Narrative review: mesenchymal-epithelial transition inhibitors—meeting their target

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Abstract: Genetic alterations in mesenchymal-epithelial transition (MET) are commonly found in solid tumors, especially in non-small cell lung cancer (NSCLC). However, agents targeting MET have not progressed until recently. Advancements in our understanding of the role of various *MET* aberrations in carcinogenesis have allowed MET-directed therapy to find its way to clinic use. Of all *MET* alterations, *MET* exon 14 skipping (*METex14* skip⁺ or *MET*^Δ14), stands out as a true oncogenic driver. Recently, MET tyrosine kinase inhibitors (TKI) targeting *METex14* skipping were able to demonstrate significant improvement in clinical outcomes including response rate and progression free survival. Of these, capmatinib was granted accelerated approval by the FDA in May 2020 for patients with advanced NSCLC harboring *METex14* skip alterations. Tepotinib, another TKI, has shown significant activity in a phase II trial and received breakthrough therapy designation from the FDA in September 2019. *MET* amplification (*MET*^Amp) and overexpression are usually a late phenomenon in tumorigenesis and aggravate malignant properties of transformed cells. Capmatinib and savolitinib have shown activity in patients with NSCLC with high levels of *MET*^Amp. Several other agents are being developed and under evaluation in clinical trials involving multiple tumor types. In addition to TKIs, MET overexpression is also an appealing target for development of antibody conjugated chemotherapy. Understanding the mechanisms of resistance to MET TKIs and alterations in anti-tumor immunity through MET inhibition are clinically relevant areas that need further exploration.

Keywords: Mesenchymal-epithelial transition (MET); METexon14 skipping; non-small cell lung cancer (NSCLC)

Introduction

Receptor tyrosine kinases (RTK) regulate vital cellular processes in both physiologic and pathologic conditions. Mesenchymal-epithelial transition (MET) kinase is a unique RTK that has pleiotropic effects. Under physiologic conditions, MET kinase reprograms certain cells to detach from tissues, helps them survive without a matrix, and through these effects assists them in migrating and facilitates their proliferation at new or different sites. This process is common during human development and evident in adult life during wound repair. This is referred to as 'invasive growth' or 'epithelial-to-mesenchymal transition' (1-3). It is a canonical attribute of malignancy where properties of cell-stemness and dissemination are activated concomitantly. Constitutive or aberrant activation of MET kinase can trigger and/or sustain malignant processes. Abnormal activity of MET kinase enables cancer cells to adopt unfavorable circumstances and it is common in various

types of malignancies (1,3). Though *MET* alterations occurs in various malignancies, however they have emerged as an important target for therapy in non-small cell lung cancer (NSCLC). In recent years, significant progress has been made in this regard. This review focus on the importance of *MET* alterations in NSCLC and provide an update on drugs targeting MET. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/tlcr-20-588).

MET receptor and pathway

MET is a cell surface RTK encoded by the *MET* proto-oncogene, located on chromosome 7q21-31. It is expressed in the epithelial cells of many organs including lungs, liver, pancreas, prostate, kidneys, muscle, and bone marrow, during both embryogenesis and adulthood. MET receptor is a disulfide-linked heterodimer consisting of α- and β-chains. The α-chain is present only extracellularly and is heterodimerized to the amino-terminal of the β-chain to form the Semaphorin domain which serves as a ligand-binding site. The β-chain has three extracellular domains: semaphorin, plexins, semaphorins and integrins (PSI) and immunoglobulin-plexin-transcription (IPT), and a transmembrane domain. The β-chain also has three intracellular regions: the juxtamembrane region containing the receptor downmodulation c-Cbl-binding domain, the kinase domain (catalytic region) and the carboxy-terminal tail, essential for downstream signaling (docking region). Hepatocyte growth factor (HGF) is the ligand for the MET receptor and induces homodimerization and phosphorylation of two tyrosine residues (Y1234 and Y1235) within the catalytic region, which regulate kinase activity. The carboxy-terminal tail includes tyrosine residues (Y1349 and Y1356) and serves as a docking site upon phosphorylation for intracellular adaptor proteins, leading to downstream signaling through MAPK/RAS, PI3K/Akt, STAT3/5, Wnt/catenin and FAK pathways as shown in *Figure 1* (1-3).

MET alterations in NSCLC

Dysregulation of the MET pathway in cancer can occur through a variety of mechanisms including gene mutation, amplification (*Amp*), rearrangement, and protein overexpression (1,2,4). Both germline and sporadic *MET*-activating point mutations have been identified in renal papillary carcinomas; however, these are rare in NSCLC

(5,6). *MET*-rearrangement is also an extraordinarily rare oncogenic event in NSCLC and has been reported in only a few cases to date (7). Relevant alterations of *MET* in NSCLC include *MET* exon 14 skipping mutation (*METex14* skip$^+$) and *MET*^{Amp}.

