MET targeting: time for a rematch

Jonas P. Koch[1,2], Daniel M. Aebersold[1,2], Yitzhak Zimmer[1,2], Michaela Medová[1,2]

[1]Department for BioMedical Research, Inselspital, Bern University Hospital, and University of Bern, 3008 Bern, Switzerland.

[2]Department of Radiation Oncology, Inselspital, Bern University Hospital, and University of Bern, 3010 Bern, Switzerland.

Corresponding author: PD Dr. Michaela Medová, Department for BioMedical Research, Inselspital, Bern University Hospital, and University of Bern. Murtenstrasse 35, 3008 Bern, Switzerland. Phone Nr.: +41316323565. E-mail: michaela.medova@dbmr.unibe.ch

Conflict of interest statement: The authors have no conflicts of interest to declare.

Running title: MET targeting in cancer

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

52 (canonical isoform, www.ncbi.nlm.nih.gov/gene/4233). *MET* transcription is controlled by a variety of

53 transcription factors: HIF-1α under hypoxic conditions, AP-1 upon HGF stimulation, members of the PAX

54 family, NF-κB, Ets1, SP1, YB1 and the TCF family of transcription factors downstream of the Wnt pathway

55 [2]. Additional mechanisms of regulation, including epigenetic modifications such as DNA methylation,

56 histone acetylation and RNA interference have been studied and were summarized by Jack Zhang and Andy

57 Babic (2015) [8]. The major mRNA isoform resulting from splicing is translated into a single 170 kDa chain

58 in the ER [9]. Subsequently, this precursor is glycosylated in the Golgi apparatus and cleaved by furin in

59 the post-Golgi compartment into α (50 kDa) and β (145 kDa) chains, which remain linked by a disulfide

60 bond to form the mature form of MET. This mature MET will localize to the cell membrane with a single-

61 pass transmembrane β subunit and the α subunit being entirely extracellular [8]. Several functional domains

62 span the length of the receptor: on the extracellular part, a SEMA domain encompasses the α and part of the

63 β chains, followed by a PSI (plexin-semaphorin-integrin) domain and four IPT (immunoglobulin-plexin-

64 transcription factor) domains. The intracellular section of the receptor consists of a juxtamembrane (JM)

65 domain, a tyrosine kinase (TK) domain and a carboxyl-terminal multifunctional docking site (MFDS) [10].

66 On the extracellular side, the SEMA domain is essential for the dimerization and activation of MET [11] as

67 well as for binding of HGF [10], although the IPT domains have also been shown to have a high affinity for

68 HGF binding [12]. Between these two sections, the PSI domain contains several disulfide bonds necessary

69 for the proper orientation of the receptor towards the ligand [13]. Two regulatory phosphorylation sites

70 reside in the JM domain, directly below the cell membrane: serine 985 and tyrosine 1003 [14,15]. The

71 tyrosine kinase domain of MET is below the transmembrane domain and contains two tyrosine residues at

72 positions 1234 and 1235. The phosphorylation of these sites is an essential step of the activation of the MET

73 receptor, leading to the phosphorylation of two additional tyrosines (1349 and 1356) in the carboxyl-

74 terminal docking site, enabling recruitment of adapter proteins and transduction of the signal [16]. See

75 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

100 indirectly through Grb2, or directly thanks to a MET binding domain, whereas it can only bind other RTKs

101 indirectly [24]. Acting together, these adapters either activate signaling cascades or recruit other proteins,

102 which will themselves signal downstream. This causes the activation of pathways essential for growth,

103 proliferation and cell motility through the following signaling cascades. Through binding and activation of

104 the PI3K subunit p85, MET induces Akt signaling, leading to the activation of mTOR, a complex

105 responsible for cellular growth and protein translation [16]. Additionally, Akt affects the p53 pathway by

106 activating MDM2 while inactivating pro-apoptotic factors such as BAD and thus offers protection from

107 apoptosis [25]. Finally, Akt activates positive cell cycle regulators such as Myc and cyclin D1 by inhibiting

108 GSK3β [26]. Another major signaling pathway downstream of MET is the MAPK cascade. By recruiting

109 SOS via Grb2, MET activates the small GTPase Ras, which subsequently activates Raf, a kinase responsible

110 for the phosphorylation of MEK1/2. Activated MEK1/2 will phosphorylate the next kinases in the cascade:

111 the Mitogen-Activated Protein Kinases (MAPK) ERK1/2. Active ERK1/2 translocate into the nucleus,

112 where their kinase activity promotes the stabilization of transcription factors responsible for motility and

113 cell cycle progression in the G1-S transition [27,28].

