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Author manuscript

*Cancer Discov.* Author manuscript; available in PMC 2021 January 04.

Published in final edited form as:

*Cancer Discov.* 2020 July ; 10(7): 922–934. doi:10.1158/2159-8290.CD-19-1446.

## Targeting MET Dysregulation in Cancer

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### Abstract

Aberrant MET signaling can drive tumorigenesis in several cancer types through a variety of molecular mechanisms including *MET* gene amplification, mutation, rearrangement, and overexpression. Improvements in biomarker discovery and testing have more recently enabled the selection of patients with MET-dependent cancers for treatment with potent, specific, and novel MET-targeting therapies. We review the known oncologic processes that activate MET, discuss therapeutic strategies for MET-dependent malignancies, and highlight emerging challenges in acquired drug resistance in these cancers.

### INTRODUCTION

The *MET* proto-oncogene encodes the tyrosine kinase receptor of the hepatocyte growth factor (HGF) and regulates embryogenesis, wound healing, liver regeneration, angiogenesis, and immunomodulation, among other physiologic processes (1-5). In cancer, aberrant MET oncogenic signaling has been known to play a role in promoting tumor invasion, angiogenesis, and metastasis; however, the initial development of targeted therapies against MET in unselected patient populations and across different tumor types did not translate into improved clinical outcomes (1,6-8). More recently, advances in the identification of new

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Conflict of interest statement

G.R. Consultant/advisory board : Amgen, Pfizer, Roche. Travel grants: Pfizer, AstraZeneca.

J.C. Consultant: Soltego and Kymera Therapeutics. Shareholder: M3 bioinformatics & technology Inc.

P.A.J. Consultant: AstraZeneca, Boehringer Ingelheim, Pfizer, Merrimack Pharmaceuticals, Roche/Genentech, Chugai Pharmaceuticals, Acea Biosciences, Ignyta, LOXO Oncology, Eli Lilly pharmaceuticals, Araxes pharmaceuticals, SFJ Pharmaceuticals, Voronoi, Daiichi Sankyo, Biocartis, Novartis, Takeda Oncology. Stock Ownership: Gatekeeper Pharmaceuticals, LOXO Oncology, Sanofi. Research Funding: Astellas Pharmaceuticals, AstraZeneca, Daiichi Sankyo, PUMA, Eli Lilly pharmaceuticals, Boehringer Ingelheim, Takeda Oncology, Revolution Medicines. Patents, Royalties, Other Intellectual Property: LabCorp

M.M.A. Consultant/advisory board: Bristol-Myers Squibb, AstraZeneca, Achilles, AbbVie, Neon, Maverick, Nektar, Hegru, Syndax, Gritstone. Institutional research funding: from Bristol-Myers Squibb, AstraZeneca, Lilly, Genentech.

biomarkers of MET dysregulation in cancer have renewed immense interest in identifying MET-dependent malignancies and in developing effective treatment options.

MET is a single-pass transmembrane receptor composed of an extracellular domain, transmembrane and juxtamembrane domains and a tyrosine kinase domain. The extracellular portion of MET is the binding site for its ligand, HGF, and contains a semaphorin (SEMA) domain, as well as plexin-semaphorin-integrin (PSI) and the Ig-like, plexins, transcription factors (IPT) domains (9). Upon ligand binding, MET homodimerization results in the phosphorylation of key intracellular tyrosine residues at positions Y1234/35 within the kinase domain and Y1349/56 in the docking site(10). These events directly recruit downstream effectors including the SRC proto-oncogene and signal transducer and activator of transcription 3 (STAT3), as well as adaptor proteins like the growth factor receptor-bound protein 2 (GRB2) and SHC, leading to downstream activation of the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR pathways which promote cell migration, proliferation and survival (9,11). MET protein receptor stability and degradation is regulated by the intracellular juxtamembrane domain which is encoded in part by *MET* exon 14 and contains the tyrosine Y1003 residue that, when phosphorylated, serves as the binding site for the casitas B-lineage lymphoma (CBL) E3 ubiquitin ligase (12). CBL-mediated ubiquitination results in receptor internalization from the cell membrane to endocytic vesicles and subsequent proteasomal degradation (13,14). Exon 14 in *MET* is 141 nucleotides long, spanning from nucleotides c.2888 to c.3028, corresponding to amino acids p.D963 to p.D1010 (NM\_000245.2, variant 2). Of note, in an alternative splice isoform of *MET* which is 54 nucleotides longer (NM\_001127500.2 Variant 1), exon 14 spans from nucleotides c.2942 to c.3082, corresponding to amino acids p.D981 to p.D1028. This alternative numbering of nucleotides and amino acids has led to some confusion in the literature. In this review, we will primarily use the shorter isoform (variant 2) when referring to *MET* sequences but will indicate the corresponding sequence variant of the longer isoform (variant 1).

The oncogenic role of MET was first described with the discovery of the *TPR-MET* genomic rearrangement induced by the exposure of a non-tumorigenic human osteogenic sarcoma cell line to the carcinogen N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) (15). Since then, across diverse tumor types, multiple biological alterations in *MET* have been discovered including exon 14 skipping mutations, activating mutations in the kinase domain, gene amplification, and protein overexpression. Recognition and detection of these *MET* biomarkers have fueled the clinical development of MET tyrosine kinase inhibitors (TKIs), antibodies, and antibody-drug conjugates (ADCs) aimed at targeting MET or its interactions with HGF or other binding partners.

