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*Review Article*

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# Targeting c-MET: An Effective Anti-Cancer Therapeutic Strategy?

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**ABSTRACT**
The mesenchymal-epithelial transition factor (MET) proto-oncogene encodes the receptor tyrosine kinase c-MET, a critical regulator of cellular proliferation, survival, and motility. Aberrant c-MET activation, most commonly through gene amplification and exon 14 skipping mutations, drives oncogenesis across multiple malignancies and promotes tumour progression and therapeutic resistance. The oncogenic roles of c-MET have established it as an important pharmacological target. This review aims to critically evaluate c-MET-targeted pharmacological strategies, including tyrosine kinase inhibitors (capmatinib, tepotinib and cabozantinib) and antibody-based approaches (rilotumumab and onartuzumab). Small-molecule inhibitors have demonstrated clinical efficacy, particularly in c-MET exon 14 skipping-positive non-small-cell lung cancer, whilst antibody approaches have shown limited clinical benefit, reflecting ligand-independent activation and pathway redundancy. Resistance mechanisms, including secondary kinase domain mutations, bypass signalling, and downstream pathway reactivation, further limit a durable response. Emerging strategies, including biomarker-guided trial design and antibody-drug conjugates, aim to overcome these challenges by aligning therapy with tumour-specific c-MET dependency and optimising drug design for target selectivity. Collectively, the evidence suggests that for durable benefit from c-MET-targeted therapies, there is a need for accurate identification of c-MET-dependent tumours coupled with molecular optimisation of drug design for improved specificity.

## Introduction

The proto-oncogene encoding mesenchymal-epithelial transition factor (c-MET), is also known as hepatocyte growth factor receptor (HGFR). Under physiological conditions, c-MET signalling regulates embryogenesis, tissue repair, and cellular motility through tightly controlled activation by hepatocyte growth factor (HGF) and is essential for the survival and function of normal cells [1,2]. In cancer, dysregulation occurs via MET gene amplification, c-MET overexpression, exon 14 skipping, and tyrosine kinase domain mutations (among others), and results in constitutive activation of downstream pathways promoting proliferation, invasion, metastasis, angiogenesis and therapeutic resistance [2]. The oncogenic function of c-MET establishes it as an attractive pharmacological target across multiple malignancies; however, clinical responses to c-MET-targeted therapies have been variable due to the complexity of c-MET signalling and tumour dependency. This review evaluates the rationale behind current pharmacological strategies for targeting c-MET, the clinical translation of MET-targeted therapies, focusing on tyrosine kinase inhibitors and antibody-based approaches, and mechanisms of resistance, along with emerging strategies aiming to improve clinical efficacy.

## Structure and Physiological Function of c-MET

### Structural organisation

C-MET is a class IV receptor tyrosine kinase expressed as a single-pass transmembrane protein (Figure 1). It consists of an extracellular domain, a hydrophobic transmembrane sequence, and an intracellular portion that possesses tyrosine kinase activity and is essential for signal transduction [3]. The protein is translated as a single-chain precursor consisting of a 50 kDa extracellular α-subunit and 145 kDa transmembrane β-subunit. It is subsequently glycosylated in the Golgi reticulum and cleaved by furin, a cellular protease, in both alpha and beta chains. The extracellular chains are linked via a disulfide bond, forming the extracellular heterodimer that binds its ligand, HGF [1,3].

C-MET consists of three domains: an extracellular domain, a transmembrane (TM) domain, and an intracellular domain. The extracellular portion of the receptor consists of 3 domains: Semaphorin domain (SEMA), a plexin-semaphorin-integrin (PSI) domain, and four immunoglobulin-plexin-transcription repeats (IPT) [1,3-5]. The SEMA domain is a seven-bladed beta-propeller and includes the binding site for the c-MET ligand, HGF [1,3]. The intracellular region includes the juxta-membrane

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(JM) domain, the kinase domain (A-loop), and the carboxyl-terminal sequences, otherwise known as the multi-functional docking site (MFDS) [3]. Key phosphorylation sites are located within the JM domain and the kinase domain, as indicated at positions S985, Y1003 (CBL binding site), Y1230, Y1234, Y1235, Y1349, and Y1356 [1,3,6,7]. The binding of HGF results in the phosphorylation and activation of downstream signalling cascades, via the GAB1adaptor protein. Activation of MAPK, P13K/AKT, PLCPKC and JAK/STAT pathways leads to subsequent transcription of downstream target genes involved in proliferation, migration/invasion and survival [8,9].

