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MINI-REVIEW

C-Met as a potential target for the treatment of gastrointestinal cancer: current status and future perspectives[†]

Running title: c-Met in gastrointestinal cancers

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ABSTRACT

Aberrant activation of the HGF/c-Met signalling pathways is shown to be related with cell proliferation, progression, metastasis and worse prognosis in several tumor types, including gastrointestinal cancers, suggesting its value as a stimulating-target for cancer-therapy. Several approaches have been developed for targeting HGF and/or c-Met, and one of them, crizotinib (dual c-Met/ALK inhibitor), is recently been approved by FDA for lung-cancers with ALK-rearrangement. The main aim of current review is to give an overview on the role of c-Met/HGF pathway in gastrointestinal cancer, in preclinical and clinical trials. Although several important matters is still remained to be elucidated on the molecular pathways underlying the antitumor effects of this therapy in gastrointestinal-cancers. Further investigations are warranted to recognize the main determinants of the activity of c-Met inhibitors, for parallel targeting signalling pathway associated/activated via MET/HGF pathway or in response to the cell resistance to anti-c-Met agents. Additionally, identification of patients that might benefit from therapy could help to increase the selectivity and efficacy of the therapy. This article is protected by copyright. All rights reserved

Key words: c-Met/HGF pathway, c-Met inhibitors, resistance to targeted agents, upper gastrointestinal cancers.

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INTRODUCTION

C-MET/HGF SIGNALING PATHWAY IN GASTROINTESTINAL CANCER

C-Met, the receptor tyrosine kinase encoded by MET proto oncogene located on chromosome 7 band 7q21–q31 that encoded a 1408 amino acid transmembrane glycoprotein[1] .C-Met is expressed in both normal and malignant cells which is an epithelial/endothelial cell surface transmembrane receptor with specificity for hepatocyte growth factor (HGF) or also known as scatter factor (SF) [1-3].

C-Met is structurally different from other receptor tyrosine kinase subfamilies, being a disulfide-linked heterodimer comprised of an extracellular and a transmembrane region, a cytoplasmic part consist of a tyrosine Kinase and a docking site domain. The extracellular region is composed of the cysteine-rich domain, Sema domain, and four immunoglobulin-like domains[4].

This pathway could leads to the activation of downstream signal transduction pathways, including the mitogen-activated protein kinase (MAPK) cascades ((ErK1) and ErK2, p38 and JNKs), (PI3K–Akt) axis, PLC γ, FAK, STATs, and (IκBα) (NF-κb) complex, responsible for controls proliferation, cell survival, tissue homeostasis , morphogenesis, angiogenesis, cell scattering, development, migration and invasiveness.[5, 6] In embryo, c-MET is required for the development of limb muscles, kidney, liver, diaphragm, tongue, brain, placenta, ovary, and testis [7-10].In adult, c-MET and its ligand is implicated in hematopoiesis, liver regeneration and wound healing [11-13].

C-MET is activated through overexpression of the protein as a result of focal genomic amplification, gene rearrangement, transcriptional up regulation, gene copy-number gain, failure of c-MET proteolysis and changes in ligand-dependent autocrine or paracrine mechanisms[14, 15]. Maus and colleagues evaluated the c-MET mRNA expression in 25 tumor specimens; resectable pancreatic adenocarcinoma who underwent both surgery and

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adjuvant chemotherapy, and 19 pancreatic stromal tissues. C-MET amplification was significantly ($P<0.05$) varied between pancreatic stromal and tumor tissues (Median: 1.0, 95%CI: 0.37-5.05 versus 3.8, 95%CI: 0.78-12.27) [16-18]. In gastric cancer, metastatic head and neck squamous cell carcinomas, childhood hepatocellular carcinoma, ovarian cancer and, lung cancer, Missense mutations in MET (primarily in the kinase domain) have also been exist [19-24].

In particular, c-Met is amplified in more than 30% of lung cancer EGFR inhibitors resistance patients. It has been reported that NSCLC cells resistant to gefitinib (EGFR inhibitor), had MET expression and activation of the tyrosine kinase Src, which is involvement in tumor development, proliferation and migration of many solid tumors[25-27].Also, the over-expression may be mediated by gene amplification, transcriptional and post-transcriptional mechanisms. Mostly in cancer, MET activation occurs through a ligand-dependent mechanism [19, 20, 22].In glioblastomas and multiple myeloma, this stimulation is often autocrine while in some cancers it is by paracrine stimulation [20] .

Mechanisms of raised Met activity in malignancies include ligand-independent activation by HGF ligand autocrine overexpression, transcriptional upregulation of other oncogenes, such as K-RAS and, extracellular matrix proteins and environmental situations, including hypoxia, and inflammatory or pro-angiogenic factors created by the reactive stroma surrounding different kinds of cancer [28-31].In this regard, numerous studies in preclinical models have indicated that the activation of HGF/c-Met signalling could triggers cell invasiveness and metastases. However, the suppression of overexpressed MET genes in tumor cells disrupts tumor growth and metastasis [3, 32] .

In summary, *MET* appears to play a role in oncogenesis, progression and malignant migration of different tumors, including upper gastrointestinal cancers[33, 34].Various promising

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approaches have been existed to use C-met RTK as survival prognostic factors, potential therapeutically target, distinguished subset of locally advanced or metastatic cancer [35].

2) TARGETING MET/HGF PATHWAY

Many documents have emphasized the prognostic value of c-Met and its robust association with invasiveness, propagation and poor survival in several cancers including upper gastrointestinal [36-40].Perturbation of the HGF/Met signaling has been shown in gastroesophageal, gastric, colorectal and pancreatic cancers [41-43].It has been shown that treatment high MET amplification cell lines of gastric cancer with the c-Met inhibitor PHA-665752 evokes great apoptosis. Thus MET amplification may introduce as a subset of gastric cancers that are uniquely sensitive to interruption of this pathway and treated with c-Met inhibitors in define patient group[44].Another study by Lee et al, illustrated that either increased MET copy number and/or c-Met overexpression in gastric cancers were associated with poor prognosis[45].Therefore, evaluation of HGF and c-Met expression status provides clinically useful information for peritoneal metastasis and prognosis in patients. Thus inhibiting this pathway might be clinically benefit for the treatment of gastric cancer.

