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The Met receptor tyrosine kinase: A key player in oncogenesis and drug resistance

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ABSTRACT

The Met receptor tyrosine kinase (RTK) is an attractive oncology therapeutic target. Met and its ligand, HGF, play a central role in signaling pathways that are exploited during the oncogenic process, including regulation of cell proliferation, invasion, angiogenesis, and cancer stem cell regulation. Elevated Met and HGF as well as numerous Met genetic alterations have been reported in human cancers and correlate with poor outcome. Alterations of pathways that regulate Met, such as the ubiquitin ligase c-Cbl are also likely to activate Met in the oncogenic setting. Moreover, interactive crosstalk between Met and other receptors such as EGFR, HER2 and VEGFR, underlies a key role for Met in resistance to other RTK-targeted therapies. A large body of preclinical and clinical data exists that supports the use of either antibodies or small molecule inhibitors that target Met or HGF as oncology therapeutics. The prognostic potential of Met expression has been suggested from studies in numerous cancers including lung, renal, liver, head and neck, stomach, and breast. Clinical trials using Met inhibitors indicate that the level of Met expression is a determinant of trial outcome, a finding that is actively under investigation in multiple clinical scenarios. Research in Met prognostics and predictors of drug response is now shifting toward more sophisticated methodologies suitable for development as validated and effective biomarkers that can be partnered with therapeutics to improve patient survival.

Contents

Abbreviations: ALK, Anaplastic lymphoma kinase; AML, Acute myeloid leukemia; Bid, Twice daily; CI, Confidence interval; CRPC, Castration-resistant prostate cancer; CSC, Cancer stem cell; DCR, Disease control rate; EGFR, Epidermal growth factor receptor; EMT, Epithelial–mesenchymal transition; ERK/MAPK, Extracellular signal-regulated kinase/Mitogen-activated protein kinase; FGFR, Fibroblast growth factor receptor; FISH, Fluorescent in situ hybridization; Gab1, Grb2-associated binding protein; Grb2, Growth factor receptor-bound protein; HCC, Hepatocellular carcinoma; HER2, Human epidermal growth factor receptor 2; HGF/SF, Hepatocyte growth factor/scatter factor; HNSCC, Head and neck squamous cell carcinoma; HR, Hazard ratio; IHC, Immunohistochemistry; MIT, Microphthalmia transcription factor-associated tumor; MITF, Microphthalmia transcription factor; MTC, Medullary thyroid carcinoma; NSCLC, Non-small cell lung cancer; ORR, Overall response rate; OS, Overall survival; PCR, Polymerase chain reaction; PDGFR, Platelet-derived growth factor receptor; PET, Positron emission tomography; PFS, Progression-free survival; PI3K, Phosphatidylinositol 3′ kinase; PR, Partial response; PTP1B, Protein tyrosine phosphatase 1B; Qd, Once daily; RCC, Renal cell carcinoma; RNA, Ribonucleic acid; RTK, Receptor tyrosine kinase; SD, Stable disease; SEMA, Semaphorin; TPR, Translocated promoter region; VEGF, Vascular endothelial growth factor; VEGFR, Vascular endothelial growth factor receptor.

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1. Introduction

The practice of oncology is undergoing a paradigm shift toward precision medicine. Understanding of the molecular pathways involved in cancer has been exploited to develop treatments tailored to the molecular profile of the individual patient. Receptor tyrosine kinases (RTKs) are ideal targets for this approach as they are frequently key drivers of tumorigenesis. Of particular interest is the Met RTK which plays a central role in epithelial tissue remodeling and morphogenesis and is deregulated in cancer. Met was identified as a prognostic marker in many cancers including lung, renal, liver, head and neck, stomach and breast, and elucidation of the oncogenic potential of Met led to the development of therapeutic agents targeting receptor activation, thereby delaying tumor progression and improving clinical outcomes in patients. However, challenges remain as to the identification of tumors most likely to respond to Met activity blockade. Thus, focusing on the development of validated biomarkers to drive utilization and effectiveness of Met-based interventions in cancer management is an unmet need. This review discusses the current status of Met prognostic and therapeutic research in oncology.

2. Biology of the Met receptor

2.1. Structure and expression patterns in normal state

Met belongs to a family of RTKs that share sequence and structural homology and includes Ron, the receptor for macrophage stimulating protein, and Sea, a Ron homologue expressed in chicken tissues (Huff et al., 1993; Gaudino et al., 1994). The high affinity ligand of Met is the hepatocyte growth factor/scatter factor (HGF/SF), a plasminogen-related growth factor involved in epithelial tissue remodeling and cell migration (Bottaro, 1991; Naldini et al., 1991a,b). While HGF is expressed by cells of mesenchymal origin, Met is predominantly expressed in cells of epithelial origin, as well as in endothelial cells, neuronal cells, melanocytes, hematopoietic progenitors, and also B cells and antigen-presenting dendritic cells (Beilmann et al., 1997; van der Voort et al., 1997; Organ & Tsao, 2011).

The Met receptor is a 190 kDa glycoprotein heterodimer consisting of an amino-terminal extracellular 45 kDa α-chain and a membrane spanning 145 kDa β subunit (Fig. 1). The β subunit is composed of extracellular semaphorin (SEMA) and immunoglobulin-like (Ig-like) domains separated by a Plexin, Semaphorin and Integrin cysteine-rich (PSI) domain (Gherardi et al., 2012). The SEMA–PSI domain was shown to provide a binding site for the α-chain of the ligand HGF (Merchant et al., 2013). The Met transmembrane domain is followed by a juxtamembrane domain containing a key tyrosine residue (Y1003) involved in Met downregulation and an intracellular portion containing the catalytic kinase domain (Peschard et al., 2001). A carboxy-terminal multisubstrate docking site recruits signaling adaptors and effectors following receptor activation (Gherardi et al., 2012).

2.2. Hepatocyte growth factor/Met mediated signaling

2.2.1. Met signaling

Met-mediated signaling has recently been reviewed in detail (Trusolino et al., 2010; Organ & Tsao, 2011). Briefly, under normal circumstances ligand-mediated homodimerization/oligomerization results in autophosphorylation of kinase domain tyrosine residues Y1234 and

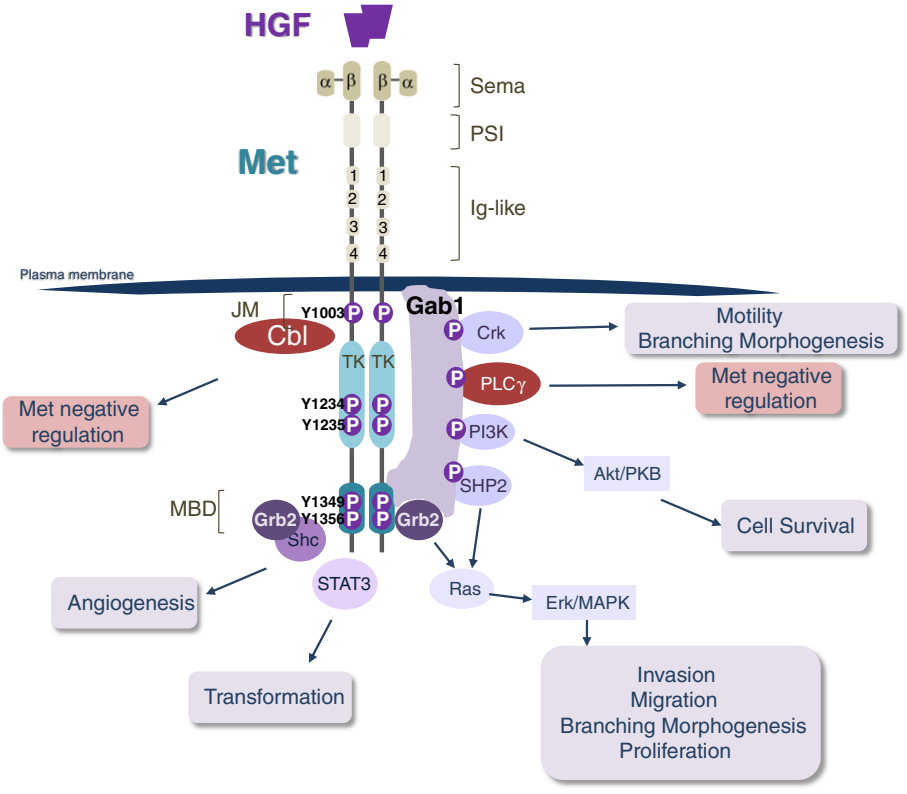

Fig. 1. HGF/Met mediated signaling and biological activities. Following HGF-mediated dimerization and autophosphorylation of the Met receptor, signaling proteins are recruited to the carboxy-terminal docking site, either directly or indirectly through Grb2 and Gab 1. This leads to activation of downstream pathways such as Erk/MAPK and Akt/PKB, and translates into biological responses such as cell transformation, survival, migration, dispersal, proliferation, and angiogenesis. Cbl: (*Casitas B-lineage Lymphoma*) E3 ubiquitin-protein ligase; Crk: (*CT10 regulator of kinase*) adaptor protein; Gab1: Grb2-associated binding protein; Grb2: growth factor receptor-bound protein 2; PI3K: phosphatidylinositol 3′ kinase; PLCγ: phospholipase C γ; Ras: (*Rat sarcoma*) small GTPase; SHIP1: Src homology 2-containing inositol 5-phosphatase 1; Shc: Src homology 2 domain-containing protein; SHP2: Src homology domain 2 (SH2)-containing tyrosine phosphatase; Src: tyrosine-protein kinase CSK; STAT3: signal transducer and activator of transcription 3. Ig-like 1–4: immunoglobulin-like domains 1–4.

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Y1235 (Fig. 1), followed by phosphorylation of carboxy-terminal tyrosines, mainly Y1349 and Y1356, providing docking sites for signaling proteins that are essential for Met-mediated biological activities (Rodrigues & Park, 1994; Zhu et al., 1994; Kamikura et al., 1996; Organ & Tsao, 2011; Gherardi et al., 2012). Signaling proteins directly or indirectly recruited to the phosphorylated docking site include the growth factor receptor-bound protein 2 (Grb2) adaptor, the non-receptor tyrosine kinase Src, Src homology 2 domain-containing (Shc) adaptor protein, the p85 subunit of phosphatidylinositol 3′ kinase (PI3K), phospholipase C γ (PLCγ), tyrosine phosphatase SHP2, Src homology 2-containing inositol 5-phosphatase 1 (SHIP1), signal transducer and activator of transcription 3 (STAT3) and the multisubstrate docking protein Grb2-associated binding protein (Gab1) (Ponzetto et al., 1993, 1994; Fixman et al., 1995, 1996; Boccaccio et al., 1998; Stefan et al., 2001). When phosphorylated, Gab1 links Met to signaling proteins such as SHP2, p85-PI3K, PLCγ and the adaptor protein Crk, and promotes the activation of the Erk/MAPK and Akt/PKB pathways (Holgado-Madruga et al., 1996; Maroun et al., 1999, 2000; Lamorte et al., 2002). Although Gab1 also signals downstream from other RTKs, its interaction with Met is unique in terms of mode of recruitment and phosphorylation kinetics. In addition to its indirect recruitment to Met through Grb2, Gab1 can directly bind to docking site Y1349 (Lock et al., 2000, 2003). Thus, unlike the transient Gab1 signals generated following epidermal growth factor receptor (EGFR) activation and leading to proliferation, Met activation induces prolonged and sustained Gab1 phosphorylation required for Met-induced branching tubulogenesis, an inherent morphogenic program of kidney, breast, and lung epithelia (Maroun et al., 2000; Lock, Maroun et al., 2002).

In non-tumorigenic cells, HGF-mediated Met activation is a tightly controlled process. Met is internalized by endocytosis, leading to localization to multivesicular bodies and degradation. This process involves ubiquitination of Met which is mediated by the E3 ubiquitin ligase c-Cbl. c-Cbl is recruited to Met-Y1003 in the juxtamembrane domain and mediates ubiquitin transfer to Met. This provides ubiquitin recognition motifs for the recruitment of Met to multivesicular bodies and efficient signal termination following Met degradation (Peschard & Park, 2003). Met signaling is also attenuated by tyrosine-specific phosphatases, including protein-tyrosine phosphatase 1B (PTP1B, known as PTPN1), T-cell phosphatase (TCPTP/PTPN2), and density enhanced protein tyrosine phosphatase-1 (DEP-1) (Palka et al., 2003; Sangwan, Paliouras et al., 2008). Deregulation of these pathways occurs in cancers and has been shown to contribute to the oncogenic potential of Met (further discussed below).

2.2.2. Interactions of Met with other partners

Signaling through Met rarely occurs in isolation. Multiple interactions with other cell membrane proteins serve to adapt signaling amplitude and duration. Moreover, these interactions could diversify signals to achieve distinct biological outputs. Cooperation with integrins, class B Plexins and CD44 variants have recently been reviewed (Lai et al., 2009; Organ & Tsao, 2011) (Fig. 2A). Both HGF-dependent and independent mechanisms have been invoked. Integrin clustering at the cell surface results in HGF-independent Met phosphorylation (Wang et al., 1996). Furthermore, Met has been shown to interact with integrin α6β4 in a HGF-dependent manner, resulting in integrin phosphorylation and enhanced invasion. The synergy between certain integrins and Met can be mediated in part by the focal adhesion kinase (FAK) upon phosphorylation by Met (Chen & Chen, 2006).

