MET as a Therapeutic Target: Have Clinical Outcomes Been "MET" in Lung Cancer?

Arin Nam and Ravi Salgia

Abstract Targeted therapy is an especially attractive approach for treating lung cancer since overactivation of oncogenic proteins often drives disease progression. In particular, dysregulation of the MET receptor tyrosine kinase (RTK) pathway via genetic mechanisms, such as gene amplification and exon 14 skipping mutations, has been identified. With significant advancements made in the realm of targeted therapeutics, such as small molecules and antagonistic antibodies, developing novel strategies to target MET is at the forefront of lung cancer treatment. This chapter will introduce the MET signaling pathway and various genetic abnormalities implicated in lung cancer. Then, the currently used MET-targeted therapies and investigative agents will be highlighted along with their status in clinical trials. The final section will shed light on preclinical data revealing possible mechanisms of resistance to MET-targeted therapy.

Keywords Targeted therapy · MET · Receptor tyrosine kinase · Lung cancer · Exon 14 skipping

Introduction

Lung cancer remains to be the most commonly diagnosed and fatal cancer type among both men and women in the United States and worldwide [1, 2]. Lung cancer is typically classified as non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), which account for 85% and 15% of cases, respectively. NSCLC diagnoses can be further identified based on subtypes, such as adenocarcinoma,

A. Nam
Department of Medical Oncology and Experimental Therapeutics,
City of Hope National Medical Center, Duarte, CA, USA

R. Salgia (✉)
Department of Medical Oncology and Therapeutics Research,
City of Hope National Medical Center, Duarte, CA, USA
e-mail: rsalgia@coh.org

R. Salgia (ed.), *Targeted Therapies for Lung Cancer*, Current Cancer Research,
https://doi.org/10.1007/978-3-030-17832-1_5

squamous cell carcinoma, and large cell carcinoma. Current treatment for early-stage NSCLC is surgical removal of the tumor and sometimes treated with adjuvant chemotherapy alone or in combination with radiation. Late-stage NSCLC is usually treated with conventional chemotherapy, targeted therapy, immunotherapy, alone or in a combined regimen. Treatment options for SCLC remain quite limited to traditional chemotherapy alone or in combination with radiation [1]. Although patients may initially respond to these therapeutic regimens, often times, tumors acquire resistance to these agents, and the disease progresses as reflected by a dismal 18% five-year survival rate [1]. Developing additional targeted therapies is particularly an attractive approach for lung cancer because overactivation of certain proteins plays a key role in lung tumorigenesis.

Several receptor tyrosine kinases (RTKs), which constitute the largest family of tyrosine kinases [3], have been identified to be upregulated in lung cancer, contributing as important drivers of disease progression. RTKs are a subclass of tyrosine kinases that mediate cell-to-cell communication and control a wide range of biological functions, including cell growth, motility, differentiation, and metabolism [4]. All RTKs share a similar protein structure comprised of an extracellular ligand-binding domain, a single transmembrane helix, and an intracellular region that contains a juxtamembrane regulatory region, a tyrosine kinase domain (TKD), and a carboxyl (C-) terminal tail [5]. The extracellular domain of the RTKs binds specific ligands, such as growth factors, cytokines, and hormones, that can activate various intracellular signal transduction cascades including survival and migration [6]. However, abnormal expression and/or signaling of RTKs are implicated in many types of cancer that fuel its progression via unregulated proliferation and invasion through surrounding tissue [7]. Ninety unique kinase genes can be identified in the human genome of which 58 are of the receptor type, distributed into 20 subfamilies [3].

This chapter will focus on one member of the RTK family namely MET or hepatocyte growth factor receptor (HGFR) that plays an important role in lung cancer [8, 9]. First, the structure and function of MET will be described together with its normal function within the cell. The following section will outline various abnormalities in lung cancer that have been frequently identified in patients. The remaining sections will discuss various therapeutic approaches targeting MET signaling in lung cancer as well as the more recent developments regarding mechanism(s) of resistance to these agents.

Structure and Function

Gene

The human gene encoding MET is ~126 kilobases and is located on chromosome 7, locus 7q21–q31. MET was originally discovered in 1984 as a partner in the fusion oncogene TPR-MET of an immortalized cell line derived from osteosarcoma [10].

Upon treatment of this cell line with the carcinogenic compound *N*-methyl-*N*′-nitronitrosoguanidine, genetic fusion was induced between the TPR gene on locus 1q25 and the MET gene on locus 7q31 [10]. At least three different isoforms are reported. The most commonly expressed isoform encodes for the protein precursor that is 1390 amino acids long.

Protein

When the precursor is posttranslationally cleaved and glycosylated, a 50-kDa alpha chain and a 140-kDa beta chain are produced. The alpha chain is linked via disulfide bonds to the extracellular portion of the beta chain, which also includes the transmembrane and intracellular portions of the receptor. Sharing domain homology with other protein structures, the beta chain is comprised of: the semaphorin domain, plexin-semaphorin-integrin (PSI) domain, four immunoglobulin-plexin-transcription (IPT) repeats, transmembrane domain, juxtamembrane domain, tyrosine kinase domain, and the C-terminal region (Fig. 1).

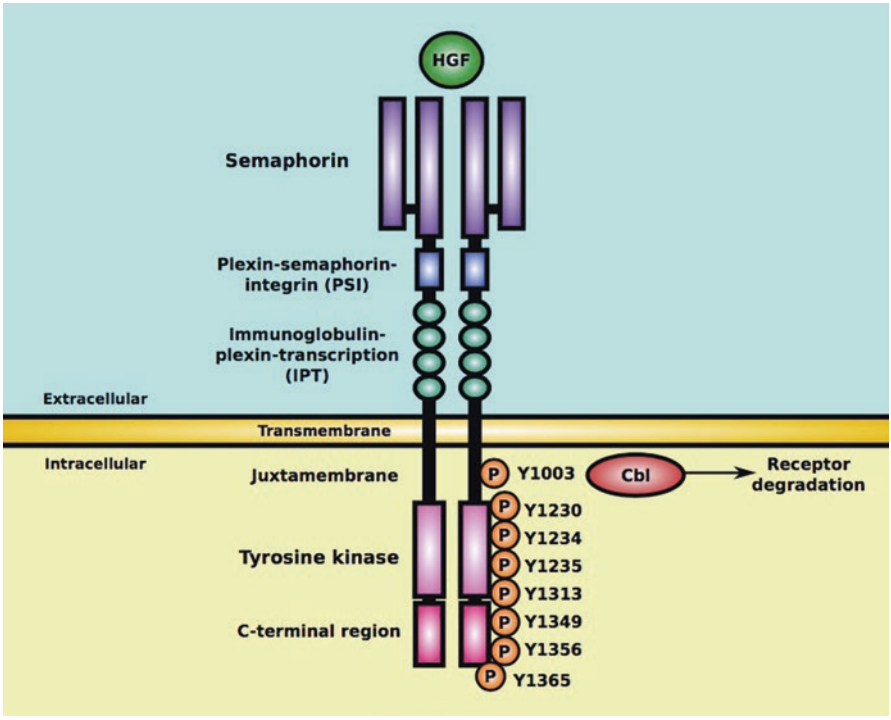

Fig. 1 MET structure, domains, and phosphorylation sites

Ligand HGF

Hepatocyte growth factor (HGF), also known as scatter factor (SF), is the only known natural ligand that binds to the MET receptor and activates it. It resembles other growth factors in the plasminogen-related growth factor family [11] and is secreted by mesenchymal cells as a precursor that is proteolytically cleaved by HGF activator (HGFA). Active HGF is produced in the form of a disulfide-linked heterodimer. HGF has six domains: the N-terminal domain, four kringle domains, and the C-terminal domain. The ligand binds to the receptor at the semaphorin domain, a seven beta-propeller structure where blades 2 and 3 form the active binding site for HGF [12].

