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REVIEW ARTICLE

HGF/MET pathway aberrations as diagnostic, prognostic, and predictive biomarkers in human cancers

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ABSTRACT

Cancer is a major cause of death worldwide. MET tyrosine kinase receptor [MET, c-MET, hepatocyte growth factor (HGF) receptor] pathway activation is associated with the appearance of several hallmarks of cancer. The HGF/MET pathway has emerged as an important actionable target across many solid tumors; therefore, biomarker discovery becomes essential in order to guide clinical intervention and patient stratification with the aim of moving towards personalized medicine. The focus of this review is on how the aberrant activation of the HGF/MET pathway in tumor tissue or the circulation can provide diagnostic and prognostic biomarkers and predictive biomarkers of drug response. Many meta-analyses have shown that aberrant activation of the MET pathway in tumor tissue, including *MET* gene overexpression, gene amplification, exon 14 skipping and other activating mutations, is almost invariably associated with shorter survival and poor prognosis. Most meta-analyses have been performed in non-small cell lung cancer (NSCLC), breast, head and neck cancers as well as colorectal, gastric, pancreatic and other gastrointestinal cancers. Furthermore, several studies have shown the predictive value of MET biomarkers in the identification of patients who gain the most benefit from HGF/MET targeted therapies administered as single or combination therapies. The highest predictive values have been observed for response to foretinib and savolitinib in renal cancer, as well as tivantinib in NSCLC and colorectal cancer. However, some studies, especially those based on MET expression, have failed to show much value in these stratifications. This may be rooted in lack of standardization of methodologies, in particular in scoring systems applied in immunohistochemistry determinations or absence of oncogenic addiction of cancer cells to the MET pathway, despite detection of overexpression. Measurements of amplification and mutation aberrations are less likely to suffer from these pitfalls. Increased levels of MET soluble ectodomain (sMET) in circulation have also been associated with poor prognosis; however, the evidence is not as strong as it is with tissue-based biomarkers. As a diagnostic biomarker, sMET has shown its value in distinguishing cancer patients from healthy individuals in prostate and bladder cancers and in melanoma. On the other hand, increased circulating HGF has also been presented as a valuable prognostic and diagnostic biomarker in many cancers; however, there is controversy on the predictive value of HGF as a biomarker. Other biomarkers such as circulating tumor DNA (ctDNA) and tumor HGF levels have also been briefly covered. In conclusion, HGF/MET aberrations can provide valuable diagnostic, prognostic and predictive biomarkers and represent vital assets for personalized cancer therapy.

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Abbreviations: ADAM: a disintegrin and metalloproteinase; AUC: area under the curve; CBL: casitas B lineage lymphoma proto-oncogene; CI: confidence interval; CNG: copy number gain; DFS: disease free survival; EGFR: epithelial growth factor receptor; FAK: focal adhesion kinase; FISH: fluorescence in situ hybridization; GaB1: GrB2-associated binding protein 1; GrB2: growth factor receptor-bound protein 2; HGF: hepatocyte growth factor; HIF: hypoxia-inducible factor; HR: hazard ratio; IGF1R: insulin-like growth factor 1 receptor; IHC: immunohistochemistry; JM: juxtamembrane; MET: mesenchymal-epithelial transition tyrosine kinase receptor, c-MET; NSCLC: non-small cell lung cancer; ORR: overall response rate; OS: overall survival; PCR: polymerase chain reaction; PFS: progression free survival; PI3K: phosphoinositide 3-kinase; PLC-γ: phospholipase Cγ; RFS: relapse free survival; ROC: receiver operating characteristic; RTK: receptor tyrosine kinase; RT-PCR: reverse transcriptase- polymerase chain reaction; sMET: soluble MET, soluble truncated

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Supplemental data for this article can be accessed here.

ectodomain of MET protein; STAT3: signal transducer and activator of transcription 3; TGF-α: transforming growth factor-α; TKI: tyrosine kinase inhibitor; VEGFR: vascular endothelial growth factor receptor

I- Introduction

The incidence and mortality of cancer are rapidly growing throughout the world. The latest GLOBOCAN report from the World Health Organization shows that cancer is the first or second most common cause of death before the age of 70 years in 91 out of 172 countries [1]. An estimated 75 million people will be living with cancer by 2030, while 21 million new cancer cases and 13 million deaths currently occur every year worldwide [2–4].

Mesenchymal-epithelial transition tyrosine kinase receptor (MET, c-MET) belongs to the family of receptor tyrosine kinases (RTKs) that is encoded by *MET* proto-oncogene located on human chromosome 7 (7q21-31) [5,6].

Since the discovery of MET and its native ligand, hepatocyte growth factor (HGF) in the mid-1980s, aberrant activation or dysregulation of this proto-oncogene has been suspected to be associated with the pathophysiology of several cancers [7]. Starting from the initial findings on the oncogenic role of *MET* mutations in papillary renal carcinoma [8], and followed by discoveries of other mutations in different human cancers [9], several lines of research in the past few decades have provided strong evidence for an important role of MET in human cancers [10,11] including gastrointestinal [12,13], lung [14,15], breast [16], cervical [17] and thyroid cancer [18]. As a result, some therapeutic agents against this pathway have found their way to routine cancer management protocols, and several others are under pre-clinical and clinical investigation [11,13,19,20].

MET is synthesized as a 170 kD single-chain precursor protein (pro-MET) which undergoes proteolytic cleavage, generating a 50 kD extracellular α-subunit and a 145 kD transmembrane β-subunit. The α-subunit (N-terminal peptide) is linked to the β-subunit by a disulfide bridge [21–24]. The β-subunit consists of an extracellular ligand-binding domain, a single-pass transmembrane domain, and an intracellular segment. The cytoplasmic domain includes a juxtamembrane (JM) domain involved in MET post translational regulation and a catalytic kinase domain that is responsible for tyrosine kinase activity and that modulates multiple downstream signaling pathways (Figure 1) [10,25–28].

Hepatocyte growth factor (HGF), also known as scatter factor, is the natural endogenous ligand of the MET receptor and is secreted predominantly by mesenchymal cells as an inactive precursor (pro-HGF). For HGF to be activated, pro-HGF is proteolytically cleaved at the Arg494-Val495 bond by enzymes such as serum HGF activator and cellular type II transmembrane serine proteinases to generate mature HGF [29]. The mature bioactive form of HGF is a disulfide-linked heterodimer composed of α-chain (69 kD) and β-chain subunits (34 kD) [5,28].

MET signaling, which is normally activated by the binding of its natural ligand, HGF, results in receptor dimerization and phosphorylation of two tyrosine residues, Tyr1234 and Tyr1235 in the kinase catalytic domain [30,31]. Subsequent phosphorylation of the docking site residues, Tyr1349 and Tyr1356, leads to the recruitment of a network of intracellular adapter and effector proteins such as phosphoinositide 3-kinase (PI3K), phospholipase Cγ 1 (PLCγ1), growth factor receptor- bound protein 2 (GrB2), GrB2-associated binding protein 1 (GaB1), and signal transducer and activator of transcription 3 (STAT3). Consequently, MET mediated activation of several intracellular signaling pathways, including the PI3K)/Akt, STAT3, SRC/FAK (FAK, focal adhesion kinase) and mitogen-activated protein kinase (MAPK)/ERK pathways, occurs [7,25,28, 32–34]. Activation of these pathways results in the emergence of diverse cellular hallmarks of cancer including cell proliferation, survival, inhibition of apoptosis, migration, invasion and metastasis (Figure 1) [6,25,28,31,35].

HGF/MET signaling is tightly regulated by various control mechanisms that attenuate or terminate the activated pathways. One such mechanism, which negatively regulates receptor signaling, is the internalization and degradation/recycling of the MET receptor via the recruitment of casitas B lineage lymphoma proto-oncogene (CBL), a ubiquitin-protein ligase. The ubiquitination of phosphorylated MET can occur through the direct interaction of CBL with Tyr1003 in the JM domain or indirectly by its binding to Tyr1356 via the Grb2 adaptor protein [10,36,37]. Another mechanism of MET downregulation is provided by the activity of tyrosine-specific phosphatases including PP2A, DEP-1, SHP2 and PTP1B [11,36].

Ectodomain shedding and regulated proteolysis also lead to downregulation of MET activity. The MET receptor is proteolytically cleaved by sheddase enzymes including the members of “a disintegrin and metalloproteinase”

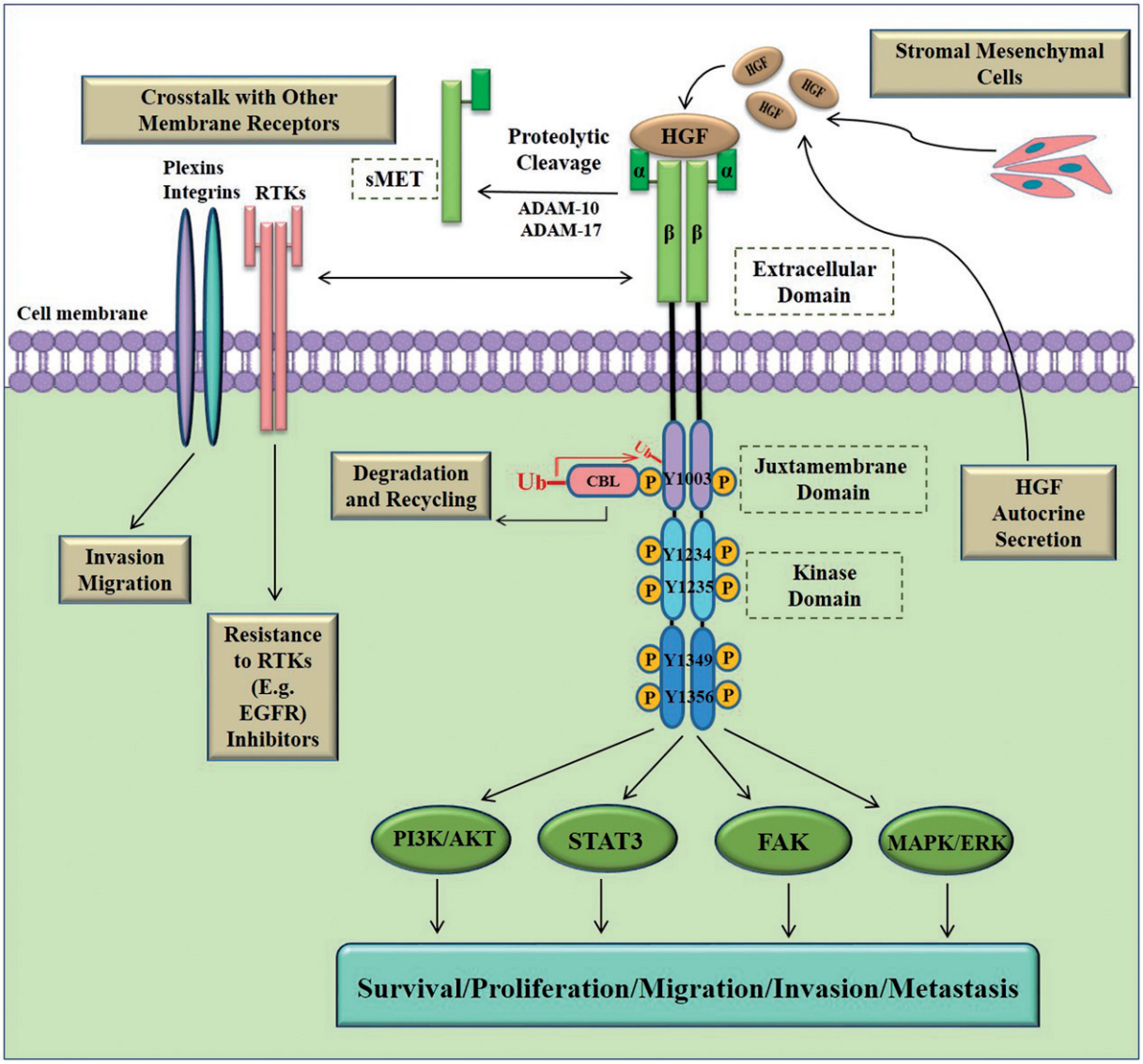

Figure 1. HGF/MET signaling pathway. The binding of hepatocyte growth factor (HGF), the natural ligand of MET tyrosine kinase receptor, induces receptor dimerization. Upon dimerization, transphosphorylation of tyrosine 1234 and 1235 residues in the kinase domain activates the kinase activity of the receptor. This is followed by further phosphorylation of Tyr1349 and Tyr1356 residues in the multifunctional docking site. This provides functional recognition sites for a variety of adaptor/effector proteins and subsequent activation of many downstream signaling pathways including MAPK, PI3K/AKT, FAK and STAT3 among others. Downstream signaling basically instigates cellular proliferation, survival, motility, migration, and invasion. Downregulation of MET receptor is initiated by recruiting CBL and ubiquitin mediated degradation as well as extracellular shedding. MET is proteolytically cleaved by ADAM-10 and ADAM-17 resulting in the formation of soluble MET ectodomain (sMET), which is secreted in the extracellular space and can be ultimately found in the circulation. The crosstalk between MET and other membrane receptors such as plexins, integrins, and EGFR and other RTKs promotes metastasis, invasion, and drug resistance. ADAM: a disintegrin and metalloproteinase family; CBL: casitas B lineage lymphoma proto-oncogene; STAT3: signal transducer and activator of transcription 3; FAK: focal adhesion kinase; MAPK: mitogen-activated protein kinase; PI3K: phosphoinositide 3-kinase; RTK: receptor tyrosine kinase.