## MOLECULAR MECHANISMS OF MET ACTIVATION IN CANCER

### *MET* exon 14 alterations

Approximately 3% of advanced non-small cell lung cancers (NSCLC) harbor point mutations or deletions in MET exon 14 or its flanking introns which affect splicing sequences including 5'- and 3'-splice sites, the branch-point adenosine, or the polypyrimidine tract (12,16,17). These alterations result in *MET* exon 14 skipping during

pre-mRNA splicing, resulting in loss of the CBL-binding site and increased half-life of the MET receptor (Figure 1A) (18). As has been described in some hereditary syndromes, point mutations in the last nucleotide of an exon often result in exon skipping (19), and point mutations in the last nucleotide of *MET* exon 14 (c.3028 = c.3082; D1010X = D1028X in the shorter and longer isoforms of *MET*, respectively) also tend to cause exon 14 skipping. Additional point mutations causing amino acid substitution of the Y1003 residue (=Y1021), such as Y1003C or Y1003F, are predicted to cause a similar biologic effect through loss of the CBL binding site without causing exon 14 skipping (20).

Splice site and Y1003X mutations differ from other mutations within exon 14, like T992I (=T1010I). The oncogenic potential of this variant is controversial, as some preclinical studies suggest that it imparts greater tumor growth and invasion potential whereas others report a lack of transforming capacity; this variant does not cause *MET* exon 14 skipping or seem to affect the CBL binding site (21-23).

*MET* exon 14 mutant NSCLC tends to occur in older patients (median age ~72) with a history of tobacco use, but can also be found in never smokers (24). These alterations are most commonly detected in lung adenocarcinomas, but are also enriched in pulmonary sarcomatoid (pleomorphic) carcinomas and can be found in squamous and adenosquamous NSCLC, and also rarely in other cancer types like gliomas and unknown primary tumors (16,25,26). De novo *MET* exon 14 alterations are almost always mutually exclusive with other oncogenic driver mutations like *KRAS*, *EGFR*, *ALK*, *ROS1*, and *RET* (16,24), and commonly co-occurring genomic alterations include mutations in *TP53*, loss of *CDKN2A/B*, and amplifications of *MET*, *MDM2*, and *CDK4/6* (16,24,26).

The large diversity of *MET* genomic alterations leading to exon 14 skipping can pose a challenge for the routine detection of these mutations and deletions in clinical practice. Current methods used to identify lung cancers harboring *MET* exon 14 mutations include DNA next generation sequencing (NGS) platforms, Sanger sequencing of exon 14 and its flanking introns, and the detection of *MET* exon 14 skipping using RNA-based assays like reverse transcription polymerase chain reaction (RT-qPCR) and RNA based NGS (27). At present, there are no certified companion diagnostic tests for the detection of *MET* exon 14 skipping alterations that are recommended to identify patients for treatment with specific *MET* inhibitors; however NGS and RT-qPCR assays appear to demonstrate higher sensitivity compared to Sanger sequencing (28). With greater use of tumor- and blood-based NGS, these alterations are being identified with increased frequency in patients whose tumors undergo broad panel-based sequence analysis (29). With mounting evidence that *MET* exon 14 mutant NSCLC can respond to *MET* tyrosine kinase inhibitors (see "Targeting *MET* alterations in cancer"), the inclusion of this promising biomarker in clinical sequencing assays among patients with advanced NSCLC should be strongly encouraged (30).

### **MET kinase domain mutations**

Activating oncogenic mutations can also occur in other domains of *MET*, including in the tyrosine kinase domain (TKD), leading to ligand-independent receptor phosphorylation and signaling (Figure 1B) (31). Activating hereditary or sporadic point mutations in the *MET* TKD are found in about 13-20% of type 1 papillary renal cell carcinomas (pRCC) and result

in constitutive MET receptor activation by affecting the inhibitory conformation of the activation loop, favoring kinase domain phosphorylation and prompting the downstream oncogenic signaling cascades (31-36). The variety of *MET* activating mutations found in pRCC include: V1092I (V1110), H1094Y/R/L (H1112), H1124D (H1142), L1195F/V (L1213), F1200I (F1218), V1188L (V1206), Y1220I (Y1238), D1228H/N (D1246), Y1230C/D/H (Y1248), M1131T (M1149), and M1250T (M1268) (31,35,37). Additionally, higher levels of MET expression are observed in pRCC due to allelic imbalances resulting from chromosome 7 polysomy, suggesting that additive oncogenic mechanisms are required to drive MET dependency in this tumor type (38).

Early trials with MET inhibitors have shown signs of clinical activity in patients with MET-dependent pRCC (see "Targeting MET alterations in cancer"), potentially broadening the spectrum of targeted therapies in kidney cancer (39,40). Interestingly, several of these activating MET mutations can also cause resistance to MET TKIs. For example, the L1195V/F, D1228X and Y1230X mutations, which are activating *MET* mutations, also cause acquired resistance to MET TKIs in *MET* exon 14 mutant lung cancers (See "Resistance Mechanisms to MET TKI") (41-44). A similar phenomenon has been observed with activating mutations of *ALK*; for example, the *ALK* F1174L driver mutation in neuroblastoma is a known mechanism of acquired resistance in TKI-treated *ALK*-rearranged lung cancer (45,46). This suggests that TKI-resistance mutations in *MET* may also result in increases in kinase activity.

In addition to *MET* kinase domain mutations, mutations affecting the Sema domain in the extracellular compartment have been described in cancer. Sema mutations may affect ligand-binding, though the functional implications of these mutations in MET signaling and their therapeutic relevance is unknown (21,47,48).

