is produced by Exelixis. A phase I dose-escalation study evaluated the safety and pharmacokinetics of cabozantinib in 85 patients with advanced solid tumors^[38]. A total of 13 dose levels were explored at 2 different schedules of administration and formulations of cabozantinib. The maximum tolerated capsule dose was 175 mg daily.

Phase II studies

A phase II, randomized discontinuation trial (ClinicalTrials.gov Identifier: NCT00940225) is ongoing to evaluate the efficacy of cabozantinib in subjects with advanced solid tumors. Estimated sample size for this enrollment

Table 2 Adverse events related to tivantinib: An overview of data from phase I and II trials *n* (%)

Adverse event	Rosen, (2011) <i>n</i> = 79		Yap, (2011) <i>n</i> = 51		Yamamoto, (2013) <i>n</i> = 47		Santoro, (2013) <i>n</i> = 21		Santoro, (2013) <i>n</i> = 71	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Pancytopenia	NA	NA	NA	NA	NA	NA	NA	NA	2 (2.8)	2 (2.8)
Leukocytopenia	NA	1 (1.3)	2 (3.9)	1 (2.6)	22 (46.8)	8 (17.0)	8 (38)	4 (19)	5 (7.0)	3 (4.2)
Neutropenia	NA	2 (2.5)	5 (9.8)	4 (7.8)	15 (31.9)	9 (19.1)	11 (52)	8 (38)	20 (28.2)	12 (16.9)
Anemia	6 (7.6)	3 (3.8)	3 (5.9)	0 (0)	12 (25.5)	5 (10.6)	10 (48)	5 (24)	11 (15.5)	8 (11.3)
Thrombocytopenia	NA	1 (1.3)	2 (3.9)	1 (2.6)	NA	NA	3 (14)	0 (0)	6 (8.5)	4 (4.9)
Lymphopenia	NA	NA	2 (3.9)	0 (0)	7 (14.9)	1 (2.1)	2 (10)	0 (0)	NA	NA
Fatigue	11 (13.9)	1 (1.3)	10 (19.6)	1 (2.6)	19 (40.4)	1 (2.1)	6 (29)	1 (5)	7 (9.9)	3 (4.2)
Anorexia	NA	NA	4 (7.8)	0 (0)	8 (17.0)	2 (4.3)	8 (38)	0 (0)	7 (9.9)	1 (1.4)
Nausea	11 (13.9)	1 (1.3)	7 (13.7)	0 (0)	4 (8.5)	0 (0)	NA	NA	2 (2.8)	1 (1.4)
Vomiting	8 (10.1)	1 (1.3)	7 (13.7)	0 (0)	NA	NA	3 (14)	0 (0)	4 (5.6)	0 (0)
Diarrhoea	5 (6.3)	NA	5 (9.8)	0 (0)	NA	NA	6 (29)	0 (0)	5 (7.0)	0 (0)
Constipation	NA	NA	2 (3.9)	0 (0)	NA	NA	NA	NA	NA	NA
Dyspepsia	NA	NA	1 (2.6)	0 (0)	NA	NA	NA	NA	NA	NA
Dysphagia	NA	NA	1 (2.6)	0 (0)	NA	NA	NA	NA	NA	NA
Alopecia	NA	NA	1 (2.6)	0 (0)	4 (8.5)	0 (0)	4 (19)	0 (0)	3 (4.2)	0 (0)
Asthenia	NA	NA	NA	NA	1 (1.3)	NA	10 (48)	2 (10)	8 (11.3)	1 (1.4)
Abdominal pain	NA	NA	NA	NA	NA	NA	NA	NA	1 (1.4)	1 (1.4)
Hepatic failure	NA	1 (1.3)	NA	NA	NA	NA	NA	NA	NA	NA
ALT increased	NA	NA	NA	NA	3 (6.4)	0 (0)	NA	NA	NA	NA
AST increased	NA	1 (1.3)	NA	NA	NA	NA	NA	NA	NA	NA
ALP increased	NA	1 (1.3)	NA	NA	NA	NA	NA	NA	NA	NA
Hypokalemia	NA	NA	1 (2.6)	0 (0)	NA	NA	NA	NA	NA	NA
Dehydration	NA	1 (1.3)	NA	NA	NA	NA	NA	NA	NA	NA
Hyperammonaemia	NA	1 (1.3)	NA	NA	NA	NA	NA	NA	NA	NA
Hyponatraemia	NA	1 (1.3)	NA	NA	NA	NA	NA	NA	NA	NA
Hyperbilirubinemia	NA	NA	NA	NA	NA	NA	3 (14)	1 (5)	NA	NA
Rash	NA	NA	6 (11.8)	0 (0)	3 (6.4)	0 (0)	NA	NA	NA	NA
Pruritus	NA	NA	1 (2.6)	0 (0)	NA	NA	NA	NA	2 (2.8)	0 (0)
Hot flush	NA	NA	2 (3.9)	0 (0)	NA	NA	NA	NA	NA	NA
Hand-foot syndrome	NA	NA	1 (2.6)	1 (2.6)	NA	NA	NA	NA	NA	NA
Mucosal inflammation	NA	NA	2 (3.9)	2 (3.9)	NA	NA	NA	NA	NA	NA
Tongue discoloration	NA	NA	3 (5.9)	0 (0)	NA	NA	NA	NA	NA	NA
Peripheral oedema	NA	NA	NA	NA	NA	NA	3 (14)	0 (0)	NA	NA
Weight loss	NA	NA	3 (5.9)	0 (0)	NA	NA	NA	NA	NA	NA
Pyrexia	NA	NA	1 (2.6)	0 (0)	NA	NA	NA	NA	4 (5.6)	0 (0)
Sepsis	NA	NA	NA	NA	NA	NA	NA	NA	5 (7.0)	5 (7.0)
Prolonged QTc	NA	NA	NA	NA	3 (6.4)	0 (0)	NA	NA	NA	NA
Bradycardia	NA	NA	NA	NA	2 (4.3)	0 (0)	NA	NA	8 (11.3)	1 (1.4)