(ADAM) family, such as ADAM-10 and ADAM-17, as well as γ-secretase, and results in the formation of a soluble extracellular ectodomain and a intracellular MET fragment that is rapidly degraded by the proteasome [38,39]. The soluble extracellular MET fragment (sMET) can bind to HGF, sequestering it from MET receptor binding and thus antagonizing MET signaling. Moreover, the interaction of sMET with full-length MET may also lead to impaired receptor dimerization [7,40–42].

Ectodomain shedding of MET and some other transmembrane receptors may have important impacts on the pathophysiology and drug response in different

types of cancer [42]. In this context, several studies have reported that expression of sMET correlates with cancer progression [40].

I-A- The importance of HGF/MET aberrations as clinical biomarkers

HGF/MET targeted therapies have had inconsistent outcomes in different tumor types. While the outcome has been promising in several clinical trials [12,43–45], others have not been able to provide enough evidence for the clinical benefit of MET targeted small molecule inhibitors or antibodies [46–50].

The study of the correlation of MET aberrations in tumor tissue with disease prognosis helps to distinguish the tumor types in which MET signaling has the highest level of biological relevance and a significant impact on tumor behavior. Hence, in addition to MET being a prognostic biomarker, the study of MET aberrations in tumor tissue helps to select cancer patients who could potentially benefit from HGF/MET targeted therapies.

The ultimate goals of studies that examine MET pathway activation in different types of cancer is to identify a predictive biomarker that enables stratification of patients with one cancer type into subpopulations and to identify those patients who are most likely to draw benefit from HGF/MET targeted therapies. This biomarker-guided approach, which is the cornerstone of precision medicine trials, could significantly increase the efficacy of targeted therapies [51].

Several clinical studies have addressed these issues and reported MET aberrations as indicators of short survival and clinicopathological features of advanced disease in diverse types of cancer, such as gastric [52], colorectal [53], breast [54], hepatocellular [55], pancreatic [56], and lung cancer [57]. In addition, the predictive role of MET dysregulation has been explored in different settings, and some results indicate improved

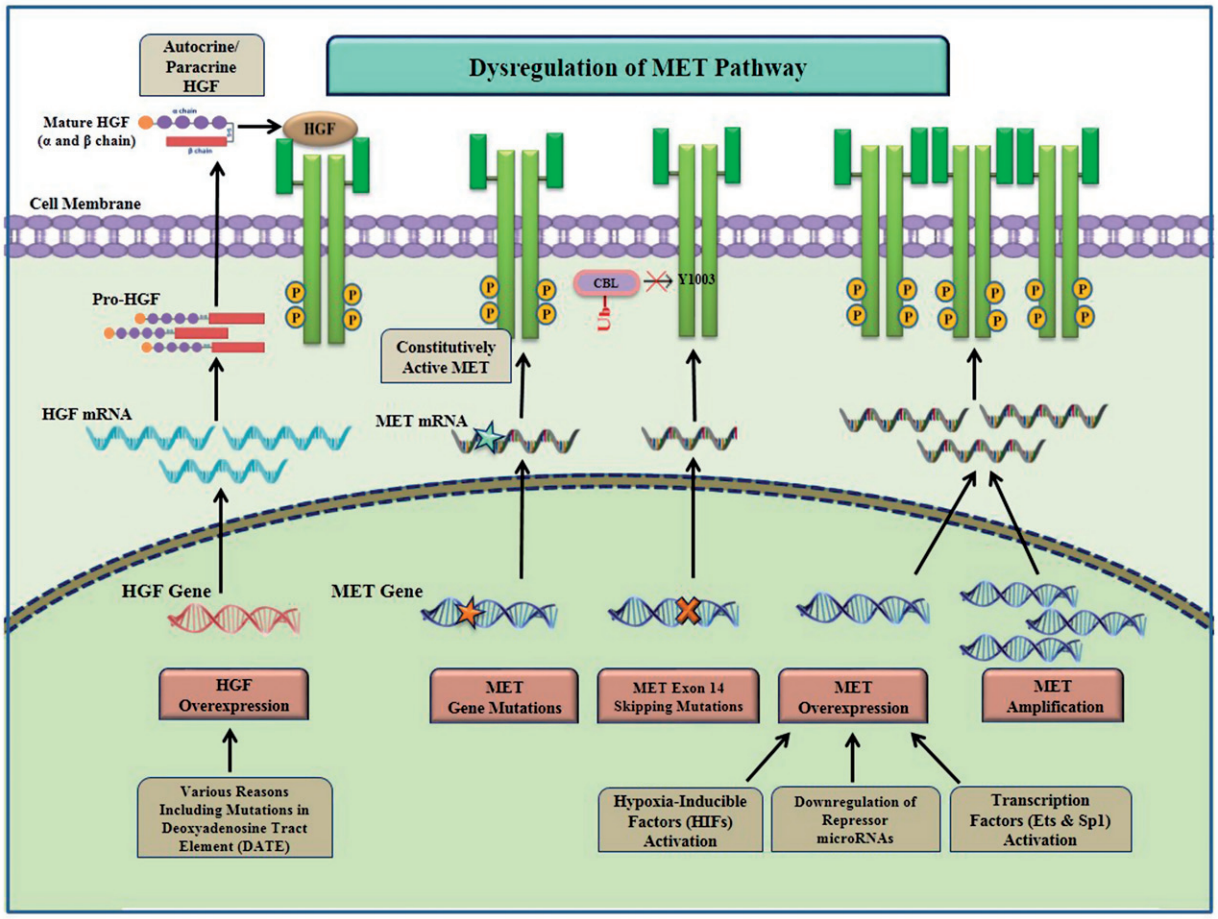

Figure 2. Aberrations in HGF/MET signaling pathway in cancer. Aberration of HGF/MET pathway may be caused by different molecular mechanisms including MET amplification, MET point mutations, exon 14 skipping mutations and excessive autocrine/paracrine HGF secretion. MET overexpression at the transcription level can be caused through transcription factors (e.g. Ets and Sp1) activation, hypoxia-inducible factor (HIF) activation and downregulation of repressor microRNAs. HGF overexpression can occur by transcriptional up-regulation due to mutations such as those in deoxyadenosine tract element (DATE) in the HGF gene promoter.

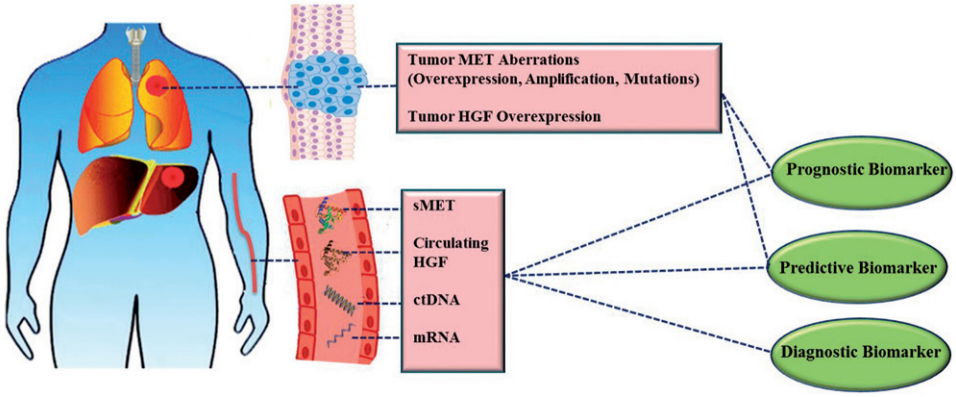

Figure 3. Available HGF/MET-related diagnostic, prognostic and predictive biomarkers in human cancers. Different tissue-based and circulation-based aberrations of HGF/MET pathway can be used as biomarkers.

response to multiple MET targeted agents in MET-positive compared with MET-negative populations [58–60]. These topics are covered in the next sections.

Alterations that may lead to HGF/MET signaling pathway activation in different tumors include gene overexpression, increased gene copy number gain (CNG), mutations in the kinase or non-kinase regions of the MET receptor as well as aberrant autocrine or paracrine HGF secretion, which have been thoroughly investigated in several different cancers (Figure 2) [6,12,61,62]. These alterations and the importance of each one as a biomarker are the subject of this review and are fully discussed in the following sections (summarized in Figure 3).

II- MET aberrant activation in tumor tissue as a prognostic biomarker

MET dysregulated signaling in tumor tissue can result from various genetic alterations in cancer cells including transcriptional dysregulation, *MET* gene amplification and mutational activations such as those resulting in exon 14 skipping (Figures 2 and 3) [63]. Understanding how HGF/MET functions as a prognostic biomarker in different types of cancer may guide the identification of tumor types and subtypes that draw the maximum benefit from HGF/MET targeted therapies. Table 1 summarizes the meta-analyses of studies on aberrant MET activation in various tumor tissues.

II-A- Increased MET expression

Increased expression of MET measured at both the protein and mRNA levels has been reported in several different types of tumors (Table 1 and Figure 2) [14,84–88]. *MET* overexpression can be a result of transcriptional up-regulation due to hypoxia-inducible factor (HIF) activation or alteration in other transcription factors including Ets and Sp1 [89,90]. It can also be caused by downregulation of repressor microRNAs, such as miR-1, miR-34, and miR-449a, that target MET [90]. An abundance of MET receptor monomers on the cell membrane can induce spontaneous dimerization, phosphorylation and subsequent activation of the receptor in a ligand-independent manner, and hence result in the activation of downstream signaling pathways that ultimately lead to tumorigenesis [91].

II-A-1- Non-small cell lung cancer (NSCLC)

Data from several meta-analyses have suggested that high MET expression is a negative prognostic biomarker in different cancers (Table 1 and Supplemental Figure 1(A,B)). A meta-analysis of hazard ratios (HRs) from 18 retrospective studies that included 5516 cases with non-small cell lung cancer (NSCLC) showed that high MET expression significantly increased the risk of mortality, even when studies responsible for heterogeneity (HR 1.52, 95% confidence interval (CI) 1.08–2.15) were excluded [67]. Similarly, a meta-analysis by Pyo et al., with 4454 NSCLC cases from 22 studies, confirmed that MET positivity was significantly correlated with shorter overall survival (OS) (HR 1.551, 95% CI 1.101–2.184) [66]. They observed that MET expression was significantly higher in non-squamous cell carcinomas and in patients with higher clinical stages [66].

II-A-2- Breast cancer

In breast cancer patients, studies have shown that high levels of MET expression are associated with favorable prognosis [92,93], have no significant association [94,95], or report statistically significant association between MET overexpression and poor prognosis

Table 1. Overview of meta-analysis studies on aberrant MET activation in tumor tissue as a prognostic biomarker in different types of cancer.

