Targeting the MET gene for the treatment of non-small-cell lung cancer.

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Abstract

Recently, a better understanding of the specific mechanisms of oncogene addiction has led to the development of antitumor strategies aimed at blocking these abnormalities in different malignancies, including lung cancer. These abnormalities trigger constitutive activation of tyrosine kinase receptors (RTKs) involved in fundamental cell mechanisms such as proliferation, survival, differentiation and migration, and consequently the aberrant signaling of RTKs leads to cancer growth and survival. The inhibition of aberrant RTKs and downstream signaling pathways has opened the door to the targeted therapy era.

In non-small-cell lung cancer (NSCLC), molecular research has allowed the discrimination of different aberrant RTKs in lung cancer tumorigenesis and progression, and thus the identification of several targetable oncogenic drivers. Following the development of small molecules (gefitinib/erlotinib and crizotinib) able to reversibly inhibit the epidermal growth factor receptor (EGFR) and signaling pathways mediated by anaplastic lymphoma kinase (ALK), respectively, the MET signaling pathway has also been recognized as a potential target. Moreover, according to current knowledge, MET could be considered both as a secondary oncogenic mechanism and as a prognostic factor. Several therapeutic strategies for inhibiting activated hepatocyte growth factor receptor (HGFR) and the subsequent downstream signaling transduction have been improved in order to block tumor growth. This review will focus on the MET pathway and its role in resistance to EGFR TK (tyrosine kinase) inhibitors, the different strategies of its inhibition, and the potential approaches to overcoming acquired resistance.

Keywords

Hepatocyte growth factor; MET; Kinase inhibitors; Targeted therapies; NSCLC

Abbreviations

RTKs, tyrosine kinase receptors; NSCLC, non small cell lung cancer; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; MET, hepatocyte growth factor receptor; HGF, hepatocyte growth factor; HGFR, hepatocyte growth factor receptor; Sema, semaphorin; PSI, plexin-semaphorin-integrin; SCLC, small cell lung cancer; MTD, maximum tolerated dose; AEs, adverse events; PFS,progression free survival; OS, overall survival; ITT, intent to treat; IHC, immunohistochemistry; FISH,fluorescent in situ hybridization; HR, hazard ratio

1. Introduction

Recently, improved understanding of the molecular mechanisms underlying oncogene addiction has led to the classification of non-small-cell lung cancer (NSCLC) into different molecular types and to the introduction of new targeted agents which have dramatically changed the natural history of this disease. Excellent examples of these agents

comprise erlotinib and gefitinib for NSCLC patients whose tumors harbor drug-sensitizing mutations in the EGFR TK domain [1], [2] and [3] and, more recently, crizotinib for NSCLCs carrying ALK translocations [4], [5], [6], [7] and [8].

Among different targets, the proto-oncogene *c-MET*, its product (HGFR, hepatocyte growth factor receptor) and its ligand (hepatocyte growth factor, HGF) have also been recognized as molecular targets. Indeed, aberrant MET pathway activation has been identified as an important oncogene addiction mechanism in different solid tumors [9] and [10] and it seems to correlate with poor clinical outcome and metastatic progression [11], [12], [13] and [14].

HGFR/HGF signaling has therefore become a new potential target for anticancer therapy through different blocking strategies, and new compounds have been tested to overcome resistance mechanisms.

2. HGFR/HGF structure and normal functions

2.1. HGFR

The *MET* gene is located on chromosome 7q21-31 and encodes a protein product called the HGF receptor (HGFR). The HGFR is a single-chain heterodimer consisting of an extracellular α-chain linked by a disulfide bond to a transmembrane β-chain possessing intracellular catalytic activity (Fig. 1 A).

