c-Met targeting in advanced gastric cancer: An open challenge

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Abstract

Despite significant improvements in systemic chemotherapy over the last two decades, the prognosis of patients with advanced gastric and gastroesophageal junction adenocarcinoma (GC) remains poor. Because of molecular heterogeneity, it is essential to classify tumors based on the underlying oncogenic pathways and to develop targeted therapies acting on individual tumors. High-quality research and advances in technology have contributed to the elucidation of molecular pathways underlying disease progression and have stimulated many clinical studies testing target therapies in an advanced disease setting. In particular, strong preclinical evidence for the aberrant activation of the HGF/c-Met signaling pathways in GC cancers exists. This review will cover the c-Met pathway, the mechanisms of c-Met activation and the different strategies of its inhibition. Next, we will focus on the current state of the art in the clinical evaluation of c-Met-targeted therapies and the description of ongoing randomized trials with the idea that in this disease, high quality translational research to identify and validate biomarkers is a priority task.

Introduction

Gastric and gastroesophageal junction adenocarcinoma (GC) is the fifth most common cancer in the world, with approximately one million new cases being diagnosed annually, and GC remains the third leading cause of cancer-related deaths worldwide, accounting for 8% of total cancer cases and 10% of total cancer deaths [1–4]. Moreover, despite recent progresses in diagnostic and therapeutic modalities, the outcome of patients with GC remains poor, especially for advanced stages with a 5-year survival for advanced or metastatic disease still <10% and a median overall survival (OS) limited to 1 year [5,6]. Palliative chemotherapy remains the mainstay of treatment for locally advanced or metastatic disease, with a platinum-containing regimen representing the current standard first-line treatment. The addition of a third drug (usually epirubicin or a taxane) to a platinum-based doublet may be a valuable option for selected fit patients. As with other cancers, recent progress in the molecular profiling of GC has led to the understanding that GC is a heterogeneous disease, with a number of driver mutations having been acknowledged to be action targets in ~40% of GC [7–11]. This finding led to the design of several targeted therapies and to progress in clinical outcomes in the past several years. These results may help to elucidate this disease, although more molecular studies are definitively needed to understand what proportion of patients could benefit from this approach.

Trastuzumab, a human epidermal growth factor receptor type 2 (HER2) monoclonal antibody, was the first such agent receiving Food and Drug Administration (FDA) and European Medicine Agency (EMA) approval because it was shown to improve overall response rate (ORR), progression free survival (PFS), and overall survival (OS) when added to cisplatin-based chemotherapy in patients with HER2 over-expressing GC [12–15]. However, HER2 over-expressing tumors represent approximately 20% of the total numbers of GC cases, and the need for additional targeted agents is urgent [13–15]. With the exception of trastuzumab in HER2-positive GC, and potentially ramucirumab (an anti-VEGF monoclonal antibody) in the relapsed setting [16,17], recent Phase III studies of other agents targeting oncogenic mediators, such as VEGF-A, EGFR and mTOR, in non-enriched patient populations have not been demonstrated to improve survival [18–27].

Of the remaining potential drug-action targets thought to play a role in GC, hepatocyte growth factor (HGF) and its receptor, the trans-membrane tyrosine kinase c-Met, have been recently indicated as survival prognostic factors, as well as potential therapeutic
targets in a distinguished subtype of locally advanced or metastatic gastric cancer, and are currently being subjected to intensive clinical investigation [5,28].

The aim of this comprehensive review is to summarize the available data and the status of ongoing randomized studies of anti-c-Met agents in advanced/metastatic GC, as well as to elucidate issues and challenges in the identification of c-Met biomarkers to facilitate patient selection.

