

Spotlight on Tepotinib and Capmatinib for Non-Small Cell Lung Cancer with MET Exon 14 Skipping Mutation

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Abstract: Mesenchymal-epithelial transition (MET) receptor tyrosine kinase is overexpressed, amplified, or mutated in 1–20% of NSCLC. MET dysregulation is associated with a poor prognosis. Recently, development of targeted therapies against MET exon 14 mutations has demonstrated efficacy and tolerability in early trials. Here we focus on tepotinib and capmatinib in regards to molecular characteristics, early preclinical and clinical data, and the emerging role in future studies and clinical practice.

Keywords: tepotinib, capmatinib, mesenchymal-epithelial transition inhibitors, MET, RET, non-small cell lung cancer

Introduction

Lung cancer is the leading cause of cancer death, accounting for almost 25% of cancer-related deaths. Development of targeted therapies has significantly improved overall survival (OS) and quality of life for non-small cell lung cancer (NSCLC) patients demonstrating oncogenic driver mutations.^{1,2} The mesenchymal-epithelial transition (MET) receptor tyrosine kinase is overexpressed in 20% of NSCLC^{3–5} and amplified in 1–5% of NSCLC.⁶ The MET exon 14 (METex14) skipping mutation occurs predominantly in NSCLC⁷ with a prevalence of 3–4% of NSCLC cases.^{7,8} MET dysregulation is associated with a poor prognosis in NSCLC^{9–11} and there was an unmet need for therapeutic blockade of this oncogenic driver. A retrospective analysis showed that use of MET-TKIs improves overall survival in NSCLC patients with METex14 skipping mutations with a hazard ratio of 0.11.¹²

The MET proto-oncogene is located on 7q31 of chromosome 7 and encodes a receptor tyrosine kinase. The MET receptor is expressed by epithelial cells of many solid organs such as liver, pancreas, prostate, kidney, muscle, and bone marrow.^{13,14} MET binds to its ligand, hepatocyte growth factor (HGF), causing autophosphorylation of tyrosine residues Y1234 and Y1235 which serve as docking sites for proto-oncogenes such as SRC and intracellular molecules such as PI3K, STAT3, and SHP2.⁷ This in turn activates signaling pathways involved in embryogenesis, cell proliferation, tissue regeneration, wound healing, and formation of nerve and muscle.¹⁵ MET dysregulation in certain types of cancer can occur as gene amplification, point mutations, fusions, exon 14 skipping mutations, or protein overexpression. MET exon 14 skipping mutations (METex14) in NSCLC is the first subtype of MET alterations to have Food and Drug Administration (FDA) approved targeted therapy. Clinically, METex14 mutations are found in patients with a median age at diagnosis of 72.5 years, smoking history, female, and pleomorphic carcinoma or adenosquamous cell carcinoma.^{7,16,17}

Historically, METex14 aberrations have been challenging to detect due to their heterogeneity. Immunohistochemical studies detect MET overexpression, which may occur due to increased gene copy number and gene amplification as well as METex14 mutations.¹⁸ Additionally, immunohistochemical staining may be due to a high degree of observer variability in interpretation.⁴ DNA-based assays include either Sanger single gene or next-generation sequencing (NGS

panels). Sanger sequencing has high specificity but low sensitivity compared to NGS panels,¹⁹ making NGS more widely implemented in clinical practice. Hybrid capture-based NGS panels have produced fewer false-negative results compared to whole-exome panels.^{17,20,21} RNA-based PCR assays detect a fusion transcript between MET exon 13 and 15. The interpretation of the PCR-based assays are more straightforward but are limited by a primer to specific sequences, thus making them unable to detect novel mutations. One study found that RNA-based assays detected a higher proportion of METex14 skipping mutations than DNA-based assays.²² Liquid biopsies detecting mutations in cell-free DNA and circulating tumor cells have been used in clinical trials^{8,23} with high sensitivity.

