MET Exon 14 Skipping Alterations in Non-small Cell Lung Carcinoma—Current Understanding and Therapeutic Advances

Rashmi Shah,[1,2] Deepu Alex,[3] and Zhaolin Xu[1,2]

1. Department of Pathology, Dalhousie University, Halifax, NS, Canada; 2. Department of Anatomical Pathology, Queen Elizabeth II Health Science Centre, Halifax, NS, Canada; 3. Department of Pathology and Laboratory Medicine, BC Cancer, Vancouver, BC, Canada

Abnormal activation of mesenchymal epithelial transition (MET) receptor tyrosine kinase is associated with oncogenesis. Various underlying mechanisms, including alteration, amplification, gene rearrangement, and exon skipping in the transcript account for abnormal *MET* signaling. One of the critical alterations in *MET* leading to non-small cell lung carcinoma (NSCLC) is *MET* exon 14 (*METex14*) skipping, a driver mutation, which accounts for approximately 3–4% of lung adenocarcinoma. *METex14* skipping results in the formation of a functionally active and stable truncated receptor lacking the juxtamembrane regulatory domain responsible for *MET* ubiquitination. Several MET kinase inhibitors have been developed targeting MET receptors, and many are in clinical trials. The US Food and Drug Administration has recently approved capmatinib (Tabrecta™; Novartis, Basel, Switzerland) for the treatment of NSCLC with *METex14* skipping alteration. We review the current understanding of the implications of aberrant MET activation in NSCLC harboring *METex14* skipping alteration, available diagnostic options, potential therapies in the pipeline, and the future clinical landscape for such alterations.

Keywords

Non-small cell lung cancer, *MET* exon 14 skipping, *METex14,* diagnostic method, therapeutic intervention, targeted therapy, MET inhibitors, clinical trials

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Corresponding Author: Zhaolin Xu, Department of Anatomical Pathology, Queen Elizabeth II Health Science Centre, 5788 University Ave. Rm 734, Halifax B3H 1V8, NS, Canada. E: zhaolin.xu@nshealth.ca

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Advanced non-small cell lung carcinoma (NSCLC) treatment paradigms have evolved during the past decade. Identification of tumor-specific molecular alteration in cancer driver genes has led to the development of targeted therapies.[1–3] Most of the tumors harboring such alterations are sensitive to tyrosine kinase inhibitor (TKI) drugs, making such oncogenic drivers promising targets for the development of antitumor therapeutics.[4,5]

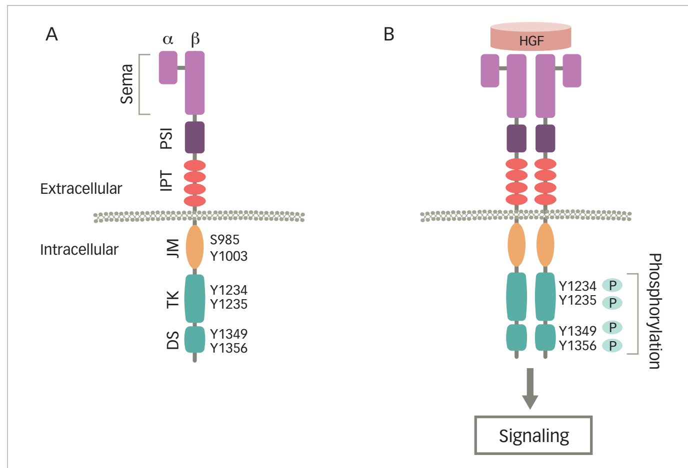
MET is a proto-oncogene that can act as an oncogenic driver after certain genomic alterations. It is expressed in many epithelial as well as mesenchymal cells, including hepatocytes, hematopoietic cells, and neuronal cells, and is essential for important biological processes, such as embryonic development and organogenesis.[6,7] However, mutations and its aberrant activation can promote tumor development and cancer progression by dysregulating downstream signaling pathways.[8,9] Initially, abnormal MET signaling was believed to be the mechanism of resistance acquired by NSCLC tumor cells against certain therapeutics.[10–12] Further reports demonstrated the role of *MET* alterations in sustained MET pathway dysregulation, leading to oncogenesis.[13–15] Clinically, NSCLCs with *MET* alterations are associated with poor prognosis, and these alterations have been recognized as an important therapeutic target in various cancers, including NSCLC.[16–18]

In this review, we discuss the current understanding of the implications of aberrant *MET* activation in NSCLC harboring *MET* exon 14 (*METex14*) skipping alteration, available diagnostic options, potential therapies in the pipeline, and the future clinical landscape.

Structure and function of the MET receptor

MET was first identified in a chemically treated human-osteosarcoma-derived cell line as a transforming gene from a fusion of TPR-MET.[19] The *MET* gene is located on chromosome 7q31 in the human genome, which spans about 125 kb DNA and contains 21 exons and 20 introns.[20] MET is encoded as a precursor, which is modified into a mature protein by proteolytic cleavage between its α and β subunits.[21] A mature MET protein is composed of a small α subunit (50 kDa) and a larger β (145 kDa) subunit linked together by a disulfide bridge.[8] The α subunit and a portion of β subunit together form the extracellular region of the heterodimer protein, while the remainder of the β subunit comprise the transmembrane and intracellular regions (*Figure 1A*).