Signaling

Like other RTK activation pathways, such as RON and Sea [13], ligand binding induces receptor dimerization and activation of the tyrosine kinase. In the active state, MET autophosphorylation and recruitment of a number of signal transducer molecules initiate several signaling cascades as seen in Fig. 2. Phosphorylation at Y1230, Y1234, and Y1235 turn on the activation loop at the catalytic domain [14]. As a result, the multisubstrate docking site located at the C-terminal region becomes activated and is able to recruit intracellular adaptor molecules that can be recognized by certain motifs like the Src homology-2 domain. Phosphorylation at Y1349 and Y1356 is required to directly bind Src and Shc and indirectly bind Gab1 [15, 16]. Only phosphorylation at Y1356 is required for binding growth factor receptor protein 2 (Grb2) to the YXN motif at Y1349, phospholipase C-γ (PLC-γ) to the YXXL motif at Y1365, phosphoinositol 3-kinase (PI3K) to the YXXM motif at Y1313 [17], and Shp2. Recruitment of these various signal transduction molecules can activate several downstream pathways: (1) Ras/Raf pathway is activated and involved in cell scattering and proliferation [18]; (2) PI3K pathway, downstream of Ras or recruited directly, is involved in cell migration via cytoskeletal reorganization through paxillin and FAK and also triggers a survival signal through AKT recruitment and activation [19, 20]; (3) MAPK pathway is activated through recruitment of Gab1/Grb2/SOS molecules as well as Ras/Raf to prompt cell survival and proliferation [21]. From ligand binding to activation of several signal transduction cascades, many biological changes occur within the cell, such as transcriptional regulation and gene expression, in order to trigger cell growth, differentiation, survival, and cytoskeletal reorganization. Phosphorylation at Y1003 in the juxtamembrane domain is required for recruiting the E3 ubiquitin ligase, Cbl. Cbl facilitates the ubiquitination of MET by acting as an adaptor for endophilin in order to direct receptor internalization within clathrin-coated vesicles. These vesicles can then be trafficked to endosomes for ultimate lysosomal degradation [22]. Aberrant signaling at any or multiple points from ligand binding to downstream changes in cellular function can give rise to cancer cell differentiation, progression, and/or metastasis [23].

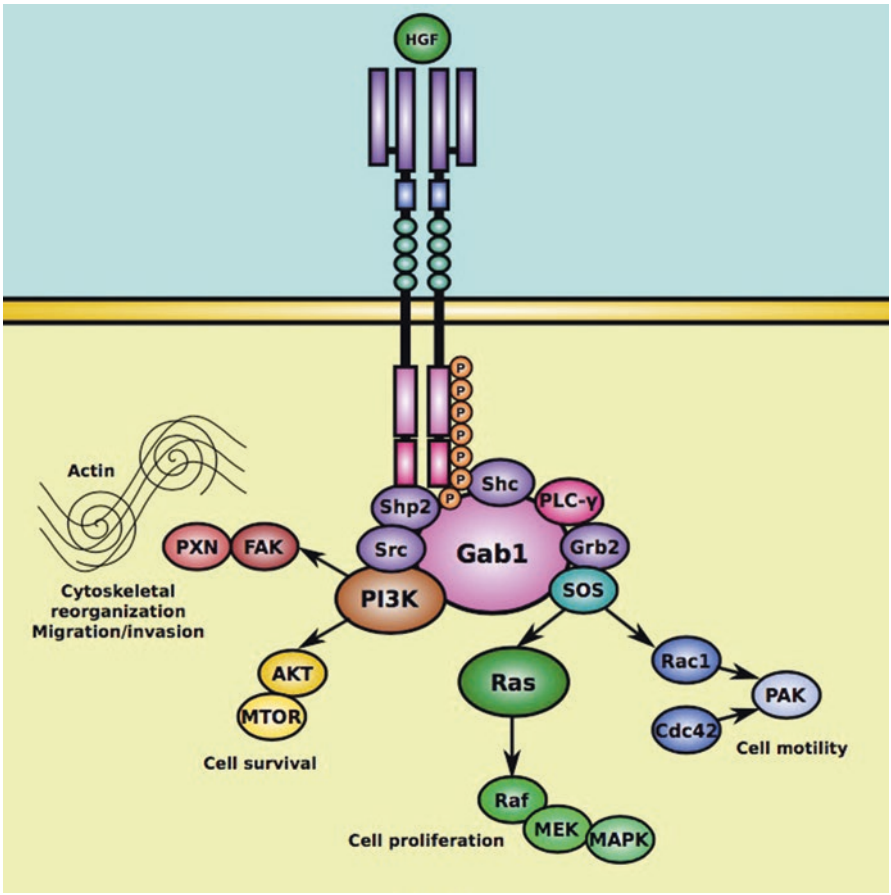

Fig. 2 MET downstream effector molecules and signaling cascades

Normal Function

Activation by MET of the various downstream pathways initiate the regulation of normal cellular processes, such as cell survival, differentiation, and migration. MET also plays an essential role in embryonic development, specifically migration of mesenchymal cells and neuronal precursors for muscle and nervous tissue organogenesis [24]. In adults, MET can be activated to prompt wound healing and tissue remodeling [25]. Hematopoietic cells can also utilize MET activation for differentiation and proliferation to generate mature blood cells [26].

Abnormalities in Lung Cancer

Since dysregulation of the MET/HGF signaling axis plays a key role in tumorigenesis and metastasis, this section highlights the various factors at the genetic level, such as gene amplification and mutations, resulting in phenotypes of receptor overexpression and constitutive kinase activation.

Gene Amplification/Receptor Overexpression

Amplification of MET at the genetic level has been observed in both NSCLC and SCLC, resulting in receptor overexpression at the protein level. In 25% of NSCLC primary tumors, a two to ten-fold higher levels of MET expression and ten to hundred-fold higher levels of HGF expression were observed when compared to adjacent normal tissue [27]. Immunohistochemical (IHC) staining of tissue from lung cancer patients (n = 32) showed MET expression in all samples. Sixty-one percent of NSCLC, 60% of carcinoids, and 25% of SCLC tumor tissues showed strong expression of MET, and no significant staining was observed in normal tissue [28]. In order to determine whether there is an accompanying increase in receptor activity, IHC staining for phospho-MET at catalytic residues Y1003 or Y1230/1234/1235 showed that in SCLC tissues, all samples stained positive for pY1003 and 50% of samples expressed pY1230/1234/1235 [28]. For NSCLC, 44%/33% of adenocarcinoma, 86%/57% of large cell carcinoma, 71%/0% of squamous cell carcinoma, and 40%/0% of carcinoid samples stained positive for pY1003 and pY1230/1234/1235, respectively. It is also worth mentioning that the invasive front of NSCLC tissues showed relatively higher levels of phospho-MET, suggesting the role of activated MET in tissue invasion [28].

