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REVIEW

Targeting the MET-Signaling Pathway in Non-Small–Cell Lung Cancer: Evidence to Date

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Abstract: The c-MET proto-oncogene (MET) plays an important role in lung oncogenesis, affecting cancer-cell survival, growth and invasiveness. The MET receptor in non-small–cell lung cancer (NSCLC) is a potential therapeutic target. The development of high-output next-generation sequencing techniques has enabled better identification of anomalies in the MET pathway, like the MET exon-14 (METex14) mutation. Moreover, analyses of epidermal growth factor-receptor (EGFR) and mechanisms of resistance to tyrosine-kinase inhibitors (TKIs) demonstrated the importance of MET amplification as an escape mechanism in patients with TKI-treated EGFR-mutated NSCLCs. This review summarizes the laboratory findings on MET and its anomalies, trial results on METex14 alterations and MET amplification in non-EGFR mutated NSCLCs, and acquired resistance to TKI in EGFR-mutated NSCLCs. The outcomes of the first trials with anti-MET agents on non-selected NSCLC patients or those selected for MET overexpression were disappointing. Two situations seem the most promising today for the use of anti-MET agents to treat these patients: tumors harboring METex14 and those EGFR-sensitive mutation mutated under TKI-EGFR with a MET-amplification mechanism of resistance or EGFR-resistance mutation.

Keywords: non-small–cell lung cancer, MET exon 14, MET amplification, MET pathway

Introduction

Targeted therapies have profoundly modified the prognoses of lung cancers with oncogenic mutations, achieving notably improved progression-free (PFS) and overall survival (OS) rates compared to reference chemotherapy regimens. That is particularly true for first- or second-line treatment of metastatic non-small–cell lung cancers (NSCLCs) harboring an epidermal growth factor-receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) translocation.[1–5] Targeted therapies have also shown their efficacy in patients carrying the v-RAF murine sarcoma viral oncogene homolog B ($BRAF^{V600E}$) mutation, tyrosine-protein kinase-1 protooncogene (ROS1) or rearranged-during-transfection (RET) translocation.[6–8] More recently, the efficacy of targeting the neurotrophic tropomyosin receptor kinase (NTRK) in all patients whose cancers express it (making it a marker for tumor-agnostic therapy) was demonstrated.[9] In other contexts, knowledge remains more fragmented, despite a potentially oncogenic target, with therapies having only modest activities. That is the case for NSCLCs expressing human epidermal growth factor receptor-2 (HER2), Kirsten rat-sarcoma viral oncogene (KRAS) or those with c-MET proto-oncogene (MET) protooncogene-pathway abnormalities.[10–12]

The MET pathway was identified in the 1980s and its carcinogenic role in lung cancer has been recognized since the 1990s.[13,14] It is a complex pathway, poorly

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understood, with anomalies, ranging from MET overexpression, rare translocations, amplifications, de novo or acquired under tyrosine-kinase inhibitors of epidermal growth factor-receptor (EGFR) (EGFR-TKIs) and, finally, mutations, particularly of MET exon-14 (METex14) mutations. Numerous molecules targeting this pathway or its ligand, hepatocyte growth factor (HGF), are at various stages of development.

This review summarizes the data available on our understanding of the different molecular MET alterations, the results obtained with agents targeting this pathway and the contribution of immunotherapy to treating these patients.[15,16]

The MET Pathway and Its Alterations

The *MET* gene is located at 7q21–q31 on chromosome 7. It is comprised of ~125 kb and 21 exons.[17,18] *MET* is a heterodimer tyrosine-kinase receptor with extracellular, transmembrane, juxtamembrane and kinase domains.[19,20]

MET binding to its exclusive ligand, HGF, leads to homodimerization and phosphorylation of the intracellular tyrosine residues.[18] Receptor activation stimulates downstream signaling pathways, such as extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase-Akt (PI3K)/protein kinase B pathways and JAK/STAT (Janus kinase/signal transducer and activator of transcription).[20] Those pathways are known to be involved in cell proliferation, migration, motility angiogenesis, survival and the epithelial-to-mesenchymal transition.[21,22]

During embryogenesis, MET and HGF favor the formation of trophoblasts and placental hepatocytes.[23] In adults, the two proteins are strongly expressed in a wide variety of tissues and can be regulated positively in response to a tissue lesion.[18]

Deregulation of the MET pathway in oncology can be manifested in several ways: genetic mutation, amplification, rearrangement or overexpression of proteins. Other than NSCLC, breast, colon, kidney and stomach cancers overexpress MET. MET amplification is found in colon, esophageal and stomach cancers.[24–28]

Overexpression

Overexpression of MET or its ligand HGF, without amplification or mutation, is possible. This overexpression seems to induce activation independent of the MET ligand, phosphorylation and activation of downstream signaling pathways.[29]

Immunohistochemistry (IHC) is able to detect MET or HGF overexpression with several antibodies that are commercially available.