Figure 1: Structure of MET receptor



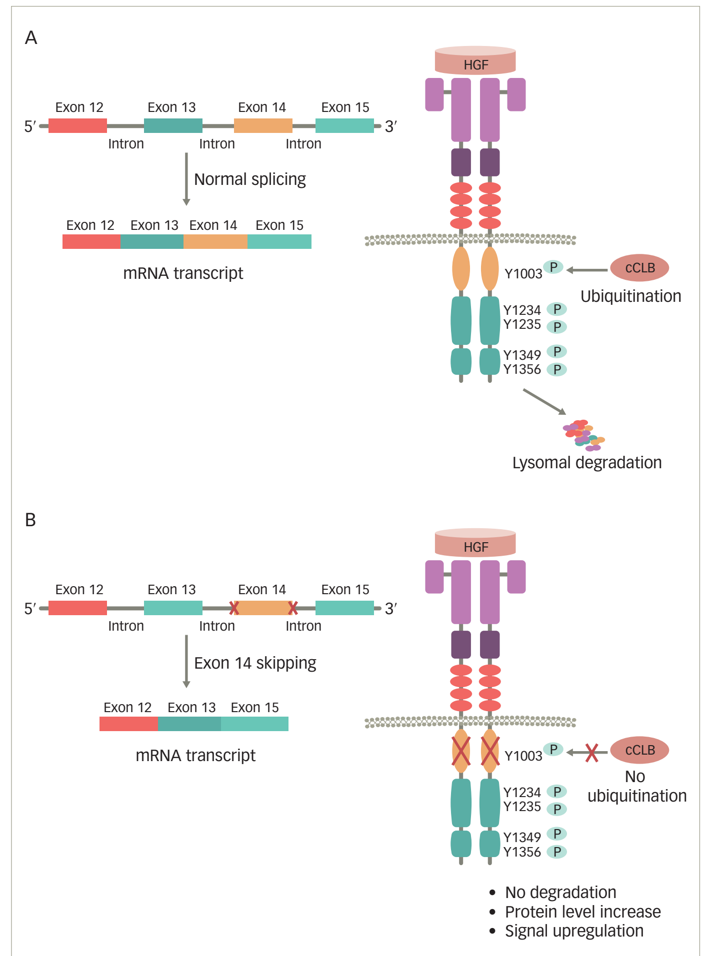
A: Schematic representation of MET receptor and its domain architecture. Important residues in regulatory, catalytic, and docking regions are shown. B: Activation of MET receptor. HGF binding to the N-terminal domain of MET results in its dimerization and autophosphorylation, leading to downstream signaling. Phosphorylation of tyrosine residues in regulatory, catalytic, and docking sites are shown.
DS = docking sites; HGF = hepatocyte growth factor; IPT = immunoglobulins-plexins-transcription factors; JM = juxtamembrane; MET = mesenchymal epithelial transition; PSI = plexins-semaphorins-integrins; Sema = semaphorin domain; TK = tyrosine kinase.

The extracellular component of MET contains three domains. N-terminal Sema (Sema-phorin) is the largest domain comprising 500 residues, which encompasses the α and a part of β subunits. The domain is essential for the ligand binding,[22] dimerization, and activation of MET.[23,24] The Sema domain is followed by the plexins-semaphorins-integrins (PSI) domain, containing four disulphide bonds, which are essential for the proper orientation of the receptor for ligand binding.[25] The PSI domain is connected to the transmembrane helix of MET through the immunoglobulin-plexins-transcription factor domain. The intracellular portion of the receptor includes a juxtamembrane (JM) domain, a tyrosine kinase (TK) catalytic domain, and a C-terminal multifunctional docking site.[22] Binding of its ligand, hepatocyte growth factor (HGF), which is also known as scatter factor, is essential for the activation of the kinase activity.[26,27] HGF is the only MET receptor ligand known so far and binds to the receptor with high affinity.[22,28]

MET signaling and its dysregulation in NSCLC

HGF binding to MET causes dimerization of the receptor leading to the autophosphorylation of intracellular residues Y1234 and Y1235 in the kinase domain followed by phosphorylation of two additional tyrosine residues, Y1349 and Y1356, in the C-terminal outside of the kinase domain (*Figure 1B*). Phosphorylation of the C-terminal residues leads to the formation of the docking site, which is necessary for the engagement of signaling partners.[29] Subsequently, adapter and effector proteins, such as GRB2 (growth factor receptor bound protein 2), GAB1 (GRB2 associated binding protein 1) and SHC (Src homology 2 domain-containing), bind to the docking site triggering downstream signaling.[30–36] MET signaling plays a crucial role in executing various cellular functions.[37–39] To maintain functional balance and cellular integrity, MET activity is regulated through various mechanisms. The active MET receptor can phosphorylate at residue Y1003 in the JM domain, a site for the recruitment of E3-ligase Casitas B-lineage lymphoma (CBL), and subsequently undergo ubiquitin-mediated lysosomal degradation, leading to the downregulation of *MET* (*Figure 2A*).[40–42] Additionally, it has been shown that phosphorylation of S985 at JM domain acts as a counterbalance to receptor activation, by

Figure 2: *MET* splicing event involving exon 14 and its consequences to MET stability



A: Normal MET splicing (left) leads to the biosynthesis of the normal MET receptor that can be targeted by E3-ubiquitin ligase cCBL and directed for lysosomal degradation (right). B: Mutations in the splice junctions of METex14 *can lead to exon skipping (left) resulting in the mature MET receptor that lacks juxtamembrane regulatory domain (right). Consequently, the receptor cannot be targeted by cCBL, impairing its lysosomal degradation thereby leading to the accumulation of the protein and increased receptor activity. CBL = Casitas B-lineage lymphoma; HGF = hepatocyte growth factor; MET = mesenchymal epithelial transition; mRNA = messenger RNA.*

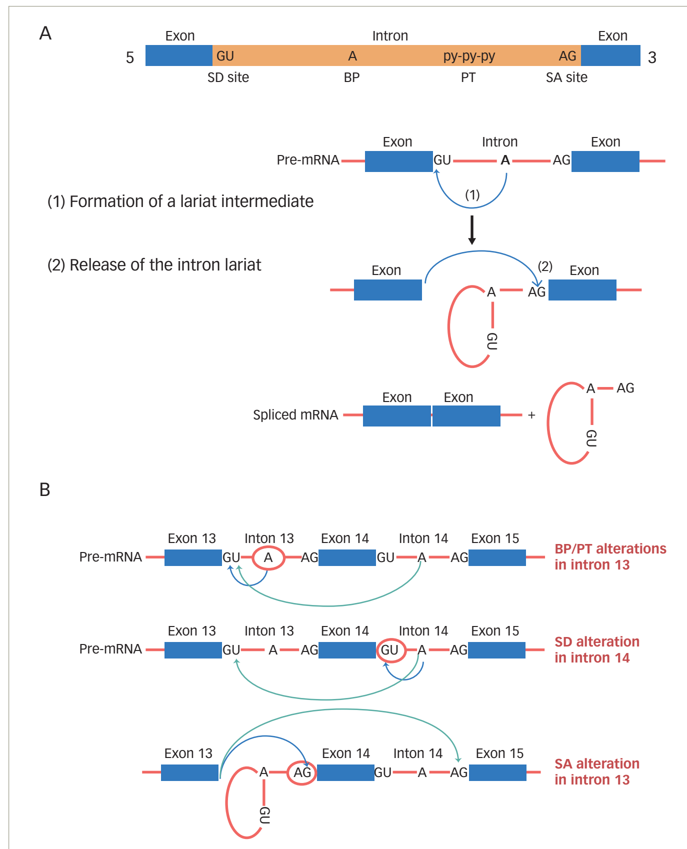
negatively regulating its activity, even in the presence of HGF.[43,44] Furthermore, proteolytic cleavage of MET by ADAMs (a disintegrin and metalloproteinase) and gamma-secretase may also contribute to the downregulation of MET receptor activity.[45,46]