Another significant partner that regulates Met biological responses is the CD44 family which bridges extracellular matrix components to cytoskeletal reorganization (Fig. 2b). CD44 bound to extracellular

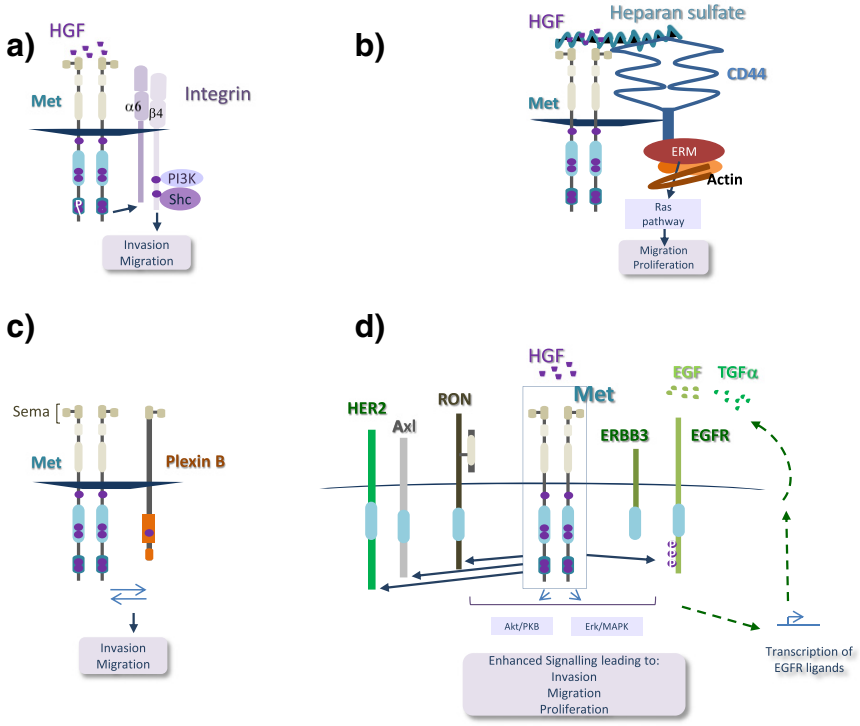

Fig. 2. Interactions between Met and other membrane receptors. **a**) HGF-dependent association of Met with integrin α6β4 leads to phosphorylation of the β4 cytoplasmic domain and enhanced invasion. **b**) CD44 bound to extracellular heparin sulfate acts as a co-receptor to present HGF to Met leading to Met phosphorylation. Activated Met leads to downstream activation of the Ras pathway via recruitment of the actin-binding proteins ezrin, radixin, moesin to the CD44 intracellular domain and enhanced migration and proliferation. **c**) Interaction between the semaphorin-like domains on Met and class B plexins leads to semaphorin-dependent, but HGF-independent activation of both Met and plexin. **d**) Transactivational cooperation between Met and receptor tyrosine kinases including HER2, Axl, Ron, ErbB3 and EGFR contributes to the development of resistance to targeted therapies by enhancement of downstream pathways such as Akt and ERK/MAP kinase. In addition, HGF-independent synergistic activation is observed between Met and EGFR and indirect transactivation of EGFR by Met occurs via the upregulation of EGFR ligands by Met-driven pathways. PI3K: phosphatidylinositol 3′ kinase; Shc: Src homology 2 domain-containing protein; ERM; ezrin, radixin, moesin; Sema: semaphorin-like domain; EGF: epidermal growth factor; TGF: transforming growth factor.

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heparin sulfate can act as a co-receptor presenting HGF to Met (Lai et al., 2009). Following Met activation a CD44 variant (CD44v6) promotes intracellular complex formation between Met binding partners and ezrin, radixin and moesin resulting in efficient downstream activation of the Ras pathway (Orian-Rousseau, Morrison et al., 2007). The collaboration of Met and CD44 is thought to support the metastatic process in cancer cell lines, and functional significance of this interaction was demonstrated in synaptogenesis in vivo in mouse models (Matzke et al., 2007). Met has been shown to associate with the class B Plexin family of transmembrane proteins leading to semaphorin-dependent activation/phosphorylation of both Met and Plexin and resulting in enhanced migration and invasion (Lai et al., 2009; Trusolino et al., 2010). This HGF-independent function has been attributed to the presence of a SEMA domain in the extracellular portion of Met which is homologous to the SEMA domain in plexins and provides a means of association of these collaborators. Under certain circumstances ligand binding to Plexin B (SEMA4D binding to Plexin B1) leads to Met phosphorylation and activation of small GTPases like Rac, to enhance invasion (Giordano et al., 2002) (Fig. 2c).

Key functional interactions occur between Met and other RTKs (Fig. 2d). Met and EGFR are frequently co-expressed and have been shown to functionally cooperate during kidney development (Ishibe et al., 2009). Met can be transactivated following EGFR activation, in the absence of HGF, and simultaneous activation of Met and EGFR is synergistic (Puri & Salgia, 2008). The interaction of Met with other RTKs including Ron, Axl and members of the EGFR and VEGFR families has been revealed in multiple systems and is involved in the regulation of oncogenic pathways and the manifestation of resistance to targeted therapies (Sections 3.3 and 3.4 below).

2.3. Hepatocyte growth factor/Met biological activities

During normal development, HGF/Met signaling is central to tissue remodeling and morphogenic differentiation. Multiple genetic ablation models including conditional knock outs revealed that Met is essential for placental and liver development as well as migration of myogenic precursor cells (Schmidt et al., 1995; Uehara et al., 1995; Ebens et al., 1996). The Met pathway also plays a critical role in organ regeneration and wound healing as supported by increased HGF levels in patients with liver or renal failure, or following tissue damage such as liver cirrhosis and renal fibrosis (Tsubouchi et al., 1991; Kawaida et al., 1994; Nakamura et al., 2000). An underlying Met-driven mechanism in the processes of tissue remodeling and morphogenic differentiation is the transient epithelial–mesenchymal transition (EMT). This process is characterized by loss of epithelial differentiation, cell dispersal and migration as well as the degradation of extracellular matrix. In the context of Met-driven cancer, tight regulation of these events is lost leading to invasion and metastasis (Baum et al., 2008; Lim & Thiery, 2012). Met is also implicated in angiogenesis and the regulation of endothelial cell function. In multiple models, activation of Met resulted in the induction of pro-angiogenic factors such as vascular endothelial growth factor (VEGF), and the cooperation with VEGFR2 pathways correlated with early onset of tumor formation (Dong et al., 2001; Saucier et al., 2004).

Met is expressed in cells of hematopoietic origin and dendritic cells, and plays a role in the regulation of immune functions. In B cells, Met is implicated in cell homing to lymph nodes, and in monocytes, in triggering an invasion program (Beilmann et al., 1997; van der Voort et al., 1997; Galimi et al., 2001). Met activation was associated with downregulation of dendritic cell (DC) functions and immune responses in several models including allergic airway inflammation, collagen-induced arthritis and experimental autoimmune encephalomyelitis. In these studies, Met activation caused inhibition of antigen presentation by DCs, decreases in infiltrating inflammatory cells and T cell activation markers along with increases in Tregs and IL-10 production (Okunishi et al., 2005; Benkhoucha et al., 2010). However, in other studies, activation of Met in skin-resident DCs was necessary for the migration of DCs to draining lymph nodes, consistent with the roles of Met in cell motility and invasion (Baek et al., 2012). It is possible that the role of Met and HGF in the regulation of immune functions is distinct in different disease/circumstance settings and further studies are required to reconcile these observations.

3. Met in cancer

3.1. Met alterations associated with cancer

HGF/Met alterations leading to deregulation of downstream signaling are major contributors to tumorigenesis and cancer progression (Christensen et al., 2005). Met was discovered as the TPR–MET oncogene resulting from chromosomal rearrangement between sequences encoding the translocated promoter region (*tpr*) and the MET kinase domain in chemically transformed human osteogenic sarcoma cells (Cooper et al., 1984) and subsequently identified in gastric tumor cell lines and biopsy samples (Soman et al., 1991). Since then, numerous Met alterations including driver mutations have been reported in human cancers, and are suggested to contribute to oncogenic progression (Christensen et al., 2005; Sattler & Salgia, 2009; Van Andel Institute, 2013) (Table 1).

3.1.1. Met mutations

Met mutations, although rare, are detected across the different Met domains. Present in all hereditary papillary renal cell carcinoma (RCC), mutations are also detected in a subset of sporadic papillary RCC, childhood hepatocellular carcinoma (HCC), gastric, head and neck, breast, and ovarian carcinomas, in addition to non-small cell lung cancer (NSCLC) (Schmidt et al., 1997, 1999; Park et al., 1999; Lee et al., 2000; Ma et al., 2005, 2008; Seiwert et al., 2009a,b; Ludovini et al., 2012).

3.1.1.1. Kinase domain mutations. Germline and somatic missense mutations (including Y1230C/H/D, Y1235D, M1268T) were the first identified in papillary RCC (Schmidt et al., 1997, 1999). These mutations were linked with the development of hereditary papillary RCC and have been functionally characterized in multiple cellular settings (reviewed in Goetsch & Caussanel, 2010). While kinase domain mutations could stabilize Met in an active conformation, leading to constitutively elevated kinase activity, the activation of these mutants was also shown to be HGF-dependent (Michieli et al., 1999). More recently, kinase domain mutations (D1246N, M1268T) were related to enhanced Met trafficking in papillary RCC cell lines, increased accumulation of Met in the recycling endosomal compartments and avoidance of lysosomal degradation which resulted in enhanced Met signaling and cell migration (Joffre et al., 2011).

Distinct kinase domain mutants drive different signaling pathways (Giordano et al., 2000). These observations were corroborated in in vivo findings demonstrating that expression of the M1248T kinase mutant in C57BL/6J mice led to carcinomas and lymphomas whereas expression of D1226N, Y1228C, and combined M1248T/L1993V was associated mainly with sarcomas and lymphomas (Graveel et al., 2004). More recently, expression of the highly active M1248T/L1993V in the FVB/N murine background led to aggressive mammary carcinoma with similar features to basal breast cancer, whereas expression of the same mutations in the C57BL/6J background did not cause mammary tumors, suggesting not only that different mutations can drive the development of distinct cancers but also can be influenced by genetic modifiers (Graveel et al., 2010). Tyrosine kinase domain mutations were also described in childhood HCC and head and neck squamous cell carcinoma (HNSCC) (Park et al., 1999; Di Renzo et al., 2000), where the Y1253D activating point mutation was associated with shorter metastasis-free survival (Ghadjar et al., 2009).

3.1.1.2. Juxtamembrane domain mutations. Mutations in the Met juxtamembrane domain have been reported in lung cancer, HNSCC,

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Table 1
Most common Met alterations in selected human cancers.

Cancer	Met alterations			
	Met protein overexpression	High HGF expression	Point mutations	Gene amplification/high copy number
Lung	14%–61% NSCLC (Ma et al., 2005, 2008; Park et al., 2012) 25%–67% adenocarcinoma; 57% SCC (Christensen et al., 2005; Ma et al., 2005)	NSCLC (Christensen et al., 2005; Van Andel Institute, 2013)	4% NSCLC (Ludovini et al., 2012) *Juxtamembrane and Sema domain* — NSCLC (Sadiq & Salgia, 2013)	2%–21% gene amplification, 9% polysomy in NSCLC (Beau-Faller et al., 2008; Okuda et al., 2008; Cappuzzo et al., 2009; Toschi & Cappuzzo, 2010; Park et al., 2012)
Head and neck	52%–68% HNSCC (Christensen et al., 2005)	HNSCC (Kim et al., 2007)	*Kinase domain* — 3% HNSCC (Seiwert et al., 2009a); 26%–50% HNSCC metastases (Di Renzo et al., 2000; Lorenzato et al., 2002) *Juxtamembrane and Sema domain* — 9% (Seiwert et al., 2009a)	
Gastric	24%–46% gastric carcinoma (Christensen et al., 2005; Lee et al., 2012)	87% intestinal type gastric carcinoma (Wu et al., 1998)	*Juxtamembrane domain* — gastric carcinoma (Lee et al., 2000)	2%–24% (38% type IV) gastric carcinoma (Christensen et al., 2005; Lennerz et al., 2011; Lee et al., 2012; Kawakami et al., 2013) 16% high chromosome 7 polysomy gastric carcinoma (Lee et al., 2012)
Colorectal	50% colorectal cancer; 70% metastases (Di Renzo et al., 1995; Christensen et al., 2005)			10% colorectal cancer; 89% metastases (Di Renzo et al., 1995; Christensen et al., 2005)
Kidney	90%–100% papillary, 100% collecting duct, 92% urothelial, 78% clear cell (Christensen et al., 2005; Choi et al., 2006)	Clear cell RCC (Tanimoto et al., 2008)	*Kinase domain* — 100% hereditary papillary RCC (Schmidt et al., 1997) 13% sporadic papillary RCC (Schmidt et al., 1999)	Chromosome 7 trisomy (Christensen et al., 2005)
20% carcinoma (Christensen et al., 2005)			*Kinase domain* — 30% childhood HCC (Park et al., 1999)	

HCC: hepatocellular carcinoma; HGF: hepatocyte growth factor; HNSCC: head and neck squamous cell cancer; NSCLC: non-small cell lung cancer; RCC: renal cell carcinoma.

gastric cancer, and melanoma (Lee et al., 2000; Ma et al., 2003; Ma et al., 2005; Puri et al., 2007; Ma et al., 2008; Seiwert et al., 2009a,b). Mutation of Y1003, the binding site for c-Cbl involved in the downregulation of Met signaling, was associated with increased Met phosphorylation in NSCLC and melanoma tumor tissue and a cytoplasmic expression pattern suggestive of constitutive activation (Ma et al., 2005; Tretiakova, Salama et al., 2011). Another mutation is R988C-Met which induced morphological changes when expressed in fibroblasts, concomitant with increased phosphorylation of Met downstream targets (Ma et al., 2003). In addition, a Met alternative splice variant resulting in the deletion of exon 14 within the juxtamembrane domain was detected in approximately 3% of NSCLC patients and resulted in the loss of the juxtamembrane c-Cbl binding site (Seo et al., 2012). Although insufficient to drive transformation, these alterations cause functional gains in Met signaling.

3.1.1.3. Extracellular domain mutations. Mutations in the extracellular domain were reported in a number of tumors, including melanoma, lung, breast, and ovarian cancers (Ma et al., 2008). Mutations in the SEMA domain were described in lung cancer. Of these, the N375S mutation was most frequently detected in squamous cell carcinoma, male smokers and East Asian patients. This mutation, believed to be a germline polymorphism, is associated with decreased affinity for HGF and sensitivity to small-molecule inhibitors (Krishnaswamy et al., 2009). No difference in postoperative survival was observed between patients with or without the N375S mutation in a recent prognosis study. However, since a decrease in the sensitivity of the N375S to Met inhibition was observed, further analyses in clinical settings are needed (Shieh et al., 2013).

