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REVIEW

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Advances in MET tyrosine kinase inhibitors in gastric cancer

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ABSTRACT Gastric cancer is among the most frequently occurring cancers and a leading cause of cancer-related deaths globally. Because gastric cancer is highly heterogenous and comprised of different subtypes with distinct molecular and clinical characteristics, the management of gastric cancer calls for better-defined, biomarker-guided, molecular-based treatment strategies. MET is a receptor tyrosine kinase mediating important physiologic processes, such as embryogenesis, tissue regeneration, and wound healing. However, mounting evidence suggests that aberrant MET pathway activation contributes to tumour proliferation and metastasis in multiple cancer types, including gastric cancer, and is associated with poor patient outcomes. As such, MET-targeting therapies are being actively developed and promising progress has been demonstrated, especially with MET tyrosine kinase inhibitors. This review aims to briefly introduce the role of MET alterations in gastric cancer and summarize in detail the current progress of MET tyrosine kinase inhibitors in this disease area with a focus on savolitinib, tepotinib, capmatinib, and crizotinib. Building on current knowledge, this review further discusses existing challenges in MET alterations testing, possible resistance mechanisms to MET inhibitors, and future directions of MET-targeting therapies.

KEYWORDS Gastric cancer; MET alterations; MET tyrosine kinase inhibitors; savolitinib; MET testing

Introduction

Gastric cancer is one of the most common cancers worldwide and a leading cause of cancer-related deaths[1,2]. In 2020 alone there were > 1 million new cases of gastric cancer and an estimated 769,000 gastric cancer-related deaths globally, ranking fifth for incidence and fourth for mortality among all cancer types[1]. Gastric cancer has a poor overall 5-year survival rate of 32.4%, likely because > 60% of gastric cancer cases are only detected at an advanced stage, which is associated with poorer survival compared to localised disease[3]. Gastric cancer is highly heterogenous, comprised of different subtypes with distinct molecular and clinical characteristics, and calls for better-defined, biomarker-guided, molecular-based treatment strategies[4]. In addition to human epidermal growth factor receptor 2 (HER2), Claudin 18.2, and programmed death-ligand 1 (PD-L1), MET, a type of receptor tyrosine kinase (RTK), has also emerged as a prominent biomarker candidate and therapeutic target for gastric cancer in recent years[4].

The *MET* oncogene was initially isolated in 1984 from a human osteosarcoma-derived cell line[5]. The MET ligand was shown to be hepatocyte growth factor (HGF) in 1991[6]. HGF/MET signalling mediates important physiologic processes, such as embryogenesis[7], muscle development[8,9], and tissue regeneration[10]. However, MET also has multifaceted roles in tumor biology through oncogene addiction, expedience, and inherence,[11] and participates in tumor proliferation[12], invasion, and metastasis[13]. Aberrant MET activation has been demonstrated in multiple cancer types, such as lung[14], liver[15], and gastric cancers[16].

Given the growing evidence of MET involvement in tumour biology, MET-targeting therapies are being actively researched in various cancer types, most notably lung cancer in which several MET tyrosine kinase inhibitors (TKIs) have already been approved for treating non-small cell lung cancer (NSCLC) with *MET* exon 14 skipping mutations[17], and the second largest body of research involving gastric cancer[18]. This review

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briefly introduces the role of MET alterations and summarizes in detail the current evidence and ongoing studies involving MET TKIs in gastric cancer. This review also discusses the challenges in MET alteration testing and other future research directions, which will be essential for further realising the potential of MET-targeting therapies in a framework of biomarker-guided precision medicine in gastric cancer.

MET alterations in gastric cancer

MET alterations at the protein and genomic levels can lead to aberrant MET pathway activation (**Figure 1**)[21]. MET protein overexpression leads to excessive kinase activation[22] and it can occur in the absence of *MET* genomic alterations[21]. As the most common type of MET alteration in gastric cancer, MET protein overexpression has been reported in 39%–60% of cases, as detected by immunohistochemistry (IHC)[18,22-24]. Several forms of MET alterations are possible at the genomic level. First, *MET* gene amplification occurs in 4%–7% of gastric cancers[22,23] and is usually detected using fluorescence *in situ* hybridization (FISH) or next-generation sequencing (NGS)[25]. Research involving NSCLC has shown that *MET* amplification is a driver of acquired drug resistance[21]. Second, two main types of *MET* gene mutations can result in aberrant MET pathway activation: 1) mutations or deletions on or flanking exon 14 can lead to exon 14 skipping and the loss of the casitas B-lineage lymphoma (CBL)-binding site, which in turn hampers degradation of MET through CBL-mediated ubiquitination[21]; and 2) point mutations, such as mutations in the MET kinase domain, can lead to constitutive activation of MET and