Alterations in *MET* can result in the dysregulation of *MET* signaling, which is present in various solid tumors including NSCLC and is associated with tumor progression and metastasis.[47–49] Gene amplification, rearrangement, and skipping alterations, which lead to the overexpression and impaired degradation of MET, are the major underlying factors of aberrant MET activation.[50,51] Alteration or deletion of crucial residues in regulatory domain interfere with mechanisms that help to maintain MET receptor turnover leading to its accumulation and hyperactivation.[52–54]

METex14 skipping alteration in NSCLC

Skipping of *METex14* in NSCLC was first reported in 2005.[55] Substitutions or deletions at 3′ splice site in intron 13 or the 5′ end splice site of

Figure 3: Molecular mechanism of *MET* splicing and exon 14 skipping



A: Schematic representation pre mRNA splicing mechanism. GU: 5′ splice donor (SD) site, AG: 3′ splice acceptor (SA) site, A: branch point (BP) and PY-PY-PY: poly-pyrimidine tract (PT). The SA is flanked upstream by the BP and PT sites, resulting the exclusion of the intron forming of a lariat.
B: Molecular mechanism involved in METex14 *alterations. Molecular alterations in intron 13 or 14 involving donor or receptor sites can result in exon 14 skipping.*
BP = branch point; MET = mesenchymal epithelial transition; SA = splice acceptor; SD = splice donor; PT = poly-pyrimidine trace.

intron 14 results in *METex14* skipping.[56,57] This somatic alteration, at or around the splice junction of *METex14*, leads to the loss of exon 14 in the transcript and synthesis of the MET protein with an in-frame deletion of 47 amino acids in the JM domain (including residue Y1003) ablating the CBL-mediating ubiquitination and degradation of the receptor (*Figure 2B*).[24,58] Consequently, *METex14* skipping results in increased levels of MET protein, which can drive activation of downstream signaling pathways that promote tumor development.[57,59]

Splicing occurs through two sequential steps involving various parts of the intron. The splice donor site and the splice acceptor site are present at the 5′ and 3′ ends, respectively. The splice acceptor site is flanked upstream by the branch point and poly-pyrimidine tract sites (*Figure 3A*). First, the branch point nucleotide performs a nucleophilic attack on the first nucleotide of the intron at the splice donor site. This forms an intermediate loop or lariat. Subsequently, the 3′ end of the released exon performs a similar nucleophilic attack on the last nucleotide of the SA thereby fusing the exons and releasing the intron lariat.[60,61] Most *METex14* skipping alterations involve the branch point, poly-pyrimidine tract or splice acceptor site in intron 13 or the splice donor site in intron 14. As shown in *Figure 3B*, these alterations interfere with the splicing mechanism leading to exon 14 skipping.

Interestingly, *METex14* skipping alterations are primary oncogenic drivers in NSCLC, as these alterations are most likely to be mutually exclusive to other known oncogenic drivers, such as *KRAS*, *EGFR*, *ALK*, *ROS1* or *RET*.[57,62,63] Approximately 3–4% of NSCLCs harbor the *METex14* alteration (*Table 1*).[18,57,63–68] They are associated with some histologic subtypes of NSCLC but are not related to tumor stage. Among the histological subtypes, *METex14* skipping alteration is commonly found in sarcomatoid carcinoma (4.9–31%),[69–72] adenosquamous carcinoma (4–8%),[18,73,74] adenocarcinoma (3–4%),[1,18,57,65,75,76] and squamous cell carcinoma (2%).[74,77] Also, among adenocarcinomas, the predominant subtypes are acinar (35–52.9%) or solid subtypes (35.3–53%).[64,70,73,74,77] Clinically, *METex14* skipping abnormality is found mostly in patients of advanced age.[18,63,68,70,73,74,77,78]

Detection of *METex14* skipping alteration

Immunohistochemical analysis is a routine practice for the detection of *MET* overexpression. However, this technique on its own cannot specifically confirm *METex14* skipping or an underlying alteration. Therefore, DNA- and RNA-based molecular assays are preferred methods for the detection of *METex14* alteration. DNA-based sequencing assay can detect *MET* alterations such as insertions, deletions, point mutations, or duplications in splice sites, which may cause exon 14 skipping. Identification of such mutational hotspots leading to *METex14* skipping alteration are used to predict the possible skipping event. However, *METex14* skipping is associated with more than 120 reported sequence variants in splice sites, which makes it challenging to detect these mutations using only DNA-based assays.[57,63] Therefore, analysis of RNA transcripts allows for the verification of fusion between exons 13 and 15.[83] In ideal cases, both DNA- and RNA-based assays are used to complement each other for reliable detection of *METex14* alterations (*Table 1*).[1,18,63–82]

Reverse transcription polymerase chain reaction (RT-PCR), quantitative real time RT-PCR, and Sanger sequencing are the routine approaches used for the analysis of mutations and *METex*14 alteration.[18,73] mRNA transcript can be reverse transcribed using RT-PCR and corresponding complementary DNA is sequenced using Sanger techniques to verify exon 14 skipping from the sample. However, efficiency of the method relies on the quality of RNA, which is often derived from formalin-fixed paraffin-embedded or frozen tissue.[83] Sanger sequencing of *METex14* and its splice sites is still in routine practice for small scale analysis covering a portion of genomic region, which is performed using the PCR amplicon from genomic DNA covering exon 13 and exon 15, or cDNA from *MET* transcript. However, the European Society for Medical Oncology (ESMO) guidelines has proposed next-generation sequencing (NGS) and RNA sequencing, if possible, to detect *METex14* alteration in its updated guidelines on September 2020.[84,85]

