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New Drugs

The promise of selective MET inhibitors in non-small cell lung cancer with *MET* exon 14 skipping

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ABSTRACT

Dysregulated activation of the MET tyrosine kinase receptor is implicated in the development of solid tumors and can arise through several mechanisms, including gene amplification, overexpression of the receptor and/or its ligand hepatocyte growth factor (HGF), and the acquisition of activating mutations. The most common activating mutations cause exon 14 to be skipped during *MET* mRNA splicing. This in-frame deletion, known as *MET* exon 14, results in production of a shortened receptor that lacks a juxtamembrane domain but retains affinity for HGF. However, the negative regulatory function located within this protein sequence is lost, leading to receptor accumulation on the cell surface and prolonged activation by HGF. *MET* mutations causing exon 14 skipping appear to be true oncogenic drivers and occur in patients and tumors with distinct characteristics.

Increasing evidence suggests that tumors carrying such mutations are sensitive to MET inhibition, raising the hope that selective MET inhibitors will provide patients with optimal anticancer activity with minimal toxicity.

We discuss the prospects for selective MET inhibitors in the treatment of non-small cell lung cancer harboring *MET* exon 14 skipping.

Introduction

Molecules that inhibit receptor tyrosine kinases (RTKs) have shown promise as therapies in a range of tumor types. This is because activated RTKs are able to act as primary driver oncogenes: through acquired mutations, they can initiate carcinogenesis and play a key role in tumor development. For example, oncogenic activation of the epidermal growth factor receptor (EGFR) through *EGFR* mutation is observed in non-small cell lung cancer (NSCLC), and such tumors are sensitive to EGFR-targeted tyrosine kinase inhibitors (TKIs). Although the MET RTK is also often aberrantly active in NSCLC, its clinical significance in NSCLC was primarily thought to be in conferring resistance to certain therapies, including EGFR TKIs. However, interest in MET as a therapeutic target, particularly in NSCLC, has increased with the realization that it may act as a bona fide primary oncogenic driver when activated by mutations causing skipping of exon 14 in the *MET* gene (*MET* exon 14).

To date, there have been three therapeutic approaches to targeting MET: MET TKIs, anti-MET or anti-hepatocyte growth factor (HGF; natural ligand of MET) antibodies, and anti-MET antibody–drug conjugates [1,2]. Anti-MET antibodies have failed to show efficacy better than placebo in patients selected for MET overexpression; two phase III trials were halted due to poorer survival with anti-MET antibodies than with placebo [3,4]. Anti-MET antibody–drug conjugates are a more recent approach; telisotuzumab vedotin, an anti-MET antibody conjugated with monomethyl auristatin E (a tubulin polymerization inhibitor), has shown favorable antitumor activity in patients with NSCLC and MET overexpression in a phase I study and is being investigated in a phase II trial (NCT03539536) [5–7]. MET TKIs have been investigated in patients with NSCLC harboring MET overexpression, *MET* amplification, or *MET* exon 14 skipping; case reports have reported activity in NSCLC with *MET* fusions [8–10].

In this review, we discuss the prospects for selective MET TKIs in the treatment of NSCLC harboring *MET* exon 14 skipping.

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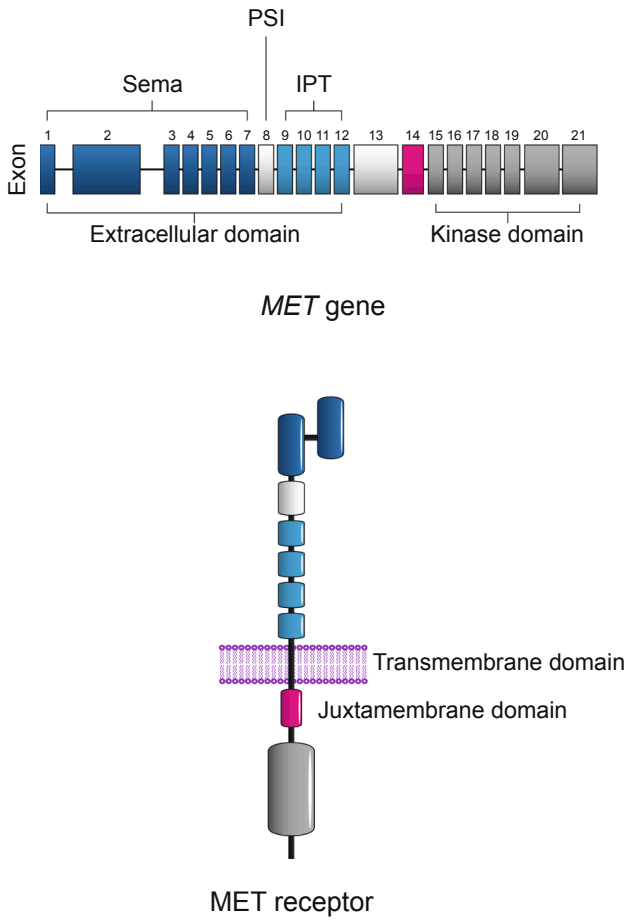

Fig. 1. MET gene and the encoded MET receptor. IPT: found in Immunoglobulins, Plexins, Transcription factors; PSI: found in Plexins, Semaphorins, Integrins; Sema: semaphorin domain.

The MET receptor tyrosine kinase

The *MET* gene is located on human chromosome 7 (7q31), includes 21 exons and 20 introns, and encodes a protein with an apparent molecular weight of 190 kDa [11] (Fig. 1). MET is a RTK normally expressed by epithelial cells, and is also found on endothelial cells, neurons, hepatocytes, and hematopoietic cells [12]. MET has one known natural ligand: HGF. HGF binding to MET induces receptor dimerization and autophosphorylation of tyrosine residues located in the intracellular portion of the receptor [13] (Fig. 2). These residues can also be transphosphorylated by other RTKs, such as the EGFR and, in particular, receptor originated from Nantes (RON), a receptor with structural homology to MET that appears to be required for oncogenic addiction to MET in some circumstances [14,15]. Phosphorylation of tyrosine residues in the MET cytoplasmic tail creates docking sites that engage molecules involved in intracellular signaling pathways, including mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K), signal transducers and activators of transcription (STAT), and nuclear factor kappa B (NFκ-B) [13]. These pathways regulate the transcriptional activity of genes that mediate the cellular effects of MET activation.

Phosphorylation of tyrosine residue Y1003 in the cytoplasmic juxtamembrane domain, encoded by exon 14 of *MET*, creates a docking site for the E3 ubiquitin ligase Casitas B-lineage lymphoma (CBL), initiating the ubiquitination of MET and removal of HGF-bound MET from the cell surface [16]. MET activity depends upon a dynamic balance between MET activation and its removal from the cell surface, with both processes driven by binding of HGF [17]. CBL can also be deleted or mutated in NSCLC, which can lead to activation of MET [16,18].

