Available online at www.sciencedirect.com

ScienceDirect

Chronic Diseases and Translational Medicine 3 (2017) 148−153

www.keaipublishing.com/en/journals/cdtm/

www.cdatm.org

Perspective

Targeting *MET* in cancer therapy

Hong-Nan Mo, Peng Liu*

Department of Medical Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China

Received 23 December 2016

Available online 19 July 2017

Abstract

MET encodes a receptor tyrosine kinase c-MET for hepatocyte growth factor (HGF). The specific combination of c-MET and HGF activates downstream signaling pathways to trigger cell migration, proliferation, and angiogenesis. *MET* exon 14 alterations and *MET* gene amplification play a critical role in the origin of cancer. Several monoclonal antibodies and small-molecule inhibitors of c-MET have been evaluated in clinical trials. In patients with advanced non-small cell lung cancer, cabozantinib and crizotinib showed clear efficacy with a generally tolerable adverse events profile. In gastrointestinal cancers, most phase III trials of MET inhibitors showed negative results. In hepatocellular carcinoma, based on the encouraging results of some phase II studies, a series of phase III trials are currently recruiting patients to access the efficacy and safety of *MET* inhibitors.

Keywords: Proto-oncogene protein c-MET; Antineoplastic agents; Protein kinase inhibitors; Molecular targeted therapy

Introduction

MET, also known as the N-methyl-N′-nitroso-guanidine human osteosarcoma transforming gene, is a proto-oncogene encoding a receptor tyrosine kinase c-MET for hepatocyte growth factor (HGF).[1,2] The binding of HGF results in c-MET dimerization and autophosphorylation, which in turn activates the mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K), v-src avian sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (SRC), and signal transducer and activator of transcription (STAT) signaling pathways.[3] c-MET activation is normally essential for cell morphogenesis, scattering and motility, proliferation, and protection from apoptosis.[3] The *MET* pathway plays an important role in wound healing, post-injury response, and degenerative diseases such as renal and lung fibrosis.[4]

Aberrant *MET* expression is widely observed in various malignancies, particularly non-small cell lung cancer (NSCLC), gastrointestinal (GI) cancer, and hepatocellular carcinoma (HCC).[5−8] *MET*-receptor overexpression, genomic amplification, mutation, or alternative splicing results in cellular deregulation of

* Corresponding author.

E-mail address: 13910216310@163.com (P. Liu).

Peer review under responsibility of Chinese Medical Association.

Production and Hosting by Elsevier on behalf of KeAi

http://dx.doi.org/10.1016/j.cdtm.2017.06.002

MET.[9] Several agents targeting *MET* have been examined in clinical trials, but the results range from relatively high response rates to prominent failure. This review summarizes *MET* pathway dysregulation in cancers and the use of *MET* inhibitors to treat advanced cancers.

c-MET pathway

The *MET* gene is located on chromosome 7q21–q31 and is approximately 125 kb long with 21 exons. c-MET is a heterodimer composed of a 50-kDa highly glycosylated alpha-chain subunit and 145-kDa beta-chain.[10] This transmembrane protein consists of a large extracellular region, membrane-spanning segment, and intracellular tyrosine kinase domain.[11] c-MET is the only known high-affinity receptor for HGF and is widely expressed in cells of epithelial-endothelial origin, including liver cells, fibroblasts, hematopoietic cells, and keratinocytes.[12]

HGF, also known as scatter factor, was initially identified as a growth factor for hepatocytes and fibroblast-derived cell motility factor.[13] HGF forms a heterodimer consisting of a 69-kDa alpha-chain subunit and 34-kDa beta-chain, linked by a disulfide bond. HGF can induce cell dissociation and movement, promote mitosis, and induce morphogenesis of epithelial cells. In addition, it can stimulate the growth of vascular endothelial cells and increase extracellular matrix protein hydrolysis.

