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**C-MET inhibitors for advanced non-small cell lung cancer**

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Key words: Met pathway, non-small cell lung cancer, target therapy, c-Met inhibitors, Epidermal growth factor receptor tyrosine kinase inhibitors
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Abstract

Introduction: The role of the c-mesenchymal-epithelial transition factor (c-MET) signaling pathway in tumor progression and invasion has been extensively studied. C-MET inhibitors have shown anti-tumor activity in NSCLC both in preclinical and in clinical trials. However, given the molecular heterogeneity of NSCLC, it is likely that only a specific subset of NSCLC patients will benefit from c-MET inhibitors. Emerging data also suggest that MET inhibitors in combination with EGFR-TKIs (epidermal growth factor receptor tyrosine kinase inhibitors) may have a role in therapy for both EGFR-TKI resistant and EGFR-TKI naïve patients. The challenges ahead are in the identification of the molecular subtypes that benefit most.

Areas covered: This review summarizes the current understanding of c-MET biology in relation to studies evaluating c-MET inhibitors in the treatment of NSCLC.

Expert opinion: MET inhibitors have the potential to benefit subsets of NSCLC patients with specific genetic alterations. Exon-14 skipping mutations appear so far to be the most promising molecular subset that is sensitive to MET inhibitors, whereas overexpression, amplification and point mutations of MET seem more challenging subgroups to target. Combination with other target agents, such as EGFR inhibitors, may represent a promising therapeutic strategy in specific areas (e.g. EGFR-TKI resistance).
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Article Highlights

- Mechanisms of activation of MET that have been detected in NSCLC may be through a variety of alterations, such as protein overexpression, gene amplification and MET exon 14 skip mutation.
- Patients with MET alterations may benefit from MET inhibitors therapy; several MET inhibitors have been evaluated in phase III trials, but to date the results of clinical studies have been negative.
- More recently small molecule inhibitors such as tivantinib, crizotinib and savolitinib exhibited some promising activity, suggesting the need of proper selection of patients.
- Dysregulation of the MET pathway is known to confer primary or secondary resistance against EGFR TKIs. Based on this rationale the combinations of savolitinib with osimertinib or gefitinib showed clinical activity in patients with EGFR mutation-positive NSCLC with MET-amplification who had progressed following prior treatment with an EGFR inhibitor.
- Further studies are warranted to select candidates for MET inhibitors in NSCLC based on robust biomarkers.
Review

1 Introduction

Non-Small cell lung cancer (NSCLC) is the most common cause of cancer-related death worldwide. Most patients who have NSCLC present with advanced or incurable disease, and chemotherapy generally results in modest improvement of survival. Recently immunotherapy has revolutionized the treatment of NSCLC, with several immune check-point inhibitors already on the market; however, the majority of NSCLC patients do not respond to PD-1/PD-L1 inhibition and patients with driver mutations appear to be less sensitive to this approach.

In the last decade, a number of subtypes of NSCLC, mainly adenocarcinomas, have been identified, which are characterized by a single oncogenic event, which drives the tumor growth. Mutations in the epidermal growth factor receptor (EGFR) gene, BRAF V600E mutations, and rearrangements in the anaplastic lymphoma kinase (ALK) and ROS1 genes represent distinct molecular subtypes of adenocarcinomas, which are sensitive to specific targeted therapies. Approximately 25% of Caucasians with adenocarcinoma of the lung have a targetable driver mutation. In Asians, however, EGFR sensitizing mutations alone represent up to 40-50% of patients with adenocarcinoma. An increasing number of molecular subgroups are being discovered, which may increase this percentage in the next few years. Among these are genetic alterations of c-Met, NTRK translocations, and RET translocations.

1.1 Overview of MET Signaling in NSCLC

C-MET gene is located on chromosome 7q21-31, encodes for a protein tyrosine kinase, which belongs to the HGF (hepatocyte growth factor) receptor family, and regulates important cellular processes, such as differentiation, proliferation, cell cycle, motility, and apoptosis. HGF, the sole ligand for c-MET, is a paracrine signaling molecule produced and secreted by mesenchymal cells during development. HGF is produced as an inactive single-chain precursor that is processed to an active heterodimer of one alpha and one beta chain linked by a disulfide bond. C-MET is produced as a single-chain precursor and subsequently processed to a mature receptor composed of an extracellular alpha subunit disulfide bond to a beta subunit (1). The extracellular portion of c-MET is composed of a Sema domain (homologous to semaphorins), a cysteine-rich, Met-related-sequence domain, and four immunoglobulin (Ig)-like modules responsible for binding HGF. The intracellular portion of c-MET is composed of a juxtamembrane domain, a tyrosine kinase domain, and a C-terminal regulatory tail responsible for signal transduction (2). The Tyrosine residues (3) in the tyrosine kinase domain control the kinase activity of c-MET, while the tyrosine residues in the C-terminal regulatory tail are important for recruitment of downstream adapters, including growth factor receptor-bound protein 2 (GRB2) protein and GRB2-associated binding protein 1 (GAB1) (Figure 1). Binding of HGF to the extracellular domains of MET (4) leads to homodimerization, and transphosphorylation of tyrosine kinase residues in the catalytic domain, followed by auto-phosphorylation, which acts as a platform for the adaptor protein binding. The adapter protein GAB1 expands the number of sites for signaling molecules (5,6) and this leads to activation of multiple downstream pathways involved in oncogenesis, such as PI3K, MAPK and STAT3 (7-10). Prolonged or continuous activity of the c-MET receptor with subsequent catalytic activation of signal transduction cascades induces excessive cell proliferation and is related to the development and progression of neoplastic disease.

In NSCLC aberrant activation of the MET pathway may occur through a variety of mechanisms. Over-expression of MET protein is the most frequent (25-75%) (11-16), whereas MET gene amplification is reported in 2-4% previously untreated NSCLC (17) and 5-20% of patients with EGFR-mutated tumors and acquired resistance to EGFR TKIs. (18). Another emerging aberrant activation of MET pathway is through a splice mutant of MET that leads to skipping of exon 14
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(METex14) and induces prolonged signaling and oncogenic capacity (19,20). Mutations leading to exon 14 skipping have been reported in approximately 3-4% of NSCLC cases (21). METex14 alterations are diverse and this diversity may be challenging for diagnostic testing. Only recently these mutations were recognized, thanks to improvement of next generation sequencing (NGS) platforms (22).

Dysregulation of the MET pathway in NSCLC induces cancer invasion and metastasis (23) and interplay with other signaling pathways such as the EGFR pathway (17,18). Amplification of MET has been shown to be responsible for acquired resistance to gefitinib by driving ERBB3 (human epidermal growth factor receptor 3) -dependent activation of PI3K, a pathway utilized by EGFR/ERBB family receptors (18). The frequency of Met amplification was initially reported to be about 20%, however in later studies it was reported to be < 10%. c-MET amplification occurs independent of the EGFR T790M mutation, a second-site point mutation associated with 50-60% of acquired resistance to first and second generation EGFR TKIs. (17). As a result, aberrant cMET is important for selection of the target population because its activation or amplification are known to confer primary or secondary resistance against EGFR TKI. The in vitro study by Engelman et al (18), showed that EGFR-TKI resistant cell lines have MET amplification, and by inhibiting MET expression through shRNA the sensitivity to EGFR-TKIs was restored. These data provide a rationale to develop clinical studies of MET inhibitors alone or in combination with EGFR-TKI in NSCLC (especially TKI-resistant patients), both as primary or secondary strategies to prevent or overcome EGFR-TKI resistance.