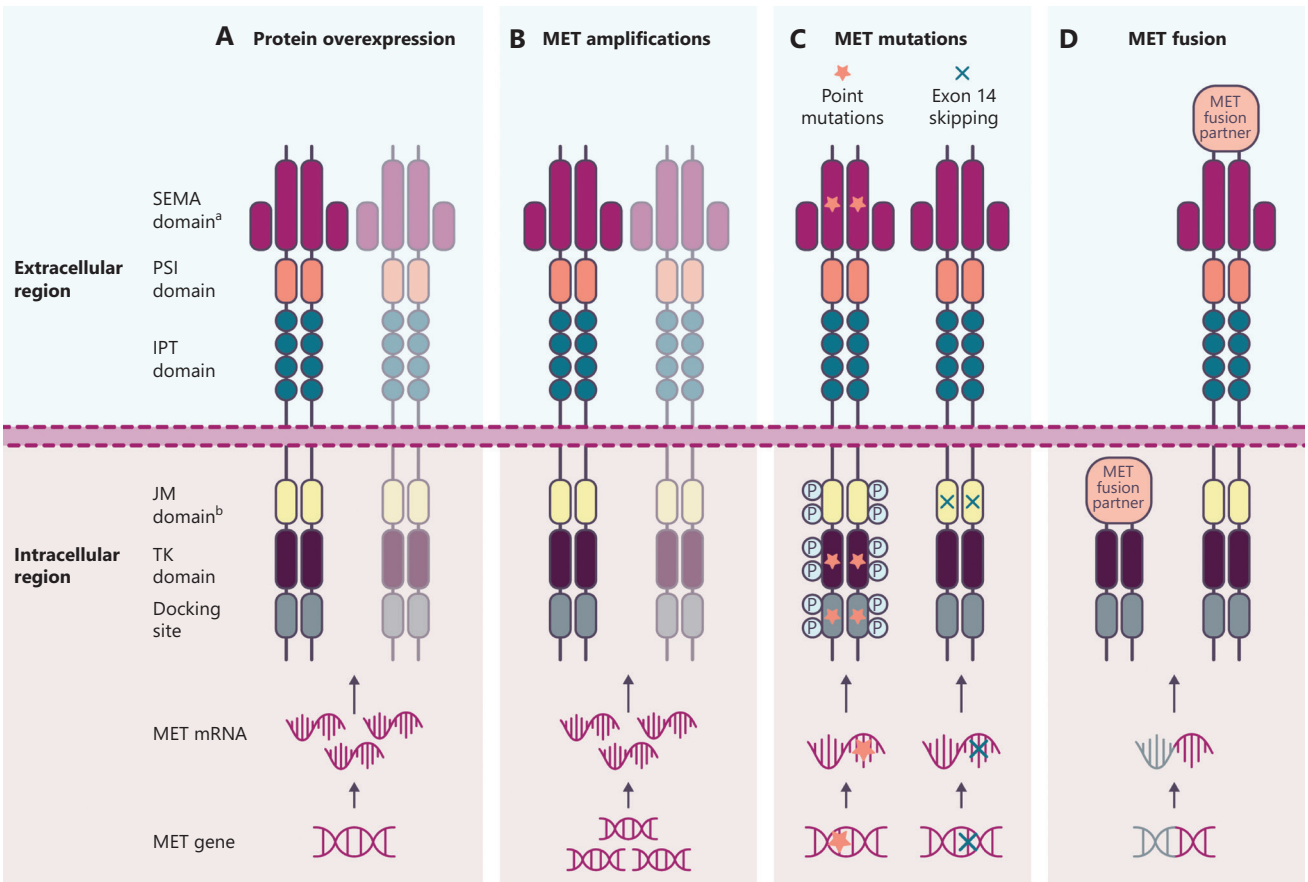

Figure 1 Different types of MET alterations that lead to aberrant MET activation (adapted from Heydt et al.[19]). A. Protein overexpression. B. *MET* amplification. C. *MET* mutations, including exon 14 skipping and MET kinase domain mutations. D. *MET* fusion. a: The SEMA domain serves as the binding site for HGF[20]; b: The casitas B-lineage lymphoma binding site is found within the JM domain[19]. HGF, hepatocyte growth factor; IPT: immunoglobin plexin transcription factor; JM, juxtamembrane; PSI, plexin semaphoring integrin; SEMA: semaphorin; TK, tyrosine kinase.

downstream signalling[19,21]. Various *MET* mutations are identified in 1%–2% of gastric cancers[22] and NGS is increasingly being used to detect such mutations[19]. Lastly, chromosomal translocations may cause the MET tyrosine kinase domain to be fused with a molecular partner and give rise to oncogenic fusion proteins, such as TPR-MET[26], that exhibit constitutive kinase activation[21]. *MET* fusion is rare in gastric cancer and is usually tested using an RNA-based NGS approach[19].

MET alterations may be associated with an unfavourable prognosis with respect to invasive/metastatic processes and survival, as well as with more frequent immunotherapy-related adverse events (AEs) in patients with gastric cancer. Peng et al.[27] performed a meta-analysis that included 14 studies with 2,258 gastric cancer patients. The hazard ratios for mortality of patients with MET overexpression and *MET* amplification were 2.42 (95% CI: 1.66–3.54) and 2.82 (95% CI: 1.86–4.27), respectively, indicating that MET overexpression and *MET* amplification are adverse prognostic factors for gastric cancer[27]. In a study involving gastric cancer patients receiving chemotherapy, An et al.[28] reported significantly shorter medians of overall survival (mOS) (6.3 *vs.* 15.1 months; $P < 0.01$) and progression-free survival (mPFS) (3.6 *vs.* 7.0 months; $P < 0.01$) in patients with than without MET overexpression. Similarly, patients with a *MET* amplification had a significantly shorter mOS (5.7 *vs.* 15.5; $P < 0.01$) and mPFS (3.6 *vs.* 6.9 months; $P < 0.01$) than patients without a *MET* amplification[28]. Patients with MET alterations were more likely to have immune-related AEs compared to patients without MET alterations in a study involving patients receiving PD-1 immunotherapy (100.0% *vs.* 27.3%; $P = 0.09$)[29]. A recent in-depth analysis involving patients with *MET*-amplified gastric cancer in clinical practice and case accumulation showed that patients with *MET*-amplified gastric cancer have the following clinical characteristics: poorly differentiated tumours[28]; peritoneal metastases[30]; and pulmonary lymphangitis carcinomatosis (PLC)[31]. Taken together, these findings suggest that increased attention should focus on identifying gastric cancer patients with MET alterations, especially *MET* amplification.

As our understanding of MET's role in gastric cancer continues to expand, there is a growing effort to explore the use of MET-targeting therapies in gastric cancer. Currently, MET inhibitors investigated for treating gastric cancer mostly fall into two main categories: monoclonal antibodies targeting MET and/or HGF with limited clinical benefits demonstrated to date; and MET TKIs[24]. MET TKIs include MET-selective and multi-target TKIs, the targets of which include MET. Moreover, there have been recent, promising findings, especially in studies involving several MET-selective TKIs. The key milestones in MET TKI development for gastric cancer are summarized in **Figure 2**.

Current evidence of MET-selective TKIs

As of 2023, a remarkable number of MET TKIs, including MET-selective TKIs and multi-target TKI, the targets of which include MET, have undergone preclinical assessment for gastric cancer but relatively few MET TKIs have entered clinical trials. Herein the findings on the key TKIs will be detailed, followed by a brief summary of other TKIs in development.