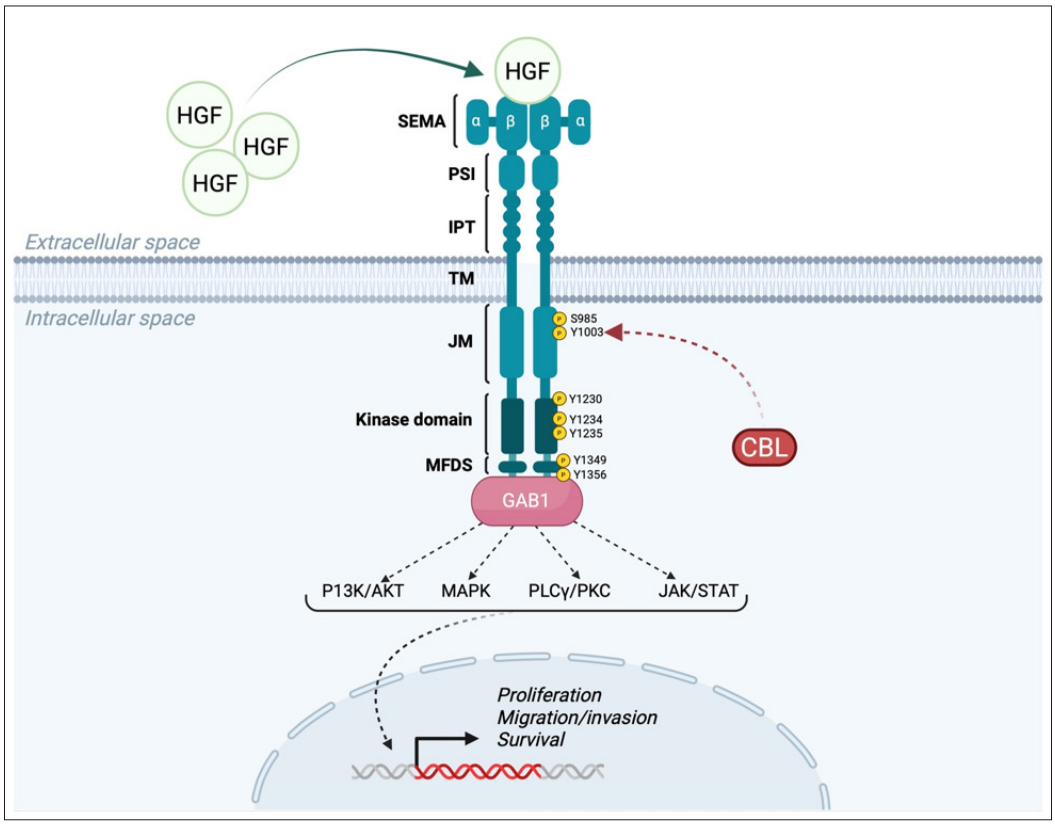


**Figure 1:** Structure of c-MET.
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## Canonical Signalling

HGF is the only known ligand for c-MET and acts as a trigger for various cellular processes [3]. HGF binding induces homo-dimerization and transphosphorylation of Y1234 and Y1235 in the activation (A) loop of the kinase domain [3,4]. Y1349 and Y1356 are subsequently phosphorylated, forming a tandem SH2 recognition motif that recruits several signalling effectors, including GAB1, GRB2, SHC, CRK, PI3K, PLCY, SRC, SHIP2, and STAT3 [3,4]. The GAB1 adaptor protein can bind directly to phosphorylated c-MET or through GAB2 and creates a binding site for more downstream adaptors (see Figure 1) [2,3]. C-MET is essential for many physiological processes such as embryogenesis, organogenesis, cell motility, proliferation, liver regeneration and wound healing [8]. The receptor acts to control several downstream signalling cascades (Figure 1), such as the mitogen-activated protein kinase (MAPK), phosphatidylinositol-3 kinase (P13K)/AKT, phospholipase C (PLC) pathway, and Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways [2,5,7]. These are known to promote cell migration, proliferation, invasiveness, angiogenesis, and survival [6]. Aberrant HGF/c-MET signalling can lead to uncontrolled proliferation and survival, which can contribute to the development, progression and survival of cancer [5].