2 Targeting MET

Multiple MET inhibitors have been tested in preclinical studies and human trials. C-MET inhibitors can be classified into three groups; small-molecule tyrosine kinase inhibitors of the c-MET receptor (multi-kinase inhibitors and selective MET inhibitors) (table 1); monoclonal antibodies against c-MET and against the HGF ligand (table 2).

Small-molecule tyrosine kinase inhibitors block intracellular signaling pathways in tumor cells, and most of them are ATP binding competitors. Type I inhibitors bind to the active protein kinase conformation (DFG-Asp in), while Type II inhibitors bind to a DFG-Asp out inactive conformation. Type II inhibitors act by inducing a conformational shift in the target enzyme such that the kinase is no longer able to function.

Monoclonal antibodies inhibit the HGF-c-MET axis by blocking the binding of HGF to c-MET or by targeting c-MET on the cell surface.

Here, we review c-MET inhibitors currently under development in non-small cell lung cancer.
2.1 Multi-kinase MET Inhibitors

2.1.1 Crizotinib (PF-02341066)

Crizotinib is a multi-targeted TKI, initially developed as a small molecule MET inhibitor. It is FDA approved for patients with advanced NSCLC with ALK or ROS1 fusions. In preclinical tumor xenograft studies, crizotinib inhibited the HGF-stimulated growth and survival of cell lines, decreasing c-MET phosphorylation. In MET amplified lung cancer cell lines crizotinib induces apoptosis and inhibition of AKT and extracellular signal-regulated kinase phosphorylation. Crizotinib demonstrated superiority over conventional chemotherapy in metastatic ALK-positive NSCLC in first-line (24) and second-line (25) in two randomized phase III trials (PROFILE 1014 and PROFILE 1007), achieving higher response rates (RR) and a significantly longer progression-free survival (PFS). The most common adverse reactions (ARs) reported in the crizotinib arms were vision disorders, elevated transaminases, diarrhea, and nausea. The most frequent serious adverse events (AEs) were dyspnea (4.1%) and pulmonary embolism (2.9%). Fatal AEs occurred in 2.3% of patients, due to septic shock, acute respiratory failure, and diabetic ketoacidosis; however the majority of ARs in the crizotinib arm were grade 1 and 2. Crizotinib has also been approved as a first-line treatment for advanced NSCLC patients with ROS1 fusions, based on a single arm phase II trial (26).

Recently a study showed activity of crizotinib in patients with NSCLC harboring activating mutations that cause MET exon 14 skipping with 8 responses out of 18 patients treated (44% [95% confidence interval: 22%-69%]) (27).

A multicenter retrospective analysis suggested that treatment of MET exon 14 mutant NSCLC with a MET inhibitor, including crizotinib, is associated with an improvement in overall survival. Of the 34 patients with MET exon 14 mutant NSCLC who never received a MET inhibitor, the median overall survival (mOS) was 8.1 months whereas the mOS was 24.6 months in 27 patients who received at least one MET inhibitor (including crizotinib, glesatinib, capmatinib, and ABBV-399). A model adjusting for administration of a MET inhibitor as first- or second-line therapy as a time-dependent covariate demonstrated that treatment with a MET inhibitor was associated with a significant prolongation of survival (HR 0.11, 95% CI 0.01-0.92, P = 0.04). Among 22 patients treated with crizotinib, the median PFS was 7.36 months (28).

In another study efficacy and safety data were presented in 13 patients with advanced c-MET-amplified NSCLC, classified as low, (FISH ratio ≥1.8-≤2.2), intermediate (>2.2-<5) and high (≥5) level amplification. MET amplification status was determined by FISH. Four partial responses (PRs) (33% 95% CI: 10%-65%) were observed: 1 in the intermediate level and 3 in the high level amplification groups. Median duration of response was 35 weeks [95% CI: 16-112] and median treatment duration was 15.7 weeks, with a tolerable safety profile (29). Furthermore crizotinib was evaluated in combination with other targeted therapies, including erlotinib (30), and dacomitinib, first and second generation EGFR inhibitors, respectively (31). Unfortunately these combinations were associated with substantial toxicity (grade 3 or 4 treatment-related adverse events in 43% of patients) but only minimal activity. Based on these results no further studies have been planned.
2.1.2 Cabozantinib (XL184, BMS-907351)

Cabozantinib is an oral TKI with significant activity against c-MET, VEGFR2, KIT, TIE3, FLT3, and RET. Cabozantinib was tested in a phase II randomized discontinuation study in multiple solid tumor types, including NSCLC and it showed an ORR (overall response rate) ≥10% in the NSCLC cohort and a reduction in the sum of target lesion size in 301 of 526 (57.2%) patients across all tumor types (32).

Recently a randomized, phase II trial enrolled 42 patients to erlotinib, 40 patients to cabozantinib, and 43 patients to erlotinib plus cabozantinib; 111 patients (89%) were included in the primary analysis. The PFS of erlotinib alone arm (median 1.8 months [95% CI 1.7-2.2]) was significantly improved in the cabozantinib arm (4.3 months [3.6-7.4]; hazard ratio [HR] 0.39, 80% CI 0.27-0.55; one-sided p=0.0003) and in the erlotinib plus cabozantinib arm (4.7 months [2.4-7.4]; HR 0.37, 0.25-0.53; one-sided p=0.0003).

The most common grade 3 or 4 adverse events were diarrhea (8%, 8%, 28%, respectively), hypertension (0%, 25%, 3%), fatigue (13%, 15%, 15%), oral mucositis (0%, 10%, 3%), and thromboembolic events (0%, 8%, 5%). One death due to respiratory failure occurred in the cabozantinib group, deemed possibly related to either drug, and one death due to pneumonitis occurred in the erlotinib plus cabozantinib arm. The authors concluded that in patients with wild-type EGFR NSCLC, cabozantinib alone or combined with erlotinib has clinically meaningful, superior efficacy to that of erlotinib alone, with additional toxicity that was generally manageable (33).

Cabozantinib is also under evaluation as single agent in previously untreated NSCLC patients positive for RET, ROS1 or NTRK fusions. Cabozantinib had a 28% ORR in 26 patients with RET-rearranged lung adenocarcinomas (34).

The combination of cabozantinib and erlotinib is being investigated in previously treated wild-type EGFR NSCLC patients with increased MET activity (overexpression, amplification, or mutation) (NCT01639508). Cabozantinib alone is being investigated in a phase II clinical trial in both unselected and c-MET amplified (determined by FISH ratio > 2.0) NSCLC patients with brain metastases (NCT02132598).

