## EDITORIAL

# Anti-MET-targeted therapy for NSCLC: has it come of age?

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Lung cancer molecular-targeted therapy has made its way into the standard of care in clinical cancer therapy in recent years. Recent clinical data also provided strong rationale for the first-line use of small molecular inhibitors against EGFR, gefitinib or erlotinib, in non-small-cell lung cancer (NSCLC) patients harboring EGFR-TKI-sensitizing mutations [1]. Molecularly matched targeted therapy represents a newly emerged paradigm that is founded upon the concept of 'oncogene addiction'. This paradigm is further consolidated by the successful development and now clinically approved use of crizotinib, a dual ALK and MET inhibitor, in NSCLC expressing the *ALK* 2p23 fusion oncogenic rearrangement as in *EML4-ALK*. Nonetheless, both EGFR and ALK inhibitors only target relatively small fractions of the NSCLC population, and resistance inevitably developed despite initial responses [2,3]. Further novel targeted-therapy development clearly remains a top priority to impact lung cancer.

Of interest is that crizotinib was initially developed in preclinical studies and in the initial Phase I study to be a MET receptor-kinase inhibitor, but was promptly shifted into being developed as an ALK-targeted therapeutic, and successfully so, after the discovery of *EML4-ALK* in NSCLC [4]. MET signaling cascade plays key roles in developmental signaling regulation in embryogenesis and early development. By contrast, MET signaling in adult tissues is typically in quiescence physiologically, except in processes of homeostasis such as wound healing. In human cancers, a dysregulated MET pathway is very commonly involved in tumorigenesis, tumor invasion and progression, and tumor metastasis [5,6]. MET, along with its specific natural ligand HGF (also called scatter factor), has been under extensive preclinical investigation for over 25 years. The MET/HGF signaling axis is now recognized as a 'druggable target' and is included as one of the 'hallmarks of cancer' [7] based on its role in "activating invasion and metastasis" [6]. The first selective preclinical MET inhibitors, SU11274 and PHA665752, used to validate MET targeting therapy in lung cancer, were reported back in 2003–2005 [8–10]. Currently, there are many experimental therapeutic agents targeting against MET and HGF that are already under clinical development in various phases in multiple cancer types. As the therapeutic target, MET receptor protein overexpression can activate the signaling pathway via transcriptional activation (e.g., through hypoxia), genomic amplification, or downregulated receptor proteolysis (e.g., through juxtamembrane CBL-binding domain mutation).

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Paracrine and autocrine ligand stimulation by HGF can further activate a wild-type, mutated or overexpresssed MET receptor. MET is highly expressed in lung cancer and phospho-MET was identified to be most prominently expressed in lung cancer when compared with other common solid tumor types [11]. A recent phosphoproteomic survey of RTKs in lung cancer tumor tissues identified

MET as the most highly tyrosine phosphorylated RTK among others in the study [12]. Agents that are under development to therapeutically target the MET/HGF-signaling pathway include small-molecule inhibitors (both ATP-competitive and -noncompetitive), as well as monoclonal antibodies, against both the ligand HGF and/or the MET receptor itself.

Several MET and HGF antibodies have been developed for therapeutic targeting. Initial efforts in developing bivalent antibodies to target MET proved difficult, primarily as the antibodies ending up being agonistic rather than antagonistic in the activities against the target receptor. This bottleneck limitation was ultimately overcome by the development of a 'one arm' engineered antibody (OA-5D5, MetMAb; Genentech, CA, USA), consisting of a monovalent Fab fragment with murine variable domains for both the heavy and light chains fused to human IgG1 constant domains (humanized). MetMAb antibody (onartuzumab, Genentech/Roche) Phase I clinical trial studies were initiated in October 2007. A global randomized, double-blind Phase II study comparing onartuzumab plus erlotinib with placebo plus erlotinib in second-/third-line NSCLC has recently been completed. In this trial, patients with MET-positive tumors (≥50% of tumor cells stain 2+ or 3+ intensity by immunohistochemistry [IHC]; Met Dx+) who received onartuzumab + erlotinib had nearly twofold reduction in the risk of disease progression (progression-free survival [PFS] median: 3.0 vs 1.5 month; hazard ratio [HR]: 0.47, p = 0.01) and threefold reduction in the risk of death compared with erlotinib alone (median: 12.6 vs 4.6 month; HR: 0.37; p = 0.002) [13]. Conversely, the MET-IHC-low/-negative group had worse overall survival (OS) in the combined MET–EGFR inhibition group than EGFR TKI alone plus placebo treatment arm (HR: 3.02; p = 0.021). This pivotal trial highlighted the importance of patient preselection for MET-targeted therapy. It also demonstrated MET receptor expression level as tested in IHC to serve as a sensitive predictor of benefit from onartuzumab, and therefore a predictive biomarker. These results lend support for further investigation of the MET antibody as a potential personalized MET-targeting cancer therapeutic for NSCLC patients, presumably with MET IHC intensity 2+ or 3+, and a Phase III clinical trial has recently been activated. A few other preclinical HGF/MET antibodies have also been developed and reported, such as the monovalent DN-30 Fab antibody against MET [14], and AMG 102 (Amgen, CA, USA) monoclonal antibody against HGF [15].

