Anti-MET Targeted Therapy Has Come of Age: The First Durable Complete Response with MetMAb in Metastatic Gastric Cancer

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Summary: The MET/hepatocyte growth factor (HGF) signaling pathway plays important roles in oncogenesis and tumor progression in a variety of human cancers. MET/HGF drives an invasive signaling program that can be dysregulated in human cancers through a number of activating mechanisms, including mutations, overexpression, amplification, alternative splicing, and HGF ligand-induced autocrine/paracrine loop signaling. As a testimony of MET-targeting therapeutics is beginning to come to clinical fruition, Catenacci and colleagues report the first case of durable complete response under an anti-MET receptor monoclonal antibody, MetMAb, in a patient with chemotherapy-refractory, advanced gastric cancer metastatic to the liver, found to have high MET gene polysomy and remarkably high serum HGF level. Serum and tissue studies also revealed predictive biomarkers for therapeutic response to MET inhibition. Cancer Discovery; 1(7); 550–4. © 2011 AACR.

Commentary on Catenacci et al., p. 573 (1).

In this issue of Cancer Discovery, Catenacci and colleagues (1) report the first durable complete response (CR) obtained with MetMAb, a molecularly targeted anti-MET receptor monoclonal antibody, in a patient with chemotherapy-refractory gastric cancer with liver metastasis. They describe a 48-year-old woman with advanced gastric cancer who was treated with MetMAb antibody as part of a phase I clinical trial and experienced a clinical CR lasting approximately 2 and a half years. The primary tumor was found to have both high MET gene polysomy, and autocrine ligand production of the hepatocyte growth factor (HGF) was present at a remarkably high level before treatment. More interestingly, this response of tumor shrinkage to MetMAb came after a previous initial transient partial response followed by disease progression on a multitargeted MET/VEGF receptor 2 (VEGFR2) small-molecule kinase inhibitor.

The cancer eventually recurred when the patient was off MetMAb therapy, which was discontinued because of adverse effects. Disease progression manifested as a peritoneal deposit invading the transverse colon and a gastrohepatic ligament node. Compassionate use of MetMAb therapy at time of recurrence further achieved a mixed response—a partial response of the 2 initial lesions but with the development of multiple new foci of carcinomatosis. When we consider that advanced gastric cancer is typically a refractory disease, difficult to treat, and has a very poor prognosis, this case report is quite noteworthy. Moreover, this timely report provides a good lesson in the optimization of the strategies of development of MET targeting clinical therapeutic agents.

The MET receptor tyrosine kinase (RTK) was first identified as the product of a fusion oncogene TPR-MET, generated from a chromosomal translocation induced by the treatment of a human osteogenic sarcoma cell line with the chemical carcinogen N-methyl-N′-nitrosoguanidine. The resulting 65-kDa cytoplasmic TPR-MET fusion oncoprotein forms a TPR (translocated promoter region) leucine zipper-mediated dimer that is constitutively activated in a ligand-independent fashion. Later, the full-length MET protooncoprotein was identified, which encodes the cell surface receptor for a specific natural ligand, HGF, also known as scatter factor. The MET/HGF signaling pathway is quite unique in its regulation of a wide array of mitogenic, motogenic, and invasive signals (Fig. 1). Ligand activation of MET occurs via a combination of signaling mechanisms, including autocrine loops (intratumoral HGF), paracrine loops (stromal/mesenchymal microenvironmental HGF), or endocrine loops (circulatory HGF). In vivo autocrine activation in HGF- or MET-transgenic mice has also been reported to promote hepatocarcinogenesis.