MET Overexpression and Correlation with Paxillin

MET is able to affect cell motility by regulating cytoskeletal reorganization through actin polymerization and depolymerization. Upon phosphorylation of key focal adhesion molecules, such as paxillin, FAK, and Pyk2, by the MET kinase, filopodia and lamellipodia formation and retraction were observed [29]. Activated paxillin by MET induces an interaction with the cytoskeleton, resulting in cell motility and migration [30]. It has been shown that the correlated activity between MET and paxillin coincide with their expression in tumor tissue. An increase in paxillin expression with higher NSCLC disease stage has been observed as well as a correlation between high paxillin expression and copy number of the MET gene [31]. In contrast, SCLC has relatively low levels of paxillin [32]. Thus, this correlation is not observed in this lung cancer type.

MET Overexpression and Mitochondrial Dynamics

Lung cancer cells with MET overexpression are highly dependent on receptor signaling to sustain viability. These overexpressing cells are more sensitive to MET inhibitor (MGCD 516) than cells with lower MET expression [33]. Interestingly, signaling of dynamin-related protein-1 (DRP1), a mitochondrial protein involved in the fission process, is attenuated when treated with this MET inhibitor [33]. As a result, mitochondrial morphology appears to be more elongated.

Missense Mutations in the Juxtamembrane and Semaphorin Domain

The MET gene is a target for several missense mutations that cause dysregulation of receptor function. Mutations are primarily found within the juxtamembrane region and semaphorin domain for lung cancer. Although mutations can be found in the MET tyrosine kinase domain in head and neck cancers [34], glioblastomas [35], and hereditary papillary renal carcinomas [36], none are found in lung cancer. Missense mutations in the juxtamembrane domain cause aberrant receptor signaling due to this region's key role as a regulator site for catalytic function of tyrosine kinases. In NSCLC, R988C, T1010I, and S1058P mutations increase phosphorylation of MET and downstream signal transduction molecules, enhance tumorigenicity, cell motility, and alter cellular morphology. These mutations also contribute to a stronger response to inhibition with small molecule compounds targeting MET [28]. Missense mutations can also be found in the semaphorin region, E168D, which can alter the binding of HGF and subsequent receptor dimerization and activation [37]. Another missense mutation found in the semaphorin domain, N375S, conferred resistance to MET inhibitors and was most frequently detected in tumor tissues of East Asians (13%) and not detected in that of African Americans (0%) [38].

Modeling Mutations in Caenorhabditis elegans

Modeling a cancer phenotype in a multicellular organism can be achieved with *Caenorhabditis elegans,* especially in a high-throughput manner. The phenotype of the nematode's vulva reflects any developmental abnormalities. In wild-type N2 adult worms, a "normal" vulva is apparent, however, the cancer phenotype exhibits a multivulval characteristic [39]. Various transgenic worms with MET missense mutations have been used as a model for determining phenotypic changes and developmental abnormalities. For example, transgenic worms expressing wild-type human MET genes exhibited ectopic hypodermal growth in the posterior region,

but transgenic worms expressing the R988C mutant MET construct exhibited a tumor-like growth of vulva-forming cells [40]. Using these transgenic worms as a model, exposure to nicotine and other smoke toxins resulted in a multivulval-resembling phenotype, suggesting synergy between MET and nicotine. [40] This model system may be useful to study other environmental toxins as well as dysregulation of other oncogenes.

Exon 14 Skipping Mutation

A shorter variant of the MET receptor was first discovered in mice in 1994 that led to tumorigenicity in vivo [41]. We were the first to identify exon 14 splicing mutation in NSCLC and SCLC [28, 37]. This variant lacked a portion of the juxtamembrane domain, which is a key regulatory site for kinase activity. In patients' genomic data, mutations were found to occur near splice sites that cause exon skipping within the MET gene in multiple tumor types, including lung cancer [42]. Primarily found in lung adenocarcinomas, exon 14 of the MET gene is susceptible to mutations near the splice site. This mutation results in exon 14 skipping during the splicing process from pre-mRNA to the mature mRNA. Because exon 14 encodes for the juxtamembrane portion of the protein that includes residue Y1003, mutations that cause exon 14 skipping produces a protein lacking this key domain and kinase regulatory site [43]. Phosphorylation at Y1003 is required for binding the E3 ubiquitin ligase, Cbl, which promotes MET ubiquitination, internalization, and degradation. However, if the MET protein product lacks this site as a result of exon 14 skipping, the receptor half-life is prolonged, resulting in MET overexpression and extended catalytic function within the cell [43]. Cbl mutations have also been found to be highly prevalent in MET-mutated NSCLC that enhance cell viability and motility [44]. Altered Cbl in NSCLC cells have higher MET expression than wild-type cells and are more sensitive to MET inhibitor SU11274. [45]

Modeling Mutations with DNA Walks and Their Fractal Patterns

DNA walks depict nucleotide sequence patterns that can be used to model wild-type genes and mutated counterparts. In particular for the MET gene, point mutations create larger gaps in the pattern, generating an increase in self-similarity or fractal dimension. On the other hand, MET deletion mutations, as seen in exon 14 skipping, decrease fractal dimension in the pattern because of a reduction in nucleotide variance [46]. This type of modeling has potential predictive capabilities for exon 14 deletions. One can introduce unknown exon 14 alterations to the

genetic sequence, generate a DNA walk, and compare the fractal dimension to known patterns that lead to exon skipping [46].

Various Therapeutic Approaches and Outcomes

The shift from traditional cytotoxic chemotherapy to a more targeted approach has given clinicians and researchers insight into biomarker-based therapies and drug development. Because abnormal signaling in the MET axis can be implicated in lung cancer as well as other types of solid cancers, it represents an attractive target for developing small molecule compounds and biological antagonists, such as antibodies, that block HGF-binding and/or MET activation as seen in Fig. 3. Screening for patients with genetic alterations in MET, as well as EGFR, has allowed clinicians to treat patients with targeted therapies and improve overall survival, since often times, patients with EGFR mutations develop resistance to EGFR inhibitors due to MET overexpression/amplification. In this section, several small molecule inhibitors and biological antagonists will be described in addition to their mechanisms of action and current status in clinical trials.

