

MET inhibitors for treatment of advanced hepatocellular carcinoma: A review

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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 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

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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.
INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common malignancy and the third major cause of tumor-related death in the world\(^\text{[1]}\). 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\(^\text{[2,3]}\), 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\(^\text{[4]}\), the long-term overall survival remains very poor in patients with advanced HCC\(^\text{[5,6]}\). The only drug approved by the United States Food and Drug Administration for the treatment of advanced HCC is sorafenib\(^\text{[7,8]}\), 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\(^\text{[9-12]}\). Accordingly, the agents inhibiting other deregulated signaling pathways, such as the hepatocyte growth factor (HGF)-MET axis, are emerging\(^\text{[13-16]}\).

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 (MNN HOS) transforming gene\(^\text{[15,16]}\). 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\(^\text{[14-16]}\). They can lead to tumor cell growth, proliferation, invasion, and metastasis\(^\text{[17]}\). MET overexpression or activation can be observed in 20%-48% of HCC patients and predicts a worse survival\(^\text{[18-21]}\). Experimental evidence also demonstrates that MET inhibition can be negatively associated with the growth of MET-positive HCC cells\(^\text{[22]}\). 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, cabozaatinib (XL184), crizotinib (Xalkori, PF-02341066), foretinib (GSK1363089 or XL880), gol-vatinib (E7050), MGCD265, and MP470. Among them, tivantinib, cabozaatinib, INC280, MSC2156119J, gol-vatinib, 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\(^\text{[23-25]}\). In the first study by Rosen et al\(^\text{[23]}\), 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\(^\text{[24]}\), 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\(^\text{[25]}\), 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 I dose should be 360 mg twice per day\(^\text{[23,24]}\). Given that tivantinib could be rapidly metabolized by CYP2C19\(^\text{[24]}\), 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\(^\text{[26]}\).

Based on the findings regarding the recommended dose of tivantinib in Western patients\(^\text{[22,23]}\), Santoro et al\(^\text{[26]}\) 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\(^\text{[27,28]}\) conducted a phase I b, multi-center, 3 + 3 dose-escalation trial to explore the safety...
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[35] 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 ≥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 enrolment
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.

In the trial reported by Verslype et al. and Cohn et al., 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).
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 II trial of tivantinib which enrolled the participants with MET-high advanced HCC\textsuperscript{[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\textsuperscript{[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, Falchuck et al\textsuperscript{[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)\textsuperscript{[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\textsuperscript{[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\textsuperscript{[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)\textsuperscript{[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)\textsuperscript{[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,
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 Ⅲ 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.

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