Current and future treatment options for *MET* exon 14 skipping alterations in non-small cell lung cancer

Ther Adv Med Oncol

2021, Vol. 13: 1–16

DOI: 10.1177/1758835921992976

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***Abstract*:** It has been over three decades since the hepatocyte growth factor (HGF) ligand and its receptor MET proto-oncogene (MET) pathway was established as promoting cancer growth and metastasis. *MET* exon 14 skipping (*METex14*) alterations occur in 3–4% of all non-small cell lung cancer (NSCLC) patients, typically in elderly patients (older than 70 years), and result in constitutive activation of the MET receptor by altering a region required for receptor degradation. Multi-kinase inhibitor of MET, such as crizotinib, and more recently selective MET inhibitors, such as capmatinib and tepotinib, have demonstrated clinical efficacy and safety in *METex14* NSCLC patients in clinical trials. These results have led to the approval of MET inhibitors by regulatory agencies across the globe. The success also fueled the excitement of further development of therapeutic strategies to target *METex14* in lung cancers. This article provides an overview of the clinical development program targeting *METex14* in NSCLC, including small molecular tyrosine kinase inhibitors and anti-MET antibodies. Furthermore, combination therapy immune checkpoint inhibitors or other targeted therapies are also under development in various patient populations, with acquired resistance immune or targeted therapy. Clinical trials in different development stages are ongoing and more drugs targeted to c-MET will be available for NSCLC patients with *METex14* skipping mutations in the future.

Keywords: antibody, hepatocyte growth factor, *MET* exon 14 skipping, non-small cell lung cancer, tyrosine kinase inhibitor

Received: 1 October 2020; revised manuscript accepted: 13 January 2021.

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Introduction

Therapeutic strategies targeting *EGFR*, *ALK*, *ROS1*, and other driver oncogenes have revolutionized the treatment landscape of non-small cell lung cancer (NSCLC) and improved patient outcomes.[1] Most recently, *MET* exon 14 skipping (hereafter referred to as *METex14*) has joined the group of actionable driver oncogenes for NSCLC. MET is a transmembrane receptor tyrosine kinase (RTK), encoded by *MET* gene, and activated by its stromal ligand hepatocyte growth factor (HGF).[2] Activation of MET-HGF promotes proliferation and metastasis of cancer cells. MET protein is an established driver of oncogenesis based on three types of genomic alterations: amplification, mutation, and fusion. The exon 14 of the *MET* encodes the intracellular juxtamembrane (JX) domain, which contains PKC phosphor-site (S985), caspase cleavage site (D1002), and E3 ubiquitin ligase CBL (Casitas-B-lineage lymphoma) docking site (Y1003), all controlling downregulation of RTK activity (Figure 1a).[3–7] The alteration disrupts intronic splice sites that flank exon 14, including the splice acceptor site of intron 13 and the splice donor site of intron 14, or mutation within the exon 14 coding sequence itself, and all result in exon 14 skipping in the transcript. The most common of these mutations are base substitutions, followed by indels. Therefore, alterative splicing events leading to the skipping of *MET* exon 14 result in activating the MET-HGF pathway and promoting tumor cell proliferation, migration, and preventing apoptosis (Figure 1b).

