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REVIEW

Targeted Treatment of Non-Small Cell Lung Cancer: Focus on Capmatinib with Companion Diagnostics

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Abstract: *MET* dysregulation promoting tumorigenesis in non-small cell lung cancer (NSCLC) is associated with worse outcomes following chemotherapy as compared to non-driver mutated NSCLC and occurs either through mutations causing *MET* exon 14 skipping (*MET*ex14) or gene amplification and overexpression that result in enhanced receptor signaling. Capmatinib is the first FDA-approved targeted therapy for NSCLC with *MET*ex14 skipping mutations, approved in 2020. FoundationOne® CDx, a comprehensive genomic profiling test for solid tumors, was concurrently approved as a companion diagnostic for capmatinib use. The GEOMETRY mono-1 phase II trial of capmatinib monotherapy demonstrated an overall response rate (ORR) of 68% in treatment naïve (n=28) and 41% in pre-treated (n=69) *MET*ex14 skipping advanced NSCLC; in *MET* amplified advanced NSCLC (gene copy number ≥ 10) ORRs of 40% in treatment naïve and 29% in pre-treated disease was seen. This review outlines the clinical data supporting capmatinib approval in the treatment of NSCLC and FoundationOne® CDx approval as a companion diagnostic. We detail the practical clinical administration of capmatinib, including dosing and toxicity management, compare capmatinib to other approved and investigational MET-targeted therapies, discuss limitations of capmatinib, and highlight ongoing trials of capmatinib in combinatorial approaches.

Keywords: capmatinib, *MET* exon 14 skipping, non-small cell lung cancer, FoundationOne CDx

Introduction

In the era of precision oncology, many patients with NSCLC have benefited from an increasing number of targeted therapies against common driver mutations. At the same time, the field of cancer diagnostics is growing apace with molecular techniques like next-generation sequencing (NGS) that have paved the way for individualized cancer treatment in the clinic. New targeted therapies and companion diagnostics are being rapidly developed and approved for oncogene driven cancers that have previously lacked effective treatments, including NSCLC driven by aberrant MET activity.

MET is a proto-oncogene that contributes to both de novo tumorigenesis and drug-resistance in NSCLC due to gain-of-function alterations including *MET*ex14 or *MET* gene amplification.[1] Following results from the phase II GEOMETRY mono-1 open-label, multicenter clinical trial, capmatinib received accelerated FDA-approval in May 2020, alongside FoundationOne® CDx, as the first targeted therapy and companion

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diagnostic for *MET*ex14 skipping NSCLC.[2] In this review, we outline the preclinical, clinical, and safety data of capmatinib and describe data supporting FoundationOne CDx test as the companion diagnostic to capmatinib for *MET*ex14 NSCLC. We also discuss current ongoing trials and future directions for this promising therapeutic agent and alternative therapies for MET-driven NSCLC to provide clinical context for using capmatinib in this rapidly evolving field.

Pathogenesis, Diagnosis, and Prevalence of MET Alterations in NSCLC

Mesenchymal–epithelial transition (MET), a transmembrane receptor tyrosine kinase that binds the ligand hepatocyte growth factor (HGF), is expressed in many epithelial cell types and plays diverse roles in development and tissue regeneration.[3] In normal tissue, homodimerization and phosphorylation of MET results in activation of downstream RAS, PI3K-AKT, Wnt, and STAT growth signaling pathways. In MET-altered tumors, over-activation of these downstream pathways contributes to oncogenesis (Figure 1).[4,5]

MET dysregulation is both a primary oncogenic driver and a secondary resistance mechanism in many cancers contributing to tumor cell growth, survival, and invasion.[5] Two primary molecular mechanisms underlie oncogenic MET alterations: mutations causing *MET* exon 14 skipping and *MET* gene amplification, which have similar tumorigenic effects, yet distinct diagnostic and therapeutic considerations. *MET*ex14 skipping is a gain-of-function mutation caused by a wide variety of genetic alterations in splice sites surrounding exon 14 or within exon 14, which encodes a juxtamembrane domain ubiquitination site that acts as a key negative regulatory element to promote receptor degradation and prevent MET oversignaling.[6,7] This group of somatic mutations promotes aberrant *MET* transcription with fusion of exons 13 and 15, resulting in exclusion of the regulatory domain and upregulated signaling by the mutant MET receptor.[8] Due to the diversity of mutations causing *MET*ex14 skipping, NGS, which detects the various splice site mutations, and RT-PCR, which detects the truncated template after