### ***MET* amplification**

In addition to MET kinase domain and exon 14 mutations, another mechanism of oncogenic activation is focal genomic amplification of wild-type *MET* located on chromosome 7 (Figure 1C) (49-51). There is no clear consensus about the optimal molecular test and or cutoff to define *MET* amplification clinically. Using fluorescent in situ hybridization (FISH), *MET* amplification can be measured by estimating the ratio between the number of *MET* copies in relation to the copies of the chromosome 7 centromere (CEP7). This distinguishes focal *MET* amplification from MET polysomy, where the gene copy number (GCN) of *MET* is increased due to an increase in the number of copies of chromosome 7. In *MET* amplified tumors, the MET/CEP7 ratio is high, whereas in polysomy, similar MET and CEP7 signals are observed. Different cutoffs of MET/CEP7 ratios have been explored to define *MET* amplification (41-43); one schema classifies tumors as MET/CEP7 low ( 1.8 to 2.2), intermediate (>2.2 to <5), or high ( 5). Higher MET/CEP7 ratios 5 seem to better predict responses to treatment with MET inhibitors, and may also identify a subgroup of lung cancers that are more likely to be dependent on MET signaling, because at high levels of *MET* amplification, there is less overlap with other oncogenic alterations involving genes such as KRAS, EGFR, and ALK compared to lower *MET* levels (52,53). Most recently, this classification was modified to use a MET/CEP7 ratio 4 to identify high levels of *MET*

amplification, which also correlated with responses to MET TKIs (53). To differentiate *MET* polysomy from amplification in treatment-naïve EGFR-mutant lung cancers, another approach defined *MET* amplification as the combination of both *MET* copies per cell  $\geq 5$  and a MET/CEP7 ratio  $\geq 2$  (49). By this method, true *MET* amplification was detected in 3% of cases and *MET* gain by polysomy was observed in 23% of cases, showing that more stringent biomarker definitions can accurately identify true *MET* amplification. In addition to FISH, recent advances in NGS platforms have enabled the identification of focal *MET* amplification, although criteria for optimal copy number cut-offs to define *MET* amplification by this technique are lacking (54).

Identifying tumors with high-level *MET* amplification is both prognostic and predictive in different tumor types, including gastric cancer and NSCLC (55,56). *De novo MET* amplification occurs in ~1% of NSCLC and has been associated with poor survival in patients with surgically resected early-stage disease (50,57,58). In *MET* exon 14 mutant lung cancer, concomitant *MET* amplification is found in ~15% of cases, showing that MET dependency in lung cancer can be driven by synergistic genomic events (26). In addition to lung cancer, *MET* copy number alterations are often present in other tumor types, including ~6% of gastroesophageal carcinomas (59). Similarly, *MET* amplification in this setting is associated with higher histological grade, advanced disease and an unfavorable prognosis (60).

*MET* amplification is a common determinant of acquired resistance to EGFR tyrosine kinase inhibitors (TKIs) in patients with lung cancers harboring *EGFR* sensitizing mutations (8). This has been reported in ~5% of tumors upon progression to first generation EGFR TKIs and ~10% of patients treated with osimertinib (a mutant-selective EGFR TKI) for EGFR T790M positive NSCLC (61,62). *MET* amplification has also recently been shown to cause resistance to anaplastic lymphoma kinase (ALK) inhibitors in ALK-rearranged NSCLC (63). In these settings, enhanced MET signaling leads to sustained bypass activation of downstream oncogenic pathways, resulting in apoptosis inhibition and enhanced tumor proliferation (8). This has guided the design of clinical trials testing the activity of EGFR and MET inhibitors in combinations such as gefitinib (a first-generation EGFR TKI) and capmatinib (a type Ib MET TKI), or osimertinib with savolitinib (a type Ib MET TKI) (see "Targeting MET alterations in cancer") (64,65). Given the implications of *MET* amplification both in cancer biology as a promising therapeutic target, clearer guidelines for identifying *MET* amplification consistently and reproducibly in clinical samples is warranted.

### ***MET* Fusions**

Another common genomic mechanism of oncogenic activation is through chromosomal translocations, in which the functional domain (such as a kinase domain) from one protein becomes ectopically expressed through its fusion to another gene. Rearrangements involving the kinase domain of *ALK*, *ROS1*, *RET*, and *NTRK* occur in lung cancer and other tumors and are predictive biomarkers of clinical benefit with selected tyrosine kinase inhibitors (66-69). Typically, the fusion partner contains a dimerization domain, which results in the constitutive activation of the tyrosine kinase domain (Figure 1D).

Although rare, *MET* rearrangements have been reported across a variety of tumor types. Interestingly, the oncogenic potential of *MET* rearrangements have been known for decades, with the original characterization of the *TPR-MET* fusion protein in a human osteogenic sarcoma cell line (15). In addition to the constitutive activation of MET by homodimerization, in the *TPR-MET* rearrangement, the juxtamembrane domain encoded by exon 14 is lost, further contributing to the oncogenic potential of this fusion through loss of this degradation domain (70).

*MET* rearrangements have been identified in patients with NSCLC (~0.5%), pediatric (10%) and adult glioblastomas (3%), and as single case reports in patients with salivary secretory carcinoma and infantile spindle sarcomas (71-75). Since the discovery of the *TPR-MET* fusion, several fusion partners have been identified and characterized including *HLA-DRB1*, *KIF5B*, *PTPRZ1*, *STARD3NL* and *ST7*. Interestingly, a *ST7-MET* fusion was reported as an acquired resistance mechanism to the third-generation ALK TKI lorlatinib, in a patient with *EML4-ALK* rearranged NSCLC, which was targetable by dual ALK-MET inhibition (63). In secondary glioblastoma, *PTPRZ1-MET* fusions are detected in 14% of cases and are associated with detrimental survival outcomes (76). Tumors bearing *MET* fusions may be sensitive to treatment with MET TKIs (see "Targeting MET alterations in cancer").

### ***MET* overexpression**

In the absence of *MET* amplification or other genomic alterations, MET can be also overexpressed in a variety of tumor types including gastroesophageal adenocarcinoma, cholangiocarcinoma, colon cancer, kidney cancer, glioblastomas and lung cancer (77-81). Elevated levels of MET expression have been associated with enhanced tumor invasion, metastases, and poor survival outcomes in patients with gastrointestinal malignancies (82,83). MET overexpression is also common in NSCLC, and has been found in about 20-25% of cases by immunohistochemistry (IHC); however the impact of MET overexpression as an independent prognostic factor in this disease is controversial (81,84).