2.1.3 Foretinib (GSK1363089)

Foretinib is a multi-targeted kinase inhibitor, targeting MET, RON, AXL, TIE-2, VEGF receptors and ROS-1. Two phase I trials have been published: the first investigated foretinib administered for 5 consecutive days every 14 days; in the second study foretinib was administered once daily for 28 days. Both trials were conducted in patients with metastatic solid tumors. Dose-limiting toxicity (DLTs) in the first study included grade 3 elevations in aspartate aminotransferase and lipase, whereas in the second trial hypertension, dehydration and diarrhea were described. Additional AEs in both studies included hypertension, fatigue, diarrhea, vomiting, proteinuria, and hematuria. No responses were observed (35, 36). Recently a phase I study of foretinib plus erlotinib was performed in patients with previously treated advanced NSCLC demonstrated responses in unselected patients, but also increased toxicity (37). No pharmacokinetic interaction was seen and the recommended phase II dose (RP2D) was defined as erlotinib 150 mg daily x 14 days with foretinib 30 mg added on day 15 (continuous dosing in 28-day cycles). Responses were seen in 17.8% of response evaluable patients (5/28). In 18 samples, baseline MET expression detected by immunohistochemistry, uncontrolled for EGFR genotype, appeared associated with response.
2.1.4 Glesatinib (MGCD265)

Glesatinib is a small molecule tyrosine kinase inhibitor of MET and Axl, which demonstrated anti-tumor efficacy in xenograft models of MET exon 14 skipping mutants and MET amplification (38). Glesatinib is a type II kinase inhibitor that binds to the inactive MET conformation enabling inhibition of MET activation loop mutations recently implicated in resistance to Type I MET inhibitors.

In a Phase I study 12 patients with advanced solid tumors received glesatinib 600mg, 1200mg or 1050 mg BID. 1050 mg BID was defined as the MTD with no DLTs in 3 patients (39). Recently a global, open-label, parallel arm, phase II trial evaluating the tumor response to glesatinib in patients with metastatic platinum pretreated NSCLC exhibiting an activating genetic alteration of MET (exon 14 skipping, MET amplification) has been closed to accrual (40) (NCT02544633) and the results are pending. Patients were assigned to one of four cohorts based on the type of MET dysregulation and detection method: mutations in tissue, amplification in tissue, mutations in circulating DNA (ctDNA), and amplification in ctDNA. A phase II trial of glesatinib in combination with Nivolumab in NSCLC patients is ongoing (NCT02954991).

2.1.5 S49076

S49076 is a potent inhibitor of MET, AXL/MER and FGFR. It has also shown activity against Aurora B. S49076 blocked MET-driven migration in lung carcinoma cell lines. In a phase I study patients with advanced solid tumors received S49076 orally once-daily or twice-daily in continuous 21-day cycles at escalating doses, followed by an expansion phase at the RP2D. A total of 103 patients were treated and the RP2D was defined at 600 mg once daily in continuous dosing. Overall, 83 patients (81.4%) had drug-related adverse events, the majority (93%) of which were grade 1–2. The clinical benefit rate was 23%, and 9 patients had long-term stable disease (≥ 6 months) (41). S49076 is being evaluated in a single-arm phase I/II study in combination with gefitinib in EGFR mutated NSCLC patients who progressed on EGFR TKIs (42). S49076 is also being investigated in combination with radiotherapy, based on demonstration of improvement in the antitumor efficacy of radiation treatment in vitro and in orthotopic tumor models in vivo (43).

2.2 Selective MET Inhibitors

2.2.1 Capmatinib (INCB28060)

Capmatinib is a highly selective, oral MET inhibitor. In a phase I study the RP2D was established at 400 mg BID (44). Eligible patients had documented c-MET positive (H-score ≥ 150 or c-MET/centromere ratio ≥ 2.0 or gene copy number [GCN] ≥ 5 or IHC 2+ or 3+) NSCLC. The study also evaluated an additional NSCLC group with EGFR wild type and centrally assessed c-MET IHC 3+. Forty-three patients were enrolled in the NSCLC expansion groups. The most common AEs were nausea (47%), vomiting (37%), peripheral edema (35%), decreased appetite (33%), and fatigue (33%). The most common grade 3/4 AEs were anemia, hypokalemia, and pneumonia (all 7%). In the group of c-MET positive NSCLC patients, 5/26 patients had partial responses (19%); 2 patients in the initial group had c-MET exon 14 mutations and both experienced a PR. In patients with cMET IHC 3+, 5/17 had PR (29%). In patients with cMET GCN ≥ 5, 5/8 had PR (63%).

A combination of capmatinib and gefitinib was tested in a phase II study in patients with EGFR mutations after disease progression on gefitinib. An ORR of 18%, and a disease control rate (DCR) of 80% were observed in 65 evaluable patients. More responses were seen in tumors with MET amplification (45). Similar results were reported with the combination of capmatinib and
erlotinib, in a study of 18 patients with MET overexpressing tumors, EGFR mutated tumors and following a prior EGFR TKi treatment. Common drug-related adverse events of any grade were diarrhea and rash (47% each), fatigue (40%), increased AST and ALT (27% each), nausea, anorexia and paronychia (27% each). Drug-related grade 3/4 AEs were anorexia, increased amylase or lipase and neutropenia (all 7%). Of the 12 evaluable patients, 6 had stable disease (3 EGFR mutated) and 2 with EGFR mutated tumors had a minor response (10-29% decrease in target lesion size). Seven patients received treatment for ≥ 3 months (5 EGFR mutated). (46).

2.2.2 Tivantinib (ARQ197)

Tivantinib is a non-ATP-competitive c-MET inhibitor. A phase II, double-blind, randomized open-label study evaluated the combination of erlotinib (150 mg daily) and tivantinib (360 mg BID daily) every 4 weeks in comparison with erlotinib 150 mg daily and placebo, in previously treated locally advanced or metastatic NSCLC patients. One hundred and sixty-seven patients were enrolled: 10% in the combination arm versus 18% in the standard arm presented an EGFR mutation, and 26% versus 26.5% had 4 or more MET gene copy number, respectively. The ORR was 10% for erlotinib plus tivantinib versus 7% for the control arm. Median PFS was 3.8 months for the tivantinib plus erlotinib arm versus 2.3 months for the erlotinib plus placebo arm (HR=0.81, P=0.24). Median OS was 8.5 for the investigational arm versus 6.9 months for the control arm (HR=0.87, P=0.47). Pre-planned exploratory survival analysis in non-squamous histology showed a trend of benefit from the combination arm in both PFS (HR=0.71) and OS (HR=0.72). A subgroup analysis showed an advantage in terms of PFS for EGFR wild type (HR=0.70), KRAS mutated patients (HR=0.76) and for Met FISH positive patients (HR=0.45). Treatment was well tolerated both in the investigational and in the control arms: low grade rash (9.5%, 7.2%, respectively) and diarrhea (7.1%, 7.2%), fatigue (4.8%, 6%), nausea (1.2%, 4.8%), vomiting (3.6%, 1.2%), dyspnea (7.1%, 13.3%), anemia (6%, 7.2%) were the most common toxicities (47).