Rearrangement

The first *MET* rearrangement was described in the 1990s with the tryptophan (*TRP*) gene.[30] Other rearrangements have since been found, notably in NSCLCs: kinesin family member 5B (*KIF5B*), F-actin–capping proteins bind in a Ca^{2+} (*CAPZA2 (2)*), cluster of differentiation 47 membrane protein (*CD47 (2)*), testin (*TES*), caveolin-1 (*CAV1*), integrin subunit alpha-9 (*ITGA9*), human leukocyte antigen (*HLA-DRB1*), transcription factor EC (*TFEC*), cortactin-binding protein-2 (*CTTNBP2*), ankyrin-1 (*ANK1*), steroidogenic acute regulatory-related lipid-transfer domain containing three N-terminal–like proteins (*STARD3NL*).[31]

Amplification

Amplification is an increased gene-copy number (GCN), linked to the focal duplication of a gene via breakage–fusion–bridge mechanisms.[32] A higher GCN can also be secondary to polysomia of chromosome 7 (caused by chromosomal duplication, for example).[33,34] MET amplification deregulates the MET signaling pathway by overexpression of the protein and constitutive activation of kinases.[33] The number of *MET* copies can be evaluated by fluorescence in situ hybridization (FISH) or quantitative polymerase chain reaction. When using FISH, the *MET*/CEP7 (centromeric portion of chromosome 7) ratio remains unchanged, whereas, with amplification, the *MET* GCN increases at the expense of the number of centromeres, which results in a higher *MET*/CEP7 ratio.[33]

New techniques of hybridization capture-based next-generation sequencing (NGS) can analyze gene amplifications. The GCN modifications can be identified by comparing tumor sequences in targeted regions to a normal diploid sample.[35] Unlike FISH, NGS and multiplex polymerase chain reaction are able to analyze in parallel other genes of interest to look for concomitant alterations having a clinical impact.[36]

No international consensus has been reached on the *MET*/CEP7 ratio threshold enabling characterization of a real amplification. Camidge et al proposed a classification scheme with several *MET*/CEP7-ratio categories (low, 1.8–2.2; intermediate, >2.2 and <5; and high, ≥5) but another classification (which changed the intermediate class to >2.2 and <4; and high to ≥4) has been applied in clinical settings when treating patients with MET inhibitors.[37] Other scores

exist: ≥5 *MET* signals per cell (Capuzzo scoring system) and a *MET*/CEP7 ratio ≥2 (PathVysion).[38,39] Their harmonization seems essential to enable comparisons among studies and available data.

Mutations

METex14 mutations provoke the suppression of the juxtamembrane domain or abnormal splicing leading to the suppression of the juxtamembrane domain that prevents the degradation of the MET receptor, which leads to increased MET-receptor activity. There can be punctual mutations at the Y1003 catalytic site (*Sema-3C*, encoded by exon 2) and the juxtamembrane (encoded by exons 14 and 15) domains. In NSCLCs, punctual MET mutations are often situated in the extracellular or juxtamembrane domains (exon 14).[40] The first NSCLC patients with METex14 mutations were described in 2005.[41]

In the absence of mutation, the introns adjacent to METex14 in the premessenger RNA (pre-mRNA) are spliced, which gives rise to an mRNA containing METex14 that becomes the functional MET receptor. METex14 codes for a part of the of the juxtamembrane domain containing Y1003, the binding site of E3 ubiquitin ligase c-Cbl (proto-oncogene Casitas B-lineage lymphoma). Ubiquitination marks the MET receptor for degradation.[42] These mutations lead to METex14 skipping, which yields a truncated MET receptor lacking a Y1003 c-Cbl–binding site. The loss of that site leads to less ubiquitination of the MET protein and its degradation, and prolonged MET activation that favors the tumor oncogenicity.[43] MET overexpression detectable by IHC for it may detect the degradation of the protein.

METex14 alterations are highly variable and represent a diagnostic challenge. Substitutions or insertions of bases at splice sites in introns 13 and 14, respectively at 3′ and 5′ termini, for example.[42–45] METex14 mutations are mutually exclusive from other mutations, suggesting its role as a true oncogenic driver. Based on an analysis of 933 non-squamous NSCLCs, no patient with a METex14 mutation had any other associated oncogenic abnormality.[45,46]

Epidemiology of the MET Pathway in NSCLC

MET Overexpression

Its frequency ranges between 22% and 75%, depending on the series.[47–52] MET overexpression is considered a poor-prognosis factor.[48,52] A meta-analysis including 18 studies (5516 NSCLC patients) showed that MET overexpression was associated with a significantly increased risk of death (hazard ratio (HR): 1.52 [95% confidence interval (CI): 1.08–2.15]).[52] Another meta-analysis of 4454 NSCLC patients (based on 22 studies) confirmed that IHC MET-positivity was significantly associated with worse OS (HR: 1.55 [95% CI: 1.10–2.18]).[53]

Rearrangements

The prevalence of *MET* rearrangement is unknown. Based on a series of 2410 NSCLC patients, that rate was 0.04% (one patient with *MET*–ATXN7L1 (ataxin-7-like protein-1) fusion).[54]

Amplification

De Novo Amplification

The reported frequency of de novo MET amplification in NSCLCs ranges from 1%–5%, depending on the level of preselection, the assay and the positivity threshold applied.[4,38,46,55,56] No consensus has yet been reached on the definition of MET positivity based on GCN. Different classification thresholds among studies has complicated comparisons of reported *MET*-amplification/GCN gain relative to the underlying frequency.[47–49,57] These amplifications are more frequent in poorly differentiated adenocarcinomas with a poor prognosis.