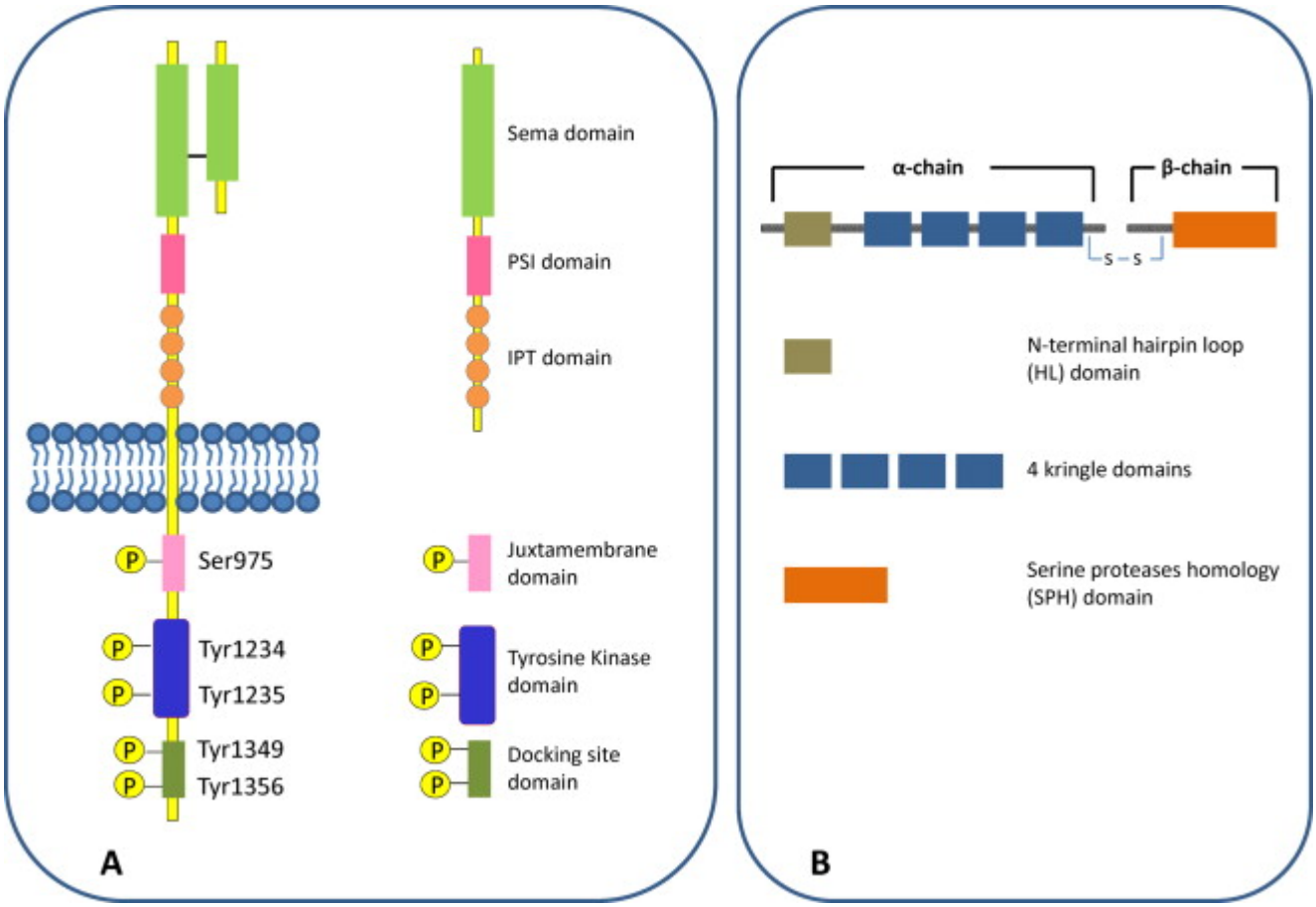

Fig. 1.
Structures of the c-MET receptor (A) and HGF (B).

The extracellular domain is composed of several domains. The semaphorin (Sema) domain, a key site for ligand binding and receptor dimerization, includes the entire α-chain and the N-terminal part of the β-chain; a plexin–semaphorin–integrin (PSI) domain and four immunoglobulin-like (IPT) domains follow, which in turn are connected to the intracellular part of the β-chain (Fig. 1A).

The intracellular domain (Fig. 1A) is composed of: (1) a juxtamembrane region which contains both a serine residue (Ser975) and a tyrosine residue (Tyr1003); these are responsible for inhibiting the MET kinase activity and for degrading the receptor, respectively; (2) a catalytic region which contains two tyrosine residues (Y1234 and Y1235) that modulate the enzyme activity; and (3) a C-terminal tail, the so-called docking site [15], which contains two other tyrosine residues (Y1349 and Y1356) capable of recruiting many intracellular effectors, such as the p85 regulatory subunit of PI3K, Src and GRB2[15] and [16], and adaptors such as SHP2, PLCγ1 and GAB1 [15], [16] and [17], as well as STAT3[18] and [19] (Fig. 2).

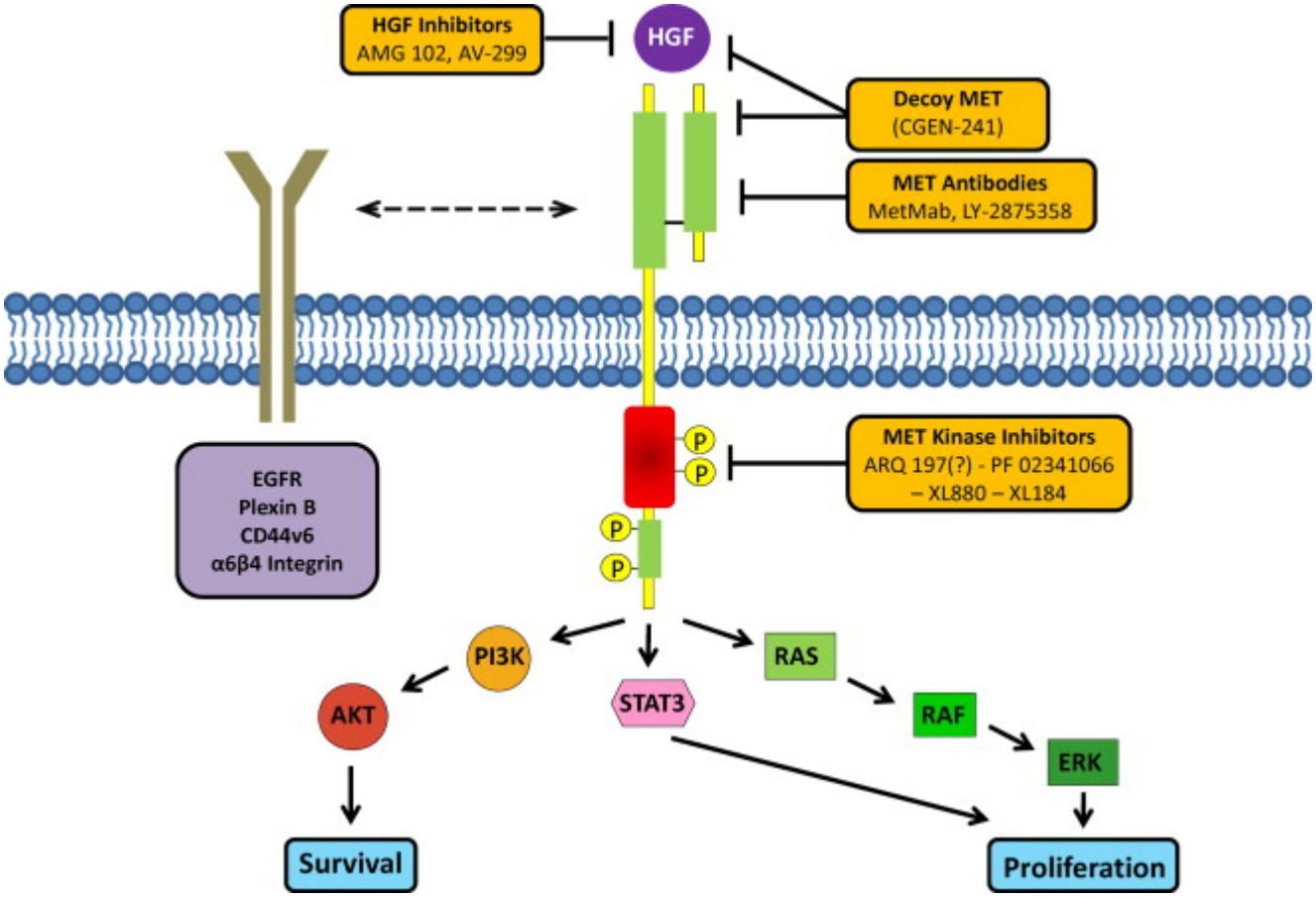

Fig. 2.
MET signaling pathways and different blocking mechanisms. In addition to ligand–receptor interaction, a network of signaling co-receptors – such as the EGFR/ERB family, CD44v6, plexinB and α6β4 integrin – can interact with MET, even in an HGF-independent manner, promoting cell proliferation, invasive growth and survival. HGF inhibitors interfere with HGF binding to MET; MET antibodies prevent receptor dimerization; decoy MET prevents both HGF binding to receptor and MET dimerization; MET kinase inhibitors block MET kinase activity. ARQ 197 (?): question mark indicates that this compound is not a bona fide c-MET inhibitor.

