MET targeting: time for a rematch

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Abstract

MET, the receptor tyrosine kinase (RTK) for hepatocyte growth factor, is a proto-oncogene involved in embryonic development and throughout life in homeostasis and tissue regeneration. Deregulation of MET signaling has been reported in numerous malignancies, prompting great interest in MET targeting for cancer therapy. The present review offers a summary of the biology of MET and its known functions in normal physiology and carcinogenesis, followed by an overview of the most relevant MET-targeting strategies and corresponding clinical trials, highlighting both past setbacks and promising future prospects. By placing their efforts on a more precise stratification strategy through the genetic analysis of tumors, modern trials such as the NCI-MATCH trial could revive the past enthusiasm for MET-targeted therapy.

The MET receptor tyrosine kinase

Genesis of the MET field

MET (also called c-Met or HGFR) is known as the receptor tyrosine kinase (RTK) for hepatocyte growth factor (HGF) and its functions are essential for both embryogenesis and tissue regeneration [1]. However, MET was originally discovered as a potent oncogene more than 30 years ago, and its role in cancer development has been the object of numerous studies since the initial characterization [2].

In 1984, Cooper *et al.* reported the identification of a chemically-induced oncogene in a human osteosarcoma cell line and suggested to name it MET, a reference to the mutagenic compound that was used in their study: *N*-**met**hyl-*N'*-nitro-*N*-nitrosoguanidine [3]. While they initially mapped MET to chromosome 7 and excluded any relation to other oncogenes known at the time, two more years were needed to demonstrate that the generated active oncoprotein actually was the result of the fusion of two separate loci from distinct chromosomes. This genetic rearrangement consisted of a sequence derived from chromosome 1 on the 5' end (called tpr; translocated promoter region) and a section of the MET proto-oncogene from chromosome 7 on the 3' end, leading to the strong expression of a chimeric mRNA due to the tpr-originating sequence [4]. This resulted in the expression of a truncated cytoplasmic protein exhibiting constitutive activation because of the spontaneous dimerization enabled by the leucine zipper domain of tpr [5]. Quickly thereafter, MET was shown to have homology with both the growth factor receptor and the receptor tyrosine kinase families [6], followed by the demonstration that it was indeed the receptor tyrosine kinase for HGF, which was incidentally shown to be identical to another MET ligand called scatter factor (SF) [7].

These initial discoveries laid the groundwork for the investigation into the structure and biological functions of MET, presented below.

MET: gene, RNA and protein structure

The locus encoding human MET is positioned on the long arm of chromosome 7 (7q31.2) and consists of 24 exons transcribed into a 6637 nucleotide long mRNA, translated into a 1390 aminoacid long protein

(canonical isoform, www.ncbi.nlm.nih.gov/gene/4233). *MET* transcription is controlled by a variety of transcription factors: HIF-1α under hypoxic conditions, AP-1 upon HGF stimulation, members of the PAX family, NF-κB, Ets1, SP1, YB1 and the TCF family of transcription factors downstream of the Wnt pathway [2]. Additional mechanisms of regulation, including epigenetic modifications such as DNA methylation, histone acetylation and RNA interference have been studied and were summarized by Jack Zhang and Andy Babic (2015) [8]. The major mRNA isoform resulting from splicing is translated into a single 170 kDa chain in the ER [9]. Subsequently, this precursor is glycosylated in the Golgi apparatus and cleaved by furin in the post-Golgi compartment into α (50 kDa) and β (145 kDa) chains, which remain linked by a disulfide bond to form the mature form of MET. This mature MET will localize to the cell membrane with a single-pass transmembrane β subunit and the α subunit being entirely extracellular [8]. Several functional domains span the length of the receptor: on the extracellular part, a SEMA domain encompasses the α and part of the β chains, followed by a PSI (plexin-semaphorin-integrin) domain and four IPT (immunoglobulin-plexin-transcription factor) domains. The intracellular section of the receptor consists of a juxtamembrane (JM) domain, a tyrosine kinase (TK) domain and a carboxyl-terminal multifunctional docking site (MFDS) [10].

On the extracellular side, the SEMA domain is essential for the dimerization and activation of MET [11] as well as for binding of HGF [10], although the IPT domains have also been shown to have a high affinity for HGF binding [12]. Between these two sections, the PSI domain contains several disulfide bonds necessary for the proper orientation of the receptor towards the ligand [13]. Two regulatory phosphorylation sites reside in the JM domain, directly below the cell membrane: serine 985 and tyrosine 1003 [14,15]. The tyrosine kinase domain of MET is below the transmembrane domain and contains two tyrosine residues at positions 1234 and 1235. The phosphorylation of these sites is an essential step of the activation of the MET receptor, leading to the phosphorylation of two additional tyrosines (1349 and 1356) in the carboxyl-terminal docking site, enabling recruitment of adapter proteins and transduction of the signal [16]. See Figure 1 for a schematic representation of MET.

HGF/SF: gene, RNA and protein structure

HGF was initially isolated from rat platelets in 1987 and cloned in 1989 [17] while SF was independently described at the same time as a factor of cell motility [18]. The gene encoding HGF is located on chromosome 7 (7q21.11) and contains 18 exons, transcribed into a 5987 nucleotide long mRNA, itself translated into a 728 aminoacid long protein (www.ncbi.nlm.nih.gov/gene/3082). Transcriptional regulation of this locus is controlled by, among other factors, TNFα, IL-6, TGFβ, CRE, and estrogens [19]. HGF is secreted as a single chain that is proteolytically cleaved into α (69 kDa) and β (34 kDa) subunits by various proteases such as urokinase, matriptase and hepsin [20]. The two subunits remain linked by a disulfide bond and bind heparin in the extracellular matrix via the α subunit [17,21]. The α chain contains an N-terminal loop followed by four Kringle domains (K 1-4) while the β subunit is homologous to serine proteases of the chymotrypsin family but has no enzymatic activity (SPH domain) [22,23]. The α chain of HGF is sufficient for binding with the IPT domains of MET with a high affinity, but the β subunit is necessary for proper MET activation by receptor homodimerization and binds the SEMA domain with lower affinity [12,21]. See Figure 1 for a schematic representation of HGF.

MET in development and tissue regeneration

MET activation and signal transduction pathways

As presented above, MET is a transmembrane protein activated by its homodimerization upon binding of HGF. The signaling pathways activated by this event described below affect the cellular processes presented in the next section.