Small molecule MET inhibitors can be divided into three types; type I, II and III. Type I inhibitors include crizotinib (type Ia), tepotinib and capmatinib (type Ib). They block ATP binding, preventing the phosphorylation and activation of the receptor (Figure 1). Type II inhibitors include cabozantinib and competitively bind to a hydrophobic pocket adjacent to the ATP binding site. Type III inhibitors bind to allosteric sites rather than the ATP binding site.²⁴ Tivantinib is an example of a type III inhibitor but its trial was terminated early due to futility.²⁵

Recently, development of targeted therapies against METex14 mutations have demonstrated efficacy and tolerability in trials. Here we discuss tepotinib and capmatinib in regard to molecular characteristics, early preclinical and clinical data, and their emerging role in future studies and clinical practice.

Tepotinib

Tepotinib (TEPMETKO) is a novel agent that targets and selectively binds MET to disrupt oncogenic signaling and promote tumor cell death (Figure 1).²⁶ On September 11, 2019, the FDA granted Breakthrough Therapy Designation to tepotinib in metastatic NSCLC patients with METex14 skipping mutations who progressed on platinum chemotherapy. Tepotinib gained accelerated approval on February 3, 2021 for this indication.²⁷

Structural Characteristics

Tepotinib (TEPMETKO[®], EMD Serono) was synthetically designed to target c-MET thus inhibiting downstream signaling pathways. It binds c-MET in a U-shaped geometry with both hinge and activation loop residue Y¹²³⁰ to prevent ATP-binding.²⁶

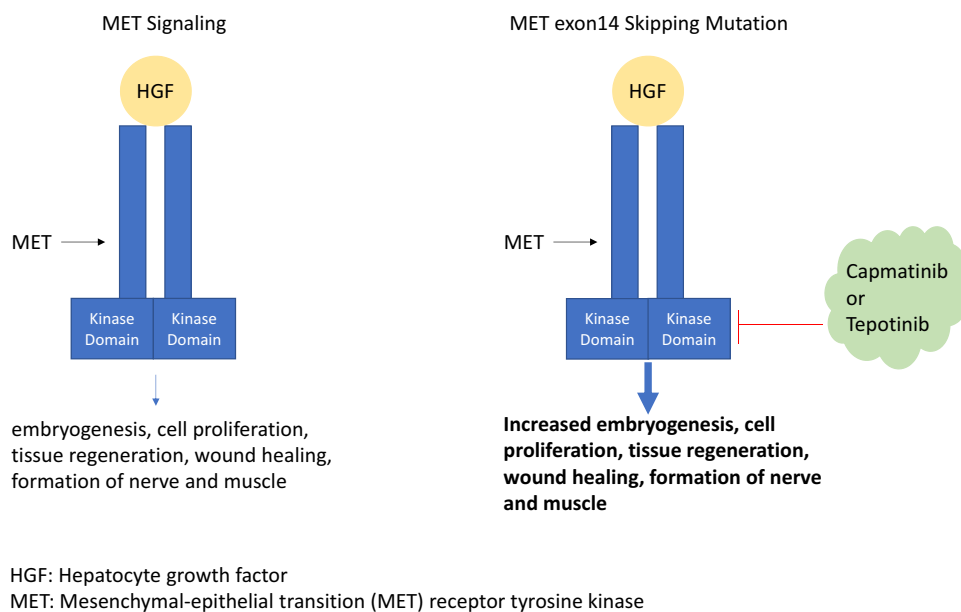


Figure 1 Describes the normal MET signaling function (left) and pathogenic effects due to MET exon 14 skipping mutations (right). Capmatinib and tepotinib inhibit the hepatocyte growth factor (HGF).

Pharmacodynamic Properties

Tepotinib was shown to inhibit MET kinase with an average IC₅₀ of 1.7 nmol/L. Screening against more than 400 kinases showed the high selectivity of tepotinib for MET.^{28,29} As shown by the fact that among a panel of 242 protein kinases, only IRAK4, TrkA, Axl, IRAK1 and Mer were inhibited by more than 50% in the presence of tepotinib at 10 nmol/L and with formal IC₅₀ determinations revealing values between 615 and 2272 nmol/L, tepotinib is unlikely to have pharmacologically relevant inhibitory activity against these off-target protein kinases.²⁶ At 1 micrometer, only MET was inhibited in a panel of over 305 kinases.