3.1.2. Gene amplification and high gene copy number

In preclinical models, *MET* amplification is one of the most sensitizing alterations to Met blockade strategies (Smolen et al., 2006; Lutterbach et al., 2007). *MET* amplification was detected in NSCLC, gastric carcinoma, esophageal carcinoma, medulloblastoma, and glioblastoma (Table 1). In lung adenocarcinoma, multiple studies indicate a correlation between *MET* amplification and poor prognosis and survival, although *MET* amplification in the absence of resistance to EGFR inhibition is a rare event (reviewed in Cappuzzo et al., 2009; Go et al., 2010; Toschi & Cappuzzo, 2010; Chen et al., 2011; Tanaka et al., 2012). Additionally, high *MET* gene copy number (polysomy) is also associated with poor outcome in NSCLC (Beau-Faller et al., 2008; Okuda et al., 2008; Park et al., 2012). A correlation between increased *MET* gene copy number and high protein expression was observed supporting ligand-independent Met activation (Dziadziuszko et al., 2012). In gastric cancer, *MET* amplification is reported with frequencies ranging between 2% and 24% (Table 1), and there was a lower survival rate for patients with elevated *MET* copy number (Christensen et al., 2005; Smolen et al., 2006; Lennerz et al., 2011; Lee et al., 2012; Kawakami et al., 2013) and in colorectal cancer, the frequency of *MET* amplification increased significantly following progression to metastatic disease, suggesting a role for gene amplification in the induction of invasive phenotype (Di Renzo et al., 1995).

It is noticeable that studies to date have reported a variable rate of *MET* amplification in tumor specimens. This may be due in part to differences in genetic background, but is likely also related to the different methods used to detect amplification (FISH versus PCR for example), and/or the lack of consistent criteria for defining a high degree of amplification. It is noteworthy that one study showed a lack of *MET* amplification in tumors from 38 patients analyzed by fluorescent in situ hybridization (FISH), although 29% (11/30) of tumor specimens did demonstrate high *MET* polysomy, high levels of Met mRNA and protein expression (Janjigian et al., 2011). Differing ratio cutoffs have been used for *MET* copies to Chromosome 7 controls such as CEP7, and in some studies *MET* polysomy is used as an indication for high *MET* copy numbers (Ou et al., 2011b). Thus, a *MET*/*CEP7* ratio >2.2 indicating "true" *MET* amplification may be predictive of clinical responses, but not *MET* polysomy in the absence of homogenously staining regions (HSR). This is supported by preclinical and early clinical studies suggesting that sensitivity to Met agents (PF-2341066 and PHA-665752) is dependent on the level of *MET* amplification (Smolen et al., 2006; Lennerz et al., 2011; Barretina et al., 2012).

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3.1.3. Increased protein expression

Increased Met expression is reported in many human tumors including NSCLC and hepatocellular carcinoma (HCC) and correlates with poor prognosis (short overall and disease-free survival). Elevated Met levels were associated with tumor aggressiveness in basal breast tumors and estrogen receptor/progesterone receptor/human EGFR receptor 2 (HER2)-negative (triple-negative) tumors (Graveel et al., 2009; Ponzo et al., 2009). High levels of Met expression were also detected in HER2 positive cancers (Paulson et al., 2013). Consistently, in colorectal cancer, Met was overexpressed in 50% of primary tumors, and in 70% of metastases, suggesting a selection process in favor of an invasive and highly proliferative phenotype associated with Met overexpression (Di Renzo et al., 1995; Christensen et al., 2005). The direct consequence of Met overexpression was assessed in a cell culture model, where Met overexpression induced malignant transformation of primary human osteoblasts into osteosarcoma, potentially due to ligand-independent receptor clustering leading to receptor dimerization/oligomerization, and activation (Patane et al., 2006).

In the absence of gene amplification, Met overexpression can be mediated by transcriptional regulation. This is observed during hypoxia following induction by hypoxia inducible factor (HIF-1α) and alterations in transcription factors such as Ets and Sp1, or repressors such as micro RNAs including miR-1, miR-34, and miR-449a promote enhanced cell invasion (Gambarotta et al., 1996; Boon et al., 2002; Pennacchietti et al., 2003; Migliore et al., 2012). The wnt/βcatenin pathway was also shown to affect Met expression in colorectal cancer models (Boon et al., 2002). While elevated Met expression has been consistently shown to be prognostic in many settings and indications, there is more limited data to support the predictive value of elevated Met expression. Ongoing late-phase clinical investigations with Met-targeted agents will provide insight into the clinical relevance and functional value of high levels of Met expression.

3.1.4. Increased ligand expression

High levels of HGF were detected in plasma and tumors of cancers of various origins including NSCLC, HNSCC, gastric, and clear cell RCC, in addition to breast cancer, acute myeloid leukemia (AML), osteosarcoma, melanoma, and glioma and have been associated with poor patient outcome and resistance to targeted therapy (Jin et al., 1997; Kentsis et al., 2012; Van Andel Institute, 2013). In mammary epithelial cells, it was shown that increased HGF expression was mediated by transcriptional activation involving STAT3 and c-Src (Wojcik et al., 2006). HGF can also be co-expressed with Met in cancer cells forming an autocrine receptor activation loop. Co-expression of HGF and Met has been described in 50% of AML tumor samples, and also in breast carcinoma, osteosarcoma and melanoma (Kentsis et al., 2012; Van Andel Institute, 2013). Autocrine activation of Met can drive the metastatic process as demonstrated when HGF and Met co-overexpressing NSCLC cells were implanted orthotopically in nude rats leading to development of spontaneous metastases to the bone, brain and kidney (Navab et al., 2009). HGF is frequently co-expressed with Met in glioblastoma (GBM) and in in vivo GBM models, autocrine Met activation precluded sensitivity to Met inhibitors (Koochekpour et al., 1997; Xie et al., 2012). Thus, the levels of HGF expression in tumor tissues may be relevant for predicting clinical responses to Met-targeted agents. This is supported in a report where retrospective demonstration of stromal HGF expression was linked with improved clinical responses in patients treated with ficlatuzumab, an anti-HGF in development (discussed in Section 4.1.2).

3.1.5. Met activation gene signatures

To further understand the mechanisms through which Met activation regulates cancer development and progression, gene expression profiles were analyzed in multiple settings. In HCC, gene expression profiles were compared between primary wild-type Met-expressing and Met-deficient hepatocytes. This signature of Met transcriptional targets was consistent with roles in oxidative stress response, cytoskeletal reorganization, motility, and angiogenesis and was linked through comparative functional genomics to a cohort of HCC samples including liver metastases specimens (Kaposi-Novak et al., 2006). Cluster analyses showed that a subset of the samples sharing this signature corresponded to patients with increased vascular invasion and microvessel density, decreased mean survival and presence of liver metastases (Kaposi-Novak et al., 2006). Interestingly, this activation signature was recently applied to a dataset from patients with breast cancer, and segregated significantly with tumors corresponding to the basal subtype, identifying patients with poor outcome. The significance of Met in basal subtype breast cancer was further supported by immunohistochemistry analyses showing increased levels of Met expression and activation as detected using phospho-specific Met antibodies. Furthermore, coexpression of Met with the EMT regulator, SNAIL, was a predictor of poor outcome (Ponzo et al., 2009). In a different transgenic mouse model with a breast-targeted activated Met variant (M1248T, Y1003F/M1248T) and conditional loss of p53, the gene expression signature corresponded to a subset of triple-negative breast cancers with a "claudin-low" signature consistent with EMT. Met inhibition in this model reversed the EMT phenotype, restored claudin expression and cell–cell junctions and reduced metastatic tumor growth suggesting that Met activity was associated with an aggressive phenotype. These studies were corroborated in breast cancer patients where coexpression of Met and missense TP53 in ER/PR negative patients was associated with poor patient outcome (Knight et al., 2013). In addition to providing insights into Met-dependent oncogenic pathways and disease progression such studies supported the development of Met-targeted agents in selected indications.

3.1.6. Alterations of other pathways affecting Met activation

Molecular alterations in other components may additionally affect Met activation status. As described above, Met phosphorylation/activation is regulated by phosphatases (Palka et al., 2003; Sangwan et al., 2008). Therefore, loss-of-function of Met-targeted phosphatases may lead to enhanced Met activation as has been demonstrated for the tyrosine kinases EGFR and HER2 in a recent study where loss of PTPN12 was associated with mammary epithelial cell proliferation and transformation and RTK activation (Sun et al., 2011). In the case of PTP1B, it was also shown that loss of this phosphatase altered Met trafficking to the late endosomal compartment, and delayed Met degradation resulting in sustained Met activation and downstream MAP kinase signaling pathway (Sangwan et al., 2011). Met activation was also shown to be regulated by glycosylation. Overexpression of the core 1β1,3-galactosyltransferase (C1GALT1) resulted in enhanced HGF-mediated cell proliferation by a mechanism involving enhanced Met-dimerization which was reversed by Met blockade using a small molecule Met inhibitor. C1GALT1 was frequently found to be overexpressed in HCC, correlated with advanced disease stage and predicted poor survival. Such studies suggest that RTKs including Met may be mediating oncogenic functions of C1GALT1 (Wu et al., 2013).

Mutations within the E3 ubiquitin ligase c-Cbl have been characterized in lung cancer and may be significant for the regulation of Met activity. As mentioned above, Met signaling can be sustained in the absence of downregulation and degradation through c-Cbl. Eight somatic mutations were discovered upon sequencing coding regions of *c-CBL*, three were located with the tyrosine kinase binding domain and the remaining distributed in the RING finger, the proline rich and the c-terminal domains (Tan et al., 2010). These mutations were not mutually exclusive with Met mutations and when tested (for example Q249E), conferred increased cell viability and motility, consistent with results observed upon c-Cbl knockdown. Loss of heterozygosity (LOH) at the *c-CBL* locus on chromosome 11 was also detected in several tumor samples (Tan et al., 2010). Since multiple alternate pathways can directly affect the status of Met activation, it will be intriguing to monitor these pathways, such as the loss of relevant phosphatases or mutations in c-Cbl, in clinical trials to evaluate a potential for predicting response to Met-targeted agents.

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3.2. Met in cancer stem cells

Consistent with its involvement in tumorigenesis, Met is activated and overexpressed in cancer stem cells (CSCs), a highly clonogenic and invasive subset of cancer cells involved in cancer initiation and progression (Boccaccio & Comoglio, 2006). In prostate cancer, immunoflurescence staining revealed that Met was co-expressed with stem-like markers in the invasive cell front (van Leenders et al., 2011). Furthermore, high HGF and Met expression levels were detected in stem-like cells and promoted cell proliferation in an autocrine and paracrine manner which was inhibited using anti-HGF antibody (Nishida et al., 2013). In another study, HGF stimulation of prostate cancer cells induced the expression of a stem-like signature and a stem cell phenotype which was blocked by Met small-molecule inhibitors SU11274 and PHA665752 (van Leenders et al., 2011). A similar association between Met expression and cancer stem cells phenotype was observed in a mouse model of basal-like breast cancer, where constitutive Met activation resulted in the loss of differentiation of mammary luminal progenitor cells and acquisition of a stem cell-like phenotype (Gastaldi et al., 2013). Met is highly expressed in pancreatic CSCs and co-expression of Met and CD44 promoted tumor formation in a mouse model, a response that was blocked by Met inhibitors (Li et al., 2011). In glioblastoma-isolated CSCs, studies using short hairpin RNA demonstrated a role for co-expressed Met and HGF in the maintenance of stemness and an invasive phenotype (Joo et al., 2012). Moreover, in in vivo GBM xenograft models, inhibition of Met either using an anti-HGF antibody or the Met-targeted small molecule inhibitor, crizotinib, resulted in a decrease in the expression of stem cell markers such as CD133, Sox2 and Nanog. Along with a decrease in tumor growth, treatments with these anti-Met agents also resulted in the depletion of tumor cells with self-renewal and sphere-forming ability (Rath et al., 2013). Thus, given the involvement of Met in cancer stem cell self-renewal and propagation, and the contribution of these cells to tumor heterogeneity and resilience to multiple therapies including radiotherapy, targeting Met may offer a therapeutic avenue in this indication, and identification of Met alterations, diagnostic indicators of patients most likely to respond (Boccaccio & Comoglio, 2013).

3.3. Met involvement in resistance to cancer treatments

In addition to its role as an oncogenic driver, increasing evidence implicates Met as a common mechanism of resistance to targeted therapies including approved EGFR and VEGFR inhibitors.

Mechanisms of resistance to EGFR inhibitor therapies have been well characterized particularly in NSCLC patients (Lin & Bivona, 2012). While the T790M "gatekeeper" mutation in the EGFR kinase domain is a predominant mechanism of resistance, activation of alternate pathways play key roles in a subset of patients (20% for upregulation of Met pathway) (D'Arcangelo & Cappuzzo, 2013). The activation of Met-dependent signaling pathways as a consequence of *MET* amplification or upregulation of HGF expression was coupled with resistance to EGFR inhibitors (Bean et al., 2007; Engelman et al., 2007; Yano et al., 2008, 2011). Mechanisms mediating this resistance involve transactivation of HER3 and downstream PI3K/Akt, and could be reversed upon Met inhibition (Bean et al., 2007; Engelman et al., 2007; Tang et al., 2008). In other studies, HGF contributed to resistance to EGFR therapies via recruitment to the EGFR complex of other metastasis promoting RTKs such as Axl and EphA2, thus bypassing EGFR inhibition and leading to enhanced survival (Gusenbauer et al., 2013). HGF-mediated Met activation was also shown to play a role in resistance to irreversible EGFR inhibitors (Yamada et al., 2010). These data provide a rationale for treatment of patients who progress on EGFR therapies and display *MET* amplification or increased HGF expression, with anti-Met agents. Interestingly, it was demonstrated that a *MET*-amplified subpopulation of cells existed prior to anti-EGFR therapy supporting upfront co-treatment of patients with Met and EGFR therapies (Turke et al., 2010). Further support comes from preclinical experiments showing that co-treatment with anti-Met and EGFR inhibitors significantly enhanced tumor growth inhibition and caused regression (Bonfils et al., 2012; Wang et al., 2012). The involvement of Met in resistance to EGFR inhibition has recently been extended to colorectal carcinoma where *MET* amplification was associated with resistance to cetuximab and panitumumab (Bardelli et al., 2013). Taken together these results provide a strong rationale for the use of Met inhibitors to overcome drug-resistance to EGFR therapies.