The level of MET expression is usually assessed in formalin-fixed paraffin-embedded (FFPE) tissues with the SP44 antibody and is scored using a semiquantitative approach ranging from 0 to 3+. There is no agreed-upon threshold to define high MET expression, but some studies have been performed in cases with a MET staining level of moderate (2+) or strong (3+) intensity in 50% of tumor cells (85). Thus far, MET overexpression by IHC has not been demonstrated to be an effective biomarker as has not successfully predicted responses to treatment with MET targeted therapies (86). In addition, MET expression by IHC has a weak correlation with MET/CEP7 ratio (50,87). In a study of pulmonary sarcomatoid carcinomas, the reported sensitivity and specificity of MET IHC positivity for detecting MET amplification by FISH is 50% and 83%, respectively, with a positive predictive value of 21.4% and a negative predictive value of 94% (87). Therefore, MET IHC positivity is not a surrogate nor an effective screening tool for identifying *MET* amplification.

## TARGETING MET ALTERATIONS IN CANCER

There are currently no approved drugs with an on-label indication for the treatment of patients with MET-dysregulated cancer. However, several pharmacological agents are in clinical development including: MET tyrosine kinase inhibitors, monoclonal antibodies directed against the SEMA domain or HGF, antibody-drugs conjugates, and bispecific antibodies (Table 1).

Small molecule inhibitors of the kinase domain are typically classified into three types: type I inhibitors, which bind to the active conformation of the kinase in the ATP pocket; type II inhibitors, which bind to the inactive conformation of the kinase in the ATP pocket; and type III inhibitors, which are non-ATP-competitive allosteric inhibitors, binding outside the ATP pocket (88). Several type I MET TKIs are currently in clinical development, and are further subdivided according to their interaction with the solvent front residue G1163: type Ia inhibitors like crizotinib (Xalkori, Pfizer) interact with this residue, and type Ib inhibitors like tepotinib (MSC2156119J, Merck), capmatinib (INC280, Novartis), and savolitinib (AZD6094, AstraZeneca) and APL-101 (Apollomics) which are independent of G1163 interaction (89). In addition, type II MET inhibitors include cabozantinib (Cabometyx, Exelixis), foretinib (XL-880, GlaxoSmithKline), merestinib (LY2801653, Lilly), and glesatinib (MGCD265, Mirati Therapeutics). In addition to TKIs, a number of MET-directed therapies are currently in development which target the MET extracellular domain including: a mixture of monoclonal antibodies (Sym015), a METxMET bispecific antibody (REGN5093), an EGFR-MET bispecific antibody (JNJ-61186372) and a MET antibody-drug conjugate (ABBV-399, telisotuzumab vedotin).

Several clinical trials are studying the efficacy of MET TKIs in the treatment of patients with *MET* exon 14 mutant NSCLC. Results presented in studies of crizotinib (NCT00585195), capmatinib (NCT02414139), tepotinib (NCT02864992), and savolitinib (NCT02897479) have shown a response rate to type I TKIs ranging from 32% to 68% (Table 1) (90-94). Early reporting shows median progression free survival (PFS) times ranging from 5.4 months to 12.2 months depending on the drug and the line of therapy (Table 1) (90-92). Whether outcomes are improved based on line of therapy, first line versus second or subsequent lines, remains unknown and future studies will be needed to define the optimal treatment sequencing approach in the context of other treatment options like immunotherapy and chemotherapy (91,95). In addition to type I MET inhibitors, clinical trials with type II TKIs like cabozantinib (NCT01639508) and merestinib (NCT02920996) are ongoing. Although additional prospective data are needed to assess the efficacy of available MET inhibitors in the central nervous system, intracranial responses have been reported with agents such as cabozantinib, capmatinib, and PLB-1001/CBT-101/APL-101 (76,91,96).

Beyond *MET* exon 14 mutant NSCLC, MET TKIs have been explored in the setting of *MET* amplification, either de novo, or in the setting of acquired resistance to EGFR TKIs. Given the lower incidence of de novo *MET* amplification in the absence of other oncogenic drivers, that population has been slower to enroll, but preliminary data has shown that in patients with high levels of *MET* amplification, defined as a MET/CEP7 ratio  $\geq 4$ , about 40% of patients achieved an objective response to crizotinib with a median PFS of 6.7 months (53)

(Table 1). In the setting of acquired resistance to first- or second-generation EGFR TKIs, the combination of gefitinib with capmatinib (NCT01610336) and osimertinib with savolitinib (TATTON study) can overcome MET bypass activation (64,65). This was replicated in patients previously treated with third-generation EGFR inhibitors with concurrent or acquired *MET* amplification, where the combination of osimertinib and savolitinib demonstrated responses in 30% of patients with a median progression-free survival of 5.4 months (65). This combination is being further explored prospectively in the SAVANNAH (NCT03778229) and ORCHARD studies (NCT03944772), which also aim to refine the optimal method and tool for defining *MET* amplification in a clinically-relevant setting.

In papillary renal cell carcinomas harboring *MET* kinase domain mutations, there are limited data on the efficacy of MET TKIs. In a phase II study of savolitinib among patients with MET-driven pRCC, the objective response rate was 18% and the median PFS was 6.2 months (95% CI: 4.1-7.0) (40). A confirmatory trial is being conducted comparing savolitinib to sunitinib as first line treatment for patients with pRCC (SAVOIR, NCT03091192). Furthermore, a phase II study of the dual MET/ VEGFR2 inhibitor foretinib (GSK1363089, GlaxoSmithKline) in patients with MET-altered pRCC (including germline mutations, somatic *MET* mutations, amplifications or chromosome 7 duplications) showed a 13.5% response rate and a median PFS of 9.3 months (95% CI: 6.9-12.9)(39). Together, these early studies support the development of MET TKIs for the treatment of *MET*-driven papillary renal carcinomas; however, to identify which specific activating mutations are sensitive to MET TKIs, detailed genomic information among responders and non-responders should be made available from these studies. MET TKIs have also been reported to have activity against tumors that harbor *MET* fusions, as has been illustrated in case reports of patients with NSCLC and primary brain tumors treated with crizotinib or the MET inhibitor PLB-1001/CBT-101/APL-101, respectively (71,72,76,97).