The specific combination of c-MET and HGF induces a conformational change in the c-MET receptor protein, and its intracellular protein tyrosine kinase domain is activated by autophosphorylation. The downstream MAPK, PI3K, SRC, and STAT signaling pathways are successively phosphorylated and activated.[14] The waterfall-like phosphorylation reactions amplify the signal step-by-step. Eventually, the c-MET pathway triggers a variety of cellular responses, including cell migration, mitogenesis, morphogenesis, proliferation, and angiogenesis.[4]

In some NSCLCs, the c-MET pathway is thought to be the primary driving mechanism, particularly *MET* exon 14 (METex14) alterations and *MET* gene amplification. METex14 alterations are detected in approximately 3–4% of lung adenocarcinomas and 20–30% of pulmonary sarcomatoid carcinomas.[15] These alterations result in decreased degradation of c-MET, sustained *MET* overexpression, and oncogenesis. Next-generation sequencing is the most frequently used tool for diagnostic testing of METex14 alterations.[16,17] The prevalence of *MET* amplification in NSCLC ranges from 1% to 5%. The fluorescence *in situ* hybridization can be used to determine the ratio of MET to the centromeric portion of chromosome 7 (CEP7) to distinguish between polysomy and true *MET* amplification (MET/CEP7 ratio > 5).

As *MET* mutations are exceedingly rare in GI cancers, *MET* is mainly activated by receptor overexpression or genomic up-regulation.[8] *MET* amplification appears to be rare in GI cancers, with reported incidences of 0–5%.[18]

c-MET signaling promotes hepatocyte proliferation and regeneration, suggesting a potential tumor-promoting role in HCC.[19,20] c-MET transcription and expression is increased in 30–100% of HCC compared to the surrounding tissue, while HGF expression is decreased in tumors compared to that in the surrounding liver tissue.[7,21]

The c-MET pathway exhibits significant cross-talk with other signaling pathways. Interactions between MET and HER2 family members have emerged as a major mechanism of tumor progression and treatment resistance. MET signaling has also been shown to interact with the vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR) pathways.[22] *MET* activation increases VEGF-A expression to promote angiogenesis and endothelial cell growth.

c-MET deregulation plays important roles in tumor formation, growth, maintenance, and invasion. It has implicated in several cancers, including lung, colorectal, liver, and gastric carcinoma. Therefore, c-MET has become an attractive target for cancer treatment and drug development.

Inhibit *MET* for malignancy

Currently, there are three main methods for inhibiting the kinase activity of c-MET: preventing the extracellular combination of c-MET and HGF with neutralizing antibodies or biological antagonists; preventing phosphorylation of tyrosine in the kinase domain using small-molecule inhibitors; blocking c-MET kinase-dependent signaling through relevant signal transducers or downstream signaling components.

Several small-molecule inhibitors and monoclonal antibodies of c-MET have been evaluated in preclinical studies. Crizotinib is a dual c-MET and anaplastic lymphoma kinase (ALK) inhibitor that has been approved for treating ALK-positive NSCLC.[23] Cabozantinib is a multikinase inhibitor that targets c-MET, VEGFR2, AXL, KIT, TIE2, FLT3, and RET.[24] Tivantinib is a non-adenosine triphosphate (ATP) competitive c-MET inhibitor.[25] Foretinib is a multikinase inhibitor of

MET, c-ros oncogene (ROS), Recepteur d'Origine Nantais (RON), AXL, TIE2, and VEGFR2. Onartuzumab is a humanized monovalent monoclonal antibody directed against c-MET, with potential antineoplastic activity.[26] Rilotumumab is a humanized, monoclonal antibody that neutralizes HGF. Most of these c-MET inhibitors have been evaluated in clinical trials.