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; NA: Not available.

is 1300 patients with different types of tumors. The trial plans are as follows: all subjects will receive cabozantinib for 12 wk; subsequently, the subjects with a partial or complete response will continue to receive cabozantinib until disease progression; on the other hand, the subjects with a stable disease will be randomly allocated into a cabozantinib or placebo group; and the subjects with a progressive disease will discontinue the drug. The subjects will be unblinded until disease progression. The preliminary results regarding metastatic non-small cell lung cancer and advanced HCC have been reported in ASCO annual meeting abstracts^[39-41].

In the trial reported by Verslype *et al*^[40] and Cohn *et al*^[41], 41 patients with advanced HCC and Child-Pugh class A who received ≤ 1 prior systemic regimen were enrolled. Half of them received a prior sorafenib. In

the lead-in stage, the patients received 100 mg daily over 12 wk. According to the original RECIST criteria, 2 of 36 patients who were evaluable for the tumor assessment at the 12th week achieved a confirmed partial response. The overall disease control rate (partial response + stable disease) at the 12th week was 68%. In the randomization stage, one additional patient achieved a confirmed partial response. Given the clinical benefits of cabozantinib in advanced HCC patients, its efficacy should be further confirmed.

Phase III studies

A phase III, randomized, double-blind, controlled trial is ongoing to compare the efficacy of cabozantinib vs placebo as the second-line treatment modality for advanced HCC patients who have received a prior sorafenib (ClinicalTrials.gov Identifier: NCT01908426)^[42].

A total of 760 subjects will be recruited into this trial. The primary endpoint is the overall survival and the secondary endpoints include the progression-free survival and objective response rate. Notably, in contrast to the phase III trial of tivantinib which enrolled the participants with MET-high advanced HCC^[36], the trial of cabozantinib does not screen the participants according to the MET expression.

INC280

Phase I studies

INC280, which is produced by Novartis Pharmaceuticals, is a highly selective MET inhibitor. In a phase I dose-escalation study, Bang *et al.*^[43] evaluated the safety and tolerability of INC280 in 32 patients with advanced solid tumors that were refractory to the current therapy or for which the effective therapy was lacking. Eligible patients also had a confirmed MET dysregulation. The researchers recommended that the phase II dose should be 600 mg twice a day. Dose expansion is ongoing in patients with non-small cell lung cancer, HCC, and other tumors.