A role for Met in resistance to anti-HER2 therapies was suggested in multiple models. High gene copy number of *MET* and *HGF* correlated strongly with poor outcome and resistance to trastuzumab in HER2-positive metastatic breast cancer (Minuti et al., 2012). Preclinical experiments indicated that trastuzumab-resistant HER2-positive breast cancer cell lines and primary tumors also exhibit elevated expression of Met and HGF (Shattuck et al., 2008). Furthermore, Met blockade using RNA interference or small-molecule inhibitor SU11274 inhibited phosphorylation/activation of Erk and Akt and sensitized cells to anti-HER2 treatment, suggesting that activated Erk and Akt were involved in Met-mediated resistance to trastuzumab (Shattuck et al., 2008). Additional evidence from gastric cancer models further indicate Met and ensuing Erk and Akt activation as a mechanism of resistance to the EGFR/HER2 inhibitor lapatinib (Chen et al., 2012).

It is now well established that crosstalk between the Met and VEGFR pathways supports tumor vascularization and progression. Met interacts with VEGFR2 to promote robust endothelial branching tubulogenesis, as well as growth and survival in in vitro and in vivo models. This process involves the upregulation of multiple genes including cytokines, chemokines and other signal transduction effectors (Gerritsen et al., 2003). Additionally, stimulation of Met and VEGFR2 synergistically activates the Erk and p38 pathways. However, while Met and VEGFR2 both activate FAK, the kinetics as well as cytoskeletal remodeling mediated by small GTPases Rho and Rac is distinct (Sulpice et al., 2009). Importantly, Met–VEGFR pathway interactions are implicated in the emergence of resistance to anti-VEGFR2 therapies. In glioblastoma, an initial response to the VEGF antibody bevacizumab is transient and often followed by radiographic progression attributed to resistance to this anti-angiogenic therapy (Bergers & Hanahan, 2008). Gene expression studies comparing primary glioblastoma to bevacizumab-treated tumors revealed *MET* as one of the most upregulated genes. Moreover, in a bevacizumab-resistant glioblastoma model genetic ablation of Met reversed resistance and reduced tumor cell invasion and survival (Jahangiri et al., 2013). Thus, Met activation is implicated in the upregulation of alternate pathways that help evade VEGFR2 inhibition and result in increased vascularization, invasiveness and metastasis (Ebos et al., 2009; Paez-Ribes et al., 2009). Data from several preclinical models suggested that Met upregulation both in tumor cells and endothelial cells is related to vascular pruning, hypoxia and elevation of hypoxia-inducible factor Hif1a. In these models, dual blockade of Met and VEGFR2 using small molecule inhibitors or antibodies reduced metastasis and improved survival compared to single pathway blockade (You et al., 2011; Sennino et al., 2012). The upregulation of Met as a consequence of VEGFR2 inhibition was also observed in lymphatics in RIP-Tag2 transgenic mice, driving lymphangiogenesis and providing a mechanism for lymph node metastases. Combined inhibition of Met and VEGFR2 with selective agents reversed lymph node metastasis in this model (Sennino et al., 2013). Interestingly, a novel hypoxia-independent but anti-VEGF-dependent pathway leading to Met activation was recently described (Lu et al., 2012). In this model, PTP1B (PTPN1) was recruited to a Met/VEGFR2 complex in a VEGF-dependent manner resulting in the inhibition of Met phosphorylation, and the abrogation of Met-dependent activities including tumor cell migration. In contrast, Met activation resulted as a consequence of VEGF ablation leading to increased invasiveness, along with corresponding changes in markers of EMT. This response was reversed upon Met knockdown (Lu et al., 2012). Importantly, in clinical samples from GBM patients treated

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with bevacizumab, Met phosphorylation correlated with mesenchymal markers such as vimentin and CD44 and moreover, significantly higher levels of mesenchymal markers were associated with bevacizumab-resistant tumors (Lu et al., 2012). Together these results suggested that targeting simultaneously the Met and VEGFR pathways represents a promising approach to cancer treatment by directly targeting multiple pathways involved in angiogenesis, tumor survival and metastasis.

Met activation was identified as one of the alternate pathways associated with resistance to the BRAF inhibitor vemurafenib, which targets the BRAF activating mutant V600E, in melanoma (Chapman et al., 2011). Exogenous stimulation of melanoma cells with HGF resulted in resistance to vemurafenib in vitro and in vivo (Straussman et al., 2012; Wilson et al., 2012). Furthermore, in patient-derived melanoma cell lines in which *MET* amplification and activation is an underlying mechanism of primary resistance to vemurafenib, genetic ablation of *MET* together with BRAF inhibition efficiently reduced cell growth and invasion (Vergani et al., 2011). Importantly, stromal HGF expression in patients with mutant BRAF correlated with Met phosphorylation/activation and primary resistance to vemurafenib (Straussman et al., 2012). The mechanisms involved in primary resistance to BRAF inhibition include Erk/MAPK and PI3K/Akt activation and were described both in cancer cell lines and patient-derived melanoma cells (Straussman et al., 2012; Wilson et al., 2012).

It has become clear that RTK activation drives alternate pathways as a common mechanism of resistance to targeted therapies. While activation can be achieved through gene amplification or increased protein expression, recent studies have further dissected the role of ligand-mediated activation of RTKs in the emergence of drug resistance (Harbinski et al., 2012; Wilson et al., 2012). Using high-throughput screening of a cDNA library for secreted proteins, it was shown that Met, HER family receptors, and fibroblast growth factor family receptors (FGFR) compensate for each other through ligand-mediated activation of redundant downstream pathways regulating cancer cell growth and survival (Harbinski et al., 2012) (Fig. 2d). Consistent with these findings, Met and HER2 were found to contribute to emerging resistance to the FGFR inhibitor AZ8010 in HNSCC (Singleton et al., 2013). Thus, knockdown or drug inhibition of Met and HER2 resulted in sensitization of cells to AZ8010; further, optimal inhibition of cancer cell growth was obtained with triple combination of Met, HER2, and FGFR inhibitors (Singleton et al., 2013).

In addition to its role in resistance to targeted therapies, Met has also been implicated in resistance to systemic chemotherapy (Guryanova & Bao, 2011). For example, Met expression was elevated in HNSCC tumors following cisplatin treatment, and Met-positive HNSCC cells demonstrated increased metastasis (Sun & Wang, 2011). In cervical cancer cell lines, cisplatin-induced Met expression was observed and mediated by platelet-derived growth factor α (PDGFRα) activation (Kina et al., 2013). Alternatively, in ovarian cancer cells, increased Met expression mediated through downmodulation of the Met repressor miR-31 induced resistance to taxanes (Mitamura et al., 2013). Met is also thought to play a role in resistance to radiation therapy (Ganapathipillai et al., 2008). In fibroblast cultures, activation of Met resulted in DNA repair signaling. In cancer cell lines radiation induced the upregulation of Met transcription, Met overexpression and activation, radioresistance and increased invasiveness. In this context, Met inhibition with small molecule inhibitors (PHA665752 or JNJ-38877605) reestablished cell sensitivity to radiation (De Bacco et al., 2011).

3.4. Mechanisms of resistance to Met inhibitors

Met-targeted agents are currently undergoing clinical trials with early evidence of activity, which will undoubtedly be accompanied by an increased interest in mechanisms of resistance to these agents. Potential mechanisms of resistance to Met-targeted agents have been identified in preclinical assessments. In gastric carcinoma cells (Met-dependent GTL16 cells) exposed to increasing doses of Met-selective inhibitors (PHA-665752 or JNJ38877605) the underlying mechanism of resistance was ascribed to *MET* amplification with subsequent amplification and overexpression of *KRAS* (Cepero et al., 2010). Met mutation in the activation loop (Y1230H) has been associated with resistance to Met inhibitors (PHA-665752 and PF-2341066) (Qi et al., 2011). This mutation causes a conformational change to destabilize the Met auto-inhibitory conformation, leading to persistent Met phosphorylation, and preventing Met interaction with inhibitors. Overexpression of this mutant in carcinoma cells was sufficient to drive resistance to Met inhibitors (Qi et al., 2011). In the same study, an alternate mechanism of resistance to Met inhibition involved the activation of EGFR following an elevation in the expression of its ligand, transforming growth factor α (TGFα). In this context, inhibition of both Met and EGFR was required for efficient inhibition of cell viability (Qi et al., 2011).

Increased HGF expression resulting in Met activation via an autocrine or paracrine loop may create a compensatory effect leading to Met-targeted drug resistance. In AML cells, drug resistance to a Met-selective inhibitor (crizotinib) was linked to upregulation of HGF expression and restoration of Met signaling (Kentsis et al., 2012). In cells where Met was co-expressed with an altered FGFR, knockdown of FGFR1 prevented HGF upregulation in response to chronic crizotinib treatment, and combination of Met and FGFR inhibition (with crizotinib and PD173074, respectively) synergized to overcome crizotinib resistance (Kentsis et al., 2012). Taken together, these data suggest that resistance to Met inhibition involves multiple mechanisms including upregulation of Met-mediated signals, mutations in the Met kinase domain, and upregulation of alternative pathways involving other RTKs such as EGFR and FGFRs, the latter providing potential for combination of targeted therapies for improved clinical responses.

Although clinical data on mechanisms of resistance to Met therapies is scarce, a recent case report documented disease recurrence in a metastatic gastric cancer patient treated with onartuzumab after an initial complete response that lasted two years (Catenacci et al., 2011). This patient exhibited *MET* polysomy and a particularly high level of circulating HGF which significantly diminished upon treatment with onartuzumab. Analyses aimed at the identification of a mechanism for the recurrence revealed a lack of *MET* amplification, and evidence for a potential increase in Met expression (Catenacci et al., 2011). Additional studies showed transient *KRAS* amplification which was not sustained at the time of recurrence (Catenacci et al., 2011). Thus, the molecular mechanism for resistance to the Met therapy in this patient remains to be determined. However, as clinical trials with Met agents progress, it will be critical to ensure collection of tumor samples at the time of progression to investigate molecular basis of resistance, to help design future trials aiming for success.

4. Drug development

Several drugs that target HGF/Met, including both antibodies and small molecule inhibitors have reached clinical evaluation or shown promise in preclinical models (Table 2). Antibodies targeting either HGF or Met prevent the ligand–receptor interaction and consequently impact downstream Met signaling. Small molecule inhibitors are generally designed to target the active site of the receptor, inhibiting phosphorylation and recruitment of signaling effectors. Sub-classes were suggested based on the small molecule chemotype and binding mode to the Met kinase (Dussault & Bellon, 2009). Class I inhibitors are believed to be ATP-competitive inhibitors of the activated kinase, interact with Y1230 and as a consequence are generally weak inhibitors of Met Y1230 mutants. Class II inhibitors are also ATP-competitive but interact in a more extended conformation engaging additional residues in the kinase domain available upon conformational changes (Dussault & Bellon, 2009; Underiner et al., 2010). A third unique mode of action was identified for the non-ATP competitive inhibitor tivantinib (ARQ197) that binds to an inactive Met conformation, favoring stabilization of the receptor in an auto-inhibited conformation (Eathiraj et al., 2011).

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Table 2
Drugs targeting HGF/Met.

Drug	Company	Molecular targets
Small molecule inhibitors		
Crizotinib (Xalkori; PF-02341066)	Pfizer	Met, ALK, ROS1
Cabozantinib (Cometriq, XL184)	Exelixis	Met; VEGFR2, VEGFR-1, and -3, RET, KIT, TRKB, FLT-3, AXL, and TIE-2
Tivantinib (ARQ197)	Arqule	Inactive or unphosphorylated c-Met
Foretinib (GSK1363089; XL880)	GSK/Exelixis	Met; VEGFR2; KIT, Flt-3, PDGFR β, Tie-2
INC280 (formerly INCB28060)	Novartis	Met
Golvatinib (E7050)	Eisai	c-Met, VEGFR-2
MGCD265	MethylGene	Met, VEGFR 1,2,3, Axl
LY-2801653	Eli Lilly	Met, MST1R, FLT3, AXL, MERTK, TEK, ROS1, DDR1/2, MKNK1/2
AMG 208	Amgen	Met
AMG 337	Amgen	Met
EMD 1214063	Merck Serono	Met
MK-8033	Merck	Met; Ron
ASLAN002 (BMS-777607)	ASLAN Pharmaceuticals	Met, Axl, Ron, Tyro3
Volitinib (HMPL-504)	Hutchison Medipharma Limited	Met
MK-2461	Merck	Met, FGFR, PDGFR
MSC2156119J	Merck	Met
Sar125844	Sanofi	Met
Tas 115	Taiho	Met/VEGFR
Antibodies		
Onartuzumab (MetMab)	Genentech (Roche)	Met
Rilotumumab (AMG102)	Amgen	HGF
Ficlatuzumab (AV-299)	Aveo	HGF
TAK-701	Takeda Pharmaceuticals Co	HGF
LY-2875358	Eli Lilly	Met
ABT-700	AbbVie	Met
ARGX111	arGEN-x	Met

4.1. Efficacy and safety results from Phase II and III clinical trials

4.1.1. Small-molecule inhibitors

4.1.1.1. Crizotinib. Crizotinib is a multi-targeted receptor tyrosine kinase inhibitor that inhibits Met, anaplastic lymphoma kinase (ALK) and ROS1. This drug was approved for treatment of NSCLC patients who express an altered form of ALK (EML4-ALK), after a rapid and focused development path, culminating in a Phase III trial that showed marked improvements in efficacy outcomes for patients on crizotinib monotherapy, as compared with standard second-line chemotherapy (Shaw et al., 2013) (Table 3). Patients who received crizotinib had a significantly longer median progression-free survival (PFS) (7.7 months vs 3.0 months chemotherapy; $P < .001$), and higher overall response rate (65% vs 20%; $P < .001$) (Shaw et al., 2013). Crizotinib maintained superiority versus each cytotoxic agent in separate subgroup analyses (Solomon et al., 2013) and significantly greater improvement in quality of life measures were observed among patients treated with crizotinib versus those treated with chemotherapy (Hirsh et al., 2013). Common side effects among patients who received crizotinib were mild vision disorders, diarrhea and nausea (Shaw et al., 2013), although cases of asymptomatic profound sinus bradycardia have also been documented (Ou et al., 2011). In addition, there is a case report of a patient who developed fatal severe acute interstitial lung disease after crizotinib therapy (Tamiya et al., 2013).