Another commonly adopted paradigm of inhibiting MET/HGF signaling is the use of small-molecular TKIs against the MET receptor. Tivantinib (Daiichi Sankyo, NJ, USA/ArQule, MA, USA) is the most advanced, having had the first ever MET-targeting Phase III clinical study in advanced NSCLC (MARQUEE) completed recently. It is the first-in-class non-ATP competitive small molecule that selectively targets MET, its method of action being to lock the kinase in a 'closed' and 'inactive' conformation when bound to the drug. In the ARQ197-209 global, randomized, placebo-controlled Phase II clinical trial comparing erlotinib plus tivantinib (ARQ197) with erlotinib plus placebo in advanced NSCLC patients, the final PFS was prolonged in the tivantinib plus erlotinib (combined MET–EGFR inhibition) group [16]. Median PFS was 3.8 month in tivantinib-plus-erlotinib arm and 2.3 month in placebo-plus-erlotinib arm (HR: 0.81; p = 0.24). The planned multivariable Cox regression model in the intention-to-treat population adjusting for key prognostic factors yielded significant improvement in PFS with a HR of 0.68 (95% CI: 0.47–0.98; p <0.05). The difference in OS in the two arms was not statistically significant. Moreover, a preplanned subset analysis showed a statistically significant improvement in both PFS (adjusted HR: 0.61) and OS (adjusted HR: 0.58) in patients with 'nonsquamous' histology who were treated with the combined MET/EGFR-inhibition approach with tivantinib plus erlotinib. This preplanned analysis supports the notion that nonsquamous tumors may indeed be enriched for MET expression, as implicated in existing literature. Preliminary biomarker analysis in this Phase II study demonstrated that 75% of tumors among nonsquamous population had MET-positivity by IHC, compared with only 12% of squamous tumors. Most interestingly, exploratory analyses also showed PFS was significantly better in the tivantinib arm among patients with mutated *KRAS* (median PFS: 2.3 vs 1.0 month; HR: 0.18), and a similar trend in patients with wild-type *EGFR* [17].

Finally, tivantinib was also found in an exploratory analysis of time-to-development of new metastasis to significantly delay new tumor metastases among patient treated with tivantinib plus erlotinib (median: 7.3 vs 3.6 months; HR: 0.49; p <0.01 in the intention-to-treat population), raising early clinical evidence that inhibiting MET in human cancer can impact the tumor progression, presumably by inhibiting MET-signaling-mediated tumor invasion and metastases. Furthermore, this effect was observed to be more pronounced in nonsquamous patients. The final result of the Phase III nonsquamous cell NSCLC trial of tivantinib plus erlotinib versus placebo plus erlotinib (MARQUEE [Interim analysis showed no difference in the overall survival as primary end point, although

there is a statistically significant PFS difference. The trial study has been halted as per the sponsor's press release on 2 October 2012]) is highly anticipated, in order to validate the notion of improved efficacy of combined MET/EGFR TKI therapy and especially that within the mutated *KRAS* and wild-type *EGFR* patient populations.

Other HGF-/MET-targeted agents that have been in clinical trials include foretinib (XL880), ficlatuzumab (AV-299) and cabozantinib (XL184). A growing list of other MET- or HGF-targeting agents continues to emerge and some of the agents are currently still under preclinical and early clinical development. To this end, it is of interest to note that there is indeed a recent US FDA-approved kinase inhibitor that possesses anti-MET activity – crizotinib (Pfizer, NJ, USA). Crizotinib was approved in August 2011 for patients with *ALK* 2p23 translocation-positive NSCLC, although it was initially developed both preclinically and clinically with the intension of being a MET inhibitor. A recent case report also described a NSCLC patient with *de novo MET* amplification, but without *ALK* rearrangement, who achieved a rapid and durable response to crizotinib, indicating that it is also a clinically *bona fide* MET inhibitor [18].