114 Additional pathways are activated by MET, such as the STAT-3 cascade and NF-κB signaling. STAT-3

115 binds and is phosphorylated by MET, leading to its translocation into the nucleus where it acts as a

116 transcription factor for several genes related to proliferation, differentiation and morphological changes such

117 as the formation of tubules [29]. NF-κB is part of a family of rapid-acting transcription factors kept inactive

118 in the cytoplasm by IκB, which is itself controlled by IKK. Through the PI3K-Akt pathway, MET activates

119 IKK, which subsequently phosphorylates IκB, promoting its ubiquitination and degradation, releasing NF-

120 κB. Free NF-κB translocates into the nucleus and promotes the transcription of mitogenic, anti-apoptotic

121 and general cell-protective genes [30]. One more signaling axis worth mentioning, as it is connected to

122 epithelial-mesenchymal transition (EMT) via the promotion of cell migration and anchorage-independent

123 growth, occurs through FAK via the activation of Src by MET. Activated FAK regulates cell-matrix

124 adhesion as well as cytoskeleton reorganization and promotes cell invasion [31]. This process is assisted by

125 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

152 tightly regulated RTK involved in numerous cellular pathways. As MET has been shown to be crucial in

153 many processes in embryonic development and tissue repair, these pathways have been the object of

154 thorough studies, which are summarized in the next section.

The physiological functions of MET

156 As mentioned earlier, MET was initially discovered because of its oncogenic potential. However, the normal

157 function of MET is to act as essential regulator of various cellular function playing a pivotal role in the

158 development of various tissue types, as well as an important factor for tissue repair [1].

159 MET is mostly expressed by epithelial cells of various tissues and organs (including the gastrointestinal

160 tract, lung, liver, kidney, thyroid and skin) as well as some endothelial cells, cells in the hematopoietic

161 lineage, B cells and in neurons of various brains structures, while HGF is mainly expressed and secreted by

162 mesenchymal cells such as fibroblasts as a cytokine that modulates the proliferation of epithelial cells [44–

163 49]. As the other name of HGF – scatter factor – suggests, it also affects the "scattering" of MET-expressing

164 cells and controls invasive growth by its motogenic, mitogenic and morphogenic properties [50]. MET acts

165 as the main coordinator of the various stages of this complex program that involves proliferation, matrix

166 degradation, survival and migration: together MET and HGF form the basis for epithelial and mesenchymal

167 interaction, wound closure and angiogenesis at various stages of life [51]. As such, MET signaling is

168 essential *in vivo*: deletion of HGF was shown to impair proper placental and fetal development in mice,

169 leading to *in utero* death. Among the affected tissues, liver was strongly impacted and showed drastic size

170 reduction [52]. By virtue of being expressed in many more organs, MET signaling is key for the

171 development of additional types of tissues, including the pancreas, muscles and various types of neurons

172 [53–55]. It regulates angiogenesis by promoting VEGF signaling while downregulating TSP-1, and thus

173 stimulating endothelial cell motility [45,56], and can also promote hematopoiesis [46]. As a token of the

174 pleiotropic functions of MET, a recently discovered mutation in the fourth IPT domain (F841V) has been

175 linked to hearing loss in humans [57].

176 MET functions are not limited solely to development: by promoting proliferation and invasion, it is a crucial

177 component of wound repair when the invasive growth of remaining cells needs to be reactivated to

178 reconstitute the damaged tissues. Along with other factors, MET signaling plays a key role in liver and

179 kidney regeneration [58,59]. Bone remodeling also involves MET signaling as both osteoclasts and

180 osteoblasts express MET and osteoclasts secrete HGF, leading to a crosstalk between these cell types to

181 ensure proper bone resorption and deposition [60]. Beyond its functions directly involved in repair, MET

182 signaling plays a protective role in damaged tissues (such as ischemic cardiac muscle) by protecting cells

183 from apoptosis [61]. As a whole, the HGF-MET tandem can be described as a crucial factor for cellular

184 proliferation, growth and motility. While these functions are essential for normal life, they can be hijacked

185 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

189 The initial discovery of MET was made by the generation of an artificially induced oncogenic fusion protein,

190 and while this particular rearrangement was later also observed in human gastric cancerous lesions, a

191 plethora of different mechanisms leading to MET deregulation can naturally occur at all stages of

192 carcinogenesis and caught the interest of researchers promptly after the initial discovery of tpr-MET [62].