c-Met pathways and gastric oncogenesis

The receptor tyrosine kinase c-Met, encoded by MET proto-oncogene located on the 7q31 locus, is an epithelial/endothelial cell surface transmembrane receptor with specificity for hepatocyte growth factor (HGF) or scatter factor (SF), and it is the only known high affinity ligand [29–31]. c-Met is structurally distinct from most receptor tyrosine kinase subfamilies, being a disulfide–linked heterodimer composed of an extracellular and a transmembrane region, the latter with a transmembrane and a cytoplasmic portion composed of a tyrosine Kinase and a docking site domain. Following binding of the active heterodimer HGF resulting from the conversion of its inactive precursor through proteolysis, the c-Met receptor undergoes dimerization and autophosphorylation on two tyrosine residues in its catalytic domain (Y1234 and Y1235) [32,33]. Other tyrosine residues located outside the kinase domain (Y1349 and Y1356) are subsequently phosphorylated, forming a multifunctional docking site that recruits several Src-homology-2 domain (SH2 domain)-containing effectors, such as PI3K [34], the non-receptor tyrosine kinase Src [34], the growth factor receptor-bound protein 2 (Grb2) and SH2 domain-containing protein (SHC) adapters [34–36], SHP2 (also known as PTPN11; an upstream activator of Src and ras) [36], phospholipase Cγ1 (PLCγ1) [34], the transcription factor STAT3 [37,38], and Grb2-associated-binding protein 1 (GAB1) [39,40]. As a whole, this apparatus leads to the efficient activation of downstream signal transduction pathways that include the mitogen-activated protein kinase (MAPK) cascades (extracellular signal-regulated kinase 1 (ErK1) and ErK2, Jun amino-terminal kinases (JNKs) and p38), the phosphoinositide 3-kinase–Akt–signal transducer and activator of transcription proteins (STATs), and the nuclear factor-κB inhibitor-α (IκBα)–nuclear factor-κB (NF-κB) complex, responsible for driving proliferation, cell survival, morphogenesis, cell migration, and invasiveness [39,41–43].

Further levels of complexity are provided by the interaction of several signal modifiers, including c69β4 integrin, which works as a signaling platform that potentiates HGF-triggered activation of Ras, and PI3K [44,45]; Class B plerin, which transactivates c-Met in response to semaphorin stimulation and leads to the execution of c-Met-dependent biological processes [46,47]; transmembrane cell adhesion molecules CD44v6 and CD44v10 [48,49] (and more recently the intercellular adhesion molecule 1 (ICAM-1) [50], which link the c-Met cytoplasmic domain to actin microfilaments through GRB2 and intermediate ezrin, radixin and moesin (ERM) proteins, facilitating c-Met-induced activation of Ras by the guanine nucleotide exchange factor son of sevenless (SOS); and death receptor FAS (also known as CD95 and TNFRSF6), which interacts with the c-Met extracellular domain, thereby preventing FAS receptor–FAS ligand (FASL) recognition and FAS self-aggregation, and limiting apoptosis through the extrinsic pathway [51]. In addition, the G-protein-coupled receptor (GPRC) agonists lysophosphatidic acid (LPA), bradykinin, thrombin and carbachol can induce c-Met phosphorylation, although the functional consequences of these interactions are still unclear [52].

Interestingly, functional interactions have been reported between HGF receptors and epidermal growth factor receptors, enabling the activation of c-Met after the stimulation of cells with the EGFR ligands EGF or transforming growth factor (TGF–α) [53]. c-Met can be transactivated following EGFR activation in the absence of HGF, and simultaneous activation of c-Met and EGFR is synergistic. An indirect transactivation of EGFR by c-Met also occurs via the upregulation of EGFR ligands by Met-driven pathways [54]. Evidence also exists for c-Met interactions with the other EGFR family members, ERBB2 and ERBB3, causing transactivation of both receptors [55,56]. Transactivational cooperation between c-Met and EGFR has been reported to enhance the malignant invasive phenotype and is involved in the development of resistance to targeted therapies by strengthening of downstream pathways such as Akt and ERK/MAP kinase. As a whole, the list of cell surface receptors that play a role in c-Met signaling is growing constantly (recepteur d’origine nantais (RON), platelet-derived growth factor receptor (PDGFR), Axl) [57–59] and highlights the importance of personally targeted cancer therapies, depending on the expression of these RTKs in specific patients.