Has anti-MET-targeted therapy for NSCLC come of age? Yes, indeed. However, based on the two recent sets of promising Phase II clinical trial data from onartuzumab and tivantinib, both tested in combination with erlotinib, do we know the optimized strategy to target the 'MET pathway' in NSCLC yet? The answer to this question is, perhaps, 'maybe'. Indeed, many questions still remain unresolved. One key concept in MET-targeted therapy that we need to keep in min,d is that one should expect it to be different from the paradigm in EGFR-targeted therapy, or even the EML4-ALK-targeted therapy. *MET* does not have to be mutated or chromosomally rearranged to be activated in lung cancer cells, whether constitutively or ligand dependent. The role of wild-type *MET* genotype in lung cancer biology is relatively more important than that of wild-type *EGFR* or *ALK* in the disease. The optimal patient subgroup that would most benefit from MET-inhibitor treatment also remains to be fully defined. To date, several biomarkers, including HGF serum level, tumor *MET* gene amplification and receptor protein overexpression, have been studied in both preclinical models and ongoing clinical trials. Reliable and validated predictive biomarker for MET-targeted therapy is still urgently needed. Nonetheless, a confounding issue here is that many MET-targeting agents in clinical trial studies are in fact multi-targeted inhibitors, except perhaps

for tivantinib and onartuzumab. Abnormally high HGF serum or plasma levels have been associated with advanced disease and poor outcomes for several cancers. Plasma HGF concentrations have been reported to correlate to response to XL184 [19]. Recently, a case report of durable complete response of gastric cancer with onartuzumab found that the patient had a remarkably high serum HGF level before onartuzumab treatment and experienced rapid and sustained drop in HGF level post-treatment [20,21]. *MET* amplification has been shown to correlate with drug sensitivity in preclinical models and is incorporated in Phase II and ongoing Phase III tivantinib clinical trials. MET overexpression, as determined by IHC staining, is showing promise as a predictive biomarker, illustrated by the onartuzumab Phase II study results. Further work in developing this as a companion diagnostic test is ongoing.

The best strategy of using MET-targeted inhibition as a single agent or in combination with other targeted agents, especially EGFR TKI, remains to be determined. Currently, most Phase II and III trials testing MET agents are being conducted in combination with erlotinib. Recent data implicate that MET inhibition either alone, or in combination with EGFR TKI, may indeed have a role in primary therapy of EGFR-TKI naive NSCLC patients. Our recent study showed that MET activation is not involved in the early reversible adaptive resistance in tumor cells that evaded erlotinib inhibition, but a dependence on BCL-2/BCL-xL prosurvival signaling is key [22]. In addition, a number of potential opportunities exist in combining MET inhibition with other targeted agents, such as a HGF antagonist, other targeted receptor kinase agents, or downstream signaling effector inhibitors, for example, PI3-K/AKT/mTOR inhibitors, MEK inhibitor or BH3 mimetics. Finally, there would certainly be great opportunities to explore combining MET-targeting agents with radiation or even chemoradiation to impact lung cancer, especially in the locally advanced stage III therapy setting, where erlotinib has failed in previous clinical studies.

Third, HGF has emerged as a molecular target as well as MET receptor itself. Recent data supporting the role of paracrine HGF in mediating acquired resistance, not only in EGFR-TKI-targeted therapy in NSCLC [23] but also in other disease-type targeted therapeutics, such as vemurafenib in mutant-*BRAF* inhibition in melanoma [24], certainly open up a wide array of therapeutic opportunities to target HGF in lung and other cancer types. Ficlatuzumab (AVEO, MA, USA) is a humanized anti-HGF IgG1 monoclonal antibody with potent MET-signaling inhibition. Phase I studies of ficlatuzumab combining with EGFR inhibitors showed

a favorable tolerability profile and some early clinical activities. AMG 102 is another novel, fully humanized monoclonal antibody that selectively targets HGF. A Phase I/II trial of AMG 102 with erlotinib or cytotoxic chemotherapy in advanced NSCLC is currently ongoing.

Finally, the potential acquired-resistance mechanisms against MET-targeting inhibition and strategies to overcome its resistance are equally important to be understood. Prior experience in other targeted therapeutics, such as erlotinib against mutant *EGFR* and crizotinib against *EML4-ALK,* suggests that acquired resistance is thus far unavoidable. Proactive efforts in identifying potential resistance mechanisms in MET-targeted inhibition would be needed to accelerate the discovery of newer co-targeting strategies to dampen drug resistance. The best effort to re-biopsy tumor tissues in sites of progressive resistant disease should bring forth renewed understanding of the MET pathway in lung cancer biology and therapeutics, and could have a long-lasting impact in advancing our rational therapeutic strategies in lung cancer.

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