



A narrative review of MET inhibitors in non-small cell lung cancer with *MET* exon 14 skipping mutations

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Abstract: Treatment of advanced non-small cell lung cancer (NSCLC) has radically improved in the last years due to development and clinical approval of highly effective agents including immune checkpoint inhibitors (ICIs) and oncogene-directed therapies. Molecular profiling of lung cancer samples for activated oncogenes, including epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*), c-ros oncogene 1 (*ROS1*) and *BRAF*, is routinely performed to select the most appropriate up-front treatment. However, the identification of new therapeutic targets remains a high priority. Recently, *MET* exon 14 skipping mutations have emerged as novel actionable oncogenic alterations in NSCLC, sensitive to MET inhibition. In this review we discuss: (I) *MET* gene and MET receptor structure and signaling pathway; (II) *MET* exon 14 alterations; (III) current data on MET inhibitors, mainly focusing on selective MET tyrosine kinase inhibitors (TKIs), in the treatment of NSCLC with *MET* exon 14 skipping mutations. We identified the references for this review through a literature search of papers about MET, *MET* exon 14 skipping mutations, and MET inhibitors, published up to September 2020, by using PubMed, Scopus and Web of Science databases. We also searched on websites of main international cancer congresses (ASCO, ESMO, IASLC) for ongoing studies presented as abstracts. *MET* exon 14 skipping mutations have been associated with clinical activity of selective MET inhibitors, including capmatinib, that has recently received approval by FDA for clinical use in this subgroup of NSCLC patients. A large number of trials are testing MET inhibitors, also in combinatorial therapeutic strategies, in *MET* exon 14-altered NSCLC. Results from these trials are eagerly awaited to definitively establish the role and setting for use of these agents in NSCLC patients.

Keywords: MET; *MET* exon 14 skipping mutations; MET-tyrosine kinase inhibitors (TKIs); non-small cell lung cancer (NSCLC)

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Introduction

Therapeutic management of advanced lung cancer has strikingly and ceaselessly evolved in recent years for the development and approval for clinical use of an increasing number of highly effective agents, including molecularly targeted drugs and immune checkpoint inhibitors (ICIs). Biomarker testing is routinely performed in non-small cell lung cancer (NSCLC) patients because multiple targeted therapies are currently available, including epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1) tyrosine kinase inhibitors (TKIs) (1). The approval of the combination of dabrafenib and trametinib for *BRAF*-mutant NSCLC patients has further enlarged the number of predictive biomarkers that need to be screened at baseline to define the optimal therapeutic approach (2,3). Immunotherapy has become part of the treatment for patients without driver alterations (EGFR or ALK). The ASCO and OH Joint Panel Guideline recommends pembrolizumab for non-squamous cell carcinoma and SCC with high PD-L1 expression [tumor proportion score (TPS) $\geq 50\%$] (4,5). Combination of chemotherapy and immunotherapy is recommended for most patients with negative or low positive PD-L1. Recently, additional actionable oncogenic alterations other than *EGFR*, *ALK*, *ROS1* and *BRAF*, have emerged, including *MET* alterations, *RET* and *NTRK* rearrangements (6-13). Herein, we describe *MET* exon 14 alterations and review current available data from clinical trials with *MET* inhibitors in *MET* 14 altered-NSCLC patients. Demonstration of clinical efficacy of selective *MET* TKIs in this subgroup of patients underlines the need to routinely include *MET* exon 14 mutation screening as part of the molecular testing panels performed for advanced NSCLC.

We present the following article in accordance with the Narrative Review Checklist (available at <http://dx.doi.org/10.21037/tlcr-20-1113>).

Methods

We performed an updated literature search for papers published up to September 2020 on the role of *MET* in non-small lung cancer using the following medical research databases: PubMed, Scopus and Web of Science. We also searched for abstracts on main international cancer congresses (ESMO, ASCO, IASLC) websites. We included in the search strategy the following terms: “*MET*”, “*MET*

deregulation”, “*MET* and lung cancer”, “*MET* exon 14 skipping mutations”, “*MET* inhibitors” (see Key Search, in Appendix 1). For clinical trials, we collected and reviewed data of both completed and ongoing studies.

Discussion

MET signaling pathway

The *MET* receptor is encoded by the *MET* oncogene, located on the long arm of human chromosome 7 (7q31). This oncogene was first identified in a human osteogenic sarcoma cell line containing a transforming fusion protein, TPR-*MET*, resulting from a rearrangement between the translocated promoter region (*TPR*) on chromosome 1 on the 5' end, and the *MET* gene on chromosome 7 on the 3' end (14,15). *MET* was shown to have homology with the receptor tyrosine kinase (RTK) family and to recognize the hepatocyte growth factor (HGF) as ligand (Figure 1) (16-18). *MET* expression is regulated at multiple layers by various mechanisms, such as DNA methylation and histone acetylation, alternative splicing, protein translation, posttranslational modifications and protein degradation (19,20). The receptor encompasses several functional domains: the extracellular portion contains a region of homology to semaphorins (Sema domain), which includes the full α chain and the N-terminal part of the β chain, a plexin-semaphorin-integrin (PSI) domain and four immunoglobulin-plexin-transcription factor (IPT) domains. The intracellular part of the receptor consists of a juxtamembrane domain, a catalytic tyrosine kinase (TK) domain, and a carboxy-terminal regional multisubstrate docking site, capable of recruiting multiple downstream adaptors with Src homology-2 (SH2) domain (21). Its physiological ligand is the HGF/scatter factor (HGF/SF), a two-chain (α and β) protein produced by the activation through site-specific proteolysis of pro-HGF, a single-chain, inactive molecule (22-24). HGF/SF contains two *MET*-binding sites, one in the NK1 fragment, and one in the SPH domain. Ligand binding induces *MET* homodimerization and autophosphorylation of tyrosine residues of its catalytic domain. Other tyrosines (1,349 and 1,356) are then phosphorylated within the docking site and allow recruitment of a large variety of downstream effectors, including growth factor receptor-bound protein-2 (GRB2), GRB2-associated binding protein 1 (GAB1), phospholipase C γ 1 (PLC γ 1), SRC, the p85 regulatory subunit of phosphatidylinositol-3 kinase (PI3K) and the