Although the primary focus of crizotinib has been on the ALK target, substantial data supports its role as a Met-targeted agent. In preclinical studies, crizotinib selectively inhibited Met, and potently inhibited HGF-stimulated endothelial cell survival or invasion in vitro (Zou et al., 2007). In vivo, the drug also reduced tumor burden and survival in a xenograft model of ovarian cancer metastasis (Zillhardt et al., 2010). Recently it was reported that a patient with advanced squamous cell carcinoma (SCC) experienced a major partial response on crizotinib monotherapy regime (Schwab et al., 2013). This tumor was Met-amplified in the absence of ALK or ROS1 expression, supporting the potential of crizotinib as a Met-targeted therapeutic in this indication. Retrospective analyses in clinical samples from patients with NSCLC and GBM also support the clinical activity of crizotinib in *MET*-amplified patients (see Section 5.1). Ongoing trials including the Phase II CREATE trial will assess both ALK and Met mutations in other tumor types including anaplastic large cell lymphoma, papillary RCC and soft tissue sarcomas. Crizotinib is also in development for treatment of NSCLC expressing the target ROS1 (U.S.National Institutes of Health, 2013).

4.1.1.2. Cabozantinib. Cabozantinib is an orally bioavailable tyrosine kinase inhibitor targeting Met, VEGFR2, RET, Kit and Flt3, currently approved for the treatment of patients with progressive, metastatic medullary thyroid carcinoma (MTC) (Exelixis Inc., 2013). The efficacy of cabozantinib was first demonstrated in a Phase I trial in patients with metastatic differentiated thyroid cancer (Cabanillas et al., 2012) and a subsequent Phase III trial showed significant anti-tumor efficacy of cabozantinib in a subset of thyroid carcinomas characterized by frequent RET mutations (Schoffski et al., 2012; Sherman et al., 2013). In patients with radiographically progressive MTC, cabozantinib monotherapy significantly prolonged PFS compared to placebo (11.2 months vs 4.0 months; hazard ratio [HR] 0.28; $P < .001$) (Table 3), and PFS improvement was reported for all RET mutation subgroups (hereditary or sporadic) (Elisei et al., 2013). Overall tumor response was reported in 28% of patients (0% in placebo group), over a median duration of 14.6 months (Elisei et al., 2013) and the most frequent adverse events were diarrhea, hand–foot syndrome, decreased weight, decreased appetite, nausea and fatigue (Schoffski et al., 2012).

While RET is a known driver in MTC, cabozantinib is also under investigation in other tumor types where coverage of Met may be a significant determinant of efficacy. Interestingly, significant tumor regression and resolution of bone metastases was demonstrated in multiple tumor types in a Phase II randomized discontinuation trial of cabozantinib 100 mg monotherapy including a cohort of patients with metastatic castration-resistant prostate cancer (CRPC). In this cohort, cabozantinib treatment resulted in partial response in 5% of patients at the end of the 12-week lead-in phase, and disease control rate (DCR) was 66% (Smith et al., 2013) (Table 3). Median PFS was 23.9 weeks (95% CI: 10.7–62.4) for 14 patients subsequently assigned to cabozantinib, compared with 5.9 weeks (95% CI: 5.4–6.6) for placebo patients (Smith et al., 2013). Follow-up analyses reported median overall survival (OS) of 10.8months (95% CI: 9.1–13.0) for all CRPC patients treated with cabozantinib and

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Table 3
Targeted Met inhibitors — results of Phase II and III clinical trials.

Drug	Phase	Population	Intervention	Efficacy outcomes			Main adverse events
				Progression-free survival, median (95% CI)	Overall survival, median (95% CI)	Response rate, %	
Crizotinib	III	Locally advanced or metastatic ALK-positive lung cancer (Shaw et al., 2013)	Crizotinib 250 mg oral bid vs chemotherapy (pemetrexed or docetaxel)	Months: Crizotinib: 7.7 Chemotherapy 3.0	Crizotinib: HR for death: 1.02 (0.68–1.54); $P = .54$	Crizotinib: 65% (58–72) Chemotherapy: 20% (14–26); $P < .001$	Visual disorder, gastrointestinal side effects, and elevated liver aminotransferase levels
Cabozantinib	III	MTC with documented radiographic disease progression (Elisei et al., 2013)	Cabozantinib 140 mg oral qd vs placebo	Months: Cabozantinib: 11.2 Placebo: 4.0 HR: 0.28 (0.19–0.40); $P < .001$ (1-year PFS rate: 47.3% vs 7.2% placebo)	Data not mature	ORR Cabozantinib: 28% Placebo: 0%; $P < .001$ (median duration of response 14.6 months)	Diarrhea, hand–foot syndrome, decreased weight, decreased appetite, nausea, fatigue, dysgeusia, hair color changes
Cabozantinib	II	Metastatic CRPC (Scher et al., 2013; Smith et al., 2013)	Cabozantinib 100 mg oral qd vs placebo	Weeks: Cabozantinib: 23.9 (10.7–62.4) Placebo: 5.9 (5.4–6.6) HR: 0.12; $P < .001$	10.8 (95% CI: 9.1–13.0)	PR: 5% SD: 75% DCR (week 12): 66%	Fatigue, decreased appetite, diarrhea, nausea, weight loss, hand–foot syndrome, taste alterations
		Metastatic NSCLC (Hellerstedt et al., 2012)		Overall: 4.2 months		PR: 10% SD: 48% DCR (week 12): 38%	
		Metastatic refractory RCC (Choueiri et al., 2012)		Overall: 14.7 months	Not reached at median follow-up of 14.7 - months	PR: 28% SD: 52% DCR (week 12): 72%	
		HCC (Verslype et al., 2012)		Overall: 4.4 months	15.1 (8.9–18.3)	PR: 5% SD: 78% DCR (week 12): 66%	
		Metastatic breast cancer (Winer et al., 2012)		Overall: 4.3 months		PR: 14% SD: 57% DCR (week 12): 48%	
		Metastatic uveal melanoma (Daud et al., 2013)		Overall: 4.8 months	12.6		
		Metastatic melanoma (Gordon et al., 2012)		Overall: 4.2 months		PR: 5% SD: 57% DCR (week 12): 46%	
		Ovarian cancer (Buckanovich et al., 2011)		Not reached (median follow-up 4 months (range: 1–11)		ORR (week 12): 24% DCR (week 12): 58%	Hand–foot syndrome (10%), diarrhea (8%), fatigue (4%)
Foretinib	II	Metastatic gastric cancer (Shah et al., 2013)	Foretinib 240 mg oral qd for 5 days then every 2 weeks (intermittent cohort) or foretinib 80 mg oral qd (daily cohort)	Months: Overall: 1.7 (1.6–1.8); Intermittent cohort: 1.6; Daily cohort: 1.8	Months: Intermittent cohort: 7.4 Daily cohort: 4.3	ORR: Intermittent cohort: 0% (0.0–8.0) Daily cohort: 0% (0.0–13.7)	Intermittent cohort: fatigue (43.8%), hypertension (35.4%), nausea (27.1%), diarrhea (27.1%) Daily cohort: fatigue (46.2%), hypertension (15.4%), nausea (26.9%), diarrhea (11.5%)

Foretinib	II	Papillary RCC (Choueiri et al., 2013)	Foretinib 240 mg oral qd on days 1–5 every 14 days (intermittent cohort) or foretinib 80 mg oral qd (daily cohort)	Months: Overall: 9.3 (6.9–12.9); Intermittent cohort: 11.6 (5.8–17.0); Daily cohort: 9.1 (5.78–10.91)	Median OS not reached 1-Yr survival: 70% overall (64% intermittent cohort, 76% daily cohort)	13.5% (6.7–23.5)	Hypertension (81%), fatigue (73%), diarrhea (55%) High rate of non-fatal pulmonary embolism
Foretinib	II	Triple-negative breast cancer (Rayson et al., 2012)	Foretinib 60 mg oral qd				Fatigue (64%), nausea (55%), diarrhea (41%), hypertension (32%), vomiting (27%), anorexia (23%) and rash (14%)
Foretinib	II	Advanced HCC (Yau et al., 2012)	Foretinib 45 mg or 30 mg oral qd	TTP, median: 4.2 months (2.7–7.5)		ORR: 24% (11–40)	Hypertension (36%), decreased appetite (23%), and pyrexia (21%)
Foretinib	II	Recurrent or metastatic HNSCC (Seiwert et al., 2009b)	Foretinib 240 mg oral qd	3.65 months (3.42–5.32)	5.59 months (3.71–not reported)	Best response: SD (median duration 4.11 months)	Fatigue (50%), constipation (36%), hypertension (36%), anorexia (29%), dysphagia (29%), weight loss (29%), increased alanine transaminase (29%), increased aspartate transaminase (29%), dyspnea (29%), headache (29%), and mucosal inflammation (29%)
Tivantinib	III	Non-squamous NSCLC with wt EGFR (Kyowa Hakko Kirin Co Ltd, 2012)	Tivantinib in combination with erlotinib				Trial discontinued due to high frequency of interstitial lung disease
Tivantinib	III	Non-squamous NSCLC with wt EGFR (ArQule Inc., 2012)	Tivantinib in combination with erlotinib	Statistically significant improvement			
Tivantinib	II	HCC (Santoro et al., 2013a)	Tivantinib 240 mg or 360 mg oral bid, or placebo	TTP, median months: Tivantinib: 1.6 (1.4–2.8) Placebo: 1.4 (1.4–1.5) HR 0.64 (0.43–0.94) $P = .04$ *Met-high subgroup*: TTP, median months: Tivantinib: 2.7 (1.4–8.5) Placebo: 1.4 (1.4–1.6) HR 0.43 (0.19–0.97) $P = .03$ PFS, median months: Tivantinib: 2.2 (1.4–4.6) Placebo: 1.4 (1.4–1.4) HR 0.45 (0.21–0.95) $P = .02$	Months: Tivantinib: 6.6 (4.6–9.0) Placebo: 6.2 (3.8–9.4) HR: 0.90 (0.57–1.40); $P = .63$ *Met-high subgroup*: Tivantinib: 7.2 (3.9–14.6) Placebo: 3.8 (2.1–6.8) HR 0.38 (0.18–0.81) $P = .01$	DCR: 44% tivantinib, 31% placebo *Met-high subgroup*: 50% tivantinib, 20% placebo	240 mg: neutropenia (21%), asthenia (18%), anemia (15%), decreased appetite (9%), thrombocytopenia (9%), bradycardia (9%) 360 mg: neutropenia (29%), anemia (16%), fatigue (16%), decreased appetite (11%), diarrhea (11%), thrombocytopenia (8%), leukopenia (8%), vomiting (8%)
Tivantinib	II	Metastatic colorectal cancer expressing wild-type KRas (Eng et al., 2013)	Tivantinib 360 mg bid plus irinotecan and cetuximab	Months: 8.3 (tivantinib) 7.3 (control)		ORR: 45% tivantinib arm, 33% control arm	Elevated neutropenia in tivantinib arm
Tivantinib	II	Advanced or recurrent gastric cancer (Muro et al., 2012)	Tivantinib 360 mg bid	43 days (29–92)		No ORR	Well tolerated
Tivantinib	II	Microphthalmia transcription factor-associated (MiT) tumors (Wagner et al., 2012)	Tivantinib 120 mg oral bid, then 360 mg bid	Months: 3.6 (1.9–5.6)	Months: 21.4 (14.2–29.2)	PR: 2.1%; SD: 57%; ORR (PR + SD): 60%	Fatigue (49%), nausea (43%), vomiting (28%), anemia (17%), neutropenia (13%) and leukopenia (13%)

bid: twice daily; CI: confidence interval; CRPC: castration-resistant prostate cancer; DCR: disease control rate; HCC: hepatocellular carcinoma; HR: hazard ratio; MTC: medullary thyroid carcinoma; NR: not reported; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; qd: once daily; RCC: renal cell carcinoma; SD: stable disease.

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approximately half of these patients had improvements in bone disease and related pain (Scher et al., 2013). In patients with metastatic refractory RCC, overall PFS was 14.7 months, and DCR was 72% (Choueiri et al., 2012). DCR rates in other populations in this trial ranged from 38% for metastatic NSCLC to 66% for HCC (Gordon et al., 2012; Hellerstedt et al., 2012; Verslype et al., 2012; Winer et al., 2012). In all patient populations, the most frequent adverse events during the lead-in stage of this Phase II discontinuation trial included fatigue, decreased appetite, diarrhea, nausea, and weight loss and common grade 3 adverse events were fatigue, hypertension, and hand–foot syndrome (Smith et al., 2013). Given the known roles of the Met receptor in processes fundamental to metastasis, a Met-targeted therapeutic would be predicted to impede this process, which is a significant complication for the majority of advanced prostate cancer patients. Thus far the data available in prostate cancer from other Met-targeted agents is too limited to determine whether the potential effects observed in cabozantinib studies are reflective of targeting Met.