2.2. HGF

HGF, the unique ligand of HGFR, belongs to the plasminogen family. It has a high affinity for HGFR and leads to activation of its receptor only in its cleaved mature form: a disulfide-bonded heterodimer which consists of an N-terminal domain, four domains known as kringle domains, and a C-terminal domain (Fig. 1B). The HGF residues that form the receptor binding site are unknown, although several studies have pointed out different roles for the α- and β-chains [20], [21] and [22]. In particular, it would seem that a high-affinity site in the α-chain is able to bind to the receptor in a manner independent of HGF maturation, even though the binding with a low-affinity site, accessible only when HGF is fully active, is necessary for receptor dimerization.

2.3. MET signaling activation and its normal function

Upon Sema domain–HGF binding, the MET receptor dimerizes and phosphorylation of its TK domain leads to the activation of different important pathways, such as PI3K–Akt signaling [15] and [16], Ras–MAP kinase cascades [16] and [23], STAT and the nuclear factor-κB complex [24] and [25], which promote cell proliferation, angiogenesis, morphogenesis, survival, cell scattering, migration and invasiveness (Fig. 2).

Moreover, HGFR can crosstalk with other pathways, such as the EGFR/ERBB family of receptors [26], even through its ligand TGF-α and K-RAS signaling [27], and it has been shown that these activated signaling pathways may be sensitive to MET inhibition both in *vitro* [28] and in *vivo* [29] (Fig. 2).

Nevertheless, it is noteworthy that a hypoxic status in tissues enhances both HGF levels and HGFR expression [30]. MET activation can also occur by semaphorins after HGFR–plexins interaction[31] and [32] (Fig. 2). In fact, HGFR and some classes of plexins share a highly homologous Sema domain, so that HGFR can be transactivated after oligomerization with plexins in response to their semaphorin ligands, also in the absence of its ligand. Moreover, MET signaling activity can be maintained even after receptor internalization [33], [34], [35], [36], [37], [38], [39] and [40]. After being internalized from the cellular membrane, the MET receptor continues to be active through its recruitment into early endosomes, favoring either HGF-induced cell migration via protein kinase C (PKC) and extracellular signal-regulated kinase (ERK), or phosphorylation and subsequent translocation into the nucleus of STAT3.

HGFR and its ligand are widely expressed in a variety of normal cells and tissues of epithelial and mesenchymal origin, respectively, and MET signaling activation has a key role in both embryonic and adult life. In particular, during embryonic development MET signaling transduction plays a crucial role in several processes, such as motogenesis [41], [42], [43] and [44], angiogenesis [45] and [46], mitogenesis [47] and morphogenesis [48] and [49]. In adult life, its signaling transduction has an important role in tissue repair and organ regeneration following acute tissue injury [50].

3. MET signaling in NSCLC

Several studies have demonstrated that an aberrant MET signaling pathway plays an important role in promoting tumor growth, progression and invasion in many cancers [51] and [52].

3.1. The different mechanisms of aberrant MET signaling activation

MET receptor overexpression has been reported in both small-cell lung cancer (SCLC) and NSCLC [53],[54] and [55] and, in particular, has been identified in up to 40% of lung cancer tissues [56]. A significant correlation between MET receptor overexpression/hyperactivation and poor outcome has been demonstrated in different solid tumors [11], [13] and [14]. HGFR overexpression, high MET gene copy number and MET gene amplification, as well as high HGF levels, also have a negative prognostic significance in NSCLC [12], [57], [58], [59], [60], [61], [62], [63] and [64]. Besides being a consequence of HGF or HGFR overexpression – usually due to transcriptional upregulation – aberrant MET signaling can be also caused by gene amplification, activating gene mutations, or alternative splicing [53], [56] and [65].

3.1.1. HGF/HGFR overexpression

High HGF levels secreted by both primary and metastatic tumors (autocrine mechanism) and mesenchymal cells (paracrine mechanism) have been reported as ligand-dependent mechanism of aberrant MET signaling activation [66], [67], [68], [69] and [70]. Others studies have pointed out the importance of other tissue and transcriptional factors such as cytokines, growth factors and ETS (transcriptional factors involved in tumor invasion program), in

inducing MET upregulation and ultimately receptor overexpression, regardless of HGF stimulation [30], [71], [72], [73], [74], [75] and [76].

Hypoxic conditions can also stimulate both higher HGF levels and HGFR transcriptional levels via hypoxia-inducible factor-1α (HIF-1α), which renders the cells more sensitive to HGF stimulation in the tumor invasion process; therefore, MET overexpression by itself nourishes this hypoxia-dependent invasion mechanism [30].

3.1.2. MET gene mutations

Activating point mutations in the MET coding sequence have been reported as somatic and germline variants in many solid tumors, albeit infrequently. In NSCLC, MET gene mutations can occur in the semaphorin extracellular domain, in the juxtamembrane region and also in the kinase domain. Missense mutations found in the Sema domain, encoded by exon 2 and necessary for MET dimerization, have been reported as germline mutations [77]. The mutations found in the juxtamembrane domain, encoded by exons 14–15, seem to be involved in tumorigenesis [78], [79], [80] and [81]. Nevertheless, the MET juxtamembrane region, necessary for receptor downregulation, contains a tyrosine residue (Tyr1003) which is able to bind to the c-Cbl TK domain; this complex in turn promotes MET polyubiquination and receptor degradation. A point mutation in this tyrosine residue does not permit the formation of the complex and polyubiquination, leading conversely to MET oncogenic activity [82].

Mutations in the MET tyrosine kinase domain [53] and [83], primarily described in patients with hereditary and sporadic papillary renal cell carcinoma [84] and head/neck squamous-cell carcinoma [85], have been found rarely in NSCLC as a secondary event resulting from exposure to prior therapies, such as tyrosine kinase inhibitors [86] and [87].

