Cancer Letters 588 (2024) 216780

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

# Unlocking c-MET: A comprehensive journey into targeted therapies for breast cancer

Parham Jabbarzadeh Kaboli [a], Hsiao-Fan Chen [a], Ali Babaeizad [b], Kiarash Roustai Geraylow [b], Hirohito Yamaguchi [a], Mien-Chie Hung [a,c,*]

[a] Graduate Institute of Biomedical Sciences, Institute of Biochemistry and Molecular Biology, Research Center for Cancer Biology, Cancer Biology and Precision Therapeutics Center, and Center for Molecular Medicine, China Medical University, Taichung, 406, Taiwan
[b] Faculty of Medicine, Semnan University of Medical Sciences, Semnan, Iran
[c] Department of Biotechnology, Asia University, Taichung, 413, Taiwan

ARTICLE INFO

*Keywords:*
c-MET receptor
Breast cancer
Hepatocyte growth factor receptor
Targeted therapy
Tumorigenesis
Clinical approach

ABSTRACT

Breast cancer is the most common malignancy among women, posing a formidable health challenge worldwide. In this complex landscape, the c-MET (cellular-mesenchymal epithelial transition factor) receptor tyrosine kinase (RTK), also recognized as the hepatocyte growth factor (HGF) receptor (HGFR), emerges as a prominent protagonist, displaying overexpression in nearly 50% of breast cancer cases. Activation of c-MET by its ligand, HGF, secreted by neighboring mesenchymal cells, contributes to a cascade of tumorigenic processes, including cell proliferation, metastasis, angiogenesis, and immunosuppression. While c-MET inhibitors such as crizotinib, capmatinib, tepotinib and cabozantinib have garnered FDA approval for non-small cell lung cancer (NSCLC), their potential within breast cancer therapy is still undetermined. This comprehensive review embarks on a journey through structural biology, multifaceted functions, and intricate signaling pathways orchestrated by c-MET across cancer types. Furthermore, we highlight the pivotal role of c-MET-targeted therapies in breast cancer, offering a clinical perspective on this promising avenue of intervention. In this pursuit, we strive to unravel the potential of c-MET as a beacon of hope in the fight against breast cancer, unveiling new horizons for therapeutic innovation.

## 1. Introduction

Breast cancer, accounting for 24.5% of all new cancer cases among males and females, is the most prevalent malignancy among women, with 2,261,419 newly diagnosed patients and a staggering 684,996 associated deaths in 2020 [1]. Its complex nature makes prognosis and treatment outcomes highly variable, underscoring the significance of subtype classification. Currently, breast cancer is categorized into four primary subtypes, primarily hinging on hormone receptor (HR) and human epidermal growth factor receptor-2 (HER2) expression; $HR^+$ and $HER2^-$, $HR^+$ and $HER2^+$, $HR^-$ and $HER2^+$, and triple-negative breast cancer (TNBC) devoid of HR and HER2 receptors. Hormone therapies, such as estrogen receptor (ER) antagonists and aromatase inhibitors, are used for $HR^+$ cases, while HER2-targeted therapies like trastuzumab and pertuzumab are employed in $HER2^+$ breast cancer [2,3]. Yet, TNBC, marked by the absence of these therapeutic targets, emerges as the most aggressive and unfavorable subtype, demanding innovative approaches [4]. In recent years, several novel treatments for TNBC have been approved, including Poly (ADP-ribose) polymerase (PARP) inhibitors, programmed cell death protein 1 (PD-1) inhibitors, and TROP2-targeting antibody-drug conjugates, significantly broadening therapeutic horizons. Nonetheless, resistance remains a persistent challenge across all breast cancer subtypes, cementing its status as a formidable adversary for patients battling this disease [2,5].

Receptor tyrosine kinases (RTKs) play pivotal roles in cellular processes spanning development, proliferation, survival, differentiation, motility, and tissue homeostasis. However, aberrant RTK activity is a hallmark feature of various malignancies, encompassing multiple solid tumors and hematologic cancers. Among these, the cellular-mesenchymal epithelial transition factor (c-MET), also known as hepatocyte growth factor (HGF) receptor (HGFR), plays a critical role as an RTK encoded by the *MET* proto-oncogene, predominantly expressed in

* Corresponding author. Graduate Institute of Biomedical Sciences, Institute of Biochemistry and Molecular Biology, Research Center for Cancer Biology, Cancer Biology and Precision Therapeutics Center, and Center for Molecular Medicine, China Medical University, Taichung, 406, Taiwan.
*E-mail addresses:* mhung@cmu.edu.tw, mhung77030@gmail.com (M.-C. Hung).

