

MET inhibitors in combination with other therapies in non-small cell lung cancer

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Abstract: MET and its ligand hepatocyte growth factor/scatter factor (HGF) influence cell motility and lead to tumor growth, invasion, and angiogenesis. Alterations in MET have been observed in non-small cell lung cancer (NSCLC) tumors, with increased expression associated with more aggressive cancer, as well as acquired resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI). MET inhibitors act via two basic mechanisms. Small molecule inhibitors antagonize ATP in the intracellular tyrosine kinase domain of MET, with studies on the following agents reviewed here: tivantinib (ARQ-197), cabozantinib (XL-184), crizotinib (PF-02341066), amuvatinib (MP470), MGCD265, foretinib (EXEL-2880), MK2461, SGX523, PHA665752, JNJ-38877605, SU11274, and K252A. The monoclonal monovalent antibody fragment onartuzumab (MetMab) is also discussed here, which binds to and prevents the extracellular activation of the receptor by ligand. MET inhibition may both overcome the negative prognostic effect of MET tumor expression as well as antagonize MET-dependent acquired resistance to EGFR inhibitors. Here we discuss MET inhibitors in combination with other therapies in lung cancer.

Key Words: Non-small cell lung cancer; targeted therapies; tyrosine kinase inhibitors; MET



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Introduction and impact of the MET signaling axis

Lung cancer remains the leading cause of cancer-related deaths in the United States, estimated to be responsible for 160,000 deaths in 2012, and worldwide killing of more than 1.3 million people annually (1,2). MET is a transmembrane receptor tyrosine kinase (RTK) that binds with high affinity to the ligand hepatocyte growth factor/scatter factor (HGF) (3), and is instrumental in growth of normal epithelial tissues like liver, gastrointestinal tract and kidney (4). MET was first discovered to be linked to cancer in papillary renal cell carcinoma (5), and its function has since been found altered in a variety of cancers including lung cancer (6,7). Upregulation of MET enhances autocrine signaling with HGF and downstream activation of the central proliferation and anti-apoptotic signaling pathways, Ras/Raf/ERK/MAP kinase

and PI3 kinase/AKT (8,9); and results in motility, growth, angiogenesis, and invasion in cancers (4,9). Somatic intron mutations in *MET* create an alternate splicing transcript which deletes the juxtamembrane domain of MET, creating an activated protein with enhanced downstream signaling (10). As previously reviewed, MET is dysregulated via a variety of mechanisms in cancer including *MET* chromosomal rearrangements, somatic and germline mutations, gene amplification, transcriptional upregulation, and autocrine stimulation via HGF (11).

Increased MET signaling in non-small cell lung cancer (NSCLC) is linked to a relatively unfavorable prognosis. In a study that looked at circulating MET in NSCLC, higher levels were associated with higher nodal stage (P=0.011) and earlier recurrence than lower levels [HR 3.9, 95% confidence interval (CI), 1.17-13.33, P=0.027] (12). In another retrospective study, increased *MET* gene copy number

(GCN) of ≥ 5 copies/cell were found in 11% NSCLC patients and negatively affected survival (25.8 months in MET positive versus 47.5 months in MET negative tumors, $P=0.005$) (13). MET also participates in other signaling networks that are important in lung cancer. For example, the epidermal growth factor receptor (EGFR) pathway acts synergistically with MET to increase phosphorylation and activation of downstream effectors, likely through the tyrosine kinase partner ERBB3 (14). Inhibition of both MET and EGFR *in vitro* decreases cell proliferation by more than double (65.2% versus 21.5-25.5%) than either pathway alone (15). MET amplification or increased HGF expression is associated with 5-50% of acquired resistance to EGFR tyrosine kinase inhibitors (TKIs), like gefitinib or erlotinib (16,17). Theoretically the combination of a MET TKI plus an EGFR TKI may overcome this resistance (14,18-20). Alteration of the MET pathway has also been identified in small cell lung cancer, though the clinical significance is not yet understood (21,22). Based on MET's importance in cancer development and cross talk between pathways for which there are targeted therapeutics in development, here we review clinical studies involving MET inhibitors in combination with other therapies in the treatment of lung cancer.

Tivantinib (ARQ 197; ArQule, Woburn, Massachusetts)

Tivantinib mechanism of action

Tivantinib is an oral small molecule TKI that binds to the inactive form of MET (23-26). It has shown antitumor activity in xenograft models of colon, gastric, and breast cancer (23). Tivantinib has been studied alone and in combination with other targeted therapeutics, like erlotinib and sorafenib, in a variety of solid tumors.

Tivantinib monotherapy

Five phase I trials were conducted with tivantinib (27). Tivantinib demonstrated linear pharmacokinetics (PK) and inter-patient variable metabolism due to the genetic polymorphism of cytochrome P450 CYP2C19 (28,29). ARQ-101 included 74 patients with metastatic solid tumors (4 with NSCLC), and recommended a phase II dose of 360 mg orally twice daily (bid) of the crystalline formulation (30-32). 3 patients had a partial response (PR) and 40 had stable disease (SD), including two patients with NSCLC, for up to 20 weeks. Because maximum tolerated

dose (MTD) was not reached, ARQ-103 (n=51 patients, 1 with NSCLC) was conducted and recommended the phase II dose of 300 mg bid of amorphous formulation (25), which is equivalent to the previously recommended dose of the crystalline formulation (unpublished data, clinicaltrials.gov NCT00658554). Best tumor response was stable disease in 14 patients for ≥ 4 months. Correlative studies demonstrated a decrease in phosphorylated MET and total MET in 15 available tumor biopsies; decrease in circulating tumor cells in 58% (n=25) of samples; and no significant change in dynamic contrast enhanced magnetic resonance imaging. In these studies, tivantinib was well tolerated with toxicities of greater than 5% including fatigue and nausea, and dose limiting toxicities (DLT) of hematologic cytopenias including febrile neutropenia, fatigue, vomiting, and dehydration (25,32).