MET/HGF is greatly expressed in human epithelial tissues, with its mediation of proliferation, survival, motility, scattering, and invasion playing critical roles in early embryonic development. In adult tissues, the MET/HGF axis is primarily quiescent in its invasive growth signaling program, except in processes such as tissue repair. In human cancers, dysregulated MET/HGF signaling leads to aberrantly activated proliferative and invasive signaling programs that promote malignant transformation, epithelial–mesenchymal transition, cell motility and migration, cell scattering, angiogenesis, invasion, and metastasis (2). The role of MET in human cancer was first established with the identification of germ-line and somatic kinase domain mutations in hereditary and sporadic papillary renal cell carcinoma, respectively (3). Subsequently, MET missense mutations, alternative splicing defects, and genomic amplification events were identified and catalogued in a wide variety of human hematologic and solid malignancies (http://www.vai.org/met). Of particular interest, various MET missense mutations affecting the Sema domain have also been uncovered in thoracic cancers.
views and colleagues (6) demonstrated that even a modest increase in MET activation can initiate tumorigenesis and that both the MET mutational spectra and the host stromal tissue background can have profound influence on the type of tumor generated. Hence, personalized combinational MET-targeting therapies would have to take into accounts of any interaction of genetic modifiers and MET oncogenic signaling. This finding is relevant in understanding the mixed response profile seen in the patient under a specific MET targeted agent as in the patient described by Catenacci and colleagues (1).

The MET/HGF signaling pathway is recognized as one of the hallmarks of cancer in activating invasion and metastasis that can be therapeutically targeted (Fig. 1; ref. 7). Multiple studies during the past 2 decades have established MET as an attractive and validated molecular target in cancer therapy. Agents that are under development include small molecule inhibitors—both ATP-competitive and non-competitive, as well as monoclonal antibodies—against both the ligand HGF and/or the MET receptor itself. The molecular determinant(s) of response and resistance to MET/HGF targeting therapeutic agents have become one of the most crucial yet challenging questions to be resolved in drug development against this pathway.

Several MET/HGF antibodies have been developed for targeting the pathway. Earlier efforts in developing therapeutic...
antibodies to target MET were largely unsuccessful as a result of the antibodies ending up possessing agonistic rather than antagonistic activities against the target receptor. This obstacle turned out to be attributable to the bivalent nature of the antibodies that would inadvertently dimerize and hence activate the MET receptors kinase trans-autophosphorylation. This limitation was ultimately overcome by the development of the one-arm engineered antibody (OA-SD5, MetMAb; Genentech), which consists of a monovalent Fab fragment with murine variable domains for both the heavy and light chains fused to human IgG1 constant domains (humanized).

Preclinical murine orthotopic xenograft modeling with the administration of MetMAb intratumorally demonstrated the antibody's potent inhibitory efficacy against in vivo cell growth of HGF-driven U87 glioblastoma, which expresses MET and HGF (8). MetMAb was also found to significantly inhibit orthotopic pancreatic KP4 tumor growth and improve survival (9). Ultimately, MetMAb antibody phase I clinical trial studies were initiated in October 2007.

The pace of clinical development of MET targeting therapeutics has been remarkably fast in recent years. A global, randomized, double-blind phase II study in which investigators compared MetMAb plus erlotinib with placebo plus erlotinib in the second-/third-line treatment of advanced non-small cell lung carcinoma (NSCLC) has been completed recently (10). In the MET-immunohistochemistry (IHC)-positive group (n = 65), MetMAb plus erlotinib resulted in a clinically and statistically significant improvement in both progression-free-survival (median, 2.9 vs. 1.5 months) and overall survival (median, 12.6 vs. 3.8 months). However, the MET-IHC–low/negative group had a worse overall survival in the MetMAb plus erlotinib than the placebo plus erlotinib treatment arm. This is one of the first MET targeting agents that has well-designed incorporation of companion diagnostic assays for predictive biomarker development and is highly commendable. In the MetMAb trial, according to the trial investigators, the overall survival benefit (or the trend of OS benefit) was not exclusive to EGFR mutations or MET FISH+ (≥5 copies) and was observed in FISH-/IHC+ patients, suggesting IHC as a more sensitive predictor of benefit from MetMAb. These results lend support for further investigation of MetMAb as a potential personalized MET targeting cancer therapeutic for NSCLC patients, and a phase III clinical trial has just begun.