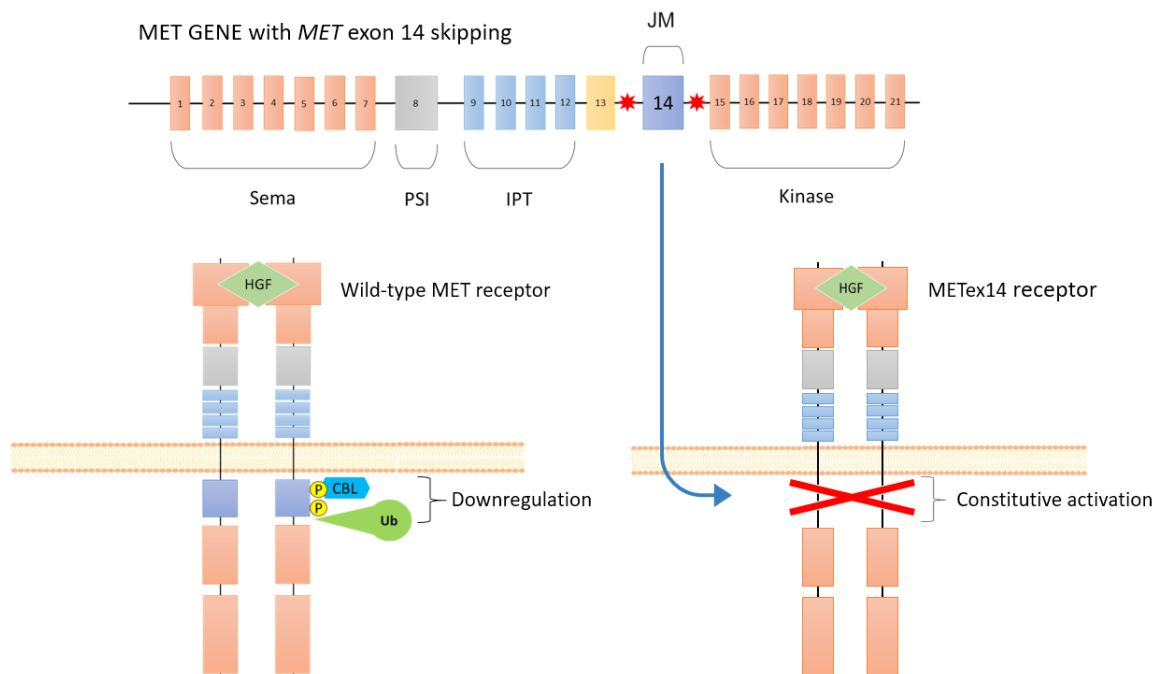


Figure 1 MET wild type and MET with exon 14 skipping mutations leading to loss of the juxtamembrane domain and constitutive activation. IPT, immunoglobulin-plexin-transcription; HGF, hepatocyte growth factor; PSI, plexin-semaphorin-integrin; JM, juxtamembrane.

signal transducer and activator of transcription 3 (STAT3) (6,25). MET activates multiple signal transduction pathways, including the RAS-mitogen-activated protein kinase (MAPK) cascade, the PI3K-AKT pathway, the Signal Transducer and Activator of Transcription (STAT) and NF- κ B pathway, involved in cell proliferation, differentiation, cell motility, invasion and survival. Moreover, by regulating cell-matrix adhesion and promoting cytoskeletal changes and cell migration, MET plays a key role in epithelial to mesenchymal transition (EMT) (6,24). The pleiotropic biological effects of MET activation also rely on crosstalk and signaling cooperation with various surface membrane proteins (26), including the MET homologue RON, and other TKs, such as ROR1, CD44, integrins, plexin B1 and EGFR. Similar to other RTKs, MET is downregulated through a variety of mechanisms. On ligand activation, MET is internalized through clathrin-mediated endocytosis, as a mechanism to prevent sustained signaling activation. The internalized receptor is delivered to endosomal compartments and can be degraded or recycled to plasma membrane. A key protein involved in internalization and degradation is the E3 ubiquitin ligase casitas B-lineage lymphoma (CBL), that recognizes the phosphorylated Tyr1003 in the juxtamembrane domain, encoded by exon 14

of *MET*, and recruits regulatory components of endocytic vesicles, while on the other hand, engages ubiquitin ligases to ubiquitylate MET that is then degraded in a proteasome-dependent manner (27-29). Other mechanisms involved in MET downregulation have been described, including proteolysis by ADAM metalloproteases and shedding of the extracellular domain (30).

While HGF is mainly expressed and secreted by mesenchymal cells, such as fibroblasts, MET is wider expressed by epithelial cells of a variety of tissues, but also found on endothelial cells, neurons, hepatocytes, and hematopoietic cells, and has been demonstrated to be involved in a variety of physiological processes during embryonic development and in tissues repair in adults [reviewed in (24)].

MET alterations driving tumorigenesis

A deeper knowledge of the biology of this receptor in normal tissues has been helpful for understanding the roles of HGF and MET in cancer. Indeed, aberrant HGF-MET signaling promotes tumor proliferation, invasive growth, angiogenesis and metastasis (6). MET expression and signaling is essential for expansion and maintenance of

cancer stem cells (CSCc) (31).

MET constitutive activation is a common event in several cancer types and can be the result of various mechanisms, including excessive autocrine or paracrine production of HGF, MET overexpression or genetic abnormalities of *MET*, such as gene copy-number amplification and point mutations. Other mechanisms include inadequate internalization and degradation and receptor crosstalk (6,32).

MET overexpression, due to increased gene copy number or transcriptional regulation, is commonly detected in many different solid tumors, including lung cancer, and correlates with poor prognosis (33-36). *MET* amplification, found in a small percentage of tumors, leads to kinase overexpression and constitutive activation of downstream survival signals and has been demonstrated to be an acquired resistance mechanism to different classes of EGFR TKIs (37,38). Activating point mutations in the kinase domain occur in different sporadic and inherited cancers and data suggest a correlation with progression and metastasis. These mutations, such as D1228N, Y1235D, and M1250T, lead to constitutive MET activation and can contribute to tumor development (7). In lung cancer, oncogenic mutations can be also found in the Sema domain (exon 2), and the juxtamembrane domain (exon 14) (6,7). *MET* mutations located within the Sema domain could affect ligand binding rather than promoting kinase activity (6). The expression of MET variants harboring point mutations within the juxtamembrane domain, including R988C and T1010I, was correlated with enhanced tumorigenicity and metastatic potential in lung cancer (39).

However, different studies have described *MET* mutations identified outside the kinase domain as germline polymorphisms (7,40-42) that do not induce kinase activation and may not act as oncogenic alterations. Hence, it remains crucial to fully elucidate the functional consequences of *MET* mutations and their relevance in oncogenesis. Dysregulation of the MET pathway can also occur through gene rearrangements, giving rise at fusion proteins encompassing the MET intracellular domain fused with a dimerization motif that potentially leads to a constitutive dimerization and activation of the receptor. The first to be identified in lung cancer was *TPR-MET* (14,15). New MET fusion proteins have been uncovered by RNA sequencing analysis from The Cancer Genome Atlas (TCGA) data and found to occur at low frequencies in different tumor types (43). A kinesin family member 5B gene (*KIF5B*)-*MET* fusion was detected in a sample from a patient with lung adenocarcinoma (43). More recently,

other *MET* fusion partner genes have been identified in lung cancer patients by using next-generation sequencing (NGS) technologies. These genes include StAR-related lipid transfer domain-3 N-terminal like (*STARD3NL*), human leukocyte antigen (*HLA*)-*DRB1*, *CD47* and ataxin 7-like 1 (*ATXN7L1*) (44-47). MET fusions are oncogenic in cellular models, suggesting may be suitable for targeted inhibition in lung cancer. Moreover, some studies have demonstrated a significant association with clinical response to crizotinib (44-46), suggesting a potential role of MET rearrangements as predictive biomarkers to MET inhibitors.

MET exon 14 skipping mutations

Somatic mutations affecting splicing sites of exon 14 of the *MET* gene, encoding for the juxtamembrane region, were first reported in small cell lung cancer. In this study, two tumor samples were found to harbour a two base-pair insertion within the intron 13 of *MET*, that could potentially cause alternative mRNA splicing and skipping of exon 14.