Tivantinib combination therapy

Phase I study tivantinib and erlotinib

A phase I study (ARQ 197-111) combined tivantinib in 3 dose cohorts up to 360 mg bid with the standard dose erlotinib (EGFR TKI) 150 mg oral daily (33). All patients had CYP2C19 genotyping performed and inpatient dose escalation was allowed. Tissue was not required for the study, but when available was tested for mutations in EGFR and KRAS by polymerase chain reaction (PCR), and MET and EGFR amplification by fluorescent in situ hybridization (FISH). Thirty-two patients (mean age =60 years) enrolled had received a median of 3 previous chemotherapies (range, 1-8 chemotherapies), and the most common tumor type was NSCLC (n=8). Six out of eight NSCLC patients had stable disease (3-23 months), of which some had prior exposure to erlotinib. One out of 5 NSCLC patients had an EGFR mutation and 3 out of 6 had MET amplification. Patients with increased MET GCN (3.5-4.5 copies per cell) stayed on study longer than those who did not (14.7 versus 8.6 months). Median progression free survival (PFS) was 4.1 months (95% CI, 2.0-8.1 months). Adverse events (AE) were frequent (87.5%) and included those not seen when tivantinib was used as single agent including grade 1-2 rash and bradycardia. However, previously reported gastrointestinal (GI) symptoms were prevalent along with hematologic toxicities at higher doses (>360 mg bid). The pharmacokinetics of tivantinib were not linear and there were no obvious drug interactions. The recommended phase II dose was tivantinib 360 mg oral bid and erlotinib 150 mg oral daily, although the MTD was not reached.

Phase II study tivantinib and erlotinib

In a randomized double blind phase II study, erlotinib 150 mg oral daily combined with tivantinib 360 mg oral bid (ET) was compared to erlotinib 150 mg oral daily plus placebo (EP) in pre-treated stage IIIB or IV NSCLC patients (34). Patients could not have been exposed to EGFR TKIs, a difference from the phase I trial, and crossover was allowed at progression. The primary end point was PFS and the study was powered to detect a 1.5 month improvement in the ET arm (35). Eighty-four patients were treated with ET and 83 patients with EP. The median age was 63 years and majority of patients were Caucasian, male, current or former smokers, had adenocarcinoma histology (60%), and had received one prior chemotherapy. As KRAS and EGFR status were not used at randomization, there were approximately double the number of patients with tumors harboring a KRAS mutation (10 versus 5) and half the number of patients with tumors harboring EGFR mutations (6 versus 11) in the tivantinib arm, which favored the placebo arm. The majority of patients (73 versus 37) were *MET* GCN negative as determined by FISH. At a median follow up of 11 months, the trial did not meet its primary endpoint; however, median PFS favored the ET arm (3.8 months versus 2.3 months; HR 0.81, 95% CI, 0.57-1.16, $P=0.24$). The pre-planned PFS hazard ratio (HR) adjusted for clinical and molecular variables favored the ET arm with PFS HR 0.68 (95% CI, 0.47-0.98, $P=0.04$). Median overall survival (OS) was not statistically significant different (8.5 months ET versus 6.9 months EP; HR 0.87, 95% CI, 0.59-1.27, $P=0.47$). Significant benefit was seen with tivantinib in the non-squamous group with adjusted PFS HR 0.61 (95% CI, 0.39-0.98, $P=0.04$) and OS HR 0.58 (95% CI, 0.34-0.99, $P=0.04$). In the intention to treat (ITT) population on tivantinib, there was an increase in median time to new metastases and the benefit was again, more evident in the non-squamous group (11 months ET versus 3.6 months EP, HR 0.46, 95% CI, 0.26-0.82, $P<0.01$). Patients with KRAS mutation tumors had a statistically significant improvement in PFS in the ET arm (HR 0.18, 95% CI, 0.05-0.70, $P=0.013$, interaction $P=0.06$), and there was also a trend for improvement in the patients with EGFR wild type tumors (HR 0.70, 95% CI, 0.44-1.10, $P=0.12$) and higher *MET* GCN. This regimen may serve as a niche in patients with tumors with KRAS mutations and increased resistance to EGFR TKIs (36). There is an ongoing trial of this combination versus single agent chemotherapy in pretreated advanced NSCLC with KRAS mutations [NCT01395758]. The combination is well

tolerated with the most frequent toxicities including rash and diarrhea and both arms had similar rates of grade 3-5 toxicities including anemia and neutropenia.

Phase III study tivantinib and erlotinib

The phase III randomized trial (MARQUEE) studied this combination in stage IIIB/IV non-squamous NSCLC patients with 1 or 2 prior chemotherapies and no prior therapy with an EGFR or MET inhibitor (37). Unlike the phase II trial, patients were randomized by EGFR and KRAS mutation status. They were also tested for but not stratified by tumor MET expression by IHC, *MET* GCN by FISH, and circulating hepatocyte growth factor (HGF). The trial was terminated in October 2012 after interim analysis showed it would not meet its primary endpoint of overall survival in the approximately 1,000 patients enrolled (<http://investors.arqule.com/releasedetail.cfm?ReleaseID=710618>). The full results including subset analyses and correlative studies are awaited. The Phase III ATTENTION study of this combination is still ongoing in Asia [NCT01377376].