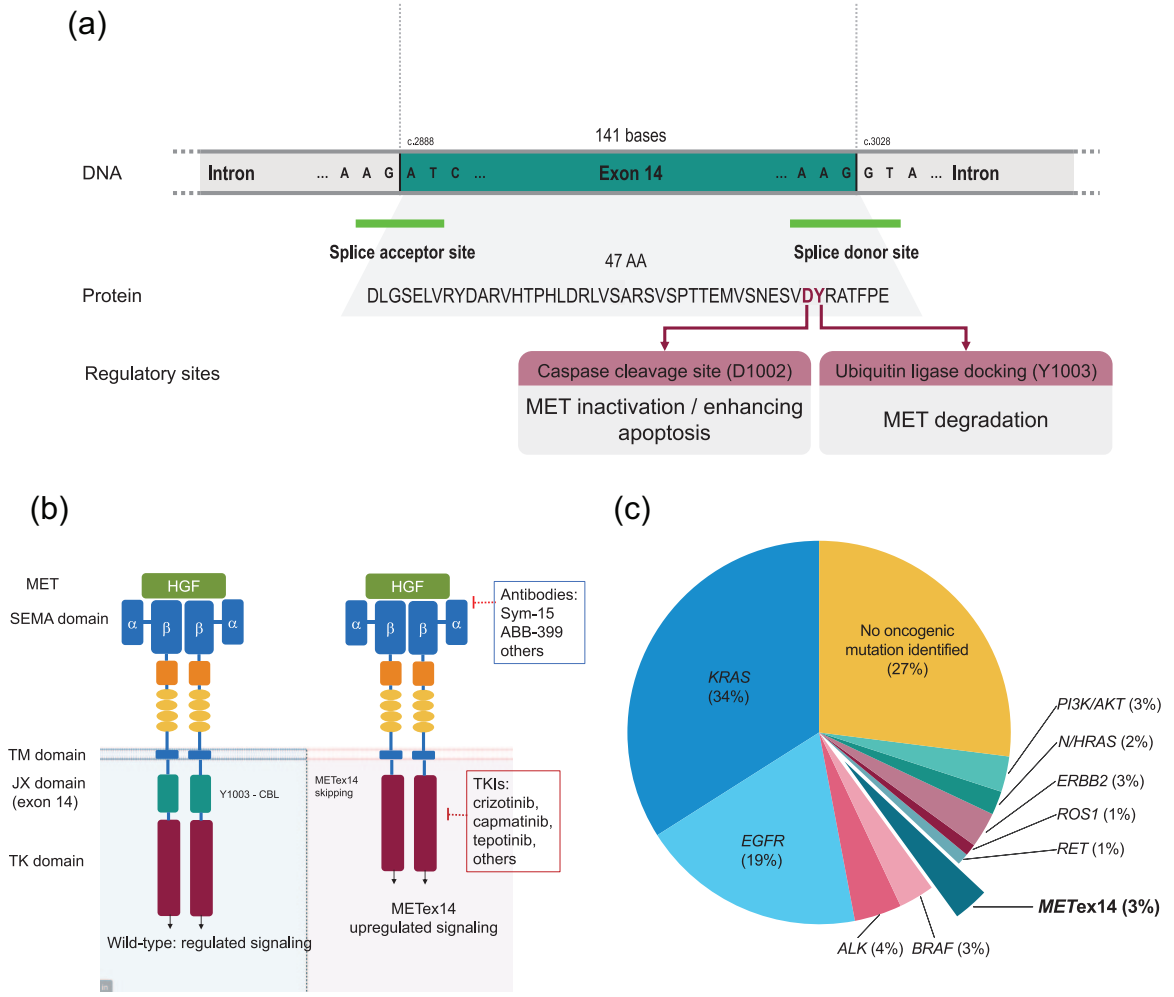

Figure 1. *METex14* in non-small lung cancers. (a) schematic diagram of genomic areas flanking *MET* exon 14 and key amino acid residuals within exon 14. (b) Skipping of *MET* exon 14 leads to upregulated *MET* signaling. Tyrosine kinase inhibitors (TKIs) and antibody-based therapies are two major therapeutic approaches to target *METex14*. (c) Incidence of known driver oncogenes for lung adenocarcinoma.
CBL, Casitas-B-lineage lymphoma; JX, juxtamembrane; SEMA, sema homology region; TK, tyrosine kinase; TKIs, tyrosine kinase inhibitors; TM, transmembrane.

The first alternative splicing event of *METex14* was described in mouse models, which was a 141-basepair deletion and results in a 47-amino-acid JX region deletion of the MET protein.[8] This deletion in *METex14* JX region promoted tumorigenesis and formation.[9] Alterations in this region in patients with NSCLC were first reported by Ma *et al.*[10] and explored in a large cohort since late 2015.[11] Since then, *METex14* has been studied in NSCLC and other tumors as an oncogenic driver, and ignited the enthusiasm for the development of therapeutic agents to target this new driver. In this review, we summarize characteristics of *METex14* NSCLC, and discuss the promise of selective MET inhibitors, small molecule inhibitors and antibody-based approaches, in the treatment of NSCLC patients harboring *METex14* skipping alterations. We also discuss immunotherapy strategies under development.

Clinicopathologic characteristics of *METex14* splicing alterations in NSCLC

Hundreds of different alterations have been described that lead to exon 14 skipping in NSCLC, including point mutations, deletions, insertions, or complex mutations (indels) that all affect conserved sequences of splice donor or acceptor sites located within the exon–intron boundaries (Figure 1a). Due to the nature of

METex14 being a heterogeneous RNA splicing alteration, an effective next-generation sequencing (NGS) assay is needed to capture the genetic changes. Generally speaking, hybrid-based DNA sequencing platforms could be more sensitive than the amplicon-based DNA sequencing platforms, whereas the RNA sequencing platform can directly identify the loss of exon 14 transcription and therefore may be the most definitive.[12] Nowadays, with MET exon 14 skipping becoming an established actionable oncogene for lung cancer, many NGS platforms have optimized the assays with high depth of coverage surrounding the MET gene, which improves the detection sensitivity.

Studies from different countries have reported that the prevalence of *METex14* in lung adenocarcinoma was around 3% (Figure 1c),[8] higher than squamous cell carcinoma (1%)[13] and small cell lung cancer (0–0.2%), but much lower than adenosquamous (6%) and pulmonary sarcomatoid carcinoma (9–22%). *METex14* alterations have also been observed at higher frequency in females than males, and the median age was reported from 71.4 years to 76.7 years.[14–19] NSCLC with MET exon 14 skipping mutations appeared to be a highly aggressive subtype. Some 88.2% (out of 34 with metastatic disease) of *METex14* NSCLC patients had metastases at more than one single site, and 22.6% (out of 84) total *METex14* NSCLC patients had multifocal disease.[14] Gow *et al.*[20] showed that the median overall survival (OS) of stage IV *METex14* NSCLC patients ($n=18$) was 6.7 months, without significant difference when compared with the patients with negative driver mutation ($n=210$; 11.2 months). Another retrospective study conducted by Awad *et al.*[21] reported 34 stage IV *METex14* NSCLC patients who never received *MET* inhibitors, and the median OS was 8.1 months.

Small molecule inhibitors targeting *METex14* NSCLC

Two classes of *MET*-targeting therapeutics are now in clinical development for *METex14* NSCLC: small molecular *MET* tyrosine kinase inhibitors (TKIs) and antibody-based therapies against MET/HGF (Figure 1b). In 2020, two MET TKIs received regulatory approval for *METex14* NSCLC: tepotinib by Japanese Ministry of Health, Labor and Welfare (MHLW) and capmatinib by US Food and Drug Administration (FDA), representing a major achievement for MET TKI development.

TKIs for MET are generally classified as type I, type II, and type III. Type I MET inhibitors bind to the ATP-pocket in the active form (DFG-in) of MET, and are subdivided into Ia and Ib. Type Ia, such as crizotinib, interacts with the Y1230 residue, the hinge region, and the solvent front G1163 (analogues to the same position as G1202 of *ALK* gene and G2032 of *ROS-1* gene). Type Ib, such as capmatinib, tepotinib, savolitinib, has strong connection with the Y1230 residue and the hinge, but no interaction with G1163. Each of these TKIs has demonstrated promising efficacy for advanced *METex14* NSCLC. Newer type I inhibitors, Bozitinib and TPX-022, are under clinical evaluation currently. Type II inhibitors, such as cabozantinib, merestinib, glesatinib, bind the ATP-pocket in the inactive state (DFG-out) by extending to a hydrophobic back pocket. Both type I and type II are ATP-competitive inhibitors.[22] Tivantinib is a type III inhibitor, which binds to allosteric sites distinct from the ATP binding site, and is reported to be non-ATP competitive.[23] Tivantinib has been previously studied in NSCLC patients, and was discontinued due to futility in an interim analysis;[24] however, *METex14* was not evaluated in this trial. Many other small molecule inhibitors targeting MET are under various stages of development, such as glumetinib (SCC244), AMG-337, foretinib (GSK1363089, XL880), S49076 and SAR125844.