The recommended dose is 500 mg daily orally once daily after food.^{29,30}

Pharmacokinetics

The median time to maximum dose was 8 to 10 hours after initiation.³¹ The C_{max} and area under the curve (AUC) increased with increasing dose. A dose proportional increase was seen for once-daily doses up to 450 mg. When taken with food, the bioavailability is 71.6%. Food was shown to increase AUC 1.6-fold and C_{max} 2-fold.³¹ The half-life of tepotinib is 32 hours following oral ingestion. Tepotinib is metabolized by CYP3A4 and CYP2C8, which may have implications for drug interactions.

Preclinical Studies

In vivo murine xenograft models of cancer cells, tepotinib was associated with tumor regression regardless of hepatocyte growth factor impact on MET activation.²⁶

In preclinical models, regression of orthotopic brain metastases have been reported with tepotinib administration. Mazieres et al demonstrated that the fraction of unbound tepotinib in rat brain tissue (0.4%) was low compared with plasma (4%), indicating high binding within the brain. In orthotopic brain models, tumors from MET-driven NSCLC brain metastases regressed significantly with a mean tumor volume reduction of 63% for LU5406 and 84% for LU5349.³¹

Clinical Trials

Phase I

After a Phase I study of 149 patients with solid tumors (NCT01014936), the recommended dose for Phase II trials was determined to be 500 mg once daily. In this trial, patients received oral tepotinib every 21 days on one of three dose escalation regimens: R1 (n=42) – 30–400 mg daily for 14 days; R2 (n=45) – 30–315 mg daily three times per week; or R3 (n=62) – 300–1400 mg daily.²⁹ Although the maximum tolerated dose was not reached, six patients (R1 n=1, R2 n=3, R3 n=2) reported dose-limiting toxicities. The dose of 500 mg daily was shown to achieve at least 95% MET inhibition in 90% or higher of patients. Treatment related AEs include fatigue, peripheral edema, decreased appetite, nausea, vomiting, and increased lipase.²⁹

Phase 2

In the phase II open-label VISION trial, Paik et al studied tepotinib 500 mg daily in advanced or metastatic NSCLC patients with METex14 skipping mutations (Table 1).⁸ They compared DNA-based liquid biopsy and RNA-based tissue biopsies. They found similar outcomes in both biopsy groups with ORR 46% (95% CI: 36–57) with median DOR 11.1 months (95% CI: 7.2, could not be estimated). In this trial, 28% of participants experienced grade 3 or higher adverse events, most commonly peripheral edema (7%).

Tepotinib has demonstrated intracranial activity. The VISION trial cohort A enrolled 22 patients with neurologically stable baseline brain metastases. Mazieres et al reported efficacy from 21 patients who had at least nine months of follow up.³² The confirmed systemic best overall response was partial response in 52.4% (95% CI 29.8–74.3, 11 patients/21). Median duration of response was 9.5 months (95% CI 5.5-NE) and median PFS was 9.5 months (5.7–11.2).

Table I MET-Targeted Therapy

Study Drug	Trials	Population	Number Participants	Primary Outcome	Results	Secondary Outcome	Results	Secondary Outcome	Results
Capmatinib	Phase I NCT 01610336	NSCLC EGFR-mutated and MET amplified or overexpressed	161	ORR	23%				
	Phase II GEOMETRY NCT 02414139	NSCLC with METex14 skipping mutations	373	ORR	41% (95% CI 29–53) in pretreated and 68% (95% CI 48–84) in treatment naive	PFS	5.42 months (95% CI 4.17–6.97) pretreated and 9.13 months (95% CI 5.52–13.86) treatment naive		
	Phase I NCT01324479	MET positive solid tumor including NSCLC	131	Dose Limiting Toxicity	Recommended Phase II dose: 400mg BID tablets/ 600mg BID capsules				
	Phase I NCT01911507	Capmatinib and Erlotinib combination NSCLC	35	Max tolerated dose	600mg BID	Toxicities, ORR, DCR, PFS	Toxicities: Neutropenia		
Tepotinib	Phase II VISION NCT 02864992	NSCLC with MET exon 14 skipping mutations or MET amplification	337	ORR	46% (95% CI 36–57)	DOR	11.1 months (95% CI 7.2 – not estimatable)	Grade 3 or 4 AE	28%
	Phase II INSIGHT NCT 01982955	NSCLC with high MET expression or MET amplification after EGFR-TKI failure	88	OS	17.3 (95% CI 12.1–37.3) tepotinib + gefitinib vs 18.7 (95% CI 15.9–20.7 chemo)	PFS	4.9 months (95% CI 3.9–6.9) vs 4.4 months (95% CI 4.2–6.8)		
Savolitinib	Phase IB TATTON NCT 02143466	NSCLC both EGFR-mutated and MET amplified	344	DOR	7.1 months (SD 7.6) savolitinib v 5 months (SD 7.7) osimertinib	DOR	7.1 months		
	Phase II NCT 02897479	Sarcomatoid carcinomatoma with METex14 skipping mutations	76	ORR	38.7%	PFS	6.9 months (4.57–8.25)	OS	12.5 months (10.48–21.39)
Glumetinib (SCC244)	Phase II Glory	NSCLC harboring MET exon 14 skipping mutations	69	ORR	60.9% (95% CI 48.4–72.4)	PFS	7.6 months (4.2- not estimable)	AE ≥ grade 3	43.8%