Cabozantinib (XL-184; Exelixis, South San Francisco, CA)

Cabozantinib mechanism of action

Cabozantinib is a small molecule TKI of MET which also has activity against the VEGFR2, RET, AXL, KIT, FLT-3 and TIE-2 kinases, which are important mediators of tumor cell growth and angiogenesis. It is orally bioavailable and administered once daily. Cabozantinib has been tested in a variety of preclinical and xenograft models, and exerts antitumor effects in mice injected with cells expressing MET and VEGF (38), as well as mouse models of pancreatic neuroendocrine cancer and prostate cancer (39,40). Preclinical efficacy appears to be associated with the inhibitory effects against both MET and VEGFR.

Cabozantinib monotherapy

Multiple phase I studies have been conducted with cabozantinib. In solid tumors, the XL184-001 study treated 85 patients with escalating doses of cabozantinib, with a MTD of 175 mg orally daily (by salt weight, which equals 138 mg freebase equivalent weight) (41). Of note, 35 patients were included with RET-oncogene dependent medullary thyroid cancer, of which 29% achieved partial responses (PR) and an additional 49% had some degree of

tumor shrinkage. Major observed toxicities included hand/foot syndrome, diarrhea, and increased risk of hemorrhage.

To investigate the clinical utility of cabozantinib as monotherapy, the XL184-203 phase II trial included a NSCLC cohort as well as 8 other solid tumor cohorts and utilized a randomized discontinuation design (42). Patients received cabozantinib 100 mg (freebase equivalent weight) orally daily for 12 weeks of lead-in, then patients with responses continued cabozantinib, while those with stable disease were randomized to continue either cabozantinib or switch to placebo. The 60 patients with NSCLC received a median of 3 prior lines of therapy, including 50% who had received erlotinib. The radiographic response rate was 10%, with 50% of patients having some degree of objective tumor regression, and the median PFS was 4.2 months. Patients with some degree of tumor regression included, but were not limited to, patients with tumors harboring EGFR and KRAS mutations. Interestingly, the best three responses were observed in patients of untested mutation status, and there was no clear association between histology (adenocarcinoma *vs.* squamous cell carcinoma) and response. Toxicities included fatigue, diarrhea, anorexia, nausea/vomiting, dysphonia, hypertension, and hand-foot syndrome, with one grade 5 hemorrhage reported in the lead-in stage. The disease stabilization interval among the crossover patients has not yet been reported. An interesting retrospective analysis would be to determine whether any of the best responding tumors harbored RET translocations, which have recently been reported in 1% of NSCLC (43-45).

Cabozantinib combination therapy

In NSCLC, the XL184-202 phase Ib/II study was conducted with the combination of cabozantinib with erlotinib in patients who had developed acquired resistance to erlotinib. In the phase I portion, 64 participants received escalating doses of the combination of erlotinib and cabozantinib (46). Dose limiting toxicities included diarrhea, mucositis, hand-foot syndrome, hypertension, fatigue, hypokalemia, and elevated lipase. Overall, grade 3 or higher events included 43% of patients with diarrhea, 20% with fatigue, 13% with dyspnea, and one grade 5 pulmonary hemorrhage. The MTDs of erlotinib and cabozantinib were 50 mg erlotinib with 125 mg cabozantinib (98 mg freebase equivalent), and 150 mg erlotinib with 50 mg cabozantinib (40 mg freebase equivalent). The response rate was 15%, with a confirmed partial response rate of 8%. Approximately one-third of patients had stable disease for >4 months, lasting

up to 15 months. Molecular analysis of tumors revealed no clear association between known EGFR mutations, secondary T790M mutations, and response; but one patient with an EGFR mutation and *MET* copy number gain by FISH testing did have a partial response. In the phase II expansion, patients were enrolled who failed erlotinib treatment after previous clinical benefit, with the goal of overcoming MET-dependent acquired resistance by the addition of cabozantinib. Patients were randomized to either cabozantinib or cabozantinib plus erlotinib, and the final report of this trial is awaited.

Ongoing studies with cabozantinib in lung cancer include monotherapy with 60 mg (freebase equivalent) in patients with RET translocations [NCT01639508], as well as a three arm randomized study in EGFR wild-type patients to erlotinib (150 mg) versus cabozantinib (60 mg freebase equivalent) versus the combination (150 mg erlotinib and 40 mg cabozantinib) [NCT01708954].

MetMab (Onartuzumab; Roche, Pleasanton, CA)

Onartuzumab mechanism of action and monotherapy

Onartuzumab is a monovalent one armed 5D5 (OA-5D5) monoclonal antibody (mAb) against MET that blocks binding of HGF as demonstrated in glioblastoma and orthotopic pancreatic tumor models (47,48). Onartuzumab has been studied alone and in combination with bevacizumab in a phase I trial and was well tolerated with adverse events of fatigue, peripheral edema, and hypoalbuminemia (49). Pharmacokinetic studies demonstrated linear pharmacokinetics of onartuzumab from 4 mg/kg to 30 mg/kg (mean clearance values 6.8-9.9 mL/day/kg), an elimination half-life of 8-12 days, and the recommended phase II dose of 15 mg/kg intravenous (iv) every 3 weeks (50,51).