Under normal conditions, MET expression and HGF-induced c-Met tyrosine kinase activation are tightly regulated in cells of epithelial origin (though also found on non-epithelial tissues such as endothelium, neuronal cells, melanocytes and hematopoietic cells) [60] by paracrine ligand delivery, ligand activation at the target cell surface, and ligand activated receptor internalization and degradation [61]. The oncogenic dysregulation of the c-Met signaling pathway has been reported in a wide range of human epithelial cancers, including lung, colorectal, breast, pancreatic, ovarian, hepatic and gastric cancers, representing, for many of these, an independent prognostic factor associated with worse outcomes [62–65]. c-Met activation occurs via several molecular mechanisms, including overexpression, focal gene amplification, gene copy-number gain, activating mutations, RTK transactivation or changes in ligand-induced autocrine or paracrine signaling [41,66,67]. In this regard, various studies in preclinical models have reported that activation of HGF/c-Met signaling promotes cell invasiveness and triggers metastases [31]; conversely, the suppression of overexpressed MET genes in tumor cells inhibits tumor growth and metastasis [68]. In addition, it is noteworthy that HGF–c-Met signaling stimulates tumor angiogenesis, enhancing tumor growth for cancers growth-limited by hypoxia, while a hypoxic status in tissues enhances both HGF levels and HGF receptor expression through a negative feedback-like mechanism [69].

Previous studies, both in preclinical models and in humans, have reported that the most common cause of c-Met pathway activation in GC is the MET gene amplification with subsequent protein overexpression and kinase activation. MET amplification was reported in approximately 4%–10% of gastric tumors [70,71], and c-Met protein overexpression was reported in approximately 50% of advanced gastric cancers [72].

In GC, immunohistochemistry (IHC) analyses showed that c-Met is frequently expressed (~65%), with high-intensity staining in ~20% of cases [72] with increased invasiveness and increased potential of distant metastases, mainly to the liver, resulting in worse clinical outcomes [72,73], also following potentially curative surgery [74]. However, these figures do not match with the frequency of known mechanisms of c-Met activation. In fact, activating c-Met mutations are exceedingly rare in GC, and c-Met amplification occurs in only 5%–10% of cases [70,71]. These discrepancies underscore the complexity of mechanisms that upregulate the HGF/c-Met axis [67,75,76].

Of note, c-Met activation seems to have important clinical implications. In fact, it has been shown in several studies to affect the efficacy of drugs specifically designed to target members of the EGFR family in lung, breast and colorectal cancers [77–80]. In particular, c-Met activation has been shown to confer resistance to HER2-targeted drugs in gastric cancer by way of poorly understood molecular mechanisms involving signaling crosstalk [81]. HER2 and
c-Met are usually co-expressed in 12% of unselected gastric cancers and in 24% of the intestinal subtypes [82]. This co-expression is considered of particular importance because c-Met and HER2 have been shown to be synergistically promoting cellular invasion, suggesting that tumors expressing both receptors may be more aggressive [56]. From a therapeutic point of view, c-Met expression in HER2-positive tumors may provide tumor cells with an “escape hatch”. In fact, notwithstanding the HER2 inhibition, GC cells may shift their growth dependence from HER2 to other available tyrosine kinases, or they may be less dependent upon HER2 to begin with, vastly influencing the response to HER2-targeted therapy [83]. Conversely, the down-regulation of c-Met expression with siRNA can bypass c-Met rescue effects and restore growth inhibition of the GC cells by anti-HER2 drugs. Furthermore, loss of c-Met function, through either RNA-interference-mediated depletion or small-molecule-mediated inhibition, significantly improves the response to trastuzumab [81].