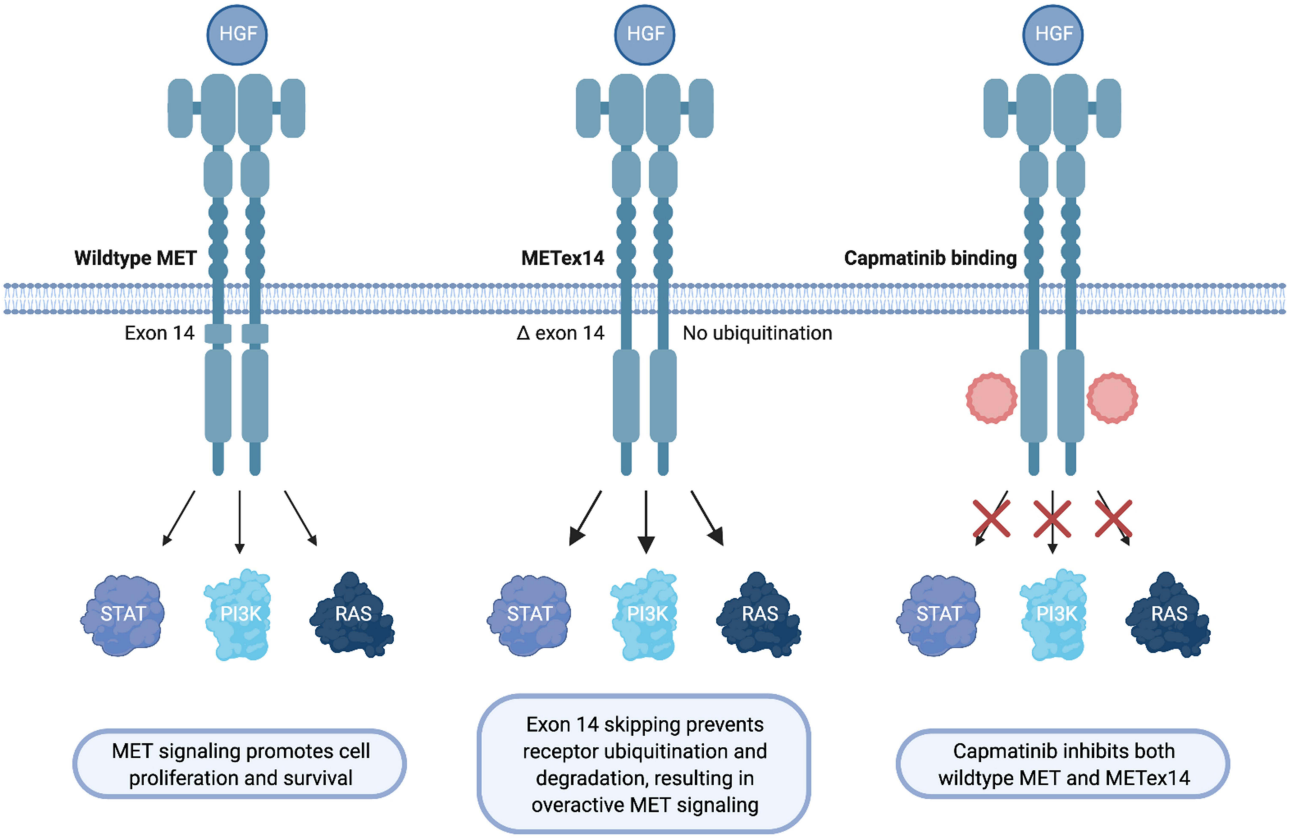

Figure 1 Capmatinib selectively targets MET on NSCLC tumor cells, inhibiting both wildtype and METex14 which lacks ubiquitination sites required for receptor degradation.