Safety, Tolerability, and Adverse Events

In the VISION trial, common adverse events included peripheral edema (63%), nausea (26%), diarrhea (22%), increased blood creatinine (18%) and hypoalbuminemia (16%).⁸

Analysis of pooled adverse effect data from five phase I and phase II studies of tepotinib 500 mg daily (NCT01014936, NCT01832506, NCT01988493, NCT02115373 and NCT02864992) showed 75.4% of participants experienced any adverse event and 22.8% experienced a grade 3 or higher adverse event. The most common adverse events included peripheral edema (33.8%), diarrhea (19.7%), fatigue (14.9%), nausea (12.7%), decreased appetite (11.8%), increased serum creatinine levels (7.9%), hypoalbuminemia (7.0%) and increased amylase levels (5.7%). Dose reductions occurred in 14.5% of patients due to adverse events and treatment was discontinued in 21.5% of patients. There were two fatal adverse events: an upper gastrointestinal hemorrhage and a hypoglycemic coma.³³

Capmatinib

Capmatinib also targets and selectively binds the MET tyrosine kinase, including mutations produced by exon 14 skipping, and inhibits cancer cell growth driven by MET aberrations (Figure 1).³⁴ Capmatinib inhibits phosphorylation of MET and its downstream effects, thus inhibiting tumor proliferation and inducing apoptosis in MET-dependent tumor cell lines.³⁵ On May 6 2020, capmatinib was approved by the FDA for use in adults with metastatic NSCLC with a METex14 skipping mutation.³⁶

Structural Characteristics

Capmatinib (Tabrecta™, Novartis) is a selective and potent small molecule MET inhibitor. It functions as an ATP-competitive type 1b MET inhibitor. The central aromatic ring of capmatinib binds to Y1230 of MET tyrosine kinase in a pi stacking interaction.³⁷ Additionally, the Y1230-capmatinib interaction is further stabilized by a salt bridge between D1228 and K1110 of the MET activation loop. The mechanism behind this interaction is similar to that of crizotinib and other selective MET inhibitors.

Pharmacodynamic Properties

The recommended dose of capmatinib is 400 mg administered twice per day to be taken orally with or without food.³⁹ The exposure-response and time course dynamics are largely unknown.

Pharmacokinetics

Capmatinib was measured with multiplex ELISA in tumor lysates from the Cancer Cell Line Encyclopedia project.³⁸ MET inhibition was detectable two hours after the last dose with residual phospho-MET recovery in two of three models 12 hours after the last dose.³⁶

In human studies, capmatinib demonstrates linear pharmacokinetics with exposure increasing in both peak plasma concentration (C_{max}) and area under the concentration-time curve dose-proportionally within the range of 200–400 mg daily.³⁹ It is rapidly absorbed with C_{max} one-to-two hours after administration. The bioavailability of over 70% was similar both with and without food. With twice per day dosing, steady state was reached by day three. The elimination half-life of capmatinib is 6.5 hours. Capmatinib is metabolized by cytochrome P450 A34 (CYP3A4) and aldehyde oxidase.