In 1994, Lee *et al.* reported an alternatively spliced short variant of MET RTK in mice which lacked the 47-amino acid juxtamembrane region of the MET receptor (8). The deleted part of the receptor contains the Y1003 residue, which serves as the binding site for E3 ubiquitin ligase c-Cbl, required for degradation and internalization of MET RTK. Subsequently, mutations in the *METex14* splice sites were reported by Ma and colleagues in small cell lung cancer in 2003 and in NSCLC in 2005 (9,10). The significance of these splice site mutations, either a single nucleotide substitution or small deletions in the 5' and 3' splice sites, can lead to 'skipping of exon 14' which encodes the juxtamembrane region and thus abolishes the c-Cbl E3 ligase binding site, resulting in decreased ubiquitination and relative increase of MET protein levels on cell surfaces (*Figure 1*) (11). Studies have found that the frequency of *METex14* skipping alterations in lung cancer is about 2–4%; however, the prevalence is higher in adenosquamous and sarcomatoid histologies (8.2% and 7.7%, respectively) (12-14). *METex14* skipping is mutually exclusive to other oncogenic drivers like *EGFR*, *ALK*, *RET* and *ROS-1* in NSCLC apart from *KRAS* as described later in this review.

MET overexpression and amplification without exon 14 skipping is usually a late phenomenon in tumor carcinogenesis, including NSCLC. *MET* is transcriptionally induced by hypoxia, NF-κB, inflammatory cytokines and pro-angiogenic factors present in the reactive stroma of NSCLC and leads to increased MET expression. However, genomic instability or unfavorable circumstances in the tumor microenvironment in an established NSCLC can lead to *MET*^{Amp} with or without MET overexpression. Both events aggravate intrinsic malignant properties of transformed cells and convey anti-apoptotic and migratory signals by activating multiple signaling pathways including MAPK, PI3K, STAT3/5, and others (2,3). *MET*^{Amp} with or without overexpression contributes to 15% of all cases of acquired resistance to third-generation EGFR TKI in patients with NSCLC harboring sensitizing *EGFR* mutations (*EGFR*^{m}) (15,16).

Targeting MET in NSCLC

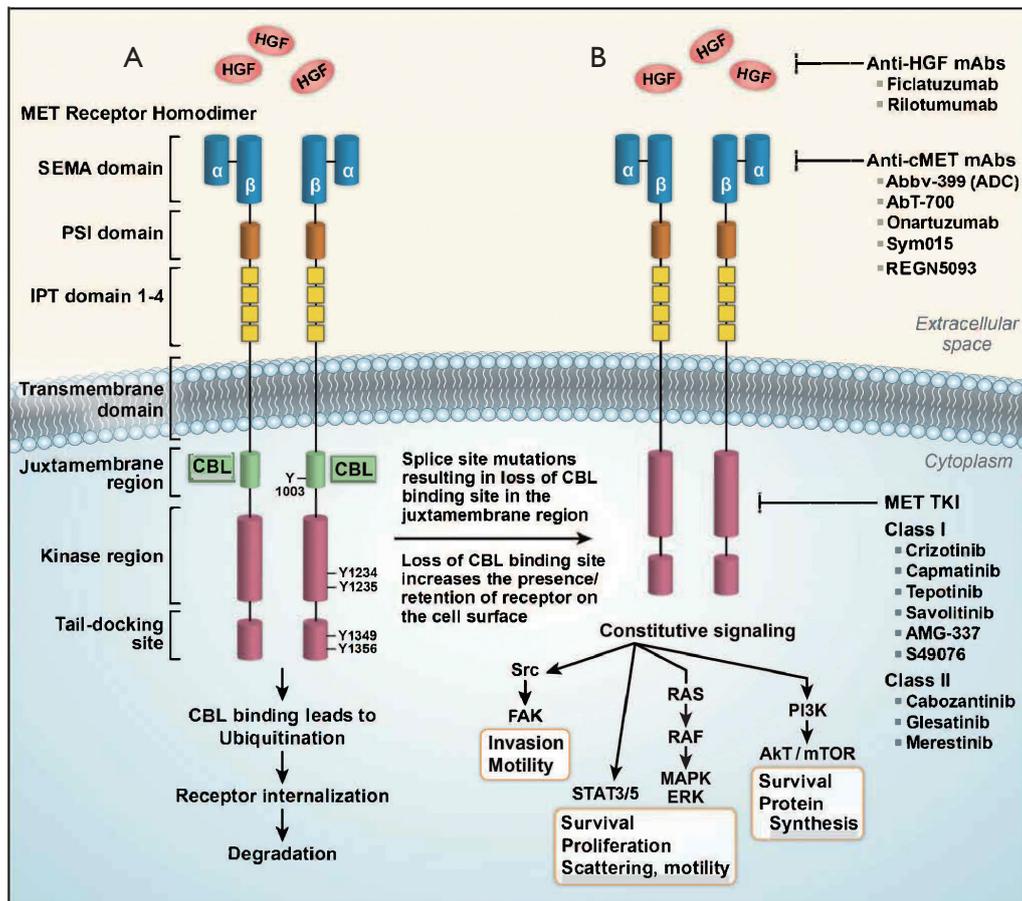Targeting abnormally active MET with monoclonal