4.1.1.3. Foretinib. Early investigation of foretinib, an oral multikinase inhibitor targeting Met, RON, Axl and VEGFR, revealed an acceptable safety profile and evidence of clinical efficacy in patients with metastatic or unresectable solid tumors (Eder et al., 2010). However, a Phase II study of single-agent foretinib for metastatic gastric cancer found minimal anti-tumor activity (Shah et al., 2013). Overall, patients treated with foretinib had a median PFS of 1.7 months (95% CI: 1.6–1.8); PFS for those administered foretinib daily was 1.8 months, and 1.6 months for patients treated according to an intermittent schedule (Shah et al., 2013). The intermittent cohort had an estimated median OS of 7.4 months, compared with 4.3 months in the daily cohort. No patient treated with either dosing schedule achieved a complete or partial response (Shah et al., 2013). Treatment-related adverse events occurred in 91% of patients; most commonly fatigue, hypertension, and diarrhea (Shah et al., 2013). Another Phase II study reported activity of foretinib among patients with advanced papillary RCC (Choueiri et al., 2013). Foretinib was administered either daily or according to an intermittent dosing schedule; the overall median PFS was 9.3 months (95% CI: 6.9–12.9), 9.1 months (95% CI: 5.78–10.91) for the daily administration cohort and 11.6 months (95% CI: 5.8–17.0) for the intermittent dosing cohort. The overall response rate was 13.5% (95% CI: 6.7–23.5), and median OS was not reached. However, the presence of a germline MET mutation was highly predictive of a response. The most frequently encountered adverse events were hypertension, fatigue and diarrhea (Choueiri et al., 2013). Foretinib is also undergoing evaluation in combination with the anti-HER2 lapatinib in $HER2^{+}$ metastatic breast cancer (Phase 1b). Preclinical data on the respective biological functions of Met and HER2 as well as the role of Met in mediating resistance to HER2-targeted therapy support a complementary efficacy profile for such a combination approach. However, combination therapy may lead to an expanded side effect profile. Recent reports indicate that foretinib is also a potent inhibitor of ROS1 fusions, including a crizotinib-sensitive ROS1 mutant (Davare et al., 2013). Patient enrichment strategies may hold the advantage of directing focus on tumors with targeted MET and/or ROS1 mutations to improve outcome, while reducing risks of toxicity.

4.1.1.4. Tivantinib. The small molecule non-ATP competitive inhibitor tivantinib has been shown to possess weak Met inhibitor activities (Munshi et al., 2010) but was also shown to alter microtubule functions thereby regulating anti-tumor responses (Basilico et al., 2013; Katayama et al., 2013). More recently, glycogen synthase 3 (GSK3) α and β were revealed as novel targets of tivantinib in cancer cells, and blocking of these targets may contribute to the tivantinib anti-tumor responses (Remsing Rix et al., 2013). As such, the relative contribution of these targets to the antitumor activity of tivantinib is not yet clarified. Nonetheless, tivantinib has been the subject of investigation in several late stage clinical trials. In a Phase II trial for patients with HCC refractory to previous treatment, tivantinib monotherapy prolonged time to progression (TTP) and PFS compared to placebo (Table 3; TTP: 1.6 months vs 1.4 months; HR 0.64; $P = .04$), but did not improve OS significantly in the overall intent-to-treat population (Santoro et al., 2013a). Subgroup analyses revealed significant survival advantage in tivantinib-treated patients that express high Met levels (Table 3; OS 7.2 vs 3.8 months, HR: 0.38, $P = .01$; TTP 2.7 months vs 1.4 months; HR 0.43; $P = .03$). A Phase III trial of tivantinib in HCC was initiated in 2013. Tivantinib monotherapy also resulted in modest anti-tumor effects in microphthalmia transcription factor (MITF)-associated (MiT) tumors in a multicenter Phase II trial (Wagner et al., 2012) (Table 3). Among 47 patients with MITF-associated MiT tumors who were treated with tivantinib, median PFS was 3.6 months (95%: 1.9–5.6) and OS was 21.4 months (95% CI: 14.2–29.2). The overall DCR was 60%, comprising 2.1% of patients who achieved a partial response, and 57% who had stable disease (Wagner et al., 2012). In a Phase II study of tivantinib monotherapy in advanced or recurrent gastric cancer, only marginal efficacy was achieved (Muro et al., 2012).

Further investigation of tivantinib efficacy was conducted in a Phase I/II placebo-controlled trial in patients with metastatic colorectal cancer expressing wild-type KRAS (Eng et al., 2013). Preclinical and clinical observations provide a strong rationale for the combination of EGFR inhibitors and Met inhibitors in CRC where Met has been identified as central to resistance to anti-EGFR therapy via a number of mechanisms including *MET* gene amplification and bypass mechanisms (see Section 3.3). In this trial, tivantinib in combination with the anti-EGFR cetuximab and antiproliferative drug irinotecan showed a trend toward improvement of PFS and OS. In addition, two randomized Phase III trials of tivantinib in combination with the EGFR inhibitor erlotinib in non-squamous NSCLC with wild type EGFR were initiated but both were halted early. In one case due to a high incidence of interstitial lung disease, and in the other because interim analysis indicated that the primary endpoint of improved overall survival would not be met (ArQule Inc., 2012; Kyowa Hakko Kirin Co Ltd, 2012). However, a statistically significant improvement in PFS was reported from this trial (ArQule Inc., 2012). Overall, the most common adverse events reported for tivantinib were asthenia, fatigue, vomiting, anemia, decreased appetite, neutropenia, thrombocytopenia and leukopenia (Wagner et al., 2012; Santoro et al., 2013a,b). As noted above, tivantinib has recently been identified as a microtubule-targeted agent. This target coverage is also supported by the safety profile of the agent in clinical trials to date as the high frequency of hematologic side effects may be reflective of a predominantly cytotoxic product profile, rather than a Met-targeted agent. In this context, the limited efficacy of tivantinib observed in the majority of trials may not be reflective of the Met-targeted agents as a class.

4.1.2. Antibodies

4.1.2.1. Onartuzumab. Onartuzumab (MetMAb) is a chimeric, humanized, monovalent monoclonal antibody directed against Met that inhibits the binding of HGF to the Met ligand binding site (Martens et al., 2006; Merchant et al., 2013). In NSCLC, anti-EGFR therapies such as erlotinib and gefitinib are effective for patients expressing activating EGFR mutations. However, these patients eventually develop resistance. Given the role of Met in resistance to anti-EGFR therapy (Section 3.3), synergistic inhibition of Met and EGFR is a promising approach in this indication. Results from a randomized Phase II trial comparing onartuzumab plus erlotinib to erlotinib plus placebo in second and third line NSCLC were very promising. Among the patients with tumors expressing high Met levels (assessed by immunohistochemistry), combination therapy resulted in clinically significant improvements of PFS and OS. In this patient subset, PFS was prolonged by two-fold in the onartuzumab plus erlotinib arm compared with erlotinib plus placebo (2.9 months vs 1.5 months; HR: 0.53 [0.28–0.99]; $P = .04$) and OS was increased by three-fold (12.6 months vs 3.8 months; HR: 0.37 [0.19–0.72]; $P = .002$) (Spigel et al., 2013). This data was strikingly distinct from the intent to treat

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population, where no increased benefit was noted for the onartuzumab/erlotinib combination (see Section 5.1 below). These results are consistent with the well documented cooperation between the Met and EGFR pathways, and a significant role of Met in EGFR-inhibitor resistance. These observations are also a strong indictment for prospective selection of patients with high Met expression as is the case in an ongoing Phase III study of patients with advanced Met-positive NSCLC (Spigel et al., 2012). Of note, despite the improved PFS and OS in the Met positive population, the overall response rate in this subset was not different between treatment groups, which may suggest that in this context Met did not serve as an independent oncogenic driver. A separate randomized Phase II study in lung cancer is assessing onartuzumab in combination with paclitaxel plus cisplatin or carboplatin as first line treatment for squamous NSCLC (U.S.National Institutes of Health, 2013). Preclinical data implicating Met in the development of chemotherapy-induced resistance support this trial rationale (Section 3.3), although the molecular mechanisms involved are not fully understood.

Beyond NSCLC, a Phase II trial in triple-negative breast cancer evaluating a combination of onartuzumab, anti-VEGF bevacizumab and paclitaxel did not meet the primary endpoint of PFS (U.S.National Institutes of Health, 2013). Onartuzumab is also under investigation in a Phase III study of patients with metastatic HER2-negative, Met-positive gastroesophageal cancer, and Phase II trials in metastatic colorectal cancer and glioblastoma (Bendell et al., 2013; Cunningham et al., 2013b; U.S.National Institutes of Health, 2013).

4.1.2.2. Rilotumumab. The efficacy and safety of rilotumumab, a human monoclonal antibody against HGF/SF, in combination with cytotoxic agents epirubicin, cisplatin, and capecitabine were assessed in a Phase I/II trial of patients with gastric or gastroesophageal junction (G/GEJ) adenocarcinoma (Davidenko et al., 2012). Rilotumumab was given at either 15 mg/kg or 7.5 mg/kg. In these patients, rilotumumab combination with chemotherapy prolonged PFS and OS modestly. When data for the two rilotumumab arms was combined, PFS was 5.7 months versus 4.2 months (HR 0.60), and OS was 10.6 months versus 8.9 months (HR 0.70) for rilotumumab plus chemotherapy compared to placebo plus chemotherapy, respectively. However, the treatment effect was found to be more pronounced in Met-positive patients (Oliner et al., 2012). In this population, PFS was 6.9 months versus 4.6 months (HR 0.44), and OS was 11.5 months versus 5.7 months (HR 0.70) for rilotumumab plus chemotherapy compared to placebo plus chemotherapy, respectively. These data suggest that prospectively selecting for Met-positive patients may be important for optimal use of rilotumumab in this indication and a Phase III trial of first-line rilotumumab in combination with epirubicin/cisplatin/capecitabine is underway for patients with advanced Met-positive G/GEJ adenocarcinoma (Cunningham et al., 2013).

Rilotumumab has also been assessed in other indications. In a Phase II study of rilotumumab in combination with panitumumab in colorectal cancer expressing wild type KRAS the response rate for the combination was found to be 31% compared to 21% for panitumumab alone (Eng et al., 2011) (Table 4). A Phase II trial of rilotumumab monotherapy for advanced or metastatic RCC showed efficacy results that were equivocal (Schoffski et al., 2011) (Table 4). PFS among patients who were administered low dose (10 mg/kg) rilotumumab every two weeks had a PFS of 3.7 months (95% CI: 1.8–7.6) compared with only 2.0 months (95% CI: 1.8–3.7) among those who received a higher dose (20 mg/kg). However, median OS was 14.9 months (95% CI: 9.4–not evaluable) in the low dose cohort, and 17.6 months (95% CI: 7.1–not evaluable) for the patients treated with higher doses. Those treated with low dose rilotumumab had an overall response rate of 2.5%, compared with 0% at higher dose. Differences between the low and high dose cohorts may stem from an imbalance of patient baseline characteristics (Schoffski et al., 2011). Phase II studies in glioblastoma and in taxane-refractory CRPC in combination with mitoxantrone did not show significant clinical activity for rilotumumab (Wen et al., 2011; Ryan et al., 2013) (Table 4). Edema was the most frequent adverse event, followed by fatigue and nausea (Schoffski et al., 2011).

4.1.2.3. Ficlatuzumab. Ficlatuzumab is a humanized antibody directed against HGF. This antibody was shown to inhibit tumor growth in multiple preclinical models including NSCLC and HNSCC as well as Met phosphorylation and Akt activation in tumor tissues. In addition, combination with EGFR inhibitors also demonstrated enhanced antitumor activities compared to treatment with either agent alone (Meetze et al., 2009, 2012). In clinical studies, ficlatuzumab demonstrated a potential benefit for the treatment of lung adenocarcinoma in a Phase II investigation of 188 Asian treatment-naïve patients (Mok et al., 2012) (Table 4). Patients unselected for EGFR mutational status were treated with ficlatuzumab in combination with the anti-EGFR, gefitinib or gefitinib alone. The treatment groups did not show a statistically significant difference in response rate or PFS. Interestingly, despite the small number of patients in subgroup analyses, a trend toward prolonged OS in patients with stromal HGF expression was reported as well as a trend for improved overall response rate and PFS for a subset of patients who received combination therapy and who had low Met expression and EGFR-sensitizing mutations. This suggested the possibility that Met inhibition delayed the onset of resistance to the EGFR therapy and disease progression. However, in this trial there was no increased clinical response in the subgroup of patients expressing high Met protein, in contrast to the findings with onartuzumab and erlotinib combination treatment (see above) (Mok et al., 2012; D'Arcangelo & Cappuzzo, 2013). The molecular basis for this discrepancy is yet to be confirmed, and may reside in the distinct anti-EGFR agents used or mechanistic differences in blocking the Met receptor with onartuzumab in combination with erlotinib compared to HGF with ficlatuzumab in combination with gefitinib. However, treatment with the anti-HGF rilotumumab did demonstrate improved clinical outcomes in Met high patients albeit in combination with epirubicin, cisplatin and capecitabine in unresectable locally advanced or metastatic gastric esophagogastric junction carcinoma patients (see above). Thus, the difference in Met levels dependence between anti-Met/onartuzumab and anti-HGF/ficlatuzumab cannot simply be accounted for by targeting Met or HGF, respectively. These results highlight the complexity in understanding the difference between targeting the receptor versus the ligand, the distinct predictive potential of expression of high/low Met levels which may be indication-specific and rely on the combination regimens.

4.2. Met inhibitors in early-stage development

Several Phase I studies of drug candidates targeting HGF/Met have been completed (Cecchi et al., 2012). These include INC280, a small molecule selective Met inhibitor, which had a favorable pharmacokinetic profile and manageable toxicity in patients with treatment-refractory neoplastic disease. Another highly selective Met inhibitor, EMD 1214063, showed antitumor activity in preclinical models and in a Phase I dose-escalation trial in patients with advanced solid tumors, where two patients showed an unconfirmed partial response and one patient prolonged stable disease. In addition, inhibition of Met phosphorylation was revealed in pre- and on-treatment tumor biopsies (Falchook et al., 2013). Early results from Phase I evaluation of TAK-701, a monoclonal anti-HGF antibody, showed that it was well-tolerated up to 20 mg/kg bi-weekly; more serious treatment-related adverse events included ileus, muscular weakness, asthenia, urinary tract infection and dehydration. LY-2875358 is a novel humanized bivalent antibody to Met that blocks HGF binding and leads to Met internalization and degradation, thus targeting both HGF-dependent and -independent Met functions (Wortinger et al., 2012; Zeng et al., 2012). In preclinical studies LY-2875358 showed promising activity, including against Met mutants that were unresponsive to onartuzumab (Zeng et al., 2013). This antibody is in Phase I combination studies with erlotinib (Goldman et al., 2013).