193 Various mechanisms have been shown to lead to MET deregulation in cancer, the most obvious one being

194 HGF-dependent: the stromal cells surrounding tumors frequently express HGF [63]. Ligand-dependent

195 activation of MET sometimes happens in an autocrine instead of paracrine fashion, however the

196 overexpression of MET is sometimes necessary for tumor cells to respond to HGF [64,65]. As a matter of

197 fact, MET overexpression is the most frequent cause of its constitutive activation in a ligand-independent

198 manner and results mostly from transcriptional upregulation. Examples of this have been reported in a

199 breadth of distinct carcinomas including thyroid, colorectal, ovarian, pancreatic, lung, and breast cancer

200   [66–71]. Hypoxia is one of the mechanisms that can trigger increased transcription of MET: as mentioned

201   above, HIF-1α can promote the transcription of MET [72]. Interestingly, MET overexpression can occur as

202   a response to radiotherapy through the ATM-NF-κB signaling pathway [73]. Activation of other oncogenes,

203   such as Ras, can upregulate MET expression as well [74]. A less common way for tumor cells to overexpress

204   MET is the amplification of its locus. Such gene amplification has been reported in esophageal

205   adenocarcinoma, medulloblastoma, cancer of the pancreas and of the gastrointestinal tract [75–78]. In lung

206   adenocarcinomas, MET amplification has also been documented as an acquired resistance mechanism to

207   EGFR targeted therapy [79]. Activation of MET due to its overexpression is thought to happen through its

208   spontaneous dimerization via the SEMA domain and is linked to cell-matrix adhesion mechanisms. [69,80].

209   However, some tumors rely on point mutations to activate MET without overexpressing it. The relevance

210   of activating MET mutations is underscored by the evidence that in HNSCC, the selection of somatic MET

211   mutations is promoted during metastatic spread [81]. These genetic aberrations include mutations in the

212   kinase domain of MET and have been described in both hereditary and sporadic forms of papillary renal

213   cell carcinomas as well as in gastric cancer [82,83]. Many of these mutations have been thoroughly studied

214   by their ectopic expression in various cellular systems, such as the NIH 3T3 mouse fibroblast model [84].

215   Ineffective downregulation of MET through the inactivation of pathways leading to MET dephosphorylation

216   or degradation can also lead to increased MET activation [85]. A relevant example of these mechanisms is

217   seen in a family of mutations leading to alternative splicing and hence skipping exon 14 of MET. The

218   resulting protein lacks a section of the juxtamembrane domain containing serine 985 and tyrosine 1003

219   which, as previously mentioned, are capital for the downregulation and degradation of MET [86]. These

220   mutations were first observed in lung cancer cases as a response mechanism to EGFR inhibition by MET

221   activation, and were later detected in subpopulations of brain and gastric cancer patients [87]. While a

222   relatively rare mutation, it could serve as a biomarker for patient stratification, as presented in later sections

223   of this review.

224　Finally, MET activation can result from the activation of other RTKs. For instance, stimulation of EGFR

225　with its ligand EGF promotes MET activation via the MAPK signaling pathway when both RTKs are co-

226　expressed [88]. Another example is RON, an RTK structurally related to MET. These receptors can interact

227　together and are sufficiently similar for the activation of one to lead to the phosphorylation of the other [89].

228　Similarly, several other RTKs, including IGF-1R and AXL, can interact with MET and cause its activation

229　[90,91].

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

231　MET deregulation can happen at any stage of cancer development, and together all the activation

232　mechanisms presented above have been shown to promote both primary tumor formation and the transition

233　to metastatic disease [66]. Various studies have associated high MET expression and activation with poor

234　outcome [92]. For instance, high expression is known to correlate with markers of negative prognosis in

235　thyroid carcinoma, is a significant negative prognostic marker in NSCLC and is a predictor of tumor

236　invasion and lymph node metastases in colon cancer [93–95]. These last two examples are representative of

237　two classes of cancer that are of particular interest in the context of MET: gastrointestinal and lung cancers.

238　While MET mutations or amplifications are rare in gastric and colorectal cancer (CRC), overexpression of

239　MET and HGF at the mRNA and protein levels is common and can be observed in up to 40-70% of patient

240　samples, correlates with tumor stage and is a prognostic marker of clinical outcome [66,96–99]. Moreover,

241　MET expression is a predictor of invasive growth in gastric cancers and is associated with higher

242　occurrences of lymph node and liver metastases [32,95,100]. Cellular and *in vivo* models of gastric and

243　colorectal cancer have confirmed these observations and show that blockade of MET signaling reduces

244　tumor growth and spread [32,101–103]. Overall, while the various methods and scoring systems used to

245　assess MET-positivity make the prognostic value of its aberrant expression difficult to gauge, systematic

246　reviews and meta-analyses associate high MET expression with higher hazard ratios and poor prognosis in

247　gastric and colorectal cancer [104]. Interestingly, MET amplification has been observed as a resistance

248　mechanism to EGFR inhibition in metastatic colorectal cancer, a phenomenon that can also occur in

249 NSCLC, either by selecting for pre-existing MET-amplified subclones or by inducing de novo copy number

250 gains [105,106]. Lung cancer studies also led to the discovery of another clinically relevant phenomenon:

251 MET exon 14 skipping mutations [107]. Because of such genetic aberrations, MET is considered a major

252 oncogene and a potential target in NSCLC [108]. Indeed, there is evidence for the efficacy of MET-targeting

253 therapies in NSCLC cases exhibiting MET alterations [86].