A few meta-analyses on the prognostic role of *MET* amplification in NSCLC have been published.[52,58,59] A meta-analysis of 21 studies that had enrolled 7647 patients showed that *MET* amplification was associated with shorter OS (HR: 1.45 [95% CI: 1.16–1.80]). Subgroup analyses based on histology and ethnicity indicated that *MET* amplification was significantly associated with shorter survival, especially for patients with adenocarcinomas (HR: 1.41 [95% CI: 1.-11–1.79]) and of Asian ethnicity (HR: 1.58 [95% CI: 1.32–1.88]).[58]

Amplification as a Resistance Mechanism in Tumors Becoming EGFR-Mutated Under TKIs

MET amplification represents a mechanism of acquired resistance in 5–20% of patients, whose NSCLCs harbor EGFR mutations and were treated with EGFR-inhibitors, particularly after first-line third-generation therapy.[60–65] In the AURA3 trial of 83 patients who cancers progressed on second-line osimertinib, 19% exhibited *MET* amplification.[66] When osimertinib was given as a first-line therapy, *MET* amplification was the most common resistance mechanism, found in 15% of

patients by NGS of circulating-tumor DNA analysis. Moreover, that percentage is expected to be higher in tissues, because of the underestimation of gene amplification in plasma.[67] Consistent with those findings, the results of several preclinical and clinical studies demonstrated that the combined use of MET inhibitors, osimertinib and other EGFR-TKIs can potentially overcome the resistance in osimertinib-resistant *EGFR*-mutant NSCLC lines with *MET*-gene amplification.[68–70]

Mutations

The frequencies of METex14 mutations was 1.7–4.3% in metastatic lung adenocarcinomas, according to NGS analyses.[46–48,55,58] METex14-skipping mutations tend to be more frequent in relatively elderly populations and mutually exclusive of other lung cancer-driver mutations.[71,72] METex14-skipping mutations have been identified across different major histological subtypes of lung cancers, eg adenosquamous (8.2%) or sarcomatoid subtypes (7.7%), adenocarcinomas (2.9%) and squamous-cell carcinomas (2.1%).[72,73]

Anti-MET Therapies

The MET pathway can be targeted via several mechanisms. Anti-MET therapies are divided among selective TKIs, nonselective (also known as multitarget) TKIs and antibodies directed against MET or its ligand HGF.[74] Table 1 summarizes the molecules being evaluated as NSCLC treatments. TKIs can be separated into three types according to their binding mechanisms and their conformations.[75,76] TKI types I and II are ATP-competitive MET inhibitors but with different selectivities, conformations and binding sites. Those two groups include the majority of TKIs currently used or being developed, such as crizotinib, capmatinib and savolitinib (type I) or cabozantinib, merestinib and glesatinib (type II). Tivantinib is an exception because its activity is only partially linked to MET inhibition (with non-ATP–competitive binding; other mechanisms are involved, eg, microtubule rupture and blocked assembly).[77] Type III TKIs bind to allosteric sites distinct from the ATP-binding site. At present, no type III inhibitor has been developed for use in oncology.[75]

Therapies Developed for Non-Selected or Selected MET-Overexpression Patients

Anti-MET results obtained for NSCLC patients not selected for a MET pathway anomaly have been disappointing, even when they were analyzed as a function of their IHC-detected MET expression.

The GO27820 study evaluated onartuzumab (Genentech, Inc, South San Francisco, CA), a recombinant, fully humanized, monovalent monoclonal antibody that binds to the extracellular domain of MET, in combination with first-line platinum-based doublet chemotherapy, in patients with squamous cell NSCLCs. Its results were considered negative, with median PFS at 4.9 months in both treatment arms. For patients whose cancers expressed IHC-detected MET, median PFS lasted 5.0 and 5.2 months, respectively, in the onartuzumab or placebo arms.[12] In another Phase II trial, onartuzumab in combination with chemotherapy comprised of platinum salt–pemetrexed–bevacizumab in patients with non-squamous NSCLC (GO27281) did not reach its principle objective, with median PFS at 5.0 months vs 6.8 months for the placebo arm. In patients with IHC MET-positive expression, median PFS was 4.8 (95% CI: 3.7–6.2) months for onartuzumab recipients vs 6.9 (95% CI: 4.9–10.9) months for the placebo arm, with an unstratified HR of 1.71.[78]

The combination of erlotinib and onartuzumab, tested in two studies, did not prolong PFS or OS in the general NSCLC population or those with MET overexpression.[79,80]

Crizotinib (PF-02341066, Xalkori, developed by Pfizer; 200 mg twice daily) was evaluated in combination with dacomitinib (NCT01121575; maximum tolerated dose: 30 mg once daily) in a Phase I study on 70 patients were treated during the dose-escalation (n=33) and expansion phases (n=37). Grade-3 or −4 treatment-related adverse events occurred in 43% of patients.[81] The crizotinib–dacomitinib combination had limited antitumor activity against advanced NSCLC and was associated with substantial toxicity. Further assessment of that combination was not pursued.