Pre-clinical data

MET-selective TKIs

Savolitinib is a MET-selective TKI developed for the treatment of metastatic NSCLC, papillary and clear cell renal cell carcinoma, colorectal cancer, and gastric cancer[32]. As early as 2015, Gavine et al.[33] demonstrated that savolitinib blocks MET signalling and tumour growth in a patient-derived xenograft (PDX) model of *MET*-amplified gastric cancer but not in a control model of 'MET-normal' gastric cancer. The same study also showed that savolitinib enhances the efficacy of docetaxel in Hs746t cell line-derived and patient-derived MET-dysregulated xenograft models[33]. Chen et al.[34] subsequently showed potent savolitinib anti-tumour activity in PDX models of advanced gastric cancer overexpressing MET and phosphorylated MET. Treatment with savolitinib inhibited MET downstream signalling pathways, as indicated by the reduction in phosphorylated AKT and ERK[34]. A more recent pre-clinical study revealed that savolitinib inhibits *in vitro* proliferation of MKN45 (characterised by *MET* amplification and overexpression of MET and phosphorylated MET) by suppressing downstream PI3K/Akt and MAPK signalling pathways[35]. Savolitinib also inhibits the growth of xenografts derived from MET-over-expressing MKN45 cells *in vivo* and exhibits synergistic activity with trastuzumab[35].

Capmatinib has been shown to be active against cancer models characterized by a variety of MET alterations, including marked MET overexpression, *MET* amplification, *MET* exon 14 skipping mutations, and MET activation *via* expression of HGF[36]. Sohn et al.[37] demonstrated that capmatinib inhibits the growth of *MET*-amplified MKN45 and SNU620 diffuse-type

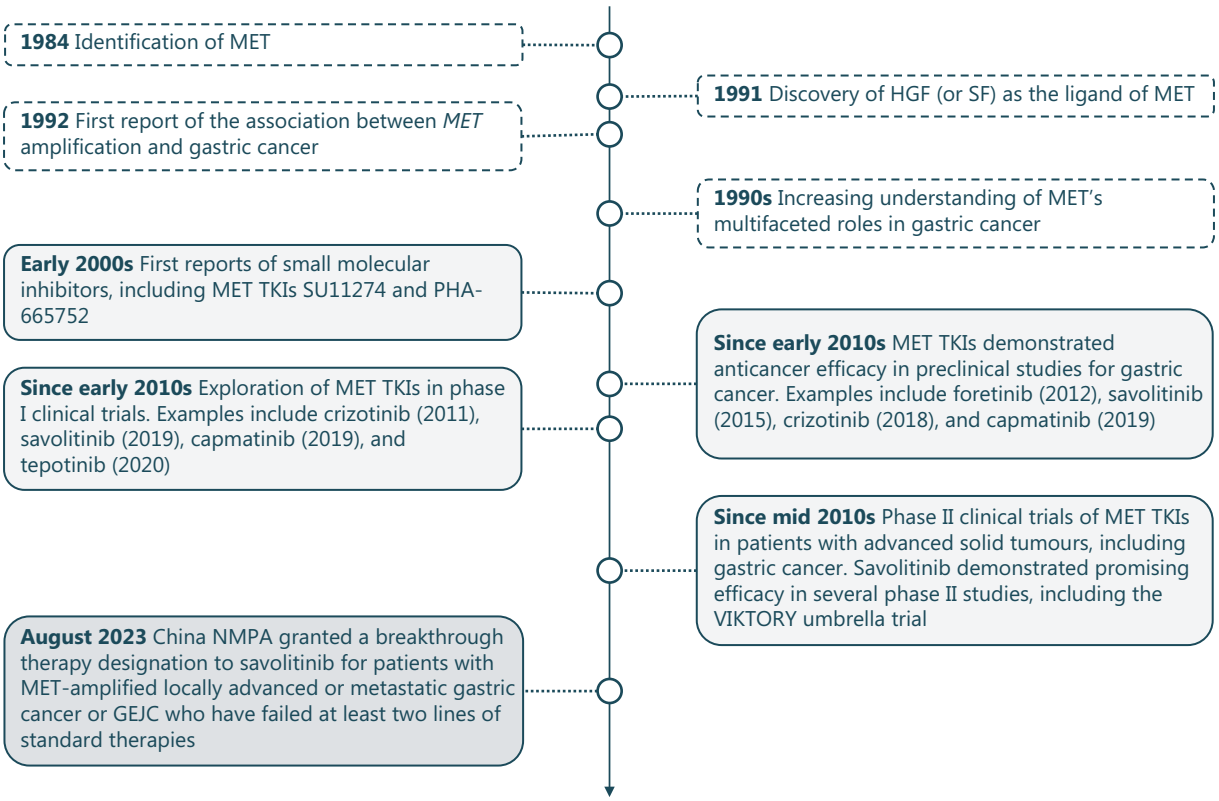

Figure 2 Key milestones of MET TKI development for gastric cancer. GEJC, gastroesophageal junction cancer; HGF, hepatocyte growth factor; NMPA, National Medical Products Administration; SF, scatter factor; TKI, tyrosine kinase inhibitor.

cells but not *MET*-reduced, intestinal-type MKN28 cells in gastric cancer models. Specifically, the highest inhibition and apoptotic rates and the lowest half maximal inhibitory concentration (IC_{50}) values of capmatinib were observed in MKN45 cells[37]. The same study also reported that capmatinib inhibits the WNT/β-catenin and EMT signalling pathways in MKN45 cells[37].

Sohn et al.[38] showed that tepotinib induces apoptosis in MET-amplified MKN45, SNU620, and KATO III cells but has no effect on MET-low MKN28 or AGS cells. Tepotinib also significantly reduces the levels of phosphorylated and total MET protein in MKN45 and SNU620 cells, and exhibits good tumour growth inhibition with increased E-cadherin and decreased levels of phosphorylated MET protein in an MKN45 xenograft model[38]. Sohn et al.[39] subsequently demonstrated anti-cancer activity with tepotinib in gastric cancer cell lines with MET exon 14 skipping mutations, as well as gastric cancer cell lines with high expression of PD-L1 and CD44. In a more recent study, Zang et al.[40] showed that tepotinib alone or tepotinib plus paclitaxel inhibit the growth of MET-positive gastric cancer cells more effectively than ramucirumab alone, paclitaxel alone, or ramucirumab plus paclitaxel.