Targeting MET with monoclonal antibodies directed against the receptor extracellular domain or the HGF ligand has been more challenging. In the randomized phase III of the monoclonal antibody onartuzumab (MetMab, Roche) in unselected patients with NSCLC, adding onartuzumab to erlotinib in patients previously treated with chemotherapy had a detrimental effect on overall survival; this therapy also showed no benefit in an exploratory analysis of patients with *MET*-amplified tumors by FISH (>5 copies) (86,98). Similarly, the addition of onartuzumab to chemotherapy treatment for patients with advanced NSCLC, gastrointestinal tumors, and glioblastoma was not effective (99-102). A similar compound emibetuzumab (LY2875358, Lilly) was initially evaluated but its development was later stopped (103). Rilotumumab, a monoclonal antibody directed against soluble HGF, also resulted in deleterious outcomes when combined with chemotherapy in patients advanced gastric and esophagogastric tumors (104). These early trials lacked adequate biomarker-enrichment and patient selection, and MET expression by IHC has not proven to be a reliable indicator of MET oncogenic dependency. The etiology of the negative impact of combining MET inhibition with chemotherapy in unselected patients is unclear, but one hypothesis is that MET inhibitors may dysregulate immune-mediated cytotoxicity and factors in the tumor microenvironment (105). For instance, MET inhibition can impair interferon gamma induction of programmed cell death ligand 1 (PD-L1) expression *in vitro*



and decrease neutrophil antitumor activity (106,107). Given these preclinical observations, the effects of MET inhibitors on tumor immunology in patients warrant further investigation.

Given the advances in the understanding of MET signaling and biomarker selection, in addition to TKIs, novel MET directed therapies are being developed. Sym015 (Symphogen A/S, Denmark) is a mixture of two IgG1 humanized monoclonal antibodies (Hu9006 and Hu9338) directed against non-overlapping epitopes in the SEMA  $\alpha$ -domain of MET (108). This combination of antibodies confers potent *in vitro* and *in vivo* activity in *MET*-amplified and *MET* exon 14 mutant models and is currently in clinical development (NCT02648724) (109). Also, the dual MET antibody REGN5093 (Regeneron) is currently being clinically developed for patients with MET-altered NSCLC (NCT04077099). In addition, the bispecific EGFR/MET antibody JNJ-61186372 (Genmab/Jansen) appears to be active in the setting of MET-amplified, EGFR-TKI resistant *EGFR*-mutant NSCLC through several proposed mechanisms including by impeding ligand-receptor binding, enhancing receptor internalization, and promoting antibody-dependent cellular cytotoxicity (ADCC) (110,111). Preliminary reports of the phase I dose escalation cohort showed encouraging clinical activity for patients with EGFR mutations (112).

In addition to antibody-based therapies, antibody-drug conjugates are also being developed to target MET. The ADC telisotuzumab vedotin (ABBV-399, Abbvie) is composed of the MET monoclonal antibody ABT-700 conjugated with monomethylauristatin E (MME), a cytotoxic microtubular inhibitor, with a cleaved valine-citruline linker, and has *in vitro* cytotoxic activity in *MET*-amplified preclinical models (113). A phase I dose-escalation study of ABBV-399 in patients with advanced solid tumors and MET overexpression, showed that this drug has a tolerable safety profile with signs of activity in patients with MET-positive NSCLC (114). A phase II study (NCT03539536) is currently enrolling patients with lung cancer to test this compound in the second- or third-line setting; identification of the optimal predictive biomarkers of response to these antibodies and ADCs will be necessary to enrich for patients who will benefit from these therapies.

## MECHANISMS OF RESISTANCE TO MET TYROSINE KINASE INHIBITORS

The diversity and complexity of biological mechanisms underlying the adaptation of cancer cells to kinase inhibitors is a matter of intense study. Established biological mechanisms of resistance to TKIs include: 1) acquisition of on-target kinase domain mutations affecting drug binding to the receptor or its ATP affinity, 2) bypass track activation of oncogenic signaling pathways, and 3) histological transformation such epithelial-mesenchymal transition or small cell lung cancer transformation (115), although in many cases, the molecular mechanisms of drug resistance are unknown.

In the *MET*-amplified or *MET* exon 14-altered NSCLC, secondary *MET* kinase domain mutations have been clinically documented and preclinically characterized to confer resistance to type I and type II MET TKIs (41,42,116). *MET* mutations in codons D1228 (=D1246) and Y1230 (=Y1248) can mediate resistance to type I MET TKIs by hindering drug binding to the receptor (117-119) (Figure 2A), but do not affect the binding of type II MET TKIs (41,120). The solvent front mutation G1163R, which is analogous to the ALK

G1202R and ROS1 G2023R TKI resistance solvent front mutations, confers resistance to the type Ia MET inhibitor crizotinib but not to type Ib or II MET TKIs (Figure 2B) (41,43). Multiple MET mutations can be detected at the time of progression to MET TKIs suggesting that polyclonal resistance can emerge in this setting (116). The efficacy of type II MET inhibitors in overcoming resistance to type I TKI-resistant tumors, particularly with acquiring mutations at residues D1228 and Y1230, is supported by preclinical rational and clinical reports (42,43,116,121).