Phase II studies

A phase II, single-arm, open-label study is being carried out to explore the efficacy and safety of INC280 as the first-line treatment modality for advanced HCC and MET dysregulation after the failure of locoregional therapies (ClinicalTrials.gov Identifier: NCT01737827). This study will exclude the patients who have received a prior systemic chemotherapy or molecular-targeted therapy for HCC. The primary endpoint is the time to progression according to the RECIST criteria. The participants will be enrolled from China, Singapore, and Thailand. The sample size should be estimated as 56 patients.

In addition, a phase II, randomized, multi-center, double-blind, placebo-controlled study has been designed to evaluate the efficacy and safety of INC280 as the second-line treatment option for advanced HCC after sorafenib is ineffective or intolerant (ClinicalTrials.gov Identifier: NCT01964235). However, it is still suspended without any patient recruitment.

MSC2156119J (EMD 1214063)

Phase I studies

MSC2156119J, which is produced by Merck KGaA, is a highly selective MET inhibitor. In a phase I dose-escalation study, Falchook *et al.*^[44] found that MSC2156119J was well tolerated and had an antitumor activity in 126 patients with advanced solid tumors (ClinicalTrials.gov Identifier: NCT01014936). The recommended phase II dose of MSC2156119J was 500 mg per day. Another Japanese phase I trial is ongoing to evaluate safety and efficacy of MSC2156119J in subjects with malignant solid tumors (ClinicalTrials.gov Identifier: NCT01832506).

Phase II studies

A phase Ib/II, single-arm, multi-center trial, which will evaluate the efficacy and safety of MSC2156119J as the second-line treatment option for MET-positive advanced HCC, is under way (ClinicalTrials.gov Identifier: NCT02115373). Additionally, a phase Ib/II, randomized, multi-center, open-label trial will compare the efficacy of MSC2156119J vs sorafenib for the improvement of the time to progression in Asian patients with MET-positive advanced HCC and Child-Pugh class A (ClinicalTrials.gov Identifier: NCT01988493)^[45]. The patient enrollment has been launched since January 2014. A total of 158 patients are estimated, including 18 and 140 patients for the phase Ib and II cohorts, respectively. The primary endpoint is the time to progression.

GOLVATINIB (E7050)

Golvatinib, which is produced by Eisai Inc., can inhibit MET and multiple members of the Eph receptor family as well as c-Kit and Ron. Two phase I dose-finding studies determined the maximum tolerated dose and safety of golvatinib monotherapy in advanced solid tumors. The first study conducted in Japan found that the maximum tolerated dose should be 200 mg twice per day^[46]; by comparison, the second study conducted in the United Kingdom demonstrated that the drug-related toxicity was manageable at a maximum tolerated dose of 400 mg once daily^[47].

An ongoing phase Ib/II study will explore the safety and efficacy of golvatinib plus sorafenib in patients with advanced HCC (ClinicalTrials.gov Identifier: NCT01271504)^[48]. Thirteen patients have been enrolled in the phase I cohort, demonstrating that the maximum tolerated dose should be golvatinib 200 mg once daily and sorafenib 400 mg twice per day. Among them, 2 and 4 patients were confirmed to have a partial response and a stable disease, respectively. In the phase II cohort, the participants are being recruited to assess whether or not the efficacy of golvatinib plus sorafenib will be superior to that of sorafenib alone.