Type I MET small molecule inhibitors

Crizotinib (XALKORI). The first targeted therapy demonstrating anti-tumor efficacy in *METex14* NSCLC was crizotinib. Crizotinib (PF02341066; Pfizer) is a type Ia inhibitor. Besides MET, it also inhibits ALK, ROS-1 and other targets. The IC_{50} of inhibiting the phosphorylation of wild-type MET *in vitro* in several human tumor cell lines ranges between 4 nM and 8 nM.[16,25–27] Many case studies reported the efficacy of crizotinib in lung cancer patients with *METex14* alterations (>10 refs since 2015). In a retrospective series of 61 patients with metastatic NSCLC, 27 including 19 adenocarcinomas were treated with a *MET* inhibitor (22 with crizotinib) and 34 were not. Median OS was 24.6 months for patients treated with a MET inhibitor compared with 8.1 months in those not receiving such a drug.[21] The median progression-free survival (mPFS) for the 22 patients treated with crizotinib was 7.4 months.

PROFILE 1001 was the first trial to formally evaluate crizotinib efficacy in *METex14* NSCLC patients. In the total of 65 evaluable patients, overall response rate (ORR) was 32% with three complete responses (CRs) and 18 partial responses (PRs). Duration of response (DOR) was 9.1 months and mPFS was 7.3 months. Objective responses to crizotinib were observed independent of *METex14* alteration splice site or mutation type.[28] The most common treatment-related adverse events (TRAEs) were edema (51%) and vision disorder (45%), which were similar to that reported previously for patients with *ALK*- or *ROS1*-rearranged NSCLC. For this trial, METex14 was detected in archival tumor tissue and baseline/end of treatment plasma samples. Tissue NGS was performed at the central laboratory Foundation Medicine, Inc. (FMI) and Cancer Genetics, Inc. (CGI). Plasma ctDNA NGS was performed at Personal Genome Diagnostics (PGDx).

A phase II, two-arm study, the METROS study with crizotinib (NCT02499614), is ongoing in pretreated NSCLC patients with *ROS-1* translocation, or *MET* amplification, or *MET* exon 14 mutation. Stage IA–IIIA NSCLC patients with surgically resectable *ALK* rearrangement, *ROS-1* rearrangement, or *MET* exon 14 mutation positive are also being recruited to evaluate the efficacy of neoadjuvant therapy with crizotinib (NCT03088930). Additionally, crizotinib is the TKI for the *METex14* arms of two large phase II basket trials: the NCI-MATCH trial (NCT02465060) in the US and the National Lung Matrix trial (NCT02664935) in the UK, for patients with *METex14* solid tumors and lung cancer respectively. Another phase II, open-label study (NCT04084717) is underway to assess the efficacy of crizotinib in metastatic NSCLC patients with a mutation in genes *ROS-1* or *MET*. Crizotinib has received FDA breakthrough designation for use in the treatment of *METex14* NSCLC.

Capmatinib (TABRECTA). Newly designed small molecule inhibitors selectively targeting MET have been developed for the treatment of *METex14* NSCLC and they have shown promising activities. Capmatinib (INC280, INCB28060; Novartis) is a highly selective and potent type Ib MET inhibitor with *in vitro* and *in vivo* activities against preclinical cancer models with *MET* activation.[29,30] Capmatinib inhibits MET kinase activity with an average IC_{50} value of 0.13 nM, and a cell-based IC_{50} of 0.3–0.7 nM in lung cancer cell lines. Two open-label, multicenter, phase I dose-escalation and expansion studies (NCT01546428, $n = 44$; NCT01324479, $n = 38$) demonstrated clinical safety and determined the dose to be safe was 400 mg b.i.d.[31,32] Preliminary anti-tumor efficacy was reported in NCT01324479 and NCT02276027 in *MET* altered tumors.[33,34]

Capmatinib efficacy in *METex14* NSCLC was established in the GEOMETRY mono-1 trial (NCT02414139), a multicenter, non-randomized, open-label, multicohort, and phase II study enrolling 97 metastatic *METex14* NSCLC patients. Patients received capmatinib 400 mg orally twice daily until disease progression (PD) or unacceptable toxicity. Among the 28 treatment-naïve patients, the ORR was 68% (95% CI: 48–84) (64% PRs and 4% CRs) with a response duration of 12.6 months (95% CI: 5.5–25.3), and the mPFS was 9.69 months. Among the 69 previously treated patients, the ORR was 41% (95%CI: 29–53) (all PRs) with a DOR of 9.7 months (95% CI: 5.5–13), and the mPFS was 5.42 months. Additionally, in this trial, 13 patients had brain metastases, with seven that had central nervous system lesions shrinkage, including four that disappeared. The drug's efficacy appeared to be independent of any specific *MET* exon 14 variant, and treatment was well tolerated, with the main side effects being peripheral edema and nausea.[35,36] With this set of results, on 6 May 2020, capmatinib received its approval by the US FDA for the treatment of metastatic NSCLC whose tumors have a mutation that leads to *MET* exon 14 skipping, as detected by an FDA-approved test.[37] In addition, FDA also approved the FoundationOne CDx assay (Foundation Medicine, Inc.) as a companion diagnostic for capmatinib.

Several phase II studies are ongoing in patients with NSCLC, including NCT03693339 in Korea and NCT03911193 in Italy. In addition, a phase II trial (NCT04460729) will formally evaluate the intracranial efficacy of single-agent capmatinib in the population of treatment-naïve or pretreated with one or two prior lines of systemic therapies for advanced stage of NSCLC with *MET* exon 14 mutation that has metastasized to brain. Furthermore, confirmatory phase II data for capmatinib in the first-line setting are pending.