3.1.3. MET gene amplification

MET gene amplification has been reported in many primary human tumors and acts as a primary “oncogenic driver” in 2–21% TKI-naïve lung adenocarcinomas [53]. *MET* amplification has also been detected as a secondary event, both in preclinical and clinical studies, in EGFR–TKI-resistant NSCLC after exposure to gefitinib or erlotinib [88] and [89] with a frequency ranging from 5% to 25% [88], [89], [90],[91] and [92]. In this NSCLC population, TKI treatment specifically selects preexisting *MET*-amplified clones in which the ERBB3/PI3K/AKT signaling pathway is active, thus suggesting the potential impact of a concomitant blockade of MET for overcoming EGFR–TKI resistance [93] and [94]. The combination treatment strategy has proved capable of also overcoming primary EGFR–TKI resistance, as recently shown in xenograft models [95]. In another study, the use of golvatinib, a multitarget small-molecule inhibitor, has been shown to restore sensitivity to EGFR–TK inhibition and to prevent the emergence of resistant cell clones after continuous HGF exposure in vitro [96]. Indeed, another mechanism of both primary and acquired resistance to EGFR–TKIs is represented by HGF overexpression [97]. Furthermore, gefitinib-resistant MET-amplified NSCLC (HCC827 GR) cells showed an increased activation of the tyrosine kinase Src [98], and the use of Src inhibitors resulted in tumor-cell inhibition and apoptosis [99].

3.2. Mechanisms of acquired resistance to MET inhibition

As is known with EGFR and ALK inhibition, MET-driven NSCLC patients treated with a specific targeted strategy also invariably develop secondary resistance mechanisms which lead to tumor progression. To our knowledge, two mechanisms are involved in acquired resistance to MET inhibition, and both of them are simultaneously present: a point mutation in the MET tyrosine kinase domain at the tyrosine residue Y1230, and TGF-α overexpression, a condition that can activate alternative EGFR pathways [100]. In these cases, a treatment strategy combining both MET and EGFR inhibitors might allow to overcome resistance [53]. Other acquired mechanisms of resistance to MET inhibition have been identified in different solid tumors, such as papillary renal-cell carcinoma; these include an increased representation of a preexisting sensitive de novo somatic M1268T mutation associated with a copy number gain and

expression of genomic duplication [101]. On the other hand, aberrant MET signaling activation can represent a mechanism of oncogene expedience as a secondary event owing to the interference of other oncogenes (K-RAS), pro-inflammatory cytokines, HGF itself, and microenvironmental conditions (hypoxia) that can enhance invasiveness and metastatic properties of neoplastic cells.

4. Current treatment strategies targeting MET in NSCLC

Different targeting strategies to inhibit the aberrant MET signaling in NSCLC have been developed. In particular, MET signaling can be blocked at the ligand–receptor level by new drugs directed against HGF (HGF antagonists) or HGFR, such as anti-MET receptor monoclonal antibodies and decoy MET (the latter has so far been tested only in preclinical phase studies), or at the tyrosine kinase domain level by small-molecule MET kinase inhibitors (Fig. 1).

Currently, many molecules, either alone or in combination with other drugs, are under investigation in clinical trials on NSCLC in order to prevent or overcome possible mechanisms of resistance. A summary of these trials is provided in Table 1 and Table 2.

Table 1.
Ongoing studies with MET inhibitors in non-small-cell lung cancer (NSCLC)

Experimental drug	Combined treatment drug(s)	Study design	Description and primary end-points
HGF inhibitors			
AMG 102 (rilotumumab)	Erlotinib	Phase I/II trial	AMG 102 + erlotinib in previously treated advanced NSCLC
			Primary: safe dose to combine with erlotinib
AV-299 (ficlatuzumab)	Gefitinib	Phase I/II trial	AV-299 + gefitinib AND gefitinib alone in NSCLC Asian patients
			Primary: DLTs and RP2D; ORR
Anti-MET monoclonal antibodies			
MetMab (onartuzumab)	Bevacizumab	4-arm phase II trial	MetMab + different chemotherapy treatments versus placebo + the same chemotherapy regimen in untreated advanced non-squamous NSCLC patients.
	Platinum-based chemotherapy doublets		Primary: PFS in both the entire population and patients with MET/IHC^{+}tumors

Experimental drug	Combined treatment drug(s)	Study design	Description and primary end-points
	Placebo		
MetMab	Platinum-based chemotherapy doublet	2-arm phase II trial	MetMab + platinum-based chemotherapy doublet versus placebo + platinum-based chemotherapy doublet in untreated advanced squamous NSCLC patients
	Placebo		Primary: PFS both in ITT population and in patients with MET-positive squamous tumors, as assessed by IHC
MetMab	Erlotinib	2-arm phase III trial	MetMab + erlotinib versus placebo plus erlotinib in pretreated NSCLC patients with MET-positive tumors
	Placebo		Primary: OS
MET tyrosine kinase inhibitors			
PF 02341066 (crizotinib)	PF 00299804	2-arm phase I trial	PF 02341066 + PF 00299804 versus PF 00299804 followed by PF 02341066 plus PF 00299804 in advanced NSCLC patients
			Primary: safety profile
PF 02341066	PF 00299804	Phase I trial	PF 02341066 + PF 00299804 in pretreated advanced NSCLC patients.
			Primary: safety profile
ARQ 197	Sorafenib	Phase I trial	ARQ 197 + sorafenib in advanced solid tumors
			Primary: MTD and/or RP2D
			Secondary: PK; antitumor activity; changes of HGF, VEGF and c-MET in peripheral blood
ARQ 197	Erlotinib	2-arm phase II trial	ARQ 197 + erlotinib versus single-agent chemotherapy in previously treated advanced NSCLC carrying K-RAS mutation

Experimental drug	Combined treatment drug(s)	Study design	Description and primary end-points
	Pemetrexed		Primary: PFS
	Docetaxel		
	Gemcitabine		
ARQ 197	Erlotinib	Phase II trial	ARQ 197 + erlotinib in advanced NSCLC patients with tumors harboring EGFR mutation progressing on EGFR TKI monotherapy
			Primary: ORR
ARQ 197	Erlotinib	2-arm phase III trial	ARQ 197 + erlotinib versus placebo + erlotinib in pretreated advanced non-squamous EGFR wild-type NSCLC Asian patients
	Placebo		Primary: OS
XL184 (cabozantinib)	Erlotinib	Phase I/II trial	XL184 + erlotinib (Part 1) AND XL184 + erlotinib compared to XL184 alone (Part 2) in NSCLC patients beyond erlotinib progression
			Primary: safety, tolerability and MTD; PK; PD; ORR
XL184	Placebo	Phase II discontinuation trial	Responding patients will continue treatment, those with stable disease will be randomized to continue XL184 until disease progression versus placebo; a non-randomized expansion cohort is expected for patients receiving placebo. Patients progressing on XL184 will discontinue study treatment.
			Primary: efficacy
			Secondary: safety and tolerability; PK and PD; correlation between MET expression and clinical outcome
XL184	Erlotinib	3-arm phase II trial	Erlotinib versus XL184 versus erlotinib plus XL184 as 2nd or 3rd line therapy in metastatic EGFR wild-type NSCLC patients.