Tivantinib (formerly ARQ 197; ArQule, Woburn, MA; Daiichi Sankyo, Tokyo, Japan) a non-ATP–competitive small-molecule MET inhibitor (TKI) was evaluated in three trials (NCT00777309, MARQUEE, ATTENTION) in combination with erlotinib, as second- or third-line therapy for advanced NSCLC.[82–84] None of the three trials obtained positive results. The ATTENTION study was stopped, after 307 patients had been randomized, as recommended by the Safety Review Committee because of the very different between-group frequencies and impacts of interstitial lung disease: 14 (three deaths) tivantinib recipients and six (0 deaths) placebo-group patients.[84]

Cabozantinib, an available oral TKI active against MET and vascular endothelial growth-factor–receptor-2 (VEGFR2),

Table 1 Agents Being Evaluated as Treatments for Non-Small–Cell Lung Cancers

Inhibitor	Compound	Drug Target	Company
Type			
Multikinase			
Ia	Crizotinib	MET, ALK, ROS1	Pfizer
II	Cabozantinib	MET, RET, KIT, AXL, VEGFR2	Elexis
II	Glesatinib	MET, AXL, TIE2, VEGFR	Mirati Therapeutics
II	Merestinib	MET, AXL, ROS1, TIE2, DDR, FLT3, RON, MERTK, MKNK1/2	Lilly
II	S49076	MET, AXL, FGFR1,2,3	Servier
II	Foretinib	MET, RON, MERTK, VEGFR2	GSK
Selective MET			
Ib	AMG337	MET	Amgen
Ib	Savolitinib	MET	AstraZeneca
Ib	Tepotinib	MET	Merck
I	Tivantinib		Arqule
I	Bozitinib (PLB1001) SAR125844		CBT
II	MK-8033	MET/RON	MSD
Ib	Capmatinib	MET	Novartis
I	JNJ-61,186,372 (OMO1)	MET	Janssen
Anti-MET Antibody			
	Onartuzumab		Genentech
	Emibetuzumab		Lilly
	ABT-700		AbbVie
	Tesolituzumab vedotin (ABBV-399)		AbbVie
	JNJ-61,186,372		Janssen
Anti-HGF Antibody			
	Rilotumumab		Amgen
	Ficlatuzumab		Aveo

Abbreviations: *ALK*, anaplastic lymphoma kinase; *DDR*, discoidin domain-receptor tyrosine kinase; *FGFR*, fibroblast growth factor receptors; *FLT-3*, FMS-like tyrosine kinase-3; *HGF*, hepatic growth factor (MET ligand); *MER*, myeloid-epithelial-reproductive; *MERTK*, MER tyrosine-kinase receptor; *MKNK1/2*, MAP kinase-interacting serine/threonine-protein kinase 1/2; *RON*, Recepteur d'Origine Nantais kinase or macrophage stimulating-1 receptor MST1R; *ROS1*, tyrosine-protein kinase-1; *TAM*, tyrosine-protein kinase receptor (*TYRO3*), tyrosine-protein kinase receptor (*AXL*) and (*MER*) receptor tyrosine kinase subfamily; *VEGFR*, vascular endothelial growth factor receptor.

RET, ROS1, tyrosine-protein kinase receptor (AXL), tyrosine-protein kinase *KIT* (KIT), and tyrosine kinase with immunoglobulin and EGF homology domains (TIE2/TEK), was tested alone and combined with erlotinib, as second- or third-line therapy for NSCLCs. That study included 125 patients: 42 assigned to receive erlotinib, 40 cabozantinib and 43 the combination. PFS was significantly longer for the cabozantinib (4.3 months, HR: 0.39 [80% CI: 0.27–0.55]; P=0.0003) and erlotinib plus cabozantinib arms (4.7 months, HR: 0.37 [80% CI: 0.25–0.53]; P=0.0003) than erlotinib alone (median: 1.8 months). For the 74/125 patients with IHC-detected MET-positive expression, median PFS lasted 1.8 months for patients randomized to erlotinib vs 5.0 months for patients given cabozantinib alone or in combination. This agent is not currently being evaluated in any study.[85]

An ongoing phase II study (NCT03539536) is evaluating telisotuzumab vedotin (ABBV-399), an anti-MET antibody, as second-line therapy for NSCLCs, especially IHC MET-positive NSCLCs, as assessed by an AbbVie-designated IHC laboratory or known documented *MET*-gene amplification.

The results with anti-MET agents have been disappointing in patients with tumors overexpressing MET. Notably, onartuzumab, tivantinib and cabozantinib yielded negative findings (Table 2).

MET Rearrangement

At this time, no molecule is being developed to overcome this anomaly. However, published case reports have described crizotinib efficacy against NSCLCs harboring a *KIF5B–MET* rearrangement.[86]

MET-Amplified NSCLCs

De Novo Amplification

Results obtained with agents tested in patients with this genetic abnormality are summarized in Table 2. In the two arm, non-comparative phase II METROS trial, among the 16 patients with *MET* amplification (Camidge-classification intermediate for 14 patients or high for 2) treated with oral crizotinib (250 mg twice daily), the objective response rate (ORR) was 31.3% (95% CI: 5.2–71.4), with respective median PFS and OS at 5.0 (95% CI: 2.7–7.3) and 5.4 months (95% CI: 3.4–7.4).[87] The AcSé phase II trials on 25 crizotinib-treated patients with *MET* amplification (GCN>6), the ORR was 16%, and the respective median PFS and OS were 3.2 (95% CI: 1.9–3.7) months and 7.7 (95% CI: 4.6–15.7) months.[88]

Tivantinib also yielded disappointing results for patients with *MET* amplification (defined as GCN>4): median PFS last 3.6 months for those given the erlotinib–tivantinib combination, as for those taking erlotinib alone.[83] Other molecules, like tepotinib or capmatinib, are being tested to treat this anomaly.