Tepotinib (TEPMETKO). Tepotinib (EMD1214063; Merck KGaA) is another highly selective and potent type Ib *MET* inhibitor. Preclinical studies reported that tepotinib could inhibit HGF-induced

MET phosphorylation in cancer cell lines with an average IC_{50} of 3 nM and induced regression of human tumors in xenograft tumor models regardless of whether MET activation was HGF dependent or independent.[38,39]

A first-in-human phase I trial (NCT01014936) of tepotinib in patients with advanced solid tumors was conducted in 149 patients (including 17 lung primary tumors) without identification of maximum-tolerated dose at 1400 mg daily and the recommended phase II dose (RP2D) of tepotinib was established as 500 mg once daily, supported by translational modeling data as sufficient to achieve ⩾90% c-MET inhibition in ⩾90% of patients.[40]

Tepotinib demonstrated clinically meaningful efficacy in advanced *METex14* NSCLC patients, in the open-label, multicenter, multicohort phase II VISION study (NCT02864992). The study includes three cohorts: cohort A – patients with *MET* exon 14 skipping mutation; cohort B – patients with *MET*-amplified disease; cohort C – currently enrolling patients with *MET* exon 14 skipping mutations for confirmatory analysis of the results in cohort A. As of January 2020, a total of 152 patients confirmed with *MET* exon 14 skipping based on tissue or liquid biopsy had received tepotinib (at a dose of 500 mg orally once daily) and 99 patients (89 patients were adenocarcinoma) were eligible for outcome analysis. The ORR as determined by an independent review was 46% (95% CI: 36.4–56.8; all PRs) with a disease control rate (DCR) of 65.7%. The mPFS was 8.5 months and the median duration of OS was 17.1 months (95% CI, 12.0–26.8), although data were immature at the time of analysis.[41] TRAEs were reported in 89% of the safety population. Peripheral edema was the most common TRAE of grade 3 or higher (in 7%) led to a dose reduction in 16% of the patients, and also a dose interruption in 18%. In March 2020, tepotinib received Japanese MHLW approval, and also on the agency's fast track path with US FDA. Archer®MET CDx has been approved for the detection of METex14 both in blood and tissue samples from patients with advanced NSCLC for consideration of tepotinib treatment.

Savolitinib. Savolitinib (AZD6094, volitinib, HMPL-504; AstraZeneca) is another potent (IC_{50} 4 nM) and selective (>650 folds selectivity over 265 kinases), type Ib, small molecule *MET* TKI. Studies across a panel of cancer cell lines demonstrated selectivity for *MET*-driven disease, with *MET*-amplified cell lines being most sensitive (IC_{50} of 1 nM) and also suggesting limited off-target activity. In preclinical models, savolitinib demonstrated inhibition of HGF-mediated *MET* phosphorylation and dose-dependent tumor growth and downstream signaling,[42] and was highly efficacious at blocking the growth of cancer cell lines harboring *METex14*.

A phase II clinical study (NCT02897479) conducted in China demonstrated preliminary efficacy and safety of savolitinib in patients with pulmonary sarcomatoid carcinoma and other type of *METex14* NSCLC. In the most recent updated report on this trial,[43] for *MET* treatment-naïve patients ($n = 70$, 57.1% with lung adenocarcinoma), the ORR was 47.5% (95% CI: 34.6–60.7), and DCR was 93.4% (95% CI: 84.1–98.2), and 58.1% of the patients were treated for more than 6 months. The mPFS was 6.8 months (95% CI: 4.2–13.8). TRAEs leading to treatment discontinuation occurred in 14.3% patients, among which liver injury and hypersensitivity were most common (each 2.9%). In addition, the study showed that savolitinib can penetrate the blood–brain barrier (BBB) and was also effective in patients with brain metastases. On 29 May 2020, the New Drug Application for savolitinib for the treatment of *METex14* NSCLC has been accepted for review by the China National Medical Products Administration.

Bozitinib. Bozitinib (APL-101, PLB1001, CBT101; Apollomics Inc) is a highly selective and specific MET inhibitor (8 nM) with robust activity in gastric, lung, hepatic, and pancreatic *in vivo* models.[44] Bozitinib had higher apparent permeability and lower efflux rate than other *MET* inhibitors (crizotinib, cabozantinib, and foretinib) in a preclinical cell model, and showed superior specificity in MET inhibition and was permeable in crossing the BBB in cell and rat models. Hu *et al.*[45] evaluated the mutational landscape of 188 secondary glioblastoma (sGBM) patients and identified that *METex14* was detected in 14% (95% CI: 8.0–23.5) of sGBM cases and associated with worse prognosis. In the subsequent phase I clinical trial (NCT02978261) evaluating bozitinib in sGBM patients carrying PTPRZ1-MET fusions and/or *METex14* ($n = 6$), two achieved PR, two achieved stable disease (SD), and two had PD, with little side effects, and recommended bozitinib monotherapy dosage as 300 mg b.i.d.

NCT03175224 is a phase I/II international multicenter, open-label study evaluating the safety, pharmacokinetics, and preliminary efficacy of bozitinib in NSCLC patients with *METex14* and c-MET dysregulation advanced solid tumors. Based on completion of the phase I and approval from the study's safety review committee to advance the trial, the phase II portion of the study, titled SPARTA, was initiated in May 2020. Another phase II study (NCT04258033) has recently been initiated in Guangdong, China, and will include 185 participants with advanced NSCLC harboring MET dysregulation to assess the efficiency and safety of bozitinib.

TPX-0022. TPX-0022 (Turning-point Therapeutics), a type I kinase inhibitor with a novel macrocyclic structure, has been designed and optimized to inhibit MET/CSF1R/SRC with enzymatic kinase inhibition IC_{50} values of 0.14, 0.71, and 0.12 nM, respectively. Given TPX-0022 is a cyclic compound, not a linear compound like all the existing TKIs, TPX-0022 cannot be classified as Ia or Ib. TPX-0022 potently inhibited cell proliferation of the *MET*-amplified gastric cancer cell lines with a value of $IC_{50} < 0.2$ nM that was comparable with capmatinib and was more than 10-fold more potent than crizotinib. TPX-0022 also demonstrated inhibition to tumor growth by inducing tumor-associated macrophages to a more M1 phenotype and increasing the cytotoxic T cells.[46]

The first-in-human ongoing phase I clinical trial (NCT03993873) is being conducted in the US to determine the safety and preliminary efficacy of the novel *MET*/*CSF1R*/*SRC* inhibitor TPX-0022 in patients with advanced solid tumors harboring genetic alterations in *MET*, including NSCLC with *METex14*.

