Future directions in the evaluation of c-MET-driven malignancies

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***Abstract*:** The c-MET (mesenchymal–epithelial transition factor) receptor tyrosine kinase is an exciting novel drug target in view of its key role in oncogenesis, as well as its association with disease prognosis in a number of malignancies. Several drugs targeting c-MET are currently showing promise in clinical trials and will hopefully validate positive observations from preclinical studies. The potential efficacy of these different therapeutic agents is expected to be influenced by the mechanism of aberrant hepatocyte growth factor (HGF)/c-MET signaling pathway activation in a particular cancer, but presents a promising strategy for cancer treatment either as a single agent or as part of a combination therapeutic approach. However, there is an ongoing need to improve and accelerate the transition of preclinical research into improved therapeutic strategies for patients with cancer. The main challenges facing the development of HGF/c-MET-targeted agents for cancer treatment include the discovery of rationally designed anticancer drugs and combination strategies, as well as the validation of predictive biomarkers. This paper discusses these issues, with a particular focus on future directions in the evaluation of c-MET-driven malignancies.

***Keywords*:** c-MET, drug development, targeted therapy, treatment resistance, patient selection, biomarkers

Introduction

Recent research has demonstrated that the c-MET (mesenchymal–epithelial transition factor) receptor tyrosine kinase and its ligand hepatocyte growth factor (HGF) (also known as the 'HGF/MET axis') regulate a range of cellular functions [Yap and de Bono, 2010; Ma *et al.* 2003; Trusolino and Comoglio, 2002; Bladt *et al.* 1995; Schmidt *et al.* 1995].

Under normal physiological conditions, HGF-induced c-MET tyrosine kinase activation is tightly regulated by paracrine ligand delivery, ligand activation at the target cell surface, and ligand-activated receptor internalization and degradation [Cecchi *et al.* 2010]. The importance of the HGF/c-MET pathway in the control of tissue homeostasis is supported by the well established protective activity of HGF in several degenerative diseases, including progressive nephropathies [Okada and Kalluri, 2005; Liu and Yang, 2006], liver cirrhosis [Ueki *et al.* 1999] and lung fibrosis [Watanbe *et al.* 2005]. However, activated c-MET signaling caused by deregulation of normal cellular functions is clearly implicated in oncogenesis, leading to cell growth, proliferation, angiogenesis, invasion, survival, and metastasis [Liu *et al.* 2008; Ma *et al.* 2008; Birchmeier *et al.* 2003]. Activation of the c-MET signaling pathway can occur *via* activating mutations, overexpression of the kinase itself or its ligand HGF, or by autocrine, paracrine, or endocrine loop regulation [Cecchi *et al.* 2010].

c-MET as a key target in oncological drug development

Clinically, c-MET has gained considerable interest through its apparent deregulation by overexpression or mutation in various cancers, including non-small cell lung cancer (NSCLC) [Ma *et al.* 2003, 2005; Kong-Beltran *et al.* 2006]. Overexpression of c-MET, along with HGF, also appears indicative of an increased aggressiveness of tumors [Boccaccio and Comoglio, 2006]. The deregulation of c-MET identifies it as an important therapeutic target in the development of future anticancer therapies. There is an increasing body of evidence that supports c-MET as a key target in oncology, for example through the development of small

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molecules or biological inhibitors. In addition, inhibition of c-MET affects downstream signal transduction with resulting biological consequences in tumor cells [Christensen *et al.* 2005]. The mutation or gene amplification of *MET* in selected clinical populations also suggests that certain patients may be exquisitely sensitive to targeted therapies that inhibit the HGF/MET axis [Christensen *et al.* 2005].

c-MET also has prognostic implications in patients with cancer [Beau-Faller *et al.* 2008; Boccaccio and Comoglio, 2006; Cheng *et al.* 2005]. Firstly, overexpression of circulating c-MET in patients with NSCLC has been significantly associated with early tumor recurrence [Cheng *et al.* 2005] and patients with adenocarcinoma and *MET* amplification have also demonstrated a trend for poor prognosis [Beau-Faller *et al.* 2008]. Cappuzzo and colleagues have provided clear evidence that increased *MET* gene copy number is a negative prognostic factor, further supporting anti-c-MET therapeutic strategies in this disease [Cappuzzo *et al.* 2009]. Of note, data from the same study indicated that epidermal growth factor receptor (EGFR) gene gain has no prognostic function in NSCLC, supporting its role as a predictive factor for improved survival in patients with NSCLC exposed to EGFR tyrosine kinase inhibitors (TKIs) [Cappuzzo *et al.* 2009].