In the MARQUEE phase III study, patients with NSCLC previously treated with one or two systemic regimens, including a platinum doublet, were assigned to receive erlotinib 150 mg daily plus oral tivantinib 360 mg twice daily or erlotinib plus placebo until disease progression. Tumor specimens were evaluated for EGFR and KRAS mutations, MET expression, and MET gene amplification. The study enrolled 1,048 patients and was discontinued for futility at the interim analysis. OS did not improve with the combination (median OS, 8.5 v 7.8 months, respectively for erlotinib plus tivantinib or erlotinib plus placebo; hazard ratio [HR], 0.98; 95% CI, 0.84-1.15; P = .81), even though the PFS was increased (median PFS, 3.6 v 1.9 months, respectively; HR, 0.74; 95% CI, 0.62 to 0.89; P < .001).Exploratory subgroup analyses suggested OS improvement in patients with high MET expression (HR 0.70; 95% CI, 0.49 to 1.01). Most common adverse events occurring in the two arms respectively were rash (33.1%, 37.3%), diarrhea (34.6%, 41.0%), asthenia or fatigue (43.5%, 38.1%), and neutropenia grade 3-4 (8.5%, 0.8%). These findings were confirmed by a phase III study conducted in Asian, wild type EGFR patients after failure of a prior chemotherapy. A median OS of 12.7 and 11.1 months, respectively [hazard ratio (HR)=0.891, P=0.427]. Median PFS was 2.9 and 2.0 months, respectively (HR=0.719, P=0.019). Commonly observed grade ≥3 adverse events in the tivantinib arm were neutropenia (24.3%), leukopenia (18.4%), febrile neutropenia (13.8%), and anemia (13.2%)(49).
2.2.3 Teponitinib (EMD 1214063)

Teponitinib is a highly selective c-MET TKI, showing activity in c-MET-overexpressing liver cancer models (50). Currently tepotinib is being evaluated in a phase II study in NSCLC patients with MET exon 14 skipping mutations (NCT02864992). The trial is randomizing 156 patients with c-MET positive/T790M negative tumors who have failed first-line EGFR TKI to tepotinib in combination with gefitinib or pemetrexed in combination with cisplatin or carboplatin. The final data from a phase Ib trial of tepotinib in combination with gefitinib in patients with c-MET positive/EGFR-mutant NSCLC conducted in Asia showed 4 confirmed partial response out of 8 evaluable patients with an acceptable safety profile. In the study 18 patients received tepotinib 300 or 500 mg QD combined with gefitinib 250 mg QD (T300G250 or T500G250). The primary objective was to determine the recommended phase II dose (RP2D) of tepotinib in combination with gefitinib; secondary objectives included safety and antitumor activity. Tepotinib 500 mg QD was confirmed as the RP2D. The best overall response was partial response in 6 patients; 4/7 patients with IHC 3+ tumors responded (all treated with T300G250) vs 2/11 with IHC 2+ tumors. Response duration was 4.2–12.5 months. Four of 18 patients (IHC 2+, n = 3) had stable disease. 8 patients experienced progression free survival > 5 months, and 3 patients > 10 months. Recently a preclinical study has provided new evidence that tepotinib in combination with EGFR TKI is effective in NSCLC xenografts harboring c-MET abnormalities that are resistant to EGFR TKI treatment (51). A phase Ib of tepotinib in combination with gefitinib in EGFR mutant NSCLC, with acquired resistance to any first or second generation EGFR TKI in first line, T790M negative c-MET positive, is currently under clinical evaluation (NCT01982955). The preliminary results showed durable responses observed in EGFR mutant / MET IHC 3+/polysomy (ISH+) patients, with 4 PRs out of 6 patients who were MET ISH+. These combinations appear promising and more studies seem warranted.

2.2.4 Savolitinib (AZD6094, HMPL-504, volitinib)

Savolitinib is a selective small molecule MET inhibitor. In preclinical models the combination of savolitinib and gefitinib demonstrated higher efficacy than either compound alone (52). A phase Ib study tested savolitinib plus gefitinib in patients with EGFR mutant, MET amplified NSCLC patients, who had progressed after EGFR-TKI (53). The study had 2 phases: safety run-in phase (n~12) and expansion phase (n~20). MET status was not required for the safety run-in but MET amplification by tumor biopsy confirmation was mandatory in the expansion phase. Thirteen patients completed the DLT assessment with fixed dose of gefitinib 250 mg QD in combination with savolitinib at 600 mg QD (n = 6) and 800 mg QD (n = 7). No DLT were observed in the 600mg QD cohort and one potential DLT of grade 3 febrile neutropenia in the 800 mg QD cohort. Eleven patients were evaluable for response and 12 were evaluable for safety analysis. Most common drug-related AEs across both dose levels were mild nausea (40%), blood bilirubin increased (30%), and vomiting (30%). Two confirmed PRs (MET amplification was negative) were reported. The safety and tolerability of savolitinib as monotherapy in advanced wild type EGFR NSCLC is currently under clinical evaluation (NCT01985555). Savolitinib is also being evaluated in a phase II trial in combination with osimertinib for T790M mutation positive patients who developed resistance to osimertinib (NCT02143466). The preliminary results showed safety and clinical activity of savolitinib in combination with osimertinib: in 66 patients treated, the most common adverse events were nausea (44%), vomiting (35%), fatigue (30%), and decreased appetite (30%). A partial response was seen in 33% of patients previously treated with third-generation TKI, including osimertinib (n=30). In those patients where MET-positive status was determined centrally, preliminary data showed partial response in 28% of patients previously treated with T790M-directed EGFR TKI (n=25).
2.2.5 SAR125844

SAR125844 is a selective MET kinase inhibitor with a favorable preclinical toxicity profile, supporting its clinical development in patients with MET-amplified tumors (54). A phase I study showed a manageable safety profile and encouraging anti-tumor activity in c-MET-amplified Asian patients with advanced solid tumors (55). In this study 38 Asian patients were treated: 19 in the dose-escalation cohort and 19 in the dose-expansion cohort. No DLTs were observed during the dose-escalation phase. The MTD was not reached, and 570 mg/m² intravenously weekly infusion was selected as the RP2D in Asian patients. Of 19 patients treated in the expansion cohort at 570 mg/m², one experienced a DLT (transaminase and creatinine increases that were reversible after dose omission and reduction) during cycle 1. Treatment-emergent adverse events were observed in 36 patients (94.7%) and considered drug related in 22 patients (57.9%). Serious AEs were reported in eight patients (21.1%); none were considered drug related. The most frequent AEs were nausea (36.8%), vomiting (34.2%), decreased appetite (28.9%), and fatigue or asthenia, constipation, and abdominal pain (21.1% each). There were no deaths due to adverse events. Nine patients had at least one dose modification, and one patient had an infusion interrupted because of a grade 2 infusion-related reaction. Two cases of transaminase increase (grade ≥ 3) led to dose modification. A phase II study assessing SAR125844 as monotherapy in patients with NSCLC harboring MET gene amplification (NCT02435121) has been completed; the results are pending.

2.3 Anti-MET and Anti-HGF Antibodies

2.3.1 Anti-Met antibodies

2.3.1.1 Onartuzumab (MetMab)

Onartuzumab is a fully humanized, monovalent monoclonal anti-Met antibody, which binds the sema domain of Met, thereby blocking the binding of the HGF α-chain to c-MET. The efficacy of onartuzumab was demonstrated in several preclinical studies (56). A phase I trial investigated IV MetMab in advanced solid tumors: MetMab was administered every three weeks, both as single agent and in combination with bevacizumab 15 mg/kg every three weeks, until progression. Most frequent MetMab AEs as single-agent were: fatigue (56%), peripheral edema (35%), decreased appetite (32%), constipation (29%), nausea (27%), vomiting (24%) and hypoalbuminemia (24%); there was no consistent relationship between AEs and dose level. Grade 3 AEs were peripheral edema (9%), abdominal pain, AST increase, fever and hyponatremia. No grade 4 toxicity was observed. The combination arm had similar toxicities; no grade 3 or 4 toxicity was observed. MTD was not reached. The best response was stable disease (57).