Accumulating studies indicated the prognostic value of c-Met in pancreatic cancers. There is compelling documentation revealing c-Met expression in developing pancreatic embryo bud and marking best candidate stem/progenitor cells in the embryonic and adult pancreas, while low amplification of c-Met has been observed in normal adult differentiated pancreatic cells[46].In pancreatic cancer, interactions among cancer cells and fibroblasts, across c-Met, and factors affecting the cancer/stroma interaction increase pancreatic cancer progression play a crucial role in invasiveness and aggressive behaviour [47-49].

Several studies reported that pancreatic ductal adenocarcinoma (PDAC) cells with up regulated c-Met are resistant to gemcitabine (nucleoside analog), as the first line chemotherapy in treatment of PDAC [43, 50, 51].Moreover, amplification of c-Met mediates

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radioresistance [52] and resist to lapatinib (either HER2/neu or EGFR inhibitor) inhibition of HER2-overexpressed gastric cancer cells[53].These results indicated that kinase switching or a parallel mechanism might lead to resistance to gemcitabine. Future investigations should attend on finding the structure, mechanism and specific program of resistant tumors, in order to develop/design reasonable combination therapies including c-Met inhibitors.

In the past decades, several therapeutically mechanisms have been advanced to target aberrant HGF/Met pathway, including first; inhibition of HGF, second; suppression of Met with Met antibodies and blocking Met with TK inhibitors [54].The first two strategies goal at preventing the interaction of ligand-receptor hence disrupts receptor dimerization, while the latest approach suppresses the activity of Met kinase. Moreover, small molecule Met inhibitors can join to c-Met through tree ways:(1) hinge region with a U-shaped conformation; (2) C-helix; [55] or (3) sniping the interactions between the activity major catalytic residues, e.g. tivantinib as a non-ATP competitive c-Met inhibitor[56].

Several new c-Met inhibitors have been developed in upper gastrointestinal cancer, and most of them have evaluated in phase I/II/III clinical trials (Table 2). The strategies and potentially of each agent depend on the particular mechanism of behaviour of these drugs in HGF/Met signalling aberration. Some of the inhibitors, high selective to multi-target, and might be used single-agent or in combination with other therapy. In particular, Ficlatuzumab and TAK-701 are either humanized IgG1 monoclonal antibodies against HGF. A phase I trial evaluated the safety, tolerability, pharmacodynamics, and pharmacokinetics of Ficlatuzumab alone and in combination with erlotinib in advanced solid tumors patients [57].These findings indicated that combination treatment was high safe, well tolerated and more effective than single-target therapies. In addition, several phase II trials are developed for investigating the therapeutic role of both these monoclonal antibodies.

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In a double blind randomized phase II clinical trial, 128 chemotherapy pre-treated NSCLC patients were received MetMab(a recombinant anti-human c-Met monoclonal antibody) [58] and erlotinib or placebo plus erlotinib. This study showed MetMab in combination with erlotinib improved significantly overall survival (OS) (12.6 vs. 4.6 months; hazard ratio (HR) = 0.37, p = 0.002) and progression free survival (PFS) (3.0 vs. 1.5 months; HR= 0.47, p = 0.01), only in patients whose tumors had a high expression (2+ or 3+)c-Met protein. In contrast, in patients with low expression (0 and 1 +), combination of MetMab to erlotinib had an adverse event [59].

MGCD265 is a small multi-targeted TKI with anti-antineoplastic activity, which binds to and blocks the phosphorylation of several RTKs, including the c-Met receptor; macrophage-stimulating 1 receptor (MST1R or RON);Tek/Tie-2 receptor; and VEGFR types 1, 2, and 3. Suppression of these RTKs may lead to Inhibition of angiogenesis and cancer cell progression in tumors expressing these RTKs. In another phase I study, a total number of 28 patients with advanced malignancies was enrolled and treated by MGCD265. This therapy was well tolerated in all patients [60-62].

Another study by Beeram and colleagues tested the effect of MGCD265 plus docetaxel in 34 patients with metastatic or advanced solid tumors. This trial demonstrated the objective partial responses in 2 of 9 patients with NSCLC, 1 out of 1 patient with endometrial cancer and 1out of 3 patients with prostate cancer. In addition, 6 patients had a constant disease for 6 cycles or more, and treatment-related toxicity was observed in more than 2 patients. The pharmacodynamics characteristic of the patients showed that the plasma levels of VEGF and HGF were raised or decline, at day 8 in comparison to baseline of some patients, respectively. They showed that MGCD265 in combination with full-dose docetaxel was well tolerated,[63] and currently multiple on-going trials focused on this subject.

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Small-molecule inhibitors of c-Met including EMD 1204831, EMD 1214063, JNJ-38877605, INCB028060, Golvatinib (E7050) , MK-2461 and AMG 208 are with potential antineoplastic activity and suppression the ligand-dependent and/or ligand-independent activation of cMet are currently in phase I, II or III trials in patients with advanced solid tumors, particularly gastrointestinal cancers(Table 1).

2.1. *MET PATHWAY* in Gastric cancer

Gastric cancer accounts for 7.8% of global cancers. Also, it is the fourth most common form of cancer and the second major cause of cancer-related death worldwide [64-66].Nearby 85% of gastric cancers are adenocarcinomas [67]. Despite advances in early diagnosis, surgical techniques and targeted therapies including trastuzumab, [68] advanced gastric cancer remains with high incidence of metastases, recurrence, relatively poor prognosis and limited treatment choices [69].The genetic properties of gastric carcinogenesis stay not well known. A series of genetic changes involving tumor suppressor genes, oncogenes, DNA repair genes, cell-adhesion molecules, and cell-cycle regulators have been related with gastric cancer [70-74] .

Several preclinical studies have reported that the c-Met activation in gastric cancer. MET amplification was reported in nearly 4%–10% of stomach tumors, and c-Met protein overexpression responsible for 50% of advanced gastric cancers. Recently, Fuse et al. observed that among the 293 patients from nine centres, 120 (41 %) were c-MET positive. They also reported that c-MET-positive level were associated with poor prognosis[75].Wang and colleagues described that lentivirus-mediated RNA silencing of Met noteworthy inhibited peritoneal dissemination of gastric cancer, implicating that prevention of c-Met might supress development and metastatic growth of gastric cancer cells[76-77].