Resistance to established agents

c-MET is involved in resistance to established agents, such as vascular endothelial growth factor receptor (VEGFR) and EGFR inhibitors. For example, the c-MET receptor and VEGFR have been found to cooperate to promote tumor survival [Eder *et al.* 2009]. Furthermore, c-MET has additional roles in tumor angiogenesis; firstly, as an independent angiogenic factor and also one that may interact with angiogenic proliferation and survival signals promoted through VEGF and other angiogenic proteins [Eder *et al.* 2009]. Combined VEGF and HGF/c-MET signaling has also been reported to have a greater effect on the prevention of endothelial cell apoptosis, formation of capillaries *in vivo*, and the increase of microvessel density within tumors [Boccaccio and Comoglio, 2006]. For EGFR, c-MET has been implicated in cooperating as a mediator of EGFR tyrosine phosphorylation and cell growth in the presence of EGFR inhibitors [Mueller *et al.* 2008]. *MET* amplification is responsible for EGFR-TKI acquired resistance in approximately 20% of patients [Bean *et al.* 2007; Engelman *et al.* 2007]. Recent findings from Pillay and colleagues suggest that inhibition of a dominant oncogene by targeted therapy can also alter the hierarchy of receptor tyrosine kinases, resulting in rapid therapeutic resistance [Pillay *et al.* 2009].

Such findings appear to suggest that c-MET inhibition, either alone or in combination with an EGFR inhibitor, may confer clinical benefit in the setting of EGFR inhibitor resistance. Indeed, available data imply that c-MET may be a clinically relevant therapeutic target for some patients with acquired resistance to gefitinib or erlotinib, particularly given that *MET* gene amplification occurs independently of $EGFR_{T790M}$ mutations [Bean *et al.* 2007]. The presence of *MET* gene amplification in combination with gain-of-function drug-sensitive EGFR mutations could together lead to cellular changes that confer enhanced fitness to cells bearing both alterations [Bean *et al.* 2007]. However, other mechanisms could contribute to disease progression in such patients. As the mechanism of interaction between HGF/c-MET and resistance remains unclear, further research into crosstalk and balance between these two signal pathways remains critical and necessary for the development of novel anticancer therapies.

Plasticity in cancer cell 'addiction'

When considering the rational identification of responsive tumors, previous experience with EGFR TKIs has demonstrated that they are only efficacious in a small subset of tumors that exhibit genetic alterations of the receptor itself [Sharma *et al.* 2007]. However, research has also shown that cultured cell lines containing the same EGFR genetic lesions present in human tumors can undergo cell cycle arrest or apoptosis when subjected to EGFR inhibition, even under otherwise optimal conditions [Sharma *et al.* 2007]. This phenomenon, termed 'oncogene addiction', applies to all clinical scenarios in which cancer cells appear to depend on a single overactive oncogene for their proliferation and survival [Sharma *et al.* 2007; Sharma and Settleman, 2007]. For c-MET, further consideration needs to be given to the fact that genetic alterations of the kinase can induce oncogene addiction and therefore possibly aid prediction of therapeutic responsiveness. Importantly, research from Comoglio and colleagues has highlighted that preclinical

investigations of developmental c-MET inhibitors appear to utilize a vast array of differing cell lines, most of which tend not to be genetically characterized [Comoglio *et al.* 2008]. Clearly, to enable identification and recruitment of potentially responsive patients in future studies, the rational selection of genetically defined cell lines will need to become mandatory, in order to lead to the development of reliable *in vitro* models for the testing of c-MET inhibition. Future models will need to be able to clearly display signaling abnormalities of c-MET and also to respond to c-MET inactivation with a distinct and measurable phenotypic readout.

In addition to oncogene addiction, available data suggest that c-MET can act as an 'oncogene expedient' even in the absence of genetic alterations [Comoglio *et al.* 2008]. Such findings indicate that c-MET might potentiate the effect of other oncogenes, promote malignant progression and participate in tumor angiogenesis [Comoglio *et al.* 2008]. In order to identity potentially responsive tumors, the different roles that c-MET can play in malignant transformation and progression warrant further research.