Type II MET small molecule inhibitors

Cabozantinib (CABOMETYX). Cabozantinib (Cometriq, XL184, BMS-907351; Exelixis) is a type II MET inhibitor with activities against a broad range of targets, including MET, RET, AXL, VEGFR2, FLT3, and c-KIT. Currently, cabozantinib was approved by US FDA for metastatic medullary thyroid cancer (November 2012), first-line treatment of advanced renal cell carcinoma (December 2017), and hepatocellular carcinoma patients previously treated with sorafenib (January 2019).

Cabozantinib was the first orally available MET inhibitor to enter clinical trials in 2005. Cabozantinib is potent inhibitor of MET with an IC_{50} value of 1.3 nM. As cabozantinib is a type II inhibitor, it also inhibits MET-activating kinase domain mutations Y1248C/H, D1246N, or K1262R, with IC_{50}s values of 4, 5, and 14.6 nM, respectively. In mouse models, cabozantinib dramatically altered tumor pathology, resulting in decreased tumor and endothelial cell proliferation coupled with increased apoptosis and dose-dependent inhibition of tumor growth in breast, lung, and glioma tumor models.[47] Although large cohort investigation of cabozantinib in *METex14* NSCLC has not been published yet, several case reports demonstrated safety and potential activity of cabozantinib in *METex14* NSCLC.[48–50] An Italian phase II trial is currently evaluating cabozantinib in patients with *MET*-amplified NSCLC or *METex14* NSCLC (NCT03911193).

Merestinib. Merestinib (LY2801653; Eli Lilly) is also a type II potent, orally bioavailable MET inhibitor ($IC_{50} = 2$ nM). Merestinib also inhibits MST1R (RON). Preclinical studies have demonstrated that treatment with merestinib inhibited the constitutive activation of *MET* pathway signaling, and resulted in inhibition of *MET* in cell lines with *MET* alterations.[51–54]

Recondo *et al.* reported a patient harboring *MET* exon 14 skipping who experienced PD on crizotinib, and a resistance *MET* mutation of Y1230C was detected both in plasma and tumor tissue at the time of progression. This patient had a PR after switched to merestinib.[55] These results supported that merestinib may provide a therapeutic option to patients with *METex14*. The first-in-human phase I study was to evaluate the safety and tolerability of merestinib including three types of tumor without NSCLC. Overall, 60 (32%) of the 186 patients enrolled in the study had a best response of SD, and recommended a dosing of merestinib at 120 mg once daily based on acceptable exposure and safety.[56] A phase II study conducted by Awad *et al.* was to evaluate the safety and efficacy of merestinib in patients with advanced *METex14* NSCLC or patients with advanced cancer with NTRK rearrangements (NCT02920996).[54]

Glesatinib. Glesatinib (MGCD265; Mirati Therapeutics) is another orally bioavailable, type II, multi-targeted inhibitor with potential anti-tumor

activity. Glesatinib binds to and inhibits the phosphorylation of several RTKs, including the MET receptor, the TEK/TIE-2 receptor, RON, SMO, and VEGFR types 1, 2, and 3. Preclinical studies showed that glesatinib resulted in a dose-dependent inhibition of cancer cell growth with an IC_{50} value of 80 nM on NSCLC H1299 cells.[57] A patient with *METex14* NSCLC showed response to glesatinib after relapsing to crizotinib, including a reduction in size of a *MET* Y1230H mutation-positive liver metastases and concurrent loss of detection of this mutation in plasma DNA.[58]

Amethyst NSCLC trial is a global phase II trial enrolling patients with NSCLC with *MET* alterations in tumor tissue or blood and who have received prior therapy. Patients were treated with glesatinib in 21-day cycle until PD or unacceptable toxicity.[59] It was shown that in patients harboring *MET*-activating mutations in tumor tissue ($n=28$) *versus* in ctDNA ($n=8$) taking 750 mg b.i.d. tablet or 1050 mg b.i.d., ORR was 10.7% (95% CI: 2.27–28.23) *versus* 25% (95% CI: 3.19–65.09), mPFS was 3.95 (95% CI: 2.11–4.18) months *versus* 3.39 (95% CI: 1.28–not reached) months, and 1-year survival rate was 50.47% (95% CI: 27.49–69.62) *versus* 54.69% (95% CI: 13.72–83.24). The OS data were immature due to the small number of events.[60]

The above-reviewed clinical trials have indicated that ORR with *MET* small molecule inhibitors for *METex14* NSCLC patients range from 25% to 68%, with median PFS varying between 7.6 and 13.8 months (Table 1). These data were compelling to establish *METex14* as an actionable driver-oncogene for NSCLC and for oncologists to provide the approved *MET* inhibitors to *METex14* NSCLC patients. In the meantime, these data also support that acquired resistance develops over time with TKI treatment. The spectrum of resistance mechanisms to *MET* TKIs is likely to be similar to other targeted therapies, such as *EGFR* or *ALK*. Both secondary resistance mutations and bypass activation mechanisms have been reported. D1228 and Y1230 were common sites for resistance mutations for type I inhibitors, whereas L1195 and F1200 were common sites for type II inhibitor-associated resistance.[61–63] This configuration enables type II inhibitors to act against *MET* kinase domain mutations that confer resistance to type I inhibitors, and vice versa. Therefore, switching between type I and type II *MET* inhibitors might be an effective strategy in patients with acquired specific resistance mutations following either type of inhibitor exposure.[55] Other resistance mechanisms were also reported, including upregulation of bypass signaling pathways (such as *RAS-MAPK*) and/or the acquisition of additional oncogenic mutations (such as *KRAS* and *EGFR* mutations); it is recommended that a combination therapy targeting different markers may enhance clinical outcomes.[64]

Antibody-based therapies against MET/HGF

Different than ATP-competitive small molecule inhibitors interacting with the kinase domain of *MET*, antibodies against HGF and MET suppress the signaling pathway by inhibiting interactions between HGF and MET (Figure 1b). Compared with small molecule inhibitors that often target multiple RTKs, biologics more specifically inhibit the HGF/MET signaling pathway. Multiple therapeutic antibodies targeting the HGF/MET signaling pathway are currently in preclinical and clinical development. Because the mechanism of action of the antibody-based therapies is interrupting HGF/MET binding, most of the trials are selecting for *MET* over-expression, not restricted to *METex14*.