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Rilotumumab

Rilotumumab (AMG102) is a human IgG2 monoclonal antibody targeting human hepatocyte growth factor/scatter factor (HGF) that prevents the binding of HGF to its receptor [78, 79] . .The efficacy of this component in gastric cancer was reported in a randomized phase II trial at the 2011[80, 81].In 121 patients, combination of epirubicin, cisplatin, and capecitabine (ECX) was added to Rilotumumab at a dose of 15 mg/kg in 83 patients and placebo with locally advanced or metastatic gastric cancer. The toxicities were controlled and a maximum-tolerated dose was not reproted. Progression free survival (PFS) was 5.6 months in the Rilotumumab group versus 4.2 months in the placebo group (HR 0.64; p = 0.04). Median OS was 11.1 months in the Rilotumumab group and 8.9 months in the placebo group (HR 0.73; p = 0.2). In the subgroup biomarker analysis, there was a statistically significant PFS and OS benefit in patients administrated with Rilotumumab with high c-Met. OS was 11.5 against 5.7 months (HR 0.29; P = 0.012) for c-Met-high tumors (more than 50 percent cells c-Met positive) compared to c-Met-low tumors [81].

Also, two Phase 3, multicenter randomized double-blind placebo controlled trials (RILOMET-1) [82] (and RILOMET-2)[83] evaluated the role of Rilotumumab in combination with polichemotherapy. Particularly, RILOMET-1 studied the combination of Rilotomumab (at the dose of 15 mg/kg) and ECX as a first-line treatment for untreated advanced Met-positive Gastric or Gastroesophageal Junction Adenocarcinoma. OS was the primary outcome, while secondary end-points were measured PFS, time to progression (TTP), time to response (TTR), objective Response Rate (ORR), disease-control rate (DCR), and safety. The RILOMET-2 trial studied the role of Rilotumumab plus Cisplatin and Capecitabine (CX) in c-Met-positive Asiatic patients with unresectable locally advanced or metastatic gastric or GEJ adenocarcinoma. The primary outcome of this study were PFS and

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OS, and the secondary factors were TTP, TTR ,ORR , DCR and safety characteristic, although the trial was stop.

Onartuzumab

Onartuzumab is humanized, monovalent, recombinant monoclonal antibody directed against the c-Met receptor and blocks HGF/cMet binding [84]. In a dose-escalation trial seeking the role of Onartuzumab (MetMAb) in addition Bevacizumab in advanced solid malignancies, interesting results were acquired. Particularly, a durable complete response lasting approximately two years was achieved in a metastatic female gastric cancer patient with high MET polysomy and c-Met high amplification[85] .Also, a Phase2 double-blind placebo-controlled randomized study evaluated the activity of Onartuzumab in combination with mFOLFOX6 in patients with metastatic HER2-negative Gastroesophageal Cancer. They results revealed a higher incidence of serious toxicities in the experimental arm in comparison to placebo arm. Onartuzumab plus mFOLFOX6 regimen did not add benefit with respect to PFS in patients with advanced gastroesophageal cancer [86]. Moreover, a randomized Phase III study (YO28322) trial, investigated FOLFOX6 with or without Onartuzumab in HER2-negative, c-Met-positive advanced gastric patients, although the trial was stopped [87].

Small molecule c-Met tyrosine kinase inhibitors (TKIs)

Nearly all of small molecule inhibitors of aberrant c-Met compete with adenosine triphosphate (ATP) for joining to the tyrosine kinase domain. These include Tivantinib (ARQ197) or Foretinib (GSK1363089), which is an inhibitor of AXL, RON (Receptuer d'Origine Nantaise), VEGFR2, PDGFR (platelet-derived growth factor receptor-β), KIT or AMG337.

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Foretinib

Foretinib is an oral effective multikinase inhibitor targeting AXL, RON, TIE-2, c-Met, and VEGFR2 receptors [88].Analysis of the first Phase Ib/II study in a random population of heavily pretreated patients with different tumor types, showed that 20 percent decreased in tumor size at the first 8-week assessment was detected in 6 of 12 patients with advanced gastric cancer. A phase II cohort of assessed the safety, ORR, and tolerability of 2 dosing of oral Foretinib (GSK1363089) in 74 patients with metastatic gastric cancer (93% pre-treated). The optimum response was stable disease (average duration: 3.2 months) in 23% patients taking intermittent dosing and 20% taking daily dosing. 3 out of 67 patients with tumor samples, showed MET amplification, one of whom accomplished a stable disease. Treatment-related side effects were observed in 91% of patients. Incidences of hypertension (35% versus 15%) and increased aspartate aminotransferase (23% versus 8%) were raised with intermittent dosing. Analysis of their data suggested that single-compound Foretinib failed to display efficacy in molecularly randomized subjects with metastatic gastric cancer [89].

Tivantinib

Tivantinib (ARQ197) is another non-ATP-competitive selective small-molecule inhibitor of MET and allosterically hurts kinase activation. It was first reported as a c-Met selective inhibitor in 2010 [90]. Tivantinib prevented c-Met with a calculated inhibitory constant (Ki) value ~355 nmol/L and poor inhibitory impacts on p21-activated kinase 3 (PAK3), calmodulin-dependent kinase II (CAMKII)-delta, vascular endothelial growth factor receptor-3 (VEGFR-3/Flt4), and Pim-1.Based on crystal structure of the tivantinib binding with the c-Met kinase domain disclosed that it blocks c-Met within a non-ATP competitive trend. However, Tivantinib cannot be considered as an appropriate inhibitor of c-Met [91].Although, the exploratory analysis of a phase I dose-escalation trial lasting disease stabilization for more than 32 weeks was observed in 7 of 11 patients with five various tumor

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types including gastric cancer [92].Also Tivantinib monotherapy did not confirm objective responses in 30 pre-treated metastatic gastric cancer patients with a DCR of 36.7% and average PFS of 43 days. Grade 3 or 4 toxicities were found in 43.3% of subjects [93].

AMG-337

AMG-337 is an oral bioavailable TKI with tendency for binding to c-Met, disruption c-Met signal transduction pathways and induction cell death in tumors. Kwak *et al.* represented early toxicity and efficacy results of AMG 337 in patients with gastroesophageal cancer. 13 patients with MET amplification tumors were cured, and 8 had at least an objective response. Main side effects of this agent were headache, nausea, vomiting and fatigue [94].

NCT02096666 and NCT02016534 are surveying AMG 337 in MET amplified gastroesophageal cancer patients in a non-randomized trend. There is also a phase I and randomized phase II double blinded placebo controlled study of mFOLFOX6 with or without AMG 337 in the first line therapy of patients with Her2/Neu negative and high MET expressing advanced gastric and oesophageal adenocarcinoma. In this trial, MET was assessed by FISH and IHC to establish the best method for diagnosing those patients most likely to benefit from treatment (NCT02344810) [95].