MET inhibitors in NSCLC

Targeted therapies, particularly those aimed at epidermal growth factor receptor (EGFR) and ALK, have been recommended as first-line treatments for patients with advanced NSCLC with specific gene mutations. EGFR activation stimulates c-MET phosphorylation and activation. *MET* amplification results in PI3K/AKT activation, which is associated with acquired resistance to first-generation EGFR tyrosine kinase inhibitor. Thus, *MET* inhibitors combined with EGFR tyrosine kinase inhibitors have been evaluated in several clinical trials.

A randomized controlled phase II trial compared the efficacy of cabozantinib alone or in combination with erlotinib versus erlotinib alone in patients with advanced NSCLC with wild-type EGFR.[27] A total of 111 patients were randomized and the primary endpoint of progression-free survival (PFS) was reached. Compared with erlotinib alone (1.8 months), PFS was significantly improved in the cabozantinib group (4.3 months) and erlotinib plus cabozantinib group (4.7 months). The most common grade 3 or 4 adverse events were diarrhea, hypertension, fatigue, oral mucositis, and thromboembolic events.

A phase II clinical trial suggested that only c-MET-positive tumors would benefit from combinational treatment of onartuzumab plus erlotinib, which doubled patient survival compared with the erlotinib plus placebo arm (6.4 *vs.* 12.4 months) in patients with NSCLC.[28] Unfortunately, a subsequent phase III trial that assessed the impact on overall survival (OS) of adding onartuzumab to erlotinib in patients with advanced NSCLC with *MET* overexpression showed negative results. A total of 499 patients with *MET*-overexpressing tumors were randomized. Median OS was decreased in patients who received combination therapy.[29]

In a phase II clinical trial, tivantinib increased the response rate (RR) and OS when combined with erlotinib in previously treated patients with locally advanced or metastatic NSCLC.[30] Disappointingly, two phase III studies of tivantinib in combination with erlotinib in patients with advanced nonsquamous NSCLC did not meet their primary endpoint. The ATTENTION trial randomized 307 patients to receive erlotinib with or without tivantinib.[31] The study was terminated early because of an increased incidence of interstitial lung disease in the tivantinib arm, while OS did not significantly differ between the two groups. The MARQUEE trial randomized 1048 patients to receive erlotinib with or without tivantinib.[32] This trial was terminated early because of an interim analysis revealing futility, and OS did not differ between groups.

As a dual c-MET and ALK inhibitor, crizotinib has been evaluated in patients with METex14-altered NSCLC. Its anti-tumor activity and safety profile were recently reported at the 2016 American Society of Clinical Oncology annual meeting. In the 15 response-evaluable patients, partial response was documented in 10 patients, with a generally tolerable adverse events profile.

MET inhibitors in GI cancer

Nearly 4−10% of upper GI cancers show *MET* amplification, and 50% of patients with advanced gastric cancer show c-MET protein overexpression. Patients with colorectal carcinoma (CRC) may also exhibit overexpression or amplification of c-MET, which is associated with CRC invasion and distant metastases.[33] Thus, numerous clinical trials have attempted to evaluate *MET* inhibitors alone or combined with cytotoxic chemotherapy in patients with GI cancer, most of which showed no efficacy.

A phase II trial randomized 121 GI cancer patients into rilotumumab or placebo combined with epirubicin, cisplatin, and capecitabine (ECX) groups.[34] Improved OS and PFS were observed in the rilotumumab plus ECX group, with no unexpected safety signals. However, the phase III RILOMET-1 study of rilotumumab plus ECX as a first-line therapy for *MET*-positive patients with advanced gastroesophageal adenocarcinoma (GEC) did not meet its primary endpoint of increasing OS.[35] The results showed that rilotumumab was not superior to placebo for OS; in addition, PFS and objective response rate (ORR) were statistically worse in the rilotumumab arm. This lack of efficacy was due to increased deaths in the rilotumumab arm because of disease progression and occurred regardless of the level of *MET*-positive expression. Another phase II MEGA study assessed modified FOLFOX6 (oxaliplatin, 5-fluorouracil, and leucovorin) alone or in combination with rilotumumab as first-line treatment in patients with advanced GEC.[36] This trial

also showed negative results. Adding rilotumumab appeared to be more toxic and not more effective than modified FOLFOX6 (mFOLFOX6) alone.