In a randomized phase II study, unselected NSCLC patients who had received one or two prior systemic regimens (including platinum-based chemotherapy) were assigned to receive onartuzumab plus erlotinib or placebo plus erlotinib (control arm); 26 patients (23%) harbored a KRAS mutation, and 13 (12%) had an EGFR mutation. The study showed no improvement in PFS or OS in the ITT population (n=137; PFS HR 1.09; p=0.69; OS HR 0.80; p=0.34). MET-positive patients (n=66) treated with erlotinib plus onartuzumab, showed improvement in both PFS (HR 0.53; p=0.04) and OS (HR 0.37; p=0.002). Conversely, clinical outcomes were worse in MET-negative patients treated with onartuzumab plus erlotinib (n=62; PFS HR 1.82; p=0.05; OS HR 1.78; p=0.16). MET positive control patients had worse outcomes than MET negative control patients (n = 62; PFS HR, 1.71; p= 0.06; OS HR, 2.61; p=0.004). Incidence of peripheral edema was higher in onartuzumab-treated patients. The authors concluded that onartuzumab plus erlotinib
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was associated with improved PFS and OS in the MET positive population but worse outcomes in MET negative patients (58). Consequently, a larger randomized trial enrolled 499 patients with previously treated MET-positive NSCLC stratified by EGFR mutation status, MET IHC (2+ vs 3+), number of prior treatments (1 vs 2), and histology (squamous vs non-squamous). Patients were randomized (1:1) to receive erlotinib 150mg daily plus placebo or onartuzumab 15mg/kg IV every 21 days. An independent data review recommended termination of the trial for futility, as the addition of onartuzumab to erlotinib did not improve OS (HR 1.27, p=0.068; median OS 6.8 vs 9.1 months), PFS (HR 0.99, p=0.92; median PFS 2.7 vs 2.6 months), or overall response rate (8.4% vs 9.6%; p=0.63). The most frequent adverse events that were higher in the combination arm were peripheral edema, hypoalbuminemia, back pain, dyspnea, nausea, acneiform dermatitis, and rash (59). Based on these results, onartuzumab is no longer in clinical development.

2.3.1.2 Emibetuzumab (LY2875358)

Emibetuzumab is a monoclonal antibody against c-MET that blocks HGF-c-MET binding and leads to internalization and degradation of c-MET. Emibetuzumab blocks both HGF-dependent and independent tumor growth in mouse xenograft models (60). A recent phase I clinical study tested emibetuzumab in patients with solid tumors alone and in combination with erlotinib in NSCLC patients (61). Two of the 14 NSCLC patients receiving combination treatment achieved a PR (14.3%) and four achieved stable disease. The most common emibetuzumab-related adverse events included diarrhea, nausea, and vomiting, but no dose-limiting toxicities and related serious AEs were observed. Phase II trials of emibetuzumab in NSCLC patients with EGFR mutations (NCT01897480) and in combination with the anti-VEGFR2 antibody ramucirumab (NCT02082210) are ongoing.

2.3.1.3 Telisotuzumab (ABBV 399)

Telisotuzumab is a novel, first-in-class, antibody drug conjugate against c-MET, conjugated to monomethyl auristatin E (MMAE). In a preclinical study, ABBV-399 inhibited growth in xenografts including patient-derived xenograft (PDX) models and those refractory to other c-Met inhibitors. A threshold level of c-Met expression was required for significant ABBV-399-mediated killing. In this study activity extended also to amplified MET cell lines where significant tumor growth inhibition and regressions are observed (62).

In a dose-escalation design, ABBV-399 was administered at doses ranging from 0.15 to 3.3 mg/kg every 21 days to patients with advanced metastatic solid tumors (NCT02099058). ABBV-399 was then studied in a dose-expansion cohort in 16 patients with advanced c-MET positive (immunohistochemistry H-score ≥150) NSCLC that had progressed on 2 prior lines of therapy. ABBV-399 was also studied in combination with erlotinib in 10 patients with NSCLC, 8 of whom were c-MET positive. Forty-eight patients with solid tumors received at least one dose of ABBV-399. The DLT was febrile neutropenia, which occurred in 2 patients. There were no treatment-related deaths. Single agent treatment-related adverse events occurring in at least 10% of patients (including all dose levels and all grades) were fatigue, nausea, neuropathy, decreased appetite and vomiting. Based on safety and tolerability, a 2.7 mg/kg dose was chosen for dose expansion in patients with c-MET positive advanced NSCLC. Three of 16 ABBV-399 treated c-MET positive NSCLC patients had a confirmed PR and 6 had disease control. Ten patients received ABBV-399 in combination with erlotinib: 3 of 8 evaluable patients had a confirmed PR. Two of the 3 patients with PR had an EGFR-mutated tumor. The authors concluded that ABBV-399 is well tolerated at a dose of 2.7 mg/kg every 21 days and has antitumor activity in patients with c-MET positive NSCLC both as monotherapy and in combination with erlotinib (63). An ongoing clinical study is evaluating the combination of ABBV-399 with nivolumab in subjects with advanced c-MET overexpressing NSCLC who failed one prior line of chemotherapy.
Review

2.3.1.4 ARGX-111

ARGX-111, an anti c-MET antibody, inhibits ligand-dependent c-MET activation, showing cytotoxic activity in c-MET-expressing human cancer cells. In an orthotopic mouse model of metastatic breast carcinoma, ARGX-111 decreased the number of circulating tumor cells and suppressed metastasis (64). A phase I trial in patients with advanced cancers overexpressing c-MET has recently been completed. The study had a dose escalation part (3 mg/kg q3w) and a safety expansion part (3 mg/kg q2w). The study population included 12.5% of MET amplified NSCLC patients and overall 3% (15/501) of patients were MET gene amplified (MET:CEP7 ≥ 2). The trial showed 42% DCR with 1/24 PR and 9/24 SD, 60% DCR in the safety expansion with a mean duration of treatment of 12 weeks. The most common adverse events included fatigue, constipation, nausea, decreased appetite, myalgia and vomiting. Infusion related reactions of any grade occurred in 79% of patients, but were manageable with premedication (65).

2.3.2 Anti HGF-antibodies

2.3.2.1 Ficlatuzumab (AV-299)

Ficlatuzumab is a humanized monoclonal antibody against HGF that inhibits the HGF-induced c-Met signaling pathway by neutralizing HGF/c-Met binding (66). Preclinical studies in a NSCLC xenograft model showed increased anti-cancer activity of ficlatuzumab in combination with an EGFR inhibitor (erlotinib or cetuximab) compared with single agents (67). A randomized phase II trial evaluated the combination of ficlatuzumab with gefitinib versus gefitinib alone in Asian patients with NSCLC not selected for EGFR mutational status. In a subgroup of patients with EGFR mutations and low c-MET expression, patients treated with ficlatuzumab combined with gefitinib showed improved ORR (41% vs. 22%) and median PFS (11 vs. 5.5 months). However, in the overall population no significant difference was observed in terms of RR or PFS (68).

In another phase II study a total of 188 patients were randomized to receive either gefitinib or ficlatuzumab plus gefitinib treatment. Molecular analyses included tumor EGFR mutation status. The trial showed that the addition of ficlatuzumab to gefitinib did not provide significant improvement over gefitinib monotherapy for the primary end-point of ORR or the secondary end-points of PFS and OS. For all patients, the most frequent adverse events were diarrhea, acneiform dermatitis, and paronychia. (69). The combination of erlotinib and ficlatuzumab has been evaluated in a phase II trial that enrolled previously untreated metastatic EGFR mutated NSCLC (NCT02318368). The results are pending.