**c-Met assessment**

The oncogene MET can be studied at both the protein and gene levels. Immunohistochemistry (IHC) represents the most useful technique to identify protein expression, even if it cannot establish whether the receptor over-expression is linked to gene amplification or to other mechanisms, such as transcriptional activation or hypoxia [84]. Unfortunately, a consensus on the evaluation of c-Met status with IHC is not currently available, and the literature is notably poor. The H-score is a semi-quantitative method combining staining intensity (score: 0–4) with the percentage of positive cells (score: 0–100%). Each intensity level is multiplied by the percentage of cells, and all values are summed up to obtain the final IHC score (ranging from 0 to 400). Scores from 0 to 200 are considered to be associated with negative/low expression, while scores from 201 to 400 are considered to show positive/high expression [85–87]. A modified H-score system has also been proposed. This model hypothesizes three staining intensity levels (score: 0–3), and it provides a total score ranging from 0 to 300. Cases are considered as negative (score 0–50), weakly positive (51–100), moderately positive (101–200), or strongly positive (201–300) [88]. In a second scoring system evaluating the expression of c-Met, samples are classified as negative (0, 1+), when no staining or faint staining is present in <10% of cells; ambiguous (2+), when moderate staining is present in >10% of cells; or positive (3+), when a circumferential, basolateral, or lateral signal for c-Met over-expression of protein with strong intensity is present in >10% of the cells [89].

MET amplification is studied by in situ hybridization techniques (fluorescence in situ hybridization, FISH, and single or double silver in situ hybridization, SISH). MET amplification is defined as a gene-to-centromere ratio (MET/CEP7) ≥2.2 or MET copy number ≥6 [90]. An alternative method is the same as that used for EGFR. Amplification of MET is classified into six groups as follows: (I) disomy (≥2 copies in ≥90% of cells); (II) low trisomy (≤2 copies in ≥40% of cells, 3 copies in 10%–40% of cells, >4 copies in <10% of cells); (III) high trisomy (≤2 copies in ≥40% of cells, 3 copies in ≥40% of cells, >4 copies in <10% of cells); (IV) low polysomy (≥4 copies in 10%–40% of cells); (V) high polysomy (>4 copies in ≥40% of cells); and (VI) gene amplification (defined by the presence of tight MET clusters and a ratio of MET/CEP7 ≥2, or ≥15 copies of MET/cell in ≥10% of analyzed cells). High polysomy and gene amplification are considered as a positive SISH result, while the others represent negative results [86].

**Development of c-Met-inhibitor therapies**

Greater understanding of the structure, function, and roles of c-Met in GC has led to the development of multiple compounds with different targeting strategies that are currently being tested in the clinic. In particular, c-Met signaling can be blocked at the ligand-receptor level by drugs directed against HGF (HGF antagonists) or HGF receptors, such as anti c-Met receptor monoclonal antibodies, or at the tyrosine kinase domain level by small molecule c-Met kinase inhibitors [91]. Currently, many molecules, either alone or in combination with other drugs, are under investigation in clinical trials in GC, with early data summarized below.

**Monoclonal antibodies**

Examples of the monoclonal antibodies in clinical trial data on Rilotumumab (Amen, Thousand Oaks, CA, USA) and Onartuzumab (MetMab; Roche, Basel, Switzerland) will be presented.

**Rilotumumab**

Rilotumumab (AMG102) is a human IgG2 targeting human hepatocyte growth factor/scatter factor (HGF) that blocks the binding of HGF to its receptor [92–94]. The effectiveness of this agent in GC was reported in a randomized phase II trial presented at the 2011 ESMO Congress [95,96]. In 121 patients, a combination ECX (epirubicin, cisplatin, and capecitabine) chemotherapy was administered with Rilotumumab at a dose of 15 mg/kg in 83 patients and placebo in a total of 39 patients with locally advanced or metastatic GC. The toxicities were manageable and a maximum-tolerated dose was not reached. PFS was 5.6 months in the Rilotumumab group and 4.2 months in the placebo group (HR 0.64; p = 0.04). 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 presented at ASCO 2012, there was a statistically significant PFS and OS advantage for patients treated with Rilotumumab and high c-Met overexpression by immunohistochemistry. OS was 11.5 vs. 5.7 months (HR 0.29; P = 0.012) for c-Met-high tumors (more than 50% cells c-Met positive by immunohistochemistry) compared to c-Met-low tumors [96]. Notably, the same effect was not found according to the c-Met high amplification status by FISH analysis. Moving from these results, two Phase 3 randomized double-blind placebo controlled trials (RILOMET-1 [97] and RILOMET-2 [98]) evaluating the role of Rilotumumab in combination with polichemotherapy were started. In particular, the first trial studied the combination of Rilotumumab (at the dose of 15 mg/kg) plus ECX as a first-line treatment for untreated advanced c-Met-positive GC. OS was the primary outcome, while secondary objectives were represented by PFS, time to progression (TTP), ORR, disease-control rate (DCR), time to response (TTR) and safety. Secondly, the RILOMET-2 trial analyzed the role of Rilotumumab plus CX in c-Met-positive Asian patients with locally advanced or metastatic GC. The primary end-points of this study were PFS and OS, and the secondary ones were TTP, ORR, DCR, TTR and safety profile [98]. Unfortunately, in November 2014, all clinical studies of rilotumumab in advanced gastric cancer, including the Phase 3 RILOMET-1 and RILOMET-2 trials, were closed. This decision was based on a planned safety review by the RILOMET-1 independent data monitoring committee that observed an increase in the number of deaths in the rilotumumab and chemotherapy treatment arm compared to the chemotherapy-treatment only arm. However, the data from that trial are under investigation, and no detailed results are available to date. The results of the latter interim analysis will be available shortly. A recent exposure–response analysis of Rilotumumab in GC has been published and has shown that Rilotumumab had an exposure-dependent treatment effect in patients with c-Met-positive GC [99].