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Table 4
HGF/Met antibodies — results of Phase II clinical trials.

Drug	Phase	Population	Intervention	Efficacy outcomes			Main adverse events
				Progression-free survival, median (95% CI)	Overall survival, median (95% CI)	Response rate, %	
Onartuzumab	II	NSCLC (Spigel et al., 2013)	Onartuzumab + erlotinib vs erlotinib plus placebo	Met-high subset, months: combination: 2.9 Erlotinib + placebo: 1.5 HR: 0.53 (0.28–0.99); $P = .04$	Met-high subset, months: combination: 12.6 Erlotinib + placebo: 3.8 HR: 0.37 (0.19–0.72); $P = .002$	Met-high subset: combination: 8.6% Erlotinib + placebo: 3.2%	rash, diarrhea, fatigue, nausea, decreased appetite, peripheral edema
Rilotumumab	II	Gastric or gastroesphageal junction adenocarcinoma (Davidenko et al., 2012; Oliner et al., 2012)	Rilotumumab 15 mg/kg or 7.5 mg/kg + epirubicin/cisplatin/ capecitabine vs placebo	Months: Rilutumumab arms combined: 5.7 Placebo: 4.2 HR 0.60 (0.39–0.91) Met high subset months: Rilutumumab arms combined: 6.9 Placebo: 4.6 HR 0.44 (0.20–0.96)	Months: Rilotumumab arms combined: 10.6 Placebo: 8.9 HR 0.70 (0.45–1.09) Met high subset months: Rilutumumab arms combined: 11.5 Placebo: 5.7 HR 0.34 (0.15–0.78)		Neutropenia, thrombocytopenia, deep vein thrombosis grade 3/4/5 AEs in all arms
Rilotumumab	II	Wild type KRAS-positive colorectal cancer (Eng et al., 2011)	Rilotumumab + panitumumab vs panitumumab alone	Combination: 5.2 (3.6–5.4) Panitumumab alone: 3.7 (2.5–5.3)		PR: 31% vs 21% SD: 40% vs 35%	
Rilotumumab	II	CRPC (Ryan et al., 2013)	Rilotumumab 15 mg/kg + mitoxantrone + prednisone vs rilotumumab 7.5 mg/kg vs placebo	Months: Combination: 3.0 Placebo: 2.9 HR 1.02 (80% CI: 0.79–1.31)	Months: Combination: 12.2 Placebo: 11.1 HR 1.10 (80% CI: 0.82–1.48)	NR	Peripheral edema (24%)
Rilotumumab	II	Glioblastoma or gliosarcoma (Wen et al., 2011)	Rilotumumab 10 mg/kg vs rilotumumab 20 mg/kg iv. every 2 weeks	Weeks: 10 mg/kg: 4.1 (4.0–4.1) 20 mg/kg: 4.3 (4.1–8.1)	Months: 10 mg/kg: 6.5 (4.1–9.8) 20 mg/kg: 5.4 (3.4–11.4)	CR: 0% either cohort; PR: 0% either cohort; SD: 10 mg/kg: 10% 20 mg/kg: 15%	Fatigue (38%), headache (33%), and peripheral edema (23%)
Rilotumumab	II	Advanced or metastatic RCC (Schoffski et al., 2011)	Rilotumumab 10 mg/kg vs rilotumumab 20 mg/kg iv. every 2 weeks	Months: 10 mg/kg: 3.7 (1.8–7.6) 20 mg/kg: 2.0 (1.8–3.7)	Months: 10 mg/kg: 14.9 (9.4–not evaluable); 20 mg/kg: 17.6 (7.1–not evaluable)	10 mg/kg: 2.5%; 20 mg/kg: 0%	Edema (45.9%), fatigue (37.7%) and nausea (27.9%)
Ficlatuzumab	II	Lung adenocarcinoma (Mok et al., 2012)	Combination (Ficlatuzumab 20 mg/kg + gefitinib 250 mg qd) vs gefitinib 250 mg qd	Months: Combination: 5.6; Gefitinib: 4.7 HR 0.89 (0.64–1.23); $P = .47$	OS data: not yet fully mature HR 0.84 (0.52–1.37)	Combination: 43% (32–53); Gefitinib: 40% (30–51)	Paronychia (47%), peripheral edema (38%), acne (27%), hypoalbuminuria (20%), dizziness (19%), eczema (17%), gingival bleeding (12%)

AE: adverse event; CI: confidence interval; CR: complete response; CRPC: castration-resistant prostate cancer; HR: hazard ratio; iv: intravenous; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; RCC: renal cell carcinoma; SD: stable disease.

MGCD265 is a multi-targeted kinase inhibitor which potently inhibits key pathways including Met, Axl and VEGFR1-3 that is being developed by Mirati Therapeutics. In preclinical Met-driven tumor models MGCD265 exhibited anti-tumorigenic activity that correlated with inhibition of Met phosphorylation, cell proliferation and increased apoptosis (Fournel et al., 2012). Combination of MGCD265 with the EGFR inhibitor erlotinib led to increased antitumor activity, in keeping with the synergism predicted from the crosstalk between the EGFR and Met-dependent signaling pathways (Bonfils et al., 2012). MGCD265 has an acceptable safety and tolerability profile to date with over 200 patients treated in Phase I and I/II trials (Mirati Therapeutics, 2013). MGCD265 is being assessed both as monotherapy and in combination with docetaxel or erlotinib; development will include patient selection strategies for tumors exhibiting deregulated Met and/or Axl, in order to target the population most likely to be responsive to therapy. The ability of MGCD265 to simultaneously inhibit both Met and Axl may confer specific advantages in situations where resistance to EGFR inhibitors is common, such as NSCLC and HNSCC; likewise, the anti-VEGFR activity may address or circumvent resistance to angiogenesis inhibitors.

MK-2461 is a tyrosine kinase inhibitor of Met, Ron and Flt1. This molecule inhibited phosphorylation sites in the Met juxtamembrane (Y1003) and carboxy-terminal domain (Y1349 and Y1365) as opposed to tyrosine sites within the activation loop (Y1234/Y1235) suggesting preferential binding of the molecule to activation-loop phosphorylated Met (Pan et al., 2010). In Phase I/II studies, MK-2461 had a half-life of ~6 h and was well-tolerated with few adverse events above grade 1 (Cecchi et al., 2012). Golvatinib is a Met and VEGFR-2 tyrosine kinase inhibitor that has reached Phase I/II trials in solid tumors and HCC (U.S.National Institutes of Health, 2013). In mouse xenograft and peritoneal dissemination models, golvatinib promoted tumor regression and prolonged survival of treated mice (Nakagawa et al., 2010). The drug was well tolerated and the most common treatment-related adverse events were nausea, vomiting and diarrhea (Daniele et al., 2012; Doi et al., 2012).

Anti-Met drugs in experimental and preclinical development include MGCD516 (*Mirati Therapeutics*), a small molecule with potent activity against Met, Axl, Trk, Ret, VEGFR, DDR and Eph receptor families. MGCD516 inhibits proliferation and vascularization of tumor xenograft models including those driven by Met, Ret or Axl (Beaulieu et al., 2013). BAY-853474 (*Bayer Pharma AG*) is a specific inhibitor that blocks Met phosphorylation, and T-1840383 (*Takeda Pharmaceuticals Company*) is a small-molecule kinase inhibitor against Met and VEGFR family. Both of these agents have been efficacious in tumor models (Klotz et al., 2012; Awazu et al., 2013). KRC-408 (*Department of Biomedical Sciences and NCEED, Inha University, Korea*) inhibits Met phosphorylation and downstream signaling, and has shown activity in gastric cancer and colorectal carcinoma xenograft models (Gao et al., 2013; Hong et al., 2013). TAS-115 (*Taiho Pharmaceuticals Co.*) is a dual Met/VEGFR inhibitor that showed promising anti-proliferative efficacy and tolerable safety profile (Fujita et al., 2011b,a).

4.3. Met-targeted agents summary

In summary, there is a great degree of activity in the area of Met-targeted cancer therapeutics. The most advanced small molecule inhibitors of Met also cover other targets. The specific contribution of Met inhibition to the overall activity of these agents may be difficult to isolate within the available clinical data, although results suggest that targeting Met alterations provides a clinical benefit (see Section 5). Therapeutic antibodies target specifically the Met/HGF axis and in contrast to small molecule inhibitors, the consequences of inhibiting the ligand–receptor interaction may be more readily elucidated. One shortcoming of this approach is the inability of therapeutic antibodies to block ligand-independent Met activation, but the design of novel anti-Met antibodies may overcome this limitation. Although clinical results with Met-targeted agents have not shown overwhelming results as single agents in unselected populations, improved outcomes in patients with Met alterations have been observed, supporting biomarker-driven strategies and the incorporation of patient selection moving forward (further discussed in Section 5).

To date the most promising clinical data comes from combination therapies in which Met is believed to play a role in mechanisms of drug resistance. Current combination trials with Met agents were recently highlighted (Cecchi et al.,2012). Approaches that combine inhibition of Met with other EGFR family inhibitors are likely to be more effective than Met-targeted monotherapy due to overcoming primary resistance and/or avoiding acquired resistance as well as the potential to address alteration of multiple activated pathways and tumor heterogeneity. As described in Section 3.3, Met and EGFR family are frequently co-expressed, functionally collaborate and Met/HGF have consistently been found altered in patients resistant to EGFR therapies, providing a strong rationale for combining agents targeting these pathways. There are currently ongoing trials assessing the combination of erlotinib with onartuzumab in NSCLC and cabozantinib in NSCLC. There are also clinical investigations of the dual mode Met-targeted antibody LY2875358 with erlotinib in NSCLC, the small molecule Met inhibitors INC280 in combination with gefitinib in NSCLC and MGCD265 in combination with erlotinib in solid tumors including NSCLC. In addition, foretinib is in clinical evaluation in combination with the anti-HER2 lapatinib in $HER2^{+}$ metastatic breast cancer and golvatinib in combination with cetuximab is in trials for head and neck cancer. The inhibition of Met and VEGFR pathway is likewise promising given the wealth of preclinical translational data supporting the advantages of blocking both pathways (Section 3.3 above). Several clinical trials are underway with anti-angiogenic combinations such as onartuzumab plus bevacizumab in GBM, onartuzumab plus bevacizumab and FOLFOX chemotherapy in first line metastatic CRC and onartuzumab plus the anti-angiogenic multi-kinase inhibitor sorafenib in advanced HCC.

Additional combinations with chemotherapy may also be promising, given the reports of elevated Met expression in response to chemotherapy (Section 3.3) and including onartuzumab plus FOLFOX and rilotumumab plus epirubicin/cisplatin/capecitabine in GE cancers.

Met-targeted agents in general have been shown to be relatively well tolerated with Met and HGF-targeted antibodies demonstrating a cleaner safety profile. To date, the most commonly reported adverse events related to Met pathway blockade included peripheral edema which was detected for both Met-targeted onartuzumab and HGF-targeted agents. The use of small molecule inhibitors was accompanied by a larger safety signal. However, since these agents inhibit additional non-Met targets, toxicities maybe related to the blocking of alternate pathways. For example, among the noticeable events were vascular toxicities such as hypertension potentially resulting from coverage of VEGFR2. Other side effects present a complex etiology as is the case for tivantinib where toxicities may derive from microtubule-targeted activity. Nevertheless, some reported toxicities are significant. Of note, cabozantinib prescribing information includes a boxed warning describing risks of perforations and fistulas and severe sometimes fatal hemorrhage and a trial of tivantinib in NSCLC was halted due to interstitial lung disease.

5. Met biomarkers

The frequency of Met alterations and their prognostic potential as well as the involvement of Met activation in drug resistance collectively support the development and use of Met-related biomarkers in clinical development of Met-targeted agents. High levels of Met protein and/or RNA expression were shown to be prognostic in multiple indications and the ability to predict sensitivity of cancer patients to Met-targeted agents could have significant benefit.

5.1. Clinical and preclinical research findings

Whether Met alterations are predictive of responses to Met inhibiting agents is a fundamental question under investigation in

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multiple clinical scenarios. Early results indicate improved responses in patients with high level *MET* amplification and protein expression in certain indications, suggesting that *MET* amplification and/or high level of protein expression could serve as biomarker for prospective patient selection. *MET* amplification predicted sensitivity to multiple Met-targeted agents including crizotinib in preclinical studies as well as in several clinical case reports (Lennerz et al., 2011; Ou et al., 2011b; Tanizaki et al., 2011). In a subset of esophagogastric adenocarcinoma patients, high level *MET* amplification was detected by FISH and correlated with responsiveness to crizotinib, although this response was transient (Okuda et al., 2008; Lennerz et al., 2011). Similar results were obtained in a case report of recurrent glioblastoma (Chi et al., 2012). A durable response to crizotinib was observed in a NSCLC patient with de novo *MET* amplification (Ou et al., 2011). Also a prolonged response to onartuzumab was described in a gastric cancer patient with evidence of *MET* polysomy and elevated HGF suggesting Met activation through an autocrine loop (Catenacci et al., 2011).

Multiple trials with Met-targeted agents included retrospective analysis of Met protein expression in relation with clinical responses. Of these, a single agent tivantinib study, in patients with advanced HCC expressing high Met levels (immunohistochemistry [IHC] score 2+ in ≥50% cells), tivantinib treatment resulted in statistically significant survival benefits compared to placebo (TTP HR: 0.43, $P = .03$; OS HR: 0.38, $P = .01$) (Table 3), whereas no differences were reported between treatment groups of patients expressing low Met levels (Santoro et al., 2013a). Using the same assessment criteria, a retrospective analysis of NSCLC tumors treated with tivantinib plus erlotinib failed to demonstrate a predictive value for Met expression (Zahir et al., 2012). In subgroup analyses, it was shown that Met expression could have predictive potential only in Met-positive patients with nonsquamous histology, suggesting that the clinical relevance of Met biomarker for tivantinib may vary among tumor types (Rodig et al., 2012).