MET activation induces cellular proliferation, survival, mobilization, and invasion, while altered cell morphology and remodeling of cell–cell and cell–matrix adhesions initiate epithelial–mesenchymal transition [12]. MET has a critical role in embryogenesis, enabling tissue remodeling, and in adults plays a more subtle role in tissue repair [19].

Abnormal MET activity is observed in a wide range of solid tumors [20], and can be caused by activating *MET* mutations, *MET* amplification, overexpression of MET or HGF, or transactivation by other RTKs such as RON [17,18]. *MET* aberrations are associated with rapid tumor growth, aggressively invasive disease, and poor prognosis [21], as well as resistance to anticancer therapy. Different *MET* aberrations may, however, vary in their oncogenic potential; for example, poor prognosis in NSCLC appears to be more clearly associated with *MET* amplification than with MET overexpression.

MET exon 14 skipping

Following transcription of the *MET* gene, the 21-exon precursor messenger ribonucleic acid (RNA) is spliced, guided by specific sequences in the 5′ and 3′ introns [22]. Skipping of exon 14 during splicing is associated with a mutation in one of the exon 14 splice regions located within the exon–intron boundaries (*MET* exon 14 mutation hotspots; Fig. 3), although additional genomic alterations within exon 14 have also been noted [23,24]. The resulting in-frame deletion of 141 base pairs leads to translation of a shortened MET receptor lacking the juxtamembrane domain on the cytoplasmic side of the plasma membrane. Because the deletion is in frame and exon 14 encodes a discrete domain, the resulting shortened MET receptor retains affinity for HGF and a transmembrane location with catalytic activity.

The first somatic mutation causing *MET* exon 14 skipping was found in the 5′ splice site junction of *MET* exon 14. This mutation was reported in deoxyribonucleic acid (DNA) isolated from small cell lung cancer (SCLC) in 2003, with the occurrence of mutations in NSCLC being reported in 2005 [23,24]. A mutational analysis of a series of NSCLC samples in 2006 subsequently identified a 22-base-pair deletion in the 5′ splice site junction of exon 14, a 28-base-pair deletion in the 3′ splice site, and a point mutation in the 3′ splice site, all of which generated *MET* exon 14 transcripts [25]. Moreover, in 2015, Frampton et al. conducted comprehensive genome profiling of 38,028 tumor specimens from unique patients, and identified 224 mutations responsible for *MET* exon 14 transcripts, including 126 distinct sequence variants in 221 specimens [26].

MET exon 14 skipping alterations are distinct from other *MET* aberrations and are strong oncogenic drivers

As a result of *MET* exon 14 skipping, MET lacks the juxtamembrane domain, which contains multiple sites involved in the regulation of MET signaling and cell survival, including the CBL binding site (Y1003) and associated ubiquitination sites [27] (Fig. 4). Consequently, endocytosis of HGF-activated *MET* exon 14 is compromised, leading to its accumulation as an active ligand/receptor complex on the cell surface [28] and sustained dysregulated activation of downstream signaling pathways [29]. In addition, the juxtamembrane domain is key to negative regulation of the intracellular kinase domain via protein kinase C phosphorylation of S985 [27]. Therefore, its disruption through *MET* exon 14 skipping can likely transition the closed kinase conformation to a more active conformation [30].

MET exon 14 skipping has been shown to drive the growth of tumor cells in preclinical models through high and persistent MET signaling [25,31]. *MET* exon 14 skipping is often found to be mutually exclusive with other known oncogenic drivers such as Kirsten rat sarcoma (KRAS), epidermal growth factor receptor (EGFR), and human epidermal growth

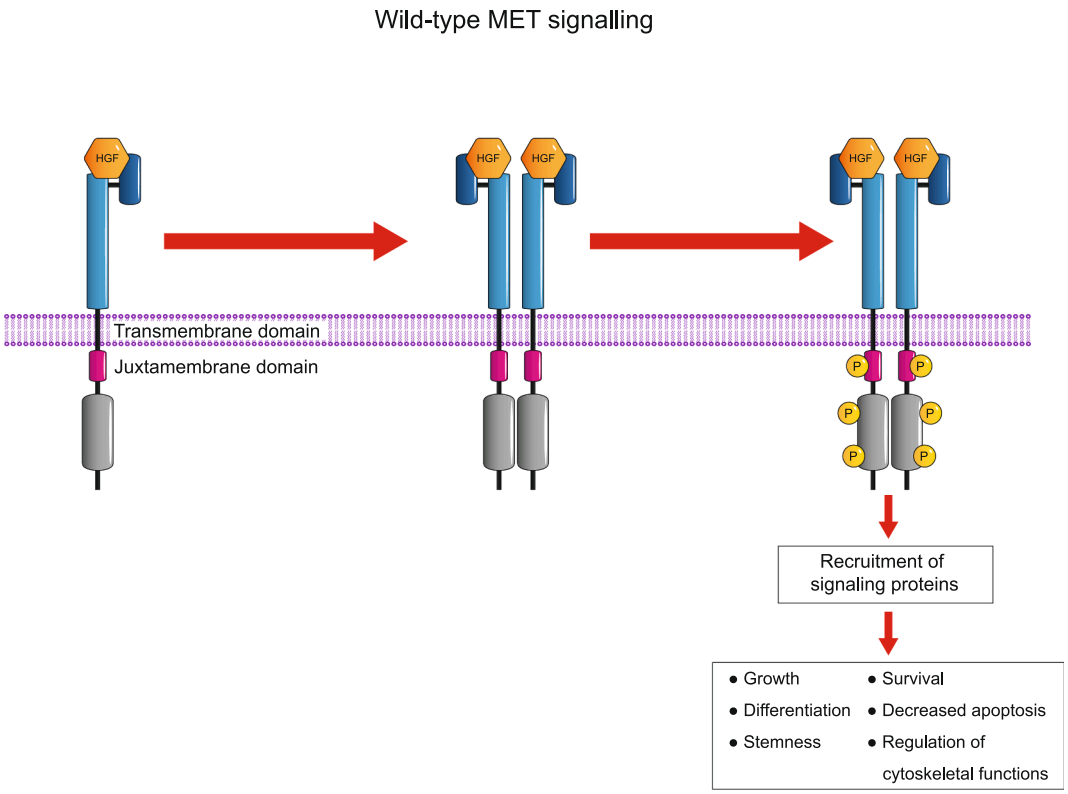

Fig. 2. Wild-type MET signaling. HGF: hepatocyte growth factor.

factor receptor 2 (HER2), indicating that *MET* exon 14 can promote oncogenesis in the absence of other oncogenic drivers [26,32].