ABT-700

ABT-700 is a bivalent humanized IgG1, c-Met targeting antibody. This agent binds to c-Met and disrupts its effective dimerization and activation motivated by HGF or by the high amount of c-Met [96]. ABT-700's is under a Phase I/Ib open label trial assessing the safety, pharmacokinetics (PK), and initial efficacy of this antibody in subjects with advanced solid tumors with c-Met overexpression. The primary data of this study was shown the safety and tolerability of ABT-700, as either monotherapy or complex with 5-fluoruracil or docetaxel, irinotecan, folinic acid and cetuximab (FOLFIRI/cetuximab) or erlotinib. Secondary results

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showed by objective response rate, PFS and time of response (NCT01472016) [97]. Results from recent studies have emphasized ABT-700 regresses tumor and inhibiting tumor growth in preclinical tumor models of lung and gastric cancers harboring amplified MET.

Crizotinib

Crizotinib is a multitargeted tyrosine kinase inhibitor that is approved for the targeting ALK-positive lung cancer; and MET tyrosine kinase [98, 99].FDA has recently approved Crizotinib for the treatment of advanced NSCLC with anaplastic lymphoma kinase (ALK) rearrangement. Preclinical in vivo and in vitro experiments have shown that crizotinib can inhibit the proliferation of MET-overexpressing gastric cancer [98, 99]. Moreover, the study by Okamoto and collaborators revealed the antitumor activity of crizotinib in gastric neoplasms xenografts positive for MET expression. This influence was resulted from upregulation of BIM expression, a proapoptotic subfamily of Bcl-2, and negatively regulated of survivin, X-linked suppressor of apoptosis protein, and c-IAP1, members of apoptosis protein family inhibitor. In contrast, they showed that forced reduction of BIM inhibited apoptotic effect of crizotinib, implicating that overexpression of BIM leads to crizotinib-induced apoptosis [99].

An analysis of a phase I trial of crizotinib in advance solid tumor patients revealed that 50 % of patients with MET-amplified gastric cancer had temporary tumor shrinkage [41]. Numerous studies of crizotinib in gastric cancer are ongoing including NCT02034981, which are examining crizotinib across many genetically defined solid tumor types including METamplified gastric cancer. A pilot study, NCT02435108, in Korea is evaluating crizotinib as third-line chemotherapy for MET-positive gastric adenocarcinoma.

Novel drug Volitinib

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Volitinib is a novel and potent c-Met small molecule tyrosine kinase inhibitor that represents advantageous preclinical pharmacokinetic and tolerance features [100, 101]. Volitinib is currently in Phase I clinical trials in China and Australia. Result of first study performed in Chinese patient revealed that Volitinib has a high selective profile across a gastric cell line panel, powerful blocking cell growth just in dysregulated cMET cell lines (EC50 values range from 0.6 to 12.5 nM/L)[102] .

KRC-00715

Newly synthesized, orally available, c-Met inhibitor, KRC-00715 with good efficacy in vitro and in vivo studies, suggested as a candidate for targeted therapy in gastric cancer by park et al. in 2016 [103].

2.2. MET PATHWAY in Colorectal Cancer

Colorectal carcinoma (CRC) is the most common malignancy. Various studies have been shown that overexpressed or amplified of c-Met is associated with CRC invasion and distant metastases [104]. Takeushi et al. revealed that c-Met overexpression is significantly related with tumor intestinal wall aggression and lymph-node metastasis [105]. Kammula et al. reported that raising c-Met and HGF mRNA expressions in colon cancer are linked to advanced disease stage and poor prognosis [106]. A Study by Al-Maghrabi et al. in 2015 demonstrated that c-MET is concomitantly overexpressed in either primary tumors and nodal metastasis. These findings indicate that high protein expression of c-MET is significantly associated with large tumor size. Controversially, they did not find any significant correlation between overexpression of c-MET protein and tumor stage, lymph node positivity, or distant propagation [107].

In a phase Ib/II, randomized, double-blind, clinical trial (NCT00788957), patients with metastatic colorectal cancer whose tumors were wild-type for KRAS received rilotumumab or AMG-479 plus panitumumab (an anti-EGFR mAb). No dose-limiting toxicities were

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reported [108]. In another phase II study, a dose of 10 mg/kg rilotumumab was used. The selected arms were panitumumab plus rilotumumab, panitumumab plus placebo, and panitumumab plus ganitumab. The ORRs were 31%, 21%, and, 22% respectively. The median PFS was 5.2, 3.7, and 5.3 months, while median OS was 13.8, 11.6, and 10.6 months in the treatment groups, respectively. Moreover their data showed that adverse effects were tolerable. Also biomarker analyses, including MET /IGF-related protein expression, failed to display conclusive predictive evidence on effectiveness of endpoints[109].In turn, several studies in CRC are ongoing including NCT01892527, NCT01075048, NCT02510001 to examine tivantinib, or crizotinib.

2.3. MET PATHWAY in Oesophageal cancer

Overexpression of c-Met in oesophageal cancer has been reported to be correlated with poor prognosis. In particular upregulation of c-Met is reported by Mesteri *et al*. in 34.4% of AC, and 7.6% of SCC. In AC c-Met expression is correlated with EGFR expression, pSTAT3 expression and lymphovascular invasion (LVI) of tumor cells.

It has been shown that the amplification of c-Met was associated with shorter disease free, disease specific and OS of AC patients ($p < 0.05$). All c-Met positive ACs with metastases were surveyed, in contrast 25% of c-Met negative primary tumors represented c-Met positive lymph node and 33% of them had distant metastases [110].

2.4. MET PATHWAY in Hepatocellular Carcinoma

Liver cancer is the sixth most common neoplasm worldwide, with reported 845582 new cases and 806873 deaths in 2015. Hepatocellular carcinoma (HCC) is the most frequent type of liver cancers [111-114]. HCC is often diagnosed at advanced stages, when often potentially curative strategies are of limited efficiencies. Despite all the progression in development of new targeted agents, the prognosis of HCC is not satisfying, with the 5- year survival incidence being at 12% [115, 116]. Accumulating evidence has determined the role of the

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tyrosine kinase receptor MET and its ligand (HGF) in tumor proliferation and metastatic invasion in HCC. The activation of the HGF/MET pathway in HCC is related with an aggressive phenotype and worse prognosis [117] .