Table 2 Clinical Trials on NSCLC Patients Without *EGFR*-Mutation(s)

***MET* Anomaly** **MET-Positivity Definition**	**Agent**	**Trial**	**Phase**	**Line**	**Population**	**Arm**	**Primary Endpoint**	**Status**	**ORR (%)**	**OS (mo)**	**PFS (mo)**
METex14 Mutation											
	Crizotinib	NCT00585195 (PROFILE-1001)	II	Any	NSCLC	Crizotinib	Safety	Ongoing	32		7.3
		NCT02499614 (METROS)	II	1st	NSCLC	Crizotinib	ORR	Ended	20	3.8	2.8
		NCT02034981 (AcSé Crizo)	II	2nd/3rd	NSCLC	Crizotinib	ORR	Ongoing	10.7	8.1	2.4
		NCT04084717 (CROME)	II	Any	NSCLC	Crizotinib	ORR	Not yet recruiting			
		NCT02465060 (NCI-MATCH)	II	Any	NSCLC	Crizotinib	Safety	Ongoing			
		NCT02664935 (Matrix)		Any	NSCLC	Crizotinib	ORR	Ongoing			
	Capmatinib	NCT02750215	II	1st and 2nd/3rd	NSCLC	Capmatinib	ORR	Complete	72/39		9.7 5.4
		NCT02414139	II	2nd/3rd	NSCLC	Capmatinib	ORR	Ongoing			
	Tepotinib	NCT02864992 (VISION)	II	Any	NSCLC	Tepotinib	ORR	Ongoing	51		
	Savolitnib	NCT02897479	II	Any	NSCLC	Savolitnib	ORR	Ongoing			
	Cabozantinib	NCT03911193	II	2nd/3rd	NSCLC	Cabozantinib	ORR	Ongoing			
		NCT01639508	II	2nd/3rd	NSCLC	Cabozantinib	ORR	Ongoing			
	Glesatinib	NCT02544633	II	2nd/3rd	NSCLC	Glesatinib	ORR	Ended			
	Merestinib	NCT02920996	II	2nd/3rd	NSCLC	Merestinib	ORR	Ongoing			
MET Overexpression											
IHC MET 2+/3+	Onartuzumab	NCT01519804 (GO27820)	II	1st	Squamous-cell NSCLC	Platinum–paclitaxel + onartuzumab	PFS	Ended	3.2	10.8	5.0
						Platinum–paclitaxel + placebo			8.6	7.9	5.2

IHC MET 2+/3+	Onartuzumab	NCT01496742 (GO27821)	II	1st	Non-squamous–cell NSCLC	Platinum–pemetrexed–bevacizumab + onartuzumab	PFS	Ended		9.9	4.8
						Platinum–pemetrexed–bevacizumab + placebo				16.5	6.9
						Platinum–pemetrexed + onartuzumab				8.0	5.0
						Platinum–pemetrexed + placebo				7.6	5.0
IHC MET 2+/3+	Onartuzumab	NCT00854308 (OMA4558g)	II	2nd/3rd	NSCLC	Erlotinib + onartuzumab	PFS	Ended			2.9
						Erlotinib + placebo					1.5
IHC MET 2+/3+	Onartuzumab	NCT01456325 (METLung)	II	2nd/3rd	NSCLC	Erlotinib + onartuzumab	OS	Ended		6.8	2.7
						Erlotinib + placebo				9.1	2.7
FISH+	Onartuzumab		II	2nd/3rd	NSCLC	Erlotinib + onartuzumab	OS	Ended	11.8	6.4	1.5
						Erlotinib + placebo			4.2	9.4	2.7
IHC MET 2+/3+	Tivantinib	NCT01244191	III	2nd/3rd	NSCLC	Erlotinib + tivantinib	OS	Ended		9.3	3.7
						Erlotinib + placebo				5.9	1.9
IHC MET 2+/3+	Tivantinib	NCT01377376	III	2nd/3rd	NSCLC	Erlotinib + tivantinib	OS	Ended			
						Erlotinib + Placebo					
IHC MET 2+/3+	Cabozantinib	NCT01708954	II	2nd/3rd	NSCLC	Cabozantinib arms	PFS	Ended			5.0
						Placebo					1.8
MET FISH+ or IHC 2+/3+	Capmatinib	NCT01911507	I	2nd/3rd	NSCLC	Erlotinib + capmatinib	Safety	Ongoing			
IHC MET+	Telisotuzumab vedotin	NCT03539536	II	2nd/3rd	NSCLC	Telisotuzumab vedotin	ORR	Ongoing			
MET amplification											
MET GCN>4	Tivantinib	NCT00777309	II	$2_{nd}/3_{rd}$	NSCLC	Erlotinib + tivantinib	PFS	Complete			3.6
						Erlotinib + placebo					3.6
FISH *MET*/CEP7>2.0	Cabozantinib	NCT02132598	II	$2nd/3_{rd}$	Non-squamous NSCLC (brain metastases)	Cabozantinib	ORR	Ongoing			

(*Continued*)

Table 2 (Continued).