## MET Regulation

The tyrosine kinase activity of the receptor can be both positively and negatively modulated through phosphorylation of tyrosine residues at differing positions. Activity is upregulated through phosphorylation of Y1234 and Y1235 within the catalytic site; these form part of the MFDS and directly mediate recruitment of downstream signalling molecules, including transducers and adaptors [3,4]. This is juxtaposed with repression through phosphorylation of S985 within the JM portion [3,4]. The receptors' stability and degradation are regulated by the JM domain encoded for in part by MET exon 14, which contains the tyrosine Y1003 residue that, upon phosphorylation, serves as the binding site for casitas B-lineage lymphoma (CBL) E3 ubiquitin ligase (Figure 1) [3,4,6]. CBL-mediated ubiquitination results in receptor internalisation and subsequent proteasomal degradation [1,6].

## Dysregulation of c-MET in Cancer

Aberrant MET signalling (Figure 2) has since been implicated across a wide range of tumour types, including non-small cell lung cancer (NSCLC), gastric cancer, breast cancer and papillary renal cell carcinoma (PRCC) [9]. Multiple biological alterations have been identified, including exon 14 skipping (METex14) mutations, overexpression of HGF, mutational activation through the kinase domain of c-MET, autocrine signalling, and MET gene amplification [2,6].

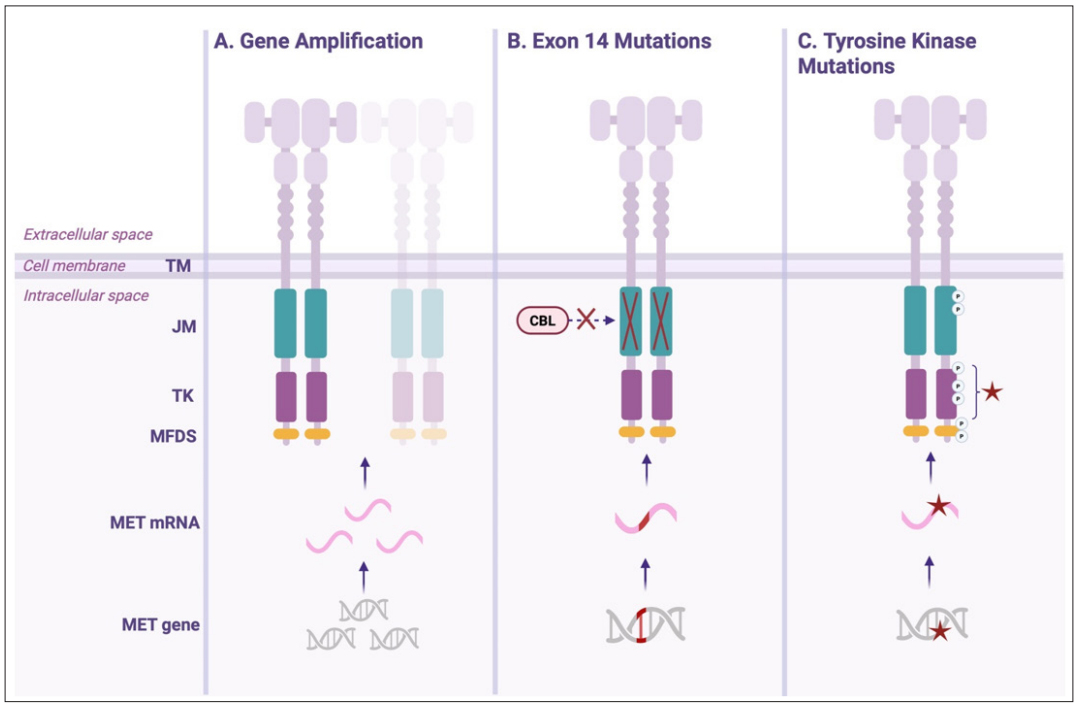


**Figure 2:** C-MET dysregulation. A) MET gene amplification leads to increased expression of the receptor, elevating MET protein levels and causing hyperactivation of downstream signalling cascades. B) METex14 results in the loss of the CBL-binding site (Y1003) within the JM domain [1]. C) Activating oncogenic mutations in the tyrosine kinase domain cause ligand-independent receptor phosphorylation, resulting in constitutive c-MET activation [1,6].
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**Gene amplification**

Gene amplification of MET can occur through polysomy (whole chromosome or genome duplication) or by amplification (regional/focal copy number increase), with the latter being the most likely to initiate oncogene addiction [10]. Amplification leads to increased expression of the receptor, elevating MET protein levels and causing hyperactivation of downstream signalling cascades [9]. Amplification of MET is seen across cancer types, occurring in 1-6% of NSCLC patients, 1-10% in gastric cancers, 3-13% in PRCCs, and 8% in breast cancers, and often confers a poor prognosis [10]. MET amplification has been shown to hold much promise as a therapeutic target (See Clinical Efficacy section) [9].