Onartuzumab combination therapy

In a phase II double blind randomized trial (OAM4558g), onartuzumab (15 mg/kg iv every 3 weeks) was studied in combination with erlotinib 150 mg oral daily (OE) versus placebo plus erlotinib (PE) in the second or third line treatment of NSCLC patients who had no previous exposure to an EGFR-TKI (52,53). Tissue was required for all patients enrolled, of which 95% were evaluable for MET IHC and 75% for *MET* FISH testing. Patients were divided into subgroups based on IHC MET expression, and the immunohistochemical "H-score" of $\geq 50\%$ of

tumor cells staining 2+ or 3+ intensity was defined as MET positive (MET+). Primary endpoints included PFS in both the MET+ population and ITT population. Secondary endpoints included OS and adverse events. In the setting of erlotinib, the majority of patients reached the goal steady state trough concentration of onartuzumab (mean value 73 µg/mL) and there were no drug interactions (51).

There were 128 patients studied, including 65 MET+ patients who had a worse overall survival compared to MET negative (MET-) patients on the placebo plus erlotinib arm (HR 2.52) (53). At a median follow up of 9.9 months, the MET+ group, specifically MET+ by FISH or MET+ by IHC (even if negative by FISH), and irrespective of EGFR status, had an improvement in both PFS and OS when given the combination of onartuzumab plus erlotinib. In the MET+ IHC group, onartuzumab improved time to progression by 2-fold [3 months (OE) versus 1.5 months (PE); HR 0.47, 95% CI, 0.26-0.85, P=0.01] and OS by 3-fold [12.6 months (OE) versus 4.6 months (PE); HR 0.37, 95% CI, 0.2- 0.71, P=0.002]. In a surrogate biomarker analysis that did not specify what chemotherapy was received, there were 12% (13/112 evaluable specimens) EGFR mutations, and these were present in 6 of 7 patients with objective responses (54). MET GCN median copies per cell was 3.44 (range, 1.6-25.0) in 96 evaluable specimens with only 8% gene amplification. KRAS mutations (n=26 specimens) did not affect OS in the onartuzumab arm. The adverse event of peripheral edema was higher in patients who received onartuzumab but otherwise toxicities were well balanced between the two arms (52). MET+ by IHC had the highest sensitivity in detecting clinical improvement with onartuzumab, and establish that diagnostics need to evolve concurrently to identify the appropriate population for targeted therapies. For example, when MET-FISH positivity is defined as ≥5 copies per cell, there was trend to an improved OS (HR 0.47, P=0.19) but not at lower copy numbers (53); and when reverse transcriptase-PCR was used, the OS benefit in MET+ patients was not present at all (HR 0.69, P=0.48) (54).

A phase III double blind randomized study, MetLUNG, is studying the combination of onartuzumab and erlotinib in MET+ (IHC) NSCLC patients who failed one to two chemotherapies (including one platinum based) (55). Patients (N=480) were randomized 1:1 to erlotinib at 150 mg orally daily with either placebo or onartuzumab 15 mg/kg iv every 3 weeks. Although all patients were positive for MET by IHC, they were stratified by degree of MET expression (2+ versus 3+) and also by prior lines of therapy, histology

(nonsquamous versus squamous), and presence or absence of EGFR mutations. This trial is ongoing with the primary endpoint of OS and secondary endpoints of PFS, response rate, safety, and PK data [NCT01456325]. Additionally there are ongoing trials of onartuzumab in combination with first line chemotherapy, including bevacizumab and platinum based chemotherapy, in patients with squamous and non-squamous NSCLC [NCT01456325, NCT00854308, NCT01519804, NCT01496742]. These trials will enroll patients regardless of MET IHC with an early safety analysis focused on those with low MET IHC scores.

Crizotinib (PF-02341066; Pfizer, New York, NY)

Crizotinib mechanism of action

Crizotinib was initially characterized as a TKI of MET before it was approved for the treatment of anaplastic lymphoma kinase (ALK) positive NSCLC (56-59). Crizotinib has most activity in MET amplified tumor lines compared to other MET alterations (60). Crizotinib acts synergistically with erlotinib in MET driven NSCLC patient derived xenografts without an ALK mutation to produce complete responses (61).

Crizotinib monotherapy

In a phase I trial, oral crizotinib 250 mg twice daily was given to ALK-positive stage III or IV NSCLC (58,59), of which majority were previously treated nonsmokers with adenocarcinoma histology (97%). Clinical activity was noted with significant durable responses: 60.8% overall response rate (ORR) (95% CI, 52.3-68.9) with 3 complete responses (CR) and 84 partial responses (PR); median duration of response (DOR) of 49.1 weeks (95% CI, 39.3-75.4 weeks); and median PFS of 9.7 months (95% CI, 7.7-12.8 months). Crizotinib was well tolerated with the most common adverse events of GI and visual disturbance (>40%), and peripheral edema (30%). Grade 3-4 events included neutropenia/lymphopenia (n=15) and elevated ALT (n=6). Tumors available from 33 patients were tested and were negative for MET amplification, suggesting that MET was not responsible for the crizotinib treatment responses (58). However, the MET alteration of MET gene amplification is relatively uncommon. In a phase II trial (PROFILE 1005), crizotinib was evaluated in at least the second line setting for advanced ALK positive NSCLC (62) with similar demographics and results to the phase I study [ORR of 53%,

median DOR 43 weeks (95% CI, 36-50 weeks), median PFS of 8.5 months (95% CI, 6.2-9.9 months)]. 29 patients had treatment related SAE including dyspnea and pneumonitis and febrile neutropenia. The phase III study demonstrated superiority of crizotinib to standard chemotherapy of either pemetrexed or docetaxel in previously treated ALK positive advanced lung cancer. Patients (n=374) showed an improvement in median PFS of 7.7 versus 3 months (HR 0.49; 95% CI, 0.37-0.64, $P<0.0001$), and an ORR of 65% versus 20% ($P<0.0001$) (63).