Tumor type	Number of analyzed studies/included patients	Aberrations	Applied method	Occurrence of MET-altered patients	Main findings	Ethnic subgroups	Impact of MET aberration on prognosis (clinical outcome)	Reference
NSCLC	21 Studies/7647 patients	Gene amplification	FISH (most commonly), qPCR and SISH	1–38.9%	High CNG was significantly associated with shorter OS (HR 1.45 [1.16–1.80], $p = .001$), but not with DFS (HR 1.37 [0.88–2.12], $p = .16$)[a]	Asian and non-Asian	Negative (only OS)	[64]
NSCLC	22 Studies/18,464 patients	Exon 14 skipping mutations	NGS/RT-qPCR/Sanger sequencing	Western patients: 3%. Asian patients: 2% (1–8.8%)	Exon 14 skipping mutations was significantly associated with shorter OS (HR 1.82 [1.04–3.19], $p = .04$)	Asian and western	Negative (OS)	[65]
NSCLC	22 studies/4454 patients	Overexpression	IHC	10.3–80.6%	MET overexpression was significantly associated with shorter OS (HR 1.55 [1.101–2.184])	–	Negative (OS)	[66]
NSCLC	18 studies/5516 patients	Gene amplification and overexpression	IHC in expression studies. qPCR, FISH, and SISH in amplification studies	13.7–68.9% for overexpression. 4–18% for gene amplification	MET overexpression was significantly associated with shorter OS (HR 1.52 [1.08–2.15], $p = .017$). High CNG was significantly associated with shorter OS (HR 1.90 [1.35–2.68], $p < .001$)[b]	Asian and non-Asian	Negative (OS)	[67]
Breast cancer	32 Studies/8281 patients	Overexpression	IHC (most commonly), RT-qPCR, RPPA	3.8–80%	MET overexpression was significantly associated with shorter OS (HR 1.65 [1.328–2.051]) and DFS (HR 1.53 [1.20–1.95])[c]. Met overexpression was significantly associated with large tumor size (OR 1.785 (1.480–2.153); high histologic grade (OR 1.547 [1.108–2.158] and distant metastasis (OR 20.431 [1.869–223.360])	Asian and non-Asian	Negative (OS, DFS)	[68]
Breast cancer	28 Studies/7830 patients	Overexpression	WB, IHC, RPPA, IS and IF	13–70.4%	MET overexpression was significantly associated with shorter PFS (HR 1.63 [1.20–2.22], $p = .002$), but not with OS (HR 1.16 [0.69–1.95], $p = .570$)	–	Negative (PFS), nonsignificant (OS)	[69]
Breast cancer	21 studies/6010 patients	Overexpression	IHC (most common), RT-qPCR, RPPA and MIP	–	MET overexpression was significantly associated with shorter OS (HR 1.52 [1.15–2.01], $p = .004$) and DFS (HR 1.60 [1.27–2.00], $p < .0001$). Subgroup analyses: MET overexpression was significantly associated with: poor OS (HR 1.62 [1.20–2.20], $p = .003$) and DFS (HR 1.52 [1.27–1.83], $p < .00001$) in Western patients but was not Asian patients[d]	Asian and Western	Negative (OS, DFS)	[70]

(*continued*)

Table 1. Continued.

Tumor type	Number of analyzed studies/included patients	Aberrations	Applied method	Occurrence of MET-altered patients	Main findings	Ethnic subgroups	Impact of MET aberration on prognosis (clinical outcome)	Reference
Colorectal cancer	6 Studies/1284 patients	Overexpression	IHC (most commonly) and PCR	28–79% (median 60.9 %) in the studies using IHC. 11.6% in the study using PCR	MET overexpression was significantly associated with shorter OS (HR 0.71 [0.54–0.92], $p = .009$) and DFS (HR 0.55 [0.38–0.79], $p = .001$)	–	Negative (OS, DFS)	[71]
Colorectal cancer	11 Studies/1895 patients	Overexpression	IHC (9 studies) and RT-qPCR (3 studies)	12–81% (median 61%)	MET overexpression was significantly associated with shorter OS (HR 1.33 [1.06–1.59]) and PFS (HR 1.47 [1.03–1.91])	–	Negative (OS, PFS)	[72]
Gastric cancer	14 Studies/2258 patients	Gene amplification and overexpression	IHC (majority of studies) and RT-PCR in expression studies. qPCR, SISH and Southern blot in amplification studies	8.3–30% in amplification studies. 24–82.4% in expression studies	MET amplification was significantly associated with shorter OS (HR 2.82 [1.86–4.27]). MET overexpression was significantly associated with shorter OS (HR 2.42 [1.66–3.54])	Asian and Caucasian	Negative (OS)	[73]
Gastric cancer	15 Studies/2210 patients	Gene amplification and overexpression	IHC (9 studies) and RT-qPCR (4 studies) in expression studies. FISH, SB and SISH in amplification studies	8–82%	MET overexpression/amplification was significantly associated with shorter OS (HR 2.112 [1.622–2.748])	Asian and Western	Negative (OS)	[74]
Head and neck cancer	16 Studies/1948 patients	Overexpression	IHC	26–82.9%	MET overexpression was significantly associated with shorter OS (HR 1.83 [1.29–2.60], $p = .0007$) and DFS (HR 1.49 [1.04–2.14], $p = .03$). MET overexpression was significantly associated with higher rate of lymph node metastasis (OR 3.26 [2.27–4.69], $p < .00001$) and higher T stage (OR 1.33 [1.03–1.71], $p = .03$)	–	Negative (OS, DFS)	[75]
Head and neck cancer	28 Studies/2019 patients	Overexpression	IHC	Level I: 41–100%. Level II: 9–90%. Level III: 0–83%	Above cutoff level II: MET overexpression was significantly associated with shorter OS ($p = 4.0 \times 10^{-6}$), positive nodal status ($p = .0001$), advanced disease stage ($p = .0007$), older age ($p = .0021$), disease recurrence ($p = .02$). Above cutoff level III: MET overexpression was significantly associated with shorter DFS/PFS ($p = 9.0 \times 10^{-6}$), OS ($p = .0004$), and larger tumor size ($p = .0046$)	–	Negative (OS, DFS, PFS depending on cut off level)	[76]

(*continued*)

Table 1. Continued.

Tumor type	Number of analyzed studies/included patients	Aberrations	Applied method	Occurrence of MET-altered patients	Main findings	Ethnic subgroups	Impact of MET aberration on prognosis (clinical outcome)	Reference
Head and neck cancer	17 Studies/1724 patients	Overexpression	IHC	–	MET overexpression was significantly associated with shorter OS (HR 2.19 [1.55–3.10], $p < .01$) and DFS (HR 1.64 [1.24–2.17], $p < .01$) and lymph node metastases (RR: 1.76 [1.26–2.45])[f]	Asian and non-Asian	Negative (OS, DFS)	[77]
Pancreatic adenocarcinoma	5 Studies/423 patients	Overexpression	IHC	27.5–60.6%	MET overexpression was significantly associated with shorter OS (HR 1.86 [1.19–2.91]) and DFS (HR 1.94 [1.46–2.56])	–	Negative (OS, DFS)	[78]
Hepatocellular carcinoma	5 Studies/1408 patients	Overexpression	IHC (most commonly) and WB	25.4–61.2%	MET overexpression was significantly associated with shorter OS (HR 1.16 [1.03–1.31], $p = .01$) and DFS (HR 1.26 [1.02–1.56], $p = .03$)	–	Negative (OS, DFS)	[79]
Biliary tract cancer	32 Studies/2885 patients	Overexpression	IHC	–	MET overexpression was significantly associated with shorter OS (HR 2.24 [1.45–3.45])[e]	–	Negative (OS)	[80]
Esophageal cancer	9 Studies/1062 patients	Overexpression	–	–	MET overexpression was significantly associated with shorter OS (HR 2.04 [1.66–2.52], $p < .001$) and DSS (HR 3.03 [2.04–4.48], $p < .001$) but not with DFS ($p = .176$)	–	Negative (OS, DSS). Not significant (DFS)	[81]
Renal cell carcinoma	12 Studies/1724 patients	Overexpression	IHC (most common) and RT-qPCR	16.7–80%	MET overexpression was significantly associated with shorter OS (HR 1.32 [1.12–1.56], $p = .0009$)	–	Negative (OS)	[82]
Cervical Cancer	9 Studies/685 patients	Overexpression	IHC	30.4–87.5%	MET overexpression was significantly associated with shorter DFS (RR: 0.59 [0.37–0.93], $p = .025$) and lymph node involvement (RR: 1.28 [1.08–1.52], $p = .005$), and lymphovascular space invasion (RR: 1.16 [1.01–1.34], $p = .038$)	–	Negative (DFS)	[83]

CI: confidence interval; CNG: copy number gain; DFS: disease free survival; HR: hazard ratio; IF: immunofluorescence; IHC: immunohistochemistry; IS: immunostaining: NGS: next-generation sequencing; OR: odds ratio; OS: overall survival, PFS: progression free survival; RPPA: reverse phase protein array; RR: relative risk; SB: Southern blot

[a]Subgroup analyses: High MET CNG was significantly associated with poor prognosis in patients with adenocarcinoma (HR 1.41, 95% CI: 1.11–1.79, $p = .005$) and Asian populations (HR 1.58, 95% CI: 1.32–1.88, $p < .00001$).

[b]Subgroup analyses: MET overexpression was significantly associated with poor OS (HR 1.89, 95% CI: 1.34–2.68, $p < .001$) in Asian patients but not in non-Asian patients. MET amplification was significantly associated with poor OS (HR 1.49, 95% CI: 1.05–2.10, $p = .025$) in adenocarcinoma patients but not in squamous cell carcinoma patients. MET amplification was significantly associated with poor OS (HR 2.22, 95% CI: 1.46–3.38, $p < .001$) in Asian patients but was not non-Asian patients. MET overexpression was significantly associated with poor OS (HR 1.69, 95% CI: 1.31–2.19, $p < .001$) in adenocarcinoma patients.

[c]Subgroup analyses: High MET CNG significantly was significantly associated poor prognosis in all methods group and non-Asian populations.

[d]Poor OS in lymph node negative breast cancer (HR 2.04, 95% CI: 1.48–2.80, $p < .0001$) and hormone-receptor positive (HR 1.41, 95% CI: 1.11–1.79, $p = .005$) and triple negative breast cancer (HR 2.31, 95% CI: 1.53–3.48, $p < .0001$), but not in human epidermal growth factor receptor (HER)-2 positive breast cancer.

[e]MET overexpression was not significantly associated with TNM stage, lymph node status and perineural invasive status.

[f]No significant relationship was between MET overexpression and advanced T stage, distant metastasis, poor tumor differentiation, and TNM stage. 95% CI are shown in brackets.

[96–99]. The conflicting results of multiple trials have been evaluated in recent meta-analyses [68,69,72]. An earlier meta-analysis of HRs from 21 studies that included 6010 breast cancer patients showed that MET overexpression was related to shorter OS (HR 1.52, 95% CI 1.15–2.01) in 17 studies that included 4228 patients as well as to shorter relapse-free survival (RFS) (HR 1.60, 95% CI 1.27–2.00) in 12 studies with 3570 patients [70]. Pooled data in the fixed-effects model showed that MET was significantly correlated with poor OS in lymph node negative breast cancer (HR 2.04, 95% CI 1.48–2.80) and with poor RFS in hormone-receptor positive (HR 1.41, 95% CI 1.11–1.79) and triple negative breast cancer (HR 2.31, 95% CI 1.53–3.48), but did not correlate with prognosis in human epidermal growth factor receptor (EGFR)-2 positive breast cancer (HR 1.20, 95% CI 0.91–1.59) [70]. Zhao et al. gathered 32 studies with 8281 patients; among these, 18 reports with 4751 cases were suitable for OS data analysis and 12 other studies with 3598 cases were available for disease free survival (DFS) data assessment. The data showed that MET overexpression was significantly associated with poor OS (HR 1.65, 95% CI 1.328–2.051) and poor DFS (HR 1.53, 95% CI 1.20–1.95). The results of subgroup analysis by immunohistochemistry (IHC) indicated a significantly poor prognosis in the patients with higher MET expression level [68].

The differences in the characteristics of breast cancer between Asian and Western populations have been discussed in various reports [100–102]. Results of subgroup analysis according to ethnicity has suggested that MET is a predictor of poor prognosis (both RFS and OS) in Western patients but not in the Asian patients [70]. These findings agreed with the results of a recent meta-analysis that showed that MET oncogenic alterations were not associated with poor prognosis in Asian patients [68].

II-A-3- Colorectal cancer

The value of MET overexpression as a prognostic biomarker in colorectal cancer was shown in two systematic reviews in 2015 [71,72]. Data from a meta-analysis of 11 studies that included 1563 patients and used the fixed-effects model demonstrated that patients with high MET expression had a significantly shorter OS (HR 1.33, 95% CI 1.06–1.59) and progression free survival (PFS) (HR 1.47, 95% CI 1.03–1.91) [72]. The second meta-analysis, with a smaller number of samples, showed a significantly shorter OS and DFS in patients with high MET expression; the data related to the subgroup examined by IHC indicated a significantly shorter DFS in the patients with MET overexpression, and suggested that patients diagnosed with stage III–IV cancer had higher MET expression level compared to those diagnosed with stage I–II [71].

II-A-4- Gastric cancer

Two meta-analyses have been performed on published articles in patients diagnosed with gastric cancer [73,74]; some of the same studies were included and analyzed in both these meta-analyses. The results of both studies revealed that higher MET expression was an indicator of poor prognosis in both early and advanced gastric cancer patients. Data from subgroup analysis related to method, race, tumor stage and type of aberration (amplification or expression) suggested that elevated MET expression had a significant negative impact on survival [73,74]. More recent published reports have confirmed these earlier findings [52,86,103,104].