**Exon 14 skipping mutations**

The MET proto-oncogene is activated by MET exon 14 skipping (METex14) in ~3% of NSCLC [8,11]. METex14 mutations are associated with a poor prognosis and are most commonly seen in older patients and those with a history of smoking [8,11]. METex14 is typically mutually exclusive with other major oncogenic drivers, suggesting its role as a primary tumour-initiating event [8]. METex14 can be triggered by over 500 different genomic alterations, including point mutations, insertions, deletions, or indels, all of which disrupt mRNA splicing through disruption to consensus sequences, including branch sites, polypyrimidine tracts, splice acceptors and splice donor sites [8]. Of these alterations, point mutations at the splice donor site are the most common [8]. METex14 increases the half-life of c-MET through evasion of CBL-mediated ubiquitination and subsequent receptor degradation [1]. Loss of this negative regulation promotes aberrant oncogenic activation of downstream signalling pathways (discussed previously) [6,11]. This is thought to drive oncogenesis through hyperactive c-MET-mediated signalling, inducing uncontrolled cell proliferation and tumour growth. Due to the oncogenic addiction seen to this receptor, there is mounting evidence that METex14 in NSCLC can be therapeutically exploited through pharmacological inhibition using MET tyrosine kinase inhibitors [6].

**Tyrosine Kinase Domain (TKD) mutations**

Activating oncogenic mutations in the TKD can lead to ligand-independent receptor phosphorylation and signalling through downstream cascades [6]. These activating mutations result in constitutive c-MET activation by affecting the inhibitory conformation of the catalytic loop, favouring phosphorylation and downstream oncogenic signalling [6]. Mutations can be hereditary or sporadic and are seen in ~13-20% of type 1 PRCC [6]. These tumours often co-present with amplified c-MET expression, suggesting the potential for additive oncogenic mechanisms required to induce tumorigenesis in these patients, and subsequently two potential pharmacological targets [6].

Collectively, these diverse mechanisms of aberrant c-MET signalling highlight not only its central role in driving tumour progression across a range of malignancies but also its potential as a therapeutic target.

**Pharmacological Targeting of c-MET**

The widespread dysregulation of c-MET and its pivotal role in tumorigenesis have established the receptor as a compelling target for pharmacological intervention. Consequently, several therapeutic strategies have been developed to inhibit c-MET signalling, most notably through small-molecule tyrosine kinase inhibitors and antibody-based approaches (summarised in Figure 3). These strategies differ in their mechanism, selectivity, and pharmacological properties, with their clinical impact being determined by tumour context and the specific molecular alteration.