In a phase Ib multicenter study performed by Santoro *et al*, 21 patients who did not respond to or had relapses after pre-treatment, received tivantinib 360 mg orally twice daily. The median age of patients was 69 years; Eastern Cooperative Oncology Group performance statuses were less than 1. Patients had preserved liver function at the beginning of the study, and they were received at least one systemic therapy. The important off-target effects were anemia (48%), neutropenia (52%), leucopenia (38%), asthenia (48%), diarrhea (29%), anorexia (38%), and fatigue (29%). The important serious side effects of this drug (grades 3-4) observed were anemia (24%), neutropenia (52%), and leucopenia (19%). In this work, the mean time lasted to progression was 3.3 months [118].

In a randomised, double-blind, placebo-controlled phase II study, tivantinib, was tested in the second-line therapy in 107 patients, of whom 77 (72%) had adequate tissue which was used to assess MET expression by immunochemistry. Of those, 37 (48%) patient had MET-high tumors. Overall, 71 patients set to tivantinib, which had a little longer TTP (1.6 versus 1.4 months (HR 0.64, P = 0.04). The major severe adverse event leading to dose was severe neutropenia in 8 of 17(47%) patients, proposing an off-target effect of this component. It is noticeable that, only patients with high tumor MET amplification derived a considerable advantage from tivantinib in TTP (2.7 vs. 1.4 months; HR = 0.43; P = 0.03) and OS (7.2 vs. 3.8 months; HR = 0.38; P = 0.01). In the placebo group, patients with MET-low tumors had a significantly longer OS (9.0 months) in comparison to patients with MET-high tumors (3.8 months; HR = 2.94; P = 0.02). In advanced HCC, the use of such a potential predictive biomarker has shown to select subjects who were most probably to advantage from treatment [119].

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Another phase III trial of tivantinib in the second-line therapy in MET-high advanced HCC patients, who failed sorafenib, is ongoing (NCT01755767)[120] .Cabozantinib (XL-184), dual MET/VEGFR-2 tyrosine kinase inhibitors, has also been shown promising results as a second-line setting in a randomised phase II study in 41 patients with advanced HCC and Child-Pugh A cirrhosis, with a 12 week median OS of 15.1 months, DCR of 68%, and PFS of 4.4 months. Three patients (8%) had an objective partial response, and 28 patients (78%) had tumor regression [121] .Most frequent grade 3/4 events were thrombocytopenia (10%), diarrhoea (17%) and palmarplantar erythrodysesthesia (15%). Cabozantinib is now in phase III trial[122, 123].

Many other MET inhibitors including golvantinib, INC-280, MSC2156119J, and foretinib are also under assessment .In particular, Foretinib was examined in a phase I/II trial as first-line therapy in Asian patients with advanced HCC and Child-Pugh A cirrhosis/no cirrhosis. In 38 patients who were received the maximum tolerated dose (30 mg daily), foretinib exhibited an ORR of 24%, DCR of 79%, TTP of 4.2 months, and OS of 15.7 months. Foretinib had an acceptable toxicity feature. The most common adverse events were hypertension, anorexia, and fever, while the most common serious adverse event were hepatic encephalopathy and ascites. Analysis of plasma biomarker from the SHARP trial advocates the concept that a low HGF level at the baseline was a predictor of net result in HCC patients [122].

2.5. MET PATHWAY in Cholangiocarcinoma

Cholangiocarcinoma (CCA) classified intrahepatic CCA, extra-hepatic CCA and gallbladder carcinoma (GBC), is the second frequent primary liver cancer [124, 125] .

CCA is identified by early lymph node and distant propagations, only 10% of patients with early stage disease are candidate for radical resection. The high incidence of unresectable tumors and recurrence after surgery cause a poor prognosis. In addition, CCA is commonly diagnosed when distant metastases or advanced local tumor infiltration are currently present

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and restrain tumor resection. The combination therapy of gemcitabine plus cisplatin remains the standard regimen for upgrade CCA [126] .

A phase II trial of cabozantinib (XL-184) in patients with advanced cholangiocarcinoma conducted by Goyal et al. evaluated the effect of dual VEGF receptor and c-MET small molecule inhibitor in patients with advanced CCA. Preliminary results, represented at the 2015 ASCO Gastrointestinal Cancers Symposium. All eligible patients had histologically confirmed unresectable / metastatic CCA and had progressed after 1/2 lines of systemic therapy. Patients were treated with cabozantinib 60mg orally daily for 28 day cycles. 19 patients (female 68%; median age 67 years old; intrahepatic versus extrahepatic CCA, 95 versus 5%; 1 versus 2 prior lines of systemic therapy, 53% versus 47%) were entered and all received at least one dose of cabozantinib. No objective responses were observed in follow-up duration (4.07 months). Eleven patients (58%) needed dose reductions. The median PFS was 1.77 months (95% CI, 1.63-5.37), and the OS was 5.20 months (95% CI, 2.70-8.17). 79% of patients showed grade 3 and 4 adverse events included, epistaxis, neutropenia, hyperbilirubinemia, , AST/ALT risen, alkaline phosphatemia, , lipasemia, anemia, and hypertension. The off-target effects were seen in two patient included bowel perforation and development an enterocutaneous fistula. Cabozantinib showed confined antitumor activity in unselected patients with advanced CCA[127].A Phase II Study of monotherapy by Cabozantinib (XL-184) in patients with advanced Cholangiocarcinoma after Progression on First or Second Line Systemic Therapy is ongoing to evaluate the role of cabozantinib. In 44 patients, 60 mg per day Cabozantinib will be administered daily and continuously for a cycle length of 28 days. The results are this trial is still unpublished [128].

2.6. MET PATHWAY in Pancreatic cancer

Pancreatic cancer is one of the leading causes of cancer related deaths with 5-year survival rate of 23%. With consideration to endocrine physiology of pancreas, the beta cell that

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responsible for insulin secretion needs HGF-MET for hypertrophy and developing in reaction to constant hyperglycemia[129]. In other word, stimulation of the HGF/MET signalling is suggested to promote beta cell proliferation later islet cell transplantation [130, 131].