II-A-5- Head and neck cancer

Several meta-analyses involving head and neck cancer patients have suggested the validity of MET overexpression as a negative prognostic biomarker [75,76]. Szturz et al. conducted a meta-analysis to explore the prognostic value of different cutoff levels of MET expression. They classified MET expression, measured by IHC, into three levels (I, II, and III) with an increasing order of positivity. Results showed that a high MET level, above cutoff level II, was associated with worse survival outcomes and higher disease stage [76]. From 16 studies, 1948 patients were included in the meta-analysis by Kim et al. [75], who found that patients with overexpression of MET had significantly inferior DFS (HR 1.49, 95% CI 1.04–2.14) and OS (HR 1.83, 95% CI 1.29–2.60) compared to those with low MET expression. Finally, another meta-analysis demonstrated that MET overexpression in the Asian subgroup had a significant association with poor OS but not with DFS [77].

II-A-6- Other cancers

The value of MET expression in tumor tissue as a prognostic biomarker has been studied in pancreatic cancer [78], hepatocellular carcinoma [79], and biliary tract [80], esophageal [81], renal [75], and cervical cancers [83]. The details of these meta-analyses are shown in Table 1. In addition, several studies confirm that high expression of MET is associated with poor survival in other less prevalent cancers. For instance, Mao et al. have shown that in cholangiocarcinoma, patients with MET overexpression had significantly shorter OS and DFS compared to those with low MET expression (OS, $p = .003$ and PFS, $p = .009$). The expression of MET in

patients with tumor tissues was significantly higher than that in adjacent tissues. Based on multivariate COX regression analysis, the high expression of MET was an independent risk factor for DFS and OS for patient with cholangiocarcinoma [105]. Another study reported similar data in patients with glottic laryngeal squamous cell carcinoma [106].

II-B- MET gene amplification

Amplification of the *MET* protooncogene or gene CNG, which causes protein overexpression and constitutive activation of the MET receptor (Figure 2), has been detected in NSCLC [107] and breast [16], gastric [52,108] and renal cancers [109]. Several methods, including fluorescence in situ hybridization (FISH) (the most widely used technique), silver in situ hybridization, quantitative polymerase chain reaction and Southern blotting, have been applied to detect *MET* gene amplification [14,85,110]. Because different techniques and criteria have been used to detect gene amplification, the prevalence of *MET* amplification in cancer patients varies greatly in the literature. For instance, the rate of *MET* amplification based on FISH analysis ranged from 1.5 to 11% among those with gastric cancer [52,111,112] and 2.4 to 4.1% for NSCLC patients [113,114], whereas the prevalence of high *MET* copy number was observed in up to ∼20% of NSCLC [115] and ∼30% of gastric cancer [116] patients by polymerase chain reaction (PCR)-based assays.

In NSCLC, the prognostic value of *MET* CNG and its association with poor overall survival was first shown by Okuda et al. [117].

There are a few meta-analyses in the literature on the prognostic role of *MET* CNG in NSCLC [64,67,118]. A recent meta-analysis combined the results from 21 studies that involved 7647 patients and showed the association between *MET* CNG and inferior OS (HR 1.45, 95% CI 1.16–1.80) [64]. Subgroup analyses based on histology and ethnicity indicated that *MET* CNG significantly correlated with shorter survival, especially in patients with adenocarcinoma (HR 1.41, 95% CI 1.11–1.79) and in Asian populations (HR 1.58, 95% CI 1.32–1.88). However, the number of studies that reported data regarding DFS seemed to be insufficient to determine a significant association of high *MET* CNG with DFS (HR 1.37, 95% CI 0.88–2.12).

The prognostic value of *MET* CNG in NSCLC was consistent with the results of two previous meta-analyses published in 2014 [67,118]. Some patient populations from these studies shared the same patient origin. It has also been noted that FISH, followed by reverse transcriptase-PCR (RT-PCR), was the most widely used method for detection of CNG [67,118].

II-C-Exon 14 skipping mutations

Exon 14 of *MET* encodes the JM domain of the receptor tyrosine kinase, which contains an important tyrosine residue (Tyr1003) and is the binding site for CBL, an E3 ubiquitin-protein ligase. Mutations that result in exon 14 splicing alterations result in the loss of this important regulatory region in the MET receptor and lead to decreased ubiquitination and hence reduced lysosomal degradation and prolonged MET signaling [85,119]. This post translational dysregulation activates MET signaling in cancer cells and promotes oncogenesis [6,120].

Exon 14-skipping mutations have been amply reported in lung cancer, with a prevalence of approximately 3–5%, and in other tumor types, with probably lower frequencies [121–123]. These mutations are very likely to confer sensitivity to MET targeted therapies [65,124,125].

The association between the *MET* mutation and the clinico-pathological features and prognosis of NSCLC has been investigated in a meta-analysis of 11 retrospective studies [65]. Data from only two studies reporting the HR on overall survival in patients with *MET* exon 14 mutations could be pooled [126,127]. The pooled results indicated that the presence of *MET* exon 14 mutations in NSCLC patients was correlated with a significantly poor prognosis (HR 1.82, CI 1.04–3.19). Of note, based on the histologic subtypes, the incidence of this mutation was detected mostly in pulmonary sarcomatoid carcinoma [65].

II-D-MET mutations

MET germline and somatic mutations have been identified across different receptor domains including the kinase, JM, and extracellular domains in several tumor types (hereditary and sporadic papillary renal cell, gastric, head and neck, breast, and ovarian cancers) [8,9,128]. However, there are few publications on the correlation between activating mutations and prognosis.

Kinase domain mutations such as Thr1191Ile (detected in hepatocellular carcinoma), Tyr1248Cys/Asp/His (sporadic and hereditary papillary renal cell carcinoma), Tyr1230Cys/Tyr1235Asp (head and neck squamous cell cancers), Asp1228Val (NSCLC), and Ala1108Ser (gastric cancer) prompt ligand-dependent or ligand-independent constitutive MET activation [9,11,129]. In the JM domain, missense mutations such as Tyr1010Ile, Arg988Cys and Pro1009Ser have been

reported in lung cancer, gastric, breast, ovarian and colorectal cancer [9]. Extracellular Sema domain mutations (i.e. Glu168Asp, Leu299Phe, Ser323Gly, and Asn375Ser) have not yet been carefully examined, but likely affect the structure of the HGF-binding region and MET receptor dimerization [12,130,131].

III- MET aberrant activation in tumor tissue as a predictive biomarker

III-A- MET activation biomarkers as a guide to stratify patients for MET-targeted therapies

The HGF/MET pathway has become an attractive therapeutic target because of its critical roles in regulating multiple processes involved in tumorigenesis and numerous pathways related to hallmarks of cancer. Several studies have addressed the important issue of using MET alterations in tumor tissue as predictive biomarkers for making clinical decisions on the administration of targeted therapies [60,132–134]. For example, in NSCLC patients, in addition to using predictive biomarkers such as EGFR mutations, PD-L1 expression and ALK/ROS1 rearrangements, which are already part of routine practice to guide therapeutic decision making, MET alterations are being considered as the next candidate to add to the list of predictive biomarkers [135].

HGF/MET targeted therapies can be divided into the following groups: (1) selective type I inhibitors that bind to the active (phosphorylated) conformation of the receptor; (2) nonselective MET kinase inhibitors, such as type II and III inhibitors, that bind to the non-active unphosphorylated conformation and allosteric site of the receptor, respectively; (3) anti-MET monoclonal antibodies; and (4) HGF-directed antibodies [136–138] (Figure 4).

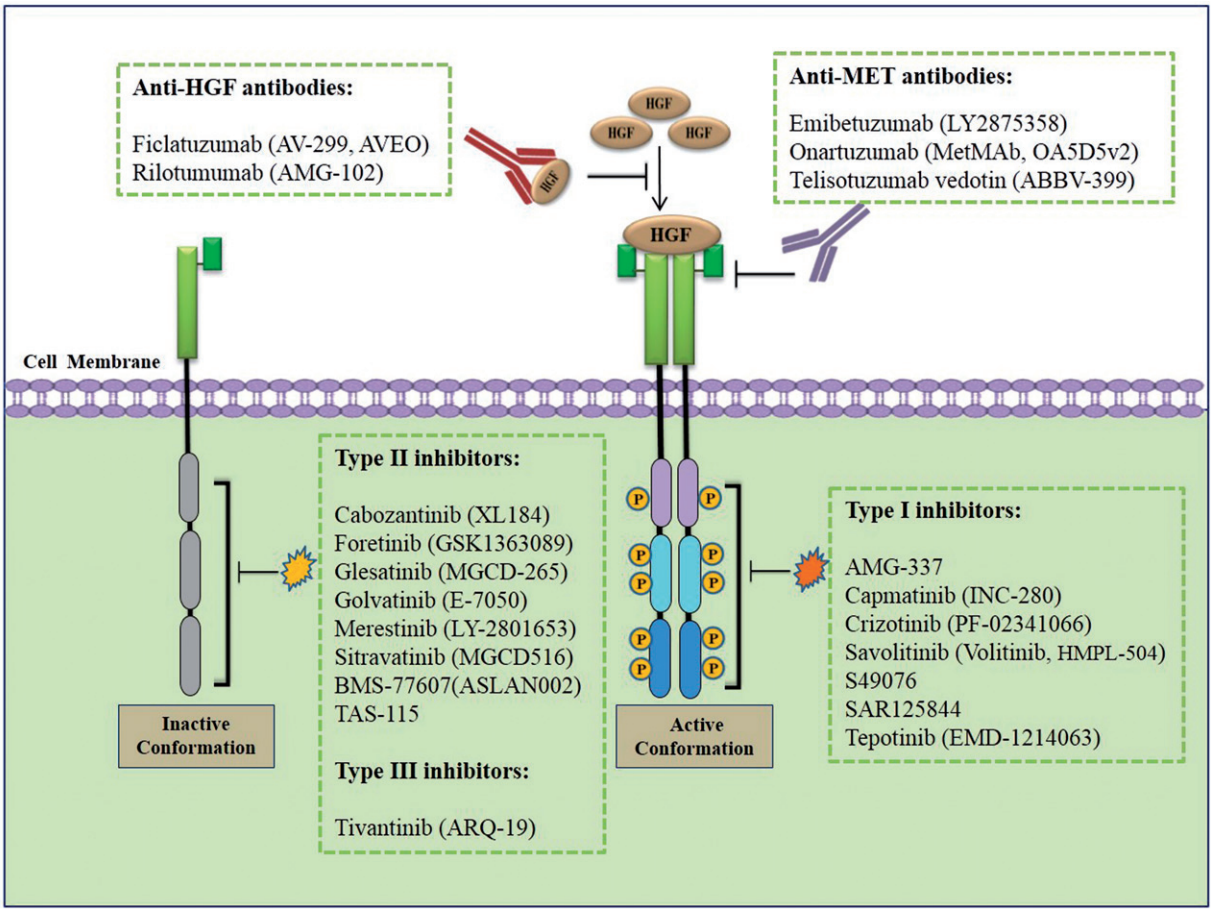

Figure 4. HGF/MET-targeted therapies for management of cancer. Several strategies to hamper the activity of the HGF/MET pathway are available to patients or are currently under clinical investigation. These include small molecule tyrosine kinase inhibitors (TKIs) and monoclonal antibodies (mAb) against MET or HGF. Small molecule inhibitors can be mainly divided into three classes, labeled as types I, II, and III. Both type I and II inhibitors bind to the ATP binding site. Type I inhibitors more efficiently bind to the active protein kinase conformation (Asp-Phe-Gly (DFG)-in), while Type II inhibitors generally bind to a DFG out inactive conformation. Type I inhibitors may also bind to the inactive conformation. Type III inhibitors are non-ATP competitive and bind to a site distinct from the ATP binding pocket. Antibodies could be directed against the MET receptor itself or its ligand HGF.

HGF/MET inhibitors have been assessed as monotherapy or in combination with other anticancer targeted therapies or cytotoxic agents [136,138]. The value of MET-related biomarkers such as *MET* overexpression, CNG and exon 14 splicing mutations to predict the response to MET targeted therapy has been documented in several clinical trials. Here, we provide an update on the most relevant data on the potential applications of MET as a predictive biomarker to identify patients most likely to benefit from therapy (Table 2).

An important biomarker-based phase II trial of savolitinib identified MET positive papillary renal cell carcinoma patients (patients with *MET* CNG, tumor HGF, *MET* overexpression or *MET* mutations). The authors observed that 40% of the cancers were MET driven, 46% were MET independent, and the status of the rest was unknown [134].