254 A more global picture of the role of MET in cancer depicts this RTK as an overall negative factor. Combined

255 data from multiple studies accessed from the cBioPortal website reveal that MET genetic alterations are

256 common in various types of cancers (Figure 2A), the highest mutation rate is observed in lung cancers

257 whereas esophageal squamous cell carcinomas show the highest amplification rate. RNA sequencing shows

258 overexpression in all cancer types: the highest median expression is found in papillary renal cell carcinoma

259 (PRCC), often combined with amplification or copy number gain, and the lowest overexpression is seen in

260 acute myeloid leukemia (AML) (Figure 2B). Strikingly, disease outcome is significantly worse for cases

261 with MET alterations compared with non-altered MET, showing a median overall survival of 66.7 versus

262 92.4 months (Figure 2C).

263 As will be discussed further below, these observations have led to a great interest in the development of

264 MET targeting compounds, in particular for the treatment of MET-addicted tumors, as covered by various

265 reviews [80,109].

MET as an addicting oncogene

267 Oncogene addiction, an expression that was first coined by Bernard Weinstein in 2002, denotes the fact that

268 despite having multiple genetic alterations, the survival and proliferation of some tumor cells rely

269 exclusively on one (or a few) specific oncogenes, the earliest examples being Myc, Ras, Bcr-Abl and

270 HER2/neu [110–114]. Thus, the inhibition of the addicting oncogene is often sufficient to induce

271 proliferative arrest, senescence, apoptosis or terminal differentiation in addicted cancer cells [115]. While

272 this phenomenon was first observed in artificial models, this field of research was quickly translated to

273 applicable treatment strategies in the clinic with oncogene-targeted therapies. Imatinib, a specific inhibitor

274   of Bcr-Abl, the product of the Philadelphia chromosome translocation and a cause of chronic myeloid

275   leukemia, showed remarkable efficacy in patients [116]. Similarly, inhibition of HER2 with the monoclonal

276   antibody trastuzumab was shown to be efficacious and well tolerated in breast cancer patients displaying

277   strong overexpression of the receptor [117]. Over the years, evidence has emerged that oncogene addiction

278   can occur in many types of cancer and for several oncogenes, including major RTKs such as EGFR, VEGFR

279   and KIT [118]. Numerous clinical trials have shown the efficacy of targeted therapies against EGFR in lung

280   cancers driven by that oncogene, significantly improving progression free-survival (PFS) compared to

281   standard of care, but most trials failed to show higher overall survival [119–122]. Similarly, additional

282   examples of therapies targeting addiction to various oncogenes, both in preclinical and clinical trials, have

283   shown strong early response but failed to elicit durable effects [123]. This can be explained by the

284   development of resistance to the therapeutic compound via one or several mechanisms including the

285   selection or acquisition of protective mutations in the target and the escape from addiction, relying instead

286   on other pathways or oncogenes for cancer cell survival and proliferation, highlighting the need for

287   combination therapy [118,124,125]. As emphasized previously, MET is a potent oncogene involved in

288   various stages of neoplastic and metastatic development as well as in resistance mechanisms to therapies

289   targeting other oncogenes. Moreover, there is evidence for MET addiction in the preclinical and clinical

290   settings, making this receptor a prime target for targeted therapy [80]. For instance, the MET inhibitor PHA-

291   665752 has proven remarkably efficient in inducing apoptosis in gastric cancer cell lines harboring

292   amplification of wild-type MET, while sparing cell lines without copy number alterations [103]. Similarly,

293   out of a panel of 35 human cancer cell lines, the eight lines with the highest expression of active MET were

294   shown to be significantly sensitive to the MET-targeting antibody ABT-700 [126]. While the most

295   promising results of MET-targeting therapies have been observed in the preclinical setting, their potential

296   translational application is supported by case reports describing encouraging results for their use in MET-

297   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

321 being studied at the preclinical level, such as SFN68, which binds HGF in complex with MET, and the

322 bispecific (MET- and serum albumin-binding) nanobodies 1E2-Alb1 and 6E10-Alb8 [137,138].

323 As mentioned before, MET targeting antibodies can elicit diverse cellular responses depending on their

324 nature and the domain they bind. R13 and R28 (OncoMed Pharmaceuticals, Redwood city, California, USA)

325 are fully human mAbs used in tandem that compete with HGF for binding and induce ADCC [139].