Multi-target TKIs

Several multi-target TKIs, including crizotinib, foretinib, and TPX-0022 (elzovantinib), have demonstrated anti-tumour activity in gastric cancer models with MET alterations[41-45]. Among the multi-target TKIs, crizotinib targets MET, anaplastic lymphoma kinase (ALK), and proto-oncogene receptor tyrosine kinase 1 (ROS1), and has been shown to decrease the viability of gastric cancer cells and induce growth arrest and apoptosis in a xenograft model[41]. More recently, Chen et al.[46] explored the use of crizotinib-based proteolysis targeting chimera (PROTAC) to induce MET degradation and reported that crizotinib-PROTAC effectively eliminates MET *in vitro* and *in vivo*, and inhibits proliferation and motility of MET-positive gastric cancer cells. In an MKN45 xenograft model, an optimized PROTAC compound (PRO-6E) showed pronounced anti-tumour efficacy at a well-tolerated dose[46].

Table 1 Other MET TKIs with published preclinical results in gastric cancer

MET TKIs	Target	Preclinical findings
AMG337[47]	MET	- Inhibited MET-dependent cell growth in multiple MET-amplified cell lines - Reduced tumour growth in MET-dependent xenograft models
SAR125844[48]	MET	- Promoted dose-dependent tumour regression in MET-amplified xenograft model at tolerated doses
KRC-408[49]	MET	- Exerted stronger anti-cancer effects than 5-FU on gastric cancer cells, especially cell lines over-expressing MET - Delayed tumour growth (dose-dependent) in xenograft model
KRC-00715[50]	MET	- Specifically suppressed the growth of MET-over-expressed cell lines - Reduced tumour size in a *in vivo* Hs746T xenograft assay
Simm530[51]	MET	- Inhibited MET-promoted cell proliferation, migration, invasion, ECM degradation, cell scattering, and invasive growth - Dose-dependent inhibition of MET phosphorylation and tumour growth in MET-driven lung and gastric cancer xenografts
Foretinib[42-44]	MET, RON, AXL, TIE-2, & VEGFR2 receptors	- Dose-dependent inhibition of the growth of MET-amplified MKN45 and SNU620 cells with concomitant induction of apoptosis - Improved the anti-tumour impact of nanoparticle paclitaxel in MET-overexpressing MKN45 cell-derived xenografts, as well as PDX
TPX-0022 (elzovantinib)[45]	MET, CSF1R, & SRC	- Inhibited MET, CSF1R, and SRC kinases; inhibited tumour growth by promoting an anti-tumour immune response

5-FC, 5-fluorouracil; ECM, extracellular matrix; PDX, patient derived xenograft; TKI, tyrosine kinase inhibitor.

Taken together, these preclinical findings have indicated the potential of MET TKIs in treating gastric cancer with MET alterations. In addition to the above-mentioned drugs, numerous other MET-TKIs have demonstrated anti-cancer activity at the pre-clinical stage, as summarised in **Table 1**.

Clinical trials

While > 12 MET TKIs have demonstrated pre-clinical anti-cancer potential in MET-altered gastric cancer models, the number of MET TKIs with safety and efficacy results available from clinical studies is much smaller. Specifically, savolitinib, crizotinib, capmatinib, and tepotinib have achieved the most promising progress thus far in gastric cancer or NSCLC. Herein the findings for these four MET TKIs are presented in detail, together with a brief summary of the other MET TKIs with the available clinical findings.

Savolitinib

In an open-label, multicentre, dose-escalation and -expansion phase I study conducted in 45 patients with advanced solid tumours in Australia, Gan et al.[52] showed that the tolerability profile of savolitinib was acceptable and the recommended phase II dose (PR2D) was established as 600 mg once daily (QD). Three patients with papillary renal cell carcinoma achieved partial responses (PRs) and all three patients had an increase in the *MET* gene copy number (GCN) and high MET protein expression, demonstrating the savolitinib anti-tumour activity in solid tumours with MET dysregulation[52]. Another open-label, multicentre, phase Ia/Ib study in Chinese patients with MET-aberrant advanced gastric cancer or NSCLC confirmed the PR2D of 600 mg QD and demonstrated 500 mg twice a day (BID) as another feasible dosage[53]. Among 14 gastric cancer patients with an increased *MET* GCN (range, 9.7–18.4), savolitinib achieved an objective response rate (ORR) of 35.7% and a disease control rate of 64.3%[53]. With respect to safety, Gan et al.[52] reported that the most frequent drug-related AEs were nausea (58%), fatigue (38%), vomiting (33%), and peripheral oedema (23%), while the most frequent drug-related AEs reported in the phase Ia/Ib study in China were nausea (29.4%), vomiting (27.1%), peripheral oedema (21.2%), decreased appetite (18.8%), and abnormal liver function (16.5%)[53].

The phase II VIKTORY umbrella trial was conducted to explore genomic profiling-guided therapy in metastatic gastric cancer patients[54]. A total of 715 metastatic gastric cancer patients were screened for pre-specified genomic biomarkers, including MET, during first-line chemotherapy or at the

time of progression following first-line chemotherapy. One hundred five metastatic gastric cancer patients were assigned to 10 different biomarker-specific treatment arms to receive the corresponding targeted therapies. Among the 20 *MET*-amplified patients who received savolitinib monotherapy, the 6-week PFS was 80.0%. The ORR was 50%, which was the highest ORR in the 10 different biomarker-specific treatment arms. Further analysis showed that patients with a *MET* GCN > 10 had an even higher ORR (70%)[54]. The most common AEs observed in patients receiving savolitinib in this study, regardless of causality and severity, were fever, anaemia, an increased alkaline phosphatase level, and a decreased neutrophil count (all 37.5%), as well as nausea, anorexia, and constipation (all 33.3%)[54]. On a related note, in a real-world cohort study involving 30 advanced gastric cancer patients matched to targeted therapies or immunotherapies, 11 patients with *MET* amplification/MET overexpression received savolitinib or crizotinib, achieving an ORR of 27%, a median PFS of 2.1 months, and a median OS of 3.7 months[55].