Upon dimerization of MET, the tyrosine residues 1234 and 1235 in the kinase domain are transphosphorylated, leading to phosphorylation of two additional tyrosine residues (1349 and 1356) in the docking domain [16]. This phosphorylated docking domain forms an SH2 recognition motif enabling the recruitment of adaptor and effector proteins such as Grb2, Gab1, SHC, CRK, PI3K, PLCγ, SHIP-2 and STAT-3 [2,16]. One remarkable difference between MET and other RTKs is that Gab1 can bind MET either

indirectly through Grb2, or directly thanks to a MET binding domain, whereas it can only bind other RTKs indirectly [24]. Acting together, these adapters either activate signaling cascades or recruit other proteins, which will themselves signal downstream. This causes the activation of pathways essential for growth, proliferation and cell motility through the following signaling cascades. Through binding and activation of the PI3K subunit p85, MET induces Akt signaling, leading to the activation of mTOR, a complex responsible for cellular growth and protein translation [16]. Additionally, Akt affects the p53 pathway by activating MDM2 while inactivating pro-apoptotic factors such as BAD and thus offers protection from apoptosis [25]. Finally, Akt activates positive cell cycle regulators such as Myc and cyclin D1 by inhibiting GSK3β [26]. Another major signaling pathway downstream of MET is the MAPK cascade. By recruiting SOS via Grb2, MET activates the small GTPase Ras, which subsequently activates Raf, a kinase responsible for the phosphorylation of MEK1/2. Activated MEK1/2 will phosphorylate the next kinases in the cascade: the Mitogen-Activated Protein Kinases (MAPK) ERK1/2. Active ERK1/2 translocate into the nucleus, where their kinase activity promotes the stabilization of transcription factors responsible for motility and cell cycle progression in the G1-S transition [27,28].

Additional pathways are activated by MET, such as the STAT-3 cascade and NF-κB signaling. STAT-3 binds and is phosphorylated by MET, leading to its translocation into the nucleus where it acts as a transcription factor for several genes related to proliferation, differentiation and morphological changes such as the formation of tubules [29]. NF-κB is part of a family of rapid-acting transcription factors kept inactive in the cytoplasm by IκB, which is itself controlled by IKK. Through the PI3K-Akt pathway, MET activates IKK, which subsequently phosphorylates IκB, promoting its ubiquitination and degradation, releasing NF-κB. Free NF-κB translocates into the nucleus and promotes the transcription of mitogenic, anti-apoptotic and general cell-protective genes [30]. One more signaling axis worth mentioning, as it is connected to epithelial-mesenchymal transition (EMT) via the promotion of cell migration and anchorage-independent growth, occurs through FAK via the activation of Src by MET. Activated FAK regulates cell-matrix adhesion as well as cytoskeleton reorganization and promotes cell invasion [31]. This process is assisted by the protective role of MET against anoikis, a form of cell death caused by cell detachment from the

126 extracellular matrix [32]. Finally, MET can also crosstalk with various other membrane proteins, forming a
127 complex network. For instance, interaction with CD44v6, a glycoprotein involved in cell-matrix and cell-
128 cell adhesion, is required for HGF-dependent activation of MET in several cancer cell lines, is crucial for
129 Ras activation through SOS and connects MET to the cytoskeleton [33]; α6β4 integrin, a receptor for
130 laminin, plays a role in MET-controlled invasive growth by associating with MET and enhancing PI3K,
131 SHC and Ras signaling [34]; and the semaphorin receptor Plexin B1, a regulator of cell-cell interaction also
132 associates with MET to enhance its activation and thus promote invasive growth [35]. Moreover, MET has
133 been hypothesized to protect cells from apoptosis by interacting with Fas and preventing FasL binding [36].

134 Under normal circumstances, MET is downregulated by various mechanisms, including negative feedbacks.
135 Notably, active MET is phosphorylated on tyrosine 1003, leading to the recruitment of Cbl, an E3 ubiquitin
136 ligase that will target MET degradation via two pathways: multiple monoubiquitination promotes its
137 trafficking to the lysosome via the endosomal network for proteolytic degradation, whereas
138 polyubiquitination promotes its proteasomal degradation [15,37]. The activation of PKC through PLCγ
139 constitutes another negative feedback mechanism, as PKC-dependent phosphorylation of MET serine 985
140 downregulates MET tyrosine kinase activity, whereas PP2A can dephosphorylate serine 985 and counteract
141 the action of PKC [14]. Ubiquitin-dependent degradation of MET is not the only proteolytic mechanism
142 downregulating MET: ADAM metalloproteases can cleave MET in the extracellular domain and cause the
143 shedding of its ectodomain, followed by cleavage of the intracellular domain by γ-secretase [38]. This acts
144 in two ways to downregulate MET: first by reducing the number of receptors available for HGF binding,
145 second by releasing the ligand-binding domain of MET proteins, which will act as decoy receptors and thus
146 reduce the amount of free HGF available for MET activation. This mechanism acts independently of MET
147 activation and enables a constant low-grade attenuation of MET signaling [39]. Finally, several
148 phosphatases have been shown to inhibit MET directly by dephosphorylating its tyrosine residues. Such
149 phosphatases include PTP1B and TCPTP (which dephosphorylate tyrosines in the catalytic domain) as well
150 as DEP1, LAR and RPTP-β (which target tyrosines in the docking domain) [40–43]. For an overview of the
151 pathways activated by MET and their biological outcomes, see Figure 1. Altogether, this depicts MET as a

tightly regulated RTK involved in numerous cellular pathways. As MET has been shown to be crucial in many processes in embryonic development and tissue repair, these pathways have been the object of thorough studies, which are summarized in the next section.

The physiological functions of MET

As mentioned earlier, MET was initially discovered because of its oncogenic potential. However, the normal function of MET is to act as essential regulator of various cellular function playing a pivotal role in the development of various tissue types, as well as an important factor for tissue repair [1].

MET is mostly expressed by epithelial cells of various tissues and organs (including the gastrointestinal tract, lung, liver, kidney, thyroid and skin) as well as some endothelial cells, cells in the hematopoietic lineage, B cells and in neurons of various brains structures, while HGF is mainly expressed and secreted by mesenchymal cells such as fibroblasts as a cytokine that modulates the proliferation of epithelial cells [44–49]. As the other name of HGF – scatter factor – suggests, it also affects the "scattering" of MET-expressing cells and controls invasive growth by its motogenic, mitogenic and morphogenic properties [50]. MET acts as the main coordinator of the various stages of this complex program that involves proliferation, matrix degradation, survival and migration: together MET and HGF form the basis for epithelial and mesenchymal interaction, wound closure and angiogenesis at various stages of life [51]. As such, MET signaling is essential *in vivo*: deletion of HGF was shown to impair proper placental and fetal development in mice, leading to *in utero* death. Among the affected tissues, liver was strongly impacted and showed drastic size reduction [52]. By virtue of being expressed in many more organs, MET signaling is key for the development of additional types of tissues, including the pancreas, muscles and various types of neurons [53–55]. It regulates angiogenesis by promoting VEGF signaling while downregulating TSP-1, and thus stimulating endothelial cell motility [45,56], and can also promote hematopoiesis [46]. As a token of the pleiotropic functions of MET, a recently discovered mutation in the fourth IPT domain (F841V) has been linked to hearing loss in humans [57].