326 SAIT301 (Samsung Inc, Yongin, Republic of Korea) is a humanized mAb that leads to MET downregulation

327 by internalization and lysosomal degradation via LRIG1 [140]. Similarly, emibetuzumab (LY2875358, Eli

328 Lilly, Indianapolis, Indiana, USA) is a humanized IgG4 that induces internalization and degradation of MET

329 and prevents HGF binding [141]. ABT-700 (AbbVie, Lake Bluff, Illinois, USA) is a humanized IgG1 that

330 blocks HGF binding and induces ADCC by recruiting natural killer cells to mediate the lysis of the targeted

331 cells [126]. An antibody-drug conjugate (ADC) has been developed from ABT-700: ABBV-399 (AbbVie).

332 This ADC is composed of the antibody and the cytotoxic microtubule inhibitor monomethylaurstatin E,

333 connected by a cleavable linker. Using an ADC could present the advantage of efficiently targeting cancer

334 cells with high expression of MET regardless of MET activation or addiction, while sparing normal cells

335 expressing lower levels of MET [142]. Onartuzumab (MetMab/OA-5D5, Genentech, South San Francisco,

336 California, USA) is a humanized monovalent antibody that competes with HGF by binding to the SEMA

337 domain of MET [143]. DN30 (Metheresis Translational Research SA, Lugano, Switzerland) is a chimeric

338 mouse IgG2A that induces ADAM-10 mediated shedding of receptor by binding the 4th IPT domain of MET

339 and altering the conformation of the receptor, which has the benefit of preventing MET activation and

340 releasing decoy MET moieties that can titer HGF away from cancer cells. The original form of the

341 compound had a flaw common to several receptor-targeting antibodies: since antibodies contain two binding

342 domains, DN30 could act as a partial agonist of MET by bringing two receptors together, leading to ligand-

343 independent dimerization and activation. This issue was solved by converting the compound to a smaller

344 monovalent Fab (MvDN30), which unfortunately had an increased renal clearance due to its small size

345 [144]. Two strategies could be explored to solve the resulting shorter half-life: stabilizing the plasma

346 availability of the compound (for example by PEGylation) or enabling continuous production of the Fab in

15

347 patients by gene transfer therapy, a route that is investigated in preclinical models of glioblastoma

348 multiforme, where MET has been described as a marker of cancer stem cells [145].

Small molecule inhibitors of MET

350 As mentioned earlier, small molecule tyrosine kinase inhibitors (TKIs) have the benefit of targeting the

351 activated receptor regardless of ligand presence by preventing ATP from reaching the ATP-binding pocket

352 of the kinase domain [146]. However, TKIs can vary in their specificity: some compounds have

353 demonstrated remarkable specificity for MET while others inhibit several kinases with varying affinities.

354 One notable exception to the ATP-competitive mode of action is the case of Tivantinib (ARQ197, Daiichi

355 Sankyo, Tokyo, Japan, and ArQule Inc, Woburn, Massachusetts, USA), which was initially presented as an

356 allosteric inhibitor of MET locking the receptor in the inactive conformation, but has subsequently been

357 shown to exert its cytotoxic activity by interfering with microtubule dynamics without affecting MET

358 activation [147]. Table 1 lists relevant examples of non-selective and selective TKIs that are at various

359 stages of clinical trials [2,109].

MET/HGF targeting in clinical trials

361 Over the years, many of the compounds presented above have progressed through clinical trials with varying

362 degrees of success. While there are too many completed and ongoing trials to be comprehensively presented

363 here, previous reviews have regularly summarized their progress, and only the most relevant examples of

364 completed or ongoing studies are highlighted below [2,80,109,133,146,148]. It should be noted that

365 currently only two non-selective MET TKIs have been approved for use, but not specifically for their MET-

366 inhibiting action: cabozantinib for medullary thyroid cancer and kidney cancer, and crizotinib for ALK and

367 ROS1 positive NSCLC [149,150]. However, these and other compounds are still being evaluated for other

368 cases, with many trials focusing on lung and gastrointestinal cancers due to the role this signaling axis plays

369 in the development and progression of these malignancies, as mentioned earlier. Nonetheless, a number of

370 studies is also being performed for other types of cancer, such as HCC, castration-resistant prostate cancer,

371 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

397 mutations [157]. The phase I PROFILE 1001 trial has also been testing the efficacy of this compound in

398 lung cancer and other solid tumors exhibiting MET, ALK or ROS1 alteration. While the study is still

399 ongoing, preliminary results have shown benefits for patients with advanced, ROS1-rearranged or MET-

400 amplified NSCLC [158,159]. Likewise, several ongoing phase II trials are evaluating the performance of

401 crizotinib in NSCLC and other cancers, focusing on genetic alterations such as MET amplification and

402 mutation (NCT02034981, NCT02499614, NCT03088930). Similar trials are also being performed for

403 gastric cancer: a pilot phase I study showed that MET-amplified gastroesophageal adenocarcinoma could

404 transiently respond to crizotinib [160], the subsequent phase II study has yet to publish conclusions

405 (NCT02435108). At the present time, the phase I MErCuRIC1 trial represents a first attempt at combining

406 crizotinib with a MEK inhibitor in a cohort of CRC patients harboring amplified MET and either wild-type

407 or mutated Ras (NCT02510001) [161].