Resistance mutations may also be found infrequently at the time of initial diagnosis prior to TKI exposure. In *MET* exon 14 mutant NSCLC, for example, the *MET* Y1230C mutation was reported to be present at a low allele frequency at baseline in a patient but later emerged as a dominant mechanism of resistance to crizotinib after treatment exposure (119). Other mutations, involving residues F1200 and L1195, affect the binding of type II inhibitors to the DFG-out conformation resulting in resistance to these compounds (Figure 2C) (43). In vitro assays suggest that F1200I also confers resistance to type I MET TKI with the exception of savolitinib (43,122). The *MET* L1195V mutation alters the C-terminus of the alpha helix conferring resistance to crizotinib and type II MET TKI (43). Understanding the implication of these secondary kinase domain mutations in conferring sensitivity or resistance to the growing repertoire of available MET TKIs may help guide clinical strategies to sequence MET inhibitors at the time of resistance.

Bypass track activation of downstream oncogenic signaling, independent of MET inhibition, can be driven by other receptor tyrosine kinases or intracellular molecules at the time of resistance to MET TKIs. Activation of the MAPK pathway has been reported to drive acquired resistance to crizotinib through the development of wild-type *KRAS* amplification or *KRAS* mutations in patients with *MET* exon 14 altered tumors (123,124). Furthermore, preclinical and preliminary clinical studies suggests that baseline *KRAS/NFI/RASA1* mutations are associated with primary resistance to MET TKIs, and efforts to correlate absence of MET or KRAS expression with a lack of response to MET inhibitors are underway (124,125). In addition, *PI3KCA* mutations and EGFR activation has been reported to drive resistance to MET inhibitors *in vitro* (126,127). Acquired *EGFR* amplification has also been detected in tumor samples from patients experiencing resistance to MET TKIs, implying that *EGFR* amplification can drive resistance to MET inhibitors, just as *MET* amplification can confer EGFR TKI resistance in EGFR-mutant NSCLC, highlighting the potential role for dual EGFR-MET inhibition in TKI-resistant NSCLC (110,116). With the expansion of MET testing in NSCLC and the improvement in access to targeted therapies with MET inhibitors, new mechanisms of resistance will be uncovered to hopefully guide the development of novel therapeutic strategies for patients.

## CONCLUSION

A more comprehensive understanding of the diverse biological mechanisms driving MET dysregulation in cancer has both fueled the development of predictive biomarkers of response to MET inhibitors and enabled design of new therapies. Biomarkers like *MET* exon 14 skipping mutations and high levels of focal *MET* amplification have been effective for identifying patients who would benefit from treatment with MET TKIs. Guidelines are

needed to improve and standardize diagnostic methods to identify MET-dependent cancers and inform drug development strategies. Clinical trials testing novel and selective MET inhibitors are ongoing and will lead to the approval of effective therapeutic options for patients with MET-dysregulated cancers.

## Acknowledgments

### Sources of funding

This work was supported by the National Cancer Institute grant R01CA222823 (P.A.J. and M.M.A.), the Conquer Cancer Foundation of the American Society of Clinical Oncology grant number 6298701 (M.M.A.).

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**STATEMENT OF SIGNIFICANCE**

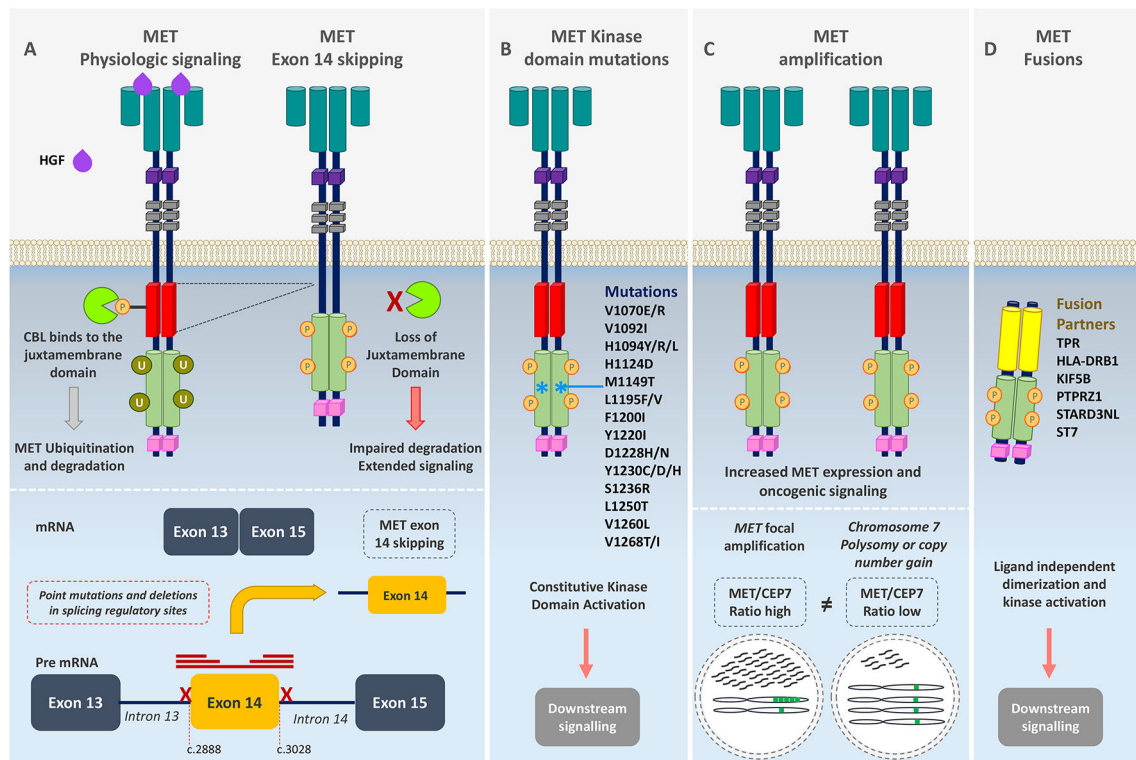
Increasing evidence supports the use of MET-targeting therapies in biomarker-selected cancers that harbor molecular alterations in MET. Diverse mechanisms of resistance to MET inhibitors will require the development of novel strategies to delay and overcome drug resistance.