FORETINIB (GSK1363089, FORMERLY XL880)

Foretinib, which is produced by GlaxoSmithKline, can inhibit MET, RON, AXL, TIE-2, and VEGFR. A phase I/II study evaluated the safety and efficacy of foretinib in Asian patients with unresectable or metastatic HCC, but without a prior sorafenib or other multi-kinase inhibitors (ClinicalTrials.gov Identifier: NCT00920192)^[49]. In the phase I cohort with a standard 3 + 3 dose escalation design, 13 patients were enrolled. The investigators found that the maximum tolerated dose should be 30 mg once daily. In the phase II expansion cohort, 32 patients further received 30 mg once daily. In 38 evaluable patients,

Table 3 Current status of MET inhibitors for the treatment of advanced hepatocellular carcinoma

First-line therapy of advanced HCC
INC280: A phase II sing-arm trial (NCT01737827)
MSC2156119J <i>vs</i> sorafenib: A phase II RCT (NCT01988493)
Golvatinib plus sorafenib <i>vs</i> sorafenib alone: A phase II RCT (NCT01271504)
Foretinib: A phase II sing-arm trial (NCT00920192)
Second-line therapy of advanced HCC
Tivantinib <i>vs</i> placebo: A phase II RCT (NCT00988741)
Tivantinib <i>vs</i> placebo: A phase III RCT (NCT01755767)
Cabozantinib <i>vs</i> placebo: A phase II randomized discontinuation trial (NCT00940225)
Cabozantinib <i>vs</i> placebo: A phase III RCT (NCT01908426)
INC280 <i>vs</i> placebo: A phase II RCT (NCT01964235)
MSC2156119J: A phase II sing-arm trial (NCT02115373)

HCC: Hepatocellular carcinoma.

the objective response rate was 24%, the disease stabilization rate was 79%, and the median time to progression was 4.2 mo. These findings supported the necessity of a randomized controlled trial in future.

CONCLUSION

MET inhibitors are being widely tested as the first-line or second-line therapy for advanced HCC after the failure of a loco-regional or systemic therapy (Table 3). At present, the most striking findings are from a phase II randomized controlled trial in which the survival benefit has been achieved in MET-positive advanced HCC patients treated with tivantinib after the failure of a systemic therapy. Notably, this trial has a relatively small sample size ($n = 108$) and only a low proportion of included patients had MET-high tumors (34%, 37/108). Certainly, the evidence from phase III randomized controlled trials should be warranted to establish the recommendations regarding the use of MET inhibitors in advanced HCC.