MET functions are not limited solely to development: by promoting proliferation and invasion, it is a crucial component of wound repair when the invasive growth of remaining cells needs to be reactivated to reconstitute the damaged tissues. Along with other factors, MET signaling plays a key role in liver and kidney regeneration [58,59]. Bone remodeling also involves MET signaling as both osteoclasts and osteoblasts express MET and osteoclasts secrete HGF, leading to a crosstalk between these cell types to ensure proper bone resorption and deposition [60]. Beyond its functions directly involved in repair, MET signaling plays a protective role in damaged tissues (such as ischemic cardiac muscle) by protecting cells from apoptosis [61]. As a whole, the HGF-MET tandem can be described as a crucial factor for cellular proliferation, growth and motility. While these functions are essential for normal life, they can be hijacked to support cancer development, which will be described in the next section.

The oncogenic facet of MET: a key player in cancer development and progression

Mechanisms of MET/HGF deregulation

The initial discovery of MET was made by the generation of an artificially induced oncogenic fusion protein, and while this particular rearrangement was later also observed in human gastric cancerous lesions, a plethora of different mechanisms leading to MET deregulation can naturally occur at all stages of carcinogenesis and caught the interest of researchers promptly after the initial discovery of tpr-MET [62].

Various mechanisms have been shown to lead to MET deregulation in cancer, the most obvious one being HGF-dependent: the stromal cells surrounding tumors frequently express HGF [63]. Ligand-dependent activation of MET sometimes happens in an autocrine instead of paracrine fashion, however the overexpression of MET is sometimes necessary for tumor cells to respond to HGF [64,65]. As a matter of fact, MET overexpression is the most frequent cause of its constitutive activation in a ligand-independent manner and results mostly from transcriptional upregulation. Examples of this have been reported in a breadth of distinct carcinomas including thyroid, colorectal, ovarian, pancreatic, lung, and breast cancer

[66–71]. Hypoxia is one of the mechanisms that can trigger increased transcription of MET: as mentioned above, HIF-1α can promote the transcription of MET [72]. Interestingly, MET overexpression can occur as a response to radiotherapy through the ATM-NF-κB signaling pathway [73]. Activation of other oncogenes, such as Ras, can upregulate MET expression as well [74]. A less common way for tumor cells to overexpress MET is the amplification of its locus. Such gene amplification has been reported in esophageal adenocarcinoma, medulloblastoma, cancer of the pancreas and of the gastrointestinal tract [75–78]. In lung adenocarcinomas, MET amplification has also been documented as an acquired resistance mechanism to EGFR targeted therapy [79]. Activation of MET due to its overexpression is thought to happen through its spontaneous dimerization via the SEMA domain and is linked to cell-matrix adhesion mechanisms. [69,80]. However, some tumors rely on point mutations to activate MET without overexpressing it. The relevance of activating MET mutations is underscored by the evidence that in HNSCC, the selection of somatic MET mutations is promoted during metastatic spread [81]. These genetic aberrations include mutations in the kinase domain of MET and have been described in both hereditary and sporadic forms of papillary renal cell carcinomas as well as in gastric cancer [82,83]. Many of these mutations have been thoroughly studied by their ectopic expression in various cellular systems, such as the NIH 3T3 mouse fibroblast model [84].

Ineffective downregulation of MET through the inactivation of pathways leading to MET dephosphorylation or degradation can also lead to increased MET activation [85]. A relevant example of these mechanisms is seen in a family of mutations leading to alternative splicing and hence skipping exon 14 of MET. The resulting protein lacks a section of the juxtamembrane domain containing serine 985 and tyrosine 1003 which, as previously mentioned, are capital for the downregulation and degradation of MET [86]. These mutations were first observed in lung cancer cases as a response mechanism to EGFR inhibition by MET activation, and were later detected in subpopulations of brain and gastric cancer patients [87]. While a relatively rare mutation, it could serve as a biomarker for patient stratification, as presented in later sections of this review.

Finally, MET activation can result from the activation of other RTKs. For instance, stimulation of EGFR with its ligand EGF promotes MET activation via the MAPK signaling pathway when both RTKs are co-expressed [88]. Another example is RON, an RTK structurally related to MET. These receptors can interact together and are sufficiently similar for the activation of one to lead to the phosphorylation of the other [89]. Similarly, several other RTKs, including IGF-1R and AXL, can interact with MET and cause its activation [90,91].

The significance of MET in cancer: a prognostic marker and a target

MET deregulation can happen at any stage of cancer development, and together all the activation mechanisms presented above have been shown to promote both primary tumor formation and the transition to metastatic disease [66]. Various studies have associated high MET expression and activation with poor outcome [92]. For instance, high expression is known to correlate with markers of negative prognosis in thyroid carcinoma, is a significant negative prognostic marker in NSCLC and is a predictor of tumor invasion and lymph node metastases in colon cancer [93–95]. These last two examples are representative of two classes of cancer that are of particular interest in the context of MET: gastrointestinal and lung cancers. While MET mutations or amplifications are rare in gastric and colorectal cancer (CRC), overexpression of MET and HGF at the mRNA and protein levels is common and can be observed in up to 40-70% of patient samples, correlates with tumor stage and is a prognostic marker of clinical outcome [66,96–99]. Moreover, MET expression is a predictor of invasive growth in gastric cancers and is associated with higher occurrences of lymph node and liver metastases [32,95,100]. Cellular and *in vivo* models of gastric and colorectal cancer have confirmed these observations and show that blockade of MET signaling reduces tumor growth and spread [32,101–103]. Overall, while the various methods and scoring systems used to assess MET-positivity make the prognostic value of its aberrant expression difficult to gauge, systematic reviews and meta-analyses associate high MET expression with higher hazard ratios and poor prognosis in gastric and colorectal cancer [104]. Interestingly, MET amplification has been observed as a resistance mechanism to EGFR inhibition in metastatic colorectal cancer, a phenomenon that can also occur in

NSCLC, either by selecting for pre-existing MET-amplified subclones or by inducing de novo copy number gains [105,106]. Lung cancer studies also led to the discovery of another clinically relevant phenomenon: MET exon 14 skipping mutations [107]. Because of such genetic aberrations, MET is considered a major oncogene and a potential target in NSCLC [108]. Indeed, there is evidence for the efficacy of MET-targeting therapies in NSCLC cases exhibiting MET alterations [86].

A more global picture of the role of MET in cancer depicts this RTK as an overall negative factor. Combined data from multiple studies accessed from the cBioPortal website reveal that MET genetic alterations are common in various types of cancers (Figure 2A), the highest mutation rate is observed in lung cancers whereas esophageal squamous cell carcinomas show the highest amplification rate. RNA sequencing shows overexpression in all cancer types: the highest median expression is found in papillary renal cell carcinoma (PRCC), often combined with amplification or copy number gain, and the lowest overexpression is seen in acute myeloid leukemia (AML) (Figure 2B). Strikingly, disease outcome is significantly worse for cases with MET alterations compared with non-altered MET, showing a median overall survival of 66.7 versus 92.4 months (Figure 2C).

As will be discussed further below, these observations have led to a great interest in the development of MET targeting compounds, in particular for the treatment of MET-addicted tumors, as covered by various reviews [80,109].