The prevalence of *MET* exon 14 skipping across different cancer types differs from those of other *MET* aberrations. *MET* amplifications and MET protein overexpression are common in many solid tumors, particularly hepatocellular carcinoma [33]. In contrast, an extensive study by Frampton et al. detected *MET* exon 14 skipping most frequently in lung adenocarcinoma (3%), other lung neoplasms (2.3%), brain glioma (0.4%), and tumors of unknown origin (0.4%) [26]. Similarly, analysis of 4422 samples from 12 different malignancies showed that *MET* exon 14 skipping was most common in lung adenocarcinoma (~3%), with lower prevalence in bladder urothelial carcinoma, head and neck squamous cell carcinoma, kidney renal clear cell carcinoma, lung squamous cell carcinoma, and colon adenocarcinoma, and none in other tumor types [34]. Comprehensive genomic profiling of 11,205 lung cancers identified 298 *MET* exon 14 NSCLC samples (2.7%) [35]. *MET* exon 14 skipping was most frequently detected in patients with adenosquamous (8.2% of 98 samples) or sarcomatoid (7.7% of 104 samples) histologies. In patients with adenocarcinoma (n = 7149), squamous cell carcinoma (n = 1206), or NSCLC histologic subtype not otherwise specified (n = 1659), *MET* exon 14 skipping was detected in 205 (2.8%), 25 (2.1%), and 49 (3.0%), respectively. At a lower frequency, *MET* exon 14 skipping was also reported in patients with large cell NSCLC (0.8%) or SCLC (0.2%). In a large cohort of Chinese patients with NSCLC, *MET* exon 14 skipping rates were 2.6% in adenocarcinoma, 4.8% in adenosquamous carcinoma, and 31.8% in sarcomatoid carcinoma [36].

The prognostic impact of *MET* exon 14 skipping has not been studied extensively, although both *MET* exon 14 skipping and high-level *MET* amplification have been found to be independent prognostic factors of poor survival in a multivariable analysis [36]. The prognosis of patients with MET dysregulation who do not receive treatment with a MET inhibitor appears to be inferior, for both NSCLC harboring *MET* exon 14 skipping or *MET* amplification, or both alterations concurrently [37,38].

In another study of East Asian patients with stage I to stage IIIA NSCLC, multivariate analysis showed that patients with tumors harboring *MET* exon 14 skipping had a higher recurrence rate post-resection than patients with *ALK* (*ALK* fusion versus *MET* exon 14 skipping, hazard ratio [HR] 0.283; 95% confidence interval [CI], 0.119–0.670; P = 0.004), although overall survival was similar to that in patients with other mutations (*EGFR* mutation, *ROS1* fusion, *ALK* fusion, *RET* fusion) or none of these mutations, after adjusting for pathologic stage and other factors [39]. Overall, there is evidence that *MET* exon 14 skipping alterations are associated with poorer outcomes in patients with NSCLC, which, together with its oncogenic driver potential and prevalence in NSCLC, makes *MET* exon 14 an attractive therapeutic target.

Tumors with *MET* exon 14 skipping are sensitive to MET TKIs

Preclinical and clinical evidence suggest that tumors with *MET* exon 14 skipping alterations are sensitive to MET TKIs (see Table 1 for an overview of MET TKIs that have shown activity and/or are in ongoing clinical development). In particular, *MET* exon 14 skipping tumor models have been shown to respond to MET TKIs [31], including capmatinib [26,40], glesatinib [41], AMG337 [42], and tepotinib [43].

The first clinical evidence of *MET* exon 14 skipping tumors responding to MET TKIs came from studies using crizotinib, an inhibitor of anaplastic lymphoma kinase (ALK), c-ros oncogene 1 (ROS1), and RON, as well as MET [16,44]. Crizotinib showed efficacy in patients with *MET* exon 14 skipping tumors, possibly due to its MET-inhibitory activity [16,45–48]. Data from a large dose-expansion cohort (N = 69) of a phase I trial with crizotinib (PROFILE 1001; NCT00585195) reported encouraging outcomes in patients with advanced NSCLC and *MET* exon 14 skipping [49]. Based on this, crizotinib received breakthrough therapy designation from the United States Food and Drug Administration (US FDA) in May 2018 for the treatment of metastatic NSCLC in patients with *MET* exon 14 skipping alterations and progression on or after platinum-based chemotherapy [48,50]. The AcSé

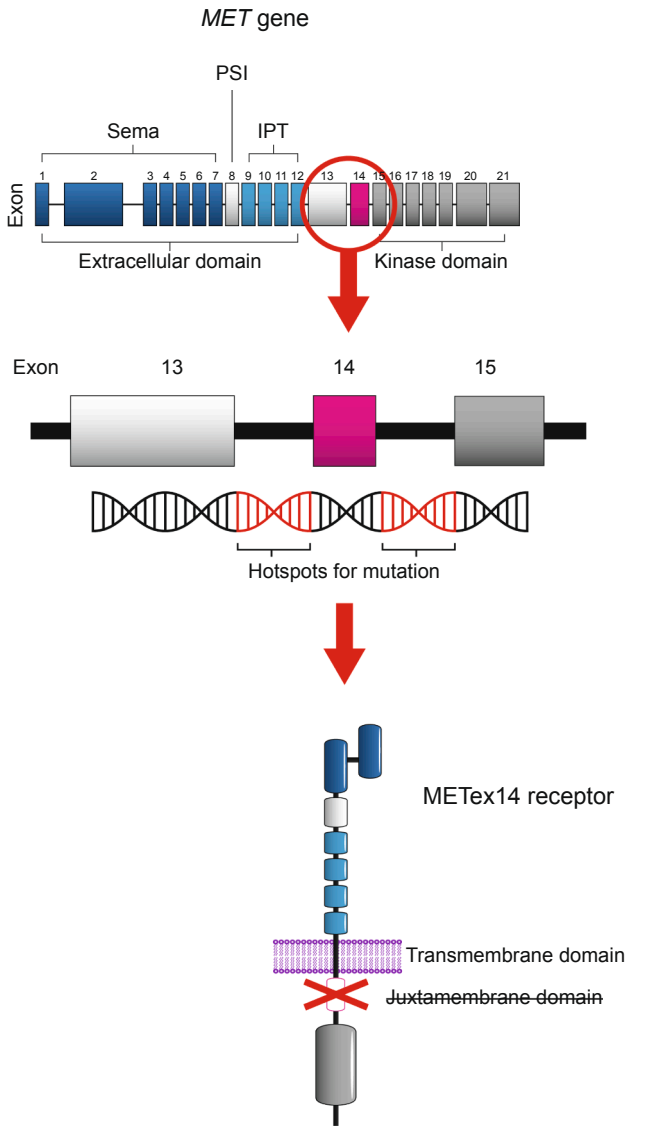

Fig. 3. *MET* exon 14 skipping and loss of the juxtamembrane domain. IPT: found in Immunoglobulins, Plexins, Transcription factors; PSI: found in Plexins, Semaphorins, Integrins; Sema: semaphorin domain.