In this issue of Cancer Discovery, Catanecci and colleagues (1) report the first durable CR obtained with MetMAb in a patient with chemotherapy-refractory gastric cancer with liver metastasis. In this case report, several salient points were raised, in that (i) the primary gastric tumor was found to have high MET gene polysomy; (ii) both MET and HGF were found expression by IHC in the primary tumor, and there was increased expression with histologic progression to the gallbladder metastasis; and (iii) the serum HGF level pretreatment was extremely high and decreased precipitously after MetMAb drug exposure, remaining at a low level even up to the time of extensive disease recurrence at multiple sites. Of note, the use of a MET TKI (also targeting VEGFR2) before the initiation of MetMAb antibody therapy raises the question of whether “vertical” inhibition of a RTK with combined targeted antibody and TKI would be a beneficial therapeutic approach.

It is particularly attractive to consider in MET/HGF pathway targeting in the context of the substantial role of HGF ligand-mediated pathway activation under various clinical scenarios. Here, the metastatic recurrence of new abdominal disease sites occurred approximately 2 years after initial CR from MetMAb therapy, whereas during most of that time the patient was not receiving MetMAb treatment because of side effects. It is certainly remarkable that the CR is so durable after only approximately 7 months of initial MetMAb therapy. The nature of the recurrent disease off active therapy calls into questions of whether it should be defined as “acquired” resistant disease. One wonders whether there is any difference in the expected clearance of MetMAb therapy versus TKI. Also, although one might expect recurrent disease after previously effective therapy would remain sensitive to the rechallenge of targeting agent (as in reported cases of erlotinib in lung cancer), this case report illustrates the possibility of tumor progression to continue with or without ongoing therapy with underlying tumor molecular evolution resulting ultimately in a more heterogeneous tumor burden at late disease stages. To this end, the “mixed response” to MetMAb retreatment during the tumor recurrence consisting of a partial response in the colonic and gastrohepatic ligament node and progression of multiple new metastatic peritoneal lesions highlights the therapeutic dilemma in the era of targeted therapy: whether one should stop the targeted drug altogether or to keep it on with addition of further therapeutics. More vigorous investigations in this area are clearly needed.

In this case report (1), it is of interest to find that pretreatment serum HGF level was remarkably high, whereas it decreased precipitously almost immediately after therapy and remained low even up to the late disease recurrence. The data suggest that there might have been a change in pretreatment HGF dependency of the original tumors into posttreatment HGF-independent state, which might have been achieved by the metastatic tumor evolution into MET overexpression. It is important to point out that in tumors under predominantly HGF-dependent activation, MET receptor expression levels might not necessarily need to be very high.

A few other preclinical HGF/MET antibodies have also been developed and reported. A mouse monoclonal antibody directed against the extracellular portion of MET (DN-30) that induces MET proteolytic cleavage (receptor “shedding”) followed by proteasome-mediated receptor degradation was shown to inhibit MET/HGF-mediated biologic activity but also resulted in partial activation of MET overexpression. It was found to have single-agent activity in human HGF-driven preclinical models, blocking HGF-mediated cell cycle progression, proliferation, migration, invasion, and survival. It potently inhibited autocrine and paracrine tumor growth in...
experimental transgenic xenograft models of human leiomyosarcoma (SK-LMS-1 and SK-LMS-1T0; ref. 12).

Another commonly adopted paradigm of inhibiting MET/HGF signaling is the use of small-molecule tyrosine kinase inhibitors against the MET receptor. The first selective preclinical MET inhibitors include SU11274 and PHA665752, which date back to 2003. Currently, there are many MET tyrosine kinase inhibitors under clinical development in many cancer types in various study phases (Fig. 1). Tivantinib (ARQ197; ArQule/Daiichi-Sankyo) is the most advanced, already having entered recently into phase III clinical trial in advanced NSCLC (Met inhibitor ARQ 197 plus erlotinib vs erlotinib plus placebo in NSCLC [MARQUEE] trial). It is the first non-ATP-competitive small molecule that selectively targets MET, with the mechanism of action as locking the kinase in a “closed” and “inactive” conformation when bound to the drug.