An ongoing Phase III trial of onartuzumab in combination with erlotinib in NSCLC is selecting for Met diagnostic-positive patients, as determined by scoring criteria established in a Phase II trial of this agent (Spigel et al., 2012, 2013). Specifically, Met-positive patients were defined as those for whom at least 50% of tumor cells stained positive for Met with IHC intensity of 2+/3+ (Spigel et al., 2012). The Phase II trial did not show significant clinical activity in unselected patients, but subgroup analyses demonstrated a benefit in PFS and OS in patients that were diagnostic-positive (see Section 4.1.2; Spigel et al., 2013). Patients who expressed low levels of Met demonstrated worse outcome than placebo and the reason for this remains unclear. Another intriguing trial is that of ficlatuzumab in combination with gefitinib, where the combination failed to significantly improve clinical outcomes in previously untreated lung adenocarcinoma patients (Mok et al., 2012). However, subgroup analyses showed that patients with low levels of Met protein (IHC intensity score 1 in ≤25% cells) showed a trend toward improvement of OS/PFS and response rate in the combination, this trend was not maintained in patients with higher Met expression. These results did not replicate the results observed with onartuzumab, and reasons for this discrepancy remain unknown (Mok et al., 2012). In a rilotumumab combination trial with epirubicin/cisplatin/capecitabine in patients with G/GEJ adenocarcinoma, the subset of tumors with high Met expression (IHC score ≥1+ in >50% cells) showed significant OS and PFS improvement for the combination compared to chemotherapy alone (see Section 4.1.2), suggesting that Met expression could be used as a predictive marker for response to rilotumumab in this setting (Oliner et al., 2012).

While several Phase II trials support the concept that high level Met expression predicts responses to Met agents, the question remains open as to whether patient selection based on Met mutations will drive clinical responses. Hints of responses come from a retrospective analysis of a Phase II trial of foretinib in papillary RCC where germline mutations of Met were predictive of clinical response (Choueiri et al., 2013). Patients carrying a *MET* germline mutation experienced partial response (5/10) or stable disease (5/10), compared to only 9% (5/57) of patients with no Met mutations (Choueiri et al., 2013). While these results are encouraging, confirmation is awaited from prospective trials.

The extent of target inhibition is central to the development strategies of target-precise agents. Potent inhibition of Met activity at drug exposures that are attainable and safe in humans is highly desirable, therefore pharmacodynamic endpoints that indicate the degree of Met inhibition are critical. Met activation can be judged by the phosphorylation status of tyrosine residues in the kinase domain or carboxy-terminal tail as a decrease in activation is associated with a reduction in Met phosphorylation. In multiple preclinical xenograft models the inhibition of Met phosphorylation was associated with tumor growth inhibition by Met-targeted agents. In foretinib studies, decreased levels of phosphorylation of downstream effectors Gab1 and Erk were used as pharmacodynamic indicators (Huynh et al., 2012). Pharmacokinetic and pharmacodynamic modeling based on readouts of Met phosphorylation/activation were used in xenograft models testing crizotinib, to establish the required level of drug exposure to reach maximal Met inhibition and guide clinical trial designs (Yamazaki et al., 2012). Importantly, in clinical pre/post treatment patient biopsies, changes in Met phosphorylation and activation of downstream signaling effectors were observed in response to several anti-Met agents (Eder et al., 2010; Yap et al., 2011; Klotz et al., 2012). For example, treatment with foretinib or tivantinib led to a decrease in the level of Met phosphorylation and activation of Erk and Akt pathways in post-treatment biopsies. However, it remains unclear whether changes in these markers are predictive of clinical responses (Eder et al., 2010; Feldman et al., 2013; Santoro et al., 2013b,a).

Additional proof of target coverage comes from evaluation of Met-related biomarkers in plasma including HGF and shed-Met, as well as angiogenic cytokines and receptors such as VEGF, soluble-VEGFR2 and interleukin IL-8 for agents co-targeting VEGFRs. Several clinical trials evaluated changes in these circulating markers. Notably, in Phase I and II trials of patients treated either with single agent onartuzumab or in combination with erlotinib, the median level of plasma HGF increased from baseline over two-fold (Penuel et al., 2013). In the absence of correlation with drug exposure, it was suggested that the increase in HGF was due to the ability of onartuzumab to displace HGF by interfering with its Met binding (Penuel et al., 2013). In these same trials and consistent with earlier data, baseline levels of HGF in cancer patients were over two-fold higher than in healthy donors. However, no correlation was observed between the levels of HGF at baseline (or upon treatment) and tumor Met expression (Penuel et al., 2013). Interestingly, in a case report of a gastric cancer patient with complete response to single agent onartuzumab, the high level of HGF significantly dropped, suggesting that this patient demonstrated autocrine Met activation resulting from increased levels of stromal HGF, contributing to the circulating pool of HGF (Catenacci et al., 2011). This pharmacodynamic effect warrants further study to confirm validity. The HGF-antibody rilotumumab also induced a significant increase in HGF suggested to be related to the augmentation of the HGF half-life as a consequence of antibody binding, and/or to a compensation mechanism increasing level of HGF expression (Gordon et al., 2010).

Shedding of the Met extracellular domain was assessed as a pharmacodynamic marker in multiple trials. A trend towards an increase in shed-Met was observed upon treatment with Met-targeted agents (Penuel et al., 2013). In the case of onartuzumab this increase was explained by altered clearance of antibody-Met complexes. Shed-Met has previously been associated with malignancy (Athauda et al., 2006). However, no trend with clinical outcome was observed (Penuel et al., 2013). Despite the lack of correlation with drug exposure or clinical outcome, taken together, these markers establish a proof of concept for drug activity and target inhibition in patients.

5.2. Challenges in biomarker development

Selection of patients most likely to respond to Met-targeted agents requires validated diagnostic tests that are accurate, dependable and

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reproducible. Similarly, in prognostic studies, determination of Met as a biomarker by statistical association between expression and disease prognosis and/or tumor response depends on the availability of validated diagnostics (de Bono & Ashworth, 2010). Clinical studies are currently ongoing to validate the use of Met markers including Met, P-Met and HGF in clinical practice. A range of diagnostic reagents are available to detect baseline expression and alterations in levels of these biomarkers. However, limitations such as differences in the antibodies used for IHC, inter-observer variability and differences in cut-offs, have limited consistency and reproducibility between evaluations, with additional variables related to differences in methods of tissue procurement and conservation. Differences in sensitivity and specificity of diagnostic antibodies limit reproducibility and may lead to distinct clinical results. For example, a study of IHC staining of tumor cells showed varying levels of Met expression when different anti-Met antibodies were used (Cousens et al., 2009). Specifically, the proportion of Met-positive cells varied between 44% and 83% with anti-Met SC-10 and Epitomics reagents, respectively.

There is currently no consensus on scoring criteria for Met assays. For example in one study, high Met levels have been defined as IHC intensity score of at least 2 when more than 75% of tumor cells were positive for Met (Mok et al., 2012) and in a different study, using SP44 anti-Met (Ventana), the scoring criteria were defined for Met-diagnostic positive as at least 50% of positive tumor cells with an intensity of 2+/3+ (Spigel et al., 2012, 2013). Due to the wide variability of results across tumor types, drug classes, and different Met antibodies used for IHC assays, distinct assay conditions may be required in different indications.

The majority of retrospective biomarker studies to date have evaluated the levels of total Met, although considering phosphorylated-Met may offer further advantages due to the potential for indicating the activation status of Met. However, establishing reagents and assay systems for the recognition of phosphorylated forms of Met has been not surprisingly challenging. On the one hand most antibodies used to date cross-react with additional phosphorylated RTKs given the high degree of conservation of the tyrosine kinase domains and on the other hand, phosphorylated tyrosine residues are particularly labile, affected by tissue procurement, fixation and conservation. Tissue snap freezing may offer an alternative but presents its own challenges. Novel techonologies exploring alternatives include a "proximity" assay that detects HGF–Met complexes as a surrogate for activated receptor (Dua et al., 2011).

Consistent criteria and validated tests are also needed for the definition and evaluation of *MET* amplification. To date FISH and other methods (PCR or comparative genomic hybridization [CGH]) used various criteria for determining *MET* amplification "positivity" (summarized in Ou et al., 2011b). It was suggested that high level *MET* amplification is defined by the presence of homogeneously staining regions, and scoring of MET/CEP7 ratio >2.2, however, optimization of these methods and validation of the scoring criteria in clinical trials are necessary to establish the use of *MET* amplification as a prospective selection biomarker.

Another challenge in biomarker development is related to the difficulty to access tumor tissues for stringent validation of marker expression profiles. Frequent/repeat tumor biopsy pre/post treatment and ideally at time of progression may not be feasible in some indications. Furthermore, increasing efforts in molecular profiling to match specific genetic alterations with appropriate therapeutic agents, and patients maintained on successive biomarker-dependent trials, limit the availability of archival biopsies. Circulating markers and surrogate tissues (blood, plucked hair) may offer alternate strategies but are subject to similar limitations involving assay validation.

5.3. Novel biomarker strategies

Key challenges in biomarker development relate to the nature of cancer itself. Molecular heterogeneity exists among patients within an indication as well as intra-patient heterogeneity due to molecular changes occurring throughout the disease process, in response to treatment and as a consequence of resistance to therapy. While protein markers are often used to assess and predict disease progression and drug response, gene expression markers may provide more reliable results, especially when these genotypic changes are within oncogenic drivers and could mediate drug effects. Therefore multiplex genotyping to simultaneously evaluate multiple targets and alterations thereof, using the same tissue specimen, will be critical moving forward (Giampieri et al., 2013). These technologies will eliminate the need for sequential testing and may provide a much needed contraction of turnaround time and costs.

As discussed above, Met alterations (mutations, exon-14-skipping, high copy number) are of significance if considered collectively within a given indication, supporting the simultaneous evaluation of these genetic alterations. Emerging technologies to identify such actionable alterations are in development, but use of such methodologies in prospective clinical settings will require robust validation in line with regulatory recommendations and guidelines. Novel technologies with potential in this area include PCR-based assays that evaluate multiple mutations simultaneously in a selected set of oncogenic drivers from genomic DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue sections, mass spectrometry-based systems (e.g. Sequenom OncoCarta) or capillary electrophoresis analyses (SNaPshot platform from Applied Biosystems) (Thomas et al., 2007; Sequist et al., 2011; Li et al., 2013). More recently, next generation sequencing combined with an exon-targeted approach has enabled the identification of specific alterations of interest including mutations, fusions and gene copy numbers (Chmielecki et al., 2010; Wagle et al., 2012). Together with the development of powerful bioinformatic tools this opens avenues for future diagnostics. These novel "high-depth" sequencing technologies will enable efficient and reliable genotyping for the development of Met-targeted agents.

Other strategies that complement Met-targeted therapeutic strategies are being explored. Among these, a number of imaging techniques including magnetic resonance imaging (MRI) and positron emission tomography (PET) have been assessed. A MRI anti-Met antibody probe was designed to detect Met expression levels in vivo in an experimental rodent model of C6 glioma (Towner et al., 2010). PET tracers 3′-deoxy-3′[^{18}F]-fluorothymidine and [^{18}F]-2-fluoro-2-deoxy-D-glucose were used as surrogate markers to assess tumor response to Met inhibitors crizotinib and rilotumumab (Cullinane et al., 2011; Rex et al., 2013). A PET imaging agent using onartuzumab (^{89}Zr-df-onartuzumab) was recently developed and its utility was assessed in gastric carcinoma xenografts (Wright et al., 2013). While these technologies offer some advantages, challenges related to test availability and costs may be limiting.

MicroRNAs may also represent novel markers of Met activity. Three candidate microRNAs that are involved in the modulation of Met expression, miR-449a, miR-340, and miR-409-3p are downregulated in NSCLC, aggressive breast cancer cell lines, and bladder cancer cells, respectively (Wu et al., 2011; Lee et al., 2013; Luo et al., 2013). In breast cancer cell lines, expression of miR-340 was found to be inversely correlated with Met expression (Wu et al., 2011). Additionally, the identification of small sets of gene signatures based on mRNA expression profiles can be helpful in predicting drug response. In a recent preclinical study, a Met gene signature (including Met and 4 proximal genes in the same chromosome) was found to be significantly more accurate in predicting sensitivity to the Met inhibitor TAS-115 than Met expression alone (Itadani et al., 2012).

6. Conclusions

Being a key oncogenic driver and contributor to drug resistance, Met is an attractive therapeutic and predictive target. Clinical trials of Met-targeted drug monotherapy have shown promising results in terms of anti-tumor efficacy and improvement of clinical outcomes in various

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types of previously treated advanced cancers. Met-targeted treatments provide new options to cancer patients for whom other therapies have not been successful. However, the greatest potential of Met-targeted agents may reside in combined approaches whereby multiple molecular drivers and mechanisms of resistance are simultaneously inhibited, either via multi-targeted small molecule inhibitors, or by combination therapy approaches. In preclinical studies using Met-targeted agents in combination therapy, drug sensitivity was restored in resistant tumors. These observations are promising in the context of drug resistance, a factor which frequently challenges treatment success. Synergistic inhibition of Met and EGFR are of particular importance for patients with lung and colorectal cancer where Met has been shown to be involved in anti-EGFR resistance. Further, biomarker development studies have helped identify several markers in the HGF/Met axis that have prognostic and predictive value. Future progress in the area of Met targeted therapies will focus on incorporation of markers to optimize patient selection and treatment strategies. Thus, precisely targeting patient populations with most chance of responding will help improve clinical outcomes thereby delaying or preventing disease progression. The HGF/Met axis has significant clinical potential, which will be realized in the context of the development and validation of biomarkers and rational mechanism-based treatment combinations.

Conflict of interest statement

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