Of note, caution should be used with other CYP3A4 inhibitors which are shown to increase capmatinib exposure, potentially increasing the incidence and severity of adverse events while CYP3A4 inducers are shown to decrease capmatinib exposure, potentially decreasing antitumor activity.³⁹

Preclinical Studies

Preclinical studies screened capmatinib against 57 different human kinases and found potent selectivity for MET within this panel.³⁵ Investigators found capmatinib activity against MET amplification, MET overexpression, METex14 skipping mutations, and MET activation via expression of HGF ligand. Cancer cell lines without MET aberrations showed poor

response to capmatinib, which suggests that strict selection criteria should be used and/or used in combination with other kinase inhibitors to combat MET resistance.³⁷ Another study of capmatinib activity in over 600 cancer cell lines in the Cancer Cell Line Encyclopedia project³⁸ showed that cell lines with MET amplification and MET overexpression were associated with dramatic sensitivity to capmatinib both in vitro and in vivo.³⁷ Overall in vivo xenografts showed a more robust response than in vitro cell lines.³⁷

Clinical Trials

Phase I

A multicenter dose-escalation and expansion of capmatinib in advanced MET positive solid tumors (NCT01324479) found 400 mg BID or 600 mg BID to be tolerable doses. The maximum tolerated dose was not reached. In heavily pretreated patients with NSCLC, the overall response rate (ORR) was 24% with median progression-free survival (PFS) 7.3 months.⁴⁰

Phase 2

The GEOMETRY trial (NCT 02414139) was a non-randomized phase II investigation of stage IIIB/IV NSCLC patients with METex14 skipping mutations (Table 1). This included 69 pretreated patients and 28 treatment naïve patients. Participants received capmatinib 400 mg BID. The ORR was 41% (95% CI 29–53) in pretreated patients and 68% (95% CI 48–84) in treatment naïve patients. A 4% complete response (CR) rate was seen in the treatment naïve cohort. The median duration of response (DOR) was 9.7 months (95% CI 5.5–13) in the pretreated population versus 12.6 months (95% CI 5.5–25.3) in treatment naïve patients. The median PFS was 5.42 and 9.69 months, respectively. Of note, capmatinib was shown to cross the blood brain barrier with a 54% intracranial response in the phase II GEOMETRY study.⁴¹

Another clinical trial in China (NCT 02276027) of 66 patients who failed prior therapy or were unable to receive chemotherapy received targeted therapy based on mutational status (capmatinib – MET, ceritinib – ALK/ROS, binimetinib – KRAS/NRAS/BRAF, and alpelisib – PIK3CA). There was an 18.8% confirmed partial response with capmatinib.⁴²

Safety, Tolerability, and Adverse Events

In the phase II GEOMETRY trial the most common adverse events included peripheral edema (52%), nausea (44%), fatigue (32%), vomiting (28%), dyspnea (24%), and decreased appetite (21%). The most common grade 3 or 4 adverse events were peripheral edema (9%), fatigue (8%), and dyspnea (7%).^{39,41} Dose interruptions due to adverse events occurred in 54% of patients due to peripheral edema, increased serum creatinine, nausea, or vomiting. Dose reductions occurred in 23% of patients due to peripheral edema, increased alanine aminotransferase (ALT), increased serum creatinine, and nausea.

Future Directions

MET TKIs for EGFR TKI Resistance

MET is implicated as the cause of acquired/adapted resistance to targeted therapies^{43–50} which further emphasizes the importance of developing potent MET inhibitors.