408 Cabozantinib is the second non-selective MET inhibitor that has been approved for use in the clinic: for

409 advanced, unresectable medullary thyroid cancer and for kidney cancer as a second-line treatment after anti-

410 angiogenic therapy [162,163]. As for crizotinib, the approved use of cabozantinib does not involve the status

411 of MET in the tumor. There is currently limited evidence for the benefit of using cabozantinib specifically

412 to target MET: a case report presented one patient with MET exon 14 skipping who showed complete

413 response, and the phase III CELESTIAL trial in HCC, a disease where MET has been implicated, showed

414 a slight but significant improvement in PFS and overall survival for patients treated with cabozantinib, but

415 did not report on a MET-specific response [157,164–166]. Several phase II trials are currently testing

416 cabozantinib specifically for lung and salivary gland cancer harboring MET alterations (NCT03729297,

417 NCT01639508, NCT03911193, NCT02132598).

418 Selective MET inhibitors are also being investigated in clinical trials, with some studies specifically

419 focusing on the status of MET in the tumors. Capmatinib displayed improvements for patients with MET-

420 overexpressing or amplified NSCLC in a phase I trial, and a phase Ib/II study with EGFR-targeted therapy-

421 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].

468 Early trials have been criticized for casting too wide a net by selecting patients using MET detection by IHC

469 [181]. Therefore, the focus shifted to the detection of genetic alterations showing a better correlation with

470 the response to MET-targeted therapies, such as MET amplification or MET exon 14 skipping mutations.

471 However, MET amplification assessment by fluorescence in situ hybridization (FISH) is controversial as

472 well. Some trials deem that duplication of the whole chromosome 7 is not enough to depict true MET

473 amplification, and consider that only the amplification of the MET locus, defined by a high ratio of MET to

474 centromere 7 (MET/CEP7), represents an oncogenic event [181]. What MET/CEP7 threshold should be

475 applied remains controversial: some trials selected patients with a ratio higher than 2, whereas others defined

476 MET amplification as a MET/CEP7 higher than five, the most stringent threshold suggesting that less than

477 1% of the patients might exhibit true amplification, whereas less stringent settings include up to 7% in the

478 MET-amplified group in gastric or lung cancer studies [181,182]. The stratification of patients harboring

479 MET exon 14 skipping mutations, which is already being applied in some trials as presented above, could

480 be a viable alternative selection strategy, enabled by the non-intrusive detection in circulating tumor DNA

481 [157,179]. Nevertheless, it is important to remember that MET exon 14 skipping only occurs in up to 4%

482 of NSCLC cases, and selecting such a small subset of patients could exclude other potential responders

483 [183]. Regardless of the stratification method, it has become clear that only a minute fraction of tumors

484 exhibit MET addiction, and thus the potential response to standard anti MET treatments might only prove

485 effective for a very limited population [157,181]. However, recent advances in the field of immunotherapy

486 could extend MET targeting therapies to tumors expressing MET without addiction to the oncogene, as

487 presented in the next section.

The rise of personalized immunotherapy

489 The generation and injection of chimeric antigen receptor (CAR) T-cells is a type of adoptive

490 immunotherapy and a promising method currently being developed for the treatment of cancer. The

491 principle behind CAR T therapy is the genetic engineering of a patient's T-cells *ex vivo* to express an

492 artificial receptor (CAR) targeting a surface protein specifically expressed by the targeted tumor cells.

493 Modified T-cells are then infused into the patient, where they can target tumor cells independent of the

494 major histocompatibility complex and trigger tumor cell death primary by cytolysis and by extrinsic

495 apoptosis induction [184]. Thus, as opposed to TKIs and mAbs which can only affect MET-addicted cells

496 or cells that express high levels of MET, this therapeutic approach can potentially be used to target cells

497 expressing the target at a level too low for standard targeted therapy, or those that are not addicted to the

498 target [185,186]. Currently, CAR T-based therapies have shown the most promise for hematologic

499 malignancies, while their application to solid tumors remains a challenge [187]. Nevertheless, efforts are

500 being made to target proteins such as EGFR [188], EphA2 [189] and HER2 [190]. Similarly, MET has been

501 the object of recent studies evaluating its potential as a CAR T target. In order to overcome the challenge of

502 solid tumor invasion by T-cells, Tchou and colleagues assessed the feasibility of intratumoral injection of