Crizotinib combination therapy

A phase I/II study is ongoing with the combination of crizotinib 150 mg bid or 200 mg bid with erlotinib 100 mg daily in patients with pre-treated NSCLC and no prior MET targeted therapy (64). Twenty-five patients have enrolled and median duration of therapy is similar at the lower combination dose (6.6 weeks, n=18) and the higher combination dose (6.9 weeks, n=7). Five patients had DLT's (all resolved) at both dose combinations with predominance of GI events: grade 2 vomiting, grade 2 esophagitis and dysphagia, grade 3 diarrhea and dehydration, grade 3 esophagitis, and grade 3 dry eye. The most common treatment related AE's included grade 1-2 diarrhea (72%), rash (56%), and fatigue (44%); and 6 patients had to discontinue therapy. There was one partial response at the higher dose of crizotinib of 61 weeks duration and 9 with stable disease (duration 7-54 weeks). Pharmacokinetics demonstrated a drug interaction with increase in erlotinib AUC by 1.8 fold. The MTD was reached of erlotinib 100 mg daily and crizotinib 150 mg bid [NCT00965731]. As seen in *Tables 1* and *2*, there are a variety of crizotinib combination trials that are recruiting with pan-Her inhibitor PF-0299804 [NCT01441128], ganetespib (STA 9090) [NCT01579994], and pazopanib [NCT01548144].

MET inhibitors in clinical development

Amuvatinib (MP470; Astex, Pleasanton, CA)

Amuvatinib (MP470) was developed for activity against imatinib resistant gastrointestinal stromal tumors (GIST), in which cKIT is downregulated, and tyrosine kinase receptors, AXL and MET are upregulated (65). Amuvatinib is a multi-targeted inhibitor of MET, AXL, and platelet derived growth factor receptor alpha (PDGFR α). It also acts as a radiosensitizer via inhibition of homologous recombination protein RAD51 (66,67), a known poor

prognostic marker in NSCLC with decreased median survival time of 19 versus 68 months (68). Amuvatinib plus erlotinib have shown synergy with enhanced downstream AKT inhibition and tumor suppression in prostate cancer xenograft mice (69).

In early phase I cancer studies, amuvatinib dry powder capsules (DPC) did show activity but low systemic exposure, and a new lipid suspension formulation (LSC) was tested (70). In three phase I studies (n=58 healthy subjects), the new LSC suspension, multiple dosing regimens, and high fat meals increased drug exposure. A phase Ib study of a standard 3+3 design, enrolled cancer patients to receive amuvatinib (DPC) uninterrupted in combination with five standard of care chemotherapy regimens (21 day cycles) (71,72). Amuvatinib doses were escalated from 100 mg oral daily to 400 mg oral twice daily until the MTD of the drug with each regimen was reached. A total of 100 patients (mean age =58) were enrolled, of which 90% were pretreated. The standard of care chemotherapy regimens included: paclitaxel and carboplatin (n=23), carboplatin and etoposide (n=22), topotecan (n=15), docetaxel (n=15), and erlotinib (n=20). There were no drug interactions except with the docetaxel arm and the MTD was not reached. The most common treatment related AEs were expected of each chemotherapy regimen. Clinical activity was noted with 12 partial responses, with majority in the platinum based chemotherapy arms (n=11), and 5 of 11 small cell lung cancer and neuroendocrine tumor patients (72) and 1 NSCLC patient (71). Forty four patients had stable disease, for an overall disease control rate of 56% (95% CI, 46-66). Pharmacodynamic studies confirmed Rad51 inhibition and increased DNA damage on skin biopsies. Amuvatinib may serve a niche in small cell lung cancer, and a study is ongoing in those who have progressed on platinum and etoposide [NCT01357395].

MGCD265 (Methylgene, Montreal, Canada)

MGCD265 is an oral TKI of MET, VEGFR (1-3), Tie and Ron (73). Non-small cell lung cancer xenograft models including one that harbored the TKI resistant EGFR mutation T790M, combined MGCD265 with either docetaxel, paclitaxel, or erlotinib. Each combination elicited greater tumor response than either agent alone, and displayed antiangiogenic properties with docetaxel (74).

In a phase I study, MGCD265 was given orally from 24 mg/m² daily to 235 mg/m² twice daily uninterrupted to patients with advanced solid malignancy until disease