Onartuzumab was evaluated in the METGastric study, a phase III study of onartuzumab plus mFOLFOX6 in patients with metastatic *HER2*-negative and *MET*-positive GEC.[37] The phase II YO28252 study was conducted in parallel with METGastric, which also examined first-line onartuzumab plus mFOLFOX6 in the same target population.[38] Their results were consistent: addition of onartuzumab to mFOLFOX6 was ineffective in these patients. In patients with metastatic CRC, negative study data were published for onartuzumab. A phase II study (GO27827) revealed that onartuzumab combined with FOLFOX plus bevacizumab did not significantly improve efficacy outcomes.[39]

Only one study has evaluated foretinib in patients with metastatic gastric cancer. This phase II cohort of 74 patients with metastatic gastric cancer failed to display efficacy.[40]

In patients with advanced CRC, a phase II study found that tivantinib in combination with irinotecan and cetuximab was well tolerated, but did not significantly improve patient survival.[41] Tivantinib combined with cetuximab after resistance to cetuximab or panitumumab in patients with *MET*-high/*KRAS* wild-type metastatic CRC is being evaluated in an ongoing clinical trial (NCT01892527).

A phase II study of cabozantinib was performed for patients with advanced refractory cholangiocarcinoma, which showed limited activity and significant toxicity.[42] The median PFS was 1.8 months and median OS was 5.2 months. Grade 3/4 adverse events including neutropenia (5%), bowel perforation (5%), and hypertension (11%) occurred in 89% of patients. Notably, one patient with a *MET*-high tumor remained on treatment for 278 days.

Several c-MET inhibitors have been developed and evaluated in patients with GI cancer. However, most of the results were negative. Numerous phase II/III clinical trials have reported a lack of improvement in efficacy with *MET* inhibitor in these patients. It remains unclear whether other biomarkers (rather than *MET* immunohistochemistry) or small molecule inhibitors are more appropriate for inhibiting this oncogenic pathway.

MET inhibitors in HCC

Most patients with HCC have advanced disease at the time of diagnosis. For those who cannot undergo surgery or locoregional therapies, the options for systemic therapy are limited. In patients with advanced HCC, cytotoxic chemotherapy treatment showed no efficacy. Sorafenib showed a significant survival benefit in large randomized trials[43,44] and is recommended for patients with advanced HCC with good liver function. For *MET* inhibitors, several phase II clinical trials reported clinically meaningful anti-tumor activities in these patients, and randomized phase III studies are currently underway.

A phase II single-arm study evaluated the safety and activity of foretinib in the first-line setting in patients with advanced HCC.[45] The ORR was 22.9%, PFS was 4.2 months, and OS was 15.7 months. The most frequent adverse events were hypertension, decreased appetite, ascites, and pyrexia.

A phase II randomized controlled trial compared the efficacy and safety of tivantinib versus placebo as second-line therapy in 108 patients with advanced HCC. In subgroup analysis of patients with high c-MET expression, tivantinib significantly prolonged PFS and OS.[46] Unfortunately, tivantinib failed to improve OS or PFS compared with placebo as a second-line therapy for patients with *MET*-overexpressing inoperable HCC in the phase III METIV-HCC study.[47]

A phase II trial evaluated the efficacy of cabozantinib in advanced solid tumors, among which 41 patients with advanced HCC were enrolled.[48] Three of 33 patients evaluable for tumor assessment achieved a partial response. The most common related adverse events were hand-foot syndrome, diarrhea, and thrombocytopenia. A randomized phase III trial, CELESTIAL, is currently recruiting patients with advanced HCC to compare the efficacy of cabozantinib and placebo as a second-line treatment after sorafenib.

