c-MET: an exciting new target for anticancer therapy

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The c-MET receptor tyrosine kinase, along with its ligand hepatocyte growth factor (HGF), plays an important role in the regulation and control of tissue homeostasis under normal physiological conditions [Yap and de Bono, 2010; Ma *et al.* 2003; Trusolino and Comoglio, 2002; Bladt *et al.* 1995; Schmidt *et al.* 1995]. However, the HGF/c-MET pathway (also known as the ‘HGF/MET axis’) has also been implicated in the regulation of cancer cell growth, angiogenesis, invasion and metastasis [Liu *et al.* 2008; Ma *et al.* 2008; Birchmeier *et al.* 2003]. Activation of the c-MET signaling pathway can occur *via* a number of mechanisms, including activating mutations, overexpression of c-MET itself or HGF, or through autocrine, paracrine or endocrine loop regulation [Cecchi *et al.* 2010]. Research studies have also demonstrated that c-MET has prognostic implications in patients with cancer [Beau-Faller *et al.* 2008; Boccaccio and Comoglio, 2006; Cheng *et al.* 2005].

It is now clear that c-MET is involved in resistance to established agents, such as vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR) inhibitors. For example, increased tumor survival through the cooperation between the c-MET receptor and VEGFR has previously been reported [Eder *et al.* 2009]. In addition, c-MET appears to act as an independent angiogenic factor and also one that may interact with angiogenic proliferation and survival signals that are promoted through VEGF and other angiogenic proteins [Eder *et al.* 2009]. Thus, there may be therapeutic utility to suppressing c-MET activity when targeting angiogenesis and to prevent the potential dissemination of cancer cells, which would be promoted as a result of intratumoral oxygen deprivation.

It is a logical step to consider the prevention of c-MET dependent neoplastic processes and to target distinct functions of c-MET as a novel strategy of treating invasive tumors of high metastatic potential. Preclinical studies have shown that in animal models, the inhibition of c-MET or neutralization of its ligand impairs tumorigenic and metastatic properties of cancer cells [Corso *et al.* 2008; Petrelli *et al.* 2006]. In line with this, inhibition of the c-MET pathway using novel inhibitors of the c-MET receptor tyrosine kinase appears to be a promising treatment option. Indeed, the prevalence of HGF/c-MET pathway activation in human malignancies has driven a rapid growth in oncology drug development programmes, with several new agents targeting c-MET now in clinical trials. These agents include direct inhibitors of HGF and/or its binding to c-MET, antibodies targeted at c-MET, and small molecule c-MET tyrosine kinase inhibitors.

Results from recent clinical trials evaluating c-MET inhibitors appear promising. The phase II clinical trial of the specific c-MET inhibitor tivantinib (ARQ 197) demonstrated antitumor activity in non-small cell lung cancer (NSCLC), when administered in combination with erlotinib [Schiller *et al.* 2010]. Progression-free survival (PFS) was prolonged in patients who received erlotinib and tivantinib (16.1 weeks), in contrast with those in the erlotinib and placebo arm (9.7 weeks). Patients with nonsquamous histology appeared to gain the greatest benefit, with a 9.2-week improvement in median PFS and a 13.7-week improvement in median OS with the combination therapy. Tivantinib has now entered phase III development. MetMab, a monovalent monoclonal antibody (mAb) directed against c-MET, is currently in phase II development. A recent phase II clinical trial using MetMab in

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combination with erlotinib to treat NSCLC patients whose tumors expressed high levels of c-MET resulted in a tripling of patient survival from 4.6 to 12.6 months [Spigel *et al.* 2011]. Another agent that has reached phase II/III clinical trials is cabozantinib (XL184), a potent tyrosine kinase inhibitor that blocks c-MET, VEGFR2, AXL, KIT, TIE2, FLT3 and RET signaling. Impressively, clinical studies with cabozantinib have demonstrated tumor shrinkage in almost 60% of glioblastoma patients [Wen *et al.* 2010].

The efficacy of the myriad of therapeutic agents currently in clinical development is likely to be influenced by the underlying mechanism of aberrant HGF/c-MET signaling pathway activation in different cancers. Such inhibitors of the HGF/c-MET axis will hopefully offer a promising new strategy for cancer treatment, either as a single agent or as part of a combinatorial therapeutic approach. Several clinical trials are already underway to determine whether the combination of c-MET tyrosine kinase inhibitors given together with either targeted agents against EGFR/VEGF or chemotherapy is a clinically effective therapeutic approach.

There is an urgent need to accelerate the transition of preclinical research into better therapeutic approaches for patients with cancer [de Bono and Ashworth, 2010; Yap *et al.* 2010]. The main challenges facing the effective development and use of HGF/c-MET targeted therapies for cancer treatment include optimal patient selection and diagnostic/pharmacodynamic biomarker development, as well as the identification and testing of rationally designed antitumor drugs and combination strategies. For the ongoing development of c-MET inhibitors to result in a clinically effective therapeutic approach, it is important to highlight that a requirement for this may be the selection of a target patient population and a practical but analytically validated predictive biomarker assay to identify them in a clinical context [de Bono and Ashworth, 2010; Yap *et al.* 2010]. Future challenges will also involve the investigation and dissection of other vital crosstalk mechanisms involving the c-MET signaling pathway, which could lead to greater improvements in the efficacy of novel antitumor therapies and have an impact on patient survival.

The articles contained within this supplement are based on content presented at the satellite

symposium 'c-MET: an exciting new target for anticancer therapy' which took place during the Targeted Anticancer Therapies meeting in Paris, 2011. Topics covered include the c-MET signaling pathway, c-MET as a potential therapeutic target and biomarker, ongoing clinical trials evaluating c-MET-inhibiting drugs, and future directions in the laboratory and the clinical evaluation of c-MET-driven malignancies.

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Conflict of interest statement

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