Table 1 Currently recruiting and active MET inhibitor trials, targeting lung cancer patients <i>clinicaltrials.gov</i>				
Phase	MET inhibitors +/- other therapy	Eligibility	Primary outcome	ClinicalTrials.gov
Phase 1B/2 open label [†]	INC280 (po) + gefitinib	NSCLC (EGFR mutated, <i>MET</i> amplified) with acquired resistance to EGFR TKI	Ph1b: DLT Ph2: ORR	NCT01610336
Phase 1 open-label [†]	Crizotinib + Pan-Her Inhibitor (PF-0299804)	Locally advanced or metastatic NSCLC with acquired resistance to erlotinib or gefitinib	Safety	NCT01441128
Phase 1 open label ^{†¶}	Crizotinib + panHER inhibitor (PF-00299804) vs. PF-00299804	Advanced NSCLC with acquired resistance to erlotinib or gefitinib	AE, DLT	NCT01121575
Phase 1/2 open-label randomized [‡]	Crizotinib + Erlotinib vs. Placebo + Erlotinib	Locally advanced or metastatic lung adenoca progressed after 1-2 chemo tx	Ph1: PK Ph2: DOR, ORR, and OS	NCT00965731
Phase 2 open-label [§]	Crizotinib	East Asian ALK+ locally advanced or metastatic NSCLC (non squam), progressed after 1 chemo tx	Obj RR	NCT01500824
Phase 3 open-label randomized [§]	Crizotinib vs. Pem + Cisplatin (or Carboplatin)	Asian ALK+ locally advanced, recurrent or metastatic NSCLC (non squam) untreated	PFS	NCT01639001
Phase 1/2 open-label ^{¶¶}	Crizotinib + ganetespib (STA-9090)	ALK+ locally advanced or metastatic lung adenoca	MTD	NCT01579994
Phase 1/2 open-label randomized ^{¶¶}	Foretinib (EXEL-2880) + erlotinib vs. erlotinib	Locally advanced or metastatic NSCLC with known EGFR status progressed after 1-2 chemo tx	Ph1: RP2D, safety, tolerability, DLT, and PK Ph2: ORR	NCT01068587
Phase 3 double-blind randomized ^{¶¶}	Tivantinib (ARQ 197) + erlotinib vs. placebo + erlotinib	Locally advanced or metastatic non squam NSCLC progressed after 1-2 chemo tx (platinum doublet)	OS	NCT01244191
Phase 3 double blind randomized [‡] (ATTENTION)	Tivantinib + erlotinib vs. placebo + erlotinib	Locally advanced or metastatic non squam NSCLC with wild type EGFR progressed after 1-2 chemo tx (platinum doublet)	OS	NCT01377376
Phase 2 open-label [†]	Erlotinib + Tivantinib separate doses for CYP2C19 EM or CYP2C19 PM	Locally advanced or metastatic NSCLC with EGFR mutation progressed after first EGFR TKI monotox	Obj RR	NCT01580735
Phase 1	Tivantinib + erlotinib	Advanced/recurrent NSCLC with ≥ 1 prior chemo tx (EGFR TKI considered one tx) for CYP2C19 PM	DLT	NCT01251796
Phase 2 open-label randomized [†]	Tivantinib + erlotinib vs. single agent chemo tx (Pemetrexed, or Docetaxel, or Gemcitabine)	KRAS+ locally advanced or metastatic NSCLC and at least one prior chemo tx	PFS	NCT01395758

Table 1 (continued)

Table 1 (continued)

Phase	MET inhibitors +/- other therapy	Eligibility	Primary outcome	ClinicalTrials.gov
Phase 1b/2 open-label randomized [†]	Ph1: Cabozantinib + Erlotinib Ph2: Cabozantinib + Erlotinib vs. Erlotinib	Ph1: Stage IIIB/IV NSCLC Ph2: Stage IIIB/IV NSCLC with progressive disease and acquired resistance to erlotinib monothx	Ph1: safety, tolerability, MTD, PD, PK Ph2: Obj RR, PD	NCT00596648
Phase 2 open-label randomized ^{§¶}	Erlotinib; or Cabozantinib; or Erlotinib+ Cabozantinib	EGFR wild type stage IV non squam NSCLC progressed after 1-2 chemo tx (platinum based) + erlotinib naive	PFS	NCT01708954
Phase 2 open-label [†]	Cabozantinib	Unresectable or metastatic NSCLC with KIF5B/RET+ or related variant RET fusions	ORR	NCT01639508
Phase 2 open-label [†]	Amuvatinib	SCLC with disease progression on platinum-etoposide (PE) chemo or relapse w/i 90 days after PE	Obj RR	NCT01357395
Phase 3 double-blind randomized [†] (MetLung)	MetMab (Onartuzumab) + Erlotinib vs. Placebo + Erlotinib	MET+ (IHC) stage IIIB/IV NSCLC; available EGFR testing; 1-2 prior chemo tx (platinum based)	OS	NCT01456325
Phase 2 double-blind randomized ^{†¶}	MetMab +erlotinib vs. MetMab + placebo	Stage IIIB/IV NSCLC with progression after at least one chemo tx	PFS and PFS in MET+	NCT00854308
Phase 2 double-blind randomized ^{†¶}	MetMab/paclitaxel/ platinum (PP) vs. Placebo/ PP	Stage IIIB/IV squam NSCLC untreated; Met IHC assay and EGFR tested	PFS and PFS in MET+	NCT01519804
Phase 2 double-blind randomized [†]	MetMab + Bev vs. Bev+ placebo; and MetMab+pem/carbo (PC) vs. PC + placebo	Stage IIIB/IV non squam NSCLC untreated	PFS and PFS in MET+	NCT01496742

[†]trials recruiting. *Table 1* abbreviations in order of appearance: po = oral; NSCLC = non-small cell lung cancer; EGFR = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor; Ph = phase; DLT = dose limiting toxicity; ORR = overall response rate; AE = adverse event; adenoca = adenocarcinoma; chemo = chemotherapy; tx = regimen; PK = pharmacokinetics; DOR = duration of response; OS = overall survival; ALK = anaplastic lymphoma kinase; non squam = non squamous; obj RR = objective response rate; pem = pemetrexed; PFS = progression free survival; MTD = maximum tolerated dose; RP2D = recommended phase 2 dose; EM= extensive metabolizer; PM= poor metabolizer; monothx= monotherapy; PD = pharmacodynamics; SCLC = small cell lung cancer; w/i = within; MET+ = MET positive; IHC = immunohistochemistry; squam = squamous; bev = bevacizumab; carbo = carboplatin

progression (75,76). As of January 2012, a total of 56 patients (median age =61 years) were enrolled (76). Six patients had stable disease for ≥ 6 cycles (range, 6-12 cycles). Dose limiting toxicities occurred at daily doses ≥ 250 mg/m² and included grade 2 hypertension and grade 3 elevated lipase, fatigue, and pituitary hemorrhage. Pharmacokinetics were linear and the half-life was long (26 + hours) (77), and twice daily compared to daily dosing increased exposure along with MET and VEGFR inhibition (76). Other

variables including intermittent dosing schedules and a capsule formulation have been tried and demonstrate efficacy and are well tolerated (77-79).