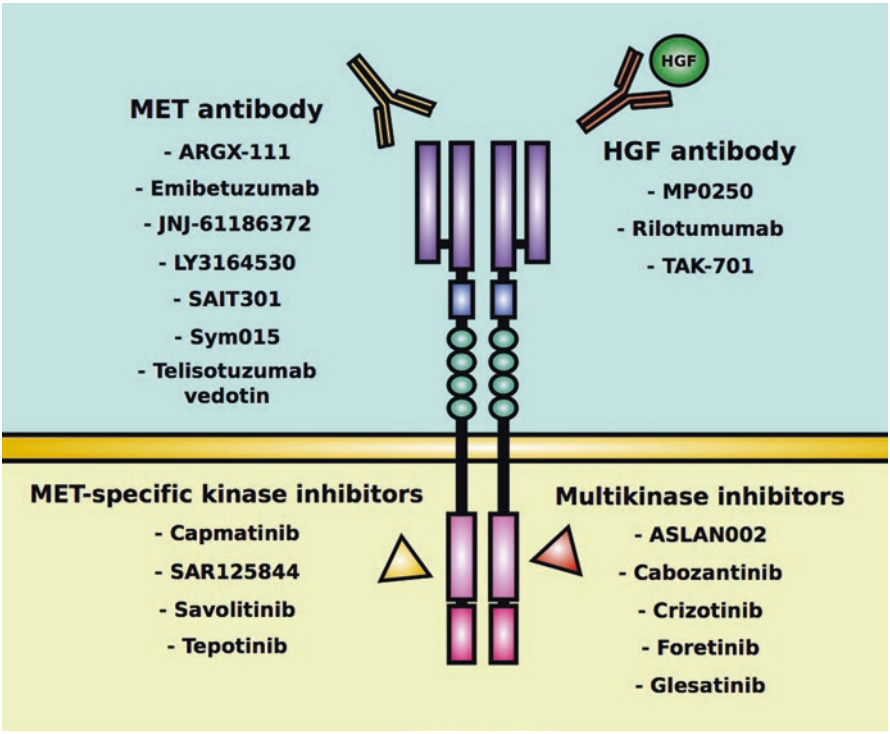

Fig. 3 Current therapeutic approaches targeting MET

Small Molecule Inhibitors Against MET

Small molecule kinase inhibitors or tyrosine kinase inhibitors (TKIs) that block receptor activation have shown promise in clinical settings where dysregulated signaling of these receptors drive cancer progression. When these agents bind to the receptor, activation of downstream signaling events is prevented and thus, tumor cells are directed to apoptosis. These types of inhibitors are an appealing strategy for developing targeted therapies because of their small size (<500 Da), cost-effectiveness, and availability, as compared to monoclonal antibodies. First generation TKIs, such as crizotinib and cabozantinib, also target other types of RTKs and hence, they are classified as a multikinase inhibitor. The primary drawback to inhibitors that target a wider range of receptor kinases is toxicity, drawing attention toward the need for more specific RTK inhibitors. Recently developed small molecule inhibitors against MET, such as capmatinib, have exhibited more potent activity and selective binding for the MET receptor than other kinases [47]. These MET-specific inhibitors have shown promise in clinical trials especially for patients with MET amplification and/or exon 14 skipping mutations. [42]

Overcoming EGFR Inhibitor Resistance with MET Inhibitors

Several clinical trials for MET inhibitors are in combination with EGFR inhibitors because research has shown that cancer cells develop resistance to EGFR-targeted therapies via MET overactivation [48]. Crosstalk and synergism between MET and EGFR signaling was found to occur in NSCLC cell lines to promote cancer progression [49]. When EGFR signaling is blocked, tumorigenic cells take advantage of alternate signaling pathways, such as MET, to overcome inhibition and reactivate downstream signaling cascades that drive cancer progression.

The remainder of this section will highlight several small molecule inhibitors of MET that have shown significant clinical efficacy and describe their mechanisms of action and current stage in clinical trial investigations. Table 1 presents a more extensive list of ongoing clinical trials with the various MET inhibitors.

Small Molecule Tyrosine Kinase Inhibitors

Cabozantinib (XL184)

Cabozantinib is a small molecule multikinase inhibitor that targets MET as well as other receptor tyrosine kinases, such as VEGFR2, AXL, and RET. A phase Ib/II study investigated safety and pharmacokinetics in NSCLC patients with EGFR mutations that were previously treated with erlotinib. Treatment with a combination

Table 1 Current status of MET-targeted agents in clinical trials

Drug	Manufacturer	Conditions	Combination	Phase	NCT	Study Start Date
Small molecule inhibitors against MET						
ASLAN002 (BMS-777607) *Small molecule inhibitor against MET and RON*	Bristol-Myers Squibb	Malignant solid tumor	–	I, completed	NCT01721148	October 2012
Cabozantinib (XL184) *Multikinase small molecule inhibitor against MET, VEGFR2, AXL, RET*	Exelixis	NSCLC with brain metastases	–	II, recruiting	NCT02132598	December 2015
Capmatinib (INC280) *MET small molecule inhibitor*	Novartis	NSCLC	–	II, recruiting	NCT02414139	June 11, 2015
			Erlotinib	Ib, recruiting	NCT02468661	September 23, 2015
			EGFR TKI Nazartinib (EGF816)	I/II, recruiting	NCT02335944	January 13, 2015
			PD-1 antibody Nivolumab	II, recruiting	NCT02323126	February 9, 2015
		Recurrent NSCLC	Erlotinib	I, recruiting	NCT01911507	July 2013
		Solid tumors, MET dysregulated	–	I, completed	NCT02925104	December 14, 2016
		NSCLC, METex14 skipping alterations	–	II, recruiting	NCT02750215	May 2016
Crizotinib (PF-02341066) *Multikinase small molecule inhibitor against MET, ALK, ROS1*	Pfizer	NSCLC	–	II, recruiting	NCT03088930	December 13, 2017
			Erlotinib	I, completed	NCT00965731	January 2010
			Rifampin, Itraconazole	I, recruiting	NCT00585195	April 19, 2006

(continued)

Table 1 (continued)

Drug	Manufacturer	Conditions	Combination	Phase	NCT	Study Start Date
Foretinib (GSK1363089) *Small molecule inhibitor against MET and VEGFR2*	GlaxoSmithKline	Lung cancer	Erlotinib	I/II, completed	NCT01068587	December 2009
Glesatinib (MGCD265) *Small molecule inhibitor against MET and AXL*	Mirati Therapeutics	NSCLC	Nivolumab	II, recruiting	NCT02954991	November 2016
SAR125844 *MET small molecule inhibitor*	Sanofi	Malignant neoplasm	–	II, completed	NCT02435121	November 2015
Savolitinib (AZD6094) *MET small molecule inhibitor*	AstraZeneca	NSCLC	Gefitinib	I, not yet recruiting	NCT02374645	April 2015
			Osimertinib (AZD9291)	I, recruiting	NCT02143466	August 5, 2014
		Tumors	–	I, recruiting	NCT01985555	May 2013
Tepotinib (MSC2156119J) *MET small molecule inhibitor*	Merck	NSCLC	Gefitinib	I/II, not yet recruiting	NCT01982955	December 23, 2013
		NSCLC, METex14 skipping alterations	–	II, recruiting	NCT02864992	September 13, 2016
Antibodies against MET/HGF						
ARGX-111 *MET antibody*	argenx	Cancer, overexpressing MET	–	I, completed	NCT02055066	January 2014
Emibetuzumab (LY2875358) *MET monoclonal antibody*	Eli Lilly	Solid tumors	Ramucirumab	I/II, completed	NCT02082210	March 7, 2014
		NSCLC	Erlotinib	II, not yet recruiting	NCT01897480	August 28, 2013