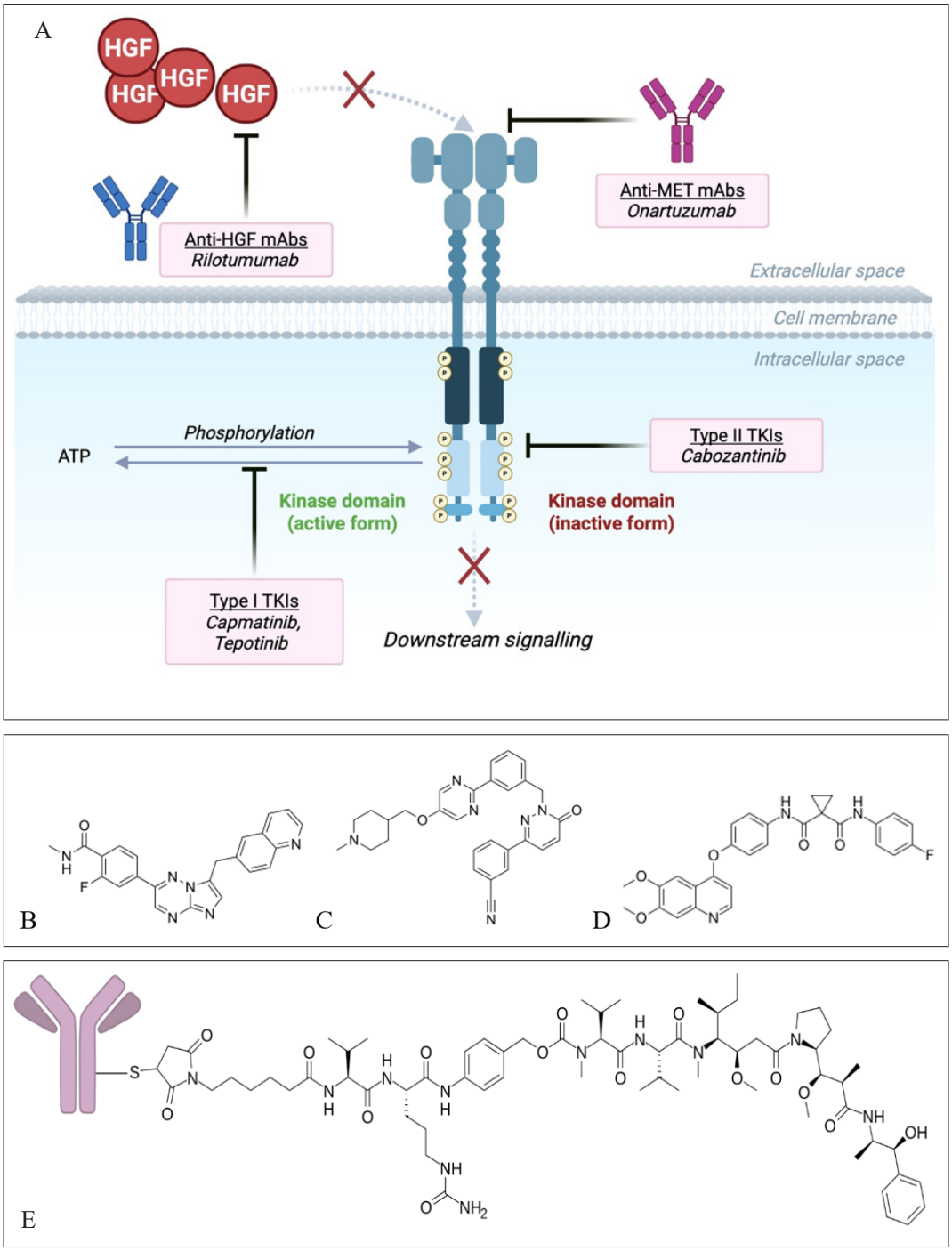


**Figure 3:** Pharmacological targeting of c-MET (A). Intracellularly, type I MET TKIs capmatinib (B) and tepotinib (C) bind the kinase domain in its active form; type II MET TKIs (e.g. cabozantinib; D) bind the ATP-binding pocket of the kinase domain in its inactive form. Both inhibit ATP phosphorylation and activation of downstream signalling cascades. Extracellularly, Anti-HGF mAbs (e.g. rilotumumab) inhibit ligand-induced activation, and anti-MET mAbs block the extracellular HGF-binding region, preventing HGF binding and downstream signalling. E) c-MET-directed antibody-drug conjugate (ADC) telisotuzumab vedotin delivers monomethylauristatin E (MMAE) a potent antimitotic agent derived from marine mollusc Dolabella auricularia.
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**Small-molecule tyrosine kinase inhibitors (TKIs)**

Small-molecule TKIs suppress c-MET by competitively binding to the ATP pocket of the catalytic domain, thereby preventing receptor phosphorylation and activation of downstream oncogenic pathways [1,10]. These inhibitors can be Type I or Type II, denoting the region of the ATP pocket they bind. Type I inhibitors bind the kinase ATP pocket in its active state [1,10,12,13]. Type II binds to the kinase in its inactive state, when the ATP-binding pocket is slightly more open, allowing these agents to be more potent against mutations that destabilise the activation loop binding site of type I inhibitors (see resistance section) [1,10,12,13]. Type I TKIs can be further classified into Type Ia and Ib, which interact with different residues in the ATP-binding pocket. The activity of these MET TKIs varies depending on the specific mutation observed [10].

Second-generation TKIs, such as capmatinib and tepotinib (Figure 3B and C), were developed through structural optimisation of first-generation compounds to increase selectivity and potency for c-MET and reduce off-target effects [12,14]. Structurally, these compounds are Type Ib TKIs, binding the active conformation of the MET kinase domain through a U-shaped binding mode and strong interactions with key residues such as Y1230, enhancing affinity and selectivity relative to first-generation compounds [14,15]. Both capmatinib and tepotinib are highly potent, orally bioavailable, reversible TKIs, suitable for systemic delivery [14,15].

In contrast, cabozantinib is a Type II compound (Figure 3D). Type II are less specific than Type I TKIs, frequently exhibiting multi-kinase activity, allowing for targeting of additional receptors, including VEGFR2, and FLT3 in the context of cabozantinib [1,12]. Cabozantinib's dual-kinase abilities lie within its ability to bind both the hinge region of c-MET and the VEGFR-2 active site, inhibiting downstream signalling cascades [16]. This bifunctional inhibition profile aims to suppress parallel oncogenic signalling pathways involved in tumour progression but has the potential for greater off-target effects [12,16].