alternative splicing, are the most sensitive and comprehensive diagnostic tools for these mutations.[8,9] Diagnosis of *MET* amplification is defined by fluorescence in-situ hybridization (FISH) analysis reporting *MET*-to-chromosome 7 centromere (*MET*/*CEP7*) ratio or NGS reporting gene copy number (GCN) per cell. A previous study seeking to define *MET* amplification analyzed the mean *MET*/cell and mean *MET*/*CEP7* using FISH in 686 cases of NSCLC. The authors defined high amplification as *MET*/cell ≥7 or *MET*/*CEP7* ≥5, intermediate amplification as *MET*/cell ≥6 to <7 or *MET*/*CEP7* >2.2 to <5, and low amplification as *MET*/cell ≥5 to <6 or *MET*/*CEP7* ≥1.8 to ≤2.2. *MET*/cell <5 and *MET*/*CEP7* <1.8 were defined as no amplification. While the boundaries of amplification levels differ widely in the field, using these author-defined breakdowns between high, intermediate, and low amplification, the authors concluded that *MET*/cell ≥7 or *MET*/*CEP7* ≥5 were associated with the strongest responses to MET inhibition. They thus concluded that these diagnostic criteria are indicative of high *MET* amplification.[10]

In NSCLC, *MET* dysregulation is a prognostic biomarker associated with poorer outcomes.[11–13] *MET*ex14 most frequently presents as a primary driver mutation, occurring in 3–4% of patients with NSCLC overall and 8–22% of patients with the rare NSCLC subtype pulmonary sarcomatoid carcinoma.[7,14–16] The frequency of *MET* amplification in NSCLC is difficult to define given the varied definitions and cutoffs applied, but in one comprehensive analysis, *MET* amplification defined as *MET*/*CEP*7 ≥2.0 or *MET*/cell ≥6 occurred de novo in approximately 3% of treatment-naive patients with NSCLC.[17] MET amplification occurs more commonly as a resistance mechanism in approximately 20% of patients on anti-EGFR TKI therapies.[17,18] Concurrent MET amplification occurs in 15–21% of *MET*ex14 NSCLC,[14,19] while other driver mutations (ie, EGFR, ALK, ROS1, BRAF) are rarely found in *MET*ex14 tumors,[19] suggesting that *MET*ex14 skipping is an independent driver of oncogenesis. Brain metastases develop in 20–40% of patients with *MET*ex14 NSCLC, a frequency similar to that of all stage IV NSCLC.[20,21] Despite the prevalence of MET-driven NSCLC, prior to the approval of capmatinib for *MET*ex14 NSCLC in May 2020, targeted treatment had been primarily limited to off-label use of multi-kinase inhibitors crizotinib and cabozantinib.

Capmatinib for the Treatment of *METex14* Skipping and MET Amplified NSCLC

Capmatinib is a type I MET inhibitor with high potency (IC_{50} = 0.13 nmol/L) and selectivity.[22] The ATP-competitive TKI binds to both wild-type and exon 14 skipped MET protein products (Figure 1) and demonstrated selectivity for MET kinase and its disease variants in a screen of over 400 candidate kinases.[23] The medication is orally bioavailable and is metabolized primarily by CYP3A4 and aldehyde oxidase.[24]

Preclinical studies of capmatinib found that it effectively inhibited MET receptor signaling, halting tumor growth and inducing apoptosis. Capmatinib displayed activity in mouse xenograft models bearing tumors from lung and liver cancers with *MET*ex14 or *MET* amplification.[22,23] Treatment with capmatinib also restored sensitivity to erlotinib, an anti-EGFR TKI, in NSCLC cell lines that had acquired resistance post-TKI.[25] Interestingly, in vivo experiments studying capmatinib in combination with standard chemotherapy in mice found that capmatinib not only increased the antitumor efficacies of cisplatin and doxorubicin but also limited their respective nephrotoxicity and cardiotoxicity.[26]

A Phase I trial of capmatinib in MET-positive advanced NSCLC and other solid tumors determined the recommended Phase 2 dose of 400 mg tablets BID or 600 mg capsules BID.[27,28] The study demonstrated safety and clinical activity in predominantly pretreated patients (95% had received at least one prior line of systemic therapy) with various MET alterations including *MET*ex14 and amplification with GCN ≥ 6.[27] The most common adverse events (AEs) were GI-related toxicities and peripheral edema.