crizotinib program developed by the French National Cancer Institute performed biomarker testing to identify patients with molecular alterations targeted by crizotinib and enrolled them into a phase II study of crizotinib [51]. Tumor samples of 1192 NSCLC patients were tested for *MET* mutations (exons 14 and 16–19) using next-generation sequencing: 74 (6.2%) were positive and 28 enrolled in the study (25 patients had *MET* exon 14 skipping). In these 25 pretreated patients, an encouraging overall response rate of 40% was reported. However, a phase II trial of crizotinib in 26 patients with pretreated NSCLC with *MET* amplification (n = 16) or *MET* exon 14 mutation (n = 10 [one patient had both *MET* amplification and *MET* exon 14 mutation]) (METROS study, NCT02499614) recently reported limited benefit in terms of objective response rate (ORR), progression-free survival, or overall survival among patients with *MET* exon 14 skipping [52]. A phase II study of crizotinib in Japanese patients with NSCLC harboring *MET* alterations is ongoing (Co-MET; UMIN000031623). Nineteen patients with *MET* exon 14 skipping will be recruited in Cohort A; Cohort B will recruit ten patients with tumors harboring *MET* amplification. The primary endpoint is ORR [53].

The TKI cabozantinib, which inhibits multiple RTKs in addition to MET, has also been reported to have efficacy in *MET* exon 14 skipping tumors [54,55]. An Italian phase II trial is currently evaluating cabozantinib in patients with *MET*-amplified NSCLC or *MET* exon 14 skipping NSCLC (CABinMET study, NCT03911193). A phase II trial of the multitargeted TKI merestinib (LY2801653) [56] in patients with advanced NSCLC with *MET* exon 14 skipping is ongoing (NCT02920996). An overview of pivotal clinical trials of MET inhibitors in patients with NSCLC harboring *MET* exon 14 skipping is presented in Table 2.

A multicenter retrospective analysis conducted to determine whether treatment with MET TKIs impacts survival in patients with NSCLC harboring *MET* exon 14 skipping found that, of 27 patients with metastatic disease who received at least one MET TKI (including crizotinib, glesatinib, and capmatinib), median overall survival was 24.6 months. A model adjusting for first- or second-line MET TKI therapy as a time-dependent covariate showed that MET TKI treatment significantly prolonged survival versus no MET TKI treatment (HR 0.11; 95% CI, 0.01–0.92; P = 0.04) [57]. Further data from 87 patients with *MET* exon 14 skipping NSCLC reported a median overall survival of 25.3 months for those who had received a MET inhibitor (n = 36) versus 10.9 months for those who had not (n = 51) [38]. *MET* exon 14 skipping NSCLC tumors can also express high levels of programmed cell death-ligand 1 (PD-L1) [38,58,59]; however, notably, this does not appear to translate into clinical benefit with PD-L1-targeted immunotherapies [58,59]. This finding, together with the evidence of clinical activity of MET inhibitors, suggests that targeted therapy with selective MET inhibitors is a more appropriate treatment choice than immunotherapy in patients with NSCLC harboring *MET* exon 14 skipping.

Given that *MET* exon 14 skipping alterations drive carcinogenesis through MET activity in the absence of other oncogenic drivers, it is likely that despite the lack of selectivity of the aforementioned TKIs, MET inhibition is central to their activity in tumors harboring *MET* exon 14 skipping. However, appropriate trials of agents that are potent and selective inhibitors of MET will confirm this.

Selective MET inhibitors are promising therapies for patients with *MET* exon 14 skipping-positive tumors

MET-selective TKIs are attractive potential treatments for *MET* exon 14 skipping tumors because they target only the activity associated with this primary driver. Thus, unlike non-selective MET inhibitors, they cause little off-target toxicity. Reduced toxicity improves tolerability and enables dosing at levels that cause profound inhibition of MET kinase activity, thus maximizing efficacy. Based on this rationale, several selective MET inhibitors are being investigated in patients with *MET* exon 14 skipping lung tumors, including capmatinib, savolitinib, and tepotinib (Table 1, Table 2).

Capmatinib (INC280) is an oral, adenosine triphosphate (ATP)-competitive MET inhibitor that has shown potent and selective inhibitory activity against MET *in vitro*, as well as antitumor activity in MET-dependent cell lines and in a MET-driven mouse xenograft model [60,61]. A phase I study (NCT01324479) recruiting patients with advanced NSCLC and aberrant MET expression identified four patients harboring *MET* exon 14 skipping. Of these, two patients had a confirmed partial response and one a complete response [62]. A current phase II trial of capmatinib (GEOMETRY *mono-1*; NCT02414139) includes cohorts of patients with advanced *EGFR* wild-type, *ALK* rearrangement-negative NSCLC with *MET* alterations, including *MET* exon 14 skipping, who are either treatment naïve or have received 1–2 prior lines of therapy, but not with a MET inhibitor. Data from 97 capmatinib-treated patients with *MET* exon 14 skipping advanced NSCLC, reported a higher ORR in treatment-naïve patients (which included patients with *MET* gene amplifications) than in the subgroup who had received 1–2 previous lines of therapy. Additionally, progression-free survival was also higher in treatment-naïve patients, while duration of response was similar between groups [63]. Notwithstanding these promising response results, longer-term data will be required to