Experimental drug	Combined treatment drug(s)	Study design	Description and primary end-points
			Primary: PFS
GSK 1363089 (foretinib)	Erlotinib	2-arm phase I/II trial	GSK 1363089 + erlotinib versus erlotinib alone in previously treated NSCLC patients
			Primary: RP2D of GSK 1363089 in combination with erlotinib; safety, tolerability and DLTs; PK; toxicity; ORR
INC280	Gefitinib	Phase Ib/II	INC280 + gefitinib in EGFR-mutated and c-MET amplified NSCLC patients who have progressed after EGFR inhibitor treatment
			Primary: DLTs (Phase I) and ORR (Phase II)
			Secondary: OS, safety, inhibition of c-MET signaling, PK

PK, pharmacokinetics; PD, pharmacodynamics; MTD, maximum tolerated dose; DLTs, dose limiting toxicities; RP2D, recommended phase 2 dose; HGF, hepatocyte growth factor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; DCR, disease control rate; ORR, objective response rate; PFS, progression free survival; OS, overall survival; ITT, intent to treat; IHC, immunohistochemistry.

Table 2.
Ongoing phase I/II studies with new small molecules targeting MET

Trials (ClinicalTrials.gov Identifier)	Experimental drug(s)	Mechanism of action	Description and End-points
NCT01014936	EMD 1214063	MET kinase inhibition	Open-label, dose-escalation, first-in-man, non-randomized trial in patients with advanced solid tumors under different regimens.
			Primary: MTD
			Secondary: safety profile and tolerability; PK; PD; safety profile; anti-tumor effects, and PK/PD in subjects with and without specific c-Met alterations, anti-tumor effects and others
NCT01253707	AMG 337	MET kinase	Open-label, first-in-human, sequential dose-

Trials (ClinicalTrials.gov Identifier)	Experimental drug(s)	Mechanism of action	Description and End-points
		inhibition	escalation and expansion trial in adults with advanced solid tumors.
			Primary: safety and tolerability; PK and MTD
			Secondary: clinical response and tumor anti-proliferative response
NCT00813384	AMG 208	MET kinase inhibition	Open-label, first-in-human, sequential dose-escalation and expansion trial in adults with advanced solid tumors.
			Primary: MTD; clinical response; PK; safety and tolerability
			Secondary: decrease in tumor cell proliferation according to PET scanning; tumor volume changes according to CT/MRI scanning; biomarkers on skin specimens; correlation between c-MET expression, amplification or mutation and response
NCT01721148	BMS 777607	MET kinase inhibition	Phase I multiple ascending dose study in patients with advanced/metastatic solid tumors
			Primary: MTD
			Secondary: PK and antitumor activity
NCT01428141	E7050	MET kinase inhibition (and VEGFR2)	Phase I study in adults with advanced solid tumors (and gastric cancer).
			Primary: MTD
NCT01433991	E7050	MET kinase inhibition	Open-label phase Ib/II study to assess the combination of E7050 and E7080 in adults with advanced tumors (dose-escalation part) and with recurrent glioblastoma or unresectable stage III/IV melanoma (expansion cohort and phase II)

Trials (ClinicalTrials.gov Identifier)	Experimental drug(s)	Mechanism of action	Description and End-points
	E7080	Multi-target inhibition	Primary: DLTs and MTD (phase Ib), antitumor activity (Phase II)
			Secondary: PK and PD of the two drugs, administered alone or in combination; antitumor activity
NCT00697632	MGCD265	Multi-target inhibition (including MET Kinase)	Open-label, phase I dose-escalation study to evaluate MGCD265 administered without interruption in patients with advanced tumors
			Primary: safety and tolerability
			Secondary: PK, PD and clinical response
NCT00975767	MGCD265	Multi-targets inhibition (including MET kinase)	Phase I/II study combining MGCD265 with erlotinib or docetaxel in patients with advanced tumors and advanced NSCLC
	Erlotinib		Primary: safety profile (phase I); antitumor activity (Phase II)
	Docetaxel		Secondary: PK, PD and antitumor activity (Phase I); safety profile (Phase II)
NCT01588821	Cabozantinib	Multi-target kinases inhibition (including MET and VEGFR2)	Phase II trial in patients with advanced solid (except breast and prostate) tumors and bone metastases
			Primary: effect on bone biomarkers, such as NTx, CTx and others
			Secondary: rate of SRE; QoL; ORR; correlation between response and MET amplification; response in metastatic bone sites; time to SRE

MTD, maximum tolerated dose; PK, pharmacokinetics; PD, pharmacodynamics; PET, positron emission tomography; CT, computed tomography; MRI, magnetic resonance imaging; VEGFR2, vascular endothelial growth factor receptor 2; DLTs, dose-limiting

toxicities; NTx, N-terminal telopeptide; CTx, C-terminal telopeptide; SRE, skeletal-related events; QoL, quality of life; ORR, objective response rate.

4.1. HGF antagonists

AMG-102 (rilotumumab) and *AV-299* (ficlatuzumab) are the two anti-HGF monoclonal antibodies currently in the most advanced phases of clinical investigation.

4.1.1. AMG-102

AMG-102, a fully human anti-HGF IgG2 monoclonal antibody, has shown preclinical activity both in vitro and in vivo by enhancing temozolomide and docetaxel efficacy in xenograft models overexpressing the HGF/MET pathway [102]. In the ensuing phase I trial, the maximum tolerated dose (MTD) was set at 20 mg/kg and was administered according to a 2-week schedule; the main adverse events (AEs) were fatigue, nausea, constipation, peripheral edema and hypertension of low to moderate grade [103]. This experimental drug has also shown good tolerability in association with antivascular agents [104]. *AMG-102*in association with standard chemotherapy in patients with advanced or metastatic gastric or gastroesophageal junction cancers has shown encouraging results, particularly in those with MET-positive tumors [105]. This compound is currently under evaluation in MET-positive gastric and gastroesophageal junction cancers and in pretreated NSCLC in combination with erlotinib.

4.1.2. AV-299

AV-299, a human anti-HGF IgG1 monoclonal antibody, showed a good tolerability profile and additive activity when combined with chemotherapy and an anti-EGFR drugs [106]. In a phase I trial AV-299 was administered at the previous MTD (20 mg/kg every 2 weeks) in combination with gefitinib (250 mg once daily); five out of 15 Asian NSCLC patients achieved a response and treatment was well tolerated. The most frequent AEs were rash, cough, diarrhea, decreased appetite, edema, drug hypersensitivity reactions and fatigue [107]. A randomized phase II study is evaluating AV-299 in combination with gefitinib in never smokers or light smokers and untreated Asian patients.