The therapeutic role of capmatinib in *MET*ex14 NSCLC was further established in the stage II, multicenter, open-label GEOMETRY mono-1 trial (NCT02414139) studying capmatinib in 364 patients in various cohorts segregated by *MET*ex14 status, *MET* amplification status, and number of previous systemic therapies (Table 1).[29] The strongest responses to capmatinib were in patients with treatment naïve *MET*ex14 NSCLC with an objective response rate (ORR) of 68%, median duration of response (DOR) of 12.6 months, and median progression-free survival of (PFS) 12.4 months. Treatment naïve NSCLC patients with high *MET* amplification (GCN ≥ 10) also had robust responses to

Table 1 Responses to Capmatinib by NSCLC Cohort from GEOMETRY mono-1[29]

Cohort	*MET* Alteration	Previous Treatment	ORR	Median DOR (Months)
Cohort 1a (n = 69)	Amplification GCN ≥ 10	Pretreated	29%	8.3
Cohort 1b (n = 42)	Amplification GCN 6–9	Pretreated	12%	24.9
Cohort 2 (n = 54)	Amplification GCN 4–5	Pretreated	9%	9.7
Cohort 3 (n = 30)	Amplification GCN < 4	Pretreated	7%	4.2
Cohort 4 (n = 69)	*MET*ex14 any GCN	Pretreated	41%	9.7
Cohort 5a (n = 15)	Amplification GCN ≥ 10	Treatment naïve	40%	7.5
Cohort 5b (n = 28)	*MET*ex14 any GCN	Treatment naïve	68%	12.6

Notes: From Wolf J, Seto T, Han J-Y, et al. Capmatinib in MET exon 14-mutated or MET-amplified non-small-cell lung cancer. N Engl J Med. 2020;383(10):944–957. Copyright © 2020 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[29]

capmatinib (ORR 40%, median DOR 7.5 months, median PFS 4.2 months).[29] Interim analysis of an expansion cohort, pretreated *MET*ex14 or GCN ≥ 10 patients (n = 34), revealed an ORR of 48%, and an additional cohort of treatment naïve *MET*ex14 patients (n = 23) is currently ongoing.[29]

Intracranial disease control of capmatinib was observed in 12 out of 13 response-evaluable patients in the GEOMETRY mono-1 trial with brain metastases at baseline. Seven of the 12 patients had an intracranial response, including four complete responses.[29] The observed intracranial activity of capmatinib thus addressed a treatment limitation of *MET*-dysregulated NSCLC with crizotinib, which has poor blood–brain barrier penetration.[30]

The most common AEs of any grade observed in the GEOMETRY mono-1 trial were peripheral edema (51%) and nausea (45%). Additional AEs occurring in more than 20% of patients included vomiting, increased serum creatinine, dyspnea, fatigue, and decreased appetite. Treatment-related AEs grade ≥ 3 occurred in 13% of patients, most commonly peripheral edema, dyspnea, and increased ALT. Dose reduction occurred in 23% of patients and discontinuation in 11%. One death due to pneumonitis was attributed to capmatinib treatment.[29]

A retrospective study of a subset of patients screened for the GEOMETRY mono-1 in Korea observed a median overall survival (OS) of 21.5 months among 8 patients with MET-driven tumors (*MET*ex14 or GCN ≥ 10) treated with capmatinib, as compared to median OS of 7.5 months for MET-driven tumors treated with standard chemotherapy regimens (n = 6), and 11.3 months among *MET* wild-type controls (n = 53) on standard chemotherapy.[31] This analysis highlights the ability of targeted therapy with capmatinib to overcome the poorer prognosis of *MET* dysregulated NSCLC.