Savolitinib was the first MET-TKI to be approved in China. Savolitinib was granted approval by the Chinese National Medical Products Administration (NMPA) in June 2021 for the treatment with metastatic NSCLC with *MET* exon 14 skipping mutations in patients who have progressed after or are unable to tolerate platinum-based therapy[32]. Savolitinib was later included in the Chinese National Reimbursement Drug List for the same indication[56]. Following recent promising findings involving savolitinib in gastric cancer, the NMPA also granted a breakthrough therapy designation in August 2023 for savolitinib to be used in patients with *MET*-amplified locally advanced or metastatic gastric cancer or gastroesophageal junction adenocarcinoma who have failed at least two lines of standard therapy[56]. Additional data from the ongoing NCT04923932 trial will further validate the use of savolitinib in these patients in China[57].

Capmatinib

In a phase I dose-escalation study involving 44 Japanese patients with advanced solid tumours, including 5 with stomach cancer, 29 received capmatinib capsules with doses ranging from 100 mg QD to 600 mg BID and 15 received capmatinib tablets (200 or 400 mg BID)[58]. Dose-limiting toxicities occurred in two patients and the maximum tolerated dose (MTD) was not reached. Based on the doses investigated, the highest dose considered safe was 400 mg BID for tablets; the highest dose considered safe for capsules was not determined. Eight patients had a best overall response of stable disease (SD)[58]. Subsequently, in an open-label, multicentre, non-randomized, dose-escalation and -expansion phase I study that included MET-positive solid tumour patients, Bang et al.[59] established the recommended phase 2 dose (RP2D) of capmatinib to be 600 mg BID for capsules and 400 mg BID for tablets. Among the 38 patients participating in the dose-expansion phase of this study, SD was reported in 2 of 9 (22%) patients with gastric cancer, 5 of 11 (46%) patients with hepatocellular carcinoma, and 5 of 18 (28%) patients with other advanced solid tumour types. The most common AEs requiring a dose adjustment or interruption reported in the Japanese phase I study were an increased blood creatinine level (20.5%), nausea (13.6%), vomiting and decreased appetite (both 6.8%)[58]. The most common AEs reported by Bang et al.[59] were decreased appetite (42%), peripheral oedema (40%), vomiting (40%), and nausea (37%). Although capmatinib has demonstrated promising results in NSCLC patients with *MET* exon 14 skipping mutations and has been approved for this indication in the US and Japan[60], no phase II results of capmatinib in gastric cancer patients have been published to date.

Tepotinib

Falchook et al.[61] reported that tepotinib can be safely administered up to 1,400 mg/day based on a phase I trial in patients with advanced solid tumours with an RP2D of 500 mg QD. Additionally, patients with high MET expression appeared to benefit the most from treatment[61]. In a subsequent phase I study involving 12 Japanese patients with solid tumours, Shitara et al.[62] reported that 1 male patient with MET-expressing (IHC 2+) gastric cancer and 4 prior lines of chemotherapy achieved a best response of SD for ≥12 weeks and a PFS of 4.6 months. The most common treatment-related AEs reported by Falchook et al.[61] were peripheral oedema (12.8%), fatigue (12.8%), and decreased appetite (8.1%). Tepotinib was also well-tolerated in a subsequent Japanese study with no dose-limiting toxicities observed and most treatment-related AEs grades 1–2[62]. However, like capmatinib, although tepotinib has been approved in the US and Japan for NSCLC patients with *MET* exon 14 skipping mutations[60], there are no published results of tepotinib in gastric cancer patients beyond the phase I stage.

Crizotinib

Lennerz et al.[63] studied a gastroesophageal cancer cohort screened from 2007–2009 and reported the clinical responses of 4 additional patients with *MET*-amplified tumours who received crizotinib as part of an expanded phase I cohort

Table 2 Other MET TKIs with published phase II trial results in gastric cancer

	Phase	Population	*n*	MET TKI Dose	ORR	DCR	Median PFS (95% CI)	Common grade 3/4 AEs
AMG337 Van Cutsem et al. 2019[66,67]	II	MET-amplified G/GEJ/E cancers	45[a]	300 mg QD	18%	53%	3.4 months (2.2–5.0)	NR
Foretinib Shah et al. 2013[69,70]	II	Metastatic gastric adenocarcinoma	48	240 mg QD for 5 days[b]	0	10%	1.7 months (1.6–1.8)	AST increased, fatigue, GGT increased
			26	80 mg QD[b]	0	5%		Fatigue, hypertension, nausea, and diarrhea

AE, adverse event; AST, aspartate aminotransferase; BID, twice a day; CI, confidence interval; DCR, disease control rate; E, esophagus; G, gastric; GEJ, gastroesophageal junction; GGT, γ-glutamyl transferase; NR, not reported; ORR, objective response rate; PFS, progression-free survival; QD, once a day; TKI, tyrosine kinase inhibitor. [a]Cohort 1, including 45 patients with MET-amplified cancers; [b]During each 2-week cycle.

study. The study revealed that among patients with stage III and IV disease, the *MET*-amplified group had a substantially shorter median OS compared to the non-amplified group (7.1 months *vs.* 16.2 months; $P < 0.001$). Two of the 4 *MET*-amplified patients treated with crizotinib experienced tumour shrinkage (−30% and −16%)[63]. The AcSé-crizotinib program consists of a biomarker testing study to identify patients with tumours showing genomic alterations targeted by crizotinib, including MET alterations, and a phase II clinical trial providing access to crizotinib monotherapy[64]. Among 9 patients with chemotherapy-refractory, *MET*-amplified (GCN ≥ 6) esophogeal gastric adenocarcinoma, crizotinib monotherapy achieved an ORR of 33.3% with a median PFS of 3.2 months and a median OS of 8.1 months. Safety analysis revealed 5 patients with grade ≥3 treatment-related AEs, including 2 patients experiencing an increase in the alkaline phosphate level and 1 patient each experiencing an increase in alanine transaminase and aspartate transaminase levels, fatigue, an increase in the gamma-glutamyl transpeptidase level, and pneumonia[64]. Crizotinib has been approved by the US Food and Drug Administration for the treatment of ALK- or ROS1-positive metastatic NSCLC but not MET-positive NSCLC[65]. Additional clinical data will help better inform its potential use in patients with MET-positive gastric cancer.