4.2. Anti-HGFR monoclonal antibodies

MetMab (onartuzumab) is a humanized, monovalent, monoclonal antibody directed against the MET receptor which inhibits HGF/MET binding without exerting agonistic activity and inducing MET dimerization. It demonstrated significant antitumor activity both in glioblastoma featuring an HGF-dependent autocrine loop [108] and in pancreatic [109] xenograft models. In the following phase I trial*MetMab* was well tolerated both as a single agent and in combination with bevacizumab, and the phase II recommended dose was set at 15 mg/kg every 3 weeks [110].

More recently, a global randomized phase II study (OAM4558g) comparing *MetMab* in combination with erlotinib or placebo as second- or third-line treatment for NSCLC has been completed and the efficacy data presented (Table 3) [111]. This study showed no significant improvement in progression-free survival (PFS) or overall survival (OS) in the intent-to-treat (ITT) population (137 patients). However, according to MET status determined by immunohistochemistry (IHC), patients with MET-positive (IHC score: 2+ or 3+) tumors benefited significantly from the addition of *MetMab* to erlotinib in terms of both median PFS (HR = 0.53, $P = 0.04$) and OS (HR = 0.37, $P = 0.002$). A significant improvement in OS was also observed in MET fluorescence in situ hybridization- (FISH-) positive (HR = 0.60) and MET FISH-negative/IHC-positive (HR 0.37, $P = 0.01$) NSCLC patients, which suggests that IHC might be a more sensitive tool for predicting a clinical benefit from *MetMab*. A significant improvement in OS (HR 0.45) was also observed in MET FISH-negative/IHC-positive/EGFR wild-type NSCLCs. Conversely, the addition of *MetMab* resulted in a detrimental effect in

patients with low MET expression (0 and 1+) tumors. *MetMab* in combination with erlotinib was well tolerated. Adverse events – such as rash, diarrhea, fatigue and nausea/vomiting – were comparable between the two treatment arms; peripheral edema was the only adverse event which occurred with a significantly higher frequency in the combination drug group (22.9% versus 6.5%).

Table 3.
Randomized phase II/III trials with MetMab [111] and Tivantinib [122] and [123].

OAM4558g – Randomized phase II study to evaluate MetMab or placebo in combination with erlotinib in advanced NSCLC[111]

	n	Median OS (months)		HR	CI 95%	*p*	Median PFS (months)		HR	CI 95%	*P*
		PE	ME				PE	ME			
ITT population	137	7.4	8.9	0.80	0.50–1.28	0.34	2.6	2.2	1.09	0.73–1.62	0.69
c-MET IHC+	66	4.6	12.6	0.37	0.19–0.72	0.002	1.5	2.9	0.53	0.28–0.99	0.04
c-MET IHC–[a]	56	15.3	8.1	1.78	0.79–3.99	0.16	2.7	1.4	1.82	0.99–3.32	0.05

Randomized phase II study to evaluate erlotinib plus tivantinib versus erlotinib plus placebo in previously treated, EGFR inhibitor-naive NSCLC patients [122]

	n	Median OS (months)		HR	CI 95%	*p*	Median PFS (months)		HR	CI 95%	*p*
		EP	ET				EP	ET			
ITT population	167	6.8	8.5	0.87	0.59–1.27	0.47	2.3	3.8	0.81	0.57–1.16	0.24
Non–SQCC histology	117	6.8	9.9	0.72	0.44–1.17	0.18	2.2	4.3	0.71	0.46–1.10	0.12

Randomized phase III study to evaluate erlotinib plus tivantinib versus erlotinib plus placebo in previously treated, EGFR inhibitor-naive non-squamous NSCLC patients [123]

	n	Median OS (months)	HR	CI 95%	p	Median PFS (months)	HR	CI 95%	p
ITT population									
Erlotinib + Tivantinib	526	8.5	0.98	0.84–1.15	0.81	3.6	0.74	0.64–0.85	<0.001
Erlotinib + Placebo	522	7.8				1.9			
MET high IHC [b]subgroup population									
Erlotinib + Tivantinib	104	9.3	0.70	0.49–1.01	0.03	3.6	0.72	0.52–0.98	0.014
Erlotinib + Placebo	107	5.9				1.9			
MET low IHC subgroup population									
Erlotinib + Tivantinib	107	8.5	0.90	0.64–1.26	0.53	3.7	0.66	0.49–0.89	0.006
Erlotinib + Placebo	127	7.7				1.9			

EP: erlotinib plus placebo; ET: erlotinib plus tivantinib; SQCC: squamous cell carcinoma.

ITT: intent to treat; OS: overall survival; PFS; progression free survival; HR: hazard ratio; CI: confidence interval; IHC: immunohistochemistry.

a

Initial data cut; OS: overall survival; PFS; progression free survival; HR: hazard ratio; CI: confidence interval; ITT: intent to treat; PE: placebo plus erlotinib; ME: MetMab plus erlotinib; NA: not available; IHC: immunohistochemistry.

b

MET high IHC: ≥50% of tumor tissue stained with an intensity of 2+ and/or 3+.

MetMab also induced a 2-year complete response in a young patient with pretreated metastatic gastric cancer expressing high MET gene polysomy [112].

A randomized phase III study in pretreated NSCLC patients is currently evaluating *MetMab* in combination with erlotinib versus erlotinib alone in MET 2+/3+ tumors [113].

Another specific monoclonal antibody, LY-2875358, has been tested so far only in a phase I trial [114].

4.3. MET tyrosine kinase inhibitors

The inhibition of MET tyrosine kinase activity represents the last strategy developed to block the aberrant MET signaling pathway. A myriad new small molecules targeting the MET tyrosine kinase domain are currently under investigation in phase I–II trials, such as INC-280, EMD 1214063, EMD 1204831, PF-04217903, AMG 337, AMG 208, BMS-777607, LY-2801653, E-7050, MK2461, JNJ-38877605, MP470, SGX523, and MGCD-265 [53] and [114] (Table 2).

More recently, EMD 1214063 and EMD 1204831 showed a highly potent and reversible c-MET phosphorylation inhibition both in vitro and in vivo, which resulted in tumor regression in xenograft models in both an HGF-dependent and -independent manner [115].

Tivantinib (ARQ197), cabozantinib (XL184), foretinib (XL880) and crizotinib (PF 02341066) are in the more advanced phases of clinical development (Table 1).

