Targeting the HGF/c-Met Axis: State of Play

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In a recent issue of Molecular Cancer Therapeutics, Burgess and colleagues (1) give a detailed biochemical and functional characterization of AMG 102, a fully humanized monoclonal antibody to hepatocyte growth factor (HGF). HGF, or scatter factor, is the only known high-affinity ligand for the c-Met receptor tyrosine kinase (2). Upon ligand binding, c-Met undergoes dimerization, autophosphorylation of its catalytic tyrosines, activation of the multifunctional docking site for adapter protein binding, and engagement of key signal transduction pathways (3). These processes lead to increased cell survival, proliferation, growth, motility, and angiogenesis (2). Aberrant HGF/c-Met signaling may lead to cancer formation through different mechanisms, including activating HGF or c-Met mutations and gene amplification (3). Germline and somatic c-Met mutations have been reported in hereditary and sporadic papillary renal cell cancers (RCC; refs. 4–6), whereas c-Met amplification with consequent protein overexpression contributes to resistance to epidermal growth factor receptor (EGFR) inhibition in non–small cell lung cancer (NSCLC; refs. 7, 8). Both c-Met gene mutations and amplification have now been reported in other cancers, albeit at low frequencies, as putative genetic predictors of therapeutic sensitivity (3). The c-Met protein is also overexpressed in a range of tumor types, with this correlating with a worse outcome (2). These data show the pathogenic consequences of abnormal HGF/c-Met signaling in tumorigenesis and provide a strong rationale for targeting HGF or c-Met in cancer therapeutics.

A previous report by Burgess and colleagues in Cancer Research discussed the biochemical characterization of five different HGF monoclonal antibodies with subnanomolar affinities for HGF (9). In the February 2010 publication, Burgess and colleagues (1) detail studies that show the high potency and selectivity of the clinical candidate AMG 102 for the mature and processed form of HGF, without resulting in any alteration to the proteolytic activation of pro-HGF. AMG 102 was also shown to bind and inhibit both human and monkey HGF, but not rat or rabbit HGF. Furthermore, epitope-mapping studies using recombinant HGF molecules confirmed that amino acid residues near the NH2-terminus of the β-chain contained the epitope necessary for the binding of HGF by AMG 102. This same region has been shown in other studies to be essential for the interaction between HGF and c-Met (10, 11). These biochemical and functional studies contributed to the development of AMG 102 and supported its selection as the lead clinical candidate.

The phase I clinical trial findings of AMG 102 in patients with advanced solid tumors were recently published in Clinical Cancer Research (12). Forty patients were treated in six sequential dose-escalation cohorts (0.5, 1, 3, 5, 10, or 20 mg/kg AMG 102 intravenously every 2 weeks) and a dose expansion cohort (20 mg/kg AMG 102 every 2 weeks). Drug-related toxicities included mild fatigue and gastrointestinal symptoms. The maximum tolerated dose was not reached, although dose-limiting toxicities of hypoxia and dyspnea, and upper gastrointestinal hemorrhage were observed in the 0.5 mg/kg and 1 mg/kg cohorts, respectively. Importantly, no anti-AMG 102 antibodies were detected, and dose-proportional pharmacokinetics was reported. Increases in circulating HGF levels were dose-dependent, although soluble c-Met concentrations were unchanged across doses. No objective responses were seen, although 16 of 23 (70%) evaluable patients had a best response of Response Evaluation Criteria In Solid Tumors (RECIST) stable disease for 7.9 to 40 weeks. AMG 102 is currently being investigated as a single agent and in combination with other therapies in phase II studies.

It remains to be seen if HGF is a better target than c-Met, although apart from AMG 102, the development of clinical candidates against HGF seems to be lagging behind the plethora of c-Met inhibitors now available in clinical trials. Currently, the most selective c-Met inhibitors seem to be MetMAb (OA5D5; Genentech), a c-Met monoclonal antibody and ARQ197 (ArQule, Inc), an oral, non-ATP competitive c-Met inhibitor, with a novel mechanism of action involving the stabilization of an inactive conformation of c-Met (13). Both agents reported impressive preclinical data (14, 15), and promising results in phase I studies (16–18). Both are currently in phase II trials, including independent double-blind randomized phase II studies evaluating their combination with erlotinib (Genentech, OSI Pharmaceuticals) versus placebo-erlotinib in patients with NSCLC (19).