Based on studies of resistance to EGFR-TKIs, acquired resistance may occur through MET amplification or codriver gene alterations.⁷ In EGFR-mutated NSCLC, coexisting MET amplification is reported in 4–40% of cases. Codriver gene alterations occur through EGFR amplification (6.4–28.5%), FGFR1 alteration (4.8–16.6%), KRAS activation (8%) or BRAF activation (21.4%) or PIK3CA mutation/amplification (14.2%).^{51,52}

Preclinical data suggested that tepotinib can overcome acquired resistance to EGFR TKIs due to MET signaling pathway.⁵³ Indeed, in the phase II portion of the INSIGHT study (NCT01982955), patients with EGFR-mutant T790M negative NSCLC with either high MET expression by immunohistochemical staining or MET amplification after EGFR-TKI treatment failure were randomly assigned to tepotinib plus gefitinib or to standard platinum-based chemotherapy. At

interim data analysis, the combination of tepotinib and gefitinib significantly improved OS and PFS in the MET amplification cohort and high expression cohort. For the MET amplification cohort, the HR was 0.13 for PFS and 0.08 for OS (n=19; median PFS 16.6 months (8.3-not estimable) vs 4.2 months (1.4–7.0); HR 0.13, 0.04–0.43; median OS 37.3 months (90% CI not estimable) vs 13.1 months (3.25-not estimable); HR 0.08, 0.01–0.51). For the MET high expression cohort, the HR was 0.35 for PFS and 0.33 for OS (n=34; median PFS 8.3 months (4.1–16.6) vs 4.4 months (4.1–6.8); HR 0.35, 0.17–0.74; median OS 37.3 months (90% CI 24.2–37.3) vs 17.9 months (12.0–20.7); HR 0.33, 0.14–0.76)).³⁰

Data also suggests promising results with capmatinib. In EGFR-mutant NSCLC cell lines with developed resistance to EGFR inhibitors and MET dysregulation, capmatinib restores sensitivity to EGFR inhibitors.^{37,54} Indeed, in a phase Ib trial combining capmatinib and gefitinib in EGFR-mutated, MET amplified or overexpressing NSCLC (NCT01610336), the ORR was found to be 23%.⁵⁵ Better ORR (47%) and median PFS (5.5 months) were demonstrated in patients with a MET gene copy number of at least 6.

MET inhibitors may allow us to overcome other resistance pathways outside of EGFR. Baltschukat et al found that EML4-ALK translocated PDX cells expressed very high MET mRNA levels without MET amplification and high phospho-MET protein levels. This model did not respond to the second-generation ALK inhibitor ceritinib but when ceritinib was combined with capmatinib, tumor cells regressed.³⁷

Mechanisms of Resistance to MET TKIs

MET-TKI resistance can be acquired through secondary MET mutations or activation of alternate signaling pathways. In a prior study of crizotinib, 35% of patients developed MET mutations and 45% developed mutations in bypass pathways.⁵⁶ In vitro analysis using Ba/F3 models found MET secondary mutations of D1228 and Y1230 in the activation loop.⁵⁷ These findings are confirmed by case reports of patients with D1228 and Y1230 mutations who show resistance to MET inhibitors.^{58,59} Potential alternate pathway mutations for acquired resistance include KRAS amplification/mutation and PIK3CA mutation.⁷ Changes in MET gene copy number could be another potential mechanism of resistance although the activity of tepotinib and capmatinib in MET-amplified tumors will still need to be better established first.

Ongoing Clinical Trials

Ongoing clinical trials are listed in [Table 2](#). MET inhibitors are being combined with various immune checkpoint inhibitors (NCT04323436, NCT04139317, NCT02323126, NCT03647488). Combination strategies with EGFR TKIs are also being evaluated in the post EGFR TKI progression setting (NCT04816214, NCT03940703).

Other Agents Under Investigation

Savolitinib

Savolitinib (Orpathys, HUTCHMED, AstraZeneca) is being investigated in combination with other therapies in the treatment of NSCLC. Interim analysis of the TATTON phase Ib trial of third generation EGFR-TKI osimertinib plus MET inhibitor savolitinib in NSCLC patients with both EGFR mutations and MET amplifications showed ORR 52% with median DOR 7.1 months ([Table 1](#)).⁶⁰ The most common adverse effects were nausea (37%), diarrhea (30%), fatigue (28%), decreased appetite (28%), pyrexia (26%), and vomiting (22%). Serious adverse effects occurred in 37% of patients.