Recently, NGS has become a common diagnostic method to identify METex14 alterations. This high throughput method allows the large-scale analysis of multiple samples in a short time with comprehensive genomic coverage.[1,64,86,87] The two most popular NGS sequencing panels used for targeted sequence profiling are hybridization capture and amplicon-based sequencing panels. The hybridization capture panel allows more comprehensive profiling for all alteration types, whereas the amplicon-

Table 1: Prevalence of *METex14* skipping alteration and diagnostic method for detection used in various studies

Location	Number of patients	Histology	Diagnostic method	Median age, years (range)	*METex14* alterations	Reference
USA	230	ADC	WES	68.5 (42–86)	4.3% (10/230)	CGARN (2014)[1]
Korea	70	ADC	RT-PCR followed by gDNA sequencing	65	2.9% (2/70)	Park et al. (2015)[75]
Hong- Kong	154	ADC	PCR-sanger sequencing	64.3 (28–90)	3.9% (6/154)	Yeung et al. (2015)[76]
USA	36	PSC	WES, RT-PCR followed by sanger sequencing	69.3 (38–87)	22.2% (8/36)	Liu et al. (2015)[69]
USA	54	NSCLC	RNA sequencing followed by gDNA sequencing	75 (43–84)	18.5% (10/54) cohort of WT-*EGFR*, *KRAS*, *ALK*, *ROS1*	Heist et al. (2016)[79]
China	1,296	NSCLC	NGS, RT-PCR sanger sequencing	59 (41–77)	0.9% (12/1,296) all; 0.9% (10/1,101) of ADC	Liu et al. (2016)[80]
USA	933	NSCLC	NGS, confirmation by qRT-PCR	72.5 (59–84)	3.0% (28/933)	Awad et al. (2016)[63]
Hong Kong	687	NSCLC	PCR followed by sanger sequencing (using gDNA)	74	2.6% (18/687) all; 2.6% (10/392) ADC; 4.8% (1/21) ASC; 31.8% (7/22) PSC	Tong et al. (2016)[18]
China	1,770	NSCLC	qRT-PCR	66 (47–77)	1.3% (23/1,770) all; 1.6% (21/1,305) ADC; 4.2% (2/48) ASC	Zheng et al. (2016)[73]
USA	11,205	Lung cancers	Hybrid capture-based NGS	73 (43–95)	2.7% (298/11,205) all; 2.9% (205/7,140) ADC; 2.1% (25/1,206) SCC; 8.2% (8/98) ASC; 7.5% (8/107) PSC	Schrock et al. (2016)[74]
USA	860	ADC	Hybrid capture-based NGS	–	3.0% (26/860)	Jordon et al. (2017)[81]
Korea	795	NSCLC	qRT-PCR followed by sequencing	73 (55–81)	2.1% (17/795) ADC; 37.8% (17/45) cohort of WT-*EGFR*, *KRAS*, *ALK*, *ROS1*	Lee et al. (2017)[64]
Korea	102	ADC, PSC	qRT-PCR	73 (59–82)	8.8% (9/102) ADC; 20.0% (9/45) PSC	Kwon et al. (2017)[70]
France	231	ADC, PSC	MassARRAY iPLEX genotyping technology, sanger sequencing	61 (41–79)	5.3% (8/150) ADC; 5% (4/81) PSC	Saffroy et al. (2017)[71]
Taiwan	850	Lung cancers	RT-PCR followed by sequencing	77 (36–95)	3.3% (28/850) all; 4.0% (27/668) ADC; 1.3% (1/78) SCC	Gow et al. (2017)[77]
China	77	PSC	RT-PCR, NGS	62 (37–80)	20.8% (16/77)	Li et al. (2018)[82]
China	461	NSCLC	RT-PCR, sanger Sequencing	60 (31–87)	2.0% (9/461)	Qiu et al. (2018)[66]
USA	3,632	NSCLC	Hybrid capture-based NGS	–	3% (113/3632)	Suzawa et al. (2019)[67]
Korea	414	NSCLC	qRT-PCR and/or Sanger sequencing (followed by hybrid capture-based NGS in some of the patients)	69 (54–80)	3.14% (13/414) cohort of WT-*EGFR*, *KRAS*, *ALK*, *ROS1*; 4.8% (11/230) ADC; 9.5% (2/21) PSC	Kim et al. (2019)[65]
China	46	PSC	NGS sequencing	46 (45–80)	8.7% (4/46)	Yu et al. (2019)[72]
Netherlands	1,497	Non-SC NSCLC	Amplicon-based NGS	76.5 (53–90)	2.1% (32/1497)	Pruis et al. (2020)[78]
France	2,369	NSCLC	Sanger sequencing, NGS	75 (46–97)	2.6% (62/2,369)	Champagne et al. (2020)[68]

ADC = adenocarcinoma; ALK = anaplastic lymphoma kinase; ASC = adeno-squamous cell carcinoma; CGARN = Cancer Genome Atlas Research Network; EGFR = epidermal growth factor receptor; gDNA = genomic DNA; NGS = next-generation sequencing; NSCLC = non-small cell lung carcinoma; PSC = pulmonary sarcomatoid carcinoma; qRT-PCR = quantitative real time RT-PCR; RT-PCR = reverse transcription polymerase chain reaction; SC = squamous cell; SCC = squamous cell carcinoma; TCGA = the cancer genome atlas; WES = whole exome sequencing; WT = wild type.

based panel is ideal for analysing single nucleotide variants and indels (insertions and deletions). NGS analysis also can simultaneously detect other mutations or translocations (such as *ALK*, *ROS1*, *RET*, NTRK1, and *NRG1* fusions) in a single assay.[83] Due to the inherent difficulties in acquiring sufficient RNA material for testing, DNA-based NGS panels are used more frequently to identify *METex14* skipping alterations. Recently, the US Food and Drug Administration (FDA) approved FoundationOne® CDx (Foundation Medicine, Cambridge, MA, USA) as a companion diagnostic test for this indication.[88] Circulating tumor DNA (CtDNA) or RNA from plasma/blood samples (liquid biopsy) can also be used to identify *METex14* alterations using NGS technologies. A clinical trial (VISION; ClinicalTrials.gov Identifier: NCTO2864992) aiming to test *METex14* skipping alterations in circulating free DNA using plasma liquid biopsy is ongoing.[89] Some of the commercially available targeted NGS assays that are used to detect these alterations are compared in *Table 2*.[90–101]