REFERENCES

- 1 Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; **127**: 2893-2917 [PMID: 21351269 DOI: 10.1002/ijc.25516]
- 2 Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology* 2011; **53**: 1020-1022 [PMID: 21374666 DOI: 10.1002/hep.24199]
- 3 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]
- 4 Ulahannan SV, Duffy AG, McNeel TS, Kish JK, Dickie LA, Rahma OE, McGlynn KA, Greten TF, Altekruse SF. Earlier presentation and application of curative treatments in hepatocellular carcinoma. *Hepatology* 2014; **60**: 1637-1644 [PMID: 24996116 DOI: 10.1002/hep.27288]
- 5 Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; **61**: 69-90 [PMID: 21296855 DOI: 10.3322/caac.20107]
- 6 Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin* 2013; **63**: 11-30 [PMID: 23335087 DOI: 10.3322/caac.21166]
- 7 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]
- 8 Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, Liu J, Wang J, Tak WY, Pan H, Burock K, Zou J, Voliotis D, Guan Z. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; **10**: 25-34 [PMID: 19095497 DOI: 10.1016/S1470-2045(08)70285-7]
- 9 Kudo M, Han G, Finn RS, Poon RT, Blanc JF, Yan L, Yang J, Lu L, Tak WY, Yu X, Lee JH, Lin SM, Wu C, Tanwandee T, Shao G, Walters IB, Dela Cruz C, Poulart V, Wang JH. Brivanib as adjuvant therapy to transarterial chemoembolization in patients with hepatocellular carcinoma: A randomized phase III trial. *Hepatology* 2014; **60**: 1697-1707 [PMID: 24996197 DOI: 10.1002/hep.27290]
- 10 Llovet JM, Decaens T, Raoul JL, Boucher E, Kudo M, Chang C, Kang YK, Assenat E, Lim HY, Boige V, Mathurin P, Fartoux L, Lin DY, Bruix J, Poon RT, Sherman M, Blanc JF, Finn RS, Tak WY, Chao Y, Ezzeddine R, Liu D, Walters I, Park JW. Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized phase III BRISK-PS study. *J Clin Oncol* 2013; **31**: 3509-3516 [PMID: 23980090 DOI: 10.1200/JCO.2012.47.3009]
- 11 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]
- 12 Pfizer Discontinues Phase 3 Trial of Sutent® in Advanced Hepatocellular Carcinoma. Available from: URL: <http://cn.reuters.com/article/2010/04/22/idUS250005+22-Apr-2010+BW20100422>
- 13 Eder JP, Vande Woude GF, Boerner SA, LoRusso PM. Novel therapeutic inhibitors of the c-Met signaling pathway in cancer. *Clin Cancer Res* 2009; **15**: 2207-2214 [PMID: 19318488 DOI: 10.1158/1078-0432.CCR-08-1306]
- 14 Blumenschein GR, Mills GB, Gonzalez-Angulo AM. Targeting the hepatocyte growth factor-cMET axis in cancer therapy. *J Clin Oncol* 2012; **30**: 3287-3296 [PMID: 22869872 DOI: 10.1200/JCO.2011.40.3774]
- 15 Gherardi E, Birchmeier W, Birchmeier C, Vande Woude G. Targeting MET in cancer: rationale and progress. *Nat Rev Cancer* 2012; **12**: 89-103 [PMID: 22270953 DOI: 10.1038/nrc3205]
- 16 Scagliotti GV, Novello S, von Pawel J. The emerging role of MET/HGF inhibitors in oncology. *Cancer Treat Rev* 2013; **39**: 793-801 [PMID: 23453860 DOI: 10.1016/j.ctrv.2013.02.001]
- 17 Ma PC, Maulik G, Christensen J, Salgia R. c-Met: structure, functions and potential for therapeutic inhibition. *Cancer Metastasis Rev* 2003; **22**: 309-325 [PMID: 12884908]
- 18 Ueki T, Fujimoto J, Suzuki T, Yamamoto H, Okamoto E. Expression of hepatocyte growth factor and its receptor, the c-met proto-oncogene, in hepatocellular carcinoma. *Hepatology* 1997; **25**: 619-623 [PMID: 9049208 DOI: 10.1002/hep.510250321]
- 19 Kaposi-Novak P, Lee JS, Gómez-Quiroz L, Coulouarn C, Factor VM, Thorgeirsson SS. Met-regulated expression signature defines a subset of human hepatocellular carcinomas with poor prognosis and aggressive phenotype. *J Clin Invest* 2006; **116**: 1582-1595 [PMID: 16710476 DOI: 10.1172/JCI27236]
- 20 Ke AW, Shi GM, Zhou J, Wu FZ, Ding ZB, Hu MY, Xu Y, Song