The efficacy of onartuzumab, an anti-MET antibody (Figure 4), has been investigated in patients with MET IHC-positive NSCLC in phase I, II and III clinical trials. These studies have reported different findings (Table 2 and Figure 5) [46,49,133,142,154]. A phase II trial compared erlotinib, an EGFR inhibitor, plus onartuzumab in one group and erlotinib plus placebo in the second group of NSCLC patients who were tested for MET expression by IHC. This study showed increased PFS (HR 0.53, $p = .04$), OS (HR 0.37, $p = .002$), and overall response rate (ORR 3.2% vs. 8.6%) in MET-positive patients in the erlotinib plus onartuzumab arm of the study compared to patients receiving erlotinib and placebo. Of note, the MET-negative patients treated with onartuzumab plus erlotinib experienced worse outcomes in terms of PFS (2.01 vs. 3.02) as well as OS (8.1 vs. 15.3) [142]. Similarly, in another study with patients with advanced NSCLC, the predictive role of several biomarkers including *MET/EGFR* amplification (FISH), MET overexpression (IHC), *MET/EGFR* mRNA expression, and high-plasma HGF levels were evaluated. The authors suggested that MET-IHC overexpression was the best predictor of patient benefit from onartuzumab [133]. Despite the promising phase II data, a larger, double-blind, phase III study of onartuzumab plus erlotinib (vs. erlotinib plus placebo) that included 499 patients did not show clinical benefit in MET positive (2+/3+) metastatic NSCLC patients [49]. This was consistent with a more recent report by Wakelee et al., which evaluated onartuzumab in combination with platinum/paclitaxel/bevacizumab or platinum/pemetrexed and failed to detect any benefit of combination therapy in either the intent-to-treat population or the patients with MET-positive tumors [46].

Unlike these disappointing results, MET small molecule inhibitors, including crizotinib [125,140] and tivantinib [58,60] have shown better antitumor activities in NSCLC patients with *MET* exon 14 deletions and MET overexpression, respectively.

In gastrointestinal tumors, several clinical studies have addressed the predictive role of MET dysregulation as an actionable target. These investigations have tested HGF/MET pathway inhibitors as single agents or in combination with other therapies, and have reported different outcomes [20,47,155]. For instance, when 71 patients with advanced hepatocellular carcinoma were enrolled in a placebo-controlled double-blind phase II study, the results showed that tivantinib was associated with a trend towards improved time to progression (2.7 vs. 1.7 months, $p = .03$), PFS (2.2 vs. 1.4 months, $p = .02$), and OS (7.2 vs. 3.8 months, $p = .01$) in the MET-high patients [44]. Moreover, a recent study evaluating the effect of rilotumumab administration, an anti-HGF antibody, on clinical outcome has shown a survival benefit in MET-positive patients, [43]. However, Sakai et al. described unfavorable clinical outcomes in a non-randomized phase II trial assessing emibetuzumab, an anti-MET antibody, in Asian patients with advanced gastric adenocarcinoma with clinical predictors of MET status based on IHC and/or FISH [147]. However, in this report, out of 65 patients, only 15 patients were diagnosed as MET-positive and could be enrolled in the study.

AMG 337, a selective MET inhibitor tested in a phase II clinical trial, has shown significant antitumor effect in gastric/gastro-esophageal junction/esophageal adenocarcinoma patients with *MET* amplification, but not in *MET*-amplified NSCLC [20]. AMG 337 also showed promising results in a phase I study in patients with *MET*-amplified solid tumors [19]. The above reports are summarized in Figure 5.

As mentioned above, dysregulation of the MET pathway can arise from different mechanisms (Figure 2). Our knowledge of the nature of these aberrations may have useful clinical implications. For example, in patients with *MET* amplification, receptor activation occurs mainly via ligand-independent mechanisms; therefore, small molecule inhibitors targeting the kinase domain could be more advantageous than anti-MET/HGF monoclonal antibodies [15].

Moreover, an important challenge is to identify the patients in which tumor growth and invasion are critically dependent on MET alterations. Although MET overexpression is used frequently as a predictive factor to detect MET activation, it may not necessarily lead to oncogenic addiction in cancer cells [14,156]. Therefore,

Table 2. Overview of clinical trials examining the value of MET aberrations in tumor tissue as a predictive biomarker of drug response to guide stratification of cancer patients for HGF/MET targeted therapies.

Tumor type (stage)	Phase of study and randomization	Number of patients	Aberration type/method of detection (frequency of alterations)	Drug/antibody	Predictive value	MET aberration proved as a predictive biomarker	References
NSCLC (advanced)	II/randomized	259	MET overexpression/IHC (>60%)	Cohort 1: bevacizumab/ paclitaxel/platinum. Cohort 2: pemetrexed/ platinum + onartuzumab vs. pemetrexed/ platinum + placebo	In MET-positive patients, no improvement in OS, PFS, or ORR was observed in onartuzumab arm	N	[46]
Solid tumors including NSCLC (advanced)	I/nonrandomized	72	MET overexpression/IHC (all patients (41) in the dose escalation group). MET amplification/FISH (29 patients in the dose expansion group)	SAR125844	PR was observed in 5/29 patients with MET-amplification, but not in patients with MET overexpression	Y (In MET-amplified). N (In MET-overexpressed)	[139]
NSCLC (advanced)	I/nonrandomized	18	Exon 14 skipping/(all patients)	Crizotinib	PR was observed in 10/15 response-evaluable patients	Y	[140]
NSCLC (locally advanced or metastatic)	II/nonrandomized	45	MET overexpression/IHC (48.9%). MET amplification/FISH (6.7%)	Erlotinib + tivantinib	Combination of erlotinib/tivantinib was associated with a survival benefit in MET-positive patients compared with MET-negative group: Median PFS 4.1 vs. 1.4 months and median OS 20.7 vs. 13.9 months	YYY	[58]
NSCLC (locally advanced or metastatic)	III/randomized	1048	MET overexpression/IHC (211 patients). MET amplification/ FISH (54 patients)	Erlotinib + tivantinib vs. erlotinib + placebo	In MET-positive subgroup, tivantinib-containing treatment was associated with a survival benefit: median OS 9.3 vs. 5.9 months (HR 0.70 [0.4–1.01], $p = .03$), median PFS 3.7 vs. 1.9 months (HR 0.72 [0.52–0.99], $p = .01$). In the MET-low subgroup, tivantinib did not improve survival	YY	[60]
Solid tumors including NSCLC (-[a])	II/nonrandomized	46	MET amplification/FISH (all patients)	Crizotinib	DCR was 40% (4 PR and 8 SD; 95% CI: 23–59) in MET-positive patients	Y	[141]
NSCLC (advanced)	II/randomized	137	MET overexpression/ IHC (58% of nonsquamous and 26% of squamous cell tumors). MET amplification/FISH (8%). MET mRNA expression/RT-qPCR. HGF mRNA expression/RT-qPCR. MET exon 14/ SNA	Erlotinib + onartuzumab vs. erlotinib + placebo	In the MET IHC+/FISH– of the ITT, onartuzumab containing treatment was associated with benefit in OS (HR 0.37; $p = .01$) and PFS (HR 0.24; $p = .003$). There was no significant association between other MET aberrations and benefit of response	Y (in MET IHC+). N (other aberrations)	[133]
NSCLC (stage IIIb or IV)	III/randomized	499	MET overexpression/IHC (all patients)	Erlotinib + onartuzumab vs. erlotinib + placebo	No improvement was observed in onartuzumab arm in OS, PFS, or ORR	N	[49]
NSCLC (recurrent)	II/randomized	137	MET overexpression/IHC (52%)			YY	[142]

(*continued*)

Table 2. Continued.

Tumor type (stage)	Phase of study and randomization	Number of patients	Aberration type/method of detection (frequency of alterations)	Drug/antibody	Predictive value	MET aberration proved as a predictive biomarker	References
				Erlotinib + onartuzumab vs. erlotinib + placebo	In the MET-positive subgroup, significant improvement was observed in onartuzumab arm: Median OS 12.6 vs. 3.8 months, (HR 0.37; $p = .002$), median PFS 2.9 vs. 1.5 months (HR 0.53; $p = .04$), and ORR (not significantly different 3.2% vs. 8.6%). In MET-negative subgroup, onartuzumab versus placebo was associated with worse survival		
BC (-)	II/nonrandomized	45	MET overexpression/IHC (7%)	Foretinib	There was no association between MET positivity and benefit of response. PR was observed in MET-negative patients	N	[143]
CRC (advanced)	II/nonrandomized	41	MET overexpression/IHC (all patients). MET amplification/ SISH (In 2 of 13 evaluated patients)	Cetuximab + tivantinib	Two of 3 responding patients had MET amplification	Y (in MET amplification)	[144]
CRC (stage IV)	II/randomized	194	MET overexpression/IHC (41%)	FOLFOX/bevacizumab + onartuzumab vs. FOLFOX/ bevacizumab + placebo	In MET-positive patients, no improvement was observed in onartuzumab arm in OS, PFS, or ORR. In MET-negative patients, onartuzumab versus placebo improve PFS (11.7 vs. 10.2 months; $p = .03$)	N	[145]
Solid tumors (GEJ/GC/EC/ CRC/NSCLC, etc.) (advanced)	I/nonrandomized	111	MET overexpression/IHC (-). MET amplification/FISH & NGS (24%)	AMG 337	ORR was 9.9% (1 CR and 10 PR; 95% CI, 5.1%–17.0%) in all patients and 29.6% (1 CR and 7 PR; 95% CI, 13.8%–50.2%) in patients with MET amplified tumors. PR was observed in one patient with mesothelioma with MET overexpression	Y	[19]
Solid tumor (GC/GEJC/EC/ NSCLC) (97% metastatic disease)	II/nonrandomized	60	MET amplification/FISH (all patients)	AMG 337	ORR was 18% in MET-amplified cohort with GC/GEJC/EC. There was no association between MET amplification and a better response in NSCLC patients	Y (in GC/GEJC /EC). N (in NSCLC)	[20]
GEJ/GC (stage III [14%] and IV [77%])	III/randomized	609	MET overexpression/IHC (all patients). MET amplification/ FISH (12%)	ECX + rilotumumab vs. ECX + placebo	No improvement was observed in rilotumumab arm in OS and PFS in MET positive patients	N	[47]
GEA (-)	III/randomized	562	MET overexpression/IHC (214 patients)	FOLFOX + onartuzumab vs. FOLFOX + placebo	In MET-positive patients, onartuzumab versus placebo did not significantly improve OS, PFS, or ORR. Median OS: 11.0 vs. 9.7 months (HR 0.64 [0.40–1.03], $p = .06$), PFS: 6.9 vs. 5.7 months (HR 0.79 [0.54–1.15], $p = .22$). CR was observed in three patients in onartuzumab arm in MET-positive patients	N	[146]

(*continued*)

Table 2. Continued.

Tumor type (stage)	Phase of study and randomization	Number of patients	Aberration type/method of detection (frequency of alterations)	Drug/antibody	Predictive value	MET aberration proved as a predictive biomarker	References
GC (advanced)	II/nonrandomized	15	MET overexpression/IHC (all patients). MET amplification/ FISH (three of the nine tested patients)	Emibetuzumab	Emibetuzumab did not significantly improve PFS in MET-positive patients compared with MET-low group based on IHC and/or FISH using different cut off points	N	[147]
GEJ/GC (advanced)	II/randomized	123	MET overexpression/ IHC (30% in MET IHC 2+, 3+, 50% staining cutoff)	FOLFOX + onartuzumab vs. FOLFOX + placebo	Onartuzumab arm versus placebo did not improve OS or PFS in MET-positive patients compared with the MET-negative population using different cut points	N	[148]
GEJ/GC/EA(-)	I/nonrandomized	51	MET amplification/- (10 patients)	AMG 337	CR (1/10) and PR (4/10) was observed in a subset of patients with MET amplification	Y	[149]
GC (85% metastatic)	II/randomized	121	MET overexpression/IHC (41 patients)	ECX + rilotumumab vs. ECX + placebo	In the MET-positive subgroup, in rilotumumab arm an association was observed with an exposure-dependent survival benefit: Median PFS: (80% CI) 7.0 vs. 4.4 months and median OS: (80% CI) 13.4 vs. 5.7 months -In the MET-negative subgroup, no treatment benefit was seen with rilotumumab versus placebo	YY	[43]
HCC (advanced)	II/randomized	71	MET overexpression/IHC (48%)	Tivantinib	In the MET-positive subgroup, tivantinib versus placebo was associated with a survival benefit: Median TTP 2.7 vs. .4.0 months (HR 0·43 [0.19–0.97]; $p = .03$), median PFS 2.2 vs. 1.4 months (HR 0.45 [0.21–0·95]; $p = .02$), and median OS 7.2 vs. 3.8 months (HR 0.38 [0.18–0.81], $p = .01$). In the MET-negative subgroup, no treatment benefit was seen with tivantinib versus placebo	YY	[44]
Cholangiocarcinoma (advanced)	II/nonrandomized	19	MET overexpression/IHC (in 4 of 10 evaluated patients)	Cabozantinib	In MET-positive patients, cabozantinib did not improve OS and PFS	N	[150]
PRCC (advanced)	II/randomized	109	MET amplification/FISH & NGS (72% of type 1 PRCCs and 46% of type 2 PRCCs). MET kinase domain mutations/NGS (2% of type 1 and 12% type 2)	Savolitinib	In MET-positive patients, savolitinib was associated with a response benefit compared with MET-negative patients: ORR: 18% (PR) vs. 0% ($p = .002$); PFS: 6.2 vs. 1.4 months (HR 0.33 [0.20–0.52], $p < .001$)	YYY	[134]

(*continued*)

Table 2. Continued.

