Perspective

Combined treatment with MET inhibitors and other therapies in lung cancer

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Molecular targeted therapy has made significant progress in human cancers in the past decade and has become an integral part of modern human cancer treatment. Targeted drugs are now moving closer to be used in tailored therapy with personalized molecular predictive biomarkers assay development to couple with the therapeutics. Much progress has been made in non-small cell lung cancer (NSCLC) using the tyrosine kinase inhibitors (TKIs) erlotinib and gefitinib to target the epidermal growth factor receptor (EGFR) clinically in patients with advanced disease (1). However, the long term efficacy of the TKIs is still inevitably limited, as patients with NSCLC who initially have primary tumor response, always develop acquired resistance against EGFR-TKI monotherapy typically after 6-12 months of treatment (2). Recent research studies to elucidate mechanisms of acquired EGFR TKI resistance identified alternative molecular targets of receptor tyrosine kinases (RTKs) to be responsible, such as AXL (3), as well as MET receptor (4) and its natural ligand hepatocyte growth factor (HGF) (5), as implicated in mediating the tumor escape process.

Receptor tyrosine kinases are key regulators of a wide range of physiologic and developmental cellular functions, such as cell growth and differentiation, tissue repair and regeneration, cell survival, morphogenesis, cell motility, invasion, inflammation and angiogenesis. Dysregulation of RTK signaling by processes such as genomic amplification, overexpression, mutation, alternative splicing, or chromosomal translocation has been identified as oncogenic transformation to lead to the development of various human malignancies, and in their tumor progression to metastasis. MET is a multifaceted RTK that plays key roles in embryonic development. While MET/HGF signaling is typically quiescent in adult tissues and cells, its dysregulation can result in tumor cell proliferation, survival, motility and migration, scattering, epithelial-mesenchymal transition (EMT), angiogenesis, invasion and metastasis (1). Oncogenic MET overexpression has been demonstrated in various human cancers, including lung, ovarian, breast, liver, melanoma, gliomas, gastric, colorectal, and prostate among others (6-8). In particular, phosphorylated MET was shown to be highly expressed in lung cancer tissues among other common solid cancers in a tumor tissue microarray analysis (8) as well as a mass-spectrometry based phosphoproteomics analysis of NSCLC (9). Understanding the tumor specific MET signaling pathways at basic and translational levels over the past two decades has paved way to facilitate the development of novel MET targeted therapy to impact human cancers (6,7,10,11). Previous studies have demonstrated network interaction and cross-talk signaling between MET and other oncogenic pathways, such as RON, EGFR (ERBB1), HER3 (ERBB3), AXL, CD44, α6β4-integrin and HIF-1α (4,12-14). Some of these "bypass" or "rescue" pathways have emerged as possible mechanism contributing to acquired EGFR-TKI resistance (15). Continued and better understanding of signaling cross-talk and "rescue" pathways in recent years has paved way to improve our insight in novel strategies of combination targeted therapies to prevent or overcome acquired TKI resistance. This editorial will discuss the rationale and recent clinical study data in MET pathway antagonistic agents (1) in clinical therapeutic development in combination inhibition with other therapies in lung

cancer.

A deeper understanding of the structure-function relationship of MET receptor and its specific ligand HGF, has enabled significant progress in the clinical development of therapeutic inhibitors against the MET receptor and its ligand HGF for targeted cancer therapy. Generally, there are three main targeting cancer treatment strategies in MET/HGF pathway inhibition: HGF antibodies, MET receptor antibodies, MET receptor tyrosine kinase inhibitors (ATP-competitive and non-competitive) (TKIs). Several of these targeting agents are already moving from phase II to phase III randomized clinical trial studies recently. We will highlight the emerging clinical trial data with special emphasis on the combination targeted therapeutic approach using MET/HGF agents in lung cancer. Current and future challenges in bringing MET/HGF targeted therapy to full clinical fruition in lung cancer will also be discussed.