MET as an addicting oncogene

Oncogene addiction, an expression that was first coined by Bernard Weinstein in 2002, denotes the fact that despite having multiple genetic alterations, the survival and proliferation of some tumor cells rely exclusively on one (or a few) specific oncogenes, the earliest examples being Myc, Ras, Bcr-Abl and HER2/neu [110–114]. Thus, the inhibition of the addicting oncogene is often sufficient to induce proliferative arrest, senescence, apoptosis or terminal differentiation in addicted cancer cells [115]. While this phenomenon was first observed in artificial models, this field of research was quickly translated to applicable treatment strategies in the clinic with oncogene-targeted therapies. Imatinib, a specific inhibitor

of Bcr-Abl, the product of the Philadelphia chromosome translocation and a cause of chronic myeloid leukemia, showed remarkable efficacy in patients [116]. Similarly, inhibition of HER2 with the monoclonal antibody trastuzumab was shown to be efficacious and well tolerated in breast cancer patients displaying strong overexpression of the receptor [117]. Over the years, evidence has emerged that oncogene addiction can occur in many types of cancer and for several oncogenes, including major RTKs such as EGFR, VEGFR and KIT [118]. Numerous clinical trials have shown the efficacy of targeted therapies against EGFR in lung cancers driven by that oncogene, significantly improving progression free-survival (PFS) compared to standard of care, but most trials failed to show higher overall survival [119–122]. Similarly, additional examples of therapies targeting addiction to various oncogenes, both in preclinical and clinical trials, have shown strong early response but failed to elicit durable effects [123]. This can be explained by the development of resistance to the therapeutic compound via one or several mechanisms including the selection or acquisition of protective mutations in the target and the escape from addiction, relying instead on other pathways or oncogenes for cancer cell survival and proliferation, highlighting the need for combination therapy [118,124,125]. As emphasized previously, MET is a potent oncogene involved in various stages of neoplastic and metastatic development as well as in resistance mechanisms to therapies targeting other oncogenes. Moreover, there is evidence for MET addiction in the preclinical and clinical settings, making this receptor a prime target for targeted therapy [80]. For instance, the MET inhibitor PHA-665752 has proven remarkably efficient in inducing apoptosis in gastric cancer cell lines harboring amplification of wild-type MET, while sparing cell lines without copy number alterations [103]. Similarly, out of a panel of 35 human cancer cell lines, the eight lines with the highest expression of active MET were shown to be significantly sensitive to the MET-targeting antibody ABT-700 [126]. While the most promising results of MET-targeting therapies have been observed in the preclinical setting, their potential translational application is supported by case reports describing encouraging results for their use in MET-amplified lung and gastric cancer patients [127–129].

Targeting MET in the clinic: tools, trials, troubles and tentative treatments

Many angles of attack have been used to target the HGF-MET signaling axis in cancer cells. A wide variety of compounds have been developed, such as decoy ligands, docking site blockers and chimeric ribozyme constructs leading to the degradation of MET mRNA [130–132]. However, such strategies have not been clinically tested at this point. Therefore, the main focus of this section will be the two most commonly used categories of compounds: antibodies targeting either HGF or MET, and small molecules inhibitors of MET.

Antibodies targeting HGF and MET

Targeting oncogenes with antibodies is sometimes viewed as preferable than the use of small molecule inhibitors because antibodies can be more specific, are usually well tolerated, can elicit cumulative cellular responses and have longer half-lives, but need to be administered intravenously whereas small molecule inhibitors are available orally and can target receptors regardless of their mechanism of activation (ligand-dependent or -independent) [2,133]. There currently is a number of humanized and fully human monoclonal antibodies (mAbs) targeting MET or HGF in development or in clinical trials. The main mechanism of action of anti-HGF mAbs is to prevent the binding of HGF to MET by targeting domains required for their interaction. Antibodies targeting MET can act similarly to prevent HGF binding, but have also shown indirect mechanisms of actions such as receptor degradation or downregulation and immune-mediated antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) [133].

HGF-targeting mAbs include the fully human IgG2 rilotumumab (AMG 102, Amgen, Thousand Oaks, California, USA) preventing interaction with MET by targeting the SPH domain of HGF [134], the humanized IgG1 ficlatuzumab (AV-299, Aveo Pharmaceuticals, Cambridge, Massachusetts, USA) [135], and the mAb L2G7 (Galaxy Biotech, Sunnyvale, California, USA)/TAK-701 (Takeda pharmaceutical, Osaka, Japan) [136], all of which are under clinical investigation. Additional anti-HGF antibodies are also

being studied at the preclinical level, such as SFN68, which binds HGF in complex with MET, and the bispecific (MET- and serum albumin-binding) nanobodies 1E2-Alb1 and 6E10-Alb8 [137,138].

As mentioned before, MET targeting antibodies can elicit diverse cellular responses depending on their nature and the domain they bind. R13 and R28 (OncoMed Pharmaceuticals, Redwood city, California, USA) are fully human mAbs used in tandem that compete with HGF for binding and induce ADCC [139]. SAIT301 (Samsung Inc, Yongin, Republic of Korea) is a humanized mAb that leads to MET downregulation by internalization and lysosomal degradation via LRIG1 [140]. Similarly, emibetuzumab (LY2875358, Eli Lilly, Indianapolis, Indiana, USA) is a humanized IgG4 that induces internalization and degradation of MET and prevents HGF binding [141]. ABT-700 (AbbVie, Lake Bluff, Illinois, USA) is a humanized IgG1 that blocks HGF binding and induces ADCC by recruiting natural killer cells to mediate the lysis of the targeted cells [126]. An antibody-drug conjugate (ADC) has been developed from ABT-700: ABBV-399 (AbbVie). This ADC is composed of the antibody and the cytotoxic microtubule inhibitor monomethylaurstatin E, connected by a cleavable linker. Using an ADC could present the advantage of efficiently targeting cancer cells with high expression of MET regardless of MET activation or addiction, while sparing normal cells expressing lower levels of MET [142]. Onartuzumab (MetMab/OA-5D5, Genentech, South San Francisco, California, USA) is a humanized monovalent antibody that competes with HGF by binding to the SEMA domain of MET [143]. DN30 (Metheresis Translational Research SA, Lugano, Switzerland) is a chimeric mouse IgG2A that induces ADAM-10 mediated shedding of receptor by binding the 4th IPT domain of MET and altering the conformation of the receptor, which has the benefit of preventing MET activation and releasing decoy MET moieties that can titer HGF away from cancer cells. The original form of the compound had a flaw common to several receptor-targeting antibodies: since antibodies contain two binding domains, DN30 could act as a partial agonist of MET by bringing two receptors together, leading to ligand-independent dimerization and activation. This issue was solved by converting the compound to a smaller monovalent Fab (MvDN30), which unfortunately had an increased renal clearance due to its small size [144]. Two strategies could be explored to solve the resulting shorter half-life: stabilizing the plasma availability of the compound (for example by PEGylation) or enabling continuous production of the Fab in

patients by gene transfer therapy, a route that is investigated in preclinical models of glioblastoma multiforme, where MET has been described as a marker of cancer stem cells [145].