Figure 1 Schematic representation of MET receptor (left panel, A), homodimer with various domains and regions. The wild-type MET receptor is activated by hepatocyte growth factor (HGF). Genomic aberration at the splice sites, resulting in in-frame skipping of the juxtamembrane region encoded by exon14 lead to loss of CBL binding site as shown in the right panel (B). MET, mesenchymal-epithelial transition; Y-, tyrosine residues at various positions; TKI, tyrosine kinase inhibitor; mAbs, monoclonal antibodies; ADC, antibody conjugated chemotherapy.

antibodies (mAbs) and tyrosine kinase inhibitors (TKIs) in lung cancer has been studied for many years (13). Many early studies targeting *MET* alterations in NSCLC focused on *MET* amplification or overexpression and only showed modest, if any, benefit. This is at least partly because *MET* Amp or overexpression represented a late event in tumorigenesis and occurred to overcome unfavorable tumor microenvironments as opposed to representing a true oncogenic driver. In addition, validated tests confirming overexpression and especially amplification were not included in many of those studies (15). Several recent studies have prioritized *METex14* skipping as a target in NSCLC and have shown promising efficacy in early phase studies.

Broadly, the MET TKIs can be divided into types I, II and III (17). Types I and II confer MET inhibition by competing with ATP for binding to MET pockets. Type III are not ATP competitive, but bind to allosteric MET sites, e.g., tivantinib (ARQ 197, ArQule, Woburn, MA). Type I compounds occupy the ATP binding pocket and typically interact with methionine 1,160 residue via hydrogen bonds and π-stacking with Tyr1230. These compounds preferentially bind to inactive conformation of the MET kinase. Type II inhibitors are also ATP-competitive and bind to the ATP adenine binding site and extend to the deep hydrophobic Ile1145 subpocket near the C-helix region. These compounds have relatively higher molecular weights, possess lipophilic properties and are less selective compared

to type I inhibitors, e.g., cabozantinib, merestinib, and others. The different binding sites of MET inhibitors can also be exploited to overcome resistance to certain types of inhibitors (18).

Among the various *MET* aberrations, MET inhibitors are showing promising activity in early phase clinical trials against *METex14* skip[+] NSCLC (19,20). Below we have summarized clinical profile of such drugs (*Table 1*) and described a few newly developed agents seems encouraging in phase I studies in targeting various MET alterations. We searched the literature using the following terms: MET inhibitor, MET TKI, targeting MET and MET antibodies. Our search include PubMed database, abstracts and posters presented at various scientific meetings of American Society of Clinical Oncology (ASCO), American Association of Cancer Research (AACR), European Society for Medical Oncology (ESMO), and International Association of Study of Lung Cancer (IASLC) from January 2005 through June 2020.

Targeting MET by TKI

Type I TKIs

Crizotinib (Xalkori®, PF-02341066): Crizotinib is an approved TKI for the treatment of advanced stage *ALK* or *ROS1* rearranged NSCLC. It is also a potent MET inhibitor (28,29). Many case reports and series have shown promising activity in NSCLC patients with *METex14* skipping (30-36). The PROFILE 1001 (NCT00585195) is a phase I trial of crizotinib in advanced cancers (37). Of the 69 evaluable patients with *METex14* skip[+] NSCLC, the objective response rate (ORR) was 32%. Three patients had complete response (CR). Median time to response (TTR) was 7.6 weeks and median duration of response (mDoR) was 9.1 months. *METex14* skipping was detected in ctDNA in 48% of the patients. METROS (NCT02499614) is an ongoing phase II trial of crizotinib in pretreated advanced stage NSCLC with *ROS1* or *MET* alterations, including *METex14* skipping (21).