MET Anomaly	Agent	Trial	Phase	Line	Population	Arm	Primary	Status	ORR	OS	PFS
MET-Positivity Definition							**Endpoint**		**(%)**	**(mo)**	**(mo)**
MET GCN≥6	Capmatinib	NCT03240393	II	$2_{nd}/3_{rd}$	NSCLC	Cabozantinib	ORR	Withdrawn			
MET GCN≥4 and <6											
MET GCN≥6	Capmatinib	NCT02414139	II	$2_{nd}/3_{rd}$	NSCLC	Cabozantinib	ORR	Ongoing			
MET GCN≥4 and <6											
FISH *MET*/CEP7>2.2	Crizotinib	NCT02499614 (METROS)	II	1_{st}	NSCLC	Crizotinib	ORR	Ended	31.3	5.4	5.0
MET GCN>6		NCT02034981 (AcSé Crizo)	II	$2_{nd}/3_{rd}$	NSCLC	Crizotinib	ORR	Ongoing	16	7.7	3.2
Not reported	Tepotinib	NCT02864992 (VISION)	II	Any	NSCLC	Tepotinib	ORR	Ongoing			
Not reported	SAR125844	NCT02435121	II		NSCLC	SAR125844	ORR	Ended			

Abbreviations: FISH, fluorescence in situ hybridization; CEP7, centromeric portion of chromosome 7; GCN, gene copy number; IHC, immunohistochemistry; MET, c-MET proto-oncogene; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Amplification as a Resistance Mechanism

Several TKIs with anti-MET activity have been evaluated in this context (Table 3). According to a phase I trial combining crizotinib and erlotinib, respective maximum tolerated doses were 150 mg twice daily and 100 mg/day.[89] However, no ongoing clinical trial is testing this combination therapy. In a phase II study that combined cabozantinib (40 mg/day) and erlotinib (150 mg/day) for patients with *EGFR*-mutated tumors that progressed under EGFR-TKI, ORR was 10.8% for the 37 analyzable patients, none of whom had *MET* amplification.[90]

The combination of emibetuzumab and erlotinib versus erlotinib alone as first-line therapy for *EGFR*-mutated metastatic NSCLC, without selection according to *MET* status, yielded respective negative outcomes for its principal criterion (PFS) of 9.3 vs 9.5 months. Exploratory analysis of patients with MET-high expressing tumors (IHC MET 3+) showed that PFS was prolonged by 15.3 months (combination: 20.7 months vs 5.4 months, HR: 0.39 [90% CI: 0.17–0.91]).[91]

The combination of tepotinib plus gefitinib versus platinum–pemetrexed chemotherapy in patients with EGFR-mutated but $EGFR^{T790M}$-negative, IHC MET 2+/3+ or with *MET* amplification (GCN≥5 and/or *MET*/CEP7 ratio ≥2) that progressed under TKI, respective median PFS lasted 21.2 vs 4.2 months (HR: 0.13 [90% CI: 0.04–0.43]), and median OS of 37.3 vs 13.1 months (HR: 0.08 [90% CI: 0.01–0.51]).[92] ORR was also higher for the combination, respectively: 66.7% vs 42.9%. Patients with *MET*-amplification experienced ≥15% grade ≥3 treatment-related adverse events (increased amylase or lipase) in both arms. A new phase II study is now underway.

The tivantinib plus erlotinib combination had an ORR of 6.7% in a Japanese phase II study that had enrolled 45 patients with advanced *EGFR*-mutated NSCLC with acquired resistance to gefitinib or erlotinib and MET expression.[93] Half the patients enrolled in that study were $EGFR^{T790M}$-positive and 48.9% had high MET expression (IHC MET 2+/3+), including the three responders with both genetic anomalies.

In a phase Ib/II study on EGFR-TKI–pretreated patients, with $EGFR^{T790M}$-negative and *MET* amplification-positive (GCN≥6) NSCLCs, the gefitinib–capmatinib (400 mg twice per day) plus gefitinib (250 mg/day) achieved an ORR of 47%.[68] No significant drug–drug interactions were observed in that study. Other ongoing studies are combining capmatinib and aunazartinib or erlotinib.

The TATTON (phase Ib) study tested the combination of osimertinib (80 mg/day) and savolitinib (600 mg/day) on two cohorts of patients with *EGFR*-mutated *MET*-amplified NSCLCs.[69,70] In the first cohort of first- and second-generation EGFR-TKI–pretreated patients with $EGFR^{T790M}$-negative/MET-positive (GCN≥5 or IHC MET 3+) disease, the ORR was 52%. In the other cohort that included third-generation EGFR-TKI–pretreated patients, the combination therapy obtained an ORR of 25%.

The ongoing phase II SAVANNAH study (NCT 03778229) will further evaluate the osimertinib–savolitinib combination in first-generation EGFR-TKI–pretreated patients with *EGFR*-mutant, *MET*-amplified NSCLCs that progressed on prior osimertinib.

Emibetuzumab (LY2875358) is a humanized IgG4 bivalent monoclonal anti-MET antibody-blocking ligand-dependent and -independent HGF/MET signaling. In a study examining whether acquired resistance to erlotinib in MET-positive (expression) NSCLC patients, with a predominance of EGFR-mutated tumors, that resistance could be overcome by emibetuzumab or emibetuzumab + erlotinib; the ORRs for patients with MET overexpression (≥60%) were 3.8% and 4.8% in the combination and monotherapy arms, respectively.[94] In a phase Ib study combining tesolituzumab vedotin (ABBV-399) and erlotinib for patients with IHC *MET*-positive (H-score >150 or *MET*-amplification) NSCLCs, the ORR was 34.5% for the 29 EGFR-TKI–pretreated patients.[95]

JNJ-61,186,372, an antibody bispecific to EGFR and MET, binds the two proteins, thereby blocking their ligand binding, promoting receptor degradation and triggering antibody-dependent cellular cytotoxicity in models of EGFR-mutated NSCLC. Results of the phase I study were reported at ASCO 2019 (NCT02609776).[96] Response-assessable patients' ORR was 28% and their best timepoint response was partial. Among 47 patients with prior third-generation TKI therapy, 10 had best timepoint response of partial response (six confirmed), including four with $EGFR^{C797S}$ mutation, one with *MET* amplification and five with no identifiable *EGFR*/*MET*-dependent resistance. Enrollment in that trial's expansion phase is ongoing. It also evaluated another cohort with the combination of JNJ-61,186,372 and lazertinib (third-generation EGFR-TKI).