**Anti-c-MET/HGF antibody-based strategies**

Antibody-based approaches targeting the HGF/c-MET axis primarily function by neutralising the ligand (rilotumumab), or blocking the extracellular HGF-binding region (onartuzumab), thereby preventing HGF binding and subsequently inhibiting ligand-induced activation that drives downstream signalling (Figure 3). Unlike TKIs, which target the ATP-binding site in the catalytic domain of c-MET, antibodies directly block the interaction between HGF and c-MET [1,2]. Rilotumumab is a fully human IgG2 monoclonal antibody (mAb) for HGF, whereas onartuzumab is a murine-derived monoclonal antibody against c-MET [17,18]. This blockade induces c-MET internalisation and degradation, resulting in inhibition of the MET signalling pathway, in addition to stimulating complement cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC) [1,2,8].

**Clinical Efficacy of c-MET-Targeted Therapies**

The clinical translation of c-MET inhibition has evolved in parallel to understanding c-MET-driven oncogenesis. Whilst early therapeutic approaches yielded inconsistent results, selective second-generation inhibitors combined with biomarker-guided stratification of patients have significantly improved patient outcomes, with the FDA approval of capmatinib, tepotinib, and cabozantinib.

**Capmatinib (c-MET TKI)**

Capmatinib (Figure 3B) gained approval from the FDA (in 2022) and the EMA as a therapeutic for advanced-stage METex14-mutant NSCLC, with the FDA approval for both treatment-naïve and refractory advanced-stage METex14-mutant NSCLC, and the EMA approval in solely the refractory setting, after its clinical anti-tumour activity was established in the phase II GEOMETRY mono-1 trial (Table 1) [19-22]. In EGFR-mutant NSCLC, MET amplification is commonly seen as a mechanism of acquired resistance to EGFR TKIs. Capmatinib was shown to reverse the effects of c-MET activation on EGFR and HER3 pathways and was able to restore sensitivity to EGFR TKIs in NSCLC with acquired EGFR-TKI resistance [19,20]. The success of capmatinib highlights the success of molecular stratification from first-line TKIs. In NSCLC patients, METex14 impaired receptor degradation and sustained oncogenic signalling were shown to be effectively inhibited by ATP-competitive inhibition by capmatinib. Despite this, METex14 NSCLC accounts for only a small portion of c-MET aberrant cancers, and intrinsic or acquired resistance mechanisms frequently hinder their efficacy [20].

**Tepotinib (c-MET TKI)**

Tepotinib (Figure 3C) has shown promising results in MET-driven tumours and was approved by the FDA for use as a second-line treatment for METex14 NSCLC based upon the phase II VISION trial [22]. In this trial, tepotinib was assessed in NSCLC patients harbouring MET alterations, including METex14 and MET amplification (Table 1) [22,23]. Findings from this trial led to the approval of tepotinib by the FDA, but also the approval of its companion diagnostic assay (ArcherMET CDx) for the detection of MET alterations in 2020 in Japan [23]. The efficacy of tepotinib in NSCLC and the use of its companion diagnostic assay reinforce the importance of molecular context in determining therapeutic efficacy and response.

**Cabozantinib (c-MET TKI)**

Cabozantinib (Figure 3D) is currently FDA-approved for the treatment of several cancers, including medullary thyroid carcinoma, renal cell carcinoma and hepatocellular carcinoma [ 22]. The COSMIC-313 phase III clinical trial showed clinical efficacy from a combination of cabozantinib with nivolumab and ipilimumab (Table 1). It is worth noting that TRAEs observed are likely due to the multi-kinase activity of cabozantinib, exhibiting off-target effects due to their reduced selectivity (discussed previously) [13,24]. Cabozantinib is currently being investigated across cancer types, with several ongoing phase II clinical trials evaluating its efficacy and safety for the treatment of metastatic NSCLC with aberrant c-MET signalling [22].

**Rilotumumab (HGF mAb)**

Rilotumumab showed promising results in phase I and II trials in patients with advanced gastric and gastroesophageal cancers (GEC) [18]. However, phase III trials RILOMET-1 and RILOMET-2 were terminated prematurely due to an increase in disease-related deaths [18]. The RILOMET-1 trial in particular showed a reduced median OS in the rilotumumab-treated group in comparison to the placebo group, with this group showing a higher number of patient deaths (Table 1) [25]. Rilotumumab has not shown clinical efficacy in patients harbouring MET-positive gastric and gastroesophageal cancers [25].