A number of phase II clinical trials utilizing tivantinib (ARQ 197), which is an ATP-non-competitive specific MET inhibitor, to evaluate anti-tumor efficacies in various malignancies, including lung cancer, have been conducted. One such study, ARQ 197-209 (NCT00777309), is a global, randomized phase II trial comparing erlotinib plus tivantinib (ET) to erlotinib plus placebo (EP) in advanced NSCLC patients (16). The primary endpoint of the study was progression-free-survival (PFS), with secondary endpoints being overall response rate (ORR) and overall survival (OS). There were a total of 167 patients enrolled, randomized to erlotinib plus tivantinib (n=84) or erlotinib plus placebo (n=83). Median PFS was 3.8 months for erlotinib plus tivantinib (ET) arm and 2.3 months for erlotinib plus placebo (EP) arm (hazard ratio 0.81; 95% CI, 0.57 to 1.16; P=0.24) in the intention-to-treat (ITT) population. However, analysis adjusted for demographic and molecular imbalances between the two arms indeed demonstrated statistically significant prolonged PFS in the erlotinib plus tivantinib (ET) arm (adjusted HR 0.68, 95% CI, 0.47-0.98, P=0.04) in the intention-to-treat population (ITT), favoring the MET/EGFR combination regimen. More importantly, planned subset analysis showed significant improvement in both PFS (adjusted HR 0.61, 95% CI, 0.39-0.98, P=0.04) as well as OS (adjusted HR 0.58, 95% CI, 0.34-0.99, P=0.04) among patients with nonsquamous histology who were treated with erlotinib plus tivantinib. In addition, exploratory analysis showed significantly improved PFS in erlotinib plus tivantinib (ET) arm in small cohort of patients with KRAS mutant (median PFS 2.3 *vs.* 1 month, HR 0.18, 95% CI, 0.05 to 0.70, P=0.006) (16). These findings are keeping in line with previous work demonstrating that the HGF/MET signaling pathway appears to be more prevalent in nonsquamous NSCLC (17,18).

ARQ 197-218 (NCT01395758) is another phase II randomized, open-label trial designed to evaluate PFS among previously treated KRAS mutation positive patients with locally advanced or metastatic NSCLC, treated with erlotinib plus tivantinib versus single agent standard chemotherapy. The study is still actively open for patient recruitment.

Findings from the ARQ 197-209 phase II study prompted the MARQUEE study: a phase III, randomized, double-blind, placebo-controlled study of ARQ 197 plus erlotinib versus placebo plus erlotinib in previously treated subjects with locally advanced or metastatic, nonsquamous NSCLC (NCT01244191) (19). This large multinational study with just over 1,000 patients enrolled, has just recently been completed. The final trial results along with the pre-designed biomarkers analysis (*EGFR* and *KRAS* mutations, *MET* genomic amplification by FISH and receptor expression by IHC) will hopefully ultimately address the questions regarding the efficacy of combined MET and EGFR inhibition in mutant *KRAS* patients, and predictive biomarkers of MET targeted therapy. Interestingly, biomarker analysis from ARQ197-209 demonstrated that among nonsquamous tumors, 75% were MET-positive by IHC (2+/3+), compared with only 12% among squamous tumors. In addition, in this phase II trial, exploratory analysis demonstrated significant delay in time-to-development of new metastases among patients treated with erlotinib plus tivantinib (ET) compared with the erlotinib plus placebo (EP) arm in the ITT population (median 7.3 versus 3.6 months, HR 0.49, P<0.01), and this effect was notably more pronounced in the nonsquamous patient population. The final results from the phase III MARQUEE trial, which has recently completed accrual, are thus highly anticipated, as it will be interesting to see if these results would ultimately validate those observed in phase II study.

XL184-202 (NCT00596648) is a phase I/II, randomized, open-label trial of XL184 (cabozantinib, a multitargeted inhibitor with potent inhibition of MET, VEGFR2, and RET) either alone or in combination with erlotinib in patients with NSCLC who progressed after initial, favorable response from erlotinib. Results were reported at the 2010 ASCO Annual Meeting. Overall safety and tolerability profile of cabozantinib plus erlotinib is

acceptable without evidence of drug-drug interaction. Out of 36 assessable patients, 6 (of which at least 3 patients had prior erlotinib therapy) patients had ≥30% reduction in tumor measurements on at least 1 post-baseline scan, including 3 with a complete/partial response (1 with MET amplification). Furthermore, prolonged SD of ≥4 months was observed in some patients, including one for >9 months and one with EGFR T790M (20).

The first-in-class MET receptor antibody, onartuzumab, was tested in the OAM4558g trial, which is a global, randomized, double blind phase II study comparing onartuzumab (MetMAb, an antagonistic one-arm humanized monoclonal antibody that binds specifically to MET receptor resulting in signaling inhibition) plus erlotinib versus placebo plus erlotinib, in the second or third line setting in patients with NSCLC. Results were reported at 2011 ASCO Annual Meeting. A total of 128 patients with NSCLC were randomized to receive onartuzumab plus erlotinib or placebo plus erlotinib. Importantly, 54% of patients were found highly positive for MET receptor expression by immunohistochemistry (IHC) (2+ or 3+), which was associated with a worse outcome (OS HR 2.52, placebo plus erlotinib cohort). In the MET positive group (n=65), MetMAb plus erlotinib resulted in a statistically and clinically significant improvement in both PFS (median 3 *vs.* 1.5 months, HR 0.47, P=0.01) and OS (12.6 *vs.* 4.6 months, HR 0.37, P=0.002) (21). Currently, the phase III MetLUNG trial study is ongoing, which is a randomized, phase III, multicenter, double-blind, placebo-controlled study where patients with MET positive (Dx+ with IHC 2+/3+) tumors who failed at least 1 but no more than 2 prior lines of platinum-based chemotherapy for advanced NSCLC are eligible. About 480 patients will receive (1:1) erlotinib (150 mg PO daily) + placebo or onartuzumab (15 mg/kg IV Q3W). Patients are stratified for MET expression (2+ *vs.* 3+), prior lines of therapy (1 *vs.* 2), histology (squamous *vs.* nonsquamous) and EGFR activating mutation status (yes *vs.* no). The primary endpoint is OS; and secondary endpoints include PFS, response rates, safety, patient-reported outcomes, and PK. The MET antibody trial study using onartuzumab now further validates the importance of assessment of MET receptor expression level in tumor tissues which is emerging as a strong negative prognostic factor and a positive predictive biomarker for MET targeting therapeutics in lung cancer. Further validation in studies such as the phase III trials would be warranted and highly anticipated. Here, technical and performance issues with specific MET recognizing IHC diagnostic antibody would impact on future status of the assay to be fully implemented in clinical arena as companion diagnostics. Currently, the CONFIRM total c-MET antibody (clone SP-44) from Ventana is being used in this setting. This MET antibody as well as further novel assay platform development to better define the patient population with MET expression that could predict for therapy response, would be most important and highly warranted in conjunction with further MET targeted therapeutics clinical development.