The toxicity profile of crizotinib in NSCLC is well defined from *ALK*[+] NSCLC clinical trials (22). Most grades 1–2 adverse events (AEs) that were reported in ≥20% of patients included vision disturbances, diarrhea, peripheral edema, vomiting, constipation, elevated aminotransferases, dysgeusia and headaches. Grades 3–4 toxicities that occurred in 10% or more patients include elevation of aminotransferases and neutropenia; however, these are usually managed with temporary dose interruptions and reduction. Fatal pneumonitis is also described but few patients require permanent discontinuation of the drug in cases of grades 2–4 pneumonitis.

Capmatinib (INC280): capmatinib is a potent and highly selective MET kinase inhibitor with an IC50 value of 0.6 nM. The GEOMETRY mono-1 study is a phase II trial of capmatinib with multiple cohorts, including treatment-naïve and pretreated patients with NSCLC harboring *METex14* skipping or amplifications (19). Capmatinib was given orally at 400 mg twice daily. Of 97 patients with *METex14* skipping, 28 were treatment-naïve (cohort 5b) and 69 had received prior treatments (cohort 4). The primary endpoint was ORR, which was 67.9% (mDoR = 11.1 months) and 40.6% (mDoR =9.7 months) in the treatment-naïve and previously treated patients, respectively. Median progression-free survival (mPFS) was 9.7 and 5.4 months for systemic therapy-naïve and previously treated patients, respectively. There were 13 evaluable patients with brain metastases at baseline. Confirmed intracranial response rate was observed in 7 of 13 patients (54%), 4 of whom achieved CR. Cohort 1a (pretreated) and 5a (treatment naïve) enrolled 69 and 16 evaluable patients, respectively, with high levels of MET^{Amp} [gene copy number (GCN) ≥10]. The ORR in pretreated and treatment naïve patients with MET^{Amp} was 29% and 40%, respectively. Median PFS in both high MET^{Amp} cohorts was similar (4.07 *vs.* 4.17 months) (23). Grade ≥3 AEs included peripheral edema (7.5%), fatigue (3%), nausea (1.8%) and vomiting (1.8%). Treatment discontinuation due to treatment-related AEs occurred in 11.1%, most commonly due to peripheral edema, pneumonitis and fatigue. Based on this data, capmatinib was granted a priority review in February 2020 by the FDA for *METex14* skip[+] NSCLC in the first-line setting.

Another phase II trial (NCT02750215) is evaluating capmatinib for *METex14* skip[+] NSCLC in patients who have received prior MET inhibitors as their immediately preceding therapy. Capmatinib is also undergoing testing in combination with gefitinib in *EGFR*[m] NSCLC with MET^{Amp} following progression on EGFR TKI (NCT01610336). Some data suggest that MET signaling is also involved in facilitating an immunosuppressive tumor microenvironment. It has also been postulated that MET inhibitors could enhance dendritic cell function (38). *METex14* skip[+] cancer expresses high levels of PD-L1, yet this does not translate into significant clinical benefit with

Table 1 Reported activity of MET inhibitors in NSCLC patients harboring MET alterations

Drug, Study	Type of inhibitor (I–III)	MET kinase IC50 (nM)	Other kinases IC50 (nM)	Study type	Sample size (n)	Outcomes	Comments
Crizotinib NCT00585195, NCT02499614 (21,22)	I	8–11	ALK 24–60; ROS1 55	Phase I	65 (efficacy evaluable)	• ORR 35% • mPFS 7.3 mos • mDOR 9.1 mos	Time to response: 7.6 wks
				Phase II	26: 10 + $MET^{\Delta14}$; 16 + MET^{Amp}	ORR • MET^{Amp}: 31.3% • $MET^{\Delta14}$: 20% mPFS • MET amplification 5 mos • METex14 skip+ 2.6 mos	• Two-arm phase II study in patients with ROS1 and MET alterations • Patients with both MET amplification and METex14 skip+ included
Capmatinib NCT02414139 (19,23)	I	0.6	Highly selective for MET	Phase II	97: + $MET^{\Delta14}$; 28 treatment naïve, 69 previously treated	Treatment naïve • ORR 67.9% • mPFS 9.7 mos • mDOR 11 mos Pre-treated • ORR 40.6% • mPFS 5.4 mos • mDOR 9.7 mos	• Multi-cohort study • Demonstrated CNS activity • ORR in pretreated and treatment naïve patients with MET^{Amp} was 29% and 40% respectively
Tepotinib NCT02864992 (20)	I	1.7	Highly selective for MET	Phase II	87: 33 treatment naïve, 54 prior treated	• Treatment naïve, ORR 44–58.8% • Pre-treated, ORR 45% • mDOR 14.3 mos • mPFS 9.5–108 mos	• Two-cohort study, only METex14 skipping cohort results available • Patients with both tissue- or plasma-based assay included
Savolitinib NCT02897479 (24)	I	3–5	Highly selective for MET	Phase II	28 (efficacy evaluable)	• ORR 57.1% • Confirmed RR 42.8%	Interim results