A global, randomized, placebo-controlled phase II clinical trial (ARQ197-209) in which the authors compared erlotinib plus ARQ197 versus erlotinib plus placebo in patients with advanced NSCLC demonstrated prolonged progression-free survival in the ARQ197 group. A global randomized phase III trial (MARQUEE) of ARQ197 with similar design to ARQ197-209 in NSCLC is now ongoing.

Other MET/HGF–targeted agents that have been in clinical trials include foretinib (XL880), flicatuzumab (AV-299), and cabozantinib (XL184). There is also now a kinase inhibitor newly approved by the U.S. Food and Drug Administration, crizotinib (Xalkori, PF-2341066; Pfizer), that has anti-MET activity. Crizotinib was approved in August 2011 for patients with NSCLC whose tumors harbor an ALK 2p23 translocation (predominantly EML4-ALK) as assayed by a dual break-part probe FISH (Abbott). Intriguingly, crizotinib was initially developed both preclinically and clinically as a MET inhibitor (13).

In a recent case report authors described a NSCLC patient with de novo MET amplification, but without ALK rearrangement, who achieved a rapid and durable response to crizotinib, indicating it is also a bona fide MET inhibitor (14). Dramatic clinical improvement and radiographic regression also were observed in patients with MET-amplified esophagogastric adenocarcinoma (15) and glioblastoma multiforme (16) upon treatment with crizotinib. Hence, further exploration of clinical utility of the dual MET/ALK inhibitor crizotinib in MET-driven human cancers, including those with MET genomic amplification, would be warranted and potentially fruitful.

In summary, MET/HGF targeting has come of age to clinical fruition. Convincing evidence has accumulated in the literature to support the role of autocrine and paracrine ligand-mediated activation of MET through either overexpression or mutation of MET. MET represents one of the most frequently dysregulated human oncogenic RTK to date, rendering it an attractive therapeutic target pathway. A large number of MET and HGF targeting therapeutic agents are thus being developed at a rapid pace. We are beginning to witness response profiles from patients under MET/HGF–targeted agents, such as the one in this case report by Catenacci and colleagues (1) regarding a durable CR to MetMab. The obvious question that begs a clear answer for all clinicians, pharmaceutical manufacturers, and most importantly, our cancer patients, is how we can identify patients most likely to respond to the MET/HGF agents. What causes a tumor to be MET or HGF dependent, and thus likely to be responsive? Also, can we target tumors selectively through their MET dependence (tumorigenesis) and MET expedience (tumor progression, invasion, and metastasis)? Other than MET genomic amplification, can we predict response through HGF levels or MET protein expression/overexpression (total and/or phospho-MET)? Novel platforms of identifying MET overexpression in vivo, such as radiopharmaceutical molecular target imaging, may facilitate patient selection and clinical drug development (17).

Many of the aforementioned questions would need to be addressed through our recognition of the intrinsic complexity of the oncogenic MET signaling cascade and its underlying multifaceted activating mechanisms, both at the receptor level and at the ligand level. Determinants of therapeutic sensitivity and resistance would have to be understood in the context of the potential specific activating mechanism in the specific tissue type. Compared with the EGFR-targeted inhibition paradigm in lung cancer harboring mutated EGFR, the MET-targeted inhibition paradigm is likely to be somewhat different and more complex in personalized cancer therapy. Both “translational” (bench-to-bedside) research, which led to the current momentum in MET/HGF-targeted therapeutics development, and “reverse translational” (bedside-to-bench) research as exemplified by Catenacci and colleagues’ case report study (1), are both indispensable in the quest for developing truly personalized optimized MET therapeutic strategies.

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No potential conflicts of interest were disclosed.

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REFERENCES


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