Ongoing development of c-MET inhibitors

The prevalence of HGF/c-MET pathway activation in human malignancies has driven a rapid growth in cancer drug development programs, with several new drugs targeting c-MET showing great promise. Several c-MET inhibitors are now under evaluation in clinical trials (Table 1), and the interest around these compounds has consistently increased since an interaction between EGFR and c-MET was observed [Bonine-Summers *et al.* 2007]. Clinical trials with these agents will hopefully validate positive observations from preclinical studies. c-MET inhibitor agents under development include compounds that directly inhibit HGF and/or its binding to c-MET, antibodies targeted at c-MET, and small-molecule c-MET TKIs. The potential efficacy of each of these different therapeutic agents is likely to be influenced by the mechanism of aberrant HGF/c-MET signaling pathway activation in a particular cancer but will also hopefully offer a promising new strategy for cancer treatment, either alone or as part of a combination therapeutic approach.

Future challenges

There remains an urgent need to improve and accelerate the transition of preclinical research into improved therapeutic strategies for patients with cancer [de Bono and Ashworth, 2010]. The main challenges facing the effective use of HGF/c-MET targeted antagonists for cancer treatment include optimal patient selection, diagnostic and pharmacodynamic biomarker development, and the identification and testing of rationally designed anticancer drugs and combination strategies. If the ongoing development of c-MET inhibitors is to result in a clinically useful therapeutic approach, an absolute requirement is the definition of a target patient population and a practical but analytically validated method to identify them in a clinical context [de Bono and Ashworth, 2010].

Although traditional drug development has involved a 'compound-to-trial' process, there is increasing evidence that this should now change to a 'biology-to-trial' approach, starting with unraveling of the fundamental mechanisms of cancer targets, which may then drive initial drug discovery and subsequent clinical studies [Yap *et al.* 2010]. The 'one-size-fits-all' approach currently in use does not take into account the now well established patient-to-patient variation that exists in the molecular drivers of both cancer

Table 1. c-MET inhibitors under current development.

Agent	Company	MOA	Phase	Reference
AMG102	Amgen, CA, USA	Anti-HGF antibody	II	[Gordon *et al.* 2010]
Tivantinib (ARQ 197)	ArQule, MA, USA; Daiichi Sankyo, Tokyo, Japan	Selective c-MET TKI	III	[Yap *et al.* 2011; Schiller *et al.* 2010]
Cabozantinib (XL184)	Exelixis, CA, USA; Bristol-Myers Squibb, NY, USA	Nonselective c-MET, VEGFR2 and RET TKI	II	[Kurzrock *et al.* 2011]
MetMAb	Genentech, CA, USA	Anti-c-MET antibody	II	[Spigel *et al.* 2011]

c-MET, mesenchymal–epithelial transition factor; HGF, hepatocyte growth factor; MOA, mechanism of action; RET, rearranged during transfection; TKI, tyrosine kinase inhibitor; VEGFR2, vascular endothelial growth factor (VEGF) receptor-2.

and drug sensitivity [Janne *et al.* 2009; McDermott and Settleman, 2009]. A new paradigm is now emerging that involves the use of customized, adaptive, hypothesis-testing early trial designs, which incorporate analytically validated and clinically qualified biomarkers from the earliest possible stage (Figure 1) [Yap *et al.* 2010]. This preferred scenario recognizes that the new generation of molecularly targeted drugs has the potential for personalized medicine and the possibility of more efficacious and less toxic antitumor therapies in patients who have defined molecular aberrations. In this scenario, there is an initial need to focus on the biology of the disease, identify a possible therapeutic target, and then understand how a molecularly targeted approach could offer therapeutic benefit.

Key molecular targets or pathways which are vital to certain cancers, or that present opportunities for synthetic lethality, should be actively pursued and dissected to improve our understanding of these essential pathways and to identify predictive biomarkers that could be integrated early in the drug discovery process. A strong biological basis clearly already exists for c-MET as a therapeutic target. However, there is an ongoing need to identify an altered molecular target which will provide a therapeutic window and therefore a clear basis for selective tumor cell cytotoxicity with absolute or relative sparing of normal cells [de Bono *et al.* 2003]. Although *MET* amplification or mutations have been demonstrated in a range of cancers in preclinical studies, these have, to date, not been shown to strongly predict which patients will respond to c-MET inhibitors in the clinic [Yap and de Bono, 2010; Comoglio *et al.* 2008].