JNJ-61186372 *Bispecific antibody against MET and EGFR*	Johnson & Johnson	NSCLC	–	I, recruiting	NCT02609776	May 24, 2016
LY3164530 *Bispecific antibody against MET and EGFR*	Eli Lilly	Solid tumors	–	I, completed	NCT02221882	August 2014
MP0250 *HGF antibody mimetic, also targets VEGF*	Molecular Partners	Advanced solid tumors	–	I/II, completed	NCT02194426	February 20, 2018
Rilotumumab (AMG 102) *HGF monoclonal antibody*	Amgen	SCLC	Etoposide and cisplatin/carboplatin	I/II, completed	NCT00791154	December 2008
SAIT301 *MET antibody*	Samsung	Solid tumors	–	I, completed	NCT02296879	January 20, 2015
Sym015 *MET antibody*	Symphogen	NSCLC	–	I/II, recruiting	NCT02648724	March 2016
TAK-701 *HGF monoclonal antibody*	Takeda	Advanced solid tumors	–	I, completed	NCT00831896	March 2009
Telisotuzumab vedotin (ABBV-399) *MET monoclonal antibody*	AbbVie	Recurrent squamous cell lung carcinoma	–	II, recruiting	NCT03574753	February 5, 2018
		NSCLC	–	II, recruiting	NCT03539536	October 10, 2018
		Advanced solid tumors, with MET amplification or overexpression	Docetaxel or FOLFIRI/cetuximab or erlotinib	I, completed	NCT01472016	October 6, 2011

Accessed from ClinicalTrials.gov on January 21, 2019

of cabozantinib and erlotinib failed to show response in phase II and cabozantinib did not resensitize these tumors to erlotinib [50]. In a patient harboring a MET exon 14 skipping mutation, intracranial progression was observed with crizotinib treatment. Upon switching therapies to cabozantinib, rapid intracranial response to this small molecule was observed underscoring the potential of this strategy to overcome metastasis to the brain with MET-altered NSCLC [51]. Clinical studies with cabozantinib are currently recruiting for phase II in NSCLC patients with brain metastases.

Capmatinib (INC280)

Capmatinib is a competitive inhibitor with very potent and selective activity against MET compared to other kinases. It has been shown in vitro that cell lines made resistant to erlotinib, an EGFR inhibitor, could be resensitized after capmatinib treatment [52]. Results from a phase Ib/II study of patients with EGFR-mutated, MET-dysregulated NSCLC have shown promising responses to a combination of capmatinib and gefitinib (EGFR TKI) following disease progression from an only EGFR TKI treatment regimen. Recommended phase II dose was determined to be capmatinib 400 mg twice/day and gefitinib 250 mg once/day. Most common adverse events were nausea, peripheral edema, decreased appetite, rash, and increased amylase and lipase levels [53].

Crizotinib (PF-02341066)

Crizotinib is a small molecule inhibitor that competitively binds to the ATP-binding pocket of MET. Patients with MET amplification have shown remarkable response to this drug. Originally developed as a MET inhibitor, this compound also exhibited activity against anaplastic lymphoma kinase (ALK) [54] and ROS proto-oncogene 1 (ROS) rearrangements, leading to clinical trials targeting patients with this mutation. More recent studies have shown that patients with MET amplification and no ALK rearrangement treated with crizotinib have responded well in NSCLC [55] and squamous cell lung carcinoma [56]. We were the first to identify MET exon 14 skipping in patients and demonstrate that this variant can serve as a biomarker. Such biomarkers can aid clinical decisions by correctly identifying patients that would most likely benefit from MET-targeted therapies of differing class. Earlier this year, the US Food and Drug Administration (FDA) granted crizotinib a breakthrough therapy designation for the treatment of patients with metastatic NSCLC harboring MET exon 14 alterations that progress after receiving platinum-based chemotherapy. An expansion cohort of 21 patients from the PROFILE 1001 study with MET exon 14-altered NSCLC were treated with crizotinib 250 mg twice/day for 0.5–9.1+ months. Among 18 evaluable patients, 8 patients had partial responses and 9 patients had stable disease. None

had progressive disease. Most adverse events were grade 1 and 2 with one case of grade 3 edema and one case of grade 3 bradycardia. No grade 4 adverse events occurred [57]. This significant designation underscores the urgency for identifying additional biomarkers and our commitment to delivering personalized medicine for patients that carry these genomic alterations.

Foretinib (GSK1363089)

Foretinib is a multikinase inhibitor that targets MET and VEGFR2 and also exhibits an inhibitory effect against KIT, Flt-3, PDGFRb, and Tie-2. In vitro, foretinib blocks activation of MET and VEGFR2-induced signaling pathways. In vivo experiments show a dose-dependent decrease in tumor burden in a lung metastasis experimental model [58]. Foretinib has also shown to be effective against ROS1 mutations especially when acquired with crizotinib resistance. A clinical trial investigating the dosing and safety profile of combining foretinib and erlotinib was designed for advanced pretreated NSCLC patients. This regimen demonstrated response in an unselected group, but also some toxicity, suggesting future trial designs to select patients based on molecular profiling [59].

Glesatinib (MGCD265)

Glesatinib is a TKI that targets tumors with MET and AXL alterations. Nonclinical models have shown glesatinib to be effective in MET exon 14 skipping mutations [60]. It is currently being evaluated in phase II trials in NSCLC patients with MET alterations.

Savolitinib (AZD6094)

Savolitinib selectively inhibits the MET receptor, blocking the PI3K/AKT/MAPK-signaling pathway as well as downregulating MYC [61]. It is currently being evaluated in phase I clinical trials in combination with EGFR TKIs in NSCLC patients.

Tepotinib (MSC2156119J)

Tepotinib is a highly selective inhibitor against MET. In xenograft models, acquired resistance to EGFR TKIs via secondary EGFR T790 M mutations can be overcome with tepotinib treatment [62]. Tepotinib is currently being evaluated in combination with EGFR TKI gefitinib and also a separate trial in NSCLC patients with MET exon 14 skipping mutation and MET amplification.

Monoclonal Antibodies Against MET/HGF

Biological antagonists such as monoclonal antibodies can prevent ligand-receptor activation by either binding to the ligand or the receptor itself. As a result, downstream signaling events cannot be activated via this receptor. Several antibodies have been developed that target the extracellular portion of MET to block HGF binding as well as antibodies that target HGF to inhibit normal ligand binding to its receptor. Although monoclonal antibodies are larger in size (150 kDa) and more expensive to produce as compared to small molecule inhibitors, their target specificity is an advantage as it lessens the likelihood of toxicity to the patient.

This section will highlight several antibodies against HGF/MET that are currently under clinical investigation. Table 1 includes a more extensive list of the ongoing clinical trials with antibodies targeting HGF/MET.

Emibetuzumab (LY2875358)

Emibetuzumab is a bivalent antibody that blocks HGF- and MET-receptor interaction, leading to MET internalization and degradation [47]. A phase I study determined a tolerable dose for emibetuzumab to be 700–2000 mg as a monotherapy and in combination with erlotinib in NSCLC patients [63]. It is currently being investigated in phase II in combination with erlotinib.

Onartuzumab (MetMAb)

Onartuzumab is a monoclonal antibody that blocks the binding of HGF to the MET receptor. However, results from clinical trials in NSCLC patients show that onartuzumab is ineffective in improving clinical outcomes in (i) combination with current first-line chemotherapy in advanced nonsquamous cell NSCLC [64], (ii) combination with erlotinib in previously treated stage IIIB or IV NSCLC patients (Phase III) [65], and (iii) combination with platinum-doublet chemotherapy in advanced squamous cell NSCLC (Phase II) [66]. Patients enrolled in this trial were biomarker unselected.