Sym-015

Sym-015 (Symphogen A/S) is a mixture of two humanized IgG1 monoclonal, Hu9006 and Hu9338, which recognize non-overlapping epitopes in the Sema domain of MET, preventing the binding of HGF. This inhibits *MET*-dependent tumor cell growth, survival, angiogenesis, invasion, and metastasis.[65,66] An open-label, phase Ia/IIa clinical study of sym-015 enrolled 12 *METex14* NSCLC patients, who were treated with the recommended P2 dose as 18 mg/kg on cycle 1 day 1 followed by 12 mg/kg Q2W. Three of the 12 patients achieved PR and five achieved SD. Sym-015 was well tolerated at P2 dosage with a good response to NSCLC harboring MET exon 14 skipping mutations (NCT02648724).[67]

Telisotuzumab vedotin

Telisotuzumab vedotin (ABBV-399, ABT-700; ABBVie) is an antibody-drug conjugate composed of telisotuzumab, a monoclonal antibody against the tumor-associated antigen and proto-oncogene, MET receptor tyrosine kinase conjugated to the cytotoxic agent monomethyl auristatin E (MMAE) *via* a valine-citrulline (vc) peptide linker (vc-MMAE; vedotin), with potential tumor activity.

Table 1. Current clinical trials for METex14 NSCLC.

Treatment	Class	Cell IC_{50} (cell line), nM	Targets	Trials in METex14	Dosing and schedule	ORR	mPFS	Common TRAE reported (% of patients)	Grade 3 or 4 TRAE reported (% of patients)	Reference
Crizotinib	Ia	11 (A549)[25]	MET, ALK, ROS1	PROFILE 1001 (NCT00585195) (phase I completed in April, 2020)	250 mg BID daily, oral	Expansion cohort: advanced NSCLC patients harboring METex14 1L: 25% ($n=24$) 2L+: 36.6% ($n=41$)	1L+: 7.6 months	Safety population ($n=69$): edema (51), vision disorder (45), nausea (41), diarrhea (39), vomiting (29), fatigue (23), constipation (20)	Elevated transaminases (4), dyspnea (4), edema (1), constipation (1), bradycardia (1), hypophosphatemia (1), lymphopenia (1), pulmonary embolism (1), ILD (1)	Drilon *et al.*[28]
Capmatinib	Ib	0.7 (A549, H441), 0.4 (H596), 0.3 (H1437)[29]	MET	GEOMETRY Mono-1 (NCT02414139) (phase II started in June, 2015)	400 mg BID daily, oral	Patients with EGFR/ALK wild-type advanced/ metastatic NSCLC: Cohort 5b - treatment-naïve with METex14 regardless of MET GCN: 1L: 67.9% ($n=28$) Cohort 6 - pretreated with either MET GCN $\geqslant$10 without METex14 or METex14 regardless of MET GCN: 2L: 48.4% ($n=31$) Cohort 4 - pretreated with METex14 regardless of MET GCN: 2/3L: 40.6% ($n=69$)	1L: 9.7 months 2L: 8.1 months (not mature)	All cohorts ($n=334$): edema (52), nausea (44), fatigue (32), vomiting (28), diarrhea (18), constipation (18)	Lymphopenia (14), edema (9), fatigue (8), dyspnea (7), elevated transaminases (6), hyperkalemia (3), ILD (1.8)	Garon *et al.*[35]; Groen *et al.*[36]
Tepotinib	Ib	9 (EBC-1)[38]	MET	VISION (NCT02864992) (phase II started in September, 2016)	500 mg once daily, oral	Cohort A: patients with METex14 advanced NSCLC 1L: 44.2% ($n=43$) 2L+: 48.2% ($n=56$)	1L: 10.8 months 2L+: 11 months	Safety population ($n=152$): edema (70), nausea (34), blood creatine increased (28), diarrhea (31), hypoalbuminemia (25)	Edema (8), hypoalbuminemia (5), pleural effusion (6), elevated transaminases (4), ILD (0.7)	Paik *et al.*[41]
Savolitinib	Ib	6 (NCI-H441)[42]	MET	NCT02897479 (phase II started in December, 2016)	600 mg once daily, oral ($\geqslant$50 kg) 400 mg once daily, oral ($<$50 kg)	Cohort A: patients of prior MET treatment-naïve with METex14 advanced NSCLC 1L: 54.2% ($n=24$) 2L+: 46% ($n=37$)	1L: 5.6 months 2L: 13.8 months	Incidence $\geqslant$20%: edema, nausea, elevated transaminases, vomiting, hypoalbuminemia	The incidence of $\geqslant$grade 3 TRAEs was 41.4%	Lu *et al.*[43]

(Continued)

Table 1. (Continued)