Other clinical studies have focused on capmatinib as a salvage therapy for patients with MET-driven tumors who progress on standard TKIs. Among 15 patients with *MET*ex14 and 5 patients with *MET* amplified NSCLC pretreated with crizotinib, ORR to capmatinib was 10%, but disease control rate (DCR) was 80%, including stable disease in all 4 patients with intracranial metastases. Based on these modest results, the authors of the study suggest that capmatinib and crizotinib may have overlapping resistance mechanisms.[32]

FoundationOne® CDx as the Companion Diagnostic for Capmatinib in METex14 NSCLC

Prior to the approval of capmatinib, there was no approved standardized, comprehensive platform for diagnosing *MET*ex14 mutations, a challenging task given the diverse array of splice site mutations that could lead to exon truncation. FoundationOne CDx, an NGS-based diagnostic tool indicated and validated for all solid tumors, is currently the only FDA-approved companion diagnostic for capmatinib for *MET*ex14 NSCLC.[2]

FoundationOne CDx utilizes DNA extracted from formalin-fixed, paraffin-embedded tumor tissue specimens to detect indels and single nucleotide variants in 324 genes. FoundationOne CDx also reports on selected clinically relevant gene rearrangements, tumor microsatellite instability, and tumor mutational burden.[2] FoundationOne also offers a liquid biopsy diagnostic tool for cell-free tumor DNA (cfDNA) circulating in plasma, however this platform is not currently approved to identify *MET*ex14 skipping mutations.[33] Several institutions globally have conducted studies examining the clinical utility and cost-efficiency of FoundationOne CDx, finding that test utilization enhanced delivery of precision therapy with minimal

budget impact. These studies found that the utilization of comprehensive genomic testing for NSCLC had a budget impact per person per year of $0.71–0.8 with a 3-year gain of 680.9 life-years. FoundationOne CDx was found to have a 96.7% success rate, with earlier NGS testing maximizing clinical benefit. These studies prompted FoundationOne CDx to become a companion diagnostic for capmatinib for *MET*-dysregulated NSCLC.[34–36] Utilization of FoundationOne CDx as a companion diagnostic for other driver mutations in other solid tumors is currently being investigated, with mixed results suggesting potential applications in glioma and breast but limited utility in pancreatic ductal adenocarcinoma.[37–39]

Clinical Administration of Capmatinib and Management of Toxicities

Capmatinib is administered orally as 400 mg tablets BID or 600 mg capsules BID. The most prominent AEs associated with capmatinib treatment are nausea and peripheral edema. Other common AEs (defined as <20%) include diarrhea, fatigue, decreased appetite, and increased blood creatinine levels. Dyspnea occurs less commonly but was a treatment-related AE that contributed to the death of one patient in a phase Ib/II study of capmatinib plus gefitinib.[40]

Early management of low-grade toxicities is recommended to mitigate against more severe toxicities and preserve the ability to continue capmatinib therapy. Dose reductions first to 300 mg BID, then to 200 mg BID, with permanent discontinuation if 200 mg BID remains intolerable, are recommended for adverse event management.[24]

Peripheral edema and GI toxicity are recognized as class effects associated with MET inhibitors. Low grade peripheral edema can be treated initially with compression stockings, mobility, leg elevation, and dietary salt modification. Higher grade peripheral edema may require capmatinib dose reduction, and clinicians can consider trial of spironolactone or furosemide.[24,41,42] Taking capmatinib with food is recommended as studies with and without food restriction found that taking capmatinib with food decreased the incidence of GI toxicity without decreasing drug exposure.[29]

Patients should be closely monitored for symptoms of interstitial lung disease (ILD) and pneumonitis, such as dyspnea, cough, and fever. Any grade ILD/pneumonitis merits permanent treatment discontinuation if no other cause is identified due to the risk of death.[24,42]

Grade 3 hepatotoxicity with increased ALT and/or AST without increased total bilirubin merits withholding treatment until liver function has recovered to baseline followed by dose continuation or reduction. Treatment should be permanently discontinued for grade 4 hepatotoxicity, or grade 3 hepatotoxicity with increased total bilirubin.[24]

Capmatinib inhibits renal transporters MATE1 and MATE2-K causing the observed reversible elevated blood creatinine.[29] Although this may make the determination of renal function more challenging, increases in blood creatinine > 3 times the upper limit of normal were not reported, and no dosage adjustment was recommended with CrCl above 30 mL/min.