Therapeutic intervention of NSCLC with *METex14* skipping alteration

NSCLC characterized with *METex14* skipping alterations is targetable.[57] Although many *METex14* skipping tumors were found to express programmed death-ligand-1 (PD-L1), the overall response rate to PD-1/PD-L1-directed immune checkpoint inhibitors has been found to be low, and median progression-free survival (mPFS) was found to be short in patients with NSCLC.[102,103] It should be noted that the mutation burden is generally low in such tumors. There are three therapeutic approaches to target tumors harboring *METex14* skipping alteration:

Table 2: Next-generation sequencing assays used in the detection of *METex14* skipping in clinical studies

NGS assay	Target	Sample quantity	Number of genes covered	Detection of mutations	Turn-over time
Tumor based					
AmpliSeq for Illumina Focus Panel[90]	DNA or RNA	1–10 ng DNA or RNA	52	5% frequency	Not available
Archer® FUSIONPlex™ Lung [91,92]	RNA	FFPE tissue; 2–250 ng DNA	14	Not available	Not available
FoundationOne® CDx [93,94]	DNA	50–1,000 ng DNA	324	As low as 2–5% allele frequency	<2 weeks
Oncomine focus [95]	DNA or RNA	FFPE tissue; 7 mm thick and >5 mm sq	52	100% if mutation is >5% allele frequency	3 days
TruSight Oncology 500 [96]	DNA or RNA	40 ng DNA or RNA	523	96%	4–5 days
Liquid based					
Archer® LiquidPlex™[97]	Cell free DNA	5–10 ng DNA	28	If present in >1% sample	Not available
FoundationOne® Liquid [98]	Circulating tumour DNA	2 × 8.5 mL blood samples	70	If present in >0.5% sample	<2 weeks
Guardiant360® [99,100]	Circulating free DNA	10 mL blood sample for 5–30 ng DNA	73	If present in >0.1%	7 days
PlasmaSELECT™ 64, PGDx [101]	Circulating tumor DNA	2 × 10 mL blood samples	64	Not available	Not available

FFPE = formalin-fixed paraffin-embedded; NGS = next-generation sequencing.

- anti-MET and anti-HGF antibodies targeting the extracellular domain of the receptor;
- MET TKIs targeting the intracellular ATP binding pocket of target kinase to inhibit the autophosphorylation of the receptor; and
- antibody–drug conjugates.[65,104,105]

Clinical trials and case-reports have suggested varying degrees of responsiveness to experimental and FDA-approved small molecule TKIs against *METex14* skipping NSCLC (*Table 3*). A multicenter retrospective analysis determined that the treatment with a MET TKI was associated with a significant prolongation in survival with a hazard ratio of 0.11 compared to patients who did not receive any MET inhibitor.[106] MET TKIs are commonly divided into two types based on their targeting mechanism. Type I MET TKIs—such as crizotinib, capmatinib, tepotinib, and savolitinib—bind to MET in its catalytically active conformation where the aspartic acid-phenylalanine-glycine (DFG) motif projects into the ATP-binding site (DFG-in).[87,107,108] Type II MET TKIs—such as cabozantinib, merestinib, and glesatinib—bind to MET in its inactive DFG-out conformation.[109,110] Type I MET TKIs are further subdivided into type Ia (crizotinib) and Ib (capmatinib, tepotinib, and savolitinib) based on the interaction of TKI with G1163, a solvent residue. Various MET TKIs currently being used in clinical trials are listed in *Table 4*.

Multi-kinase MET inhibitors and their response against *METex14* skipping NSCLC

This group of inhibitors targets multiple TKs and has been used to target MET kinase. Crizotinib, cabozantinib, merestinib, glesatinib, and TPX-0022 are the major target agents in this group.

Crizotinib

Crizotinib (PF-02341066; Xalkori®, Pfizer, New York, NY, USA) was originally developed as a MET inhibitor, which showed activity against ALK and ROS1 rearrangement, and was approved as an ALK and ROS inhibitor in NSCLC.[63,64,111,112] Crizotinib was reported to have potent antitumor activity in NSCLC harboring *MET* amplification and exon 14 skipping alteration.[57,87,113] The phase I study PROFILE 1001 (ClinicalTrials.gov Identifier: NCT00585195) was expanded to evaluate the efficacy and safety of crizotinib in 69 patients with NSCLC with *METex*14 alteration. Among 65 response-evaluable patients, 5% had a confirmed complete response, 28% had a confirmed partial response, 45% had stable disease, and mPFS was 7.4 months.[87] In 2018, crizotinib received FDA breakthrough therapy designation for the treatment of patients with NSCLC with *METex*14 alterations based on a promising response rate of up to 44% in an earlier-phase study.[59] A retrospective study of 22 patients treated with crizotinib reported a similar mPFS of 7.4 months.[106] However, a phase II study (METROS; ClinicalTrials.gov Identifier: NCT0249961) reported an objective response rate (ORR) of 27% with an mPFS of 4.4 months in patients with NSCLC (n=26) with MET dysregulation with crizotinib.[114] Similarly, the AcSé phase II study (by French National Cancer Institute; ClinicalTrials.gov Identifier: NCT02034981) reported insufficient ORR (10.7%), even after two cycles of crizotinib in 28 patients with NSCLC with *METex*14 alteration.[115] Furthermore, neoadjuvant treatment with crizotinib in a locally advanced unresectable *METex14* mutated lung adenocarcinoma converted the unresectable tumor into a resectable one.[116]

Cabozantinib

Cabozantinib (XL-184, BMS-907351; Cabometyx®, Exelixis, Alameda, CA, USA) is a multi-kinase inhibitor targeting multiple TKs including MET. Patients with NSCLC with *METex14* skipping alteration have shown the partial response to therapy after treatment with cabozantib.[107,117] In a phase II study of solid tumors (ClinicalTrials.gov Identifier: NCT00940225) ORR was 10% and mPFS was 4 months.[118] Importantly, some case studies of patients with NSCLC with *METex14* alteration treated with cabozantinib showed intracranial response.[117,119] Phase II studies in patients with NSCLC with *MET* deregulation are ongoing (ClinicalTrials.gov Identifier: NCT03911193 [CABinMET study], and ClinicalTrials.gov Identifier: NCT01639508).[120]