Treatment	Class	Cell IC_{50} (cell line), nM	Targets	Trials in METex14	Dosing and schedule	ORR	mPFS	Common TRAE reported (% of patients)	Grade 3 or 4 TRAE reported (% of patients)	Reference
APL-101	Ib	5.8 (LU1901)[44]	MET	SPARTA (NCT03175224) (phase II started in May, 2020)	200 mg BID daily, oral	Cohort A-1: NSCLC METex14 (c-Met naive) for 1L; Cohort A-2: NSCLC METex14 (c-Met naive) for 2/3L; Cohort B: NSCLC METex14 (c-Met experienced, PD on prior c-Met inhibitor) Cohort C: basket of tumor types (with c-Met high-level amplifications) Cohort D: basket of tumor types (with c-Met fusions)				
TPX0022	I	<0.2 (MKN45, SNU-5)[46]	MET, Src, CSF1R	NCT03993873 (phase I started in August, 2019)	Once daily, oral	Cohort I: NSCLC METex14 (c-Met inhibitor naive); Cohort II: NSCLC METex14 (c-Met inhibitor pretreated) Cohort III: MET-amplified (NSCLC, HCC, gastric cancer, or GEJ) Cohort IV: MET KD mutations or fusions				
Cabozantinib	II	19 (SNU-5), 9.9 (Hs746T)[47]	MET, VEGFR2, RET, KIT, TIE-2, AXL	NCT03911193 (phase II started in September, 2018)	60 mg once daily, oral	Single arm: NSCLC patients with MET amplification or METex14 skipping mutation pretreated or not with MET inhibitors.		Results from a phase II study in patients with 9 different tumor types unselected driver oncogenes (NCT00950225). NSCLC cohort ($n = 60$): diarrhea (58), nausea (35), fatigue (58), decreased appetite (52), constipation (30), dysphonia (30), vomiting (30)	Fatigue (13), palmar-plantar erythrodysesthesia (10), diarrhea (7), hypertension (7)	

(Continued)

Table 1. (Continued)

Treatment	Class	Cell IC_{50} (cell line), nM	Targets	Trials in METex14	Dosing and schedule	ORR	mPFS	Common TRAE reported (% of patients)	Grade 3 or 4 TRAE reported (% of patients)	Reference
Merestinib	II	35.2 ± 6.9 (H460), 59.2 (S114)[51]	MET, TIE-1, AXL, ROS1, DDR1/2, FLT3, MERTK, RON, MKNK1/2	NCT02920996 (phase II started in November, 2016)	120 mg once daily, oral	Arm 1: NSCLC (METex14 mutation) Arm 2: solid tumor (NTRK 1,2,3 rearrangement)		Results from a phase I study in patients with advanced cancers (no lung cancer, NCT01285037). Dose confirmation cohort ($n = 69$): fatigue (41), nausea (23), edema (22), ALT increase (43), AST increased (35)	AST increased (10), fatigue (4)	He *et al.*[56]
Glesatinib	II	80 (H1299)[57]	MET, VEGFR, RON, TIE-2, AXL, SMO	Amethyst (NCT02544633) (phase II completed in January, 2019)	750 mg BID spray dried dispersion tablet or 1050 mg BID soft-gel capsule	Arm 1 (MET-activating mutations in tumor tissue): 10.7% ($n = 28$) Arm 3 (MET-activating mutations in ctDNA): 25% ($n = 8$)	Arm 1: 3.95 months Arm 3: 3.39 months	All cohorts ($n = 68$): diarrhea (84), nausea (53), vomiting (40), fatigue (48), edema (23), ALT elevated (44), AST elevated (41), decreased appetite (37), hypomagnesemia (25), dyspnea (29)	Serious AE: MI (3), pneumonia (7), dehydration (9), seizure (3), hypoxia (3), pulmonary embolism (3)	Clinical Trials.gov.[60]

GCN, gene copy number; ILD, interstitial lung disease; METex14, MET exon 14 skipping; mPFS, median progression-free survival; NSCLC, non-small cell lung cancer; ORR, overall response rate; TRAE, treatment-related adverse event.

Upon binding, internalization, and enzymatic cleavage, the cytotoxic agent MMAE is released into the cytosol, binds to tubulin and inhibits tubulin polymerization, which results in G2/M phase arrest and tumor cell apoptosis.[68,69]

Forty-six patients were enrolled in the first-in-human trial (NCT02099058)[70] of ABBV-399, and 35 (60%) of 58 patients were NSCLC with MET positivity. Of 16 patients with MET-positive NSCLC who were treated at a dose of 2.4–3.0 mg/kg, three (18.8%; 95% CI: 4.1–45.7) achieved a PR (mDOR, 4.8 months; mPFS, 5.7 months; 95% CI, 1.2–15.4). Only one patient with lung squamous carcinoma was confirmed to have *METex14* with MET immunohistochemistry (IHC)-positive, and achieved PD as the best response. An ongoing phase II clinical study (NCT03539536) is evaluating the safety and efficacy of ABBV-399 in patients with MET-positive NSCLC (MET IHC-positive or *MET* gene amplification).

As *MET* amplification is an established resistance mechanism to *EGFR* TKI therapy, many antibodies targeting MET/HGF were evaluated in the *EGFR*-mutant NSCLC with TKI resistance setting, including onartuzumab,[71–73] ficlatuzumab,[74] rilotumumab,[75] and emibetuzumab.[76] Most recently, bispecific *EGFR* and *MET* antibodies have been developed and are in development for *EGFR* and *MET* mutation lung cancers. Two promising compounds are amivantamab and LY3164530. Amivantamab (JNJ-61186372, JNJ-6372; Janssen) is an *EGFR-MET* bispecific antibody with an active Fc backbone (IgG1) that targets activating and resistant *EGFR* mutation and *MET* mutations and amplification.[77] A phase I, first-in-human, open-label, multicenter study on JNJ-6372 (NCT02609776) showed promising efficacy (36% ORR) with a manageable safety profile in patients with heavily pretreated *EGFR* exon 20 ins NSCLC.[78] Supported by this trial, FDA has granted Breakthrough Therapy Designation for JNJ-6372 for the treatment of patients with metastatic NSCLC with *EGFR* exon 20 insertion mutations, whose disease has progressed on or after platinum-based chemotherapy. LY3164530 (Eli Lilly) is another bispecific antibody targeting to both the *MET* and *EGFR* receptors, which consists of an IgG4 to *MET* (emibetuzumab, LY2875358) and a single-chain variable fragment to *EGFR* fused to the N-terminus of each heavy chain. The first-in-human study (I7H-MC-JNBA, NCT02221882)

showed an ORR of 10.3% with toxicities associated with *EGFR* inhibition.[79]