Thereafter, *MET* exon 14 (*MET*ex14) splice site mutations were reported in NSCLC and other tumor types (8,39). These mutations, including point mutations, insertions/deletions (indels) or large deletions, cause “exon 14 skipping” and permanent loss of the juxtamembrane region from the MET transcript (*Figure 1*). This region contains a tyrosine residue (Tyr1003) that, as previously commented, is responsible for efficient recruitment of the ubiquitin ligase CBL which is required for MET internalization and degradation. Moreover, the domain includes a serine residue (S985), which is phosphorylated by protein kinase C (PKC) that contributes to terminating the receptor kinase activity. Hence, loss of *MET* exon 14 leads to increased MET stability and expression on cell surface and prolonged activation of downstream signaling pathways, thus conferring oncogenic properties to cells (*Figure 1*) (48-50). Consistent with this, insertion of exon 14 into the oncogenic gene fusion *TPR-MET*, which consists of the *MET* sequence downstream from the juxtamembrane domain fused to the dimerization motif of *TPR*, resulted in decreased oncogenic potential (6,51).

MET exon 14 mutations in NSCLCs are found in approximately 3–4% of NSCLCs, mainly in adenocarcinoma, adenosquamous carcinoma, and the rare sarcomatoid histology, in older patients (52-57).

A meta-analysis including 12 studies comprising 18,464 NSCLCs, reported that the mutation is more likely to occur

in females and non-smokers (58). Contrasting results have been reported from clinical studies regarding the association of smoking status with *MET* exon 14 mutations (53,58,59). Both *MET* exon 14 mutations and *MET* amplification have been correlated with poor patient prognosis in NSCLC (54,58). Different DNA- and RNA-based techniques, including RT-PCR or NGS, have been used to identify *MET* exon 14 skipping events in lung cancer, although with some differences between these two diagnostic approaches. For example, it is difficult to obtain optimal quality and/or quantity of RNA from clinical samples (59-61).

Of note, similar to other activated oncogenes, *MET* exon 14 mutations have been shown to be mutually exclusive with other known drivers, including *EGFR*, *KRAS*, *BRAF* mutations and *ALK* or *ROS1* rearrangements, but to co-occur with other alterations, such as *MET*, *MDM2*, *CDK4* and *EGFR* amplification, and also with *PI3KCA* mutations (8,55,58,60,62).

Overall, *MET* exon 14 mutations have emerged as attractive targetable genomic alterations in NSCLCs, thus prompting a number of clinical trials testing different classes of *MET* inhibitors in this subset of patients.

Therapeutic agents against the HGF/MET axis

Several therapeutic strategies have been developed to target *MET* signaling, including anti-HGF or anti-*MET* antibodies and small molecule TKIs. These agents are currently in different stages of clinical testing.

Preclinical studies suggested that *MET* blockade was effective only in tumors harboring *MET* genomic alterations, including amplification or activating mutations; whereas targeting the HGF/*MET* pathway in tumors with wild type *MET* had little or no effect on cancer cell growth and did not influence cytotoxicity of chemotherapy (8,63). This preclinical evidence has been supported by negative results from some phase III randomized trials combining *EGFR* TKIs and *MET* inhibitors (64,65), such as the TKI tivantinib or the anti-*MET* monoclonal antibody onartuzumab, including pre-treated NSCLC patients unselected for any oncogenic alterations. Indeed, in a post hoc analysis, a longer OS with tivantinib was observed in the subgroup of patients with tumors displaying high *MET* copy number gain (64). Also, the use of the association with erlotinib in patients with *MET*-expressing tumors, as assessed by immunohistochemistry, did not show any survival benefit compared to placebo (65).

In initial reports, clinical responses to *MET* inhibition

were observed in lung cancer patients with *MET* exon 14 skipping mutations (8,48,50).

Multitarget TKIs

MET TKIs are small molecules that can generally be divided into three groups, according to their structure and mode of binding with *MET* (24,66). Type I and II are both ATP-competitive inhibitors and are those mostly being evaluated in clinical trials. Type I inhibitors occupy the ATP-binding pocket and bind to the activation loop (A-loop), with Y1230, to block catalytic activation. Type Ia, such as crizotinib, interacts with the solvent front residue G1163, while type Ib inhibitors, such as capmatinib, tepotinib, savolitinib, and APL-101, are independent of G1163 interaction. Type II inhibitors, such as cabozantinib, foretinib, merestinib and glesatinib, also occupy the ATP-binding pocket and extend to the deep hydrophobic back pocket and bind to the inactive “DFG out” conformation of *MET*. Hence, binding is independent of interactions with the A-loop. Type III are non-ATP competitive allosteric inhibitors binding outside the ATP pocket.

Crizotinib

Crizotinib is an oral small-molecule, multikinase inhibitor of *ALK*, *ROS1*, *RON* and *MET* and is currently approved for treatment of advanced NSCLC patients harboring *ALK* or *ROS1* rearrangements (67-69). Crizotinib acts as a type Ia *MET* TKI and competes for the ATP-binding site of the RTK, thereby preventing activation of downstream signaling pathways. Treatment with crizotinib of tumor cell lines with *MET* exon 14 skipping mutations impaired their viability and inhibited downstream pathways activation (50). A number of clinical reports supported this preclinical evidence by demonstrating that the use of crizotinib induced objective responses in patients with advanced NSCLC with *MET* exon 14 alterations (50,55,70-74). The antitumor activity of crizotinib in advanced, *MET*-exon 14-altered NSCLC patients was prospectively assessed in an expansion cohort of the multicenter phase 1 study, PROFILE 1001 (Table 1) (75,76). Overall, 69 patients with advanced NSCLC harboring *MET* exon 14 alterations, as assessed mostly by using DNA- or RNA-based, were included in the study. The median age was 72 years old. Most patients had adenocarcinoma and were former smokers and the majority of these had received ≥ 1 previous lines of treatment for advanced disease. Among the 65 patients evaluable for tumor response, the objective response rate (ORR) was

Table 1 MET inhibitors activity in NSCLC; published trials with multitarget TKIs

Drug	Trial	Phase	Treatment	Met-alteration	No. of pts	Efficacy outcome
Crizotinib (PF-02341066)	NCT00585195 (PROFILE-1001)	I	Crizotinib 250 mg bid	MET exon 14 skipping	69 (1 st line: 26; >2 nd line: 43)	ORR: 32%; PFS: 7.3 months; DOR: 9.1 months
				Amplification Low: ≥ 1.8 – ≤ 2.2 copies	3	ORR: 1 (33%); PFS: 1.8 months; DOR: 12.1 months
				Amplification Medium: > 2.2 – < 4 copies	14	ORR: 2 (14.3%); PFS: 1.9 months; DOR: 3.7 months
			Amplification High: > 4 copies	20	ORR: 8 (40%); PFS: 6.7 months; DOR: 5.5 months	
	NCT02499614 (METROS)	II	Crizotinib 250 mg bid	MET exon 14 skipping; MET/CEP7 ratio > 2.2	34 (2 nd line 17; >2 nd line: 5)	ORR: 7 (27%); PFS: 4.4 months; DOR: 3.7 months
	NCT02034981	II	Crizotinib 250 mg bid	c-MET > 6 copies	25	ORR: 4 (16%); PFS: 3.2 months;
				All MET-mutation cohort	28	ORR: 3 (10.7%); PFS: 2.2 months
Cabozantinib (XL184)	NCT01866410	II	Cabozantinib 40 mg daily + erlotinib 150 mg daily	MET exon 14 skipping	25	ORR: 3 (12%); PFS: 2.4 months
				MET amplifications not identified	37	ORR: 10.8%; PFS: 3.6 months; OS: 13.1 months
	NCT00940225	II	Cabozantinib 100 mg daily	None	60	ORR 10%; PFS: 4.0 months
	NCT01708954	II	Arm A: erlotinib 150 mg daily	None	40	ORR: 1 (3%); PFS: 1.8 months; OS: 5.1 months
		Arm B: cabozantinib 60 mg daily	None	42	ORR: 4 (11%); PFS: 4.3 months; OS: 9.2 months	
		Arm C: erlotinib 150 mg + cabozantinib 40 mg	None	43	ORR: 1 (3%); PFS: 4.7 months; OS: 13.3 months	
Foretinib (GSK1363089)	NCT01068587	I/II	Foretinib 30–45 mg daily +/- erlotinib (100–150 mg daily	None	31	ORR: 17.8% (baseline c-Met expression associated with response)

MET amplification can be measured by estimating the ratio between the number of MET copies in relation to the copies of the chromosome 7 centromere (CEP7). NSCLC, non-small cell lung cancer; ORR, overall response rate; bid, twice daily; PFS, progression-free survival; OS, overall survival; TKIs, tyrosine kinase inhibitors; DOR, duration of response.