Conclusions

The *MET* pathway plays a critical role in cancer origin. Several monoclonal antibodies and small-molecule inhibitors of c-MET have clinical meaningful efficacy with a manageable toxicity profile, mainly in patients with NSCLC patients and those with HCC, but not in patients with GI cancer. A series of phase III trials are underway to further access the efficacy and safety of *MET* inhibitors.

Conflicts of interest

The authors declare that they have no conflicts of interest.

References

1. Bladt F, Riethmacher D, Isenmann S, Aguzzi A, Birchmeier C. Essential role for the c-met receptor in the migration of myogenic precursor cells into the limb bud. *Nature*. 1995;376:768−771.
2. Sattler M, Salgia R. c-Met and hepatocyte growth factor: potential as novel targets in cancer therapy. *Curr Oncol Rep*. 2007;9:102−108.
3. Ma PC, Maulik G, Christensen J, Salgia R. c-Met: structure, functions and potential for therapeutic inhibition. *Cancer Metastasis Rev*. 2003;22:309−325.
4. Uehara Y, Minowa O, Mori C, et al. Placental defect and embryonic lethality in mice lacking hepatocyte growth factor/scatter factor. *Nature*. 1995;373:702−705.
5. Ichimura E, Maeshima A, Nakajima T, Nakamura T. Expression of c-met/HGF receptor in human non-small cell lung carcinomas in vitro and in vivo and its prognostic significance. *Jpn J Cancer Res*. 1996;87:1063−1069.
6. Siegfried JM, Weissfeld LA, Luketich JD, Weyant RJ, Gubish CT, Landreneau RJ. The clinical significance of hepatocyte growth factor for non-small cell lung cancer. *Ann Thorac Surg*. 1998;66:1915−1918.
7. Goyal L, Muzumdar MD, Zhu AX. Targeting the HGF/c-MET pathway in hepatocellular carcinoma. *Clin Cancer Res*. 2013;19:2310−2318.
8. Hack SP, Bruey JM, Koeppen H. HGF/MET-directed therapeutics in gastroesophageal cancer: a review of clinical and biomarker development. *Oncotarget*. 2014;5:2866−2880.
9. Yap TA, de Bono JS. Targeting the HGF/c-Met axis: state of play. *Mol Cancer Ther*. 2010;9:1077−1079.
10. Sierra JR, Tsao MS. c-MET as a potential therapeutic target and biomarker in cancer. *Ther Adv Med Oncol*. 2011;3:S21−S35.
11. Cecchi F, Rabe DC, Bottaro DP. Targeting the HGF/Met signalling pathway in cancer. *Eur J Cancer*. 2010;46:1260−1270.
12. Naran S, Zhang X, Hughes SJ. Inhibition of HGF/MET as therapy for malignancy. *Expert Opin Ther Targets*. 2009;13:569−581.
13. Schmidt C, Bladt F, Goedecke S, et al. Scatter factor/hepatocyte growth factor is essential for liver development. *Nature*. 1995;373:699−702.
14. Scagliotti GV, Novello S, von Pawel J. The emerging role of MET/HGF inhibitors in oncology. *Cancer Treat Rev*. 2013;39:793−801.
15. Drilon A, Cappuzzo F, Ou SI, Camidge DR. Targeting MET in lung cancer: will expectations finally be MET? *J Thorac Oncol*. 2017;12:15−26.
16. Lu YQ, Lu KH. Advancements in next-generation sequencing for diagnosis and treatment of non-small-cell lung cancer. *Chronic Dis Transl Med*. 2017;3:1−7.
17. Paik PK, Drilon A, Fan PD, et al. Response to MET inhibitors in patients with stage IV lung adenocarcinomas harboring MET mutations causing exon 14 skipping. *Cancer Discov*. 2015;5:842−849.
18. Janjigian YY, Tang LH, Coit DG, et al. MET expression and amplification in patients with localized gastric cancer. *Cancer Epidemiol Biomarkers Prev*. 2011;20:1021−1027.
19. Suzuki K, Hayashi N, Yamada Y, et al. Expression of the c-met protooncogene in human hepatocellular carcinoma. *Hepatology*. 1994;20:1231−1236.
20. Giordano S, Columbano A. Met as a therapeutic target in HCC: facts and hopes. *J Hepatol*. 2014;60:442−452.