Tumor type (stage)	Phase of study and randomization	Number of patients	Aberration type/method of detection (frequency of alterations)	Drug/antibody	Predictive value	MET aberration proved as a predictive biomarker	References
PRCC (stage I (17.6%), II (4.1%), III (18.9%), IV (56.8%))	II/nonrandomized	74	Germline and somatic MET mutation (10 patients). MET [7q31] amplification (two patients). Gain of chromosome 7 (18 patients)[b]	Foretinib	PR was observed in 50% (5/10) of patient with MET germline mutation compared with 9% (5/57) of patient without MET germline mutations. PR was observed in 1/5 and 1/18 of patients with somatic MET mutation and gain of chromosome 7, respectively	YYY	[151]
PC(-)	II/randomized	142	MET overexpression/IHC (92% of 73 patients)	Mitoxantrone/ prednisone + rilotumumab vs. mitoxantrone/ prednisone + placebo	No improvement was observed in rilotumumab arm in OS and PFS in MET-positive patients. In MET-negative subgroup, rilotumumab versus placebo was associated with worse survival	N	[152]
CCS (advanced)	II/nonrandomized	34	MET overexpression/(31 patients)	Crizotinib	In MET-positive patients ORR: 3.8% (PR: 1/26 [0.1–19.6]); DCR: 69.2% [48.2–85.7]). None of the MET-negative patients showed response to therapy	YY	[153]

CCS: clear cell sarcoma; CI: confidence interval; CR: complete response; CRC: colorectal cancer; DCR: disease control rate; EA: esophageal adenocarcinoma; EC: esophageal cancer; ECX: epirubicin, cisplatin, capecitabine; FOLFOX: fluorouracil, leucovorin, and oxaliplatin; GEJC: gastroesophageal junction carcinoma; GEA: gastroesophageal adenocarcinoma; GC: gastric cancer, HCC: hepatocellular carcinoma; HR: hazard ratio; IHC: immunohistochemistry; ITT: intent to treat; ORR: objective response rate; OS: overall survival, PC: prostate cancer; PFS: progression free survival; PR: partial response; PRCC: papillary renal cell carcinoma; SD: stable disease; SNA: surveyor nuclease assay; TTP: time to progression

YYY, biomarker value was proved by directly comparing MET-positive and MET-negative patients. YY, biomarker value was independently shown in MET-positive patients and MET-negative patients. Y, biomarker value was shown in MET-positive patient. N, no biomarker value was shown for MET aberration. NB, clinical trials are mainly analyzed from the viewpoint of biomarker value of MET aberrations. Efficacy of MET targeted therapies in general has not been addressed. 95% CI are shown in brackets.

[a]Not reported.

[b]Duplication of chromosome 7 either in its entirety or involving the region where MET is located.

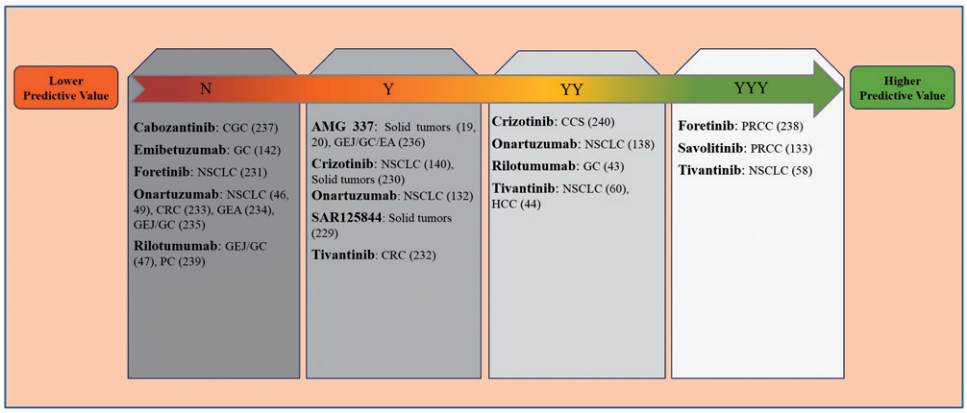

Figure 5. Potential role of tumor tissue MET aberrations to predict the response to HGF/MET targeted therapies in different cancers. The prediction of the effectiveness of MET targeted therapies based on MET biomarkers in tumor tissue are shown in a summarizing scheme. Higher predictive value indicates that MET-positive patients have benefited from treatment, while lower predictive value shows that the drug has not been effective in MET-high patients. YYY: Biomarker value was proved by directly comparing MET-positive and MET-negative patients. YY: Biomarker value was independently shown in MET-positive patients and MET-negative patients. Y: Biomarker value was shown in MET-positive patients. N: No biomarker value was shown for MET aberration. The details of the studies are reported in Table 2. Reference numbers are shown in brackets.

it has been argued that the use of IHC may have limitations in the selection of patients for anti-MET therapy.

Finally, methodologies that are applied to evaluate biomarkers need to be optimized. Scoring methods for the assessment of MET aberrations have not been validated extensively. This critical pitfall is demonstrated by the high variability in the percentage of patients who are designated as MET-high or MET-low. For example, high MET expression detected by IHC in gastric cancer ranged from 20–80% [73]. Similarly, *MET* amplification detected by FISH in NSCLC varied from 1–40% [64].

III-B- MET activation biomarkers as a guide to stratify patients with resistance to EGFR-TKIs

Functional interactions between MET and other cell surface receptors have been widely characterized [32]. MET receptors not only form homodimers but also contribute to hetero interactions with other RTKs that result in fully activated downstream signaling, just as is seen following homodimerization [32,157]. The MET signaling pathway can be activated by a variety of MET interacting molecules, for example, membrane proteins or receptors such as plexins, integrins and other RTKs such as vascular endothelial growth factor receptor (VEGFR), insulin-like growth factor 1 receptor (IGF1R), EGFR, RET and AXL (Figure 1) [157–159]. These processes may play an important role in cancer progression and specially in resistance to targeted therapies.

Among RTKs, the most studied interaction is between MET and EGFR. This communication is believed to induce MET activation in the absence of HGF after stimulation of cells with the EGFR ligands, EGF or transforming growth factor-α (TGF-α) [160].

These biological processes have important clinical implications, because EGFR-TKIs provide an important asset for management of certain subsets of NSCLC patients [161]. However, despite impressive initial responses, acquired resistance eventually occurred in a considerable number of patients. Different molecular events underlie this drug resistance, the main mechanism being the occurrence of secondary *EGFR* point mutations such as Tre790Met [162–165]. However, activation of the MET pathway has also been consistently observed as another main driver of resistance, which leads to increased downstream oncogenic signaling in the presence of continuous treatment with anti-EGFR agents [166–168].

A study that further supports these observations demonstrated that overexpression of TGF-α in colorectal cancer cells contributed to EGFR inhibition resistance by increasing EGFR/MET interaction and MET phosphorylation [169]. However, resistance could be overcome by combined inhibition of EGFR and MET, as indicated in human lung, pancreatic and breast tumor xenografts [7,170].

Some studies have addressed the important issue of the influence of the MET pathway on resistance to EGFR targeted therapies using MET aberrations in tumor tissue as predictive biomarkers [142]. MET inhibitors may be effective in overcoming this resistance and are currently being studied in several randomized clinical trials. As reported by van Veggel et al., *MET* amplification could mediate EGFR-TKI resistance in patients with *EGFR* mutation positive NSCLC. It was indeed

Table 3. Overview of studies on the value of circulating soluble MET (sMET) levels as diagnostic or prognostic biomarkers in patients with different types of cancer.

Tumor type	No. samples tested	Sample type/method of detection	Diagnostic value	Prognostic value	Notes	Reference
NSCLC	198 Patients, 54 healthy control	Plasma/ELISA	-[a]	Worse survival was observed in high sMET patients compared to low sMET subjects ($p < .001$)	A correlation was found between sMET and tissue MET expression in NSCLC patients ($p < .001$)	[57]
SCLC and NSCLC	146 Patients (14 SCLC and 132 NSCLC patients), 40 healthy control	Plasma/ELISA		sMet did not correlate with tumor size in MET-negative and MET-positive patients	sMET was correlated with tissue MET levels ($p < .05$). At cut off value, s-Met was reliable marker to predict MET overexpression in tumor tissue (89.2% sensitivity and 94.6% specificity)	[175]
Gastric cancer	290 Patients	Plasma/ELISA	Median plasma concentrations of sMET was lower in patients compared to control (1.390 vs. 1.610 ng/mL, $p < .0001$)	–	Different from most other reports, sMET levels were lower in cancer patients	[176]
Hepatocellular carcinoma	102 Patients	Plasma/ELISA	–	Higher sMET was associated with shorter OS ($p = .03$)	No association between sMET and tumor c-MET level	[55]
Prostate cancer	345 Patients, 80 healthy control	Plasma/ electrochemiluminescent immunoassay	Median sMET level in patients was significantly higher than healthy subjects ($p < .0001$)	There was no correlation between sMET level and invasive disease, metastasis and tumor grade	At cut off value ROC analysis of malignant vs. normal groups was shown 79% sensitivity and 94% specificity values (AUC = 0.8309, $p < .0001$)	[177]
Prostate cancer	156 Patients, 20 healthy control	Plasma/ electrochemiluminescent immunoassay	sMET was higher in the metastatic group compared with control ($p < .0001$)	sMET levels was elevated in patients with metastatic cancer compared to localized cancer ($p < .0001$)	–	[62]
Bladder cancer	183 Patients, 83 healthy control	Urine/ Electrochemiluminescent immunoassay	Urinary sMET levels in patients were higher than control ($p = .0004$ to $<.0001$). Median urinary sMET in patients with muscle-invasive disease was significantly higher than those with no muscle invasion ($p < .0001$)	–	Urinary sMET levels distinguished muscle-invasive patients from those without muscle invasion ($p < .0001$, AUC 0.8002, sensitivity 76%, specificity 77%)	[178]
Uveal melanoma	57 Patients, 37 healthy control	Serum/ELISA	Higher sMET was found in patients with metastatic disease compared to patients without metastasis ($p < .001$) or healthy donors ($p < .001$)	Median survival time was lower in high-sMET compared to low-sMET patients ($p = .07$). sMET levels in surviving patients with metastatic individuals was lower than deceased patients ($p = .04$)	AUCROC in patients with nonmetastatic disease vs. metastatic subjects was 0.82 ($p < .001$)	[179]
Multiple myeloma	49 Patients, 26 healthy control	Serum/ELISA	sMET levels were not different in patients and healthy individuals	The difference between the median OS in low sMET (21 months) and high sMET patients (55 months) was not statistically significant	–	[180]

AUCROC: area under the receiver operating characteristic curve; ELISA: enzyme-linked immunosorbent assay; NSCLC; non-small cell lung cancer; OS: overall survival; SCLC: small cell lung cancer
Diagnostic value: comparison of HGF levels between cancer patients and healthy individuals, or between different stages of the disease; prognostic value: association of HGF levels with prognosis in cancer patients.
[a]Not reported.

shown that 50% of patients receiving crizotinib as monotherapy or in combination with an EGFR-TKI experienced partial response; however, responses were typically not lasting, and the median PFS was only 3.5 months (95% CI 1.4–5.2) [161]. In a multicenter retrospective study, the clinical response to MET inhibitors, mostly crizotinib, was investigated in patients with metastatic *EGFR*-mutated NSCLC with *MET* amplification or overexpression as evaluated on a post-progression re-biopsy. Among patients receiving a MET inhibitor as a single agent or in combination with anti-EGFR agents, an objective response was reported in only 2 out of 19 evaluable patients [171]. Another phase II trial evaluated whether acquired resistance to erlotinib in patients who harbored MET overexpression could be overcome by emibetuzumab, a monoclonal anti-MET antibody. The ORR was increased in both the monotherapy and combination arms in MET-high patients ($\geq$60% of cells $\geq$2+ by IHC) compared with MET positive cases ($\geq$10% of cells $\geq$2+) [172]. Moreover, a combination of capmatinib (INC280) and gefitinib was assessed in a phase II study in *EGFR*-mutated NSCLC patients with acquired resistance to EGFR-TKI. Of the 65 evaluable patients with high MET expression, the ORR was 18% and the disease control rate (DCR) was 80%. A higher response rate was observed in *MET*-amplified patients (7 out of 23 patients with CNG $\geq$ 6 had partial responses (OS 30%) [173]. Moreover, a few case reports have documented complete response to crizotinib treatment in patients with MET-overexpressing NSCLC after developing EGFR-TKI resistance [174].