Therefore, MET plays a key role in pancreatic neuroendocrine cell development and proliferation. Moreover, abundant evidence is supported this idea that dysregulated MET activity in pancreatic adenocarcinoma is correlated with aggressive phenotype [132] . In a recent study, 36 pancreatic tumor samples were evaluated and MET expression value were exactly proportional to tumor grade[133]. Other histopathologic analyses demonstrated an about 5-7 folds increased in MET protein expression status in pancreatic cancer in comparison to normal pancreas samples [134, 135]. A larger group of pancreatic tumor specimens then approved increased MET protein expression compared to controls. MET aberrant expression is significantly associated with increased TNM stage [40].

Tivantinib (ARQ 197), is in phase III development for various cancers [136] especially for pancreatic cancer. It is under a randomized phase II study in treatment of patients with unresectable locally advanced or metastatic pancreatic cancer. INC280, is another c-MET inhibitor, which has been shown to reduce motility of pancreatic cancer cells with a 30% involvement of lymph node, compared to 60% involvement in the normal control group, indicating potential suppression of propagation [137].

Several in vivo and in vitro studies have reported the antitumor activity of crizotinib or PF-04217903 in pancreatic tumors with Met high amplification [43, 138, 139].

A study performed by Sennino and collaborators on pancreatic neuroendocrine tumors showed that treatment with anti-VEGF antibody lead to decline tumor burden. However, invasion and metastasis were reduced by simultaneously inhibition of c-Met by crizotinib. A same finding was observed in orthotopic Panc-1 pancreatic carcinomas treated with sunitinib in combination with PF- 04217903 in RIP-Tag2 tumors treated with Cabozantinib [62].

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In our previous study, we evaluated the therapeutic potential of crizotinib in PDAC cell lines sensitive and resistant to gemcitabine [138].

Our data showed that novel c-Met/ALK inhibitor crizotinib decreased the expression of cancer stem cell markers. Additionally, the crizotinib/gemcitabine combination was synergistic in this tumor type. Also this preclinical data revealed that this effect was correlated with enhanced apoptosis, and reduction of cell proliferation and migration. In addition, we investigated the therapeutic potential of crizotinib in vivo PDAC models. This analysis showed that this regimen reduced tumor growth and increased survival [43]. HGF/SF Mab therapies are under various phases of ongoing clinical trials for different neoplasms, including Rilotumumab from Amgen, HuL2G7 from Millennium pharmaceuticals and Ficlatuzumab from AVEO pharmaceuticals [140]. MSC2156119J is a highly selective, efficient, ATP-competitive c-Met inhibitor,which is reported to inhibit phosphorylation and downstream signalling of c-Met [141]. Bladt et al. showed that MSC2156119J is markedly associated with regression of c-Met overexpressing tumors [142].

3. CHEMORESISTANCE TO C-MET INHIBITORS

Despite the great advance of tyrosine kinase c-Met inhibitors and clinical advantages in the past decade, resistant tumor cells to targeted drugs limit the utilization of current standard therapies. Therefore, development of effective treatments and/or rational combination therapeutic strategies depends on wide insight of drug resistance mechanisms. Two important mechanisms can explain cell resistance to kinase inhibitors; First: occurrence of mutations/alteration in the amplification of targeted tyrosine c-Met or/and second: activation of alternative signalling pathways including HGF/EGFR, k-Ras, Akt/PI3K [33].Another mechanism is reported by mutation in MET activation loop (Y1230). this changes can be involved in destabilization the auto-inhibitory structural of c-Met and abrogation of aromatic stacking interaction with the inhibitor[143].Optimal targeted therapy may need the blockade

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of serial steps/parallel in signalling pathway. It has been shown that acquired resistance to anti-EGFR drugs could be obtained through c-Met overexpression phosphorylation, pursued by involvement of PI3K-based survival pathways [144].In particular, in resistant NSCLC cells have been shown that inhibition of c-Met via Golvatinib was returned sensitivity to EGFR[145].Also overexpression of wild-type KRAS gene was correlated with acquired resistance to c-Met inhibitors including PHA-665752 or JNJ38877605[146].Finally, these information can explain that a single cancer type can develop resistance through different mechanisms, advocating supplementary seeking on the molecular pathways related with restraining or suppressing resistance.

4. CONCLUSIONS:

C-Met receptor is recently being suggested as an important target for personalized cancer therapy in gastrointestinal cancers. C-Met stimulation, overexpression, or genetic aberrations have been reported in gastrointestinal cancers such as pancreatic, gastric and hepatocellular cancers, which has been shown to be associated with tumor development, progression and poor prognosis of cancer patients. Several strategies have developed to inhibit this pathway, and some of them are now under clinical trials. Crizotinib is approved for treatment of NSCLC with ALK-rearrangement, although its clinical application/utility in several gastrointestinal tumors is documented, including gastric cancers with *MET* amplification. However, several questions are still remained to be elucidated.

In aggregate future challenges should focus on the (1) optimization and evaluation of c-Met inhibitors, (2) selection of patient who might advantage from therapy, (3) detection of prognostic/predictive biomarkers that can monitor or forecast treatment response or help in management of patients; (4) targeting of other key signalling pathways, in parallel, to overcome cell resistance.

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Table **1**. Summary of c-Met or HGF inhibitors in clinical development

Compound name	Type	Target
Tivatinib	Selective kinase inhibitor; Non-ATP competitive	c-Met
Crizotinib	Multi-kinase inhibitor; ATP competitive	c-Met and ALK
Cabozantinib	Multi-kinase inhibitor; ATP competitive	c-Met and VEGFR2
JNJ-38877605	Selective kinase inhibitor; ATP competitive	c-Met
Golvatinib (E7050)	Multi-kinase inhibitor; ATP competitive	c-Met, VEGFR-2, multiple member Eph receptor family, c-Kit and Ron
MK-2461	Multi-kinase inhibitor; ATP competitive	c-Met, AKT and Ras
Rilotumumab (AMG 102)	Antibody	Human HGF
Onartuzumab (MetMab)	Monovalent monoclonal antibody	Human c-Met
PF-04217903	Selective kinase inhibitor; ATP competitive	c-Met
AMG 208	Selective kinase inhibitor	c-Met and RON
MGCD265	Multi-kinase inhibitor	c-Met, Tek/Tie-2, VEGFR and MST1R or RON
Foretinib	Multi-kinase inhibitor; ATP competitive	Met, Ron, VEGFR1 to VEGFR3, PDGFR, Kit, Flt-3, Tie-2, AXL
EMD1204831	Selective kinase inhibitor; ATP competitive	c-Met
INCB028060	Selective kinase inhibitor; ATP competitive	c-Met
EMD1214063	Selective kinase inhibitor; ATP competitive	c-Met
Amuvatinib	Multi-kinase inhibitor	c-kit, and PDGFRα c-Met, Ret oncoprotein, mutant forms of Flt3 and PDGFR
BMS-777607	Selective kinase inhibitor; ATP competitive	c-Met
AMG 337	Selective kinase inhibitor	c-Met
PF-04217903	Selective kinase inhibitor; ATP competitive	c-Met
MSC2156119J	Selective kinase inhibitor	c-Met
PF-02341066	c-Tyrosine Kinase Inhibitor	c-Met Hepatocyte Growth Factor