503 MET-targeting CAR T-cells for the treatment of metastatic breast cancer. Intratumoral injection has the

504 added benefit of reducing on-target off-tumor effect, which was further lessened by the transient expression

505 of the CAR. After observing tumor control with this approach in a mouse xenograft model, six patients were

506 enrolled for a phase 0 trial. All patients treated presented MET-positive tumors and the injection of CAR T-

507 cells was well tolerated. While no clinical response could be measured, systemic dissemination of CAR T-

508 cells remained limited and histological analysis of the sites of injection revealed the induction of necrosis,

509 immune cell infiltration and loss of MET-positive cells. This trial was limited in its scope, but serves as an

510 encouraging proof of concept, opening the door to further studies with larger cohorts and proper controls to

511 evaluate the efficacy of MET-targeting CAR T therapies [191]. While the study by Tchou *et al.* generated

512 a CAR with the single chain variable fragment of an antibody (onartuzumab), other approaches have also

513 been described. Thayaparan and colleagues generated a CAR by using the NK1 domains of HGF, hijacking

514 a natural MET-binding mechanism. They applied this approach to the treatment of mesothelioma and

515 showed positive results *in vitro* with MET-expressing cell lines. They also showed the safety and efficacy

516 of locally injected MET-targeting CAR T-cells in an intraperitoneal mouse xenograft model, leading to

517 tumor regression, albeit only when injecting high doses of CAR T-cells [192]. These promising early results

518 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].

Conclusion: the past, present and future of MET signaling-targeted 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.

569

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Figure and Table legends

1115 **Figure 1.** Schematic representation of the subunits, domains and known phosphorylation sites of MET and

1116 HGF, as well as major signaling pathways downstream of MET.
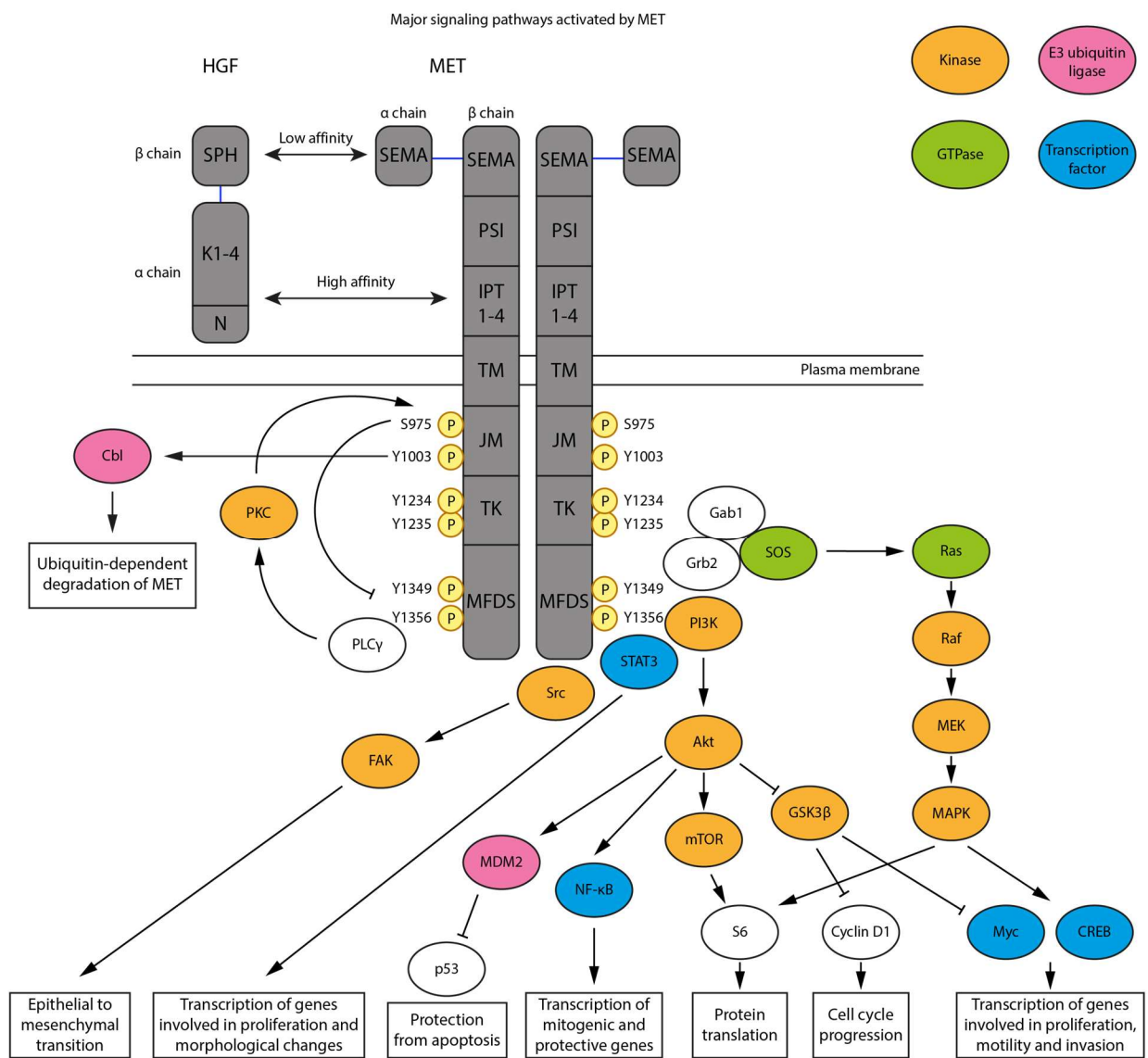
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1120   **Figure 2.** Summary of MET alterations frequency and outcome in different cancer types. Visualization of