- ZJ, Wang ZJ, Wu JC, Bai DS, Li JC, Liu KD, Fan J. Role of overexpression of CD151 and/or c-Met in predicting prognosis of hepatocellular carcinoma. *Hepatology* 2009; **49**: 491-503 [PMID: 19065669 DOI: 10.1002/hep.22639]
- 21 **Osada S**, Kanematsu M, Imai H, Goshima S. Clinical significance of serum HGF and c-Met expression in tumor tissue for evaluation of properties and treatment of hepatocellular carcinoma. *Hepatogastroenterology* 2008; **55**: 544-549 [PMID: 18613405]
 - 22 **You H**, Ding W, Dang H, Jiang Y, Rountree CB. c-Met represents a potential therapeutic target for personalized treatment in hepatocellular carcinoma. *Hepatology* 2011; **54**: 879-889 [PMID: 21618573 DOI: 10.1002/hep.24450]
 - 23 **Rosen LS**, Senzer N, Mekhail T, Ganapathi R, Chai F, Savage RE, Waghorne C, Abbadessa G, Schwartz B, Dreicer R. A phase I dose-escalation study of Tivantinib (ARQ 197) in adult patients with metastatic solid tumors. *Clin Cancer Res* 2011; **17**: 7754-7764 [PMID: 21976535 DOI: 10.1158/1078-0432.CCR-11-1002]
 - 24 **Yap TA**, Olmos D, Brunetto AT, Tunariu N, Barriuso J, Riisnaes R, Pope L, Clark J, Futreal A, Germuska M, Collins D, deSouza NM, Leach MO, Savage RE, Waghorne C, Chai F, Garmey E, Schwartz B, Kaye SB, de Bono JS. Phase I trial of a selective c-MET inhibitor ARQ 197 incorporating proof of mechanism pharmacodynamic studies. *J Clin Oncol* 2011; **29**: 1271-1279 [PMID: 21383285 DOI: 10.1200/JCO.2010.31.0367]
 - 25 **Yamamoto N**, Murakami H, Nishina T, Hirashima T, Sugio K, Muro K, Takahashi T, Naito T, Yasui H, Akinaga S, Koh Y, Boku N. The effect of CYP2C19 polymorphism on the safety, tolerability, and pharmacokinetics of tivantinib (ARQ 197): results from a phase I trial in advanced solid tumors. *Ann Oncol* 2013; **24**: 1653-1659 [PMID: 23413279 DOI: 10.1093/annonc/mdt014]
 - 26 **Santoro A**, Simonelli M, Rodriguez-Lopez C, Zucali P, Camacho LH, Granito A, Senzer N, Rimassa L, Abbadessa G, Schwartz B, Lamar M, Savage RE, Bruix J. A Phase-Ib study of tivantinib (ARQ 197) in adult patients with hepatocellular carcinoma and cirrhosis. *Br J Cancer* 2013; **108**: 21-24 [PMID: 23287988 DOI: 10.1038/bjc.2012.556]
 - 27 **Camacho LH**, Bendell JC, John-Reid L, Campos LT, Jones SF, Kazakin J, Savage R, Schwartz BE, Abbadessa G, Saleh MN. Phase Ib dose-escalation trial evaluating c-MET inhibitor ARQ 197 administered in combination with gemcitabine to patients (pts) with advanced solid tumors. *J Clin Oncol* 2010; **28** (15 Suppl): e13008
 - 28 **Camacho LH**, Pant S, Saleh MN, Abbadessa G, Kazakin J, Schwartz BE, Bendell JC. Phase Ib results of c-MET inhibitor ARQ 197 in combination with gemcitabine in a cohort of patients (pts) with advanced breast, ovarian, and uterine tumors. *J Clin Oncol* 2011; **29** (25 Suppl): 3077
 - 29 **Goldman JW**, Laux I, Chai F, Savage RE, Ferrari D, Garmey EG, Just RG, Rosen LS. Phase I dose-escalation trial evaluating the combination of the selective MET (mesenchymal-epithelial transition factor) inhibitor tivantinib (ARQ 197) plus erlotinib. *Cancer* 2012; **118**: 5903-5911 [PMID: 22605616 DOI: 10.1002/cncr.27575]
 - 30 **Puzanov I**, Sosman JA, Santoro A, Martell RE, Dy GK, Goff LW, Ma WW, Fetterly GJ, Michael SA, Means-Powell JA, Chai F, Lamar M, Strauss GM, Zucali PA, Chiang WM, Jarboe J, Schwartz BE, Adjei AA. Safety and efficacy of MET inhibitor tivantinib (ARQ 197) combined with sorafenib in patients (pts) with renal cell carcinoma (RCC) from a phase I study. *J Clin Oncol* 2012; **30** (15 Suppl): 4545
 - 31 **Means-Powell JA**, Adjei AA, Puzanov I, Dy GK, Goff LW, Ma WW, Fetterly GJ, Michael SA, Chai F, Lamar M, Schwartz BE, Sosman JA. Safety and efficacy of MET inhibitor tivantinib (ARQ 197) combined with sorafenib in patients (pts) with NRAS wild-type or mutant melanoma from a phase I study. *J Clin Oncol* 2012; **30** (15 Suppl): 8519
 - 32 **Martell RE**, Puzanov I, Ma WW, Santoro A, Dy GK, Goff LW, Fetterly GJ, Michael SA, Means-Powell JA, Chai F, Lamar M, Simonelli M, Chiang WM, Jarboe J, Schwartz BE, Adjei AA. Safety and efficacy of MET inhibitor tivantinib (ARQ 197) combined with sorafenib in patients (pts) with hepatocellular carcinoma (HCC) from a phase I study. *J Clin Oncol* 2012; **30** (15 Suppl): 4117