Immunotherapy for *METex14* NSCLC

In contrast with *EGFR*/*ALK*-positive NSCLC having zero or low PD-L1 expression, *METex14* NSCLC tumors were found to express high levels of PD-L1; 41% of 111 patients had a PD-L1 level of ⩾50% in a study from the US and 69% of 13 patients in a study from China,[80,81] and both were much higher than a large cohort analysis for 1398 unselected NSCLC cohort (20.9%).[82] Awad *et al.*[83] presented a large cohort of 1387 *METex14* NSCLC, and the results showed that *MET* exon 14-altered patients were enriched for high PD-L1 positivity *versus* wild-type NSCLC (48% *versus* 29%). Although PD-L1 expression might be high in *METex14* NSCLC, tumor mutational burden (TMB) distribution across the *METex14* tumors was much lower than general NSCLC (3.6 *versus* 7.0 mut/mb). Another study with 298 *METex14* NSCLC reported that the average TMB in cases with *METex14* was 6.9 mut/mb, compared with 10.7 mut/mb for unselected lung cancers in this cohort.[84]

The efficacy of immunotherapy for METex14 NSCLC remains controversial. Some of the case reports and case series studies showed that immunotherapy might not be effective for *METex14* NSCLC patients despite high PD-L1. One hypothesis underlying the potential inferior response to immunotherapy was low TMB. Baba *et al.* reported that a patient with 95% PD-L1 *METex14* NSCLC did not respond to pembrolizumab.[85] Reis *et al.* reported another two similar cases.[86] In a retrospective study conducted by Sabari *et al.*,[80] 24 *METex14* cancers received single-agent ($n=22$) or combination immunotherapy, including 11 patients treated as first-line therapy, and the ORR was 17% (95% CI: 6–36%), the mPFS was 1.9 (95% CI: 1.7–2.7) months. Responses to immunotherapy were not predictable by PD-L1 expression nor TMB. These findings suggest that optimized predictive markers, besides PD-L1 expression and TMB, need to be explored for immunotherapy response for *METex14* NSCLC. Furthermore, with the evident clinical activity of *MET* inhibitors, combination of *MET* inhibitors with immune checkpoint inhibitors might be a promising treatment strategy for *METex14* NSCLC patients.

A preclinical study revealed a role for the HGF/MET pathway in neutrophil recruitment and function, and suggested that MET co-treatment may improve responses to cancer immunotherapy in patients with MET-dependent tumors.[87] In an *in vitro* study of a gastric cancer cell line (Hs746T) harboring both *METex14* and *MET* amplification, it was found that MET pathway and PD-L1 expression can suppress immune cell function.[88] The COSMIC-021 trial is a multicenter phase Ib clinical trial to evaluate the safety and efficacy of cabozantinib in combination with atezolizumab in patients with multiple tumor types, including NSCLC. The dose-escalation phase of this study determined the optimal dose of cabozantinib to be 40 mg daily in combination with atezolizumab.[89] In ASCO 2020, Neal *et al.*[90] reported the results from cohort 7 of NSCLC with unknown MET status patients after prior immune checkpoint inhibitor (ICI) therapy. In the 30-patient cohort, confirmed ORR was 27%; time to response was 1.4 months; median DOR was 5.7 months; DCR was 83%; median PFS was 4.2 (95% CI: 2.7–7) months. The response rate was greater than previously observed with cabozantinib monotherapy (NCT00940225). This study demonstrated a preliminary response and acceptable safety profile of concurrent therapy with *MET* TKI and ICI; however, the *MET* gene status and PD-L1 expression has not been reported yet.

Some other studies investigating safety and efficacy of *MET* TKI combined with ICI therapy have been conducted recently, including capmatinib with anti-PD1 therapies (pembrolizumab combination NCT04139317 and nivolumab combination NCT02323126). In summer of 2020, a double-blind, placebo-controlled, randomized study evaluating the efficacy and safety of capmatinib and spartalizumab (PD-1 antibody) *versus* capmatinib and placebo as first-line treatment for advanced *METex14* NSCLC patients (NCT04323436, Novartis) just started enrollment. The primary endpoints are ORR and PFS to formally evaluate the benefit of *MET* TKI with ICI in *METex14* NSCLC.

Conclusion

METex14 skipping alterations have defined a special genomic subtype of non-small cell lung cancers. With multiple small molecule inhibitors that have demonstrated clinical efficacy and safety in clinical trials, *METex14* has been rightfully established as an actionable driver-oncogene in NSCLC. Other than developing more potent and

type II small molecule inhibitors, antibody-based therapy as well as combination immunotherapy have shown initial promise. Future prospective studies are warranted on efficacy and safety across lines of therapy to optimize clinical strategies.

Conflict of interest statement

Zhang reports research funding from Merck and Johnson and Johnson, personal fees from AstraZeneca, Bristol-Myers Squibb, GenePlus-Beijing Institute, Innovent outside the submitted work. **Heymach** receives advisory/consulting fees from Bristol-Myers Squibb, GlaxoSmithKline, Kairos Venture Investments, BrightPath Therapeutics, Hengrui Therapeutics, Eli Lilly, EMD Serono, and Foundation One Medicine, Spectrum, AstraZeneca, and research Funding from NIH/NCI, American Cancer Society, and Checkmate Pharmaceuticals, and AstraZeneca, Spectrum; and Royalties and Patents from Spectrum. **Le** receives consultant and advisory fee from Eli Lilly, AstraZeneca, EMD Serono, and research funds from Eli Lilly, Boehringer Ingelheim, and Spectrum Pharmaceuticals. All outside of the submitted work.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Lingzhi Hong is supported by MD Anderson Visiting Scholar Program, the key project from the Medical Science and Technology Department Foundation, Nanjing Department of Health, Nanjing, China (Grant No: ZKX15029). Jianjun Zhang is supported by MD Anderson Physician Scientist Award, NIH R01, AACR Johnson and Johnson Innovative Cancer Research Award, Khalifa Scholarship, and Conquer Cancer Foundation. Xiuning Le is supported by Calabresi Paul Award at MDACC (K12/NIH), Rexanna Foundation, Khalifa Scholarship, and Conquer Cancer Foundation.

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