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Table **2**. Summary of c-Met or HGF inhibitors in clinical development

Compound name	Cancer type	phase	Arm	Status	Reference
Tivatinib	Colorectal Cancer	Phase II	Tivantinib (ARQ 197)+ Cetuximab	ongoing, not recruiting	NCT01892527
	Malignant Solid Tumor ,Gastroesophageal Cancer	Phase I/II	Tivantinib + FOLFOX	completed	NCT01611857
	Inoperable Hepatocellular Carcinoma	Phase III	ARQ197 Placebo	ongoing, not recruiting	NCT01755767
	Unresectable Hepatocellular Carcinoma (HCC)	Phase II	ARQ 197 Placebo	completed	NCT00988741
	Cirrhotic Patients With Hepatocellular Carcinoma	Phase I	ARQ 197	completed	NCT00802555
	Locally Advanced or Metastatic Gastric Cancer	Phase II	ARQ 197 Oxaliplatin, capecitabine or irinotecan	withdrawn prior to enrollment	NCT01070290
	Hepatocellular Carcinoma (HCC)	Phase I	ARQ 197	completed	NCT01656265
	Advanced Solid Tumors	Phase I	ARQ 197 + Pazopanib	completed	NCT01468922
	Previously Treated Advanced/Recurrent Gastric Cancer	Phase II	ARQ 197	completed	NCT01152645
	Metastatic Colorectal Cancer	Phase I Phase II	Tivantinib (ARQ 197) + cetuximab + irinotecan Placebo + cetuximab + irinotecan	completed	NCT01075048
	Advanced Solid Tumors	Phase I/II	ARQ 197 as monotherapy or in combination with other drug(s)	Enrolling by invitation	NCT01178411
	Pancreatic Neoplasms	Phase II	ARQ 197 gemcitabine	completed	NCT00558207
	Advanced Solid Tumors	Phase I	ARQ 197 +sorafenib	completed	NCT00827177
	Hepatocellular Carcinoma (HCC)	Phase III	ARQ197 Placebo	recruiting participants	NCT02029157
	Hepatocellular Carcinoma	Phase I/II	E7050 + Sorafenib	ongoing, not recruiting	NCT01271504
	Advanced or Metastatic Solid Tumors and Previously Untreated Gastric Cancer	Phase I/II	E7050+cisplatin+capecitabine	terminated	NCT01355302
	Advanced Solid Tumors	Phase I	ARQ 197	completed	NCT00612209
	Solid Tumors	Phase I	ARQ 197 + Omeprazole/S-warfarin/Caffeine/Digoxin/Midazolam/Vitamin K	completed	NCT01517399
Crizotinib	Solid Tumors	Phase II	Crizotinib	recruiting participants	NCT02034981
	Gastric Cancer	Phase II	crizotinib	recruiting participants	NCT02435108
	Advanced Solid Tumors(hepatocellular carcinoma)	Phase I	Crizotinib + VEGF inhibitor combinations Crizotinib + axitinib Crizotinib + sunitinib Crizotinib+ bevacizumab Crizotinib + sorafenib	withdrawn prior to enrollment	NCT01441388
	Colorectal Cancer	Phase I	Crizotinib+ PD-0325901	recruiting participants .	NCT02510001
	Advanced Malignancies	Phase I	Crizotinib + Pazopanib Crizotinib + Pemetrexed	ongoing, not recruiting	NCT01548144

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			Crizotinib + Pazopanib + Pemetrexed		
	Advanced Cancers	Phase I	Crizotinib+ Dasatinib	ongoing, but not recruiting participants	NCT01744652
	Advanced Cancer with several degrees of liver dysfunction	Phase I	Crizotinib	completed	NCT01576406
	Colorectal Cancer	Phase I	Crizotinib+PD-0325901 Crizotinib+Binimetinib	recruiting	NCT02510001
	Advanced Cancer	Phase I	Vemurafenib + Sorafenib Vemurafenib + Crizotinib	recruiting	NCT01531361
	Advanced Cancer	Phase I	Crizotinib + Rifampin + Ketoconazole	recruiting	NCT00585195
	Advanced Tumors	Phase II	Crizotinib	recruiting	NCT01524926
Cabozantinib (XL184)	Refractory Soft Tissue Sarcomas	Phase II	Cabozantinib	recruiting	NCT01755195
	Advanced Malignancies	Phase II	Cabozantinib Placebo	completed	NCT00940225
	Advanced Cholangiocarcinoma	Phase II	Cabozantinib	ongoing, not recruiting	NCT01954745
	Pancreatic Cancer	Phase I	cabozantinib + gemcitabine	ongoing, but not recruiting	NCT01663272
	Colorectal Cancer	Phase I	Cabozantinib + Panitumumab Cabozantinib	recruiting	NCT02008383
	Pancreatic Neuroendocrine	Phase II	Cabozantinib	ongoing, but not recruiting	NCT01466036
	Hepatocellular Carcinoma	Phase III	Cabozantinib Placebo	recruiting	NCT01908426
	Hepatic Impairement	Phase I	Cabozantinib	completed	NCT01493869
	Solid tumors	Phase I	Cabozantinib capsules Cabozantinib tablets	completed	NCT01553656
JNJ-38877605	Advanced or Refractory Solid Tumors	Phase I	JNJ-38877605	terminated	NCT00651365
Golvatinib (E7050)	Advanced Solid Tumors	Phase I	E7050	completed	NCT00869895
	Solid Tumor Gastric Cancer	Phase I	E7050	completed	NCT01428141
	Advanced Solid Tumors	Phase I	E7050	completed	NCT00921869
	Advanced or Metastatic Solid Tumors and Previously Untreated Gastric Cancer	Phase I/II	Golvatinib + cisplatin + capecitabine	terminated	NCT01355302
	Hepatocellular Carcinoma	Phase I	E7050 + Sorafenib Sorafenib	ongoing, but not recruiting	NCT01271504
MK-2461	Advanced Cancer	Phase I	MK2461	completed	NCT00518739
	Advanced Solid Tumors	Phase I/II	MK2461	completed	NCT00496353
Rilotumumab (AMG 102)	Gastric Cancer	Phase III	(AMG102) + Epirubicin, Cisplatin+ Capecitabine (ECX) Placebo	terminated	NCT01697072
	Advanced or Metastatic Gastric or Esophagogastric Junction Cancer	Phase I/II	AMG102+Capecitabine+Epirubicin + Cisplatin Placebo+ Capecitabine+ Epirubicin+ Cisplatin	completed	NCT00719550
	Gastric Cancer	Phase III	AMG 102+ Cisplatin + Capecitabine (CX)	terminated	NCT02137343