Capmatinib can increase the risk of photosensitivity, and so proper preventative and precautionary measures are indicated. Patients should mitigate ultraviolet exposure and utilize sunscreen and protective clothing. Finally, pregnant females should be advised of the risk of fetal harm, and both males and females with reproductive potential should be advised to use effective contraception while on capmatinib and for at least one week after ending capmatinib therapy.[42]

Capmatinib in Ongoing and Future Trials

A Phase III study GEOMETRY-III (NCT04427072) of capmatinib vs docetaxel in pre-treated patients with *MET*ex14 NSCLC began in September 2020. This study should provide further insight into how capmatinib compares to cytotoxic chemotherapy in the second line.[43]

Another area of interest for MET-targeted therapy is in patients with EGFR-driven tumors that develop MET amplification, a predominant bypass resistance mechanism in anti-EGFR TKI therapy. One early-phase trial combined capmatinib and gefitinib as salvage treatment in patients with acquired resistance to gefitinib, erlotinib, or afatinib, and found that the regimen was tolerable and observed an ORR of 27% with median DOR of 5.6 months and DCR of 73%.[40] In patients with high MET-amplified tumors (GCN ≥ 6) the ORR was 47%. Similarly, a case report described that capmatinib combined with high-dose osimertinib (160 mg) induced improvement both clinically and radiologically in one patient with *EGFR*-mutant NSCLC with secondary *MET* amplification who had previously

progressed on erlotinib, high-dose osimertinib, carboplatin plus pemetrexed, atezolizumab, and crizotinib.[44] The use of capmatinib combinations in post-EGFR TKI resistance is under further investigation in a phase III trial GEOMETRY-E (NCT04816214) studying capmatinib plus osimertinib vs platinum-pemetrexed doublet chemotherapy in the second line for *EGFR*-mutant, *MET* amplified NSCLC.[45] Combination therapy with capmatinib plus nazartinib, a current investigational third-generation anti-EGFR TKI that binds EGFR T790 similar to osimertinib,[46,47] is also being investigated in a phase Ib/II study (NCT02335944) in NSCLC patients with EGFR mutations.[48]

Capmatinib has also been implicated as an immunomodulatory agent through stabilization of PD-1, resulting in decreased T cell antitumor activity.[49] Immune checkpoint inhibitors such as nivolumab are known to overcome PD-1-mediated T cell anergy and promote antitumor activity. Preliminary findings presented at the 2020 IASLC Meeting from a phase II study (NCT02323126) of capmatinib plus nivolumab found an ORR of 25% in *MET* GCN ≥ 5 NSCLC patients (n = 16) and an ORR 17% in all other patients (n = 30).[50] The addition of anti-PD-1 agent spartalizumab to capmatinib for *MET*ex14 NSCLC in the first line is also under investigation in a randomized phase II trial NCT04323436.[51] Another phase II study (NCT04139317) is comparing pembrolizumab plus capmatinib to pembrolizumab alone in patients with NSCLC with PD-L1 expression > 50%.[52] Overall, these studies will better characterize the anti-tumor effects of immune checkpoint inhibitors in combination with capmatinib.

As *MET* dysregulation is a driver mutation and potentially an actionable biomarker in multiple cancers, capmatinib is also under investigation in other solid tumors with *MET* mutations such as advanced hepatocellular carcinoma (NCT01737827), glioblastoma multiforme (NCT02386826), and papillary renal cell cancer (NCT02019693). As more mature evidence for other tumor types is awaited, capmatinib in *MET*ex14 NSCLC remains the only approved MET-specific targeted therapy.

Comparisons to Other MET Targeted Therapies

Many novel targeted therapies are in the pipeline to address MET dysregulation as an independent oncogenic driver as well as a secondary resistance mechanism to EGFR-TKI therapy in NSCLC and other cancers (Table 2).