Evaluation of Anti-MET Agents in Patients with NSCLCs Harboring METex14

The METex14 mutation clearly appears to be an oncogenic driver. According to a multicenter series of patients

Table 3 Clinical Trials on Patients with *EGFR*-Mutated NSCLC

Type of Agent	*MET* Anomaly / MET-Positivity Definition	Agent	Trial	Phase	Line	Arm	Primary Endpoint	Status	ORR (%)	OS (mo)	PFS (mo)
Multikinase Inhibitors											
	Any	Crizotinib	NCT00965731	I	2_{nd}	Erlotinib + crizotinib	Safety	Ended	NR	NR	NR
		Cabozantinib	NCT01866410	II	2_{nd}	Erlotinib + cabozantinib	ORR	Ended	10.6	13.3	3.6
		S49076	EU 2015–002646-31	I/II	2_{nd}	Gefitinib + S49076	ORR	Ended			
Selective MET Inhibitor											
	Amplification GCN≥5 and/or *MET*/CEP7≥2	Tepotinib	NCT01982955 (INSIGHT)	I/II	2_{nd}	Gefitinib + tepotinib	ORR	Ended	66.7	37.1	22.1
	Overexpression IHC MET 2+/3+					Platinum–pemetrexed			42.9	13.1	4.2
	Amplification	Tepotinib	NCT03940703 (INSIGHT 2)	II	2_{nd}	Gefitinib + tepotinib	ORR	Ended			
	Overexpression IHC MET 2+/3+	Tivantinib	NCT01580735	II	2_{nd}	Erlotinib + tivantinib	ORR	Ended	6.7	18.0	2.7
	Amplification										
	GCN≥6	Capmatinib	NCT01610336	II	2_{nd}	Gefitinib + capmatinib	ORR	Ended	42.0		5.49
	IHC MET 3+								32.0		5.45
	Amplification GCN≥6	Capmatinib	NCT02468661	I/II	2_{nd}	Capmatinib	ORR	Ongoing			
						Erlotinib + capmatinib		Ongoing			
						Platinum–pemetrexed		Ongoing			
	Any *MET*		NCT02335944	I/II	1_{st}-4_{th}	Nazartinib and capmatinib	ORR	Ongoing			
	Amplification GCN≥5 or IHC MET 3+	Savolitinib	NCT02143466	Ib	2_{nd} (after 1/2 EGFR-TKI)	Osimertinib + savolitinib	ORR	Ended	52.0		
					2_{nd} (after osimertinib)	Osimertinib + savolitinib	ORR	Ended	25.0		
	Amplification GCN≥5 or IHC MET 3+	Savolitinib	NCT03778229 (SAVANNAH)	II	2_{nd} (after osimertinib)	Osimertinib + savolitinib	ORR	Planned			

Anti-MET Antibodies										
	Overexpression IHC MET+ >60%	Emibetuzumab	NCT01900652	II	2nd	Emibetuzumab	ORR	Ended	3.8	
						Erlotinib + emibetuzumab			4.8	
	Overexpression IHC MET 3+	Emibetuzumab	NCT01897480	II	1st	Emibetuzumab	PFS	Ended		20.7
						Erlotinib + emibetuzumab				5.6
	Amplification IHC H-score>150	Tesolituzumab vedotin	NCT02099058	II	2nd	Erlotinib + tesolituzumab	ORR	Ended	34.6	
	Any *MET*	JNJ-61,186,372	NCT02609776	I	2nd	JNJ-61,186,372	Safety	Ended	28.0	
	Any *MET*	JNJ-61,186,372	NCT04077463	I	2nd	Lazertinib + JNJ-61,186,372	Safety	Ongoing		

Abbreviations: CEP7, centromeric portion of chromosome 7; GCN, gene copy number; IHC, immunohistochemistry; *MET*, c-MET proto-oncogene; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

carrying the METex14 mutation, 61/148 patients not exposed to anti-MET and for whom survival data was available, median OS lasted 8.1 [95% CI: 5.3–not reached] vs 24.6 [95% CI 12.1–not reached] months for those who had received at least one TKI anti-MET (crizotinib, glesatinib or capmatinib) during management of their NSCLCs.[97] Several MET inhibitors are under development for this indication.