Table 1 (*continued*)

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Drug, Study	Type of inhibitor (I–III)	MET kinase IC50 (nM)	Other kinases IC50 (nM)	Study type	Sample size (n)	Outcomes	Comments
AMG-337 NCT02016534 (25)	I	1	Highly selective for *MET*	Phase II	54 (efficacy evaluable)	• Cohort 1, ORR 18% • Cohort 2, no responses • mPFS 3.4 mos	• Cohort 1: gastric/gastroesophageal tumor with MET amplification (>2 GCN; n=45) • Cohort 2: other solid tumors with MET amplification (n=15) • Study terminated due to lower than expected efficacy
Cabozantinib NCT03911193	II	1.3	VEGFR 0.035; ROS1 <25; KIT 4.6; RET 5.2; AXL 7; FLT3 11.3	Phase II	25	Not available	• Ongoing Possible CNS activity
Glesatinib NCT02544633 (unpublished data from clinicaltrials.gov)	II	1	AXL 1; VEGFR 3; RON 2; TIE2 7	Phase II	68	Two $MET^{\Delta 14}$ + cohorts • ORR 10%, 25% mPFS 3.95, 3.4	Four cohorts: two with METex14 skip+, two with MET amplifications
Merestinib NCT02920996	II	35–60	FLT3 7; AXL 2; ROS1 23; DDR1 0.1; DDR2 7	Phase II	12	Not available	Ongoing
Sym015 NCT02648724 (26)	Humanized antibody mixture	NA	NA	Phase I/II	45 treated; 18 evaluable for efficacy	Includes both $MET^{\Delta 14}$ MET^{Amp} ORR was 25% regardless of	Ongoing
Telizotuzumab Vedotin NCT02099058 (27)	Antibody-drug conjugate	NA	NA	Phase I	48: includes 16 NSCLC with MET overexpression	ORR 6.3% (18.8% in NSCLC)	First in-human, phase I dose-escalation and expansion study

NSCLC, non-small cell lung cancer; nM, nano-molar; $MET^{\Delta 14}$, MET exon 14 skipping alteration; MET^{Amp}, MET amplification; ORR, objective response rate; mPFS, median progression-free survival; mDOR, median duration of response; RR, response rate; NA, not applicable; CNS, central nervous system; wks, weeks; mos, months.

immunotherapies. In a study with *METex14* skip⁺ NSCLC, incidences of PD-L1 expression of 0%, 1–49%, and ≥50% were 37%, 22%, and 41%, respectively, in 111 evaluable tumor samples (39). In response-evaluable patients (n=24), ORR was 17% with mPFS of 1.9 months in those who received single-agent or combination immune checkpoint inhibitors. PD-L1 expression did not influence outcomes. Another study (NCT04139317) is evaluating capmatinib in combination with pembrolizumab in NSCLC patients with high PD-L1 expression in the first-line setting to explore the interaction between the MET pathway and the immune-tumor microenvironment.

Tepotinib (MSC2156119, EMD1214063): tepotinib is a potent MET kinase inhibitor with an IC50 value of 1.7 nM. The phase II VISION trial (NCT02864992) is currently evaluating tepotinib in 87 treatment-naïve and previously treated patients with *METex14* skip⁺ NSCLC as confirmed by liquid or tissue biopsy (20). Tepotinib is administered orally as a 500 mg once daily dose. The primary objective is ORR which, to date, is 50% in patients who were *METex14* skip⁺ according to liquid biopsy and 45.1% in tissue biopsy patients. The most recent data reported included mDoR in the liquid biopsy and tissue biopsy groups as 12.4 and 15.7 months, respectively. Median PFS was 9.5 and 10.8 months in the liquid and tissue biopsy groups, respectively. Similar benefit has been seen in patients with CNS metastases. AEs of any grade have been found in 81.6% and grades ≥3 in 19.5% of patients. The most common AE, peripheral edema, occurred in almost 50% of patients and led to drug discontinuation in 4 (in 1 patient due to interstitial lung disease). Other less frequent AEs (grade 3 in less than 5%) included nausea, vomiting, diarrhea, and increased pancreatic and liver enzymes. Tepotinib was granted breakthrough therapy designation by the FDA in September 2019 for patients with *METex14* skip⁺ NSCLC after failure of platinum-based therapy.