Crizotinib is a multi-kinase inhibitor approved for the treatment of advanced ALK and ROS-1 driven NSCLC, with activity against MET. In the PROFILE 1001 study, crizotinib resulted in an ORR of 32% in *MET*ex14 (n=65) and 38% in *MET* amplified (n=38) tumors (GCN ≥7). Median duration of response was 9.1 months and median PFS of 7.3 months for patients with *MET*ex14 tumors.[53,54] Cabozantinib is another non-selective TKI with reported activity and off-label use in MET-driven NSCLC, currently under investigation in the Italian CABinMET study (NCT03911193) in subjects with tumors harboring *MET*ex14 mutations or *MET* amplification.[55]

The phase II VISION study of tepotinib in *MET*ex14 skipping NSCLC found an ORR 46% and median DOR 11.1 months.[56] The phase Ib/II INSIGHT study (NCT01982955) found tepotinib plus gefitinib to be superior to platinum-pemetrexed duet chemotherapy (ORR 45% vs 33%) for pretreated EGFR-positive NSCLC, particularly for tumors with *MET* amplification.[57] The most common AEs in tepotinib included peripheral edema and elevated serum amylase. Grade ≥ 3 TRAEs occurred in 28% of patients, in contrast to 37% of patients receiving capmatinib in the GEOMETRY mono-1 trial. The VISION and INSIGHT trials, along with three separately published case reports, have also indicated that tepotinib has intracranial activity.[56–60] These findings prompted FDA accelerated approval for tepotinib for *MET*ex14 skipping NSCLC in February 2021.[61] Future studies evaluating genomic or other clinical determinants of response may help better differentiate the two promising drugs.

Savolitinib is a MET-selective TKI that has activity in *MET*ex14 pulmonary sarcomatoid carcinoma, an NSCLC histology enriched for *MET*ex14, and other NSCLCs. Preliminary data from a phase II trial (NCT02897479) found an ORR of 47.5% and median DOR not reached among 61 evaluable patients, with similar AEs including peripheral edema, nausea and vomiting, elevated AST/ALT, and hypoalbuminemia.[62] CNS activity of savolitinib is yet to be fully described. For secondary *MET* amplification in pretreated EGFR-mutated NSCLC, the combination of savolitinib plus osimertinib achieved an ORR of 48% with median DOR of 9.5 months.[63] The results of this trial as well as the capmatinib plus osimertinib and capmatinib plus nazartinib trials are highly anticipated to understand whether the MET selective TKIs are tolerable and effective in combination with third-generation EGFR TKIs.

Table 2 Clinical Trials Investigating Monotherapies for *MET*ex14 NSCLC

Drug	Trial	Phase	N	Mechanism of Action	ORR for Treatment Naïve *MET*ex14 NSCLC	ORR for Pretreated *MET*ex14 NSCLC	Grade ≥ 3 TRAEs
Capmatinib[29]	GEOMETRY mono-1	II	364	Selective MET TKI	68%	41%	37%
Crizotinib[53]	PROFILE 1001	I	65	Multikinase TKI	25%	37%	29%
Tepotinib[56]	VISION	II	152	Selective MET TKI	44%	48%	28%
Savolitinib[62]	NCT02897479	II	70	Selective MET TKI	46%	40%	41%
Bozitinib[64]	NCT02896231	I	11	Selective MET TKI	NA	67%	27%

Bozitinib, another MET selective TKI, achieved an ORR of 31% in patients with MET dysregulated NSCLC, though subgroup analysis found that *MET*ex14 and *MET* amplification cohorts had higher ORRs at 67% and 41%, respectively, as compared to MET overexpression. Treatment AEs that occurred in more than 20% of patients included ALT/AST increase, bilirubinemia, peripheral edema, and QTc elongation.[64] This study excluded patients with brain metastases, so intracranial of bozitinib has not yet been assessed.

Two novel multi-kinase inhibitors with MET activity, glesatinib and merestinib, are under study for MET-driven NSCLC.[65,66] Glesatinib and merestinib are ATP-competitive type II MET TKIs that bind to the adenine-binding site, while capmatinib is an ATP-competitive type I MET TKI that interacts with the Y1230 residue to lock the kinase in an autoinhibitory conformation.[67] Glesatinib is of particular interest as it was found to have activity in vitro against MET with D1228 and Y1230 mutations that are typically associated with MET-TKI resistance.[66] In pretreated NSCLC, ORR to glesatinib was 14% in 36 patients with *MET* activating mutations and 9% in 32 patients with *MET* gene amplifications. Common AEs were similar to those of capmatinib and included diarrhea, nausea/vomiting, fatigue, increased ALT/AST, peripheral edema, fatigue, dyspnea, hypokalemia, and hypomagnesemia.[68] Merestinib demonstrated safety and clinical efficacy in a phase I trial and is currently being studied in a phase II study of pretreated *MET*ex14 NSCLC (NCT02920996).[69] Intracranial activity has not been assessed for either merestinib or glesatinib.