32%. Responses were rapid, durable (57% of patients having a response of ≥ 6 months) and were observed independent of the type of *MET* alterations (76). Interestingly, no significant difference in responses was observed between ctDNA-positive versus ctDNA-negative patients. The median PFS was 7.3 months and the probability of survival at 6 and 12 months was 87% and 70%, respectively (76). By local testing, increased concurrent *MET* copy number was observed in 2 patients, achieving durable disease control of more than 6 months. A significant association between additional concurrent genomic alterations in *TP53*, *MDM2* and *CDKN2A* and clinical outcomes was not found. The overall safety profile of crizotinib was consistent with that observed in previous studies, with edema, vision disorders, nausea, diarrhea and vomiting being the most common treatment-related adverse events (TRAEs), most of grade 1 and 2. Grade 3 included elevated transaminases and dyspnea. Permanent discontinuation for TRAEs occurred in 7% of patients. This study definitively underscores the importance of testing for *MET* exon 14 alterations in the clinic with sensitive, NGS techniques in tissue specimens, as well as in liquid biopsy. Based on initial data from this study, crizotinib as a *MET* inhibitor received breakthrough therapy designation from the United States Food and Drug Administration (US FDA) in 2018 for previously treated metastatic NSCLC in patients with *MET* exon 14 skipping. Other prospective phase II studies have evaluated crizotinib in this molecularly-defined subgroup of patients (77,78). Limited clinical benefit with crizotinib in *MET*-deregulated NSCLC patients was observed in the phase II METROS study. In the cohort including patients with both *MET* amplification and exon 14 mutations, ORR was 27%, median PFS 4.4 months, and OS 5.4 months, with no significant differences between *MET*-amplified and exon 14-mutated patients (Table 1) (78).

The above data, and results from a recent meta-analysis (79), demonstrate of crizotinib in this oncogene-addicted NSCLC subgroup is lower compared to results in *ROS1* or *ALK*-rearranged tumors, or to the efficacy of other oncogene-directed therapies, suggesting type Ia inhibitors are not the optimal agents for this subgroup of patients. Indeed, other more selective *MET* TKIs have been tested in clinical trials.

Cabozantinib

Cabozantinib (XL-184) is a small molecule, nonselective inhibitor of *MET* that targets multiple kinases, including VEGFR1-3, *RET*, *TIE2*, *FLT-3* and *KIT*, currently

approved for treatment of medullary thyroid carcinoma, renal cell carcinoma and hepatocellular carcinoma (80,81). Cabozantinib showed preclinical anti-tumor activity in a variety of mouse models, including lung cancer (82). In unselected, pretreated NSCLC patients, positive results in terms of improved PFS emerged from a randomized phase II study of cabozantinib with erlotinib or cabozantinib alone, compared to erlotinib, with acceptable tolerability (Table 1) (83). This combination was also tested in *EGFR* mutant NSCLC patients who progressed on prior *EGFR* TKI. This phase II study enrolled 37 patients, including 15 (40.5%) patients who had received more than 2 prior lines of systemic therapy. Overall, 4 (10.8%) patients had partial responses and the majority of patients (59.5%) had stable disease, with PFS and OS of 3.6 months and 13.3 months, respectively (Table 1) (84). Of note, activity was not correlated to the type of *EGFR* mutations or presence of T790M, and none of the patients with available tissue had evidence of *MET* amplification at baseline (84). Its role in patients with *MET* alterations has not been yet defined. In the study by Paik et al, cabozantinib induced a complete metabolic response as third line therapy in a patient with *MET* exon 14 alteration (50). Subsequent reports demonstrated systemic and intracranial activity of cabozantinib in this subset of patients (85,86). The agent is currently being tested in phase II clinical trials in patients with NSCLC and *MET* amplification or *MET* exon 14 skipping mutations (CABinMET study, NCT03911193) and in NSCLC with *RET* rearrangements or other oncogenic alterations, including *ROS1* or *NTRK* rearrangements and *MET* or *AXL* alterations, including amplification, mutations or protein overexpression (NCT01639508) (Table 2).

Merestinib

Merestinib (LY2801653) is an orally bioavailable, ATP-competitive, multitargeted inhibitor of *MET* and of other TKs involved in tumor cell proliferation, growth and angiogenesis, including *AXL*, *ROS1*, *VEGFR2*, *FLT3*, *DDR1-2*, *MERTK* and *NTRK1-3*, that showed tolerable safety profile and potential anticancer activity in pre-treated, advanced cancers (87,88). In preclinical *in vitro* and *in vivo* NSCLC models, this agent displayed tumor growth inhibition in tumor cell lines and patient-derived tumor xenograft models as a single agent or when used in combination with other antineoplastic drugs. In a metastatic lung orthotopic tumor model, LY2801653 treatment significantly inhibited both primary tumor growth and metastasis (89). Treatment with merestinib decreased

Table 2 Ongoing trials with MET Inhibitors in NSCLC

Drug inhibitor	Clinical trial	Phase	Drug combined
Multitarget tyrosine kinase inhibitors (TKIs)			
Crizotinib	NCT02465060 (NCI-MATCH)	II	No
	NCT02664935 (Matrix)	II	No
	NCT00965731	I	No
Cabozantinib	NCT00596648	IB/II	Erlotinib
	NCT03911193	II	No
	NCT01639508	II	No
	NCT02132598	II	No
	NCT03468985	II	Nivolumab +/- ipilimumab
Foretinib	NCT02034097	II	Erlotinib
Glesatinib	NCT02954991	II	Nivolumab
	NCT02544633	II	No
Merestinib	NCT02920996	II	No
Selective met tyrosine kinase inhibitors			
Tepotinib	NCT03940703 (INSIGHT 2)	II	Osimertinib
	NCT02864992 (VISION)	II	No
Savolitinib	NCT02897479	II	No
	NCT02143466 (TATTON)	I	Osimertinib
	NCT02374645	I	Gefitinib
	NCT03778229 (SAVANNAH)	II	Osimertinib
	NCT03944772 (OCHARD)	II	Osimertinib
	NCT02117167 (SARIF02_Lung)	II	No
Capmatinib	NCT03693339	II	No
	NCT03647488	II	Spartalizumab; docetaxel
	NCT03240393	II	No
	NCT02414139	II	No
	NCT02276027	II	No
	NCT02323126	II	Nivolumab
	NCT02335944	I/II	EGF 816
	NCT01911507	I	Erlotinib
	NCT02468661	I	Erlotinib; platinum + pemetrexed
	NCT02750215	II	No
Tivantinib	NCT01069757	I	Erlotinib
	NCT01251796	I	Erlotinib
	NCT02049060	I/II	Platinum + pemetrexed