Rilotumumab (AMG 102)

Rilotumumab is an anti-HGF antibody that prevents ligand binding to MET and its activation. A phase I/II trial of rilotumumab in combination with erlotinib was evaluated in previously treated NSCLC patients with metastatic disease. The results indicated a favorable safety profile and success in terms of disease control rate [67]. A phase Ib/II trial of rilotumumab or ganitumab in combination with etoposide

and carboplatin or cisplatin was evaluated in extensive-stage SCLC patients. This combination was determined to be tolerable, but overall outcomes in treating the disease were dismal [68].

Telisotuzumab Vedotin (ABBV-399)

Telisotuzumab vedotin (Teliso-V) is an antibody drug conjugate that targets the MET receptor. In the first in-human phase I trial for Teliso-V, NSCLC patients with MET-overexpressing tumors received monotherapy. The results of this innovative trial indicated favorable safety and tolerability responses and also showed promising antitumor activity in NSCLC patients with MET overexpression [69]. Current clinical investigations are now in phase II recruiting.

Mechanisms of Resistance

Inhibition of a specific kinase with small molecule inhibitors and/or biological antagonists adds selective pressure for tumor cells to acquire resistance through genetic mutations and nongenetic mechanisms [70]. For example, EGFR-mutated NSCLC tumors initially treated with EGFR TKIs can develop resistance to these agents through a secondary genetic mutation in the EGFR gene, activation of another receptor signaling axis, such as MET, and/or dysregulation of downstream pathways [71]. Although how lung cancer patients develop resistance to MET-targeting agents is not fully understood, this section will highlight the ongoing preclinical research to uncover the mechanisms of resistance to current MET therapeutics in solid tumors.

Genetic Mechanisms Contributing to Resistance

Acquiring a mutation at residue Y1230 in the MET activation loop was one mechanism that was observed to render MET TKI resistance in initially drug-sensitive gastric cells, in vitro and in vivo. As a result of this mutation, the interaction with the MET inhibitor is hindered and cells are able to bypass drug treatment [72]. It has also been shown in "MET-addicted" gastric cell lines that are initially sensitive to MET TKIs can acquire resistance through MET and KRAS gene amplification after incremental increases in drug concentrations. Resistant cells first acquired MET gene amplification and overexpression. Cells that subsequently harbored KRAS amplification lost dependence to MET and became dependent on wild-type KRAS as a way to become resistant to a MET TKI [73]. Although these preclinical data were observed in gastric cell lines, these findings may guide future studies investigating genetic mechanisms of resistance in "MET-addicted" lung cancer cells.

Alternative Pathways Contributing to Resistance

Various cell lines that are dependent on the MET pathway and are initially sensitive to MET TKIs, can develop resistance via kinase reprogramming. It has been shown that c-Myc is dissociated from the MET axis and overtaken by a variety of other kinases. As a result, this kinase reprogramming to take over c-Myc signaling provides a way for MET-addicted cancer cells to become resistant to agents targeting the MET axis [74]. Another mechanism by which gastric cells can become resistant to MET inhibitors is by utilizing the EGFR-signaling pathway to activate downstream effectors. This type of resistance was able to be overcome by dual inhibition of combined EGFR- and MET-targeted agents [72]. In MET-amplified NSCLC cell lines, it was found that alternative signaling pathways and downstream effectors, such as EGFR and PIK3CA were utilized to acquire resistance to capmatinib. A combination of EGFR, PIK3CA, and MET inhibitors could be an effective strategy to circumvent acquired resistance to capmatinib in MET-amplified NSCLC [75]. Lastly, in MET exon 14-mutated NSCLC, amplification and activation of KRAS was observed to mediate resistance to MET-targeted therapy in a patient-derived cell line [76] and genomic data from lung cancer patients [77]. In a patient with MET exon 14 skipping treated with crizotinib, a mutation in the MET kinase domain, D1228N, was acquired that conferred resistance to the inhibitor [78]. Other second-site mutations in the MET gene and mechanisms of resistance to MET inhibitors remain to be elucidated.

Future Directions

Much progress has been made in understanding the MET signaling axis and developing novel therapeutics to target this receptor with high specificity. However, as the landscape of precision medicine is constantly evolving, there is always more progress to be made for better and more effective clinical strategies. For example, despite the great advancements made with targeted therapies, clinical success can be out of reach for those patients that encounter severe side effects and toxicity, which remains to be a common issue among many. Furthermore, the affordability of these innovative drugs is also a challenge that impedes patients from being able to receive targeted treatments [79]. Managing these two factors is imperative as new therapeutic agents are discovered, designed, and brought into the market [79].

Inhibiting the MET/HGF signaling axis in novel ways are currently being investigated especially in the field of HGFA inhibitors and other serine protease inhibitors. These enzymes that are involved in the proteolytic cleavage of pro-HGF to active HGF can be blocked with antibodies and/or small molecules [80, 81]. Disabling the formation of active HGF may have therapeutic benefits in MET-addicted cancers since the ligand would not be able to activate the receptor. Currently, preclinical studies are extensively investigating optimal strategies for drug design [80].

As mechanisms of resistance to MET-targeted agents are continually being investigated, developing agents to overcome this resistance is crucial. Deciphering signaling pathways that are dysregulated when treated with certain agents will aid researchers and clinicians to bridge the translational gap between in vitro and in vivo models and strategies used in the clinic. Investigating novel and more effective combinatorial strategies to target MET and other RTKs can potentially attenuate the mechanisms of resistance that is acquired after MET-targeted therapy. It will also be interesting to see whether novel preclinical findings will come to clinical fruition. For example, a study that investigated simultaneously inhibiting MET and mitochondrial dynamics showed to be effective in MET-amplified NSCLC and mesothelioma cell lines. Targeting this crosstalk could possibly be an effective clinical strategy in MET-amplified NSCLC patients [33]. Lastly, a combination of MET inhibitors with immunotherapy could potentially be effective for lung cancer patients with MET exon 14 alterations since a considerable number of tumor samples were shown to express PD-L1 [82].

Discovering the MET exon 14 skipping mutation in patients and their remarkable response to MET TKIs demonstrates the need to determine additional biomarkers that will indicate good response to these agents. Equipped with the knowledge of potential biomarkers, clinicians will be able to make more effective decisions for their patients to achieve better responses to MET TKIs and monoclonal antibodies. As novel biomarkers that can be used to monitor MET-targeted agents with high specificity and sensitivity, and effective combinatorial strategies to overcome resistance are discovered, the ultimate purpose of precision medicine to guide clinical decision-making can be realized, bringing us closer to having clinical outcomes truly being "MET" in lung cancer.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68(1):7–30.
2. Bray F, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
3. Robinson DR, Wu YM, Lin SF. The protein tyrosine kinase family of the human genome. Oncogene. 2000;19(49):5548–57.
4. Du Z, Lovly CM. Mechanisms of receptor tyrosine kinase activation in cancer. Mol Cancer. 2018;17(1):58.
5. Hubbard SR. Structural analysis of receptor tyrosine kinases. Prog Biophys Mol Biol. 1999;71(3–4):343–58.
6. Lemmon MA, Schlessinger J. Cell signaling by receptor tyrosine kinases. Cell. 2010;141(7):1117–34.
7. Zwick E, Bange J, Ullrich A. Receptor tyrosine kinase signalling as a target for cancer intervention strategies. Endocr Relat Cancer. 2001;8(3):161–73.
8. Lawrence RE, Salgia R. MET molecular mechanisms and therapies in lung cancer. Cell Adhes Migr. 2010;4(1):146–52.
9. Gelsomino F, et al. Targeting the MET gene for the treatment of non-small-cell lung cancer. Crit Rev Oncol Hematol. 2014;89(2):284–99.