**Onartuzumab (MET mAb)**

Onartuzumab has been evaluated across several malignancies but has failed to show clinical efficacy in phase III trials [18]. The randomised phase III METLung trial compared the efficacy of onartuzumab plus erlotinib with placebo plus erlotinib in advanced c-MET-positive NSCLC [8,17,26]. Onartuzumab in combination with epidermal growth factor receptor (EGFR) TKI erlotinib did not improve survival rates and PFS (Table 1) [17,27]. The lack of clinical benefit portrayed by this trial may be attributed to insufficient patient selection; it is believed that MET overexpression itself may not indicate a truly c-MET-driven

carcinogenesis, as it can coexist with various oncogenic mutations, independent of METex14 [8]. Selecting patients harbouring both METex14 and MET overexpression may aid in trial outcomes for MET mAb [8].

The varied success of c-MET targeted therapy highlights the need for improved methods of trial selection and, in turn, clinical biomarker stratification to improve patient outcomes.

**Table 1: Summary of clinical trials targeting c-MET**

| Category | Drug | Classify | Trial number | Phase | Types of variation | Subgroup | ORR | mPFS | TRAEs observed |
|---|---|---|---|---|---|---|---|---|---|
| MET-TKIs | Capmatinib | Type Ib | NCT02414139 | Phase II | METex14 | Treatment-naïve patients | 0.68 | 12.4 months | 67% grade 3/4 |
| MET-TKIs | Capmatinib | Type Ib | NCT02414139 | Phase II | METex14 | Previously treated patients | 0.41 | 5.4 months | 28% grade 3 |
| MET-TKIs | Tepotinib | Type Ib | NCT02864992 | Phase II | METex14 | Liquid-biopsy group | 0.485 | 8.5 months | 28% grade 3 |
| MET-TKIs | Cabozantinib | Type II | NCT03937219 | Phase III | Not biomarker selected | Combination of cabozantinib with nivolumab and ipilimumab | 0.43 | NR* | 79% grade 3/4 |
| MET-TKIs | Cabozantinib | Type II | NCT03937219 | Phase III | Not biomarker selected | Placebo with nivolumab and ipilimumab | 0.36 | NR* | 56% grade 3/4 |
| Antibody therapy targeting MET | Rilotumumab | Monoclonal antibody | NCT01697072 | Phase III | MET overexpression | Rilotumumab and ECX | 0.298 | 5.6 months | 68% grade 3/4 |
| Antibody therapy targeting MET | Rilotumumab | Monoclonal antibody | NCT01697072 | Phase III | MET overexpression | Placebo and ECX | 0.446 | 6 months | 59% grade 3/4 |
| Antibody therapy targeting MET | Onartuzumab | Monoclonal antibody | / | Phase III | MET positive | Combination of onartuzumab and erlotinib | 0.084 | 2.7 months | 56% grade 3–5 |
| Antibody therapy targeting MET | Onartuzumab | Monoclonal antibody | / | Phase III | MET positive | Erlotinib alone | 0.096 | 1.6 months | 51.2% grade 3–5 |

**Notes**

- The table outlines key c-MET targeted therapies, including Type I and II MET TKIs and antibody-based therapies.
- Data includes trial number, phase, MET variation type, patient subgroup, overall response rate (ORR), median progression-free survival (mPFS), and treatment-related adverse events (TRAEs).
- Both experimental and control arms are shown.
- NR* = Median PFS not reached at the time of primary analysis.
- TRAEs include severe adverse events attributed to therapy.
- Studies marked with * were terminated prematurely due to increased disease-related deaths.

**Resistance to c-MET Targeted Therapy**

Despite promising clinical responses, the diversity and complexity of biological mechanisms can be adapted by cancer cells, leading to acquired resistance to c-MET-targeted therapies[6]. For TKIs in particular, resistance can be broadly categorised into on-target kinase domain mutations, off-target mutations [6].

**Mechanisms of resistance to MET TKIs**

**On-target mutations**

On-target resistance commonly arises through secondary mutations within the c-MET kinase domain, conferring resistance to type I and type II c-MET TKIs [1,6]. For example, in MET amplified or METex14 NSCLC, secondary mutations in codons D1228 and Y1230 have been found to increase resistance to type I inhibitors, such as capmatinib and tepotinib, by altering the ATP binding site, preventing the drug from binding the receptor [1,6]. These mutations, however, do not affect the binding site of type II TKIs; subsequently, type II inhibitors, such as cabozantinib, might lead to a clinical response after the acquisition of secondary mutations denoting resistance to type I TKIs [1,6]. There are, however, certain mutations that prevent both type I and type II TKIs from binding, limiting the therapeutic benefit of both classes of these inhibitors [1].