IV- Circulating MET levels as diagnostic and prognostic biomarkers

Several studies have investigated the potential utility of the soluble truncated ectodomain of MET protein (sMET) as a biomarker in different types of cancer and the correlation between sMET and tissue MET protein expression (Table 3). Most of these studies have reported that circulating MET correlates with tumor tissue expression levels [57,175,177,179,180], although this idea was rejected by one report [55]. In a study of 198 patients with NSCLC, Gao et al. observed that the plasma sMET levels were significantly correlated with tissue MET protein expression levels ($p < .001$). The OS was 9.5 vs. 22.2 months for patients with high sMet levels (>766 ng/mL) compared with patients having low levels of sMet (<766 ng/mL, respectively, $p < .001$). The average plasma sMET concentration was significantly higher in tissue MET-positive patients compared to subjects with MET-negative tumors or healthy individuals [57]. The results of multivariate analysis in another study suggested that the sMet concentration was the strongest prognostic factor for PFS after EGFR-TKI therapy (HR 3.583, 95% CI 1.379–9.312) [181].

A study by Barisione et al. evaluated the prognostic value of the serum sMET level in patients with metastatic uveal melanoma; the survival analysis revealed that cases exhibiting lower MET expression had a higher median survival time compared with patients expressing high levels [179]. In addition, this study investigated the diagnostic role of sMet by discriminating metastatic uveal melanoma from nonmetastatic uveal melanoma and healthy subjects using receiver operating characteristic (ROC) curves with area under the curve (AUC) of 0.82 (95% CI 0.68–0.95, $p < .001$) and 0.83 (95% CI 0.71–0.95, $p < .001$), respectively [179].

Kaye et al. [177] investigated the association of plasma sMET with prostate cancer. Remarkably, they identified higher levels of sMET in plasma samples of groups of patients with benign ($n = 109$) and malignant ($n = 236$) diseases when compared to 80 healthy controls ($p < .0001$). sMET could also differentiate between malignant cases and healthy individuals with an AUC value of 0.8309 (sensitivity 79%, specificity 94%, $p < .0001$). However, the median sMET level was found not to correlate with invasive disease, metastasis, pathological grade and tumor stage [177]. In contrast to these results, a study of 156 patients with localized and metastatic prostate cancer reported that soluble urinary sMET had a significant correlation with tumor metastasis. Urinary sMET showed an AUC value of 0.90 (95% CI 0.84–0.95) in discriminating localized from metastatic disease [62]. In addition, another study reported that urinary MET levels could distinguish between patients with invasive vs. not invasive bladder cancer (AUC 0.7008, $p < .0001$) [178].

In contrast to the above studies, in a case-control set of 290 subjects, the sMET level was significantly decreased among gastric cancer patients compared to controls ($p < .0001$) [176]. Intriguingly, this longitudinal cohort study showed that soluble MET levels appeared to decrease before the onset of gastric cancer [176].

Independent studies have suggested that CagA, the *H. pylori* effector protein, stimulates cancer-associated signal transduction by forming a complex with MET [182–184]. Although there was no significant genotype–phenotype interaction between soluble MET protein and single nucleotide polymorphism (SNPs) of the CagA-related genes, after adding the genetic counts of these SNPs, the diagnostic value of MET protein to distinguish gastric cancer patients from normal individuals improved significantly [176].

V- Circulating HGF levels as diagnostic, prognostic and predictive biomarkers

HGF gene expression has been shown to be upregulated by cytokines and growth factors including TNF-α, IL-1, EGF, fibroblast growth factor, platelet derived growth factor and prostaglandins as well as by interactions with other RTKs such as EGFR (Figure 2) [185–187]. In addition, HGF is frequently co-expressed with MET in cancer cells and generates an autocrine receptor activation loop [11]. In the human *HGF* gene promoter, a repeat of 30 deoxy adenosines, called the deoxyadenosine tract element (DATE), acts as a transcriptional repressor. Truncation mutations within DATE result in constitutive activation of the *HGF* promoter and subsequent aberrant *HGF* expression [186]. In breast cancer patients, 51% of African Americans and 15% of individuals of mixed European ethnic background harbored a mutant DATE variant (25 As or fewer) in their tumor cells [186].

The prognostic value of circulating HGF levels has been reported by several investigators (Table 4 and Figure 3). Most of these studies observed a negative correlation between HGF levels and survival of patients with different types of cancer; however, this association was not confirmed in all studies [196].

In addition to serving as a prognostic biomarker, HGF has the potential to serve as a diagnostic biomarker by distinguishing between cancer patients and healthy individuals, as well as to function as a predictive factor of response to therapy (Table 4). The role of HGF as a diagnostic, prognostic and predictive biomarker in different types of cancer is discussed below.

V-A- NSCLC

The assessment of sensitivity and specificity of plasma HGF levels in the study by Fang et al. suggested that HGF was not sensitive enough to detect early stage NSCLC (stage I–II) reliably; this finding may be due to the small sample size [206]. Similar observations regarding the diagnostic value of HGF were reported in a later study that included a larger number of patients [207]. The sensitivity of plasma HGF level was significantly higher in lung squamous cell cancer patients (stage III–IV) [206].

The relationship between increased HGF and clinical outcome and drug response has been explored in several studies in lung cancer patients [189,190,208,209]. In a recent study performed in 81 patients receiving anticancer treatment (53 and 48 patients received first-line and second-line therapy, respectively), high serum HGF concentration after first-line chemotherapy predicted a shorter PFS in second-line treatment compared with low serum HGF [188].

V-B- Breast cancer

The possible prognostic value of increased serum HGF levels in breast cancer was suggested for the first time by Toi et al. [210] in a Japanese cohort of patients. Serum levels of HGF were analyzed by enzyme-linked immunosorbent assay in 200 primary breast cancer patients. Increased serum HGF levels were associated with a statistically significant worse prognosis in terms of DFS ($p = .0001$). Other investigators also demonstrated that higher serum levels of soluble HGF were associated with more lymph node involvement, higher frequency of poorly differentiated tumors, more advanced cancer stages and distant metastases [211–214]. In a ROC analysis, the AUC for HGF was 0.695, which indicated that HGF could diagnose the estrogen receptor positive from the negative tumors in primary breast cancer patients [211].

However, a study by Kim et al. reported conflicting data regarding the prognostic value of HGF; when patients were divided into four groups based on their HGF levels, only those with the highest HGF levels showed a trend towards a longer DFS ($p = .008$) [191].

V-C- Colorectal cancer

A recent meta-analysis by Huang et al. combined results from nine studies that investigated the correlation between HGF and the prognosis and survival of colorectal cancer patients. The results indicated that overexpression of HGF was associated with a worse prognosis, considering both OS (HR 2.50, 95% CI 2.12–2.96) and DFS (HR 1.99, 95% CI 1.59–2.50) [53]. Toiyama et al. observed that in patients undergoing colorectal carcinoma resection, elevated serum HGF levels correlated with tumor size, lymph node metastasis, and distant metastasis [215].

In addition, the relationship between serum HGF and therapeutic responses was studied in colorectal cancer patients receiving bevacizumab and other therapies. High levels of HGF were associated with shorter PFS and OS, regardless of the type of treatment. Also, patients with lower pretreatment plasma levels of HGF showed remarkably larger benefit from bevacizumab treatment in terms of PFS and OS compared with those with high HGF concentration [192].

V-D- Esophageal cancer

In esophageal squamous cell carcinoma, Ren et al. were the first to demonstrate that serum levels of HGF were

Table 4. Overview of studies on the value of circulating HGF levels as diagnostic and prognostic biomarkers in patients with different types of cancer.

Tumor type	No. samples tested	Sample type/method of detection	Diagnostic value	Prognostic value	Biomarker value	Reference
NSCLC	81 Patients, 30 30 healthy control	Serum/ELISA	HGF was significantly increased in patients compared to healthy controls ($p < .01$)	PFS in HGF-high patients was significantly shorter compared with HGF-low patients in both first line ($p = .047$) and second-line therapy ($p = .01$)	Diagnosis: Y. Prognosis: Y	[188]
NSCLC	46 patients, 15 healthy control	Serum/ ELISA	HGF was significantly increased in patients compared to healthy controls ($p = .0004$)	Increased HGF serum levels was correlated with a shorter OS ($p = .03$)	Diagnosis: Y. Prognosis: Y	[189]
NSCLC	225 Patients	Plasma/ELISA	HGF was significantly increased in advanced stage and among smokers ($p < .05$)	HGF-high patients had significantly shorter survival ($p < .001$)	Diagnosis: Y. Prognosis: Y	[190]
Breast cancer	121 Patients	Serum/ELISA	–	Higher serum HGF level was associated with regional lymph node metastasis ($p = .017$). Higher serum HGF level was associated with longer RFS (106 vs. 85 months, $p = .008$)	Diagnosis: -. Prognosis: Y/P	[191]
Colorectal cancer	9 Studies including 777 patients	HGF levels in serum (5), plasma (2) and tissue (2)/ELISA, IHC and PCR	–	Overexpression of HGF was associated with shorter OS (HR =2.50 [2.12–2.96]) and DFS(HR 1.99 [1.59–2.50])	Diagnosis: -. Prognosis: Y	[53]
Colorectal cancer	155 Patients	Serum/ELISA	–	Longer OS ($p = .010$) and PFS ($p = .020$) observed in patients treated with bevacizumab with low HGF compared to those with high HGF	Diagnosis: -. Prognosis: Y	[192]
Gastric cancer	46 Patients	Serum/ELISA	–	High HGF was significantly associated with shorter OS (HR 3.857 [1.309–11.361], $p = .008$). There was significantly higher ORR in cases with low HGF compared to those with high HGF ($p = .014$)	Diagnosis: -. Prognosis: Y	[193]
Gastric cancer	110 Patients, 39 healthy control	Serum/ELISA	HGF was significantly increased in patients compared to controls ($p < .0001$)	Preoperative serum HGF levels were associated with disease progression ($p < .001$). No correlation between HGF and tumor diameter, invasion depth or lymphatic invasion.	Diagnosis: Y. Prognosis: Y/N	[194]
Gastric cancer	147 Patients	Serum/ELISA	–	High HGF level was significantly correlated with shorter OS ($p = .005$). Patients with advanced tumors staging had higher HGF levels ($p = .012$)	Diagnosis: -. Prognosis: Y	[195]
Esophageal cancer	78 Patients (esophageal squamous cell carcinoma ($n = 34$) and adenocarcinoma of the esophagogastric junction (AEG) ($n = 44$)	Serum/multiplex immunoassay	–	There was no association between serum HGF and OS	Diagnosis: -. Prognosis: N	[196]
Hepatocellular carcinoma	83 Patients, 63 healthy control	Serum/ELISA	HGF showed high diagnostic sensitivity (90.62%) but very low diagnostic specificity (25.81%)	–	Diagnosis: Y. Prognosis: -	[197]
Hepatocellular carcinoma	86 Patients	Serum/ELISA	–	Patients with higher baseline HGF had a significantly shorter survival in comparison with patients with a lower HGF ($p = .02$)	Diagnosis: -. Prognosis: Y	[55]

(*continued*)

Table 4. Continued.