Another phase II trial is examining savolitinib in lung sarcomatoid carcinoma and other NSCLC with METex14 skipping mutations (NCT02897479). At interim analysis, 38.7% of patients had a partial response to therapy. The most common adverse effects were nausea (41%), peripheral edema (38%), increased ALT (32%), increased AST (29%), and vomiting (21%).²³ The final analysis was presented at the European Lung Cancer Congress 2022 and reported investigator assessed median PFS of 6.9 months and median OS of 12.5 months.⁶⁵

Glumetinib

Glumetinib (SCC244) is another highly selective MET inhibitor. Results from the pivotal phase II study⁶⁶ is summarized in [Table 1](#).

Table 2 Ongoing Clinical Trials

Trial	Drug	Design	Population	Number of Participants	Primary Outcome	Secondary Outcomes	Recruiting?
NCT02750215	Capmatinib	Phase II	NSCLC with MET exon 14 alterations after prior treatment with MET inhibitor	20	RR	PFS, DOR, OS, tolerability	No
NCT04677595 (China)	Capmatinib	Phase II	Patients NSCLC MET Exon 14 Skipping Mutation	35	ORR	DOR, TTR, DCR, PFS, OS, OIRR, IDCR, TTIR, DOIR	Yes
NCT05110196 (India)	Capmatinib	Phase IV	Patients MET Exon 14 Skipping Mutation NSCLC	50	AEs	ORR, OIRR, DOR, TTR, DCR, PFS	No
NCT04926831	Capmatinib	Phase II	Neoadjuvant use in stage I-IIIa NSCLC with MET exon 14 mutation or amplification	38	MPR	pCR, ORR, DFS	Yes
NCT04323436	Capmatinib + Spartalizumab/ Placebo	Phase II	Capmatinib + Spartalizumab combination versus Capmatinib + Placebo in first line treatment MET exon 14 skipping metastatic NSCLC	31	ORR, PFS	AEs, DCR, OS, PK	Yes
NCT04427072	Capmatinib vs. Docetaxel	Phase III	Capmatinib versus docetaxel NSCLC MET exon 14	90	PFS	ORR, TTR, DOR	Yes
NCT04816214	Capmatinib + Osimertinib	Phase III	Capmatinib + Osimertinib versus platinum chemotherapy as second line treatment in metastatic EGFR NSCLC MET amplified who progressed on EGFR TKI	245	DLT, PFS	C _{max} Duration of exposure, T _{max}	Yes
NCT03693339	Capmatinib	Phase II	Capmatinib Exon 14 MET NSCLC	27	ORR	DOR, PFS, OS	Yes
NCT02335944	Capmatinib + nazartinib	Phase II	NSCLC with EGFR mutations	177	ORR	Safety, dose interruptions, DCR, PFS, DOR, OS	No
NCT04139317	Capmatinib + Pembrolizumab	Phase II	NSCLC without EGFR or ALK mutations	76	PFS	ORR, DCR, OS, antidrug antibodies	No

(Continued)

Table 2 (Continued).

Trial	Drug	Design	Population	Number of Participants	Primary Outcome	Secondary Outcomes	Recruiting?
NCT02323126	Capmatinib + Nivolumab	Phase II	NSCLC cMET positive	64	PFS	AEs, ORR, DCR, OS	No
NCT03647488	Capmatinib + spartalizumab	Phase II	NSCLC without EGFR or ALK mutations, failed chemotherapy + immunotherapy	18	OS	ORR, DCR, PFS, DOR	No
NCT02795429	Capmatinib + Spartalizumab	Phase Ib/II	HCC	89	DLT, ORR	Best response, DOR, PFS, TTP	No
NCT01737827	Capmatinib	Phase II	HCC with MET dysregulation	38	TTP	ORR, PFS, OS, DCR, AEs	No
NCT03940703 INSIGHT	Tepotinib + Osimertinib	Phase II	NSCLC	120	ORR	AEs, CR, DOR, OS, PFS	Yes
NCT04739358	Tepotinib	Phase I/II	Tepotinib efficacy in stopping spread of lung cancer with CNS metastases	65	ORR	AEs, ORR, PFS, DOR, DCR, PK parameters	No
NCT03911193	Cabozantinib	Phase II	NSCLC with MET amplification or MET exon 14 skipping mutation	25	RR (CR + PR)	PFS, OS, DCR, biomarkers	Yes
NCT02920996	Merestinib	Phase II	NSCLC with MET exon 14 alterations or NTRK rearrangements	12	ORR	DOR, OS, tolerability	No
NCT04992858	Ningetinib	Phase II	NSCLC with MET exon 14 skipping mutations	80	Recommended dose and ORR	DOR, PFS, OS, DCR, AEs	No

MET Antibodies

Antibodies against MET bind to the sema domain for HGF binding. MET antibodies are proposed to increase receptor internalization and degradation, thus inhibiting the MET signaling pathway. Currently an IgG1 monoclonal antibody Sym015 (Symphogen, Copenhagen, Denmark) is being developed for METex14 NSCLC.