Savolitinib [AZD6094, Volitinib (HMPL-504)]: savolitinib is an oral, highly potent and selective MET TKI with an IC50 value of 3–5 nM (40). The recommended phase II dose (RP2D) for savolitinib was established at 600 mg once daily in a phase I study (41). It has demonstrated anti-tumor activity in MET-driven papillary renal cell carcinoma (5). In a phase II clinical trial (NCT02897479) savolitinib is being evaluated in *METex14* skip⁺ NSCLC. Interim data has been reported (24). Of 70 patients treated, 35.7% had sarcomatoid histology, and 60% received prior treatments. Sixty-one patients were evaluable for response, of whom 47.5% achieved confirmed partial

response (PR). The mPFS was 6.8 months. The most common treatment-related AEs (≥20%) were nausea, vomiting, peripheral edema elevation of liver enzymes and hypoalbuminemia. A total of 41.4 of the patients had grades ≥3 treatment-emergent AEs, and 14.3% discontinued savolitinib due to toxicity, most commonly drug-induced liver injury. Savolitinib has been evaluated in a phase Ib study (TATTON) in combination with osimertinib in patients with *EGFRᵐ* NSCLC and *MET*^Amp (16). A total of 186 patients were enrolled in various cohorts including 2 expansion cohorts (parts B and D). Grades ≥3 AEs were observed in 79 of 138 patients (57%, part B) and 16 of 42 patients (38%, part D) who received 600 mg (8 patients in part B received 300 mg of savolitinib) and 300 mg of savolitinib once a day, respectively. ORRs were 48% in part B and 64% in part D.

AMG-337 (Amgen): AMG-337 is an oral MET TKI. In a phase I trial, AMG-337 RP2D was established at 300 mg once daily (42). Headache was the most common dose-limiting toxicity. AMG-337 showed an ORR of 29.6% in *MET*-amplified tumors with mDoR of 6.6 months. A multicohort phase II study evaluated AMG-337 in 60 heavily pretreated patients with *MET*^Amp (>2 GCN) tumors (25). Cohorts 1, 2A, and 2B enrolled 45 patients with gastric, gastroesophageal or esophageal tumors and cohort 2C enrolled 15 patients with other solid tumors. The primary endpoint of this study was ORR. This study was terminated early due to lower than expected efficacy in the phase I study. The ORR was 18% in patients with GI tumors while no patient achieved PR in cohorts of other solid tumors. Fifty-four patients were included in PFS and OS analyses. Median PFS and OS were 3.4 and 7.9 months, respectively. Another trial is currently evaluating AMG-337 in patients with clear cell sarcoma harboring *ESWR1-ATF1* gene fusion (NCT03132155).

S49076: S49076 is a potent ATP-competitive TKI that targets MET, AXL and FGFR1, 2, and 3 at clinically relevant doses. In a phase I study, peripheral edema and hypoalbuminemia were the most common drug-related AEs. RP2D was defined at 600 mg once daily as monotherapy (43). S49076 has also been evaluated in a phase Ib study in combination with gefitinib to overcome acquired resistance to EGFR TKI (first/second generation) (44). Of 17 enrolled patients, 12 had MET overexpression/ amplification, 4 had both MET and AXL overexpression, and 1 of 17 had AXL overexpression only. The most frequent drug related AEs included fatigue, diarrhea, nausea and paronychia. Among eight response evaluable patients,

one had PR, six achieved SD and one progressed.

Type II TKIs

Cabozantinib (XL184, Cabometyx®, Cometriq®): Cabozantinib is an oral TKI currently approved for advanced renal cell, hepatocellular and medullary thyroid cancers. It is currently under investigation in multiple clinical trials to explore its role in the treatment for *METex14* skip⁺ NSCLC as it has shown promising results in case series (35,45). Cabozantinib has been studied in a randomized phase II trial in non-selective patients with NSCLC along with a cohort of nine other tumor types (46). Co-primary end points were ORR PFS at 12 weeks after randomization. In 60 NSCLC patients who received 2 prior lines of therapy, ORR at week 12 was 10% and mPFS was 4.2 months. A phase II clinical trial, CABinMET (NCT03911193), is currently recruiting NSCLC patients with *MET* alterations including *METex14* skip⁺ to receive cabozantinib after progression on one or more lines of therapy. The primary objective of this trial is ORR. Given the synergistic antitumor activity of MET inhibitors and immune checkpoint blockade, ECOG-ACRIN is planning to test cabozantinib in combination with the nivolumab in NSCLC patients with *METex14* skipping.