10. Cooper CS, et al. Molecular cloning of a new transforming gene from a chemically transformed human cell line. Nature. 1984;311(5981):29–33.
11. Stoker M, et al. Scatter factor is a fibroblast-derived modulator of epithelial cell mobility. Nature. 1987;327(6119):239–42.
12. Gherardi E, et al. Structural basis of hepatocyte growth factor/scatter factor and MET signalling. Proc Natl Acad Sci U S A. 2006;103(11):4046–51.
13. Maestrini E, et al. A family of transmembrane proteins with homology to the MET-hepatocyte growth factor receptor. Proc Natl Acad Sci U S A. 1996;93(2):674–8.
14. Rodrigues GA, Park M. Autophosphorylation modulates the kinase activity and oncogenic potential of the Met receptor tyrosine kinase. Oncogene. 1994;9(7):2019–27.
15. Ponzetto C, et al. A multifunctional docking site mediates signaling and transformation by the hepatocyte growth factor/scatter factor receptor family. Cell. 1994;77(2):261–71.
16. Furge KA, Zhang YW, Vande Woude GF. Met receptor tyrosine kinase: enhanced signaling through adapter proteins. Oncogene. 2000;19(49):5582–9.
17. Maulik G, et al. Activated c-Met signals through PI3K with dramatic effects on cytoskeletal functions in small cell lung cancer. J Cell Mol Med. 2002;6(4):539–53.
18. Marshall CJ. Specificity of receptor tyrosine kinase signaling: transient versus sustained extracellular signal-regulated kinase activation. Cell. 1995;80(2):179–85.
19. Gentile A, Trusolino L, Comoglio PM. The Met tyrosine kinase receptor in development and cancer. Cancer Metastasis Rev. 2008;27(1):85–94.
20. Birchmeier C, et al. Met, metastasis, motility and more. Nat Rev Mol Cell Biol. 2003;4(12):915–25.
21. Boccaccio C, et al. Induction of epithelial tubules by growth factor HGF depends on the STAT pathway. Nature. 1998;391(6664):285–8.
22. Abella JV, et al. Met/Hepatocyte growth factor receptor ubiquitination suppresses transformation and is required for Hrs phosphorylation. Mol Cell Biol. 2005;25(21):9632–45.
23. Sadiq AA, Salgia R. MET as a possible target for non-small-cell lung cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2013;31(8):1089–96.
24. Birchmeier C, Gherardi E. Developmental roles of HGF/SF and its receptor, the c-Met tyrosine kinase. Trends Cell Biol. 1998;8(10):404–10.
25. Chmielowiec J, et al. c-Met is essential for wound healing in the skin. J Cell Biol. 2007;177(1):151–62.
26. Mizuno K, et al. Hepatocyte growth factor stimulates growth of hematopoietic progenitor cells. Biochem Biophys Res Commun. 1993;194(1):178–86.
27. Olivero M, et al. Overexpression and activation of hepatocyte growth factor/scatter factor in human non-small-cell lung carcinomas. Br J Cancer. 1996;74(12):1862–8.
28. Ma PC, et al. Functional expression and mutations of c-met and its therapeutic inhibition with SU11274 and small interfering RNA in non–small cell lung cancer. Cancer Res. 2005;65(4):1479.
29. Sattler M, et al. A novel small molecule met inhibitor induces apoptosis in cells transformed by the oncogenic TPR-MET tyrosine kinase. Cancer Res. 2003;63(17):5462.
30. Ma PC, et al. c-Met: structure, functions and potential for therapeutic inhibition. Cancer Metastasis Rev. 2003;22(4):309–25.
31. Jagadeeswaran R, et al. Paxillin is a target for somatic mutations in lung cancer: implications for cell growth and invasion. Cancer Res. 2008;68(1):132–42.
32. Salgia R, et al. Expression of the focal adhesion protein paxillin in lung cancer and its relation to cell motility. Oncogene. 1999;18(1):67–77.
33. Wang J, et al. Inhibiting crosstalk between MET signaling and mitochondrial dynamics and morphology: a novel therapeutic approach for lung cancer and mesothelioma. Cancer Biol Ther. 2018:1–10.
34. Seiwert TY, et al. The MET receptor tyrosine kinase is a potential novel therapeutic target for head and neck squamous cell carcinoma. Cancer Res. 2009;69(7):3021–31.
35. Sattler M, Salgia R. c-Met and hepatocyte growth factor: potential as novel targets in cancer therapy. Curr Oncol Rep. 2007;9(2):102–8.

36. Schmidt L, et al. Germline and somatic mutations in the tyrosine kinase domain of the MET proto-oncogene in papillary renal carcinomas. Nat Genet. 1997;16(1):68–73.
37. Ma PC, et al. c-MET mutational analysis in small cell lung cancer: novel juxtamembrane domain mutations regulating cytoskeletal functions. Cancer Res. 2003;63(19):6272–81.
38. Krishnaswamy S, et al. Ethnic differences and functional analysis of MET mutations in lung cancer. Clin Cancer Res. 2009;15(18):5714–23.
39. Salgia R. Role of c-Met in cancer: emphasis on lung cancer. Semin Oncol. 2009;36:S52–8.
40. Siddiqui SS, et al. *C. elegans* as a model organism for in vivo screening in cancer: effects of human c-Met in lung cancer affect *C. elegans* vulva phenotypes. Cancer Biol Ther. 2008;7(6):856–63.
41. Lee CC, Yamada KM. Identification of a novel type of alternative splicing of a tyrosine kinase receptor. Juxtamembrane deletion of the c-met protein kinase C serine phosphorylation regulatory site. J Biol Chem. 1994;269(30):19457–61.
42. Frampton GM, et al. Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors. Cancer Discov. 2015;5(8):850–9.
43. Kong-Beltran M, et al. Somatic mutations Lead to an oncogenic deletion of met in lung cancer. Cancer Res. 2006;66(1):283.
44. Tan YH, et al. CBL is frequently altered in lung cancers: its relationship to mutations in MET and EGFR tyrosine kinases. PLoS One. 2010;5(1):e8972.
45. Tan YC, et al. Differential responsiveness of MET inhibition in non-small-cell lung cancer with altered CBL. Sci Rep. 2017;7(1):9192.
46. Hewelt B, et al. The DNA walk and its demonstration of deterministic Chaos- relevance to genomic alterations in lung cancer. Bioinformatics. 2019. (in press)
47. Miranda O, Farooqui M, Siegfried JM. Status of agents targeting the HGF/c-Met axis in lung cancer. Cancers. 2018;10(9):280.
48. Engelman JA, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science. 2007;316(5827):1039–43.
49. Puri N, Salgia R. Synergism of EGFR and c-Met pathways, cross-talk and inhibition, in non-small cell lung cancer. J Carcinog. 2008;7:9.
50. Wakelee HA, et al. A phase Ib/II study of cabozantinib (XL184) with or without erlotinib in patients with non-small cell lung cancer. Cancer Chemother Pharmacol. 2017;79(5):923–32.
51. Klempner SJ, et al. Intracranial activity of cabozantinib in MET exon 14-positive NSCLC with brain metastases. J Thorac Oncol. 2017;12(1):152–6.
52. Lara MS, et al. Preclinical evaluation of MET inhibitor INC-280 with or without the epidermal growth factor receptor inhibitor erlotinib in non-small-cell lung cancer. Clin Lung Cancer. 2017;18(3):281–5.
53. Wu YL, et al. Phase Ib/II study of capmatinib (INC280) plus gefitinib after failure of Epidermal Growth Factor Receptor (EGFR) inhibitor therapy in patients with EGFR-mutated, MET factor-dysregulated non-small-cell lung cancer. J Clin Oncol. 2018:JCO2018777326.
54. Nwizu T, et al. Crizotinib (PF02341066) as a ALK /MET inhibitor- special emphasis as a therapeutic drug against lung cancer. Drugs Future. 2011;36(2):91–9.
55. Ou SH, et al. Activity of crizotinib (PF02341066), a dual mesenchymal-epithelial transition (MET) and anaplastic lymphoma kinase (ALK) inhibitor, in a non-small cell lung cancer patient with de novo MET amplification. J Thorac Oncol. 2011;6(5):942–6.
56. Schwab R, et al. Major partial response to crizotinib, a dual MET/ALK inhibitor, in a squamous cell lung (SCC) carcinoma patient with de novo c-MET amplification in the absence of ALK rearrangement. Lung Cancer. 2014;83(1):109–11.
57. Drilon AE, et al. Efficacy and safety of crizotinib in patients (pts) with advanced MET exon 14-altered non-small cell lung cancer (NSCLC). J Clin Oncol. 2016;34(15_suppl):108–108.
58. Qian F, et al. Inhibition of tumor cell growth, invasion, and metastasis by EXEL-2880 (XL880, GSK1363089), a novel inhibitor of HGF and VEGF receptor tyrosine kinases. Cancer Res. 2009;69(20):8009–16.