Small molecule inhibitors of MET

As mentioned earlier, small molecule tyrosine kinase inhibitors (TKIs) have the benefit of targeting the activated receptor regardless of ligand presence by preventing ATP from reaching the ATP-binding pocket of the kinase domain [146]. However, TKIs can vary in their specificity: some compounds have demonstrated remarkable specificity for MET while others inhibit several kinases with varying affinities. One notable exception to the ATP-competitive mode of action is the case of Tivantinib (ARQ197, Daiichi Sankyo, Tokyo, Japan, and ArQule Inc, Woburn, Massachusetts, USA), which was initially presented as an allosteric inhibitor of MET locking the receptor in the inactive conformation, but has subsequently been shown to exert its cytotoxic activity by interfering with microtubule dynamics without affecting MET activation [147]. Table 1 lists relevant examples of non-selective and selective TKIs that are at various stages of clinical trials [2,109].

MET/HGF targeting in clinical trials

Over the years, many of the compounds presented above have progressed through clinical trials with varying degrees of success. While there are too many completed and ongoing trials to be comprehensively presented here, previous reviews have regularly summarized their progress, and only the most relevant examples of completed or ongoing studies are highlighted below [2,80,109,133,146,148]. It should be noted that currently only two non-selective MET TKIs have been approved for use, but not specifically for their MET-inhibiting action: cabozantinib for medullary thyroid cancer and kidney cancer, and crizotinib for ALK and ROS1 positive NSCLC [149,150]. However, these and other compounds are still being evaluated for other cases, with many trials focusing on lung and gastrointestinal cancers due to the role this signaling axis plays in the development and progression of these malignancies, as mentioned earlier. Nonetheless, a number of studies is also being performed for other types of cancer, such as HCC, castration-resistant prostate cancer, renal cell carcinoma or metastatic melanoma [151]. Altogether, these trials have produced mixed results for

the use of MET/HGF-targeting compounds in the clinic. As mentioned earlier, the main mechanism of MET activation is ligand-independent and relies on the overexpression of the receptor, explaining why the majority of the currently explored strategies focus on targeting MET rather than HGF. However, HGF-targeting compounds have also been investigated and notable examples are presented below.

The anti-HGF mAb rilotumumab has undergone phase III clinical trials (RILOMET-1 and 2, NCT01697072 and NCT02137343) as first-line therapy in patients with advanced MET-positive gastric and gastroesophageal cancer, in combination with ECX chemotherapy. Unfortunately, after the promising results of a phase II trial, the RILOMET studies showed that the addition of rilotumumab to chemotherapy performed worse than chemotherapy alone, leading to the early termination of the trials [152,153]. Similarly, the phase II MEGA study compared the combination of rilotumumab plus mFOLFOX6 versus mFOLFOX6 alone as a first-line treatment for HER2-negative advanced gastric and gastroesophageal cancer but failed to show improvements with the addition of rilotumumab (NCT01443065).

The phase III METGastric study evaluated the benefits of the addition of onartuzumab to mFOLFOX6 as a first-line treatment of MET-positive but HER2-negative metastatic gastric and gastroesophageal adenocarcinoma, but failed to show any significant improvement [154]. A promising phase II clinical trial studying the addition of onartuzumab to EGFR inhibition for the treatment of advanced NSCLC showed benefit in the MET-positive population, but failed to confirm this result in a subsequent phase III trial. Two hypotheses have been proposed to explain this unfortunate turn of events: compounds preventing the interaction between MET and HGF might be ineffective in this setting (for example in the case of ligand-independent activation of MET), or the biomarkers used for patient recruitment were inadequate [155,156]. The results of additional phase III studies are still pending.

Crizotinib, as mentioned before, is a multitarget inhibitor and has been approved for the treatment of NSCLC expressing the fusion proteins EML4-ALK or CD74-ROS1, two types of cancer where its efficacy was demonstrated [149,150]. However, its pertinence as a MET inhibitor is still being evaluated. Early results of a Crizotinib trial showed some promise for the treatment of NSCLC harboring MET exon 14 skipping

mutations [157]. The phase I PROFILE 1001 trial has also been testing the efficacy of this compound in lung cancer and other solid tumors exhibiting MET, ALK or ROS1 alteration. While the study is still ongoing, preliminary results have shown benefits for patients with advanced, ROS1-rearranged or MET-amplified NSCLC [158,159]. Likewise, several ongoing phase II trials are evaluating the performance of crizotinib in NSCLC and other cancers, focusing on genetic alterations such as MET amplification and mutation (NCT02034981, NCT02499614, NCT03088930). Similar trials are also being performed for gastric cancer: a pilot phase I study showed that MET-amplified gastroesophageal adenocarcinoma could transiently respond to crizotinib [160], the subsequent phase II study has yet to publish conclusions (NCT02435108). At the present time, the phase I MErCuRIC1 trial represents a first attempt at combining crizotinib with a MEK inhibitor in a cohort of CRC patients harboring amplified MET and either wild-type or mutated Ras (NCT02510001) [161].

Cabozantinib is the second non-selective MET inhibitor that has been approved for use in the clinic: for advanced, unresectable medullary thyroid cancer and for kidney cancer as a second-line treatment after anti-angiogenic therapy [162,163]. As for crizotinib, the approved use of cabozantinib does not involve the status of MET in the tumor. There is currently limited evidence for the benefit of using cabozantinib specifically to target MET: a case report presented one patient with MET exon 14 skipping who showed complete response, and the phase III CELESTIAL trial in HCC, a disease where MET has been implicated, showed a slight but significant improvement in PFS and overall survival for patients treated with cabozantinib, but did not report on a MET-specific response [157,164–166]. Several phase II trials are currently testing cabozantinib specifically for lung and salivary gland cancer harboring MET alterations (NCT03729297, NCT01639508, NCT03911193, NCT02132598).

Selective MET inhibitors are also being investigated in clinical trials, with some studies specifically focusing on the status of MET in the tumors. Capmatinib displayed improvements for patients with MET-overexpressing or amplified NSCLC in a phase I trial, and a phase Ib/II study with EGFR-targeted therapy-resistant NSCLC showed benefits for tumors having high MET copy number gains [167,168]. Numerous

phase II trials are currently testing Capmatinib in MET-dysregulated NSCLC and HCC (NCT03693339, NCT02750215, NCT01737827, NCT01610336, NCT02414139, NCT02276027).

Tepotinib had an antitumor effect in a phase I study, which led to the start of a phase I/II study in MET-positive HCC as an alternative to sorafenib (an inhibitor of VEGFR) [169–172] and the opening of the recruitment for a phase II trial in advanced NSCLC harboring MET exon 14 skipping mutations or MET amplification (NCT02864992). Recently, a trial has been set up to assess the combination of tepotinib with a 3rd generation EGFR inhibitor to treat EGFR-mutated, MET-amplified NSCLC having acquired resistance to EGFR inhibitors (NCT03940703).