MGCD265 has been studied in a variety of advanced solid tumors including NSCLC, as a monotherapy (75-79) and in combination with either docetaxel (80,81) or erlotinib (73,82). In a phase I standard 3+3 dose escalation, MGCD265 (96 mg/m² once daily up to 162 mg/m² bid) was combined with erlotinib at 100 or 150 mg daily to determine safety (73,82),

and 45 patients have been enrolled (73,82). Dose limiting toxicity was present at the lowest dose combination and included diarrhea (n=1), and at the higher dose cohorts, rash and fatigue (n=1) and rhabdomyolysis (n=1). One of three NSCLC patients with an EGFR mutation had a partial response for 8 cycles, and 7 patients had stable disease for ≥ 6 cycles. Pharmacodynamic studies showed a decrease in HGF (MET ligand) plasma levels at day 8 of cycle one.

In a separate phase I dose escalating trial, MGCD265 was combined with docetaxel (50 then 75 mg/m² iv once every 3 weeks) in advanced solid tumors (n=34), including 9 NSCLC patients (80,81). The MTD of the microionized formulation of MGCD265 is 72 mg/m² bid and docetaxel 75 mg/m² every 3 weeks but has not been reached with the new formulation (80). NSCLC contributed to half (n=2) of the partial responses seen that lasted up to 8 cycles (81), and half (n=3) of stable disease seen that lasted ≥ 6 cycles (up to 18 cycles) (80). Four out of the 5 patients with NSCLC with PR or SD had received prior taxane therapy and 3 of their available tumor samples had high levels of MET and phosphorylated-MET expression, suggesting synergy with the combination of taxanes and MGCD265 (80). Pharmacodynamic studies also showed decreased HGF levels at day 8 compared to baseline. The combination was well tolerated with grade 3 toxicities including diarrhea, elevated lipase, neutropenia, and leukopenia (80,81). Based on MGCD265 activity in NSCLC and potential synergistic effect with taxanes, a trial is currently recruiting for MGCD265 with either docetaxel or erlotinib in taxane or erlotinib naive pre-treated advanced NSCLC patients [NCT00975767].

MET inhibitors: SGX523, Foretinib (EXEL-2880, XL 880, GSK1363089), MK2461, and others

SGX523 is a MET TKI that binds to its inactive form (83,84) and has shown activity in *MET* amplified lung cancer cell lines (83). The combination of erlotinib and SGX523 inhibited growth in a NSCLC tumor xenograft by almost 3-fold over each agent alone (85). Unfortunately, a phase I open label dose escalation study of orally administered SGX523 on a twice daily continuous schedule in advanced cancer had to be terminated because of unexpected metabolite induced renal toxicity [(86), NCT00606879].

Foretinib is an oral multitargeted TKI of primarily MET and VEGF-2 along with Kit, FLT3, platelet derived growth factor β , and Tie2 (87). Foretinib has been studied in phase I/II trials in a variety of advanced solid tumors including

mesothelioma (88). Foretinib combined with erlotinib increases sensitivity in *MET* and *EGFR* amplified lung tumor cell lines in the presence of HGF (MET ligand) (89). The first phase I study in advanced solid tumors reached a MTD of 3.6 mg/kg with a recommended dose of 240 mg for 5 days of a 14 day cycle (90) with DLT's including grade 3 transaminases and elevated lipase. The combination of foretinib and erlotinib is being compared to erlotinib in pretreated advanced NSCLC with correlative studies requiring archival tumor and EGFR status [NCT01068587].

MK-2461 is an oral multitargeted TKI of activated MET, fibroblast growth factor receptor (FGFR), and platelet-derived growth factor amongst others (91,92). Despite more potent binding to MET *in vitro*, there was more anti-proliferative activity in FGFR-2 driven cell lines (91). MK-2461 daily or bid has been studied in a phase I dose escalation trial in refractory advanced solid tumors (93). Patients (n=14) received 1-6 cycles that were well tolerated, and no tumor responses were seen. There are no trials of MK-2461 in lung cancer. Other MET inhibitors in development that show activity preclinically in lung cancer, include PHA66572 (94-99), JNJ-38877605 (100), SU11274 (101,102), and K252A (103-104).

Conclusions

MET inhibitors may add to the lung cancer treatment landscape and can enhance cell death and tumor growth when combined with chemotherapy and radiation (106). As reviewed in this paper, combination therapy with MET inhibition is under development to both increase the efficacy of primary therapies and to overcome resistance to targeted agents like erlotinib in lung cancer (14,18,19). With all targeted therapies, including MET inhibitors, resistance eventually develops. Mechanisms include mutation in MET structure and increased expression of TGF alpha/EGFR, both resulting in downstream activation of PI3K-AKT and MEK/MAP/ERK kinase pathways (107, 108), along with *KRAS* gene amplification (109). Eventually resistance also develops to combination therapies targeting MET and EGFR pathways, and STAT3 and BCL-2 signaling have been implicated (110).