There are also several phase I/II clinical trials utilizing HGF antibodies underway, such as NCT01039948 - A phase Ib/II study of ficlatuzumab (AMG 102) in combination with gefitinib in Asian subjects with NSCLC) and NCT01233687 - A phase I/II trial of ficlatuzumab (AMG 102) and erlotinib in previously treated patients with advanced NSCLC). Results from these trials are currently pending at time of publication, however they will be expected to provide important insight into alternative strategies of MET inhibition beyond the receptor level of antagonism, such as at the level of the ligand targeting. Given the recent multitudes of research findings pointing to the clinical relevance and central importance of HGF in RTK targeted therapeutic resistance, including EGFR TKI erlotinib in NSCLC and BRAF inhibitor vemurafenib in cutaneous melanoma (5,22), there would be expectedly more combinational targeting trial opportunities using HGF antagonist in the near future.

The MET/HGF signaling pathway regulates a diverse set of cancer cellular functions, including cell proliferation, survival, cell scattering and motility, invasion, epithelial-mesenchymal transition, angiogenesis, and metastasis. In addition, highly expressed levels of the MET receptor in cancer correlated with more advanced stages and poor survival/prognosis. With recent studies demonstrating dynamic interplay between various oncogenic signaling pathways, so called "cross-talk," our basic knowledge of HGF/MET biology has enabled a more thorough understanding of the complete oncogenic potential of the axis. This new insight has expanded our knowledge of the mechanisms underlying acquired resistance and, in addition, has provided a rationale for using a combined, multi-targeting inhibitory approach with the use of MET agents. Recent clinical studies of MET pathway inhibition through various strategies (MET-TKI, MET antibody, HGF antibody) in combination with other therapeutic agents, primarily the EGFR-TKI erlotinib, are mostly very promising. However, there are still a number of

remaining issues and challenges that need to be fully addressed for optimizing MET targeted therapy in full clinical fruition. Firstly, clarity in the predictor(s) of MET therapy response is urgently needed. A potential challenge here is the possibility of differing MET signaling activation mechanisms in different tumor types, or even at different stages of tumor progression, which can confound the search for the right predictive biomarkers. Given the complex and redundant nature of RTK signaling network cross-talk, predicting MET inhibitory response of a tumor merely by determining the presence of phospho-MET may or may not be unreliable, although this remains to be further defined. Secondly, the optimal strategy for utilizing MET inhibition, i.e. as single agent or in combination with other targeted agents, remains to be determined. At present, most clinical trials are analyzing MET directed agents in combination with EGFR inhibition, primarily erlotinib. In addition, future investigation into combinations of pathway selective therapies and combinational MET inhibition, such as MET-TKI with HGF targeted agents, or other targeted kinase agents, could prove to further enhance inhibition efficacy. To this end, there are now newly activated phase II studies using onartuzumab (MetMAb) in combination with cytotoxic chemotherapy in the setting of first line setting treatment in NSCLC.

Given the level of enthusiasm among investigators on this novel MET/HGF pathway targeted inhibition, and the many targeting agents to be made available for clinical development both alone and in combination regimen, the MET/HGF based therapeutic combinational opportunities in clinical testing appear not to be the ultimate limiting factor in the successful impact on lung cancer outcome. It is the translational and preclinical model studies that need to continue to match up with the clinical development. This way, a real difference can thus be made to foster the most cost-effective development of efficacious MET pathway targeted therapy. As optimists, we believe that sooner or later, we would get there. We only hope that we could get there sooner rather than later, and with most optimal and rational study trial designs, to truly achieve the next level of personalized lung cancer treatment using MET/HGF inhibitors to impact this deadly disease.

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