AMG 337 has been evaluated in a phase I trial for various advanced malignancies where it elicited a favorable response in MET-amplified tumors [173]. Unfortunately, the following phase II study was terminated early after an intermediate review revealed that the treatment had a lower-than-expected activity compared to the phase I trial, despite the selection of patients exhibiting MET amplification [173]. Another phase II study is currently recruiting patients with advanced or metastatic solid tumors harboring MET overexpression or exon 14 skipping mutations (NCT03147976).

Savolitinib is involved in numerous trials at different stages, including a phase II study in lung cancer, selecting for MET exon 14 mutated cases (NCT02897479), and several phase I/II studies in advanced gastric adenocarcinoma or metastatic CRC with MET overexpression as second- or third-line treatment, alone or combined with docetaxel (NCT03592641, NCT02449551, NCT02447380). Of note, savolitinib is also being evaluated in a phase III study in MET-driven, unresectable, locally advanced or metastatic PRCC (NCT03091192), following a promising phase II trial in a similar setting where HGF mutations or MET alterations correlated with better response (NCT02127710) [174].

The road ahead: better aiming, or better weapons?

The stratification struggles

Patient stratification for targeted therapy is not always a trivial affair: some targets can be more difficult to select than others. Whereas HER2 amplification is a common phenomenon in breast and gastric cancer (15-30% and 21-33%, respectively) [175], leading to a large population in which treatment options such as trastuzumab and lapatinib have been tested and validated, true MET amplification is a rarer occurrence. Similarly, activating mutations are less frequently observed in MET than in EGFR, which can be mutated in up to 15% of Caucasian NSCLC patients [176]. Unlike these two examples, MET alterations have been detected in less than 10% of the cases for most cancer types (see Figure 2A), and this comparatively low MET alteration frequency makes it a challenging candidate for stratification. Furthermore, not all MET alterations might lead to sensitization to targeted therapy. A recurring question in the field of targeted therapy is the validity of the target: specific kinase inhibitors can only work if the corresponding kinase is essential to the growth and survival of the cancer cells [110,118]. Such oncogene addiction can be difficult to establish outside of a preclinical cellular model, and the setbacks from early clinical trials targeting MET could have resulted from inappropriate patient selection. Indeed, patient stratification was often initially made based on MET expression in the tumor, regardless of MET activation (denoted by the phosphorylation of MET tyrosines 1234/1235), potentially rendering MET targeting ineffective [177]. Indeed, only a fraction of MET positive tumors are actually p-MET positive [178]. One would think that assessing MET phosphorylation instead of MET expression in the tumor would be a simple solution to that problem. Unfortunately, the detection of phosphorylated MET by immunohistochemistry (IHC) remains complicated: unless extreme precautions are taken in the processing of the tissue and the detection process, the phosphorylation can be lost [179]. Research from Huang and colleagues highlights the complexity of defining the proper way to measure MET expression and activation by IHC on archival tissue, their work suggests that every type of cancer might need a specific companion diagnostic, potentially each with a different antibody [180].

Early trials have been criticized for casting too wide a net by selecting patients using MET detection by IHC [181]. Therefore, the focus shifted to the detection of genetic alterations showing a better correlation with the response to MET-targeted therapies, such as MET amplification or MET exon 14 skipping mutations. However, MET amplification assessment by fluorescence in situ hybridization (FISH) is controversial as well. Some trials deem that duplication of the whole chromosome 7 is not enough to depict true MET amplification, and consider that only the amplification of the MET locus, defined by a high ratio of MET to centromere 7 (MET/CEP7), represents an oncogenic event [181]. What MET/CEP7 threshold should be applied remains controversial: some trials selected patients with a ratio higher than 2, whereas others defined MET amplification as a MET/CEP7 higher than five, the most stringent threshold suggesting that less than 1% of the patients might exhibit true amplification, whereas less stringent settings include up to 7% in the MET-amplified group in gastric or lung cancer studies [181,182]. The stratification of patients harboring MET exon 14 skipping mutations, which is already being applied in some trials as presented above, could be a viable alternative selection strategy, enabled by the non-intrusive detection in circulating tumor DNA [157,179]. Nevertheless, it is important to remember that MET exon 14 skipping only occurs in up to 4% of NSCLC cases, and selecting such a small subset of patients could exclude other potential responders [183]. Regardless of the stratification method, it has become clear that only a minute fraction of tumors exhibit MET addiction, and thus the potential response to standard anti MET treatments might only prove effective for a very limited population [157,181]. However, recent advances in the field of immunotherapy could extend MET targeting therapies to tumors expressing MET without addiction to the oncogene, as presented in the next section.

The rise of personalized immunotherapy

The generation and injection of chimeric antigen receptor (CAR) T-cells is a type of adoptive immunotherapy and a promising method currently being developed for the treatment of cancer. The principle behind CAR T therapy is the genetic engineering of a patient's T-cells *ex vivo* to express an artificial receptor (CAR) targeting a surface protein specifically expressed by the targeted tumor cells.

Modified T-cells are then infused into the patient, where they can target tumor cells independent of the major histocompatibility complex and trigger tumor cell death primary by cytolysis and by extrinsic apoptosis induction [184]. Thus, as opposed to TKIs and mAbs which can only affect MET-addicted cells or cells that express high levels of MET, this therapeutic approach can potentially be used to target cells expressing the target at a level too low for standard targeted therapy, or those that are not addicted to the target [185,186]. Currently, CAR T-based therapies have shown the most promise for hematologic malignancies, while their application to solid tumors remains a challenge [187]. Nevertheless, efforts are being made to target proteins such as EGFR [188], EphA2 [189] and HER2 [190]. Similarly, MET has been the object of recent studies evaluating its potential as a CAR T target. In order to overcome the challenge of solid tumor invasion by T-cells, Tchou and colleagues assessed the feasibility of intratumoral injection of MET-targeting CAR T-cells for the treatment of metastatic breast cancer. Intratumoral injection has the added benefit of reducing on-target off-tumor effect, which was further lessened by the transient expression of the CAR. After observing tumor control with this approach in a mouse xenograft model, six patients were enrolled for a phase 0 trial. All patients treated presented MET-positive tumors and the injection of CAR T-cells was well tolerated. While no clinical response could be measured, systemic dissemination of CAR T-cells remained limited and histological analysis of the sites of injection revealed the induction of necrosis, immune cell infiltration and loss of MET-positive cells. This trial was limited in its scope, but serves as an encouraging proof of concept, opening the door to further studies with larger cohorts and proper controls to evaluate the efficacy of MET-targeting CAR T therapies [191]. While the study by Tchou *et al.* generated a CAR with the single chain variable fragment of an antibody (onartuzumab), other approaches have also been described. Thayaparan and colleagues generated a CAR by using the NK1 domains of HGF, hijacking a natural MET-binding mechanism. They applied this approach to the treatment of mesothelioma and showed positive results *in vitro* with MET-expressing cell lines. They also showed the safety and efficacy of locally injected MET-targeting CAR T-cells in an intraperitoneal mouse xenograft model, leading to tumor regression, albeit only when injecting high doses of CAR T-cells [192]. These promising early results warrant further research into the efficacy of such therapies in the clinical setting, however the monitoring

519 and management of toxicity remains a crucial parameter to promote the application of CAR T therapies
520 [187].