2.3.2.2 Rilotumumab (AMG 102)

Rilotumumab is a fully human monoclonal antibody that selectively targets and neutralizes HGF. Results of a phase I trial in patients with solid tumors showed a maximum tolerated dose of 20 mg/kg every 2 weeks and a mean half-life of 15.4 h. All adverse events (fatigue, constipation, anorexia and nausea/vomiting) were low-grade (70). Recently a phase I/II trial evaluated rilotumumab combined with erlotinib in patients with previously treated metastatic NSCLC. 8 patients were enrolled. There were no DLTs, and only one patient had grade 3 rash that did not meet criteria for DLT. Grade 1-2 toxicities were rash, diarrhea, fatigue, hypertension, edema, lymphopenia, elevated bilirubin and alkaline phosphatase. Three patients had PR (one with EGFR mutation), 3 had stable disease, and 2 had progression (71). No further clinical investigations are under evaluation at the moment.
2.3.2.3 Other Met antibodies in development

**YYB-101** is a humanized rabbit anti-HGF antibody developed by YooYoung Pharmaceutical Co., which binds the HGF α-chain and inhibits c-MET activation in vitro and tumor growth in xenograft mouse models (72). A phase I clinical study in patients with advanced solid tumors is ongoing (NCT02499224).

**DN30** is a mouse monoclonal antibody directed against the extracellular portion of MET that induces the proteolytic cleavage of c-MET, and subsequently the release of the soluble receptor and the rapid proteasomal degradation of the intracellular portion (73). DN30 Fab reduces both HGF-dependent and HGF-independent tumor cell growth in vitro and delays tumor growth in *in vivo* models of lung carcinoma (74). However the short plasma half-life, mostly due to renal clearance, appears to severely limit its clinical application.

**HuL2G7** is a humanized antibody that binds HGF shown to overcome gefitinib resistance in EGFR-mutated human NSCLC cell lines (75). However clinical development has been halted due to an adverse toxicity profile, which included cough, abdominal pain, constipation and fatigue in a phase I study conducted in patients with advanced solid malignancies (76).

Other Anti c-MET antibodies such as **LY3164530** (Merestinib) and **JNJ-61186372** inhibit tumor cell growth by the down-regulation of both EGFR and c-MET (77). In a NSCLC xenograft model, LY3164530 showed better antitumor efficacy than combination treatment with emibetuzumab and cetuximab (78). Currently LY3164530 and JNJ-61186372 are under evaluation in phase II and I clinical studies in NSCLC patients (respectively NCT02920996 and NCT02609776).

3 Conclusions

The MET pathway appears to be important for several cancer processes and preclinical studies have demonstrated that it can be effectively targeted. In particular, MET is an appealing target in advanced NSCLC, because of the potential presence of multiple genetic alterations of MET. Several MET inhibitors have been developed, and many have undergone phase III testing already. However to date the results of clinical studies have been overall negative. The reasons for these failures may be many.

As with most targeted treatments, the selection of patients is crucial and so far it appears that the largest categories of patients entered into clinical trials of Met inhibitors have been patients with Met overexpressing or MET amplified tumors. These may not represent the most responsive groups of patients. Exon 14 skip mutations so far appear a better target for Met inhibition.

Most Met inhibitors have shown to be safe in clinical trials. However various adverse events were reported. While most adverse events occurred equally in experimental and control arms, more cases of edema and respiratory infection were found in patients on c-MET inhibitors therapy. In addition, the adverse events seemed to be drug specific. In fact all the ILD cases were found with tivantinib and crizotinib treatment and most edema cases were reported in patients on onartuzumab. In addition Asian patients have genetic polymorphisms of metabolic enzymes, that may influence exposure of small molecule inhibitors. The safety profile of monoclonal antibodies seems to be better than that of the small molecule inhibitors, because antibodies have excellent target specificity and predictable pharmacological properties. Adverse effects and dose-limiting toxicities have been reported for small-molecule inhibitors, but few dose-limiting toxicities have been reported for antibodies.
Review

Small molecule inhibitors such as tivantinib, crizotinib and more recently savolitinib exhibited some promising activity, suggesting that proper selection of patients still needs to be further improved.

Although the synergistic effect of EGFR and cMET inhibitors remains to be shown in patients, recently the combination between savolitinib with osimertinib or gefitinib showed safety and clinical activity in patients with EGFR mutation-positive NSCLC with MET-amplification who had progressed following prior treatment with an EGFR inhibitor (79).

4 Expert opinion

MET signaling is a promising target for cancer therapy. Several agents, including HGF-antagonists, anti-MET antibodies and TKIs have demonstrated some activity and several novel MET inhibitors are currently undergoing clinical investigation, showing potentially interesting preliminary results. However the trials that have been conducted highlight some critical issues and a number of questions remain to be further addressed.

First, the biology and clinical significance of MET pathway activation is still not completely understood. Met activation can occur through several mechanisms, including amplification, rearrangements, protein overexpression and mutations. Each one of these mechanisms is probably responsible for a different level of activation and potentially also qualitative differences in activation, which may respond differently to different therapeutic approaches. Also, the frequency of the mechanisms of Met activation is different in different tumor types and therefore different strategies may be required in different tumor types.

Initial trials focused on either unselected or MET-overexpressing NSCLC and those studies yielded largely negative results. It is clear that much more restrictive and well characterized groups of patients need to be defined in future studies.

Second, diagnostic tests and molecular biomarkers to identify patients who may benefit from MET inhibition are not well understood. In general MET expression by immunohistochemistry has failed to reliably identify patients who benefit, and MET amplification by FISH lacks standardization. Both assays deal with a continuous variable, and the selection of the cut-off points is crucial. Most likely only patients with a very high level of Met expression and amplification are those that may derive benefit from these treatments. On the other hand, the recent discovery of exon 14 skip mutations, afforded by improvements in NGS technology, appears to be the most promising way of selecting patients. Other mutations appear to be much more rare and of unclear significance.

The setting where Met inhibitors are developed is also crucial. It is conceivable that Met activation be different in patients who developed Met amplification after EGFR TKI treatment, than in patients who were not exposed to these drugs before. It is known that tumors that are dependent on a particular oncogenic driver, remain overall dependent on that pathway, even in the occurrence of resistance. It is so far not clear whether Met is a bona fide oncogenic driver at this point. The use of a Met inhibitor in patients with acquired resistance to EGFR TKIs may require a different strategy than in patients who were not exposed to EGFR TKIs before, and the endpoints of these studies may be different: e.g. PFS and OS in the prevention of resistance in first line, or ORR and PFS in second line.

A recent meta-analysis suggested that c-MET inhibitors significantly prolonged PFS but not OS in advanced or metastatic NSCLC patients (80). No known prognostic factors seemed to affect OS,
however, PFS was longer in Asians, non-squamous NSCLC, pretreated patients, which provided a hint for selecting subpopulations in future clinical application. In addition, this meta-analysis showed that, compared with monoclonal antibodies, only small molecule inhibitors (tivantinib and crizotinib) exhibited potentially beneficial therapeutic effects. These differences may be due to different genetic backgrounds of patients entered in the studies, in relation to the expected activity in those subgroups by different molecules. Another meta-analysis evaluated the survival benefit of MET inhibitors combined with EGFR-TKIs or standard chemotherapy in patients with metastatic NSCLC. Compared with patients in the control groups, patients who received the combination with the MET inhibitor did not show significantly improved PFS or OS, although patients with MET-high expression tumor tended to show a better survival (81).