59. Leighl NB, et al. A phase I study of foretinib plus erlotinib in patients with previously treated advanced non-small cell lung cancer: Canadian cancer trials group IND.196. Oncotarget. 2017;8(41):69651–62.
60. Engstrom LD, et al. Glesatinib exhibits antitumor activity in lung cancer models and patients harboring MET exon 14 mutations and overcomes mutation-mediated resistance to type I MET inhibitors in nonclinical models. Clin Cancer Res. 2017;23(21):6661.
61. Henry RE, et al. Acquired savolitinib resistance in non-small cell lung cancer arises via multiple mechanisms that converge on MET-independent mTOR and MYC activation. Oncotarget. 2016;7(36):57651–70.
62. Friese-Hamim M, et al. The selective c-Met inhibitor tepotinib can overcome epidermal growth factor receptor inhibitor resistance mediated by aberrant c-Met activation in NSCLC models. Am J Cancer Res. 2017;7(4):962–72.
63. Rosen LS, et al. A first-in-human phase I study of a bivalent MET antibody, emibetuzumab (LY2875358), as monotherapy and in combination with erlotinib in advanced cancer. Clin Cancer Res. 2017;23(8):1910.
64. Wakelee H, et al. Efficacy and safety of onartuzumab in combination with first-line bevacizumab- or pemetrexed-based chemotherapy regimens in advanced non-squamous non-small-cell lung cancer. Clin Lung Cancer. 2017;18(1):50–9.
65. Spigel DR, et al. Results from the phase III randomized trial of onartuzumab plus erlotinib versus erlotinib in previously treated stage IIIB or IV non–small-cell lung cancer: METLung. J Clin Oncol. 2016;35(4):412–20.
66. Hirsch FR, et al. Efficacy and safety results from a phase II, placebo-controlled study of onartuzumab plus First-line platinum-doublet chemotherapy for advanced squamous cell non-small-cell lung cancer. Clin Lung Cancer. 2017;18(1):43–9.
67. Tarhini AA, et al. Phase 1/2 study of rilotumumab (AMG 102), a hepatocyte growth factor inhibitor, and erlotinib in patients with advanced non-small cell lung cancer. Cancer. 2017;123(15):2936–44.
68. Glisson B, et al. A randomized, placebo-controlled, phase 1b/2 study of rilotumumab or ganitumab in combination with platinum-based chemotherapy as first-line treatment for extensive-stage small-cell lung cancer. Clin Lung Cancer. 2017;18(6):615–625 e8.
69. Strickler JH, et al. Dose-escalation and -expansion study of telisotuzumab vedotin, an antibody-drug conjugate targeting c-Met, in patients with advanced solid tumors. J Clin Oncol. 2018:JCO2018787697.
70. Salgia R, Kulkarni P. The genetic/non-genetic duality of drug 'resistance' in cancer. Trends Cancer. 2018;4(2):110–8.
71. Morgillo F, et al. Mechanisms of resistance to EGFR-targeted drugs: lung cancer. ESMO Open. 2016:**1**(3).
72. Qi J, et al. Multiple mutations and bypass mechanisms can contribute to development of acquired resistance to MET inhibitors. Cancer Res. 2011;71(3):1081.
73. Cepero V, et al. MET and KRAS gene amplification mediates acquired resistance to MET tyrosine kinase inhibitors. Cancer Res. 2010;70(19):7580.
74. Shen A, et al. c-Myc alterations confer therapeutic response and acquired resistance to c-met inhibitors in MET-addicted cancers. Cancer Res. 2015;75(21):4548.
75. Kim S, et al. Acquired resistance of MET-amplified non-small cell lung cancer cells to the MET inhibitor capmatinib. J Korean Cancer Assoc. 2018. (in press).
76. Bahcall M, et al. Amplification of wild-type KRAS imparts resistance to crizotinib in MET exon 14 mutant non–small cell lung cancer. Clin Cancer Res. 2018;24(23):5963–76.
77. Suzawa K, et al. Activation of KRAS mediates resistance to targeted therapy in MET exon 14 mutant non-small cell lung cancer. Clin Cancer Res. 2019;25(4):1248–60.
78. Heist RS, et al. Acquired resistance to crizotinib in NSCLC with MET exon 14 skipping. J Thorac Oncol. 2016;11(8):1242–5.
79. Beck A, et al. Strategies and challenges for the next generation of therapeutic antibodies. Nat Rev Immunol. 2010;10:345.

80. Janetka JW, Jr RAG. Inhibitors of the growth-factor activating proteases matriptase, hepsin and HGFA: strategies for rational drug design and optimization. In: Extracellular targeting of cell signaling in c.ancer. Hoboken, NJ: Wiley; 2018.
81. Kirchhofer D, Eigenbrot C, Lazarus RA. Inhibitory antibodies of the proteases HGFA, matriptase and hepsin. In: Extracellular targeting of cell signaling in cancer. Hoboken, NJ: Wiley; 2018.
82. Sabari JK, et al. PD-L1 expression, tumor mutational burden, and response to immunotherapy in patients with MET exon 14 altered lung cancers. Ann Oncol. 2018;29(10):2085–91.