 - 33 **Adjei AA**, Sosman JA, Martell RE, Dy GK, Goff LW, Ma WW, Horn L, Fetterly GJ, Michael SA, Means JA, Chai F, Lamar M, Strauss GM, Chiang W, Jarboe J, Schwartz BE, Puzanov I. Efficacy in selected tumor types in a phase I study of the c-MET inhibitor ARQ 197 in combination with sorafenib. *J Clin Oncol* 2011; **29** (15 Suppl): 3034
 - 34 **Chai F**, Abbadessa G, Savage R, Zahir H, Chen Y, Lamar M, Kazakin J, Ferrari D, Roemeling Rv, Schwartz B. Phase I experience of tivantinib in patients with hepatocellular carcinoma (HCC) or biliary tract cancer (BTC). *Ann Oncol* 2012; **23** (9 Suppl): ix245
 - 35 **Santoro A**, Rimassa L, Borbath I, Daniele B, Salvagni S, Van Laethem JL, Van Vlierberghe H, Trojan J, Kolligs FT, Weiss A, Miles S, Gasbarrini A, Lencioni M, Cicalese L, Sherman M, Gridelli C, Buggisch P, Gerken G, Schmid RM, Boni C, Personeni N, Hassoun Z, Abbadessa G, Schwartz B, Von Roemeling R, Lamar ME, Chen Y, Porta C. Tivantinib for second-line treatment of advanced hepatocellular carcinoma: a randomised, placebo-controlled phase 2 study. *Lancet Oncol* 2013; **14**: 55-63 [PMID: 23182627 DOI: 10.1016/S1470-2045(12)70490-4]
 - 36 **Santoro A**, Porta C, Rimassa L, Borbath I, Daniele B, Finn RS, Raoul JL, Schwartz LH, He AR, Trojan J, Peck-Radosavljevic M, Abbadessa G, Goldberg TR, Bruix J. Metiv-HCC: A phase III clinical trial evaluating tivantinib (ARQ 197), a MET inhibitor, versus placebo as second-line in patients (pts) with MET-high inoperable hepatocellular carcinoma (HCC). *J Clin Oncol* 2013; **31** (15 Suppl): TPS4159
 - 37 **Zahir H**, Kastrissios H, Carothers T, Jansen M, Savage R, Abbadessa G, Chai F, Schwartz B, Miller R, Tokui T. Exposure-response relationship to assess the risk of neutropenia in patients with hepatocellular carcinoma (HCC) treated with tivantinib. *Ann Oncol* 2012; **23** (9 Suppl): 244-245
 - 38 **Kurzrock R**, Sherman SI, Ball DW, Forastiere AA, Cohen RB, Mehra R, Pfister DG, Cohen EE, Janisch L, Nauling F, Hong DS, Ng CS, Ye L, Gagel RF, Frye J, Müller T, Ratain MJ, Salgia R. Activity of XL184 (Cabozantinib), an oral tyrosine kinase inhibitor, in patients with medullary thyroid cancer. *J Clin Oncol* 2011; **29**: 2660-2666 [PMID: 21606412 DOI: 10.1200/JCO.2010.32.4145]
 - 39 **Hellerstedt BA**, Edelman G, Vogelzang NJ, Kluger HM, Yassenchak CA, Shen X, Ramies DA, Gordon MS, Lara P. Activity of cabozantinib (XL184) in metastatic NSCLC: Results from a phase II randomized discontinuation trial (RDT). *J Clin Oncol* 2012; **30** (15 Suppl): 7514
 - 40 **Verslype C**, Cohn AL, Kelley RK, Yang TS, Su WC, Ramies DA, Lee Y, Shen X, Cutsem EV. Activity of cabozantinib (XL184) in hepatocellular carcinoma: Results from a phase II randomized discontinuation trial (RDT). *J Clin Oncol* 2012; **30** (15 Suppl): 4007
 - 41 **Cohn AL**, Kelley RK, Yang TS, Su WC, Verslype C, Ramies DA, Lee Y, Shen X, Cutsem EV. Activity of cabozantinib (XL184) in hepatocellular carcinoma patients (pts): Results from a phase II randomized discontinuation trial (RDT). *J Clin Oncol* 2012; **30** (4 Suppl): 261
 - 42 **Abou-Alfa GK**, Cheng AL, Meyer T, El-Khoueiry AB, Ikeda M, Chun HG, Faivre SJ, Furuse J, Knox JJ, Okusaka T, Ping J, Borgman-Hagey AE, Kelley RK, Katie R. Phase 3 randomized, double-blind, controlled study of cabozantinib (XL184) versus placebo in subjects with hepatocellular carcinoma who have received prior sorafenib (CELESTIAL; NCT01908426). *J Clin Oncol* 2014; **32** (15 Suppl): TPS4150
 - 43 **Bang YJ**, Su WC, Nam DH, Lim WT, Bauer TM, Brana I, Poon RTP, Hong DS, Lin CC, Peng B, Zhang Y, Zhao S, Kumar A, Akimov M, Ma B. Phase I study of the safety and efficacy of INC280 in patients with advanced MET-dependent solid tumors. *J Clin Oncol* 2014; **32** (15 Suppl): 2520
 - 44 **Falchook GS**, Hong DS, Amin HM, Fu S, Piha-Paul SA, Janku F, Granda JG, Zheng H, Klevesath MB, Köhler K, Bladt F, John A,