In contrast, GSK1363089 (foretinib; GlaxoSmithKline) and XL184 (Exelixis) are oral, ATP-competitive small molecule inhibitors against multiple kinases, in particular c-MET and VEGFR (20, 21). The combination seems to be rational because c-Met has indirect effects on tumor
angiogenesis, through the induction of endothelial cell proliferation and migration, VEGF expression, and inhibition of thrombospondin-1 (1). Preliminary signals of antitumor activity were observed in patients with papillary RCC treated with GSK1363089 (22, 23), and in patients with medullary thyroid cancer (24) and glioblastoma (25) treated with XL184. These results, as well as preclinical data on c-Met mutations and amplification, led to phase II single agent trials of GSK1363089, evaluating its activity in hereditary and sporadic papillary RCC and gastric carcinomas. In the papillary RCC phase II study of GSK1363089, of 26 patients with molecular evidence of c-Met activation, only 3 achieved confirmed radiological partial responses (26). Also, no objective responses were seen in the phase II gastric carcinoma trial of GSK1363089, in which a low frequency of patients were found to be c-Met amplified (27). Overall, these clinical results are disappointing and may support the need for better patient enrichment as early as possible in the drug development process (28).

The use of predictive markers is pivotal to accelerating drug development and has already been successfully applied (28). The ALK/c-Met small molecule inhibitor FF-02341066 (Pfizer) showed impressive responses when given specifically to NSCLC patients with EML4-anaplastic lymphoma kinase (ALK) fusions, with 10 of 19 such patients achieving objective responses (29). Although the antitumor responses reported seem to be solely due to ALK inhibitory effects rather than c-Met blockade, these results emphasize the importance of incorporating prospective molecular profiling, where appropriate, to optimize the development of HGF and c-Met inhibitors. Efforts should thus continue, if possible, to enrich the treated patient population with cancers driven by the HGF/Met axis to increase the odds of clinical benefit. Conversely, however, if agents targeting this pathway have anti-angiogenic properties, a more broad approach should be pursued.

As with agents targeting the vascular endothelial growth factor (VEGF) ligand and VEGF receptor (VEGFR) axis, due diligence must now be given to the development of both HGF and c-Met targeting agents, because both seem worthy of evaluation. Arguably, small molecules probably have an edge over antibodies because of their cost benefits and ease of delivery. Therapeutic antibodies may also have lower tumor penetration, although they generally have superior pharmacology, with increasing evidence that they can activate an antitumor immune response. Small molecules are, however, frequently less specific, with multiple targets, which may have implications for both efficacy and toxicity. Overall, however, HGF and c-Met inhibitors have been well tolerated in early clinical trials, although unexpected acute renal toxicity was observed in patients treated with the ATP-competitive c-Met inhibitor SGX523 (SGX Pharmaceuticals; ref. 2). This toxicity is believed to be due to the compound or a metabolite crystallizing in the kidney and not thought to be related to an “on target” c-Met inhibitory effect. This toxicity resulted in the early discontinuation of the clinical development of SGX523.

Although concerns have been raised about the relative lack of antitumor responses by RECIST observed to date in early studies of HGF/c-Met inhibitors, a similar scenario was encountered with the VEGF-targeting antibody bevacizumab, which has since been approved for a number of clinical indications. Clinical trials now need to evaluate whether, like bevacizumab, agents targeting the HGF/Met axis can also impact the angiogenesis process because this would impact the drug approval pathways pursued. The significant level of disease stabilization rates observed in the reported phase I trial of AMG 102 would support such a mechanism of action (12). Importantly, targeting this axis may not impact some of the established pharmacodynamic imaging parameters of VEGF blockade determined by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), such as k\textsubscript{trans}, unless c-Met blockade decreases VEGF levels. Measuring circulating endothelial cells and their progenitors may thus potentially be a more relevant proof-of-mechanism biomarker for the anti-angiogenic effect of these agents. Translational studies are now needed to evaluate this (2).

In the future, it is likely that the successful application of these therapeutics in cancer medicine will either be in combination with other agents or following the appropriate selection of patients for these selective inhibitors. It is envisioned that inhibitors of the HGF/c-Met pathway will have an important role to play in cancer therapeutics in the near future.

**Disclosure of Potential Conflicts of Interest**

Drs. T.A. Yap and J.S. de Bono have been involved in conducting trials of c-Met inhibitors sponsored by ArQule, Inc and Johnson and Johnson. Dr. T.A. Yap has served as a consultant for Merck. Dr J.S. de Bono has served as a consultant for ArQule, Inc, Johnson and Johnson, Genentech, Merck, Pfizer Oncology, AstraZeneca, Exelixis, and GlaxoSmithKline.

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