Combinations of Met inhibitors with other drugs, besides EGFR TKIs, will be important, and these will have to be designed with in mind a better understanding of the biology of Met activation. Several combinations that have been developed have not been based on strong preclinical rationale or careful patient selection.

Eventually tumors that initially respond to Met inhibitors will likely become resistant. Understanding of mechanisms of resistance (e.g. in tumors with exon 14 skip mutations) will be important for future development of better Met inhibitors and combinations.

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Declaration of interest
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Figure 1. Legend.
Major signaling pathways activated through c-MET. Hepatocyte growth factor (HGF) binding to c-Met results in c-MET autophosphorylation of tyrosine residues Y1234 and Y1235 within the activation loop of the kinase domain and subsequent phosphorylation of tyrosine Y1349 and Y1356. Important adapter proteins and direct kinase substrates activated downstream in the c-Met pathway include growth factor receptor-bound protein 2 (GRB2), Grb2-associated adaptor protein 1 (GAB1), phosphatidylinositol 3-kinase (PI3K), son of sevenless (SOS), rat sarcoma oncogene homolog (RAS), mitogen-activated protein kinase (MAPK), signal transducer and activator of transcription 3/5 (STAT 3/5).
Met inhibitors (antibodies against Met and HGF) and small molecule TKIs are shown. mTOR: mammalian target of rapamycin, FAK: focal adhesion kinase.
Table 1. Small molecule Met inhibitors

<table>
<thead>
<tr>
<th>Molecule and Company</th>
<th>IC50</th>
<th>Dosing and schedule</th>
<th>Patient population (ref) Met selection test</th>
<th>Most common AE reported</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Crizotinib</strong></td>
<td></td>
<td></td>
<td></td>
<td>≥25% vision disorders, nausea, diarrhea, vomiting, edema, constipation, elevated transaminases, fatigue</td>
</tr>
<tr>
<td>Pfizer</td>
<td>c-MET: 11 nM ALK: 24 nM cell-based assays</td>
<td>250 mg BID daily, oral</td>
<td>ALK+ 1/2L (24,25) ROS + 1L (26) METex14 1/2L (28,29) NSCLC 2L (30,31) Met amplification (MET/CEP7 ratio by FISH) MET ex14 (NGS)</td>
<td>≥25% vision disorders, nausea, diarrhea, vomiting, edema, constipation, elevated transaminases, fatigue</td>
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<tr>
<td><strong>Cabozantinib</strong></td>
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<tr>
<td>Exelisix</td>
<td>VEGFR2: 0.035 c-MET: 1.3 nM RET: 4 nM Kit: 4.6 nM AXL: 7 nM cell-free assays</td>
<td>60 mg daily, oral</td>
<td>Solid tumors (32) +1L NSCLC EGFR wt (33) RET rearranged (34) RET ROS1 NTRK+ or increased MET or AXL Activity (ongoing) NSCLC brain mts (ongoing) MET amplification /GCN (FISH)</td>
<td>Elevated transaminases, diarrhea, nausea, palmar plantar erythrodysesthesia AE grade 3 or higher: hypertension, fatigue, mucositis, thromboembolic events</td>
</tr>
<tr>
<td><strong>Foretinib</strong></td>
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<tr>
<td>GlaxoSmithKline</td>
<td>c-MET: 0.4 nM Tie-2: 2.1 nM VEGFR3/FLT4: 2.8 nM RON: 3nM cell-free assays</td>
<td>3.6 mg/kg, for 5 consecutive days every 14 days (35) 80 mg daily oral (36) erlotinib 150 mg daily x 14 days with foretinib 30 mg added on day 15 (continuous dosing in 28-day cycles) (37)</td>
<td>Solid tumors (35,36) +1L unselected NSCLC in combination with erlotinib (37) MET expression (IHC)</td>
<td>Elevations of AST and lipase, fatigue, hypertension, nausea, and diarrhea (35,36). Adverse events in ≥20%: diarrhea, fatigue, anorexia, dry skin, rash and hypertension (37)</td>
</tr>
<tr>
<td><strong>Glesatinib</strong></td>
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<td></td>
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<tr>
<td>Mirati</td>
<td>c-MET: 19 nM cell-based assays</td>
<td>750 mg BID daily, oral</td>
<td>Solid tumors (39) +2L post platinum MET+ NSCLC (pending results)</td>
<td>&gt;20% all grades included diarrhea, nausea, vomiting, fatigue, increase of AST, ALT, lipase</td>
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<td><strong>Review</strong></td>
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<thead>
<tr>
<th><strong>MET mutation or amplification</strong></th>
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<th><strong>S49076</strong></th>
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| **Servier** | c-MET: 2 nM  
AXL: 33 nM  
FGFR1: 65 nM  
AURORA: 500 nM cell-free assay | 600 mg once daily, oral | Solid tumors (41)  
EGFR mutated NSCLC patients progressed on EGFR TKIs in combination with gefitinib (42)  
Hypoalbuminemia, peripheral edema (93% AE grade I/II) |

<table>
<thead>
<tr>
<th><strong>Capmatinib</strong></th>
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</table>

| **Novartis** | c-MET: 0.13 nM cell-free assay | 400 mg BID daily, oral | EGFR wt, high c-MET-expressing NSCLC (44)  
EGFR mt after PD with gefitinib or erlotinib (45, 46)  
MET expression (IHC); MET amplification (FISH); MET ex14 (NGS)  
Nausea (47%), vomiting (37%), peripheral edema (35%), decreased appetite (33%), fatigue (33%). Grade 3/4: anemia, hypokalemia, and pneumonia (all 7%). |

<table>
<thead>
<tr>
<th><strong>Tivantinib</strong></th>
</tr>
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</table>

| **Tivarte** | c-MET: 0.1 μM cell-free assay | 360 mg BID daily, oral | 1L+ NSCLC with erlotinib (47,48)  
1L+ Asian NSCLC EGFR wt with erlotinib (49)  
Met expression (IHC)  
MET amplification/GCN (FISH)  
HGF expression (IHC)  
Low grade rash, diarrhea, fatigue, nausea, vomiting, dyspnea, anemia (47); interstitial lung disease (49) |

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<tr>
<th><strong>Teponitinib</strong></th>
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</table>

| **Dava** | c-MET: 4 nM cell-based assays | 500 mg QD, oral | 1-3L NSCLC with METex14 skipping mutations  
1L+ in combination with gefitinib, T790M-, MET positive (NSCLC) EGFR mt (ongoing)  
Met expression (IHC); MET amplification/GCN (FISH)  
Peripheral edema, decreased appetite constipation, nausea, fatigue, vomiting |
<table>
<thead>
<tr>
<th></th>
<th>c-MET: 5 nM cell-based assays</th>
<th>600 mg QD, oral</th>
<th>IL+ with gefitinib in EGFR mutant (53) MET amplification/GCN (FISH)</th>
<th>Nausea (40% grade 1), bilirubin increase (30%-grade 1-2), vomiting (30% -G1) (53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Savolitinib AstraZeneca</td>
<td></td>
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<tr>
<td>SAR125844 Sanofi</td>
<td>c-MET: 4.2 nM cell-based assays</td>
<td>570 mg/m² intravenously weekly</td>
<td>c-MET amplified Asian patients with solid tumors (53) MET amplification/GCN (FISH)</td>
<td>nausea (36.8%), vomiting (34.2%), decreased appetite (28.9%), and fatigue or asthenia, constipation, and abdominal pain (21.1% each)</td>
</tr>
</tbody>
</table>
### Table 2: Antibodies against MET/HGF