Table 2 (continued)

Table 2 (continued)

Drug inhibitor	Clinical trial	Phase	Drug combined
SAR125844	NCT02435121	II	No
Anti-met antibodies			
Onartuzumab	NCT01887886	III	Erlotinib
	NCT01519804	II	Platinum + paclitaxel
	NCT01496742	II	Paclitaxel, pemetrexed, bevacizumab
	NCT02031744	III	Erlotinib
	NCT02044601 (BATTLE-XRT)	I/II	Erlotinib
Telisotuzumab	NCT03574753 (Lung-MAP S1400K)	II	No
JNJ-61186372	NCT02609776	I	No
Anti-HGF antibodies			
Ficlatuzumab	NCT01039948	IB/II	Gefitinib
	NCT02318368	II	Erlotinib

NSCLC, non-small cell lung cancer.

phosphorylation of key downstream proteins, including CBL, PI3K and STAT3, and resulted in inhibition of tumor growth by inhibiting proliferation and angiogenesis in mouse xenograft models of lung cancer (90). Merestinib showed activity as single agent or when combined with the MET-targeting antibody, emibetuzumab, in a gastric cell line and xenograft model bearing *MET* exon 14 mutations (91). A phase II trial of merestinib in NSCLC with *MET* exon 14 skipping mutations or advanced solid cancers harboring *NTRK1-3* rearrangements is ongoing (NCT02920996) (Table 2).

Glesatinib

Glesatinib is an oral, ATP-competitive TKI with activity against MET, VEGFR1-3, AXL, RON and TIE2. Glesatinib is a unique type II MET inhibitor, and binds to MET independently of interactions with the A-loop, suggesting its activity against MET mutations involving the residues D1228 and Y1230 that confer resistance to type I MET inhibitors. Glesatinib demonstrated activity in tumor cell lines *in vitro* and marked regression of cell- and patient-derived tumor models harboring *MET*ex14 del mutations *in vivo*. A durable clinical response was observed in a NSCLC patient with *MET* exon 14 mutation receiving this agent (92). Glesatinib also demonstrated preclinical and clinical activity against secondary mutations within the *MET* activation loop conferring resistance to type I inhibitors (92).

A phase II trial of glesatinib in advanced, pre-treated,

NSCLC patients with activating genetic *MET* alterations (mutation or amplification), as assessed in tumor tissue or ctDNA (NCT02544633), has been completed and results are awaited (93). Another ongoing trial is evaluating this agent with the anti-PD1 nivolumab in advanced NSCLC (NCT02954991) (Table 2). High mutant allele frequency of *MET*ex14 was shown to predict tumor response to glesatinib in phase 1 and 2 studies (94).

Selective MET TKIs

Capmatinib

Capmatinib (INC280) is an oral, ATP-competitive, inhibitor of MET. Capmatinib demonstrated to be potent and highly specific against MET, with more than 10,000-fold selectivity over other human kinases, and to inhibit MET-dependent tumor cell proliferation and tumor growth in MET-driven mouse tumor models (95). Significant antitumor activity was observed in cell line- or patient-derived xenograft models with various mechanisms of MET activation, including *MET* exon 14 alterations (96). Of note, in those models where MET activation co-occurred with other oncogenic alterations, such as *EGFR* mutations, the combination of capmatinib and EGFR TKIs resulted in enhanced anticancer activity (96). In the initial report by Frampton *et al.*, two NSCLC patients with *MET* exon 14 mutations showed partial responses to capmatinib (8). These patients were included in a phase I open-label, dose-

escalation study with an expansion part (NCT01324479) to assess the safety and tolerability of capmatinib, at the recommended dose of 400 mg (tablets) or 600 mg (capsules) twice daily, in patients with advanced *MET*-dysregulated NSCLC (97). Clinically meaningful antitumor activity was observed in patients with *MET* GCN 6 and/or *MET*ex14 mutations (Table 3). Tumor responses were observed in three out of the four patients with *MET* exon 14 mutations, including one confirmed complete response. Importantly, in this phase I trial capmatinib had an acceptable safety profile. The most frequent drug-related grade 3 or 4 AEs, were nausea, peripheral edema and fatigue, occurring in 4% of patients (97). The phase II GEOMETRY mono-1 (NCT02414139) was a multicenter, non-randomized, open-label, multi-cohort, phase 2 study evaluating capmatinib (400 mg orally twice daily) in *EGFR* wild-type and *ALK*-negative NSCLC patients with *MET* alterations, including *MET* exon 14 skipping mutation or *MET* amplification. Patients were assigned to cohorts on the basis of *MET* status and previous lines of therapy. Primary endpoint was ORR assessed by a blinded independent review committee (BIRC) and secondary objectives included duration of response (DoR), PFS, OS and safety. Preliminary results from cohort 4 and 5b, including patients with *MET* exon 14 mutations (regardless of *MET* amplification status/gene copy number), pre-treated with systemic therapy (not with a prior *MET* inhibitor) or treatment-naïve, respectively, showed that the ORR and PFS with capmatinib were higher in treatment-naïve patients compared to pre-treated patients (98). Rapid and durable responses were observed across both cohorts. Capmatinib also showed significant intracranial activity and had a favorable safety profile, with the majority of the AEs being of grade 1/2. The most common treatment-related AEs were peripheral edema, nausea, increased blood creatinine and vomiting (98). On May 6, 2020, based on these positive results, the FDA granted accelerated approval to capmatinib (TABRECTA, Novartis) for adult patients with metastatic NSCLC whose tumors have a *MET* exon 14 skipping mutation and also approved the FoundationOne CDx assay (Foundation Medicine, Inc.) as a companion diagnostic for capmatinib. Recently, final results from the GEOMETRY mono-1 study have been published and showed robust antitumor activity of the agent in this molecularly-defined subgroup of NSCLC. Among NSCLC patients with *MET* exon 14 skipping mutations, ORR was 41% and DoR 9.7 months in pre-treated patients. In treatment-naïve patients, ORR and DoR were 68% and 12.6 months (Table 3). Also,

median PFS was improved in patients who had not received previous treatment (12.4 months) than in previously treated patients (5.4 months). A total of 12 out of the 13 patients evaluable by the independent neuroradiologic review committee had intracranial disease control, including 7 with an intracranial response. No significant differences in response to capmatinib according to the type of genetic alteration causing *MET* exon 14 skipping mutations or the co-occurrence of *MET* amplification were observed (99). In this study, capmatinib showed evidence of activity also in patients with *MET* amplification and GCN ≥ 10 NSCLC, although at less extent than in patients with *MET* exon 14 alterations. The ORR was 29% in pre-treated patients and 40% in not previously treated. Of note, most patients included in these cohorts of the study were male and had a history of smoking. The favorable safety profile was confirmed in these final results, showing mainly grade 1/2 and reversible adverse events; the most frequent of these were peripheral edema, nausea, vomiting and increased blood creatinine level (99).

Expansion cohort 7, including patients with NSCLC with a *MET* exon 14 skipping mutation who had not received treatment previously, is ongoing.