Other MET TKIs with published clinical trial results

Other MET TKIs with published clinical trial results include the MET-selective TKIs (AMG337[66,67] and SAR125844[68]) and the multi-target kinases [foretinib[69,70] and elzovantinib (TPX-0022[71])]. Published phase II results of these MET TKIs are summarized in **Table 2**. For AMG 337, a multicentre, single-arm phase II study yielded an ORR of 18% ($n = 8$) in 45 patients with *MET*-amplified gastric/gastroesophageal junction/esophageal adenocarcinoma [defined as a MET/centromere 7 (CEP7) ≥ 2.0] (cohort 1), while no response was observed in 15 patients with other *MET*-amplified solid tumours (cohort 2)[67]. Unlike the TKIs reviewed in Sections 3.2.1–3.2.4, the TKIs summarised in **Table 2** have not been approved for clinical use.

MET alterations testing and future directions of MET-targeting therapies

Current status and challenges in diagnostic testing of MET alterations in gastric cancer

In recent years the pace of biomarker discovery and the subsequent development of targeted therapy has increased exponentially. However, the success of targeted therapy lies not only in the development of effective treatment but also in the accurate identification of patients exhibiting specific biomarker profiles[72]. Therefore, it is necessary to reliably determine patient MET status to make therapeutic decisions regarding the use of MET-targeting therapies. Techniques for MET status identification, at either the protein or genomic level, have varied over the years. Unlike NSCLC, diagnostic assays for MET overexpression and *MET* amplification have not been standardized in gastric cancer. Although IHC and FISH are commonly used for detecting MET overexpression and *MET* amplification, respectively, these techniques have limitations and the lack of unified thresholds for predicting responsiveness to MET inhibitors remains an outstanding challenge for both[24].

IHC measures protein expression by scoring the staining intensity using a 4-point scale (0, 1+, 2+, and 3+), with 0 indicating negative and 3+ indicating strong intensity[24,73]. Although widely used to score IHC samples, this technique is only semi-quantitative and therefore highly subjective, with considerable intra- and inter-observer variability[73]. Even if scoring accuracy and reproducibility can be improved, such as

by employing highly trained pathologists with years of experience, the main challenge remains that there is currently no standard definition of IHC scores for MET nor a standard cut-off for defining MET overexpression positivity by IHC[21]. This fact is evidenced from the highly varied definitions of MET IHC scores and MET overexpression used in studies of biomarkers and MET TKIs (**Table 3**). Although some NSCLC studies have used a common cut-off value > 50% for tumour cells staining 2+ or 3+ for MET overexpression, MET overexpression detected by IHC has not been able to satisfactorily predict patient responsiveness to MET-targeting treatment[21,24]. As highlighted by El Darsa et al.[22], MET overexpression by IHC may not accurately represent the status of the gene and/or pathways involved because MET overexpression does not consistently correlate with gene amplification, transcription activation, or hypoxia. This could be an underlying reason for the inability of MET overexpression by IHC to predict treatment responsiveness. While gene amplification can be tested using FISH or NGS, there is no unified threshold for defining *MET* amplification positivity with either technique. *MET* amplification identification with FISH typically utilizes a MET/CEP7 dual probe set and thresholds for FISH positivity have included a MET/CEP7 ≥ 2.0 or ≥ 2.2[24], as well as more complex criteria, such as a MET/CEP7 < 2.0 but with > 20 copies of *MET* signals and/or clusters in > 10% of the tumor nuclei counted[82]. Some studies utilize the Cappuzzo scoring system with > 5 or ≥ 5 GCN as the cut-off[24,83]. Researchers have not identified an optimal, unified threshold. For example, a MET/CEP7 ≥ 2.0 or GCN ≥ 5 was used for patient selection in two studies on different MET-selective TKIs (capmatinib and AMG337) but neither study established a correlation to distinguish responders from non-responders using the FISH cut-off values for inclusion[59,67].

NGS may be the most promising technique for predicting responsiveness to MET inhibitors[24]. The recent VIKTORY umbrella trial revealed that a ≥ 10 *MET* GCN by tissue NGS corresponded well with high response rates to savolitinib through comprehensive biomarker group analyses[54]. Nevertheless, the use of NGS has limitations. NGS strongly depends on the quality of the DNA sample obtained and some NGS assays cannot distinguish *MET* amplification from polysomy and must be complemented by the MET/CEP7 ratio data from FISH[24]. Another point to consider for NGS is the choice between conventional tissue DNA or plasma-based circulating tumour DNA (ctDNA), also known as a liquid biopsy. Several recent studies have demonstrated a high concordance between tissue and liquid NGS[54,84]. In the above-mentioned VIKTORY umbrella trial, liquid NGS had a 89.5% concordance rate with tissue NGS with 100% specificity and 83.3% sensitivity relative to tissue, which increased to 100% if patients without detectable ctDNA were excluded[54]. As such, liquid biopsy might serve as an alternative when tissue sample is inadequate or when the patient is unfit for invasive tissue biopsy[85]. Additionally, liquid biopsy can better represent tissue heterogeneity and may help identify mechanisms of acquired resistance. Pinto et al.[85] recommended tissue NGS at disease onset to identify molecular target and liquid NGS at the time of relapse. Indeed, there is a growing interest in the use of liquid biopsy in gastric cancer testing due to its advantages, such as non-invasiveness, inexpensiveness, and the ability to capture tumour heterogeneity and provide dynamic monitoring[86-88]. However, limitations, such as low sensitivity, lack of standardized operational procedures, and limited clinical validations must be addressed for liquid biopsy to be more widely used in clinical practice[89].