521 Conclusion: the past, present and future of MET signaling-targeted 522 therapies

523 As presented in this review, the results of MET/HGF-targeting agents in clinical trials are underwhelming.
524 However, lessons can be learned from both successes and failures, which should help design future trials
525 with improved patient selection and drug combinations. It could be remarked that antibody-based therapies
526 seem to fare worse than small molecule inhibitors. However this might stem from an inferior patient
527 selection process, as it was often made on the basis of MET expression measured by IHC, a technique that
528 has limitations due to variables such as fixation and processing of the tissue or subjectivity in the scoring
529 [193]. Furthermore, measuring MET expression has the downside of not necessarily correlating with MET
530 activation, denoted by phosphorylation of tyrosine residues. Despite evidence that the presence of
531 phosphorylated MET is associated with tumor progression and is a predictor of metastasis and survival in
532 some types of tumors, assessing MET activation or addiction in this fashion has not been widely adopted
533 for patient accrual [194,195]. As is seen for EGFR-targeting therapies, where efforts are made to enrich for
534 patients with activating EGFR mutations, screening patients for genetic alterations that are associated with
535 MET activation (notably MET exon 14 skipping mutation and MET amplification), rather than simply
536 measuring MET expression, is now considered a superior selection strategy and predictor of response to
537 MET inhibition in the case of NSCLC [86,157,196,197]. Indeed, ambitious efforts are currently being made
538 to improve personalized therapy: the MATCH phase II clinical trial is aiming at stratifying patients by
539 genetic alteration instead of histology to provide them with the appropriate treatment, such as crizotinib in
540 the presence of MET overexpression or exon 14 mutations [198,199].

541 Another lesson can be learned from EGFR-targeting therapies: the inevitable rise of resistance, for example
542 as a result of the acquisition of a mutation (*e.g.* EGFR T790M) that can null the effect of the TKI or by

543 relying on another RTK such as MET [200]. In the case of EGFR, this has been addressed in two ways:
544 either by using more recent inhibitors that can overcome the protective effect of the mutation, such as
545 osimertinib, or by combining EGFR and MET inhibition [197,201]. Similar approaches could be effective
546 to face the expected emergence of resistance to MET-targeting compounds. Several such resistance
547 mechanisms in MET-driven tumors and cell lines have been documented and include the selection of
548 preexisting subclones harboring MET Y1248H (or Y1248C) mutations, rendering cells resistant to
549 crizotinib, or MET D1228V, protecting against savolitinib. While these mutated variants of MET can be
550 inhibited by glesatinib or cabozantinib, respectively, additional mutations could be selected or acquired in
551 treated cells and render them resistant to virtually any inhibitor [202–204]. Resistance to MET inhibition
552 can also occur through the amplification of HER2 or FGFR2 and de novo Ras mutations, which would
553 require the combined use of several targeted therapies preemptively or after relapse [205,206]. Drug
554 combinations can also be rationally designed to directly target processes that involve several RTKs. One
555 such example would be the combination of VEGFR and MET inhibitors, as both are involved in
556 angiogenesis [130,207]. Interestingly, such a combination could be necessary to overcome the unforeseen
557 activation of MET by the inhibition of VEGFR in a particular setting. Indeed, targeting VEGFR in
558 glioblastoma multiforme can have the unexpected effect of enhancing MET activation, leading to a more
559 invasive tumor phenotype [208].

560 Altogether, despite middling success, preclinical and clinical studies show potential for MET as a
561 therapeutic target, provided improvements in patient stratifications are made. The recent development of
562 MET targeting immunotherapy and the granting by the FDA of a priority status to both capmatinib and
563 tepotinib, based on the promising results of the GEOMETRY mono-1 (NCT02414139) and the VISION
564 (NCT02864992) studies, highlight that MET remains an appealing target and could renew interest in this
565 oncogene. Since the resistance to the inhibition of various oncogenes (such as EGFR, BRAF, MEK or
566 FGFR) can arise through the activation of MET [109], looking forward, one can expect the development of
567 combination therapies that could pre-emptively address resistance and have a synergistic effect with MET-
568 targeting therapies.

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Figure and Table legends

Figure 1. Schematic representation of the subunits, domains and known phosphorylation sites of MET and HGF, as well as major signaling pathways downstream of MET.