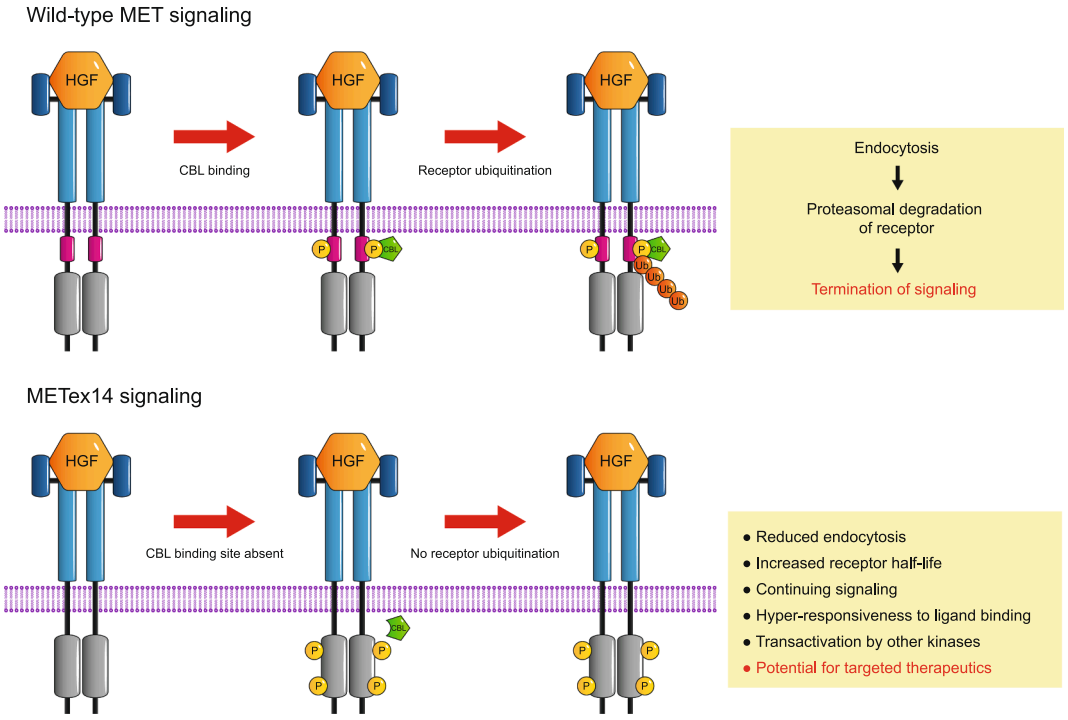

Fig. 4. Impact of *MET* exon 14 skipping on receptor ubiquitination and downstream effects. CBL: Casitas B-lineage lymphoma; HGF: hepatocyte growth factor; Ub: ubiquitination.

inform the ideal treatment sequence. Capmatinib was recently granted breakthrough therapy and orphan drug designation for patients with NSCLC harboring *MET* exon 14 skipping by the US FDA [64]. A phase II study under an umbrella trial for NSCLC is ongoing in Korea in pre-treated patients with NSCLC carrying *MET* exon 14 skipping alterations who have not received more than two lines of prior systemic therapy (STARTER_cMET study, NCT03693339). An additional phase II trial is ongoing in patients with *MET* exon 14 mutation-positive NSCLC who have received or refused prior platinum-containing chemotherapy and received MET inhibitor therapy immediately prior to trial therapy (NCT02750215). In patients with treatment-naïve NSCLC harboring *MET* exon 14 skipping, a randomized phase II trial is evaluating the combination of capmatinib with immunotherapy (spartalizumab, an anti-PD-1 antibody) compared with capmatinib alone (NCT04323436).

Savolitinib is an orally available, selective MET inhibitor that has demonstrated inhibitory activity against cell lines with exon 14 skipping mutations [65], and is being assessed in a phase II trial of patients with locally advanced/metastatic *MET* exon 14 mutation-positive NSCLC of sarcomatoid and other histologies (NCT02897479). Preliminary data from 50 patients with *MET* exon 14 skipping mutation-positive NSCLC showed an encouraging ORR [66].

Bozitinib (APL-101/PLB-1001, formerly CBT-101) is an ATP-competitive, small-molecule oral MET inhibitor currently under investigation in phase I/II trials as a single agent in patients with solid tumors, NSCLC, and glioblastomas, and in combination with PD-L1 inhibitors in patients with hepatocellular carcinoma and renal cell carcinoma. The drug has demonstrated anticancer effects in a variety of human xenograft tumor models with MET dysregulation and has shown promise in glioblastoma owing to its ability to cross the blood–brain barrier. The safety and preliminary efficacy of the drug have been demonstrated in a limited number of patients with chemotherapy-resistant, *MET*-altered gliomas [67,68]. A phase II trial is evaluating bozitinib in patients with NSCLC harboring *MET* exon 14 skipping in China (NCT04258033).

Tepotinib, an oral, ATP-competitive, and highly selective MET inhibitor, showed potent inhibitory activity against MET in cancer cell lines, and antitumor activity in mouse xenograft models of human tumors, regardless of whether MET activation was HGF dependent or independent [43]. A phase II study is ongoing, assessing tepotinib in treatment-naïve or previously treated patients with advanced NSCLC harboring *MET* exon 14 skipping as detected by tissue or liquid biopsy (VISION study, NCT02864992). The primary endpoint is ORR and preliminary data has shown encouraging signs of activity [69]. The Japanese Ministry of Health, Labour and Welfare approved tepotinib for use in patients with advanced NSCLC harboring *MET* exon 14 skipping in March 2020 [70], alongside Archer®MET companion diagnostic for detection of *MET* exon 14 skipping [71]. In September 2019, tepotinib received US FDA breakthrough therapy designation in patients with metastatic NSCLC harboring *MET* exon 14 skipping alterations who progressed following platinum-based cancer therapy [72].

Outstanding questions regarding MET inhibition in *MET* exon 14 skipping tumors

How do *MET* exon 14 mutations interact with other tumor aberrations? *MET* exon 14 mutations are notable in that they appear to drive tumors in the absence of other driver oncogenes but do co-exist with mutations in *KRAS*, *ROS1*, and *EGFR*, likely as a result of low *MET* exon 14 mutant allele frequency in these tumors [26,32,38,73,74]. Genomic profiling of 298 *MET* exon 14 NSCLC samples found concurrent *MDM2* amplification in 35% of tumors [35]. In another study, overexpression of mouse double minute 2 (MDM2) or p53 protein was found in nine (60.0%) and two (13%) tumors, respectively [39]. Resistance to crizotinib has also been shown to occur due to wild-type *KRAS* amplification [75] and *KRAS* G12 mutations have been found in 4% of patients with *MET* exon 14 mutations [76], suggesting this pathway could be a resistance mechanism to MET TKI inhibitors [77]. Therefore, it may be necessary to combine selective MET inhibitors with other targeted therapies where co-mutations have the potential to confer resistance to MET inhibitor monotherapy [74].

Has resistance to MET inhibitors been described in patients with *MET* exon 14 mutation skipping? Impressive tumor responses to MET inhibitors such as crizotinib, cabozantinib, tepotinib, and capmatinib

Table 1
Agents with evidence of activity against tumors harboring *MET* exon 14 skipping and/or that are in ongoing clinical development.