While protein overexpression and gene amplification often co-exist, MET overexpression detected by IHC is not strongly correlated with *MET* amplification[24]. This finding may be because high MET expression is not solely caused by gene amplification but also by upregulated gene transcription and changes at the translational level. Overall, poor MET status recognition at the protein and genomic levels, and the lack of unified thresholds for diagnostic criteria remain important challenges in improving the efficacy of MET-targeting therapies.

Regardless of the diagnostic test used, temporal and spatial heterogeneity of the tumour further complicates MET alteration testing in gastric cancer. Considering the remarkable plasticity of tumour tissues, Pinto et al.[85] recommended repeating NGS at the time of disease progression after targeted therapy. Indeed, in a study of anti-HER2 therapy for advanced esophagogastric cancer, *MET* amplification was detected in the post-afatinib progression sites, which may be related to anti-HER2 resistance[90]. Other researchers recommend performing the diagnostic assays on multiple samples to reduce the risk of false negativity as *MET* amplification and MET overexpression exhibit spatial heterogeneity in gastric cancer[91].

Possible resistance mechanisms to MET inhibitors

Resistance to MET inhibitors can be caused by multiple factors, including gene mutations, cross-resistance in signalling pathways, heterogeneous expression, activation of upstream

Table 3 Definitions of IHC scores and MET overexpression positivity in studies involving gastric cancer

Study	Definition of IHC scores[a]	Definition of MET over-/high expression
Studies of biomarkers		
Janjigian et al. 2011[74]	A pathologist coded MET and p-MET expression as the percentage of positive tumour cells (scale 0%–100%) with staining intensity from 0 to 3+	≥ 25% staining with intensity 2+ or 3+
Fuse et al. 2016[75]	0: no membrane reactivity or < 50% with any membrane reactivity 1+: ≥ 50% with weak or higher membrane reactivity, but < 50% with strong membrane reactivity 2+: ≥ 50% with moderate or higher membrane reactivity, but < 50% with strong membrane reactivity 3+: ≥ 50% with strong membrane reactivity	2+ or 3+
Jia et al. 2016[76]	The intensity of staining was scored as 0: no staining, 1: weak staining, 2: moderate staining, 3: strong staining The proportion of positive cells was scored as 0: 0% positive, 1: < 10% positive, 2: 10%–50% positive, 3: ≥ 50% positive	A total score was derived by adding the proportional score; ≥ 3 was regarded as high expression
Wang et al. 2017[77]	0: no membrane staining or < 10% with membrane staining 1+: > 10% with faint/barely perceptible particle membrane staining 2+: > 10% with weak-to-moderate staining of the entire membrane 3+: > 10% with strong staining of the entire membrane	2+ or 3+
Zhang et al. 2017[78]	0: no membrane and/or cytoplasm staining or < 10% with membrane and/or cytoplasm staining 1+: > 10% with faint/barely perceptible partial membrane and/or cytoplasm staining 2+: > 10% with weak-to-moderate staining of the entire membrane and/or cytoplasm 3+: > 10% with strong staining of the entire membrane and/or cytoplasm	3+
Yang et al. 2021[79]	0: no or < 50% of tumour cells with weak staining 1+: ≥ 50% with weak staining and < 50% with moderate/strong staining 2+: ≥ 50% with moderate staining and < 50% with strong staining 3+: ≥ 50% with strong staining	2+ or 3+
Studies of MET TKIs		
Kang et al. 2014[80]	Staining score: 0: no staining, 1: weak staining, 2: moderate staining, 3: strong staining Percentage of tumour area: 0 to 100 H-score = staining × percentage of tumour area	H-score > 100
Pant et al. 2017[81]	Tissue was considered positive for MET expression if > 50% of cells showed MET expression by IHC Intensity of staining was scored as: 1+: weak, 2+: moderate, 3+: strong	2+ or 3+
Shitara et al. 2020[62]	0: < 50% showed any staining 1+: ≥ 50% stained better than weakly but < 50% stained intensely or moderately 2+: ≥ 50% stained intensely or moderately, but < 50% stained intensely 3+: ≥ 50% stained intensely	2+ or 3+[b]

IHC, immunohistochemistry; p-MET, phosphorylated MET. [a]The percentages refer to the percentages of tumour cells; [b]The study did not specify the definition of MET over-expression, but a patient with IHC 2+ was considered as having MET over-expression.

signals, and changes in intracellular signalling pathways[24,92]. Knowledge of these resistance mechanisms may help to develop more effective treatment strategies to overcome the problem of MET inhibition resistance. Some important resistance mechanisms to consider are discussed below.

Heterogeneity of MET amplification

MET amplification heterogeneity in gastric cancer, occurring within the same tumour or between primary and metastatic tumours, is an important contributing factor to drug resistance[93,94]. Multi-probe FISH demonstrated

intratumoral clonal populations co-existing at submillimetre distances with distinct *MET* copy number alterations[95]. This can lead to varied therapeutic responses to MET inhibition and treatment failure due to the proliferation of non-MET amplified clones[22]. As such, intratumoral heterogeneity has been recognized as a significant barrier to the successful development of MET-targeting therapies for gastric cancer[95].

New mutations and alternative signalling pathways

Acquired resistance can also result from the emergence of new mutations within or outside the MET gene[22]. For example, mutations occurring within the MET activation loop (a drug target) may reduce binding capacity and lead to resistance to MET inhibitors. Notably, these mutations do not compromise the downstream MEK and PI3K/AKT pathways[22,96]. In the VIKTORY umbrella trial, acquired resistance through emerging mutations (MET D1228V/N/H and MET Y1230C) were observed in three patients in the savolitinib arm[97].

The crosstalk between RTKs may also contribute to drug resistance. The MET signalling pathway interacts with multiple other signalling pathways, including EGFR, HER2, and PI3K/Akt[22]. Kwak et al.[98] reported that 40%–50% of patients with *MET*-amplified gastric cancer display co-amplified HER2 and/or EGFR in the same tumour cells, which can drive *de novo* resistance. Kwak et al.[98] also identified a KRAS mutation as a novel cause for acquired resistance in a patient after 2 years of responsiveness to a MET inhibitor. This phenomenon suggests that simultaneously targeting multiple signalling pathways, such as EGFR and HER2, may be needed to prevent or combat treatment-emergent resistance in some patients with MET-addicted gastric cancer.