- Kurzrock R. Results of the first-in-human phase I trial assessing MSC2156119J (EMD 1214063), an oral selective c-Met inhibitor, in patients (pts) with advanced solid tumors. *J Clin Oncol* 2014; **32** (15 Suppl): 2521
- 45 **Qin S**, Cheng AL, Lim HY, Xu L, Bladt F, Johne A, Li C, Zheng H, Massimini G. A multicenter, randomized, phase Ib/II trial of the oral c-Met inhibitor MSC2156119J as monotherapy versus sorafenib in Asian patients with MET-positive (MET) advanced hepatocellular carcinoma (HCC) and Child-Pugh Class A liver function. *J Clin Oncol* 2014; **32** (15 Suppl): TPS4151
- 46 **Doi T**, Yoshino T, Fuse N, Bando H, Tahara M, Fujino MOK, Nishioka Y, Matsuura K, Sawada T, Ohtsu A. Phase I dose-finding study of golvatinib (E7050), a c-Met and Eph receptor targeted multi-kinase inhibitor, administered orally BID to patients with advanced solid tumors. *J Clin Oncol* 2012; **30** (15 Suppl): 3079
- 47 **Daniele G**, Ranson M, Blanco-Codesido M, Dean EJ, Shah KJ, Krebs M, Brunetto A, Greystoke A, Johnston C, Kuznetsov G, Matijevic M, Mistry B, Heras Bdl, Molife LR. Phase I dose-finding study of golvatinib (E7050), a c-Met and Eph receptor targeted multi-kinase inhibitor, administered orally QD to patients with advanced solid tumors. *J Clin Oncol* 2012; **30** (15 Suppl): 3030
- 48 **O'Neil BH**, Bendell JC, Modiano MR, Machiels JPH, Versola MJ, Hodge JP, Sawarna K, Tse N. Phase I/II study of E7050 (golvatinib) in combination with sorafenib in patients (pts) with advanced hepatocellular carcinoma (HCC): Phase I results. *J Clin Oncol* 2013; **31** (4 Suppl): 94
- 49 **Yau TC**, Sukeepaisarnjaroen W, Chao Y, Yen CJ, Lausoontornsiri W, Chen PJ, Sanpajit T, Lencioni R, Camp AC, Cox DS, Kallender H, Ottesen LH, Poon RTP. A phase I/II study of foretinib, an oral multikinase inhibitor targeting MET, RON, AXL, TIE-2, and VEGFR in advanced hepatocellular carcinoma (HCC). *J Clin Oncol* 2012; **30** (15 Suppl): 4108

P- Reviewer: Grassi G, Lin ZY **S- Editor:** Ma YJ
L- Editor: Wang TQ **E- Editor:** Zhang DN





Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgooffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>



ISSN 1007-9327