**Onartuzumab**

Onartuzumab is another humanized, monovalent, monoclonal antibody directed against the c-Met receptor. It inhibits HGF/c-Met binding without exerting agonistic activity or inducing c-Met
evaluated the activity of treatment in both patients with high baseline tumor phospho-Met/total c-Met protein ratio decreased with Foretinib (median 15% vs. 9%). Aminotransferase (23% vs. 8%) were higher with intermittent dosing.

Treatment-related adverse events were reported in 91% of patients receiving daily dosing. Of 67 patients with tumor samples, 3 showed c-Met amplification, one of whom achieved a stable disease. The best response was stable disease (median duration: 3.2 months) in subjects with c-Met amplified GC or other c-Met amplified solid tumors. In particular, a durable complete response lasting nearly 2 years was achieved in a metastatic female GC patient with high MET polysomy and c-Met overexpression [101].

Moreover, a double-blind placebo-controlled randomized Phase 2 study conducted by Shah et al. [102] evaluated the activity of Onartuzumab (at dose of 10 mg/kg) in combination with mFOLFOX6 in 123 patients with metastatic HER2-negative GC cancer. Preliminary results, presented at the 2015 ASCO Gastrointestinal Cancers Symposium, revealed a higher rate of serious toxicities in the experimental arm compared to the placebo arm (55% vs. 40%), with similar mPFS (6.77 vs. 6.97 HR 1.08, 95% CI 0.71–1.63). In particular, in the c-Met-positive subgroup, mPFS was 5.95 months for Onartuzumab and 6.8 months for placebo (HR 1.38 CI 0.60–3.20). Therefore, the addition of Onartuzumab to mFOLFOX6 did not confer an advantage in PFS in advanced gastro-esophageal cancer patients. Moving from these results, the MetGastric (Y028322) trial, a randomized Phase III study investigating FOLFOX6 with or without Onartuzumab in HER2-negative, c-Met-positive (more than 50% cells with c-Met expression measured by immunohistochemistry) advanced GC patients [105], has been recently stopped.

Small molecule c-Met tyrosine kinase inhibitors (TKIs)

The majority of small-molecule inhibitors of c-Met compete with adenosine triphosphate (ATP) for binding to the tyrosine kinase domain of a receptor such as Tivantinib (ARQ197) or Foretinib (GSK1363089), which is an inhibitor of AXL, RON (Recepteur d'Origine Nantais), VEGFR2, PDGFR (platelet-derived growth-factor receptor-β), KIT or AMG337.

Foretinib

Foretinib is an oral potent multikinase inhibitor targeting c-Met, RON, AXL, TIE-2, and VEGFR2 receptors. In the interim analysis of the first in-human Phase Ib/I trial in an unsellected population of heavily pretreated patients with different tumor types, a 20% decrease in tumor size at the first 8-week evaluation was noticed in 6 out of 12 patients with advanced GC [104].