Translating results from cancer genome mapping into clinical use will necessitate the development of analytically validated biomarker assays that can be clinically validated as potential predictors of benefit from anticancer therapies [de Bono and Ashworth, 2010]. These biomarkers will support

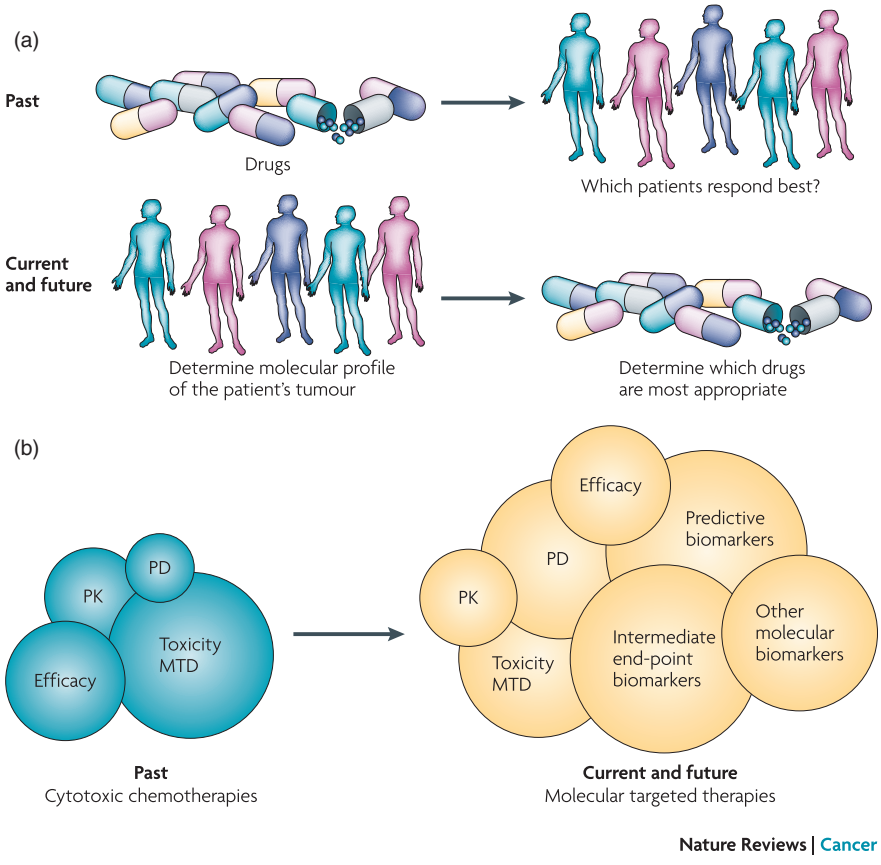

Figure 1. The shifting focus of old *versus* new phase I clinical trial designs.
PD, pharmacodynamics; PK, pharmacokinetics; MTD, maximum tolerated dose. Reprinted by permission from Macmillan Publishers Ltd: NATURE REVIEWS CANCER, Timothy A. Yap, et al. 2010a;10:514–523, © 2010.

a personalized approach as they could be used to examine intra- and inter-patient tumor molecular heterogeneity and assist selection of an optimal anticancer therapy for each individual patient. Moreover, these biomarkers could be increasingly used as intermediate endpoints of response. The upfront use and testing of putative predictive biomarkers in early clinical trial programs could minimize any possible need for retrospective subgroup dredging for predictive biomarkers in later phase trials carried out in unselected populations [Yap *et al.* 2010].

Selecting patients based on molecular predictors may help minimize the risk of late and costly drug attrition due to disease heterogeneity, accelerate patient benefit, and could also accelerate the drug approval process, which currently remains slow and inefficient. However, care should be taken when using predictive biomarkers to select patients since the potential beneficial effects of the targeted therapy in a more broadly defined patient population may be missed.

c-MET inhibitors in combination with other agents

Several different therapeutic strategies, aimed at inhibiting HGF/c-MET signaling, are currently in development, but it is still unclear if these agents will be most effective as distinct monotherapies or in combination with other agents. The combination of anti-c-MET therapeutic agents with either signal transduction inhibitors [ErbB family or mammalian target of rapamycin (mTOR) inhibitors] or with cytotoxic chemotherapies has been evaluated in preclinical studies which have provided insight into the rational development of combined therapeutic strategies for future clinical trial evaluation. Several studies have focused on the combination of c-MET inhibitors and agents targeting ErbB family members, with the rationale for this approach based on evidence of crosstalk between c-MET and other EGFR family members [Stommel *et al.* 2007; Jo *et al.* 2000]. In addition, cancers codependent on both c-MET and EGFR signaling have also been identified [Engelman *et al.* 2007], with *MET* amplification detected in patients with NSCLC who have clinically developed resistance to the EGFR inhibitors gefitinib or erlotinib [Bean *et al.* 2007; Engelman *et al.* 2007]. Several clinical trials are currently under way, which aim to determine if the combination of c-MET TKIs with EGFR, VEGF, or chemotherapy is a clinically effective therapeutic approach (Table 2).