Merestinib

Merestinib (LY2801653) is another multi-kinase ATP-competitive inhibitor of MET.[121] After the demonstration of an acceptable safety profile and potential antitumor activity in a phase I trial,[122] a phase II clinical study (ClinicalTrials.gov Identifier: NCT02920996) is ongoing for the treatment of advanced NSCLC harboring *METex14* alterations. A preclinical study demonstrated the antitumor response of merestinib in combination with emibetuzumab in

Table 3: Agents that target *METex14* in development

Agent	Company	Type of agent	Targets	Stage of development
Multi-kinase inhibitors				
Crizotinib (Xalkori®, PF-02341066)	Pfizer	Ia /ATP competitive TKI	MET, ALK, RON, ROS1	Phase II
Cabozantinib (Cabometyx®, XL184)	Exelixis	II/ATP competitive TKI	MET, VEGFR-1/2, RET, KIT, TIE2, FLT1/3/4, AXL	Phase III
Merestinib (LY2801653)	Eli Lilly	II/ATP competitive TKI	MET, AXL, RON, MERTK, ROS1, NTRK1/2/3, TEK, DDR1/2, FLT3	Phase II
Glesatinib (MGCD265)	Mirati Therapeutics	II/ATP competitive TKI	MET, AXL	Phase II
TPX-0022	Turning Point Therapeutics	I/ATP competitive TKI	MET, CSF1R, SRC	Phase I
Selective MET TKI				
Capmatinib (Tabrecta™, INC280)	Novartis	Ib/ATP competitive TKI	MET	Phase II
Tepotinib (Teometko®, EMD1214063, MSC2156119 J)	Merck	Ib/ATP competitive TKI	MET	Phase II
Savolitinib (AZD6094, HMPL-504, volitinib)	AstraZeneca	Ib/ATP competitive TKI	MET	Phase II
Bozitinib (APL-101/PLB-1001, CBT-101)	Apollomics	Ib/ATP competitive TKI	MET	Phase I
Glumetinib (SCC244)	Shanghai Haihe Pharmaceutical	II/ATP competitive TKI	MET	Phase I/II
Antibodies				
Emibetuzumab (LY2875358)	Eli Lilly	IgG4 MoAb	MET	Phase III
Sym015	Symphogen	IgG1 MoAb mixture	MET	Phase I/II
REGN5093	Regeneron Pharmaceuticals	MET bispecific Ab	MET	Phase I/II
Other				
Telisotuzumab vedotin (ABBV-399)	AbbVie	Antibody–drug conjugate	MET	Phase II

Ab = antibody; ALK = anaplastic lymphoma kinase; ATP = adenosine triphosphate; CSF1R = colony stimulating factor 1 receptor; DDR1/2 = discoidin domain receptor tyrosine kinase 1/2; FLT3 = fms-like tyrosine kinase 3; Ig = immunoglobulin; MERTK = MER receptor tyrosine kinase; MoAb = monoclonal antibody; NTRK = neurotrophic-tropomyosin receptor kinase; RON = receptor originated from Nantes; ROS1 = c-ros oncogene 1; TIE2 = tyrosine-protein kinase receptor; TKI = tyrosine kinase inhibitor; VEGFR = vascular endothelial growth factor receptor.

a mouse model with *METex14* skipping alteration.[121] Recently, merestinib demonstrated antitumor activity in a patient with lung cancer harboring *METex14* skipping and acquired resistance against capmatinib and crizotinib.[123]

Glesatinib

Glesatinib (MGCD265) is also a multi-kinase inhibitor of MET, AXL, VEGFR1/2/3, RON, and TIE2, which demonstrated antitumor activity in preclinical and clinical studies with *METex14* alteration.[109,124] A phase II study (ClinicalTrials.gov Identifier: NCT02544633) showed the antitumor activity of glesatinib in patients who had *METex14* skipping alteration and acquired resistance against crizotinib.[109,123,125]

TPX-0022

TPX-0022 is a novel multi-kinase inhibitor of MET, CSF1R, and SRC, which demonstrated antitumor activity in preclinical xenograft models.[126] A recent phase I clinical study reported that TPX-0022 was well tolerated, and responses were observed in patients with advanced solid tumors harboring genetic *MET* alterations (ClinicalTrials.gov Identifier: NCT03993873).[127]

Selective kinase MET inhibitor on *METex14* skipping NSCLC

This group of inhibitors specifically target the MET receptor by binding to the ATP binding pocket of the MET kinase. Application of such selective MET inhibitors has produced a promising response in patients with *METex14* skipping alteration. Capmatinib, tepotinib, savolitinib, and APL-101 are among the promising agents in this group.

Capmatinib

Capmatinib (INC280; Trabecta™, Novartis, Basel, Switzerland) is a highly-selective, ATP-competitive MET inhibitor and the first and only MET inhibitor approved by the FDA to target metastatic NSCLC with *METex14* skipping alteration as determined by an FDA-approved test.[128–130] The approval is based on the results from the pivotal GEOMETRY phase II study (ClinicalTrials.gov Identifier: NCT02414139). The primary efficacy outcome based on ORR was 68% and 41% among 28 treatment-naive and 69 previously treated patients, respectively, based on the blinded independent review committee assessment. The median DOR was 12.6 months (n=19) for treatment-naive and 9.7 months (n=28) for pre-treated patients.[131,132] Importantly, capmatinib also exhibited antitumor activity in patients with brain metastases in previously treated NSCLC harboring *METex14* alterations.[108,133]

Tepotinib

Tepotinib (END 1214063; Tepmetko®, Merck KGaA, Darmstadt, Germany) is an ATP-competitive and highly-selective oral MET inhibitor, which showed MET inhibitory activity in *in vitro* and *in vivo* models. It supressed MET activation by both ligand-dependent and independent mechanisms.[134]

Table 4: Clinical studies of various MET TKIs in NSCLC with *METex14* skipping alteration and observation (final/interim reports)