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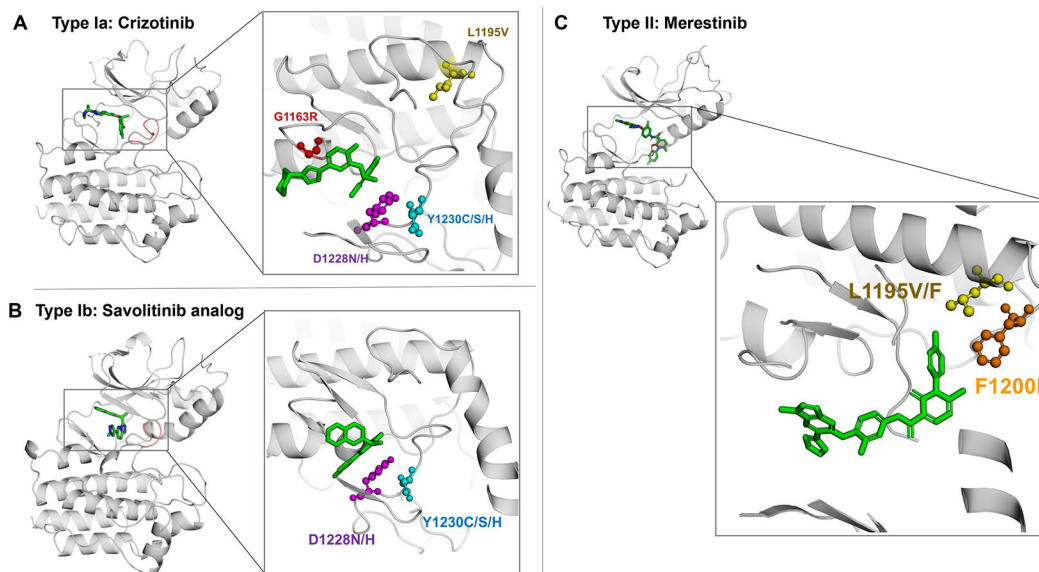
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**Figure 1. Mechanisms of MET oncogenic activation.**

(A) MET activation is initiated after ligand binding of the hepatocyte growth factor (HGF) to the SEMA domain to the extracellular portion of the MET receptor, inducing receptor dimerization and phosphorylation of the intracellular domain leading to downstream signaling of several pathways. The E3 ubiquitin ligase CBL binds to residue Y1003 in the juxtamembrane domain (encoded in part by exon 14), resulting in receptor ubiquitination and degradation. MET exon 14 alterations including mutations or deletions in splicing regulatory sites, leading to exon skipping, deletion of a portion of the juxtamembrane domain, impaired CBL binding, decreased MET turnover, and ongoing oncogenic downstream pathway signaling. (B) Point mutations in the tyrosine kinase domain result in ligand-independent MET activation through autophosphorylation of the tyrosine kinase domain, conveying sustained oncogenic downstream pathway signaling. (C) Focal *MET* amplification leads to higher levels of *MET* transcription and *MET* expression. *MET* amplification (high *MET*/*CEP7* ratio) differs from chromosome 7 polysomy or copy number gain in which the entire chromosome is duplicated (low *MET*/*CEP7* ratio). Focal *MET* amplification and, consequently high *MET* expression, leads to enhanced ligand-independent oncogenic signaling by receptor auto-dimerization or oligomerization and auto-phosphorylation. (D) Gene rearrangements involving the *MET* tyrosine kinase domain result in fusion proteins that typically self-dimerize in a ligand-independent manner, leading to phosphorylation of the tyrosine kinase domain.



**Figure 2. Mechanisms of resistance to MET tyrosine kinase inhibitors in MET exon 14 mutant lung cancer.**

Crystal modelling of the MET kinase domain and binding of MET tyrosine kinase inhibitors (green). The figure displays the position of frequently mutated residues within the MET kinase domain including G1163 (red), D1228 (purple), Y1230 (blue), L1195 (yellow), and F1200 (orange) that confer acquired resistance to MET TKIs. Panel **A** displays interaction of the type Ia MET TKI crizotinib (PDB Ref: 2WGJ) with commonly mutated residues that confer resistance to crizotinib like G1163R, D1228X and Y1230X mutations. Panel **B** shows the interaction of the type Ib MET inhibitor savolitinib analog (PDB Ref: 3ZC5) with resistance mutations including D1228X and Y1230X, but the interaction with the kinase domain is not predicted to be affected by the G1163R solvent front mutation. In panel **C**, the type II MET TKI merestinib (PDB Ref: 4EEV) is simulated bound to the kinase domain and displays the interaction of type II MET inhibitors with key residues that can cause resistance to these compounds like L1195F/V and F1200L.

**Table 1.**

Preliminary activity of MET tyrosine kinase inhibitors in the treatment of MET exon 14 mutant non-small cell lung cancer, de novo and acquired MET amplification in lung cancer and MET-dysregulated papillary renal cell carcinomas in clinical trials