Thus, in the Phase II expansion cohort of the same study safety, the tolerability and ORR of 2 dosing schedules (240 mg/d, for 5 d every 2 wk or 80 mg/d) of oral Foretinib (GSK1363089) were evaluated in 74 patients with metastatic GC (93% previously treated) [105]. The best response was stable disease (median duration: 3.2 months) in 10 (23%) patients receiving intermittent dosing and 5 (20%) receiving daily dosing. Of 67 patients with tumor samples, 3 showed MET amplification, one of whom achieved a stable disease. Treatment-related adverse events were reported in 91% of patients. Rates of hypertension (35% vs. 15%) and elevated aspartate aminotransferase (23% vs. 8%) were higher with intermittent dosing. The phospho-Met/total c-Met protein ratio decreased with Foretinib treatment in both patients with high baseline tumor phosphorylated c-Met. These results indicate that single-agent Foretinib failed to show efficacy in molecularly unsellected patients with metastatic GC [106].

Tivantinib

Tivantinib (ARQ197) is another small-molecule c-Met kinase inhibitor that binds to a region of MET outside of the ATP binding site and impairs kinase activation allosterically [107,108]. It was initially reported as a c-Met selective inhibitor in 2010 and entered into clinical trials. In the initial report, tivantinib inhibited recombinant human c-Met with a calculated inhibitory constant (Ki) of −355 nmol/L and had weak inhibitory effects on p21-activated kinase 3 (PAK3), vascular endothelial growth factor receptor-3 (VEGFR-3/Flt4), calmodulin-dependent kinase II (CAMKII)-delta and Pim-1. Tivantinib did not inhibit any of the other 225 human kinases tested, including the Ron kinase, which belongs to the c-Met family of RTKs. The crystal structure of the tivantinib in complex with the c-Met kinase domain revealed that tivantinib binds to the inactive form of c-Met, suggesting that it inhibits c-Met through a non-ATP competitive mechanism. Currently, however, Tivantinib cannot be considered a proper c-Met inhibitor. Studies on lung-cancer cell lines have shown that it acts on cells not expressing c-Met [109], and another preclinical study has shown that tivantinib inhibits microtubule polymerization independently of c-Met [107].

Although in the Phase I dose-escalation trial prolonged disease stabilization for >32 weeks was observed in 7 out of 11 patients with five tumor types including gastric cancer [110], in a Phase II trial the Tivantinib monotherapy failed to show objective responses in 30 previously treated metastatic GC subjects with a DCR of 36.7% with a median PFS of 43 days (95% CI: 29.0–92.0). Grade 3 or 4 toxicities were observed in 43.3% of patients [111].

AMG-337

AMG-337 is another orally bioavailable inhibitor that selectively binds to c-Met, disrupting c-Met signal transduction pathways and inducing cell death in tumors overexpressing c-Met protein or expressing constitutively activated c-Met protein [112]. Interim results of a multicenter, Phase Ib/Ii, single arm, two cohort study evaluating the efficacy, safety, and pharmacokinetics of AMG-337 in subjects with c-Met amplified GC or other c-Met amplified solid tumors showed that eight of 13 patients with c-Met overexpression had objective responses, which were dramatic and sustained in some instances [112]. The most common treatment-related adverse events were headache, nausea, vomiting, and fatigue. Moving from these promising results, there is now an ongoing Phase II multicenter single-arm trial investigating the role of AMG-337 (300 mg daily) in pretreated advanced gastric cancer patients. The primary outcome of this study is represented by ORR, while the secondary ones are the duration of response, TTR, PFS, OS, pharmacokinetic parameters and safety [113]. The activity of AMG-337 in combination with chemotherapy will be investigated in a Phase I/Ii randomized trial wherein patients with locally advanced or metastatic gastric cancer will be randomized to receive mFOLFOX6 plus AMG-337 (at the best dose assessed in the Phase I) or placebo. Preliminary data will be available in late 2016 [114].