Amivantamab

Amivantamab (JNJ-61186372, Rybrevant, Janssen Biotech) is a bispecific antibody that simultaneously blocks EGFR and cMET receptors. Promising results from the phase I CHRYSALIS trial provided the basis for FDA accelerated approval of amivantamab. This study assessed 81 patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations after treatment with platinum-based chemotherapy. The authors found overall response rate of 40% with median duration of response of 11.1 months.⁶¹

Immunotherapy

Retrospective studies show that PD-L1 expression is high in METex14 NSCLC.⁷ Some studies have shown promise for monotherapy with immune checkpoint inhibitors in METex14 mutated cancers, however this data is retrospective and from small cohort sizes. MET activity in immune cells is associated with immune suppression⁶² and capmatinib activity has been shown to enhance the activity of immune therapies.⁶³ Indeed, in a post hoc analysis of the GEOMETRY phase II trial, patients previously treated with immune checkpoint inhibitors were significantly more sensitive to capmatinib than those treated with chemotherapy (64 vs 32%).⁶⁴ There may be a role of combinatory approaches with MET inhibitors and immunotherapy although (immune related) adverse events must be carefully monitored. Ongoing clinical trials are listed in Table 2.

Further clinical trials are needed in MET overexpression and amplified NSCLC. Compared to MET-mutated tumors, MET overexpressed and amplified tumors are anticipated to have lower response rates and shorter survival with MET inhibitors. The most appropriate definition (or cut-off) of MET overexpression or amplification as a potential biomarker needs to be further clarified.

Additionally, more research is needed into the role of both tepotinib and capmatinib in patients with metastatic brain lesions in the front line and refractory setting. Although brain metastases are common in lung cancer, the incidence of brain metastases in METex14 NSCLC is unknown. In the VISION trial, only 11% of patients had brain metastases at study entry.⁸ In the phase II GEOMETRY study, capmatinib showed encouraging results with a 54% intracranial response.⁴⁰

Conclusion

The approval of tepotinib and capmatinib has made metastatic METex14 an actionable oncogenic driver in NSCLC, identifying a new subset of patients eligible for targeted treatment options. Tepotinib and capmatinib are potent, highly selective MET inhibitors with robust response in NSCLC. Preclinical and clinical data have shown both tepotinib and capmatinib as effective and tolerable in NSCLC patients with METex14 skipping mutations. When used in combination with EGFR TKIs, MET targeted therapies have the potential to overcome resistance to these treatments driven through the MET signaling pathway. This is of particular importance as with the frontline use of osimertinib, T790M will no longer be the resistance mechanism and we should see an increase in MET pathway related resistance to EGFR TKIs. Additionally, resistance pathways to MET TKIs themselves and strategies to overcome them must be further evaluated.

Abbreviations

ALK, anaplastic lymphoma kinase; ALT, alanine aminotransferase; AUC, area under the curve; BRAF, v-raf murine sarcoma viral oncogene homolog B1; CI, confidence interval; Cmax, peak plasma concentration; CR, complete response; CYP3A4, cytochrome p450 3A4; DOR, duration of response; EGFR, epidermal growth factor receptor; FDA, food and drug administration; HGF, hepatocyte growth factor ligand; KRAS, Kirsten rat sarcoma virus; MET, mesenchymal epithelial transition; METex14, MET exon 14 skipping mutations; NGS, next generation sequencing; NRAS, neuroblastoma rat sarcoma virus; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression free survival; TKI, tyrosine kinase inhibitor.

Ethics Approval and Consent to Participate

This report did not meet criteria for IRB approval.

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