Study	Phase	Drug	N	Line	MET alteration	ORR	PFS	DOR	Ref
<b>MET exon 14 mutations and de novo MET amplification (NSCLC)</b>									
PROFILE 1001 NCT00585195	I	Crizotinib 250mg BID	69	1 <sup>st</sup> , 26 > 2 <sup>nd</sup> , 43	MET exon 14 skipping	32%	7.3 months (95% CI: 5.4, 9.1)	9.1 months (95% CI: 6.4, 12.7)	(90)
GEOMETRY mono-1 NCT02414139	II	Capmatinib 400mg BID	28	1 <sup>st</sup> line	MET exon 14 skipping	BIRC: 67.9% Inv: 60.7%	9.69 months (95% CI: 5.52-13.86)	11.14 months (95% CI: 5.55-NR)	(91)
			69	2 <sup>nd</sup> /3 <sup>rd</sup> line		BIRC: 40.6% Inv: 42%	5.42 months (95% CI: 4.17-6.97)	9.72 months (95% CI: 5.55-12.98)	
VISION NCT02864992	II	Tepotinib 500mg/day	87	1 <sup>st</sup> : 33 2 <sup>nd</sup> : 31 > 2 <sup>nd</sup> : 23	MET exon 14 skipping	BIRC: liquid biopsy: 9.5 months (95% CI: 6.7-NR) tissue biopsy: 10.8 months (95% CI: 6.9-NR) 45.1%	BIRC: liquid biopsy: 9.5 months (95% CI: 6.7-NR) tissue biopsy: 10.8 months (95% CI: 6.9-NR)	Not reported	(92)
						Inv: liquid biopsy: 55.3% tissue biopsy: 54.9%	Inv: liquid biopsy: 9.5 months (95% CI: 5.3-21.1) tissue biopsy: 12.2 months (95% CI: 6.3-NR)		
NCT02897479	II	Savolitinib 600mg/day	34	1 <sup>st</sup> : 17 2 <sup>nd</sup> : 13 > 2 <sup>nd</sup> : 4	MET exon 14 skipping	12/31 (38.7%)	Not reported	34 weeks (range: 16-96)	(93)
METROS NCT02499614	II	Crizotinib 250mg BID	26	2 <sup>nd</sup> : 21 > 2 <sup>nd</sup> : 5	MET exon 14 skipping MET/CEP7 ratio > 2.2	7 (27%)	4.4 months (95% CI: 3.0-5.8)	Not reported	(94)
						1 (33.3%)	1.8 months (95% CI: 0.8, 14.0)	12.1 months (95% CI: 12.1-12.1)	
NCT00585195	I	Crizotinib 250mg BID	3		Low: 1.8- 2.2 copies Medium: >2.2-<4 copies	2 (14.3%)	1.9 months (95% CI: 1.3, 5.5)	3.7 months (95% CI: 3.7-3.7)	(53)
						8 (40%)	6.7 months (95% CI: 3.4, 7.4)	5.5 months (95% CI: 3.3-25.8)	
<b>MET amplification in EGFR TKI resistance (NSCLC)</b>									
NCT01610336	II	Gefitinib 250mg daily Capmatinib 400mg BID	41	Post 1 <sup>st</sup> /2 <sup>nd</sup>	Copy number < 4	5 (12%)	Copy number 6 5.49 months (95% CI: 4.21-7.29)	Not reported	(64)
			18	generation	Copy number 4 < 6	4 (22%)			
			36	EGFR TKI	Copy number 6	17 (47%)			
			4	2 <sup>nd</sup> : 86	IHC: 0	1 (25%)			
			2		IHC: +1	0 (0%)	IHC: +3 5.45 months (95% CI: 3.71-7.10)		

Study	Phase	Drug	N	Line	MET alteration	ORR	PFS	DOR	Ref
<b>MET exon 14 mutations and de novo MET amplification (NSCLC)</b>									
			16	>2 <sup>nd</sup> ; 75	IHC: +2 IHC: +3	3 (19%) 25 (32%)			
		Savolitinib 300mg or 600mg + Osimertinib 80mg/daily	51	Post 1 <sup>st</sup> /2 <sup>nd</sup> generation EGFR TKI T790M-		33 (65%)	9.0 months (95% CI: 5.5–11.9)	9.0 months (95% CI: 6.1–22.7)	
TATTON NCT02143466	Ib	Savolitinib 300mg + Osimertinib 80mg/daily	18	Post 1 <sup>st</sup> /2 <sup>nd</sup> generation EGFR TKI T790M+	EGFR mutant and MET amplification (FISH copies 5 or MET/CEP7 ratio 2, NGS 20% tumor cells and copies), or MET overexpression (3+)	12 (67%)	11-0 months (95% CI: 4-0-NR)	12.4 months (95% CI: 2.8–NR)	(65)
			69	Post 3 <sup>rd</sup> -generation EGFR TKI		21 (30%)	5.4 months (95% CI: 4.1–8.0)	7.9 months (95% CI: 4.0–10.5), 8.0 months (95% CI: 4.5–NR)	
			36	Post 1 <sup>st</sup> /2 <sup>nd</sup> generation EGFR TKI T790M-		23 (64%)	9.1 months (95% CI: 5.4–12.9)	8.0 months (95% CI: 4.5–NR)	
<b>MET kinase domain mutant/amplified (pRCC)</b>									
NCT02127710	II	Savolitinib 600mg/daily	44	1 <sup>st</sup> ; 26 > 1 <sup>st</sup> ; 18	MET mutation, polysomy, amplification	4 (18%)	6.2 months (95% CI: 4.1 - 7.0)	Range: 2.4 - 16.4 months	(40)
			46	1 <sup>st</sup> ; 23 > 1 <sup>st</sup> ; 23	MET-Independent	0 (0%)	1.4 months (95% CI: 1.4 - 2.7)		
			19	1 <sup>st</sup> ; 11 > 1 <sup>st</sup> ; 8	Unknown MET status	0 (0%)			
NCT00726323	II	Foretinib	74	1 <sup>st</sup> ; 60 2 <sup>nd</sup> ; 14	MET mutation MET amplification Chromosome 7 polysomy	10 (13.5%)	9.3 months (95% CI: 6.9 - 12.9)	18.5 months	(39)

BID, twice daily; BIRC, blinded independent review committee; DOR, duration of response; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; Inv, investigator; NSCLC, non-small cell lung cancer; NR, not reached; ORR, objective response rate; PFS, progression-free survival; pRCC, papillary renal cell carcinoma; Ref, reference.