4.3.1. Tivantinib (ARQ 197)

Until recently *tivantinib* (ARQ 197) has been considered a non-competitive ATP small molecule that inhibits in a very highly selective manner the inactive form of the MET tyrosine kinase domain. In fact, it demonstrated cytotoxic effects both in vitro and in vivo by inhibiting MET phosphorylation and its downstream effectors [116]. Conversely, as recently demonstrated in different cell models and in contrast to our previous understanding, the stabilization of microtubules represents the real mechanism of action of this compound [117]. Tivantinib showed its activity against both c-MET-dependent and -independent cell lines. In particular, in addition to inhibition of c-MET signaling, its potent activity primarily involved disruption of the microtubule dynamics via inhibition of tubulin polymerization, a mechanism similar to that of vinca alkaloids [118].

This compound has been studied in different tumor types, including NSCLC, both alone and in combination with erlotinib [119], [120] and [121]. In a phase I trial enrolling unselected patients with advanced solid tumors, six out of eight NSCLC patients treated with tivantinib plus erlotinib achieved prolonged disease stability, and the recommended phase II study dose was set at 360 mg twice daily. Combination treatment was well tolerated, and fatigue, nausea/vomiting and diarrhea were the most common treatment-related adverse events [119]. Following these results, a randomized, double-blind, placebo-controlled phase II trial, having PFS as the primary endpoint, was designed to evaluate erlotinib plus tivantinib in previously treated, EGFR-TKI-naïve, advanced NSCLC patients [122]; 167 patients were randomized in a 1:1 fashion to receive erlotinib (E) plus tivantinib (T) or placebo (P) (Table 3). For patients randomized to receive EP, crossover to ET was allowed on disease progression. Median PFS in the ITT population did not differ significantly between the two treatment arms (HR = 0.81, $P = 0.24$). After adjusting for key prognostic factors, PFS in the ITT population was significantly better in the experimental arm (HR = 0.68, $P = 0.04$). Notably, a significant advantage in terms of PFS (adjusted HR = 0.61; $P = 0.04$) and OS (adjusted HR = 0.58; $P = 0.04$) was observed in the non-squamous NSCLC subgroup treated with ET, with an impressive delay of 7.4 months in the development of new metastases. Nevertheless, the K-RAS-mutated NSCLC subgroup significantly benefited from ET treatment (median PFS 2.9 versus 1.0 months; HR = 0.18; CI95% 0.05–0.70; $P = 0.01$); also EGFR wild-type NSCLC population had a longer median PFS when treated with combined drugs (3.2 versus 1.9 months; HR 0.70; CI95% 0.44–1.10), $P = 0.12$). The most common AEs of all grades were rash, diarrhea, fatigue, anorexia, and nausea/vomiting. There were no significant differences in either overall or serious AEs between the two arms.

A phase II trial to evaluate tivantinib plus erlotinib compared to single-agent chemotherapy in previously treated advanced non-squamous KRAS-positive NSCLCs is currently ongoing.

A phase III study (MARQUEE trial) [123] in previously treated, but EGFR- and MET-inhibitors-naïve, non-squamous NSCLC patients was discontinued early because the preplanned interim analysis failed to demonstrate a significant advantage in terms of OS, its primary end-point. Final results have recently been given at the 38th ESMO Annual Meeting (Table 3). The study confirmed that in the ITT population there was a significant improvement in PFS (HR 0.74, $P < 0.001$) and ORR in favor of the combination arm, but this advantage did not translate into a significant improvement in OS (HR 0.98, $P = 0.81$). The combined treatment was generally well tolerated; patients treated with erlotinib plus tivantinib developed a higher incidence of neutropenia of grade ≥3 (10% versus 1.0%). However, in the subgroup of patients whose tumors had higher MET IHC expression (2+ or 3+), the addition of tivantinib did improve OS significantly (HR = 0.70, $P = 0.03$), suggesting the potential for efficacy in a biomarker-selected population.

CYP2C19 is known to be the main enzyme system involved in tivantinib metabolism. Specific CYP2C19 polymorphisms, expressed mainly in Asian populations (20% versus 3% in Caucasian populations), define a subgroup of patients as poor metabolizers; for these patients, the tivantinib dose has been set at 240 mg twice daily [124]. Another phase III trial (ARQ197-006) in advanced non-squamous EGFR wild-type NSCLC Asian patients is currently ongoing to evaluate the combination of tivantinib and erlotinib versus erlotinib plus placebo. Tivantinib dose administration is based on CYP2C19 polymorphism (ATTENTION, NCT01377376).

4.3.2. Cabozantinib (XL184)

Cabozantinib (XL184) is a multitarget ATP competitive inhibitor of MET, VEGFR2 and RET, and it has shown antitumor activity in experimental MET-driven and not-MET-driven models [125]. Cabozantinib has been studied either alone or in association with erlotinib in NSCLC with acquired resistance to erlotinib; the results were encouraging, with several partial responses and prolonged disease stabilization, especially in NSCLC patients with MET-amplified tumors and harboring EGFR T790M mutation [126]. In the following phase II randomized discontinuation trial, which enrolled 483 patients with different solid tumors, cabozantinib demonstrated good activity [127]. In particular, in the NSCLC subgroup ORR was 13% (6/47 patients), with a disease control rate of 40%. In the overall population, the most common AEs of grade ≥3 were fatigue (9%), hand–foot syndrome (8%) and hypertension (5%). Interestingly, the presence of EGFR/K-RAS mutations was a predictor of clinical benefit; soft tissue, visceral and bone lesions were identified as the tumor sites where the drug was more active.

In other phase II discontinuation trials, cabozantinib has been shown to be active also in advanced ovarian[128] and prostate [129] cancers.

4.3.3. Foretinib (XL880)

Foretinib (XL880, GSK1363089) is a multitarget inhibitor directed against MET/VEGFR, RON, AXL, PDGFR-β, KIT, FLT3 and TIE-2. Foretinib has shown antitumor activity in vivo [130]. Results of a phase I study enrolling 40 patients with chemorefractory advanced solid tumors [131] showed partial responses in one medullary thyroid carcinoma and in two papillary renal-cell carcinomas. MTD was set at 3.6 mg/kg administered for 5 consecutive days every 2 weeks; the investigational drug was well tolerated. Hypertension, fatigue, diarrhea, vomiting, proteinuria and hematuria were the most common adverse events. At maximum administered dose (4.5 mg/kg), grade 3 elevations in aminotransferase (AST) and lipase levels were reported.