Because c-MET activation leads to increased downstream signaling through a variety of different pathways, a combined approach that inhibits c-MET and its known downstream signaling intermediates could possibly enhance therapeutic efficacy. This approach may also be effective in cancers in which multiple receptors are concurrently activated – such as by EGFR – because these receptors typically activate the same downstream signaling proteins [Toschi and Janne, 2008]. Preclinical studies exploring a combination of anti-c-MET therapeutic agents with mTOR inhibitors have also demonstrated increased growth suppression compared with mTOR inhibitors alone [Ma *et al.* 2005].

Chemotherapy remains the mainstay of treatment for several malignancies, even though advances in the molecular knowledge of cancer continue to support the development of selective

Table 2. Combination studies: c-MET inhibitor plus other pathways.

Combination	Phase	Reference
EGFR		
Tivantinib ± erlotinib (ArQule, MA, USA; Daiichi Sankyo, Tokyo, Japan)	III	[Sandler *et al.* 2011]
MetMAb ± erlotinib (OAM4558g) (Genentech, South San Francisco, CA, USA)	II	[Spigel *et al.* 2011]
Ficlatuzumab (AV-299) ± gefitinib (Aveo Pharmaceuticals, MA, USA)	II	[Tan *et al.* 2011]
VEGF		
Rilotumumab (AMG 102) + bevacizumab or motesanib (Amgen, CA, USA)	Ib	[Rosen *et al.* 2010]
Tivantinib + sorafenib (ArQule, MA, USA; Daiichi Sankyo, Tokyo, Japan)	I	[Adjei *et al.* 2011]
Chemotherapy		
Crizotinib + pemetrexed/docetaxel (Pfizer, NY, USA)	III	[clinicaltrials.gov (trial no. NCT00932893)]
Tivantinib + gemcitabine (ArQule, MA, USA; Daiichi Sankyo, Tokyo, Japan)	I	[clinicaltrials.gov (trial no. NCT00874042)]
Tivantinib + irinotecan and cetuximab (ArQule, MA, USA; Daiichi Sankyo, Tokyo, Japan)	I/II	[Bessudo *et al.* 2011]

c-MET, mesenchymal–epithelial transition factor; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor.