Crizotinib efficacy was addressed in several case reports and Phase I–II trials (Table 2).[73,98,99] Updated results from the PROFILE-1001 study, in which 69 treatment-naïve or chemotherapy-refractory, METex14+ NSCLC patients participated, showed three complete responses and 18 partial responses (ORR, 32% [95% CI: 21–45]) with median PFS at 7.3 [95% CI: 5.4–9.1] months.[100]

In the METRO study, which included 26 crizotinib-treated patients (16 with *MET* amplification, nine harboring the METex14 mutation and one with concurrent abnormalities), the ORR was 20% for patients with METex14 mutations, with median PFS at 2.6 [95% CI: 2.2–3.0] months and median OS at 3.8 months [95% CI: 1.7–5.8]. No difference between *MET*-amplified and METex14-mutated patients was found for any clinical endpoint.[87]

In the AcSé crizotinib study,[88] among 28 patients with *MET* anomalies, 25 had the METex14 mutation; the ORR at 2 cycles was 10.7% [95% CI 2.3–28.2%]; median PFS was 2.4 [95% CI 1.6–5.9] months and median OS was 8.1 months [95% CI 4.1–12.7].

In light of the outcomes of the Profile-1001 study, in 2018, the FDA granted, crizotinib (Xalkori) a breakthrough-therapy designation for the treatment of patients with NSCLC harboring METex14 alterations that progressed after receiving platinum-based chemotherapy.

Capmatinib (INC280; Novartis), an oral, ATP-competitive, type Ib MET inhibitor has also been developed for this indication. In the phase I study, the four METex14-mutated–NSCLC patients enrolled achieved significant tumor-volume reductions (>45%).[101] In the phase II GEOMETRY mono-1 study, among the 94 METex14-mutated NSCLC patients included (69 receiving second- or third-line therapy and 25 treatment-naïve), respective ORRs were 39.1% (95% CI: 27.6–51.6) and 72.0% [95% CI: 50.6–87.9]. The median first-line PFS was 9.7 months and 5.4 months for the subsequent lines.[102] In September 2019, the FDA designated capmatinib (INC280) a breakthrough therapy as first-line treatment for patients with METex14-mutated NSCLC.

Tepotinib (EMD1214063, MSC2156119J; Merck), an oral, ATP-competitive, and highly selective MET inhibitor, was evaluated in a phase II study on patients with METex14-mutated NSCLCs. The intermediate results for 35/90 patients included and assessable showed the ORR at 51.4% [95% CI: 34.0–68.6], with median treatment duration of 9.8 [95% CI:1.1–18.0] months.[103] The FDA accorded this investigational targeted therapy breakthrough-therapy designation for patients with METex14-mutated NSCLCs that progressed after platinum-based chemotherapy.

Other anti-MET TKIs are currently being tested, like savolitinib (AZD6094, volitinib, HMPL-504; AstraZeneca) or glesatinib (MGCD265; Mirati Therapeutics) in phase II trials, but no information is available at this time (Table 2).

Immunotherapy for Patients with a MET-Pathway–Signaling Abnormality

In pathophysiological terms, the presence of a *MET* anomaly seems to induce programed cell-death protein-1–ligand-1 (PD-L1) expression.[104–106] An analysis of 622 surgical NSCLC samples showed that PD-L1 expression was significantly higher in patients with *MET* amplifications than those without. In addition, peritumoral lymphocyte infiltration was more abundant in patients with *MET* amplification.[105] In that paper, six patients with *MET* anomalies were treated with immunotherapy, which yielded three partial responses, one disease stabilization and two progressions. In an analysis of 148 patients harboring the METex14 mutation, 63% of the cohort's NSCLCs expressed PD-L1: 1–49% for 22% and >50% for 41%.[100] Their median tumor mutation burden was 3.8 mutations/megabase, lower than that of a control historical cohort, whose tumors did not carry the METex14 mutation (5.7 mutation/megabase: P<0.001).

Retrospective analysis of registries provided information on the inefficacy of immune-checkpoint inhibitors (ICIs) for patients with oncogenic driver alterations. The Immunotarget Registry included 34 patients, whose NSCLCs harbored the METex14 mutation, 30% expressing PD-L1 and their ORR was 16%, with median PFS at 4.7 months.[15] In another analysis of 30 patients with *MET* mutations, 43% expressing PD-L1, ORR was 35.7% and median PFS lasted 4.9 months.[16] ICIs do not seem to have any remarkable efficacy against *MET* anomalies but it appeared better than for other oncogenic anomalies, eg *ALK* or RET translocations. Phase I–II trials combining ICIs with anti-MET TKIs, like glesatinib, are ongoing but no information is available at this time.[105]

Conclusion

Inspired by the major breakthrough of targeted therapies in treating lung cancers, the identification of new pertinent targets remains a high priority. After the discoveries of the *EGFR* or *BRAF* mutations, or *ALK* or *ROS1* rearrangements, new, less frequent mutations have been identified, such as *RET* or *NTRK*. MET pathway anomalies also have major clinical impact, especially for patients with the METex14 mutation, for which promising therapeutics have been developed, eg first-line capmatinib or second-line crizotinib and tepotinib after chemotherapy failure. Other agents are being investigated as any treatment line in patients with metastatic MET*exon14*-mutation–positive NSCLCs.

It is necessary to distinguish between de novo amplifications and amplifications as a resistance mechanism to EGFR-TKIs. Among the latter, capmatinib, tepotinib or savolitinib have yielded promising results in combination with an EGFR-TKI, like gefitinib or osimertinib. For this indication, anti-MET or -HGF antibodies can also represent a therapeutic option.

Clinical findings about other MET anomalies, like overexpression or rearrangement, have been disappointing and do not represent an avenue for clinical research at this time.

In light of the promising results obtained for patients whose NSCLCs harbor the METex14 mutation or MET amplification as a mechanism of resistance to EGFR-TKI, inclusion of such patients in clinical trials should be strongly encouraged.

Disclosure

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