Recently, the results of a phase II study of foretinib in 74 patients with papillary renal-cell carcinoma confirmed the antitumor activity of the compound, especially in tumors with germline MET mutations [132]. At present, two phase II studies of foretinib in other cancers have been completed and results are awaited; moreover, the inhibitor is currently

under investigation in a phase I/II study in patients with previously treated, advanced or metastatic NSCLC (erlotinib versus erlotinib plus foretinib).

4.3.4. Crizotinib (PF 02341066)

Crizotinib (PF 02341066), a strong ALK inhibitor approved in August 2011 by the FDA for the treatment of ALK-rearranged NSCLC, was initially investigated as a c-MET inhibitor. Crizotinib showed a good antitumor activity in both preclinical [133] and [134] and phase I [135] studies, demonstrating that its activity correlated with its ability to inhibit MET phosphorylation. More recently, crizotinib was highly effective in a patient with NSCLC harboring a de novo MET amplification [136] and in MET-amplified gastroesophageal adenocarcinomas and glioblastoma [137] and [138]. Therefore, it is possible that crizotinib might possess a different antitumor activity according to MET gene alterations [139]. In a more recent study, Zhang et al. investigated crizotinib efficacy in different brain tumor cells. Interestingly, the authors demonstrated a heterogeneous antitumor activity and identified high HGF expression as a key determinant of major responsiveness to crizotinib through inhibition of the ERK/JAK/p53 pathway [140]. Surprisingly, a short-term pretreatment with exogenous HGF resulted in a greater cell apoptosis and tumor growth inhibition after crizotinib exposure than in non-pretreated cells both in vitro and in vivo.

Two phase I trials combining crizotinib with a pan-HER inhibitor in advanced NSCLC are currently ongoing.

4.4. On-target-based toxic effects of MET inhibition etc.

On-target toxicity refers to the exaggerated and adverse class effects due to inhibition of the direct target in normal cells and tissues.

Regarding MET inhibitors, particularly monoclonal antibodies and small molecules, these compounds have to date demonstrated few adverse effects in normal tissues. In fact, several MET inhibitors have been investigated in full doses both in combination with chemotherapy and other targeted drugs (EGFR-TK and VEGF inhibitors), and any combination treatment was well tolerated without enhanced known toxic effects. In particular, peripheral edema seems to be a peculiar on-target toxicity. Other adverse events seen in the trials with MET inhibitors – such as fatigue, anorexia, nausea/vomiting, fever and hypersensitivity reactions – arose regardless of their target.

Off-target toxicity refers to adverse effects related to inhibition activity on other targets. It occurs when a TK inhibitor causes a toxic effect by the inhibition of a kinase not known to be the target of a specific compound.

Regarding MET inhibitors, the majority of off-target adverse effects, such as proteinuria, hematuria, hypertension and bleeding, seem to be correlated with inhibition of other targets (VEGFR and others).

Drug-related toxicity refers to the physicochemical properties of a specific compound and their effects on cell compartments and metabolism.

A selective MET inhibitor, SGX523, was found to be safe and very effective in preclinical studies, but was discontinued early in a phase I trial because of the appearance of renal failure. This unexpected drug-related toxicity in humans was due to the presence of two insoluble drug metabolites that crystallized in renal tubules, leading to tubulointerstitial nephritis [141].

Although several toxicities are driven by plasma free drug levels, on-target tissue toxicities seem to be also correlated with drug concentrations in the target tissue. A recent pharmacokinetic study demonstrated that the significant liver toxicity of GEN-203, a small molecule MET inhibitor, was correlated with its lipophilic characteristics which enhance its distribution into liver tissue. By modifying the chemical properties of the compound, the authors were able to reduce its basicity and tissue concentrations, improving the safety profile of the drug [142].

5. Conclusions

Many preclinical and clinical studies have demonstrated the important role of the MET pathway in tumors, and also in NSCLC. The MET pathway can be aberrantly activated as a consequence of HGF or HGFR transcriptional upregulation, MET gene amplification and, rarely, as the final event of a MET gene mutation. Other signaling co-receptors can crosstalk with MET, even in an HGF-independent manner, providing an alternative way to induce proliferation, survival and invasive growth. On the other hand, aberrant MET signaling activation can represent an oncogene expedience to enhance invasiveness and metastatic properties of pretreated neoplastic cells.

Different compounds targeting MET have been developed and have shown antitumor activity; some of them, such as *MetMab* and tivantinib, are currently under advanced clinical development in NSCLC. A plethora of new molecules targeting MET or acting as multitarget inhibitors is emerging, but the increasing availability of new compounds might represent a double-edged sword. In fact, whereas ever-growing pharmaceutic efforts have led to the introduction of new molecules into preclinical and clinical studies, this race might generate confusion about the exact mechanisms through which these new drugs block tumor growth and those through which tumor cells are able to escape their effects. In this regard, we hope that the lesson learned from tivantinib will serve as a warning.

According to the safety profile of these drugs, overall selective MET inhibitors seem to have no particular toxicity issues, and the main expected toxicities are manageable. However, we think that our experience of the toxicity profile of these molecules is very limited, in particular regarding the late toxic effects.

Several questions remain to be answered to optimize MET-targeted therapy. First, we need to understand comprehensively if and when genetic alterations involving MET induce “oncogene addiction” or “oncogene expedience”. This is a relevant issue because of its therapeutic implications; the mechanism underlying MET oncogene addiction is not yet fully elucidated, whereas a role for MET is now emerging in oncogene expedience which can potentiate other oncogenes and accelerate tumor progression. Therefore, we need to identify definitively the subgroup of tumors that can benefit from MET inhibition. Second, the best treatment strategy has yet to be determined; in particular, we have to clarify the best drug combination treatment (MET and EGFR inhibitors, MET and other inhibitors) and if and when a MET monotarget approach might have a role. Third, we have to determine the best sequence to use and the most appropriate setting in which we should consider its use. Finally, we need to identify specific tools as predictive factors of better outcome of MET inhibition. In this regard, at present MET IHC overexpression seems to have a promising role, but other efforts are required to detect new circulating predictive biomarkers.

Understanding the specific mechanisms of drug resistance is critical in selecting and evaluating subsequent therapeutic approaches. The strategy of combining treatments targeting several molecules, or molecules blocking downstream signaling transducers, might be used in order to address the common problem of crosstalk between signaling pathways and thus the development of resistance.

With the efforts of translational and clinical research, in a few years MET-targeted therapies will surely impact on lung cancer outcome, and they must be welcomed as one of the possible therapeutic options for patients with NSCLC.

Conflict of interest statement

The authors declare they have no conflict of interest.

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