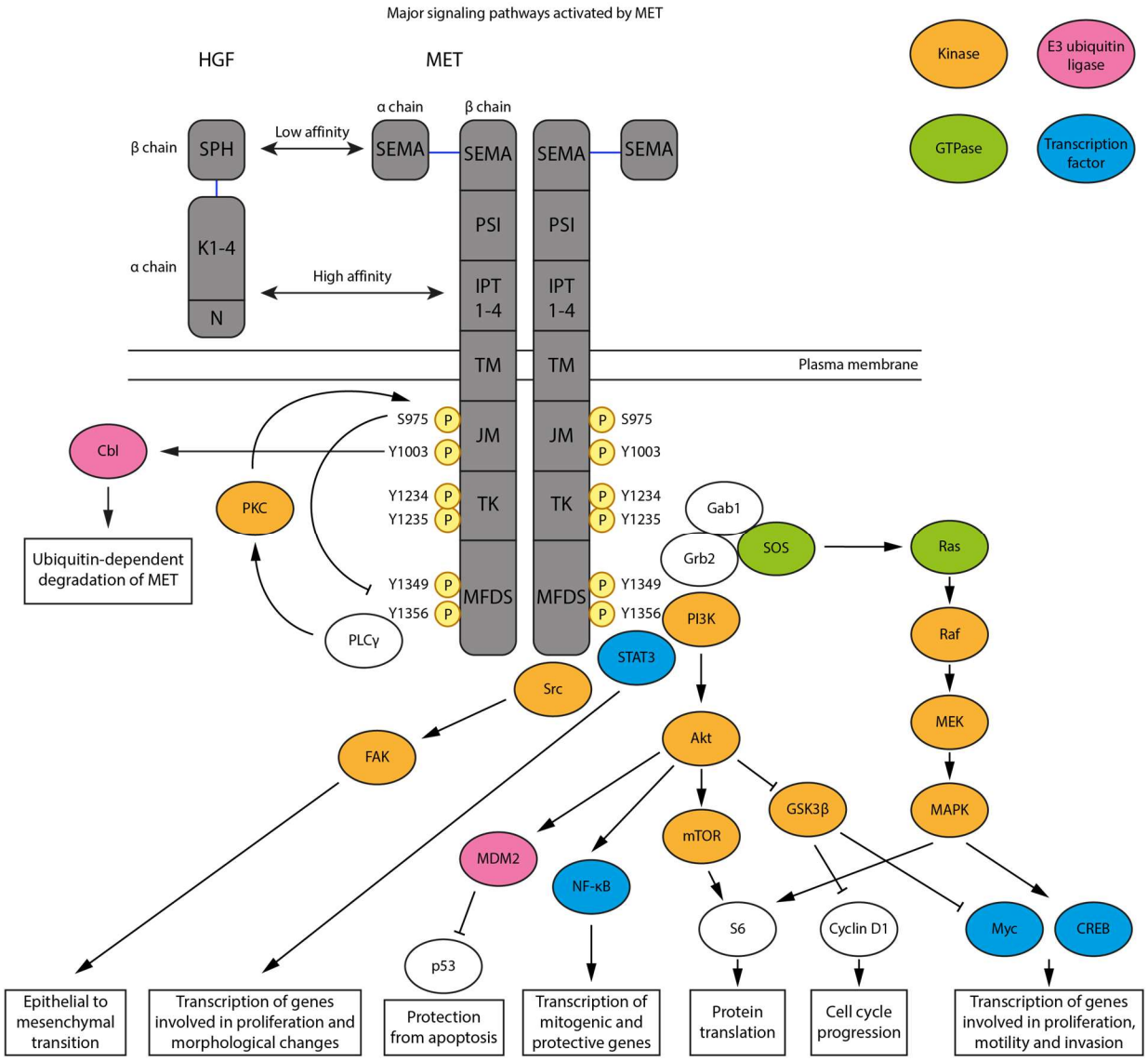
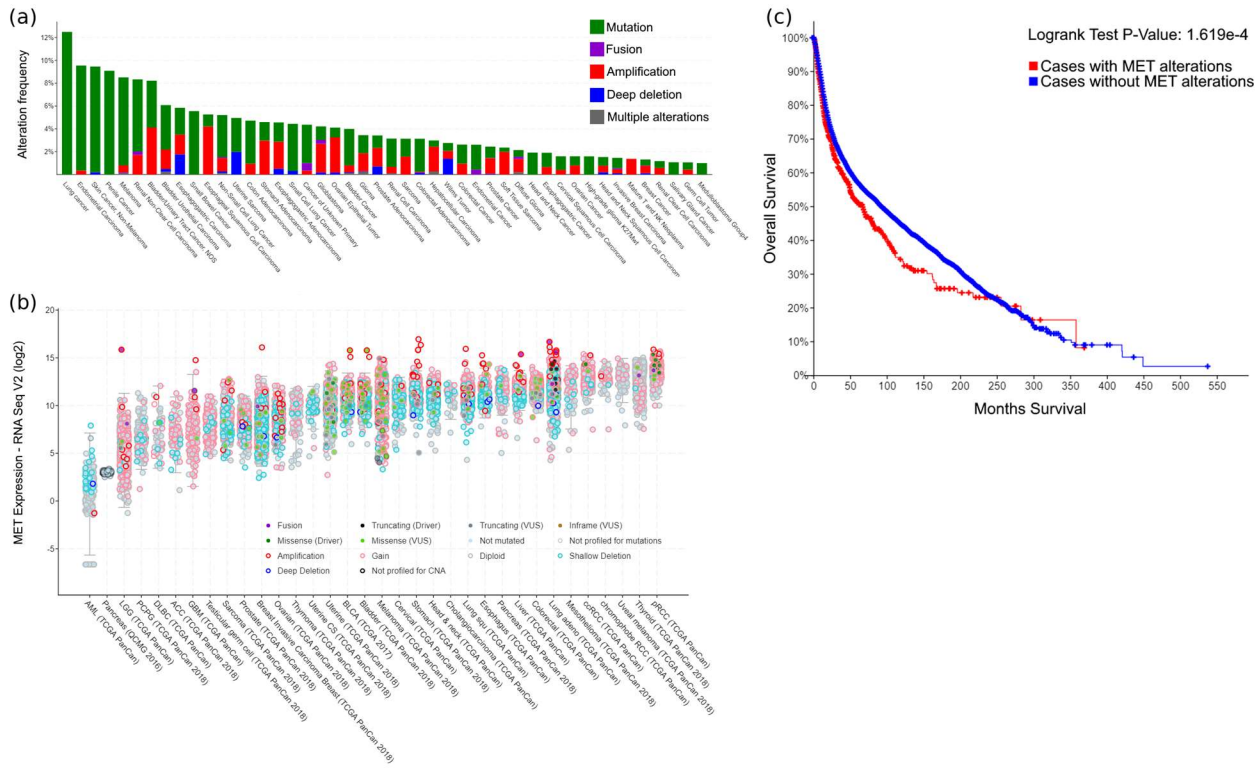


Figure 2. Summary of MET alterations frequency and outcome in different cancer types. Visualization of the data generated on cBioportal.org [209,210] from 212 studies (see link for detailed list: https://www.cbioportal.org/results/cancerTypesSummary?session_id=5d78f196e4b058f36688adc1, last accessed on the 11th of September 2019)

A. Frequency of MET genetic alterations in various cancer studies (studies with an alteration frequency lower than 1% have been excluded from the graph).

B. MET RNA expression in various types of cancer.

C. Kaplan-Meier graphs showing overall progression-free survival of cancer cases with and without MET alterations.



1132 **Table 1.** Summary of MET inhibitors in use and in development.

Compound name	Company	Targeted kinase(s)
Crizotinib (PF-02341066)	Pfizer (New York City, New York, USA)	MET, ALK, RON, AXL, TIE2, ROS1
Cabozantinib (XL184)	Exelixis (Alameda, California, USA)	MET, RET, VEGFR1-3, KIT, FLT3, TIE2, TRKB, AXL
Foretinib (XL880)	Exelixis/GlaxoSmithKline (London, UK)	MET, VEGFR2, RON, ERK, AKT, PDGFRβ, c-KIT, TIE2
Glesatinib (MGCD265)	MethylGene/Mirati Therapeutics (San Diego, California, USA)	MET, RON, VEGFR1-2, PDGFR, KIT, FLT3, TIE2, AXL
Golvatinib (E-7050)	Eisai (Tokyo, Japan)	MET, VEGFR2, RON, Eph, KIT
Merestinib (LY2801653)	Eli Lilly	MET, MST1R, FLT3, AXL, MERTK, TIE2, ROS1, NTRK1/2/3, DDR1/2, MKNK1/2, VEGFR2
PF-04217903	Pfizer	MET, ALK
AMG 208	Amgen	MET, VEGFR1-3, RON, TIE2
Capmatinib (INC280/INCB28060)	Incyte (Wilmington, Delaware, USA) /Novartis (Basel, Switzerland)	MET
Tepotinib (EMD1214063)	EMD Serono (Darmstadt, Germany)	MET
AMG 337	Amgen	MET
Savolitinib/Volitinib (AZD6094)	AstraZeneca (Cambridge, UK)	MET

OMO-1 (JNJ-38877618)	Johnson & Johnson (New Brunswick, New Jersey, USA)	ME

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