Several antibody-based anti-MET therapies are in development and under investigation at NSCLC as well. Of note, antibody-based therapies require IV infusion, which may represent a barrier compared to capmatinib, an oral medication. Telisotuzumab vedotin (teliso-v) is an antibody–drug conjugate (ADC) coupling an anti-MET antibody with the tubulin inhibitor MMAE. In pretreated patients with *EGFR* wild-type NSCLC, telisotuzumab vedotin achieved an ORR of 54% in a MET-high expressing cohort and 25% in a MET-intermediate cohort.[70]

Amivantamab is a bispecific EGFR/MET antibody that received FDA accelerated approval for *EGFR* exon 20 insertion mutated NSCLC, and the ongoing CHRYSALIS trial explores its use in MET dysregulated NSCLC in both *MET*ex14 and post-EGFR-TKI *MET* amplified cohorts.[71] Emibetuzumab is a bivalent MET/MET antibody that, when added to first-line erlotinib, increases ORR from 66% to 85% in EGFR-mutated NSCLC.[72] Another bivalent MET/MET antibody, REGN5093, is currently being studied in a first-in-human phase I/II trial for *MET*ex14 or *MET* amplified NSCLC.[73] Sym015, an antagonistic antibody mixture of two non-overlapping anti-MET monoclonal antibodies, has demonstrated promising antitumor effects in preclinical models.[74] A phase Ia/IIa trial found ORRs of 25% for both *MET*ex14 and *MET* amplified NSCLC,[75] suggesting that unlike for capmatinib, *MET*ex14 skipping mutations do not prognosticate for superior outcomes with Sym015 treatment as compared to other *MET* dysregulations. All these antibodies are expected to have poor blood-brain barrier penetration, and so further studies, potentially in combination with capmatinib or other TKIs, will provide greater insight into their utilities in targeting *MET* dysregulated NSCLC.

Limitations and Resistance to Capmatinib

As an anti-MET TKI, capmatinib can be selected for resistance due to alterations in MET kinase, bypass pathway activation, or ligand upregulation. Mutations in D1228 of the kinase domain and Y1230 of the activation loop have been identified as mechanisms of resistance in patients who progress on capmatinib treatment.[32,76,77] Alterations in MAPK, EGFR, and KRAS, as well as upregulation of the MET ligand HGF have also been suggested as potential bypass pathway mechanisms for anti-MET TKI therapy.[78–81] Treatment of post-capmatinib may thus require switching to a type II TKI (eg cabozantinib, glesatinib, merestinib), which are hypothesized to have activity against D1228 and Y1230 mutations, bypass pathway targeted therapy, or anti-HGF therapy.[82,83]

Conclusion

As the first FDA-approved targeted therapy and companion diagnostic for NSCLC with *MET*ex14 skipping mutations, capmatinib and FoundationOne® CDx address an unmet need in oncology for the diagnosis and treatment of tumors with *MET*ex14 skipping mutations. Furthermore, MET-directed therapy with capmatinib has demonstrated efficacy in tumors with *MET* amplification, both de novo amplification and secondary amplification most commonly observed as a mechanism of anti-EGFR TKI resistance, though it is not yet approved for use in these settings. The toxicity profile of capmatinib is manageable, with peripheral edema and nausea most commonly reported across all anti-MET TKIs. Compared to other MET TKIs under investigation, capmatinib demonstrates robust clinical efficacy with similar toxicity profiles. Ongoing studies of capmatinib in combination therapy with immune checkpoint inhibitors and anti-EGFR TKIs and will be closely followed to better characterize the role of capmatinib in treating MET-driven NSCLC.

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