Clinicaltrials.gov Identifier/ phase/location	Recruited patients	Population and prior treatment	Drug/dose	Responses evaluated patients	Observations (final/interim reports)
NCT00585195 (PROFILE-1001)/phase I/US	NSCLC with *METex14* skipping	69 (62% pre-treated)	cizotinib, 250 mg BID	65	ORR: 32% (95% CI: 21–45); DOR: 9.1 months (95% CI: 6.4–12.7); mPFS: 7.3 months (95% CI: 5.4–9.1)[87]
NCT02499614 (METROS)/phase II/Italy	NSCLC with *METex14* skipping or *MET* amplification	26 (100% pre-treated)	cizotinib, 250 mg BID	26	ORR: 27% (95% CI: 11–47); mPFS: 4.4 months (95% CI: 3.0–5.8); OS: 5.4 months (95% CI: 4.2–6.5)[114]
NCT02034981 (AcSé)/phase II/France	NSCLC with *METex14* skipping or *MET* amplification	28 (96% pre-treated)	cizotinib, 250 mg BID	25	ORR: 10.7% (95% CI: 2.3–28.2); mPFS: 2.4 mo (95% CI: 1.6–5.9); median OS: 8.1 mo (95% CI: 4.1–12.7)[115]
NCT02664935 (National Lung Matrix)-Arm D3/phase II/UK	NSCLC including *METex14* skipping	12 (100% pre-treated)	Multi-drug (including crizotinib, 250 mg BID)	8	ORR: 65% (95% CI: 39–86); DCB: 68% (95% CI: 39–89)[152]
NCT01324479/ phase I/global	NSCLC with *MET* dysregulated	55 (100% pre-treated)	capmatinib, 400 or 600 mg BID	55	ORR: 20% (95% CI: 10.4–33); Tumour responses in all 4 patients with *METex14*[153,154]
NCT02414139 (GEOMETRY mono 1)/phase II/global	NSCLC with *cMET* mutation or gene copy number or *cMET* dysregulation	97 (28 prior treatment-naive and 69 pre-treated)	capmatinib, 400 mg BID	28 treatment-naive and 69 pre-treated	Treatment-naive: ORR: 68% (95% CI: 48–84); median DOR: 12.6 months (95% CI: 5.5–25.3) Pretreated patients: ORR: 41% (95% CI: 29–53); mPFS: 9.7 months (95% CI: 5.5–13.0)[132,155,156]
NCT02864992 (VISION)/phase II/global	NSCLC with *METex14* skipping or *MET* amplification	99 (43 prior treatment-naive and 56 pre-treated)	tepotinib, 500 mg QD	99 combined biopsy; 66 liquid biopsy; 60 tissue biopsy	Combined biopsy (n=99): ORR: 46% (95% CI: 36–57); DOR: 11.1 months (95% CI: 7.2–NE); mPFS: 8.5 months (95% CI: 6.7–11.0) Liquid biopsy (n=66): ORR: 48% (95% CI: 36–61); DOR: 9.9 months (95% CI: 7.2–NE); mPFS: 8.5 months (95% CI: 5.1–11.0) Tissue biopsy (n=60): ORR: 50% (95% CI: 37–63); median DOR: 15.7 months (95% CI: 9.7–NE); mPFS: 11.0 months (95% CI: 5.7–17.1)[89]
NCT02897479/phase II/China	NSCLC (PSC and other NSCLC with *METex14* skipping)	70 (prior MET treatment-naive)	savolitinib, 600 mg QD or 400 mg QD	61	ORR: 47.5% (95% CI: 34.6–60.7); DCR: 93.4% (95% CI: 84.1–98.2); mPFS: 6.8 months (95% CI: 4.2–13.8)[139]

BID = twice daily; CI = confidence interval; DCB = durable clinical benefit; DCR = disease control rate; DOR = duration of response; mPFS = median progression-free survival; NE = not evaluable; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PSC = pulmonary sarcomatoid carcinoma; QD = once daily; TKI = tyrosine kinase inhibitor.

In March 2020, regulatory authority in Japan approved tepotinib for the treatment of NSCLC with *METex14* skipping alteration.[135] The approval was based on data from 99 patients with NSCLC with *METex14* skipping alteration who had been followed up for 9 months in the ongoing single-arm phase II VISION study (ClinicalTrials.gov Identifier: NCT02864992). The primary endpoint ORR of the study, as assessed by an independent review committee, was 46% with median DOR of 11.1 months for patients identified by combined biopsy (liquid/tissue biopsy). The response rate was 48% for patients in the liquid biopsy group (n=66), and was 50% for those in the tissue biopsy group (n=60).[89] The FDA granted tepotinib a breakthrough therapy designation for the treatment of NSCLC harboring *METex14* skipping alterations in September 2019. Recently, a case of antitumor activity of tepotinib in a patient with NSCLC with brain metastasis harboring a *MET* gene rearrangement was reported.[136]

Savolitinib

Savolitinib (volitinib, AZD6094, AstraZeneca, Cambridge, UK) is also a highly selective MET inhibitor.[137,138] Interim data from a phase II study (ClinicalTrials.gov Identifier: NCT02897479) reported encouraging antitumor activity and an acceptable safety profile of savolitinib in patients with *METex14* skipping NSCLC, including pulmonary sarcomatoid and other histologies. The ORR from preliminary data (n=61) was 47.5% and mPFS was 6.8 months.[139]

APL-101

APL-101 (bozitinib, CBT-101, PLB-1001), another highly selective MET TKI, has demonstrated robust anticancer activity in various human xenograft tumor models with *MET* dysregulation and bears the potential to cross the blood–brain barrier in glioblastoma.[140,141] Currently, SPARTA, a phase I/II study (ClinicalTrials.gov Identifier: NCT03175224) is evaluating antitumor activity of APL-101 in patients with NSCLC with *METex14* skipping and solid tumors with *MET* aberrations.

Glumetinib

Glumetinib (SCC244) is a highly-selective, ATP-competitive MET inhibitor. The antitumor activity of this agent was demonstrated as equivalent to capmatinib in a preclinical study.[142] Currently, phase I studies (ClinicalTrials.gov Identifier: NCT03466268) in patients with NSCLC with *MET* alterations, and another study (ClinicalTrials.gov Identifier: NCT03457532) in patients with solid tumors harboring *MET* alterations are ongoing for the evaluation of the safety and antitumor activity of glumetinib. A global phase I/II study (ClinicalTrials.gov Identifier: NCT04270591) for patients with NSCLC with *MET* alterations is also ongoing.