The three MET inhibitors furthest in development are tivantinib, cabozantinib, and onartuzumab. For example, despite setbacks for tivantinib with the negative phase III lung cancer MARQUEE study, there is still potential for benefit in the *KRAS* mutant population and in other subsets distinguished by specific biomarkers (34). Cabozantinib has also demonstrated efficacy in heavily pretreated NSCLC

Phase 1 open-label first-in-human [†]	EMD1214063-3 dose regimens	Solid tumor refractory to standard tx or no available standard tx	MTD	NCT01014936
Phase 1 open-label [†]	Crizotinib + Rifampin or Ketoconazole	Advanced cancer sensitive to crizotinib inhibition, e.g., ALK, MET, and ROS	Safety and RP2D	NCT00585195
Phase I open-label [†]	Crizotinib	Unresectable or metastatic solid tumors with hepatic impairment and no other standard tx available	PK	NCT01576406
Phase I open-label [†]	Crizotinib+ Pazopanib (P); Crizotinib + Pemetrexed (PM); P + PM; crizotinib + P + PM	Advanced cancer refractory to standard tx or no standard tx available	MTD	NCT01548144
Phase 1 open-label [†]	Tivantinib + Sorafenib	Locally advanced or metastatic solid tumors; expansion cohorts only HCC, RCC, breast cancer, NSCLC and melanoma	MTD , RP2D	NCT00827177
Phase 1 open label first-in-human [†]	AMG 337 (po)	Advanced solid tumor	Safety + tolerability, PK, MTD	NCT01253707
Phase 1 open-label first-in-human [†]	AMG 208 (po)	Advanced solid tumor refractory to standard tx or standard tx unavailable	MTD, response, PK, safety + tolerability	NCT00813384
Phase 1b open-label ^{†¶}	Tivantinib + Pazopanib	Advanced refractory solid tumors; advanced sarcoma, gastric cancer, and <i>MET</i> -expressing cancers in expansion cohort who progressed after 1 chemo tx	Safety + tolerability, MTD, decrease phosphorylated MET	NCT01468922
Phase 1 open-label [†]	Tivantinib + Temsirolimus	Unresectable or metastatic solid malignancy without standard tx available	MTD + RP2D in CYP2C19 EM	NCT01625156
Phase 1 open-label [†]	Cabozantinib	Advanced or metastatic solid tumors with no standard tx available	MTD and RP2D	NCT01553656
Phase 2 open-label [†]	Cabozantinib	Refractory or metastatic solid tumor (not breast or prostate) to bone that is refractory to or progressed after standard tx	Effect on Bone Biomarkers	NCT01588821
Phase 1 open-label [†]	Cabozantinib	Unresectable or metastatic advanced malignancy (solid tumor or lymphoma) with no standard tx available	Safety, tolerability, MTD, DLT, PK	NCT00215605
Phase 2 double blind randomized discontinuation study [†]	Cabozantinib	Advanced, recurrent, or metastatic solid tumor	Efficacy	NCT00940225
Phase 1 open label [†]	MGCD265	Unresectable or metastatic malignancy with no standard tx available	Safety and tolerability	NCT00697632

Table 2 (continued)

Table 2 (continued)

Phase 1 open-label first-in-man [†]	EMD1214063 - 3 dose regimens	Solid tumor refractory to standard tx or no available standard tx	MTD	NCT01014936
Phase 1/2 open-label [†]	MGCD265+ erlotinib; and MGCD265+ docetaxel	Unresectable or metastatic solid malignancy refractory to standard tx (no prior erlotinib or docetaxel)	PPH1: safety, MTD, DLT Ph2: antitumor activity of each tx arm	NCT00975767

[†]trials recruiting; [‡]trials active but not recruiting; [§]trials not yet recruiting; [¶]tissue required; *Table 2* abbreviations in order of appearance: tx = treatment or regimen; MTD = maximum tolerated dose; ALK = anaplastic lymphoma kinase; RP2D = recommended phase 2 dose; PK = pharmacokinetics; HCC = hepatocellular carcinoma; RCC = renal cell carcinoma; NSCLC = non-small cell lung cancer; po = oral; chemo = chemotherapy; EM = extensive metabolizers; ORR = overall response rate; DLT = dose limiting toxicity; Ph = phase

patients (including those with squamous histology) and also in combination with erlotinib in patients who had previously received an EGFR TKI (42,46). Onartuzumab has a unique MET inhibition mechanism as a monovalent one armed 5D5 monoclonal antibody and has shown significant improvement in PFS and OS in MET IHC positive tumors when combined with erlotinib (52,53). Other particularly promising MET inhibitors include crizotinib and amuvatinib, of which the latter is being tested in small cell lung cancer where the role of MET is less clear (72) [NCT01357395]. As mentioned in *Tables 1,2*, several trials are ongoing looking at MET inhibitors as monotherapy and in combination therapy in lung cancer. Other inhibitors of the MET axis are being studied, such as the HGF ligand inhibitor AMG102, in combination with platinum based chemotherapy in extensive stage small cell lung cancer [NCT00791154] and in combination with erlotinib in NSCLC [NCT01233687]. Inhibitors of the MET/HGF signaling pathway shows great promise in the treatment of lung cancer in combination with chemotherapy and with EGFR targeted agents such as erlotinib. Their true potential has yet to be reached and will hopefully be realized with better understanding of biomarkers allowing for proper patient selection.

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