Future directions for MET-targeting therapies

MET-selective TKI-based combination therapy

The application of targeted therapy in gastric cancer remains in an early stage compared to areas, such as lung and breast cancers, which has been attributed partly to the complex pathogenesis and the heterogeneity of tumour subclones in gastric cancer that may limit the efficacy of monotherapies[4,99]. As such, researchers are also actively exploring the use of MET-selective TKIs in combination with other therapies, such as chemotherapy and anti-PD-(L)1.

A prospective, open-label, single-arm, phase I trial was conducted to investigate the use of savolitinib plus docetaxel in patients with refractory cancer[100]. Among the 17 patients enrolled, most of whom were heavily pre-treated, 1 gastric cancer patient with MET overexpression (IHC 3+) and *MET* amplification (MET/CEP7 = 7.3) achieved a durable PR for 297 days. Another gastric cancer patient with a *MET* amplification (MET/CEP7 = 7.6) achieved SD for 86 days, suggesting that savolitinib plus docetaxel may help achieve a durable response in gastric cancer patients with an MET alteration[100]. Tepotinib plus paclitaxel therapy is being evaluated in an ongoing phase I/II study as a potential treatment for patients with advanced stage gastric or gastroesophageal junction cancer with *MET* amplification or exon 14 skipping mutations (**Table 4**)[101]. A study examining the alterations and prognostic values of MET, HER2, and PD-L1 in samples from a large cohort of Chinese patients revealed that MET regulated the expression of PD-L1 *in vitro* through an AKT-dependent pathway[79]. Additionally, MET inhibitors enhanced the T-cell killing ability and increased the efficacy of PD1 antibody, suggesting a potential anti-tumour synergy between MET inhibitors and anti-PD-(L)1 therapies[79]. However, a previous phase II

Table 4 Ongoing clinical trials exploring the use of MET-selective TKI in combination therapy

Trial & stage	Intervention	Patients	Estimated completion
NCT05439993 Phase I/II[101]	Tepotinib (250 mg or 500 mg daily for 28 days as one cycle) + paclitaxel (80 mg/m^2 on days 1, 8, and 15 of one cycle)	Patients with MET-amplified or MET-exon 14 altered advanced gastric and GEJC who have progressed after first-line chemotherapy	Jun 2026
NCT05620628 Phase II[102]	Savolitinib (600 mg daily for 28 days as one cycle) + durvalumab (administered at 1,500 mg every 4 weeks from day 1 of cycle 1)	Patients with advanced MET-amplified gastric cancer who failed primary chemotherapy	Dec 2025

GEJC, gastroesophageal junction cancer; TKI, tyrosine kinase inhibitor.

study of capmatinib plus spartalizumab in adult patients with advanced esophagogastric adenocarcinoma was suspended due to an unfavourable toxicity profile[103]. Currently, the combination of savolitinib plus durvalumab is being evaluated in a phase II study (VICTORY-2) for treating patients with advanced, *MET*-amplified gastric cancer (**Table 4**)[102].

Another potential direction for MET TKI-based combination therapy is MET TKI plus anti-HER2 therapy. Through a tissue microarray analysis of the expression profiles of MET, HER2, EGFR, and FGFR2 in 950 patients with gastric adenocarcinoma, Nagatsuma et al.[104] reported that > 20% of patients were positive for at least two RTKs. Multiple studies have demonstrated that a considerable proportion of gastric cancer harbours MET and HER2 co-positivity. One multicentre, retrospective study found that in 293 patients with advanced gastric cancer, a total of 24 (8%) were co-positive for MET and HER2[75]. Another cohort study showed that among 30 HER2-positive advanced gastric cancer patients, 18 (60%) were also positive for MET[35]. Of importance, MET and HER2 co-positivity has been associated with enhanced tumour invasion, suggesting that tumours co-expressing these two RTKs might be more aggressive[105]. Additionally, MET activation also affects the efficacy of anti-HER2 therapy[105]. Taken together, these findings suggest that MET TKI and anti-HER2 combination therapy may be a valuable area for future research.

Other novel MET-targeting therapies

As mentioned above, the other major class of MET-targeting therapy being investigated is monoclonal antibodies targeting MET and/or HGF, such as rilotumumab, onartuzumab, and emibetuzumab, with limited clinical benefits demonstrated so far[24]. Other novel MET-targeting therapies currently under development include MET antibody drug conjugates, such as ABBV-399[106], METxMET-M114[107], BYON3521[108,109], RC108-ADC[110], SHR-A1403[111], P3D12-vc-MMAF[112], and TR1801-ADC[113]; and bispecific antibodies targeting MET and another therapeutic target, such as PD-1[114] or claudin 18.2, which is also an emerging molecular target in gastric cancer[115].

Conclusions

Aberrant MET pathway activation represents a unique pathogenic subtype in gastric cancer, and is associated with poor patient prognosis. MET-targeting therapies have demonstrated favourable safety and efficacy, and continue to be investigated in clinical trials. Several MET TKIs, including savolitinib, have demonstrated promising efficacy, notably in extending survival duration and improving overall response time. In addition to vigorously developing MET-targeting therapies with higher efficacy, improving the accuracy in identifying patients with MET overexpression and *MET* amplification through standardizing testing methods and detection thresholds is also an important direction for future research and development. Research advances in both diagnostic and therapeutic technology hopefully would jointly open up the opportunity of introducing MET-targeting therapies into the treatment of MET-altered gastric cancer, paving the way for precision therapy for patients with advanced gastric cancer.

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Conflicts of interest statement

All authors declare no potential conflicts of interest.

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Contributed data or analysis tools: Zhi Peng, Yifan Zhang, Lin Shen.
Performed the analysis: Zhi Peng, Yifan Zhang, Lin Shen.
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