Tumor type	No. samples tested	Sample type/method of detection	Diagnostic value	Prognostic value	Biomarker value	Reference
Hepatocellular carcinoma	54 Patients	Serum/ELISA	Serum HGF was significantly increased in patients compared to control ($p < .001$)	No correlation was found between serum HGF levels and clinicopathological parameters and survival	Diagnosis: Y. Prognosis: N	[198]
Cervical cancer	426 Cases (292 CSCC patients, 43 CIN patients and 91 healthy controls)	Serum/luminex xMAP technology	HGF significantly elevated in cervical squamous cell carcinoma (CSCC) patients compared with the cervical intraepithelial neoplasia (CIN) patients and the healthy subjects ($p < .0001$)	HGF-high patients had significantly inferior OS and PFS compared to low HGF patients (OS, $p < .0001$; PFS, $p < .0001$). HGF level was associated with FIGO stage ($p = .02$), pathological grading ($p < .0001$), tumor size ($p < .0001$), pelvic lymph node metastasis ($p < .0001$), and HPV infection ($p = .039$)	Diagnosis: Y. Prognosis: Y	[199]
Glioblastoma	48 Patients	Serum/ELISA	Patients with poorly differentiated tumors had higher median serum HGF compared to patients with moderately and highly differentiated tumors ($p = .02$)	There was a correlation between low HGF levels and longer PFS in glioblastoma who received radiotherapy ($p = .041$)	Diagnosis: Y. Prognosis: Y	[200]
Ovarian cancer	172 Patients	Serum/ELISA	HGF was significantly higher in cancer patients compared to healthy control ($p < .03$)	–	Diagnosis: Y. Prognosis: -	[201]
Prostate cancer	286 Patients	Serum/ELISA	–	Higher pretreatment HGF was associated with shorter PFS in metastatic androgen dependent prostate cancer treated with androgen-deprivation therapy (HR 1.63 [1.06–2.51], $p = .03$)	Diagnosis: -. Prognosis: Y	[202]
Melanoma	101 Patients	Serum/ELISA	–	Median HGF level was higher in stage IV compared to stage I/II ($p = .032$) A significant association of high HGF concentration was found with shorter PFS ($p = .005$) and OS ($p = .03$)	Diagnosis: -. Prognosis: Y	[203]
Melanoma	29 Patients, 44 healthy control	Serum/ELISA	HGF in patients with stage III ($p = .0174$) and IV ($p = .00184$) was significantly higher compared to healthy controls	HGF-low patients showed longer PFS ($p = .0068$) and OS ($p = .039$) compared to HGF-high patients	Diagnosis: Y. Prognosis: Y	[204]
Multiple myeloma	124 Patients, 54 health control	Serum/ELISA	HGF was significantly increased in patients compared to healthy controls ($p < .0001$)	Low levels of HGF was associated with longer PFS ($p < .05$)	Diagnosis: Y. Prognosis: Y	[205]

DFS: disease free survival; HR hazard ratio; IHC: immunohistochemistry; OS: overall survival, PFS: progression-free survival
Diagnostic value: comparison of HGF levels between cancer patients and healthy individuals, or between different stages of the disease; prognostic value: association of HGF levels with prognosis in cancer patients. Biomarker value: summarizes the findings of the report; Y, confirmed biomarker value; N, no biomarker value was found; Y/P, positive correlation was found between HGF levels and prognosis; Y/N, equivocal findings; biomarker value not evaluated in the study. 95% CI is shown in brackets.

elevated in patients compared to the control group (600 vs. 214 pg/mL, respectively, $p < .001$). Higher serum levels of HGF also showed significant correlation with the stage of disease and survival [216].

Similarly, in another study, increased serum levels of HGF were found to be correlated with tumor stage ($p = .002$) and metastasis ($p < .001$) [217]. Conversely, conflicting results emerged from a study concerning the prognostic value of HGF in esophageal squamous cell carcinoma patients. No association between circulating HGF and survival or response to therapy was found in patient receiving neoadjuvant chemo(radio)therapy. These conflicting results may be explained by the long-term effect of treatment, because all samples were taken after neoadjuvant therapy [196].

V-E- Gastric cancer

Studies in gastric cancer patients have widely reported elevated serum HGF levels and their relationship with clinico-pathological features [194,218–220].

In addition, the role of serum HGF in predicting the response to treatment was evaluated by Takahashi et al. in gastric cancer patients [193]. Among 46 patients treated with trastuzumab, those with high levels of serum HGF had shorter OS (HR 3.857, 95% CI 1.309–11.361) and had a higher risk of progression compared to patients with low levels. Evidence was also provided that the serum HGF level was significantly inferior in responders compared with non-responders ($p = .014$) [193].

V-F- Head and neck cancer

Le et al. evaluated the prognostic and predictive roles of plasma HGF in 498 patients with stage III–IV head and neck cancer who received radiotherapy with cisplatin or cisplatin plus tirapazamine, a hypoxic cell cytotoxin [221]. Since *HGF* gene expression was upregulated by hypoxic conditions [221], they hypothesized that the concentration of HGF may detect a population that benefited from tirapazamine. High pretreatment HGF levels were a prognostic factor for shorter OS in patients receiving cisplatin, but not in those receiving tirapazamine/cisplatin. They also suggested that the combination of tirapazamine and cisplatin may be beneficial in patients with high HGF, but not in those with low HGF; however, these differences did not reach statistical significance [221].

It should be noted that, although circulating HGF levels could be a good biomarker to predict the response to HGF/MET targeted therapy, the situation differs with other targeted therapies or chemotherapy.

V-G- Hepatocellular carcinoma

Similar findings have demonstrated the diagnostic value of serum HGF in hepatocellular cancer [198,222,223]. However, several studies have reported conflicting results concerning the prognostic relevance of increased serum HGF levels. Rimassa et al. [55] reported that patients with higher baseline HGF had a significantly shorter survival regardless of the therapy. In another study on HCC patients, no prognostic value was reported [198].

In a cohort study, the effects of plasma HGF levels on survival and liver function were assessed in patients after radiotherapy and surgery for unresectable and resectable liver cancers, respectively. Increased plasma HGF levels significantly correlated with the CTP and MELD scores, indicators of the severity of liver disease. The authors suggested that pretreatment plasma HGF may be a useful biomarker to predict the susceptibility to radiation-induced liver dysfunction and patient survival after radiotherapy and liver transplantation [224].

V-H- Pancreatic cancer

The diagnostic value of HGF in pancreatic cancer was reported in a study by Barakat et al. who evaluated patients with periampullary cancer, benign pancreatic tumor, and chronic pancreatitis [225]. Plasma HGF levels were increased in patients with pancreatic cancer compared to normal controls, as well as in patients with benign pancreatic tumor and chronic pancreatitis. As shown by ROC curve analysis, HGF distinguished pancreatic cancer patients from subjects with benign conditions (sensitivity 84%, specificity 90%, AUC 0.919). Of note, 10 days after pancreaticoduodenectomy, the plasma HGF levels in patient were significantly higher than preoperative levels ($p = .0009$), despite removal of the tumor. However, HGF returned to preoperative concentrations by one month after surgery. In addition, patients with early tumor recurrence had higher preoperative HGF levels than patients without tumor recurrence. Similarly, in another study, after hepatopancreatic surgery, serum HGF levels were elevated compared to preoperative levels [226].

V-I- Cervical cancer

In cervical cancer, the serum HGF level showed the highest diagnostic value in comparison to other factors for distinguishing cervical squamous cell carcinoma from the cervical intraepithelial neoplasia patients and healthy controls (AUC 0.99, sensitivity 77%, specificity 54%) [199]. This study also demonstrated that serum

HGF concentrations in HPV-positive patients were higher than HPV-negative individuals. These data were consistent with a previous study that reported a strong association between HGF overexpression and cervical HPV and HIV infections [227]. In terms of the prognostic value of HGF, the study of Zhang et al. showed that cervical cancer patients with low serum HGF levels had significantly longer OS and PFS than those with high levels [199].

V-J- Multiple myeloma

The prognostic and predictive value of HGF included in serum or plasma cytokine and angiogenic factor profile analysis has been explored in different tumor types [205,228–231]. In a recent study, Saltarella et al. evaluated the panel of angiogenic factors including HGF in multiple myeloma patients; they suggested that increased plasma HGF was associated with shorter relative PFS and predicted the benefit from therapeutic regimens [205]. However, contrary to the findings of most studies evaluating angiogenic markers that have supported the role of HGF in treatment response prediction, in the study of Minarik et al., HGF was not proved to be a potential predictive factor of response to treatment in multiple myeloma patients [232].

VI- Other biomarkers

VI-A- HGF level in tumor tissue

Tumor tissue levels of HGF have also been found to correlate with poor prognosis and have been proposed as potential biomarkers [233,234]. Higher HGF expression in esophageal tumor tissue was associated with a shorter OS [196]. HGF overexpression was also observed in 67.1% of tonsillar squamous cell carcinoma patients, and patients with HGF overexpression experienced a shorter OS (49.1 vs. 93.8 months, $p = .001$) than those with a low MET expression; similar trends were observed with PFS (46.0 vs. 85.5 months, $p = .004$) [235]. Moreover, in endometrial cancer, patients with HGF-positive, fibroblast growth factor-positive tumors had an increased risk of recurrence compared with cases with negative expression of both markers (HR 9.88, 95% CI 2.63–37.16) [236].

VI-B- Circulating tumor DNA

In addition to the above-mentioned use of MET dysregulation for biomarker discovery in tumor tissue, recently a promising noninvasive method based on the detection of circulating tumor DNA (ctDNA) in blood samples has also been suggested as a cancer biomarker [237–243]. One study comparing the *MET* amplification rate in different tissue-based and blood-based analysis methods showed that the frequency of *MET* amplification using ctDNA in metastatic colorectal cancer patients after exposure to anti-EGFR antibody therapy was significantly increased compared with antibody-naïve patients ($p < .001$) [237]. Similarly, a case report of a treatment refractory patient with metastatic colorectal cancer showed that *MET* amplification was detected in ctDNA using next-generation sequencing, but not in tissue biopsy samples. The significant response that the patient experienced after treatment with the combination of cabozantinib plus panitumumab led to the suggestion that *MET* amplification in ctDNA may be a predictive biomarker for response [244]. Finally, in NSCLC, a recent study demonstrated the potential clinical utility of ctDNA as a guide for therapy when tissue DNA was insufficient or unavailable [240].

VI-C- Circulating mRNA

Circulating tumor-related genes that can be easily detected by RT-quantitative PCR in the serum or plasma of cancer patients may be reliable diagnostic and prognostic biomarkers in several types of cancer [245]. One study comparing the expression of five mRNA species, *MET, CEA, GalNAc-T, hTERT* and *MUC-1*, in peripheral blood in patients with gastric cancer showed that the *MET* mRNA level was associated with the T stage ($p = .025$), lymph node metastasis ($p = .036$), distant metastasis ($p = .031$) and disease stage ($p = .023$) [246]. Similar results were reported in a later study which showed that 41.2% of patients had serum *MET* mRNA overexpression [247].

Conclusions

Dysregulation of HGF/MET pathways in cancer cells may occur by *MET* gene overexpression, gene amplification or gene CNG, and several activating mutations including those causing exon 14 skipping. sMET and HGF levels in circulation could also be altered aberrantly.

MET aberrations in tumor tissue serve as unequivocal prognostic biomarkers in several types of cancer including NSCLC, breast, head and neck cancers as well as colorectal, gastric, pancreatic and other gastrointestinal tumors. On the other hand, the predictive value of MET activation biomarkers in tumor tissue has not always been consistent. Most studies have suggested that selection of patients based on MET biomarkers may have clinical utility by showing that MET-positive

patients, in particular NSCLC subjects, carrying any of the aberrations drew the most benefit from HGF/MET targeted therapies. However, some studies have failed to show such straight-forward associations. The root of these discrepancies may lie in the methods used for assessment of pathway dysregulations in tumor tissue.

Similar to tissue MET aberrations, increased levels of sMET in the plasma or serum in cancer patients have been mostly associated with poor prognosis; however, the evidence is not as strong as for tissue MET. As a diagnostic biomarker, sMET levels have shown their value in prostate and bladder cancer as well as in melanoma, but this role has not been solidly established yet. On the other hand, HGF aberrant signaling, mostly detected in the circulation and sometimes also in tumor tissue, has been presented as a valuable prognostic and diagnostic biomarker; however, controversies exist on its predictive value.

A frequently-encountered problem is the high variation in the prevalence of MET/HGF alterations in different reports. In this context, the main challenge is the standardization and unification of measurement techniques and scoring systems, especially those used in the determination of expression levels in tumor tissue. Another important challenge is to identify cancer types and subtypes that involve MET oncogenic addiction. This is of vital importance, because only these tumor types may benefit from HGF/MET targeted therapies.

While the prognostic value of HGF/MET biomarkers has been largely accepted, the diagnostic value of HGF/MET biomarkers is a new field with promising possibilities, and many questions remain to be answered regarding their role as biomarkers to predict the response to targeted therapies.

The HGF/MET pathway has emerged as an important actionable target across many solid tumors, and biomarker discovery has become essential to guide clinical interventions in this field. Moving along this path should pave the way towards personalized medicine.

Disclosure statement

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