1121   the data generated on cBioportal.org [209,210] from 212 studies (see link for detailed list:

1122   https://www.cbioportal.org/results/cancerTypesSummary?session_id=5d78f196e4b058f36688adc1,   last

1123   accessed on the 11th of September 2019)

1124   A. Frequency of MET genetic alterations in various cancer studies (studies with an alteration frequency

1125   lower than 1% have been excluded from the graph).

1126   B. MET RNA expression in various types of cancer.

1127   C. Kaplan-Meier graphs showing overall progression-free survival of cancer cases with and without

1128   MET alterations.
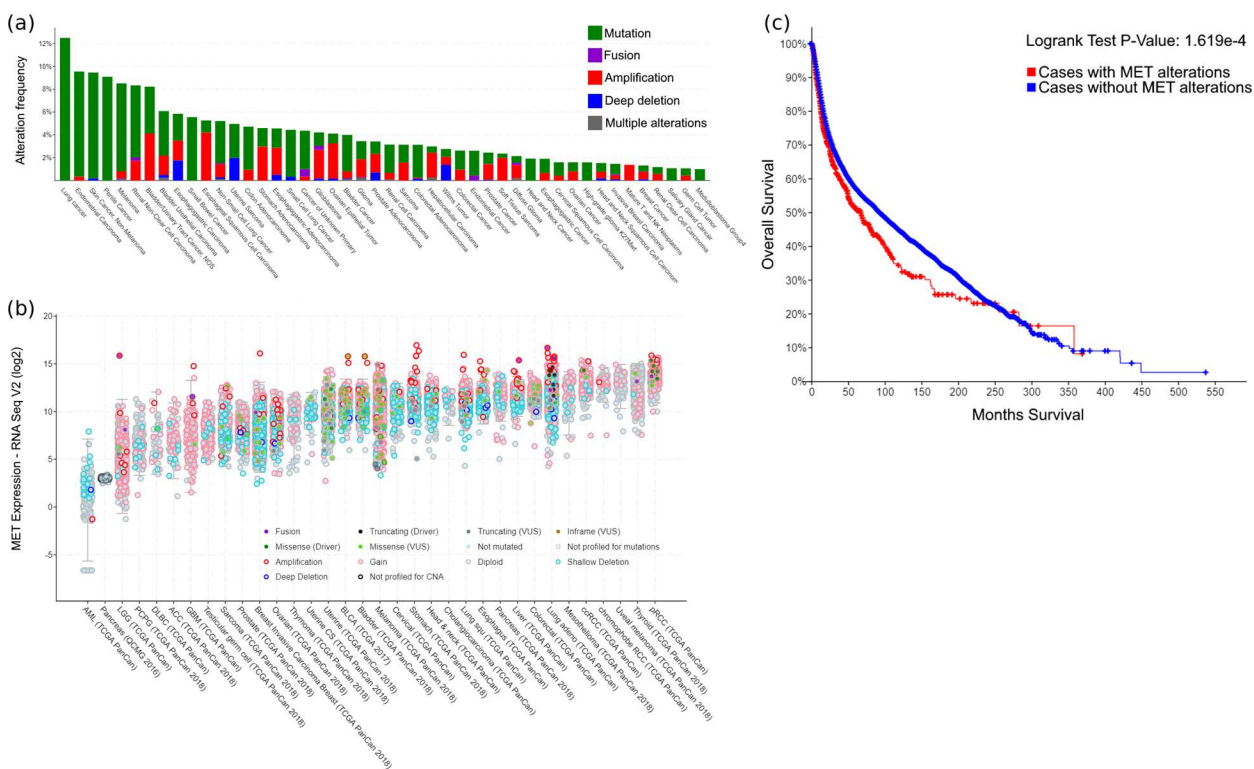
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1132   **Table 1.** Summary of MET inhibitors in use and in development.

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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