Agent	Agent type, target, and selectivity	Known target(s)	Stage of development	Evidence of activity against *MET* exon 14 skipping
Bozitinb (APL-101/PLB-1001; formerly CBT-101) (Apollomics/Beijing Pearl Biotechnology Co. Ltd.)	ATP-competitive TKI	MET	Phase I	Phase I dose-escalation trial reported signs of preliminary efficacy in two patients with *MET*-altered gliomas resistant to chemotherapy, including one with *MET* exon 14 [68]
Cabozantinib (XL184) (Exelixis)	ATP-competitive TKI	MET, VEGFR-1, VEGFR-2, VEGFR-3, RET, Kit, Tie-2, Flt-3	Phase III	Case report on activity in intracranial metastasis of *MET* exon 14 mutation-positive NSCLC [54]
Crizotinib (PF-02341066) (Pfizer)	ATP-competitive TKI	ALK, MET, RON, ROS1	Phase II	Phase I (PROFILE 1001) dose-expansion cohort data reported encouraging outcomes among patients with *MET* exon 14 skipping [49] Phase II AcSé [51] and National Lung Matrix Trial [99] studies reported encouraging responses in patients with *MET* exon 14 skipping NSCLC Phase II trial data showed limited activity in patients with *MET* exon 14 mutation-positive NSCLC [52]
Merestinib (LY2801653) (Eli Lilly and Company)	ATP-competitive TKI	RON, MET, Flt-3, AXL, MERTK, TEK, ROS1, NTRK1/2/3, DDR1/2	Phase II	Activity as a single agent and when combined with emibetuzumab in a mouse model of *MET* exon 14 skipping gastric cancer [100]
Glesatinib (MGCD265) (Mirati Therapeutics)	ATP-competitive TKI	AXL, MET	Phase II	Preclinical and clinical activity in NSCLC harboring *MET* exon 14 skipping [41,101]
AMG337 (Amgen)	ATP-competitive TKI	MET	Phase II	Preclinical data indicating activity in *MET* exon 14 skipping gastric cancer cell lines [42]
Capmatinib (INC280) (Novartis)	ATP-competitive TKI	MET	Phase II	Data from phase II GEOMETRY *mono-1* trial demonstrating activity in patients with NSCLC harboring *MET* exon 14 skipping (across treatment lines) [63]
Emibetuzumab (LY2875358) (Eli Lilly & Company)	Antagonist MAb	MET	Phase III	No activity as a single agent in a mouse model of *MET* exon 14 mutation-positive gastric cancer, but combination with merestinib may be active [100]
Savolitinib (AZD6094) (AstraZeneca)	ATP-competitive TKI	MET	Phase II	Interim data from phase II study in patients with *MET* exon 14 skipping NSCLC showed encouraging ORR [102]
Tepotinib (MSC2156119J) (Merck KGaA, Darmstadt, Germany)	ATP-competitive TKI	MET	Phase II	Interim data from phase II VISION trial demonstrating activity in patients with NSCLC harboring *MET* exon 14 skipping (across treatment lines) [69]

ALK: anaplastic lymphoma kinase; ATP: adenosine triphosphate; DDR1/2: discoidin domain receptor tyrosine kinase 1/2; FLT3: fms-like tyrosine kinase 3; MAb: monoclonal antibody; MERTK: MER receptor tyrosine kinase; NSCLC: non-small cell lung cancer; NTRK: neurotrophic-tropomyosin receptor kinase; ORR: objective response rate; RON: receptor originated from Nantes; ROS1: c-ros oncogene 1; Tie-2: tyrosine-protein kinase receptor; TKI: tyrosine kinase inhibitor; VEGFR: vascular endothelial growth factor receptor.

Table 2
Pivotal clinical trials of MET inhibitors in patients with NSCLC harboring *MET* exon 14 skipping and baseline characteristics of patients enrolled.

	Crizotinib [48,49]	Capmatinib [38,63,103]	Savolitinib [66,102]	Tepotinib [69]
Study	PROFILE 1001	GEOMETRY *mono-1*		VISION
ClinicalTrials.gov identifier	NCT00585195	NCT02414139	NCT02897479	NCT02864992
Study design	Phase I, open label, multicenter	Phase II, open label, multicenter	Phase II, open label, multicenter	Phase II, open label, multicenter
Overall patients	600 (actual)	364 (estimated)	50 (estimated)	280 (estimated)
Patients with *MET* exon 14 skipping	N = 69	N = 97 enrolled at Feb 26, 2019 cut-off Cohort 4: pretreated patients with *MET* exon 14, regardless of *MET* GCN (N = 69) Cohort 5b: treatment-naïve *MET* exon 14 regardless of GCN (N = 28) Expansion: pretreated *MET* exon 14 regardless of GCN (N = 30) Expansion: treatment-naïve *MET* exon 14 regardless of GCN (N = 27)	N = 50 enrolled at Apr 10, 2019 cut-off Additional cohort of patients pre-treated with MET inhibitor	N = 87 enrolled at Feb 18, 2019 cut-off
Recruitment as of April 2020	Complete	Complete: Cohorts 4 and 5b Ongoing: 6 and 7	Ongoing	Ongoing
Treatment	250 mg orally twice daily until disease progression, death, or unacceptable toxicity	400 mg orally twice daily until disease progression, death, or unacceptable toxicity	600 mg (BW ≥ 50 kg) or 400 mg (BW < 50 kg) orally once daily until disease progression, death, or unacceptable toxicity	500 mg (500 mg tepotinib hydrochloride hydrate, which contains 450 mg tepotinib free base) orally once daily until disease progression, death, or unacceptable toxicity
Inclusion criteria	Advanced NSCLC ECOG PS of 0 or 1	Advanced NSCLC (any histology). Stage IIIB/IV NSCLC ECOG PS 0–1 *EGFR* wt, *ALK*-negative	Histologically or cytologically documented locally advanced or metastatic PSC or other NSCLC ECOG PS 0–1 (2 may be allowed) *EGFR/ALK/ROS1* wt	Histologically confirmed advanced NSCLC (all histologies) ECOG PS 0–1 *EGFR* wt, *ALK* wt
Prior treatment	No prior MET-directed targeted therapy For pretreated patients, no major surgery, radiation therapy, or anticancer therapy within 2–4 weeks of starting study treatment	No prior MET inhibitor For pretreated patients, no previous anticancer agents within 4 weeks or ≤ 5 × half-life of the agent before first dose	No prior MET inhibitor (Cohort 1) Palliative radiotherapy allowed For pretreated patients, no radiotherapy or any anticancer therapy within 3 weeks prior to initiation of study treatment, or received TKI treatment within 2 weeks prior to initiation of study treatment	No prior MET inhibitor Palliative radiotherapy allowed For pretreated patients, no radiotherapy or anticancer therapy within 21 days prior to the first dose of trial treatment
MET exon 14 detected	*MET* exon 14 status identified by local molecular profiling Retrospective analysis for *MET* exon 14 status was performed by: Central testing of available tumor tissue (FoundationOne companion diagnostic, Foundation Medicine, Inc.) Circulating cell-free DNA analysis (PlasmaSELECT 64, PGDx)	*MET* exon 14 status determined centrally by RT-PCR Patients with *MET* exon 14 skipping had tissue biopsy samples retrospectively tested using the FoundationOne hybrid capture assay (next-generation sequencing)	*MET* exon 14 skipping identified in tumor, plasma, and/or pleural effusion. Mutations identified by local lab required to be confirmed by central lab test	Next-generation sequencing panels Guardant360® (73-gene) and Oncomine™ Focus Assay (OFA; 52-gene) were used to identify *MET* exon 14 skipping in circulating tumor DNA and tumor tissue respectively. Archer® Lung FUSIONPlex® was also used. Analyses performed by a central laboratory DNA
Brain metastases	Treated brain metastases allowed if stable for ≥ 2 weeks	Neurologically stable or asymptomatic brain metastases allowed Exclusion: symptomatic CNS metastases that are neurologically unstable or have required increasing doses of steroids within the 2 weeks prior to study entry to manage CNS symptoms		Patients who are neurologically stable on symptomatic therapy allowed. Asymptomatic untreated brain metastases ≤ 1 cm longest diameter allowed Exclusion: patients with active brain metastases or who have brain metastases as the only measurable lesion
Primary endpoint for *MET*ex14	ORR per investigator assessment (RECIST v1.0)	ORR per IRC (RECIST v1.1)	ORR per investigator assessment (RECIST v1.1)	ORR per IRC (RECIST v1.1)
Secondary endpoint for *MET*ex14	DoR, TTR, PFS, OS Safety	ORR per investigator assessment, DoR, TTR, DCR, PFS, OS Safety, PK, biomarkers, and patient-reported outcomes	DCR, DoR, TTR, PFS, 6-month PFS rate, OS Safety	ORR per investigator assessment, DoR, objective disease control, PFS, OS Safety, PK, and patient-reported outcomes