Additional Phase II trials (NCT03693339, NCT02750215) of capmatinib in patients with *MET* exon 14 mutation-positive NSCLC are ongoing, including a study of capmatinib with spartalizumab (an anti-PD-1 antibody) compared with capmatinib alone in treatment-naïve NSCLC (NCT04323436) (Table 2).

Tepotinib

Tepotinib is an oral, ATP-competitive *MET* inhibitor (type Ib). Screening against >400 kinases showed high selectivity of tepotinib for *MET*. *In vivo*, tepotinib was associated with tumor regression in murine xenograft models of human cancers, regardless of whether or not *MET* activation was dependent on HGF (100). Moreover, tepotinib showed promising clinical activity in patients with *MET*-driven tumors (101). The phase II VISION study (NCT02864992), evaluated the efficacy and safety of tepotinib in advanced NSCLC patients with *MET* alterations, including *MET* exon 14 skipping mutations and *MET* amplification. Results from patients with *MET* exon 14 skipping mutations, as detected on NGS in tissue- or liquid-biopsy, have been recently published (Table 3) (102). A total of 152 patients received tepotinib, including 11 patients with baseline brain metastases. Most of the enrolled patients were adenocarcinoma, median age was 74 years and 56 had

Table 3 MET Inhibitors Activity in NSCLC: published trials with Selective TKIs

Drug	Trial	Phase	Treatment	Met-alteration	No. of pts	Efficacy outcome
Capmatinib	NCT01610336	II	Gefitinib 250 mg daily + Capmatinib 400 mg bid	MET-amplified	100	ORR: 29%; DOR: 5.6 months; PFS: 5.5 months (in pts with GCN \geq 5 and IHC 3+)
	NCT01324479	I	Capmatinib	MET-amplified and MET exon 14 skipping (4 pts)	55	ORR: 22% (for pts with MET GCN \geq 6 ORR: 47%; for pts with MET exon 14 skipping ORR: 75%)
	NCT02414139 (GEOMETRY mono-1)	II	Capmatinib 400 mg bid	MET exon 14 skipping (in 28 (1 st line) pts EGFR wt and ALK-neg)	69 (2 nd /3 rd line)	ORR: 68%; PFS: 9.7 months; DOR: 16.6 months ORR: 41%; PFS: 5.4 months; DOR: 9.7 months
Tepotinib	NCT02864992 (VISION Cohort A)	II	Tepotinib 500 mg once daily	MET exon 14 skipping	99	ORR: 46%; PFS: 8.5 months; DOR: 11.1 months; OS: 17.1 months
	NCT01982955 (INSIGHT)	Ib/II	Tepotinib 300 mg or 500 mg + gefitinib 250 mg once daily	MET overexpression/ amplification having acquired resistance to EGFR inhibition	18 (Ib); 31 (II)	Phase II: ORR: 45.2%; PFS 16.6 months
Tivantinib (ARQ 197)	NCT01395758	II	Erlotinib 150 mg daily + tivantinib 360 mg bid (E T) vs. pemetrexed or gemcitabine or docetaxel (C)	None	51 (E T) vs. 45 (C)	ORR: 0% (E T) vs. 8.9% (C); PFS: 1.7 months (E T) vs. 4.3 months (C)
	NCT01244191 (MARQUEE study)	III	Erlotinib 150 mg daily plus oral tivantinib 360 mg twice daily (E T) or erlotinib plus placebo (E P)	MET-amplified	526 vs. 522	ORR: 10.3% vs. 6.5%; OS: 8.5 vs. 7.8 months; PFS: 3.6 vs. 1.9 months. MET+: OS: 9.3 vs. 5.9 months; PFS: 3.7 vs. 1.9 months (longer OS in patients with GCN >4)
	NCT01580735	II	Tivantinib 360 OR 240 mg twice daily/ erlotinib 150 mg four times a day	MET-amplified	45	ORR 6.7%; PFS 2.7 months; OS 18.0 months (c-Met high vs. low: mPFS 4.1 vs. 1.4 months; mOS 20.7 vs. 13.9 months)
Savolitinib	NCT00777309	II	Erlotinib 150 mg daily + tivantinib 360 mg daily vs. erlotinib + placebo	MET-amplified	84 vs. 83	ORR 10% vs. 7%; PFS: 3.8 vs. 2.3 months; OS 8.5 vs. 6.9 months
	NCT01377376 (ATTENTION)	III	Tivantinib 360 OR 240 mg twice daily/ erlotinib 150 mg	MET-amplified	154 vs. 153	ITT: ORR 5.8% vs. 4.4%; PFS 2.9 vs. 2.0; OS 12.6 vs. 3.8 vs. 12.7 months
	NCT02897479	II	Savolitinib 600 mg for \geq 50 kg or 400 mg <50 kg	MET exon 14 skipping	61	ORR was 49.2 %; DCR 93.4%; PSF 6.9 months
NCT02143466	Ib	Osimertinib 80 mg plus savolitinib 600 mg or 300 mg	MET-amplified + EGFR mutation	138	ORR 48%; PFS 7.6 months; DOR 9.5 months	
			Osimertinib 80 mg plus savolitinib 300 mg; no previous third-generation EGFR TKI, T790M negative	36	ORR 64%; PFS 9.1 month; DOR 8.0 months	

ORR, overall response rate; bid, twice daily; PFS, progression free survival; OS, overall survival; TKIs, tyrosine kinase inhibitors; DOR, duration of response; GCN, gene copy number.

received previous therapies, including immunotherapy. In the combined-biopsy group, the response rate by independent review was 46%, all were partial responses. Responses were rapid and durable (median DoR of 11.1 months). The median duration of PFS was 8.5 months in the combined-biopsy group and median duration of OS 17.1 months, according to not mature data. Clinical outcomes were similar in the two biopsy categories. Of the 51 patients who had matched baseline and on-treatment biomarker profiles from liquid biopsies, 34 (67%) had a molecular cfDNA response, of whom 24 (71%) showing radiologic response according to independent review, suggesting high concordance between molecular and clinical response. TRAEs of grade 3 or higher were reported in 28% of the patients, with peripheral edema being the main toxic effect, observed in 7% of patients. Overall, the patients' quality of life was maintained during receipt of tepotinib (102). On September 2019, the drug was granted breakthrough therapy status by the FDA for advanced NSCLC harboring *MET* exon 14 skipping alterations and, in March 2020, was first approved in Japan for the treatment of this molecularly-defined subgroup of NSCLC patients, together with its companion diagnostic assay (ArcherMET CDx) (103). Tepotinib has also demonstrated activity in the setting of acquired resistance to EGFR TKIs. Results from the randomized, phase II part of the INSIGHT trial in patients with *EGFR*-mutant NSCLC T790M-negative, with *MET* overexpression and/or *MET* amplification, and resistance to prior EGFR TKI, have been reported (104,105). Tepotinib in combination with gefitinib showed an ORR of 45.2% versus 33.3% for the chemotherapy groups (Table 3). Salient findings were found in patients with *MET* amplification where ORR was 66.7 with tepotinib plus gefitinib and 42.9% for chemotherapy. In the combination group of tepotinib plus gefitinib, median PFS was 16.6 months versus 4.2 months in the chemotherapy group, and median OS was 37.3 versus 13.1 months (104). Progression-free survival and overall survival were longer with tepotinib plus gefitinib than with chemotherapy in patients with high [immunohistochemistry (IHC)3+] *MET* protein expression. *MET* amplification correlates with the degree of *MET* expression in most cases. Importantly, tepotinib plus gefitinib was generally well tolerated (104). The trial highlights the need for tailored therapy, and that *MET* amplification could be a feasible predictive biomarker in this subset of patients, as the combination of tepotinib and gefitinib was ineffectual in patients with low *MET* expression (IHC2+ or less) (105). The INSIGHT 2 study (NCT03940703) is ongoing and will explore the benefit of

tepotinib plus osimertinib in patients with *EGFR*-mutant NSCLC who have progressed on previous EGFR TKIs due to *MET* amplification (Table 2).