21. Wu F, Wu L, Zheng S, et al. The clinical value of hepatocyte growth factor and its receptor−c-met for liver cancer patients with hepatectomy. *Dig Liver Dis*. 2006;38:490−497.
22. Zhang J, Jiang X, Jiang Y, et al. Recent advances in the development of dual VEGFR and c-Met small molecule inhibitors as anticancer drugs. *Eur J Med Chem*. 2016;108:495−504.
23. Lennerz JK, Kwak EL, Ackerman A, et al. MET amplification identifies a small and aggressive subgroup of esophagogastric adenocarcinoma with evidence of responsiveness to crizotinib. *J Clin Oncol*. 2011;29:4803−4810.
24. Grüllich C. Cabozantinib: a MET, RET, and VEGFR2 tyrosine kinase inhibitor. *Recent Results Cancer Res*. 2014;201:207−214.
25. Agwa ES, Ma PC. Targeting the MET receptor tyrosine kinase in non-small cell lung cancer: emerging role of tivantinib. *Cancer Manag Res*. 2014;6:397−404.
26. Robinson KW, Sandler AB. The role of MET receptor tyrosine kinase in non-small cell lung cancer and clinical development of targeted anti-MET agents. *Oncologist*. 2013;18:115−122.
27. Neal JW, Dahlberg SE, Wakelee HA, et al. Erlotinib, cabozantinib, or erlotinib plus cabozantinib as second-line or third-line treatment of patients with EGFR wild-type advanced non-small-cell lung cancer (ECOG-ACRIN 1512): a randomised, controlled, open-label, multicentre, phase 2 trial. *Lancet Oncol*. 2016;17:1661−1671.
28. Spigel DR, Ervin TJ, Ramlau RA, et al. Randomized phase II trial of Onartuzumab in combination with erlotinib in patients with advanced non-small-cell lung cancer. *J Clin Oncol*. 2013;31:4105−4114.
29. Spigel DR, Edelman MJ, O'Byrne K, et al. Results from the phase III randomized trial of onartuzumab plus erlotinib versus erlotinib in previously treated stage IIIB or IV non-small-cell lung cancer: METLung. *J Clin Oncol*. 2017;35:412−420.
30. Sequist LV, von Pawel J, Garmey EG, et al. Randomized phase II study of erlotinib plus tivantinib versus erlotinib plus placebo in previously treated non-small-cell lung cancer. *J Clin Oncol*. 2011;29:3307−3315.
31. Yoshioka H, Azuma K, Yamamoto N, et al. A randomized, double-blind, placebo-controlled, phase III trial of erlotinib with or without a c-Met inhibitor tivantinib (ARQ 197) in Asian patients with previously treated stage IIIB/IV nonsquamous nonsmall-cell lung cancer harboring wild-type epidermal growth factor receptor (ATTENTION study). *Ann Oncol*. 2015;26:2066−2072.
32. Scagliotti G, von Pawel J, Novello S, et al. Phase III multinational, randomized, double-Blind, placebo-controlled study of tivantinib (ARQ 197) plus erlotinib versus erlotinib alone in previously treated patients with locally advanced or metastatic nonsquamous non-small-cell lung cancer. *J Clin Oncol*. 2015;33:2667−2674.
33. Zeng ZS, Weiser MR, Kuntz E, et al. c-Met gene amplification is associated with advanced stage colorectal cancer and liver metastases. *Cancer Lett*. 2008;265:258−269.
34. Iveson T, Donehower RC, Davidenko I, et al. Rilotumumab in combination with epirubicin, cisplatin, and capecitabine as first-line treatment for gastric or oesophagogastric junction adenocarcinoma: an open-label, dose de-escalation phase 1b study and a double-blind, randomised phase 2 study. *Lancet Oncol*. 2014;15:1007−1018.
35. Cunningham D, Tebbutt NC, Davidenko I, et al. Phase III, randomized, double-blind, multicenter, placebo (P)-controlled trial of rilotumumab (R) plus epirubicin, cisplatin and capecitabine (ECX) as first-line therapy in patients (pts) with advanced MET-positive (pos) gastric or gastroesophageal junction (G/GEJ)