**Off-target mutations**

Bypass track activation allows for the cancer cells to activate downstream oncogenic signalling pathways, bypassing c-MET inhibition from TKIs, sustaining proliferation and metastasis [6,8]. Off-target mutations commonly include KRAS mutations and amplifications of signalling cascades, including EGFR, HER3, and BRAF [1,6]. Off-target mutations rely on

fundamental redundancy of signalling pathways and the ability of tumour cells to respond and adapt to c-MET-targeted therapy.

**Resistance and limitations of Antibody-Based Therapies**

Resistance mechanisms for mAb-based therapies differ mechanistically from those seen in TKIs and can arise through several tumour-intrinsic mechanisms. MET amplification is the most frequently seen MET mutation and results in constitutive auto-dimerisation, activation and oncogene addiction of c-MET, even in the absence of HGF [25]. In this context, a ligand-blocking approach seen in the anti-HGF mAb, rilotumumab, would be ineffective [25]. Lack of efficacy seen in tumours not harbouring MET amplification may be a consequence of upregulation of alternate oncogenic pathways (discussed previously), and in turn, isolated inhibition of the c-MET axis is not sufficient to inhibit tumour growth as the pathway is easily evaded [25]. The clinical efficacy of HGF-neutralising mAbs could potentially be improved through combination therapy targeting parallel pathways [25].

**Clinical implications**

There is a crucial need for comprehensive profiling of tumours both before and during treatment, as mutations can arise rapidly, denoting sensitivity and response to c-MET targeted therapies, and subsequently the treatment given to patients [1]. Understanding the consequences of secondary mutations, both off-target and on-target, inducing resistance or sensitivity to c-MET TKIs and mAbs is crucial in guiding clinical strategies against c-MET [6].

**Future Directions**

**Biomarker-Guided Trials and Therapy**

Discrepancy between preclinical and clinical activities of inhibitors for c-MET is potentially due to the selection of patients in clinical trials not correctly indicating c-MET dependency in these tumours [2]. C-MET phosphorylation has been suggested to be a more appropriate method of selection for patients for c-MET targeted therapies [2]. Recent developments in more stringent biomarker definitions have been shown to accurately identify true MET amplification [6]. Despite this, there is still a need for a broader, more comprehensive and sensitive method, using biomarker stratification of patients with c-MET mutations. This would allow for personalised medicine adapted to each patient's c-MET status to select for those who are most likely to benefit, whilst also ensuring trial results reflect pathway dependency to maximise patient response rates whilst avoiding ineffective therapy in non-c-MET addicted tumours [6,19].

**Antibody-Drug Conjugates (ADCs)**

Due to challenges with suboptimal efficacy and TRAEs, there has been a shift towards large molecules, including bi-specific antibodies and antibody-drug conjugates (ADCs) [30]. ADCs are structurally designed to combine the highly specific targeting of MET antibodies with cytotoxic drugs with potent killing effects, allowing the release of high doses of chemotherapy to tumour cells, whilst minimising off-target effects and toxicity to healthy tissues [22,30]. Telisotuzumab vedotin (Figure 3E) is an ADC containing a humanised c-MET antibody conjugated to the potent microtubule inhibitor monomethyl auristatin E (MMAE), derived from the marine mollusc Dolabella auricularia. It was assigned a breakthrough therapy for advanced, previously treated, EGFR-wild type, non-squamous NSCLC with MET overexpression, by the FDA in 2020 based on preliminary results in a phase II study and its favourable safety profile [22].

These strategies exemplify a shift towards precision oncology, combining molecular stratification with innovative pharmacology to overcome resistance and improve patient outcomes.

**Conclusion**

The clinical development of c-MET-targeted therapy reflects both the promise and complexity of targeting oncogenic signalling cascades. Current clinical and mechanistic evidence indicates that c-MET is not a universally effective therapeutic target, but rather a precision vulnerability confined to biomarker-defined contexts, in particular METex14 NSCLC, with the FDA approval of capmatinib. In addition to this, heterogeneous responses to therapy and acquired resistance highlight the challenges posed by pathway redundancy and tumour plasticity in these selected malignancies. Antibody-based approaches have further underscored the importance of understanding ligand-independent activation and appropriate patient selection in order to optimise trial and patient outcome. Future progress depends on precise molecular stratification and innovative strategies that align pharmacological design with tumour-specific c-MET dependency to achieve durable clinical benefit for patients through precision medicine.

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