Savolitinib

Savolitinib is an oral, ATP-competitive kinase inhibitor, with high activity and selectivity for *MET* (106). Savolitinib has been tested in different *MET*-driven tumors, including gastric, papillary renal cell carcinoma and NSCLC. In the multi-arm, phase 1b TATTON trial conducted in patients with advanced *EGFR*-mutant NSCLC and disease progression on a prior EGFR-TKI, osimertinib in combination with savolitinib was feasible and tolerable at the dose levels identified, and was associated with an ORR of 44% among the 18 patients enrolled (107) (Table 3). Of note, *MET* testing identified 9 patients with *MET* amplification by FISH. Among the 3 patients with *MET* amplification included in the savolitinib arm, 2 had a response. Osimertinib plus savolitinib is being studied further in patients with *MET*-driven resistance to EGFR-TKIs (SAVANNAH; NCT03778229 and ORCHARD; NCT03944772) (Table 2).

Savolitinib has also demonstrated activity against *MET* exon 14 mutations in *in vitro* and *in vivo* studies, as well as in the clinical setting (108-110). A multicenter, multicohort phase II study (NCT02897479) has been conducted to evaluate the efficacy and safety of savolitinib in unresectable or metastatic pulmonary sarcomatoid carcinoma (PSC) and other NSCLC with *MET* exon 14 mutations (110). In the cohort of *MET*-inhibitor naïve patients ORR by IRC assessment was 49.2%, all were partial responses (Table 3). Activity was observed both in PSC and other NSCLC groups. Disease control rate was 93.4% and DoR 9.6 months. Survival data were not mature. Median PFS was 6.9 months; specifically, it was 5.6 months for treatment-naïve group, including nearly half of patients with PSC and 13.8 months for previously treated patients. Tolerability was acceptable, with most TRAEs being edema, nausea, vomiting, increased AST/ALT and hypoalbuminemia. The incidence of \geq grade 3 TRAEs was 41.4% and TRAEs leading to treatment discontinuation occurred in 14.3% patients, among which liver injury and hypersensitivity were most common (110).

Other therapeutic agents targeting *MET* exon 14 mutations

Sym015

Sym015 is a mixture of two recombinant humanized

antibodies triggering non-overlapping epitopes in the extracellular domain of MET that blocks HGF-MET interaction, induces receptor internalization and degradation and stimulates CDC and ADCC *in vitro* and *in vivo*, thereby improving specificity compared to TKIs. An additional advantage of this molecule is that may circumvent intracellular acquired resistance mechanisms, such as secondary kinase mutations, to MET TKIs. Preliminary clinical activity of Sym015 from an expansion cohort of the phase 2 trial (NCT02648724) in advanced NSCLC patients with *MET* amplification/exon 14 deletion was recently reported (111). Among the 20 patients included, 5 had partial responses (ORR 25%) and the DCR was 80%. All responses were observed in the group of MET TKI-naïve patients. For patients who were prior MET TKI-treated, DCR was 60%. Median PFS for MET TKI-naïve and MET TKI pre-treated NSCLC patients was 7.4 and 5.4 months, respectively. In patients with *MET* exon 14 mutations TKI-naïve, PFS was 9.2 months. Median OS was 9.1 months for those with *MET* exon 14 mutations MET TKI-treated and not reached for overall and other subgroups. Of note, ctDNA was highly concordant with tumor for *MET* exon 14 mutations detection. Safety was assessed in 45 patients included in all cohorts of the phase 2 study. Overall, the drug was well tolerated, with 13.3% of grade 3 TRAEs, including anasarca and hypoalbuminemia, colitis and septic shock, amylase increase, hypophosphatemia and in NSCLC patients, peripheral edema and elevated liver function tests (111).

Immunotherapy in MET exon 14-mutant NSCLC

Limited clinical benefit from anti-PD1/PD-L1 directed ICIs has been reported in NSCLC patients with *MET* alterations (112-114). In a retrospective analysis evaluating ICIs activity as monotherapy in advanced NSCLC with oncogenic drivers, 36 patients with *MET* alterations (*MET* amplification n=13 or *MET* exon 14 mutation n=23) were included. Among these patients, an ORR of 16% was observed, with median PFS and OS of 3.4 and 18.4 months, respectively (112). In another study including a larger number of patients, exon 14 mutations were mainly associated with high ($\geq 50\%$) PD-L1 expression; however, the ORR with ICIs was 17% and median PFS 1.9 months (113). In this study, tumor mutational burden (TMB) was also assessed in each oncogenic subgroups. TMB is defined as the number of mutations per DNA megabase. High TMB leads to the creation of neoantigens

and increases tumor immunogenicity, which can improve the response to cancer immunotherapy. TMB in *MET* exon 14 was low compared to wild type NSCLC, as observed in other reports (62,98,113,115).

In a comprehensive genomic analysis on 60,495 NSCLC patients, *MET* exon 14 mutations, including base substitution, indels, deletions, and complex events spanning multiple functional sites of *MET*, were found in 1,387 (2.3%) of samples (62). TMB was significantly lower in *MET* exon 14-altered, compared to *MET* exon 14 wild type tumors. Moreover, *MET* exon-14-mutant NSCLC was enriched for high ($\geq 50\%$) PD-L1 expression: 48% compared to 29% in WT NSCLC. No difference in PD-L1 positivity was observed across different *MET* exon 14 alterations (62). In contrast to previous studies, a recent study reported remarkable and durable responses to ICIs in advanced *MET*-mutant NSCLC patients (115). Among 13 patients treated with ICIs, 6 (46.2%) had objective responses (4 partial and 2 complete), and response was maintained for 18–49 months. Despite these promising data, further data is needed to define the role of ICIs in this distinct subset of oncogene-addicted NSCLC (115).

Intrinsic and acquired resistance to MET inhibitors

Similar to other oncogene-directed therapies, treatment with MET TKIs can lead to acquisition of resistance by cancer cells through different mechanisms, including on-target mechanisms, such as secondary mutations within the kinase domain, and off-target mechanisms, such as activation of alternative oncogenic signaling pathways (116). In *MET* exon 14-altered NSCLC, secondary mutations in the kinase domain of *MET* have been identified, mainly in single cases, and associated with resistance to different types of MET inhibitors (92,117-125). Mutations involving the A-loop residues D1228 and Y1230 confer resistance to type I MET inhibitors by altering their binding to the kinase domain, but do not affect type II inhibitors binding, that have been shown to be effective in the presence of these mutations (92,117). In a series of lung cancer patients with *MET* exon 14 mutations receiving crizotinib, at time of progression, 9 had paired pre-/post-treatment samples to be analyzed for resistance mechanisms. Among these patients, 2 (22%) developed on-target mechanisms, including *MET* D1228N and HGF amplification and 5 (44%) were found to have potential off-target drug resistance mechanisms (123). *MET* exon 19 D1246N mutation has also been found in a patient receiving crizotinib rather than cabozantinib (124).