ABT-700

ABT-700 is a c-Met targeting antibody with significant preclinical single-agent activity against human xenograft tumors with MET amplification [115]. This antibody’s efficacy is under evaluation in a Phase I/ib open label trial evaluating the safety, pharmacokinetics (PK), and preliminary efficacy of ABT-700 in subjects with advanced solid tumors with MET amplification or c-Met overexpression. The primary end-point of this study is to assess the safety and tolerability of ABT-700, as both monotherapy and in combination with docetaxel or 5-fluorouracil, folinic acid, irinotecan and cetuximab (FOLFIRI/cetuximab) or erlotinib. Secondary endpoints are represented by Objective response rate, PFS and duration of response [115].

Discussion and future directions

Many preclinical and clinical studies have shown the important role of the c-Met pathway in tumors and in GC. The c-Met pathway can be aberrantly activated because of HGF or HGF/ c-Met overexpression. In combination with docetaxel or 5-fluorouracil, MET gene amplification and, rarely, as the final event of a MET gene mutation. Other signaling co-receptors belonging to the Sema family (RON, Plexins), such as the RET and
HER family (EGFR, HER2, HER3) members, can crossstalk with c-Met, even in an HGF-independent manner, providing an alternative way to induce proliferation, survival and invasive growth [39–43]. However, despite huge progresses made in the last decade, c-Met signaling pathways are still far from being fully elucidated in the various settings in which c-Met is involved. Furthermore, as a key element in the refinement of therapeutic strategies, as well as the prevention of resistances to c-Met targeting agents, the more accurate knowledge of molecular and biochemical functions of the c-Met pathway in the context of other relevant pathways will play an indispensable role in these goals.

Thirty years after its discovery, different compounds targeting c-Met have been developed, and many of these have been tested in early phases in GC. Monoclonal antibody Rilotumumab seemed to be the more promising because it showed clear benefits in terms of response and survival in the Phase II trial. Furthermore, Rilotumumab combined with ECX resulted in a prolonged progression-free survival compared with chemotherapy alone, especially in patients with c-Met-high tumors [95,96]. Moreover, this agent was found to be well tolerated, alleviating concerns about potential toxicities of c-Met-targeted agents in normal adult organs. Moving from these encouraging results, Rilotumumab entered late-stage in two clinical studies [98,99]. Surprisingly, in consideration of the increasing number of deaths observed in the rilotumumab and chemotherapy treatment arm when compared to the chemotherapy treatment only arm (RILOMET-1) [97], both trials have since been closed. To date, no detailed results to clarify this issue are available, and the trial lead investigators are still working to further analyze the data to clarify the potential therapeutic role of these compounds in GC, promising quick presentation and publication of records. Similarly, in spite of encouraging preliminary results, a randomized Phase III study investigating FOLFOX6 with or without Onartuzumab in HER2-negative, c-Met-positive advanced GC patients [103] has been recently discontinued due to a lack of PFS advantage, as well as a higher rate of serious toxicities in the Onartuzumab arm compared to the placebo arm. These inconsistent findings should not detract from the work that remains, and fundamental research is still fueling our knowledge of c-Met.

Conversely, no clear anti-tumor activity was identified in small-molecule c-Met tyrosine kinase inhibitors (TKIs) with the possible exception of high c-Met-positive tumors [104–115].

Novel trials are restricted to “c-Met-positive” patients, and several biomarkers are being explored to clarify the question of potential treatment benefits in selected patients according to a specific genetic/molecular profile. Future directions in the c-Met-targeted therapies research area should focus on development and validation of biomarkers to optimize patient selection and treatment strategies.

In conclusion, mounting preclinical evidence indicates that the development of HGF/c-Met inhibitors may require not only a simple assessment of “c-Met-positive” cases, but also a deep knowledge on how and to what extent tumors are HGF/c-Met addicted trough ligand-dependent and ligand-independent mechanisms. The strategies of combining treatments targeting several molecules or drugs blocking downstream signaling transducers might be used to address the common problem of crosstalk between signaling pathways and, thus, the development of resistance.

Targeting the c-Met pathway may have clinical potential in advanced/metastatic GC, even if the recent late-stage clinical trials have underlined discouraging outcomes of several anti-c-Met agents. This points to the urgent need for detailed results from these studies to clarify this issue to help inform future research and to clarify the potential therapeutic role of these compounds in GC.

Conflict of interest

None.

References