cancer: RILOMET-1 study. *J Clin Oncol*. 2015;33(15 suppl):4000.
36. David M, Florence C, Eric F, et al. FOLFOX alone or combined to rilotumumab or panitumumab as first-line treatment in patients (pts) with advanced gastroesophageal adenocarcinoma (AGEA): an open-label, randomized phase II trial (PRODIGE 17 ACCORD 20 MEGA). *J Clin Oncol*. 2015;33(15 suppl):4013.
37. Manish S, Yung-Jue B, Florian L, et al. METGastric: a phase III study of onartuzumab plus mFOLFOX6 in patients with metastatic HER2-negative (HER2-) and MET-positive (MET+) adenocarcinoma of the stomach or gastroesophageal junction (GEC). *J Clin Oncol*. 2015;33(15 suppl):4012.
38. Shah MA, Cho JY, Tan IB, et al. A randomized phase II study of FOLFOX with or without the MET inhibitor onartuzumab in advanced adenocarcinoma of the stomach and gastroesophageal junction. *Oncologist*. 2016;21:1085−1090.
39. Bendell JC, Hochster H, Hart LL, et al. A phase II randomized trial (GO27827) of first-line FOLFOX plus bevacizumab with or without the MET inhibitor onartuzumab in patients with metastatic colorectal cancer. *Oncologist*. 2017;22:264−271.
40. Shah MA, Wainberg ZA, Catenacci DV, et al. Phase II study evaluating 2 dosing schedules of oral foretinib (GSK1363089), cMET/VEGFR2 inhibitor, in patients with metastatic gastric cancer. *PLoS One*. 2013;8:e54014.
41. Eng C, Bessudo A, Hart LL, et al. A randomized, placebo-controlled, phase 1/2 study of tivantinib (ARQ 197) in combination with irinotecan and cetuximab in patients with metastatic colorectal cancer with wild-type KRAS who have received first-line systemic therapy. *Int J Cancer*. 2016;139:177−186.
42. Goyal L, Zheng H, Yurgelun MB, et al. A phase 2 and biomarker study of cabozantinib in patients with advanced cholangiocarcinoma. *Cancer*. 2017;123:1979−1988.
43. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008;359:378−390.
44. Cheng AL, Kang YK, Chen Z, et al. 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.
45. TCC Y, Lencioni R, Sukeepaisarnjaroen W, et al. A phase I/II multicenter study of single-agent foretinib as first-line therapy in patients with advanced hepatocellular carcinoma. *Clin Cancer Res*. 2017;23:2405−2413.
46. Santoro A, Rimassa L, Borbath I, et al. Tivantinib for second-line treatment of advanced hepatocellular carcinoma: a randomised, placebo-controlled phase 2 study. *Lancet Oncol*. 2013;14:55−63.
47. Lorenza R, Eric A, Markus PR, et al. Second-line tivantinib (ARQ 197) vs placebo in patients (Pts) with MET-high hepatocellular carcinoma (HCC): results of the METIV-HCC phase III trial. *J Clin Oncol*. 2017;35(15 suppl):4000.
48. Verslype C, Cohn AL, Kelley RK, et al. Activity of cabozantinib (XL184) in hepatocellular carcinoma: results from a phase II randomized discontinuation trial (RDT). *J Clin Oncol*. 2012;30(15 suppl):4007.

Edited by Pei-Fang Wei