The solvent front G1163R mutation, analogous to the *ALK* G1202R and *ROS1* G2023R, confers resistance to type Ia TKI, such as crizotinib, that mainly binds to this residue, but not to type Ib or II TKIs (92,125). Fujino *et al.* analyzed secondary mutations as resistance mechanisms to different type I, II and III MET TKIs in cell lines expressing *MET* exon 14 alterations. In this study, D1228 and Y1230 were common resistance mutations for type I TKIs, whereas the L1195 and F1200 for type II TKIs. The L1195V alters the C-terminus of the alpha-helix, and also confers resistance to crizotinib (92,125). In MET TKI-resistant tumors, alternative signaling pathways can be activated, so called bypass tracks, through different RTKs or downstream molecules activation. These off-target mechanisms include activation of crucial intracellular pathways, such as the MAPK pathway and the PI3K/AKT pathway activation. Alterations in key genes activating the MAPK pathway, such as *KRAS* amplification or *KRAS* mutations, have been described (123,126-128). Acquired gene amplification of *EGFR*, *HER2*, *HER3*, *BRAF* and *MDM2* have also been reported in resistant tumor samples (123,128).

Genomic alterations occurring at time of acquired resistance to MET TKIs were evaluated by using plasma and tissue NGS in 20 patients. On-target mechanisms of resistance were identified in 35% of patients and included *MET* mutations (H1094, G1163, L1195, D1228, Y1230), and high levels of amplification of *MET* exon 14-mutant allele, whereas off-target mechanisms were found in 45% of patients and included *KRAS* mutations and amplification of *KRAS*, *EGFR*, *HER2*, *BRAF* (128). Multiple *MET* kinase mutations were detected in some cases. The H1094Y mutation was detected in tissue after treatment with glesatinib (128). Although its impact in mediating resistance to TKI is still unknown, it seemed to reduce the ability of glesatinib to dephosphorylate MET and to be particularly sensitive to the type I MET TKI savolitinib. Two patients with on-target resistance, showed objective response when switching to a structurally different MET TKI, suggesting that the optimal therapeutic sequencing should be defined based on underlying mechanisms of resistance. Of note, activation of PIM kinases promotes resistance to MET inhibitors in NSCLC and gastric cancer cells with *MET* amplification and could have a role also in NSCLC with exon 14 mutations (129).

Phosphoinositide 3-kinases (PI3K) pathway alterations may also confer primary resistance to MET TKIs. In a recent work, tumor samples from patients with *MET* exon 14 alterations were analyzed by using targeted NGS and

immunohistochemistry. *PI3KCA* mutations were found in 2 of 65 (3%) samples and loss of PTEN in 6 of 26 (23%) samples (130). Patients with these alterations did not respond to MET TKI therapy. Interestingly, PI3K inhibition restored sensitivity to MET TKIs in *MET*ex14-mutated cell lines with a PI3K pathway alteration, thus proposing the preclinical rationale for a combined therapeutic strategy (130). Co-occurring RAS-MAPK pathway gene alterations in lung cancer patients with *MET* exon 14 mutations have been shown to correlate with decreased response to MET TKI treatment. In *MET*ex14-mutant expressing cells, resistance to MET TKI associated with *KRAS* overexpression or NF1 downregulation, was reversed with the combination of crizotinib and the MEK inhibitor trametinib. These data suggest to perform deep genomic analysis of tumor samples to find out co-occurring alterations that can potentially respond to front-line approaches with combination therapies (e.g., MET TKI and MEK inhibitor) to enhance clinical outcomes (131). The study by Rotow *et al.* (131), was performed on ctDNA by targeted NGS. The use of liquid biopsy is crucial for identification of resistance mechanisms. Liquid biopsy has the possibility to capture tumor heterogeneity and provide a wider representation of the entire genomic landscape, including primary tumor and multiple metastatic sites. In addition, the feasibility to collect multiple specimens at various time points, before and during treatment, can be exploited to track the emergence of heterogeneous mechanisms of resistance.

Most mechanisms of primary and acquired resistance to MET TKI in *MET* exon 14 mutant-NSCLC should further be elucidated. In this context, the role of other potential biomarkers, such as Y-box binding protein (YB-1) should be further analyzed (105). YB-1 is activated via AKT or ERK, or both, and has been shown to regulate the metastasis associated with the colon cancer-1 (MACC-1)-MET pathway in lung adenocarcinoma (132). The yes-associated protein (YAP1)-FOXO1 pathway has recently been associated with resistance to EGFR inhibitors (133), highlighting potential similarities among the mechanisms of resistance to different TKIs. A potential role might be played by the ATP-binding cassette transporters that have been correlated to resistance to chemotherapeutic agents and to ALK TKIs. In *MET*-amplified cells resistant to crizotinib, overexpression of ATP-binding cassette subfamily B member 1 (ABCB1) was associated with CSC-like properties and phenotype. Inhibition of ABCB1 reversed resistance to MET inhibitors (134).

Conclusions and future perspectives

Oncogene-directed therapies have markedly improved the management and prognosis of NSCLC patients over the last years. *MET* has been demonstrated to be a worthy therapeutic target in NSCLC due to its multiple roles in cancer development and progression, as well as in the acquired resistance to targeted agents, such as EGFR TKIs. A number of clinical trials are currently investigating HGF/*MET* inhibitors, as single agents or in combination with other agents, in different settings of disease (Table 2). However, a number of studies with potential effective *MET* inhibitors conducted in unselected NSCLC patient populations have reported negative results, suggesting the need of better selection of patients based on specific *MET* alterations.

MET exon 14 mutations have been identified as key oncogenic drivers in NSCLC, conferring sensitivity to *MET* TKIs in preclinical and clinical studies. The use of a *MET* TKI, including crizotinib, capmatinib and glesatinib, at any line of treatment in NSCLC patients with *MET* exon 14 mutations is associated with longer overall survival (135).

Significant clinical activity has been prospectively demonstrated by more selective *MET* TKIs in *MET*-mutant NSCLC patients, with recent approval of capmatinib by FDA for this subgroup of patients. This evidence underscores the importance of routine testing NSCLC tumor samples for *MET* alterations.

Despite promising results, many questions remain unanswered. Indeed, the optimal sequencing of *MET* TKIs remains to be determined, since the acquisition of secondary resistance mutations can impair the activity of some TKIs and enhance that of others, depending on their binding modalities. Moreover, the presence of co-occurring alterations can also confer primary resistance to *MET* blockade, thus likely explaining the lower responses of these agents compared to those observed with other TKIs, such as EGFR- or ALK-TKIs. A deeper understanding of the molecular background associated with *MET* exon 14 mutations may suggest novel rational combinatorial or sequential therapeutic strategies to improve clinical outcomes. The use of liquid biopsy, in addition to tissue biopsy, for genomic analyses can help the identification of *MET* exon 14 skipping mutations and may help track the emergence of resistant subclones over the course of treatment.

The role of *MET* gene or protein alterations in the development of resistance to EGFR TKIs in *EGFR*-

mutant NSCLC has been well established and results from trials with combination of EGFR and *MET* TKIs are encouraging (Table 2). Other combination strategies, including *MET* TKIs and ICIs, need to be further explored. Finally, although *MET* gene fusions are relatively rare, some data suggest they could represent promising predictive biomarkers for targeted therapies in lung cancer to be screened at baseline together with other more common driver alterations.

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Footnote

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