AEs from cabozantinib in NSCLC trials have been reported to be generally manageable (45,47). More common grades ≥3 toxicities have included fatigue, diarrhea and palmar-plantar erythrodysesthesia; however, these side effects are usually controlled with supportive care and adjustment of cabozantinib dose. Other AEs, such as hemoptysis or significant bleeding, have required permanent discontinuation (47).

Glesatinib (MGCD265): glesatinib is an oral TKI that inhibits MET, AXL and SMO (smoothened, a key component of sonic hedgehog pathway) receptors (48). In a phase I clinical trial (NCT00697632), one patient with *METex14* skip⁺ NSCLC, who progressed on multiple prior treatments demonstrated PR to glesatinib with 66% reduction in target lesions (18). Another *METex14* skip⁺ NSCLC patient who progressed on crizotinib after a PR and acquired Y1230H mutation developed mixed response to glesatinib in the lesion that tested positive for Y1230H mutation. Follow-up plasma DNA testing showed resolution of the Y1230H and Y1230S mutations, but persistence of the D1228N and G1163R, and a new L1195V clone was noted. This response pattern is likely indicative of the type II MET inhibition mechanism of

glesatinib (18). A phase I clinical trial determined glesatinib RP2D to be 1,050 mg BID (49). Toxicities included nausea, vomiting, fatigue, diarrhea and elevated transaminases. Glesatinib has undergone phase II evaluation in NSCLC patients with *MET* alterations in a four-arm study with two cohorts of *METex14* skip⁺ and amplified patients based on tissue *vs.* plasma tumor DNA. Response rate was modest across the different arms, ranging from 10–25% with mPFS of 3–4 months (NCT02544633). Glesatinib is currently being tested in NSCLC in combination with nivolumab (NCT02954991) in patients who have progress through platinum-based therapy. Participant selection in this study is not biomarker driven.

Merestinib (LY2801653): merestinib is an oral multi-kinase inhibitor that targets MET, NTRK, AXL, PDGFRA, FLT3 and other kinases. The first human phase I study of merestinib in advanced cancer determined RP2D at 120 mg once daily (50). The most common grade ≥3 treatment related AEs was increased transaminases (ALT, 10%; AST, 6%). The study showed one complete and three PRs in patients with cholangiocarcinoma while 60 of 186 patients achieved stable disease as their best response. Merestinib is also currently under study in a phase II trial (NCT02920996) in *METex14* skip⁺ NSCLC or other solid tumors with NTRK/TRK re-arrangement with a primary objective of ORR.

Targeting MET with antibodies

Many studies have evaluated monoclonal antibodies that specifically target the MET pathway, either by blocking the binding of HGF to MET and/or inducing internalization and degradation of MET (e.g., onartuzumab, ABT-700, emibetuzumab) or binding to HGF in the tumor microenvironment (e.g., rilotumumab, ficlatuzumab, MP0250) in patients with various malignancies (15,51,52). However, these agents have shown very modest activity in clinical trials, thus have not gained much traction. This mechanism of targeting MET is relevant to many advanced tumors where MET overexpression and/or amplification is the primary mechanism of resistance e.g., EGFR mutated NSCLC. Newer agents like amivantamab (JNJ-61186372), REGN5093 and Sym015 are under active investigation in these settings. Amivantamab is a bispecific antibody targeting EGFR/MET receptors. CHRYSALIS is an ongoing phase I study evaluating amivantamab in EGFR exon20 ins NSCLC patients (27). In 39 of 50 response evaluable patients, 36% showed ORR. The most common

AEs were rash (72%), infusion-related reaction (60%), paronychia (34%), stomatitis (16%), pruritus (14%), and diarrhea (6%). Future studies should select patients very carefully for further drug development. Sym015 comprises a mixture of two humanized antibodies directed against nonoverlapping epitopes on the MET extracellular domain (SEMA-α), allowing receptor internalization and degradation. In pre-clinical models, it showed activity against *METex14* skip⁺ and amplified tumors (53). In an ongoing phase I/II study, 45 NSCLC patients with *METex14* skip⁺ or amplification received Sym015. Of 20 patients, 5 had confirmed response (2/8 MET^{Amp} and 3/12 $MET^{Ex14\Delta}$); 11 developed SD (6/8 MET^{Amp} and 5/12 $MET^{Ex14\Delta}$), 2 progressed (2/12 $MET^{Ex14\Delta}$), and 2 were not evaluable. Median PFS was 5.5 months overall. The most common treatment-related AE in ≥10% patients were fatigue (13.3%) and peripheral edema (11.1%) (26). REGN5093 is also a bispecific antibody that binds to two distinct epitopes of MET, blocking HGF binding and inducing internalization and degradation of MET. Preclinical data is very encouraging, and a dose finding study is currently investigating NSCLC patients with various *MET* alterations (54).