(*continued on next page*)

Table 2 (*continued*)

		Crizotinib [48,49]	Capmatinib [38,63,103]		Savolitinib [66,102]	Tepotinib [69]
Baseline characteristics						
	n (%)	Overall (N = 69)	1st line Cohort (N = 28)	2nd/3rd line Cohort (N = 69)	Overall (N = 50)	Overall (N = 87)
Age	Median (range)	72 (34–91)	71 (57–86)	71 (49–90)	68.8 (52.6–85.0)	74 (39–89)
Sex	Male	29 (42)	29 (42)	10 (36)	29 (58)	47 (54)
Race	Caucasian	50 (73)	24 (86)	49 (71)	NR (likely all Asian)	66 (76)
	Asian	11 (16)	4 (14)	19 (28)		17 (20)
	Other	8 (12)	0	1 (1)		4 (5)
Smoking history	No	26 (38)	18 (64)	40 (58)	28 (56)	38 (44)
	Yes	43 (62)	10 (36)	29 (42)	22 (44)	40 (46)
ECOG PS	0	19 (28)	7 (25)	16 (23)	8 (16)	22 (25)
	1	49 (71)	21 (75)	52 (75)	41 (82)	65 (75)
	≥ 2	1 (1)	0	1 (1)	1 (2)	0
Histology	Adenocarcinoma	58 (84)	25 (89)	53 (77)	26 (52)	75 (86)
	Squamous	3 (4)	2 (7)	6 (9)	NR	7 (8)
	Sarcomatoid	6 (9)	NR	NR	20 (40)	1 (1)
	Others	2 (3)	1 (46)	10 (5)	4 (8)	4 (5)
Brain metastases		NR	3 (11)	11 (16)	11 (22)	8 (9)
No. of prior regimens for advanced diseases	0	26 (38)	28 (100)	0	18 (36)	33 (38)
	1	29 (42)	0	51 (74)	≥ 1: 32 (64)	31 (36)
	≥ 2	14 (20)	0	18 (26)	NR	23 (26)

BW: bodyweight; CNS: central nervous system; DCR: disease control rate; DNA: deoxyribonucleic acid; DoR: duration of response; ECOG PS: Eastern Cooperative Oncology Group performance status; GCN: gene copy number; IRC: independent review committee; NR: not reported; NSCLC: non-small cell lung cancer; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PK: pharmacokinetics; PSC: pulmonary sarcomatoid carcinoma; RNA: ribonucleic acid; RT-PCR: reverse transcription polymerase chain reaction; TKI: tyrosine kinase inhibitor; TTR: time to therapeutic response; wt: wild-type.

Table 3
Comparison of assays for detecting *MET* exon 14 skipping used in pivotal trials in patients with NSCLC.

Category	FoundationOne® Liquid [104]	FoundationOne® CDx [105]	Archer® LiquidPlex™ [106]	Archer® FusionPlex™ Lung [107]	Guardant360® [108]	Oncomine Focus Assay [109]	PlasmaSELECT™ 64 [110]
Biopsy type	Liquid biopsy	Tissue biopsy	Liquid biopsy	Tumor biopsy	Liquid biopsy	Tumor biopsy	Liquid biopsy
Material read	Circulating tumor DNA	Tumor DNA	Circulating free DNA	Tumor mRNA	Circulating free DNA	Tumor DNA or mRNA	Circulating tumor DNA
Sample required	2 × 8.5 mL blood samples	50–1000 ng DNA	5–10 ng DNA	FFPE tissue; 20–250 ng DNA	10 mL blood sample for 5–30 ng DNA	FFPE tissue; 7 um thick and > 5 mm^2	2 × 10 mL blood samples
Number of genes interrogated	70 genes	324 genes	28 genes	14 genes	73 genes	52 genes	64 genes
Sensitivity	Can detect mutations if present in > 0.5% sample	Can detect mutation that represents 2–5% allele frequency	Can detect mutations if present in > 1% sample	Not reported	Can detect mutations if present in > 0.1% sample	100% detection if mutation is > 5% allele frequency	Not reported
Turnaround time	< 2 weeks	< 2 weeks	Not reported	Not reported	7 days	3 days	Not reported

DNA: deoxyribonucleic acid; FFPE: formalin-fixed paraffin-embedded; mRNA: messenger RNA.