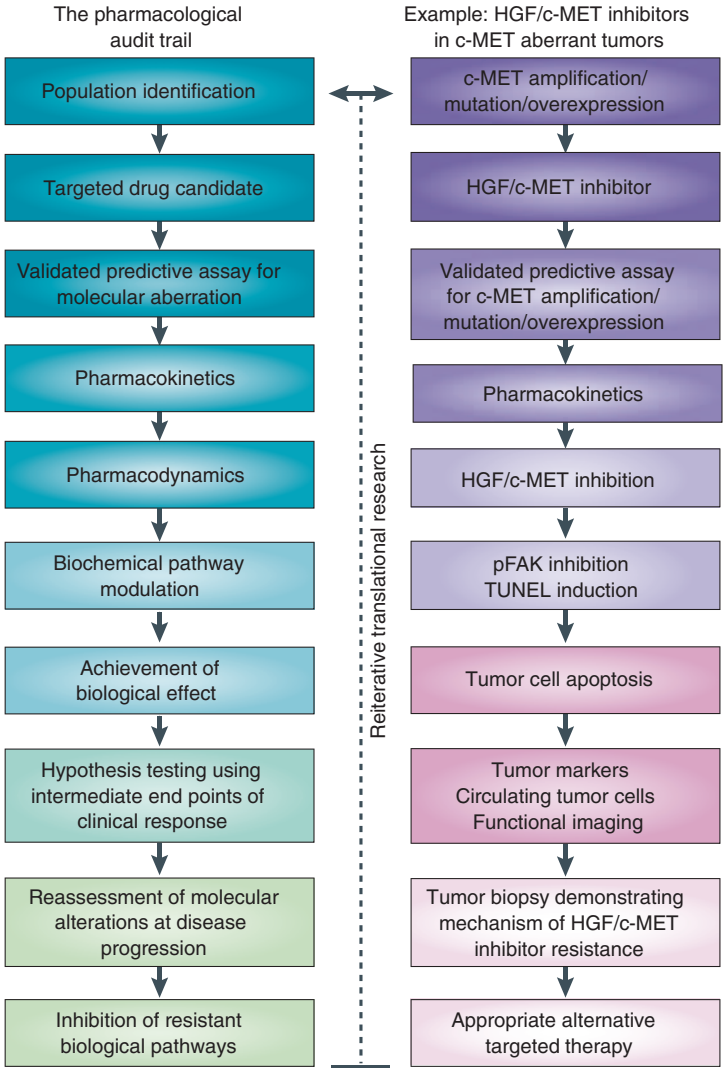

Figure 2. Pharmacological audit trail.
PARP, poly(ADP)-ribose polymerase; PBMC, peripheral blood mononuclear cell; PhAT, pharmacological audit trail. Adapted by permission from Macmillan Publishers Ltd: NATURE REVIEWS CANCER, Timothy A. Yap, et al. 2010a;10:514–523. © 2010.

targeted compounds. However, the use of conventional chemotherapy is often limited by *de novo* or acquired resistance, typically resulting from increased growth factor receptor signaling [Dai *et al*. 2005; Knuefermann *et al*. 2003]. These observations have prompted growth factor receptor inhibitors to be evaluated in combination with chemotherapy. Successful clinically validated examples of this approach include cetuximab, an anti-EGFR antibody, in colorectal cancer [Cunningham *et al*. 2004] and trastuzumab in patients with ERBB2-amplified breast cancer [Slamon *et al*. 2001]. Emerging preclinical data suggest that inhibitors of the HGF/c-MET signaling pathway may also be effective in combination with chemotherapy [Lasagna *et al*. 2006; Bowers *et al*. 2000].

The Pharmacologic Audit Trail

Pharmacodynamic and pharmacokinetic data together allow the construction of a framework, known as the 'pharmacologic audit trail' (PhAT), for rational decision making in clinical trials [Sarker and Workman, 2007; Workman, 2003, 2002]. The PhAT allows all the key stages in drug development to be linked and interpreted in relation to measured parameters (such as pharmacodynamic and pharmacokinetic parameters) and provides a stepwise 'audit' to assess the risk of failure during the development of a novel

compound at any particular stage. An updated PhAT has recently been developed to reflect the evolving drug discovery and development landscape, implementing the evaluation of potential predictive assays earlier in the drug development process and strategies to reverse resistance mechanisms (Figure 2) [Yap *et al.* 2010]. This updated version recommends inclusion of the identification and initial clinical qualification of robust predictive biomarker assays for patient selection early in the drug development process. The inclusion of intermediate endpoint biomarkers, which should be identified and studied in the audit trail as early predictors of antitumor activity, is also recommended.

Because there is an ongoing need to acquire more data from preclinical models on the relationship of anticancer drug antitumor activity and the required degree and duration of target blockade, careful assessment is warranted as to whether this is safely achievable in clinical trials and the PhAT should be seen as a useful tool.

Conclusions

Optimal methods for the assessment of HGF/c-MET overexpression or *MET* amplification have yet to be determined. Traditional histopathological diagnosis remains important when evaluating the extent of phenotypic aggressiveness, but personalized molecular diagnosis is needed to understand whether a tumor in one specific patient carries a particular genetic alteration that could be targeted by a particular therapy. In the case of c-MET, the current challenge is to identify the genetically defined responsive patient subsets that could benefit from c-MET inhibition and therefore enable appropriate patient selection strategies to be implemented in future clinical studies. This calls for a vast preclinical strategy of tumor categorization based on genetic makeup, responsiveness to c-MET inhibition and follow-up validation of surrogate indicators of c-MET activity. Treatment selection should be driven by a detailed understanding of the genetics and biology of the patient and their cancer. There is also increasing evidence for the traditional route of drug development and registration to be adapted for the development of molecularly targeted agents. Several different c-MET inhibitors are currently in development, each focusing on one or more of the steps that regulate c-MET activation. Finally, understanding the other key activated signaling pathways that occur concurrently with HGF/c-MET activation will be critical in the rational development of combination therapeutic strategies.

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Conflict of interest statement

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