Targeting MET with antibody-conjugated chemotherapy

ABBV-399 (telisotuzumab vedotin, teliso-V) is a first-in-class antibody-drug conjugate (ADC) comprised of ABT-700, a monoclonal antibody against MET, linked to monomethyl auristatin E (MMAE), a potent microtubule inhibitor via a valine-citrulline linker. Engagement of c-Met by teliso-V results in internalization of the ADC and intracellular release of MMAE after proteolysis of the linker. MMAE then binds to tubulin, thereby inhibiting mitosis and causing tumor cell death. A first-in-human phase I study enrolled 48 patients with advanced solid tumors and RP2D was defined as 2.7 mg/kg (55). The most frequent teliso-V related grades ≥3 AEs were fatigue, anemia, neutropenia, and hypoalbuminemia (4% each). Of 16 NSCLC patients with MET overexpression (defined by immunohistochemistry membrane H-score ≥150), treated with teliso-V at 2.4–3.0 mg/kg, 3 (18.8%) achieved PR with mDoR of 4.8 months and mPFS of 5.7 months. Multiple studies with ABBV-399 are being conducted in patients with NSCLC and other solid tumors expressing MET. ABBV-399 is reported to be tolerable in combination with erlotinib, an EGFR inhibitor, in a current phase Ib study (NCT 02099058). Patients with NSCLC overexpressing MET showed preliminary ORR of 28.6% in those with *EGFR* wild-type and 34.5% in those with *EGFR^m* (56).

After MET inhibitor in METex14 skip⁺ NSCLC

Resistance to MET TKIs in *METex14* skip⁺ NSCLC occurs due to acquired mutations in the MET kinase domain and through various off target mechanisms. Reports have shown the presence of mutations D1228N/V (32) and Y1230C (35,57) in the MET kinase domain in patients who progressed on crizotinib. The D1228N/V mutations was found on re-biopsy of the tumor upon progression while one of the Y1230C mutations was detected using ctDNA (35). D1246N mutation was also found after treatment with crizotinib (58,59). Switching patients to a type II inhibitor such as cabozantinib has shown some benefit (18,58,60).

In one study, nine patients with pre- and post-MET TKI therapy samples were evaluated (61). On-target resistance was found only in two patients (D1228N, n=1; HGF amplification, n=1) while off-target mechanisms were found in five patients (*KRAS* G13V, n=1; *RASA1* S742*, n=1; *MDM2* amplification, n=2; *EGFR* amplification, n=1). Another group of investigators analyzed resistance patterns from 74 patients and their findings suggested that activation of the RAS pathway conferred primary resistance to MET TKI. Several other groups have also confirmed activation of the RAS pathway in patients with *METex14* skip⁺ NSCLC who acquired crizotinib resistance (62-64). Suzawa *et al.* showed that 5 of 113 patients (4.4%) with *METex14* skip⁺ NSCLC had concurrent *KRAS G12* mutations (64). One patient acquired the *KRAS* mutation after treatment with crizotinib whereas others had the mutation prior to MET TKI therapy. In addition to patients with KRAS mutations, 3 of 113 patients in this study had amplification of wild-type *KRAS*. The co-occurrence of driver alterations in these two oncogenes was statistically significant, a very unlikely phenomenon in NSCLC patients with driver alterations in *EGFR*, *ALK*, *ROS1*, *ERBB2*, *RET*, *BRAF* genes. The combination of trametinib, an MEK inhibitor, or PI3K inhibitors with crizotinib have shown better anti-tumor activity in both *in vitro* and *in vivo* (64,65).

Summary

METex14 skipping defines a new targetable molecular alteration in NSCLC. Multiple MET TKIs have shown promising efficacy in this patient population. Based

on GEOMETRY mono-1 data, the FDA has granted accelerated approval capmatinib in patients with *METex14* skip alterations. Tepotinib is currently awaiting FDA approval in the US; however, it is currently approved in Japan for the same indication. Both agents and cabozantinib possesses CNS activity. Ongoing research to understand and evaluate primary or secondary resistance to MET TKIs in patients with *METex14* skip[+] NSCLC will be important in finding combinatorial partners. MET TKIs are also establishing a role in *EGFR*[m] NSCLC with *MET*[Amp]. MET directed antibody-conjugate therapy is also gaining potential use in various solid tumors with MET overexpression. Finally, the interaction between the MET pathway and tumor-associated immunity has yet to be characterized, a new prospect for targeting MET in cancers.

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Footnote

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