have been reported in NSCLC harboring *MET* exon 14 skipping [16,26,45–48,54,69,78]. However, several resistance mechanisms have been reported, including additional mutations in *MET* exon 14 [79,80], upregulation of bypass signaling pathways, and/or the acquisition of additional oncogenic mutations. A study of mechanisms of resistance to the MET TKIs crizotinib and glesatinib reported acquired mutated *MET* exon 14 allele amplification or MET tyrosine kinase domain secondary site mutations and bypass track activation, including amplification of wild-type *KRAS*, *BRAF*, and/or *EGFR* [81]. Interestingly, the same study showed that one patient who acquired resistance to glesatinib through mutated *MET* exon 14 allele amplification reported a confirmed partial response after switching to crizotinib [81]. Another study of paired tumor biopsies reported resistance acquired via additional MET pathway alterations or via activation of other pathways, including EGFR and RAS [82]. Assessment of cell-free circulating tumor DNA from 289 patients with NSCLC harboring *MET* exon 14 skipping found frequent RAS-MAPK pathway alterations were associated with a lower response to MET TKIs [77]. This resistance to MET TKIs was overcome by co-treatment with crizotinib and the MEK inhibitor trametinib. Another preclinical study, in which resistance was induced in a cell line harboring *MET* exon 14 skipping by exposure to high levels of MET TKIs, provided evidence that resistance to type I and II MET TKIs may often be through different pathways [83].

Taken together, these findings suggest that mechanisms of resistance to different MET inhibitors are complex and diverse, and may vary due to differing mechanisms of action of MET inhibitors [41]. Clearly, novel therapeutic strategies will be needed to combat multiple complex resistance mechanisms [81], possibly in the form of sequencing or combination approaches [77,83].

What is the optimal position in the treatment sequence for selective MET inhibitors for patients with NSCLC harboring *MET* exon 14 skipping? Most patients treated with MET inhibitors in clinical studies will have received prior therapy, although ongoing studies with capmatinib, savolitinib, and tepotinib are also enrolling previously untreated patients. Data from capmatinib suggest the objective response could be higher if MET inhibitors are used for first-line treatment [63]; however, this was not observed in the studies with tepotinib [69] or savolitinib [66]. Confirmation of whether selective MET inhibitors are most effective in first or later lines, and as monotherapy or in combination with other therapies – including chemotherapy or immunotherapies (e.g. programmed cell death-1/PD-L1 inhibitors) – will require dedicated studies.

Challenges ahead for trials of MET inhibitors in patients with *MET* exon 14 skipping tumors

A major challenge is to identify enough patients with *MET* exon 14 skipping for ongoing and planned trials. The relatively low incidence of *MET* exon 14 mutations, estimated to be approximately 3% in NSCLC, as well as additional criteria such as poor patient health and inappropriate clinical histories, limit the number of eligible patients. Until recently, screening for *MET* exon 14 skipping was technically challenging. Despite being appropriate for analyzing MET overexpression [84], immunohistochemistry has proved unsuitable for detecting *MET* exon 14 skipping, as, so far, anti-MET antibodies are not able to distinguish the exon 14-skipped splice variant from wild-type MET [85]. DNA- or RNA-based approaches are more appropriate. DNA-based sequencing approaches are able to detect a range of genomic changes in the *MET* gene (point mutations, insertions, or deletions), any of which can interfere with the exon 14 splice sites [86] and lead to exon 14 skipping. RNA-based approaches need only to detect the fusion of exons 13 and 15 in the transcribed product [86]. As such, RNA *in situ* hybridization is possible [85], although RT-PCR-based sequencing approaches are also commonly used [86,87]. However, high-quality RNA is harder to obtain than DNA, as RNA is more susceptible to degradation [86,88].

Genomic analysis of resected tumor tissue has historically been the standard of care for identifying guideline-recommended biomarkers in metastatic NSCLC [89]. The presence of *MET* exon 14 skipping can now be analyzed in circulating tumor DNA or RNA extracted from patient plasma ('liquid biopsies'). Indeed, liquid biopsies can overcome limitations imposed by tumor inaccessibility and allow the impact of therapies to be tracked over time [90–92]. Commercial liquid and tissue assays are now readily available for detection of *MET* exon 14 skipping. Assays are available that use both DNA sequencing and detection of exon 13–15 fusion in mRNA; see Table 3 for an overview of assays used in pivotal MET inhibitor NSCLC clinical trials. Other multi-gene assays are also available, as well as single tests for *MET* exon 14 skipping (such as NeoGenomics *MET* Exon 14 Deletion Analysis) [93].

The ongoing VISION trial of tepotinib is prospectively recruiting patients with tumors that are positive for *MET* exon 14 as assessed by liquid biopsy testing or tissue biopsy testing (NCT02864992). In addition to the diagnostic techniques described above, it would be useful to identify clinicopathologic features that may help to characterize a patient population with *MET* exon 14 skipping, who would most likely be amenable to treatment with selective MET TKIs. Numerous studies suggest that patients with tumors harboring *MET* exon 14 mutations tend to be of older age (median age 72–73 years in most studies) [35,36,38,39,57,94–96]. Consequently, screening for *MET* exon 14 skipping in elderly patients may be particularly beneficial [97]. Likewise, *MET* exon 14 mutations appear to be enriched in tumors with sarcomatoid carcinoma [35,36,57], and some studies suggest that they are most commonly identified in females, non-smokers, and at an earlier pathology stage [57,96]. The baseline characteristics of patients with NSCLC harboring *MET* exon 14 skipping enrolled in pivotal clinical trials for MET TKIs broadly reflect the characteristics described above (Table 2). Patients in these trials were older in age (69–74 years) and approximately 50% had a smoking history (36–62%), although proportions of female:male patients were quite variable, with the crizotinib and capmatinib trials enrolling more female patients than the savolitinib and tepotinib trials.

Conclusions

MET has been pursued as a therapeutic cancer target for many years, but phase III trials of MET inhibitors in patients with solid tumors, including NSCLC, have been largely disappointing [98]. One possible reason for trials failing to meet their efficacy endpoints is the inclusion of patients with *MET* aberrations that are dispensable for tumor growth and thus insensitive to MET inhibition. *MET* exon 14 mutations have been identified as primary oncogenic drivers, raising the possibility that tumors with these specific mutations will be largely sensitive to MET inhibitors, as supported by clinical evidence with non-selective MET TKIs. If MET activity is a primary driver of *MET* exon 14 mutation-positive tumor growth, there is good reason to suppose that selective MET inhibitors have the potential to deliver better efficacy with a favorable safety profile.

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Declaration of Competing Interest

JS and CS are employees of Merck KGaA, Darmstadt, Germany. EF reports consulting, advisory or speaker's bureau roles with AbbVie, AstraZeneca, Blueprint Medicines, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eli Lilly, Guardant Health, Janssen, Medscape, Merck KGaA, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Takeda, and Touchtime. RS and MS report no conflicts of interest.

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