<table>
<thead>
<tr>
<th>Molecule and Company</th>
<th>Dosing and schedule</th>
<th>Patient population (ref)</th>
<th>Most common AE reported</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onartuzumab</strong></td>
<td>Onartuzumab: 15 mg/kg intravenous infusion q3 weeks. Erlotinib: oral at 150 mg once daily</td>
<td>1L+ NSCLC in combination with erlotinib (58)</td>
<td>Fatigue (56%), peripheral edema (35%), decreased appetite (32%), constipation (29%), nausea (27%), hypoalbuminemia (24%) (57). Peripheral edema, back pain dyspnea, nausea, acneiform dermatitis, and rash (57,58).</td>
</tr>
<tr>
<td><strong>Aveo</strong></td>
<td>Ficlatuzumab 20 mg/kg intravenously q 2 weeks on Day 1 and Day 15 of each 28 day cycle. Erlotinib: 150 mg oral once daily</td>
<td>Asians not selected for EGFR NSCLC (68,69)</td>
<td>Diarrhea, acneiform dermatitis, and paronychia. (68).</td>
</tr>
<tr>
<td><strong>Amgen</strong></td>
<td>Rilotumumab: 20 mg/kg every 2 weeks intravenously. Rilotumumab: 15 mg/kg IV q 3 weeks; Erlotinib: at 150 mg oral daily</td>
<td>Solid tumors (70) 1L+NSCLC with erlotinib (71)</td>
<td>Grade 1-2 fatigue, constipation, anorexia and nausea/vomiting (70). Grade 1/2 rash, diarrhea, fatigue, hypertension edema, lymphopenia, elevated bilirubin and alkaline phosphatase (71).</td>
</tr>
<tr>
<td><strong>Eli Lilly</strong></td>
<td>Emibetuzumab: 750 mg once q2 weeks, intravenously</td>
<td>Solid tumors (61)</td>
<td>Diarrhea, nausea, and vomiting (61)</td>
</tr>
<tr>
<td><strong>ARGX-111</strong></td>
<td>ARGX-111: 3 mg/kg q2weeks, intravenously</td>
<td>Solid tumors overexpressing c-MET (65)</td>
<td>Infusion related reaction, fatigue, constipation, nausea, decreased appetite, myalgia, vomiting</td>
</tr>
<tr>
<td><strong>ABBV-399</strong></td>
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</tbody>
</table>
Table 3. Ongoing MET inhibitor trials, targeting NSCLC

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Clinical trial number</th>
<th>Phase</th>
<th>Drug combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib</td>
<td>NCT01639508</td>
<td>II</td>
<td>Erlotinib</td>
</tr>
<tr>
<td></td>
<td>NCT02132598</td>
<td>II</td>
<td>-</td>
</tr>
<tr>
<td>Glesatinib</td>
<td>NCT02954991</td>
<td>II</td>
<td>Nivolumab</td>
</tr>
<tr>
<td>Capmatinib</td>
<td>NCT02750215</td>
<td>III</td>
<td>-</td>
</tr>
<tr>
<td>Tepotinib</td>
<td>NCT02864992 NCT01982955</td>
<td>II</td>
<td>- Gefitinib</td>
</tr>
<tr>
<td>Savolitinib</td>
<td>NCT02143466 NCT01985555</td>
<td>I</td>
<td>Osimertinib</td>
</tr>
<tr>
<td>SAR125844</td>
<td>NCT02435121</td>
<td>II</td>
<td>-</td>
</tr>
<tr>
<td>Ficlatuzumab</td>
<td>NCT02318368</td>
<td>II</td>
<td>Erlotinib</td>
</tr>
<tr>
<td>Emibetuzumab</td>
<td>NCT01897480 NCT02082210</td>
<td>II</td>
<td>Erlotinib</td>
</tr>
<tr>
<td></td>
<td>NCT02082210</td>
<td>II</td>
<td>Ramucirumab</td>
</tr>
<tr>
<td>YYB-101</td>
<td>NTC02499224</td>
<td>I</td>
<td>-</td>
</tr>
<tr>
<td>LY3164530</td>
<td>NCT02920996</td>
<td>II</td>
<td>-</td>
</tr>
<tr>
<td>JNJ-61186372</td>
<td>NCT02609776</td>
<td>I</td>
<td>-</td>
</tr>
<tr>
<td>ABVV-399</td>
<td>NCT02099058</td>
<td>I</td>
<td>Erlotinib/Nivolumab</td>
</tr>
</tbody>
</table>

ABBvie: ABVV-399: 2.7 mg/kg q3 weeks, intravenously
Erlotinib: 150 orally once daily
c-MET positive advanced NSCLC in combination with erlotinib or alone (63)
Fatigue, nausea, neuropathy, decreased appetite and vomiting (63)
Review

References


Review

• This is one of the largest studies that have estimated the prevalence of MET in NSCLC.


• This is one of the studies that showed the correlation between MET amplification and EGFR TKI resistance in lung cancer.


•• This clinical trial investigated crizotinib in ALK positive NSCLC. The results of this study formed the basis of FDA approval.


•• This clinical trial investigated crizotinib in ROS1 rearranged NSCLC. The results of the study formed the basis of FDA approval.

•This clinical trial investigated crizotinib in MET exon 14-altered NSCLC.


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• This clinical trial investigated crizotinib c-MET-amplified NSCLC.


33 Neal J, Dahlberg S, Wakelee H, et al. Erlotinib, cabozantinib, or erlotinib plus cabozantinib as second-line or third-line treatment of patients with EGFR wild-type advanced non-small-cell lung cancer (ECOG-ACRIN 1512): a randomised, controlled, open-label, multicentre, phase 2 trial Lancet Oncology, Volume 17, No. 12, p1661–1671, December 2016

• This clinical trial investigated the combination of Cabozantinib and erlotinib in NSCLC


• This clinical trial investigated Cabozantinib in RET-rearranged NSCLC


40 Bazhenova L, Kim D, Cavanna L, et al P2.06-017 Amethyst NSCLC Trial: Phase 2 Study of MGCD265 in Patients with Advanced or Metastatic NSCLC with Activating Genetic Alterations in MET. J Thorac Oncol Volume 12, 2017 sp S1080–S1081

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Volume 81, August 2017, Pages 142-150


43 Clémenson C, Chargari C, Liu W, et al. The MET/AXL/FGFR inhibitor impairs Aurora B activity and improves the antitumor efficacy of radiotherapy Molecular Cancer Therapeutics tor S49076 2017 0.1158/1535-7163


•This clinical trial investigated Tivantinib Plus Erlotinib in Previously Treated NSCLC Patients.


53 Yang J, Yang L, Farnsworth A et al. Preliminary results of a phase Ib trial of savolitinib combined with gefitinib in EGFR-mutant lung cancer. DOI: 10.1200/JCO.2016.34.15_suppl.e20559 J Clin Oncol 34, no. 15_suppl.
Review


Review


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trial of AZD9291 combined with MEDI4736, AZD6094 or selumetinib in EGFR-mutant lung cancer. J Clin Oncol 2015 2509-2509.


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Figure 1
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