The effect of MET antibodies on *METex14* skipping NSCLC

Emibetuzumab

Emibetuzumab (LY2875358) is a humanized bivalent anti-MET antibody that has high neutralization and internalization activities. It showed potent antitumor activity to inhibit HGF-dependent and HGF-independent tumor growth in mouse xenograft models and in *MET*-positive (including NSCLC) patients.[143,144] A preclinical study revealed more antitumor activity of emibetuzumab combined with merestinib on gastric cancer with *METex14* muation.[121]

Onartuzumab

Onartuzumab is another antibody drug that has shown antitumor activity in preliminary studies. However, it failed to improve the clinical outcomes of *MET*-positive patients compared with placebo in phase III studies.[145]

SYM015

SYM015 is a combination of two humanized antibodies directed at the elimination of the MET receptors.[146] In a phase I/II study (ClinicalTrials.gov Identifier: NCT02648724), the safety and efficacy of Sym015 in patients with advanced NSCLC with *MET* amplification and exon 14 deletion were observed. Of 20 patients with NSCLC, the ORR was 25% and the disease control rate was 80%, with median PFS of 5.5 months.[147]

REGN5093

REGN5093 is a MET biparatopic antibody that blocks HGF binding and causes rapid internalization and degradation of MET.[148] A phase I/II study (ClinicalTrials.gov Identifier: NCT04077099) demonstrated the safety and tolerability of REGN5093 in patients with NSCLC with *MET* alterations.[149] This study is ongoing and is open for enrollment of patients.

The impact of antibody–drug conjugates on *METex14* alteration

Telisotuzumab vedotin

Telisotuzumab vedotin (ABBV-399) is a conjugate of a MET-targeted antibody and monomethyl auristatin E. This antibody–drug conjugate has demonstrated antitumor activity in patients NSCLC with *MET* dysregulation in a preliminary analysis from a phase I study.[150,151]

Resistance of *METex14* skipping alterations to MET TKIs

Reports suggest that patients with NSCLC with *METex14* skipping alterations are sensitive to MET TKI treatment.[87,107,111] However, emergence of primary or acquired resistance may challenge the efficacy of MET TKI-based monotherapy.[11,123,157] Clinically, the analysis of pre- and post-MET TKI treatment data from 20 patients showed 35% on-target and 45% off-target resistance acquired after the treatment.[123] Even though *MET* is exclusively a driver gene in many cancers, in some cases, *METex14* skipping alterations may exist with alterations in other driver genes, such as amplifications of *MDM2* (25–35%), *CDK4* (3–21%), and *EGFR* (6–29%), leading to MET TKI resistance. Furthermore, mutations or amplification of *KRAS* (3–7%) and *PIK3CA* (3–10%), and loss of PTEN expression (23%) may exist with *METex14* skipping alterations contributing to resistance.

The pre-existence of *MET* Y1230C on-target mutation in addition to *METex14* skipping alteration has accounted for the primary resistance to crizotinib.[158,159] *MET-D1228N*-acquired mutation was found to be responsible for the resistance to crizotinib in a patient with *METex14* skipping alteration, who did not have any additional mutation in *MET* or other driver genes before the treatment started.[11] A comprehensive analysis of secondary mutations using a Ba/F3 model resistance to eight TKIs reported that *D1228* and *Y1230* are common sites for resistance mutations for type I TKIs, whereas *L1195* and *F1200* are the mutations leading to resistance to type II TKIs. *D1228A/Y* accounts for resistance to both type I and II MET TKIs.[160]

In addition, tumor cells may activate other signaling pathways to counterbalance the MET TKI suppressed signaling. In such cases, alterations leading to overexpression of key proteins drive the activation of alternative receptors, which leads to the sustained activation of major signaling pathways (bypass signaling) and contributes to the therapeutic resistance, regardless of effective MET inhibition by MET TKI drugs. On the other hand, *MET* dysregulation, mostly due to *METex14* skipping alteration, has also been observed in NSCLC tumors because of off-target acquired resistance to EGFR TKIs.[161]

Identification of the resistance mechanism to MET TKIs is crucial for the effective treatment of NSCLC. For example, tumors developing acquired resistance against glesatinib (type II) through the amplification of the mutated *METex14* allele showed partial response after switching to crizotinib (type Ia).[160] Merestinib (type II) was reported to function better against *D1228N*-mediated acquired resistance, which developed after the application of capmatinib (type Ib).[109] Similarly, glesatinib (type II) revealed better antitumor activity in *Y1230H/S* mutation, which developed after crizotinib (type Ia) treatment.[123] Preclinical

and clinical data have demonstrated that tumors harboring *METex14* skipping alterations along with other mutations, *RAS-MAPK* or *PI3K/AKT* pathway mutations, show reduced response to MET TKIs.[162–164] Overall, the resistance mechanisms against different types of MET inhibitor can be different.[109] Therapy combining relevant inhibitors can be helpful for the treatment of NSCLC with *METex14* skipping alteration along with other driver mutations.[164,165] Extensive studies are needed to unravel the full spectrum of resistance mechanisms against the inhibitor drugs for optimising therapeutic intervention.

Conclusion and outlook

MET abnormalities due to *METex14* skipping alteration can drive cancer by upregulating receptor activity. It has become a promising target for kinase inhibitor-based targeted therapy in NSCLC, and several recent clinical trials have demonstrated the strong therapeutic effect of such inhibitors. However, it is not yet available to many potential patients who could benefit from such therapy. Firstly, current guidelines do not necessitate the analysis of *METex14* skipping alterations for a standard treatment plan, missing the identification of such mutations in many patients and consequently precluding a possible target group from receiving MET inhibitors. Secondly, many early-stage patients may not be subjected to molecular profiling due to the complexity in accessing the tissue biopsy sample. In such cases, application of liquid biopsy and ctDNA genotyping can ease sample availability, which can widen the scope of diagnosis, thereby enabling more patients to get a proper diagnosis and therapy. In addition, a detailed understanding of primary and acquired resistance mechanisms can aid in decision making for the appropriate therapeutic intervention. More clinical trials focusing on the combination of MET inhibitors with inhibitors of other signaling pathways can help to identify an appropriate drug combination in MET inhibitor-resistant cancers. ❑

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