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			placebo		
	Metastatic Colorectal Cancer	Phase I/II	Panitumumab,Ganitumab,Rilotumumab Placebo, Panitumumab,Ganitumab	completed	NCT00788957
	Advanced Solid Tumors or Advanced or Metastatic Gastric	Phase I	Rilotumumab	completed	NCT01791374
	Advanced gastroesophageal adenocarcinoma	Phase II	simplified Folfox 4 simplified Folfox 4 + Panitumumab simplified Folfox 4 + AMG 102	is ongoing, but not recruiting	NCT01443065
Onartuzumab (MetMab)	Gastric Cancer	Phase II	Placebo mFOLFOX6 onartuzumab	completed	NCT01590719
	Advanced or Metastatic Solid Tumors	Phase I	MetMAb MetMAb +bevacizumab	completed	NCT01068977
	Solid Tumor	Phase III	Onartuzumab placebo	ongoing, but not recruiting	NCT02488330
	Metastatic Colorectal Cancer	Phase II	5-FU+FOLFOX+ bevacizumab [Avastin]+ leucovorin+ onartuzumab [MetMAb] 5-FU+FOLFOX+ bevacizumab [Avastin]+ leucovorin +Placebo	completed	NCT01418222
	Metastatic HER2-Negative And Met-Positive Gastroesophageal Cancer	Phase III	Onartuzumab+ mFOLFOX6 Placebo+ Onartuzumab	completed	NCT01662869
	Advanced Hepatocellular Carcinoma	Phase I	Onartuzumab Onartuzumab+Sorafenib	completed	NCT01897038
	Neoplasms	Phase I	onartuzumab + cobimetinib onartuzumab + vemurafenib onartuzumab + vemurafenib + cobimetinib onartuzumab + vemurafenib + cobimetinib	completed	NCT01974258
	Advanced or Metastatic Solid Tumors	Phase I	Onartuzumab (MetMAb)	completed	NCT02031731
AMG 208	Advanced Solid Tumors	Phase I	AMG 208	completed	NCT00813384
MGCD265	Advanced Malignancies	Phase I	MGCD265+erlotinib MGCD265+docetaxel	terminated	NCT00975767
	Advanced Malignancies	Phase I	MGCD265	completed	NCT00679133
	Advanced Cancer	Phase I	MGCD265	recruiting	NCT00697632
	Healthy Subjects	Phase I	MGCD265	completed	NCT01930006
Foretinib (GSK1363089)	Solid Tumor	Phase I	Foretinib	completed	NCT00742261
	Liver Cancer	Phase I	Foretinib	completed	NCT00920192
	Metastatic Gastric Cancer	Phase II	Foretinib	completed	NCT00725712
EMD1204831	Advanced Solid Tumors	Phase I	EMD1204831	terminated	NCT01110083
INCB028060	Advanced Malignancies	Phase I	INCB028060	completed	NCT01072266
Amuvatinib	Solid Tumors	Phase I	Amuvatinib	completed	NCT00894894
	Malignant Disease	Phase I	MP-470 + topotecan MP-470 + docetaxel MP-470 + erlotinib MP-470 + paclitaxel/carboplatin	completed	NCT00881166

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			MP-470 + carboplatin/etoposide		
BMS-777607 (ASLAN002)	Malignant Solid Tumor	Phase I	BMS-777607	ongoing, not recruiting	NCT01721148
	Advanced or Metastatic Solid Tumors	Phase I/II	BMS-777607	completed	NCT00605618
AMG 337	Stomach Neoplasms	Phase I/II	AMG 337	ongoing, not recruiting	NCT02096666
	Advanced Solid Tumors	Phase I	AMG 337	ongoing, not recruiting	NCT01253707
	Advanced Stomach or Esophageal Cancer	Phase I/II	c-Met inhibitor AMG 337+ oxaliplatin+ leucovorin calcium+ fluorouracil placebo+ oxaliplatin+ leucovorin calcium+fluorouracil	not recruiting	NCT02344810
	Gastric/Esophageal Adenocarcinoma or Other Solid Tumors	Phase II	AMG 337	terminated	NCT02016534
PF-04217903	Advanced Cancer	Phase I	PF-04217903	terminated	NCT00706355
MSC2156119J	Solid Tumors	Phase I	MSC2156119J	completed	NCT01832506
	Hepatocellular Carcinoma	Phase I/II	MSC2156119J	recruiting	NCT02115373
	Hepatocellular Carcinoma	Phase I/II	MSC2156119J Sorafenib	recruiting	NCT01988493
	Advanced Solid Tumors	Phase I	MSC2156119J	completed	NCT01014936
PF-02341066	Advanced Cancer	Phase I	PF-02341066,Rifampin, Itraconazole	recruiting	NCT00585195
Volitinib	Advanced Gastric Cancer	Phase I	Volitinib + Docetaxel	completed	NCT02252913
	Advanced Gastric Adenocarcinoma	Phase II	Volitinib	recruiting	NCT02449551
	Advanced Solid Tumors	Phase I	Volitinib	recruiting	NCT01773018
	Advanced Gastric Adenocarcinoma	Phase I/II	Volitinib+ Docetaxel	recruiting	NCT02447406
	Advanced Gastric Adenocarcinoma Patients With MET Overexpression	Phase II	Volitinib+ Docetaxel	ongoing, not recruiting	NCT02447380
	Advanced Solid Tumors	Phase I	Volitinib	recruiting	NCT01985555

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