https://doi.org/10.1016/j.canlet.2024.216780
Received 20 December 2023; Received in revised form 18 February 2024; Accepted 29 February 2024
Available online 8 March 2024

epithelial cells across diverse tissues. Its ligand, HGF, secreted by neighboring mesenchymal cells, stimulates c-MET, though the receptor can also activate independently through interactions with other membrane receptors and lipids [6,7]. Notably, c-MET exhibits heightened expression in epithelial cancer cells within lung, esophageal, renal, and gastrointestinal tumors. Moreover, extensive research has consistently demonstrated c-MET overexpression in breast cancer, with TNBC displaying the highest levels [8–12]. Elevated serum levels of HGF have even been proposed as a prognostic indicator for breast cancer [13].

Compellingly, studies have elucidated c-MET's role in bolstering resistance to targeted therapies in TNBC and prostate cancer, hepatocellular carcinoma, and gastric cancer (GC) [14–18], rendering it an attractive therapeutic target for these cancers. Despite the approval of c-MET inhibitor capmatinib for non-small cell lung cancer (NSCLC) [19], no U.S. Food and Drug Administration (FDA)-approved c-MET inhibitor exists for breast cancer. However, tivantinib, a less specific c-MET inhibitor, has successfully completed a phase II clinical trial in TNBC patients [20].

Despite significant advances in breast cancer treatment over the past five years, an unfilled void persists in the literature—a comprehensive review addressing c-MET-targeted therapy in breast cancer. In this review, we endeavor to bridge this gap, offering insights from recent clinical studies, exploring c-MET's potential as a therapeutic target, and dissecting the intricate molecular mechanisms governing c-MET regulation.

## 2. Structural biology of c-MET and HGF

The MET gene, sprawling over 120 kb and harboring 21 exons, is located on human chromosome 7q31. The synthesis of c-MET commences as a nascent 150 kDa protein, later undergoing cleavage at residues R307-S308, orchestrated by the furin endopeptidase. This proteolytic event produces the mature c-MET heterodimer, characterized by a 32 kDa extracellular α-chain and a 120 kDa transmembrane β-chain, conjoined by disulfide bonds [21]. Within the extracellular region of c-MET, a Semaphorin (SEMA) domain, a cysteine-rich hinge known as Plexin-Semaphorin-Integrin (PSI), and four immunoglobulin–plexin–transcription domains (IPT 1–4) reside, each with its distinct role. In the intracellular domain, c-MET possesses a juxtamembrane (JM) domain, a tyrosine kinase domain, and a pivotal docking site at its c-terminus (Fig. 1a) [22]. Several mutations in c-MET, predominantly concentrated in the SEMA (E168D, L299F, S323G, and N375S) and JM (R988C, R988C + T1010I, and S1058P) domains, exert pronounced impacts on c-MET's interaction with HGF. Moreover, alternative splicing events can lead to the exclusion of the JM domain (exon 14/15), culminating in sustained c-MET activation (Fig. 1a) [23].

HGF, secreted initially as a single-chain precursor, undergoes proteolytic cleavage catalyzed by a trypsin-like protease, targeting the RV residues within the Q-L-R494-V495 motif. This process transforms HGF into a mature heterodimer comprised of a 57 kDa α-chain and a 26 kDa β-chain, united by a disulfide bond. The α-chain flaunts an N-terminal hairpin loop followed by four Kringle-like domains (K1-4), while the β-chain houses a serine protease homology (SPH) domain (Fig. 1b) [22].

Both the mature and immature forms of HGF retain the capacity to bind to c-MET, but only the mature form can activate it [24]. The HGF-α and HGF-β components boast high- and low-affinity c-MET-binding sites, respectively. HGF-β, with its low affinity, forms a binding liaison with the α-SEMA domain. At the same time, HGF-α, the high-affinity counterpart, has been reported to engage with either the SEMA domain or the IPT 3–4 domain. Recent findings, however, underline the pivotal role played by the IPT1-2 domain in stabilizing two c-MET dimers and a single HGF dimer, facilitating c-MET tetramerization (Fig. 1c). Intriguingly, this study suggests the existence of four interfaces between c-MET-SEMA αβ and HGF-α, enabling a single HGF molecule to concurrently bind with two c-MET receptors (Table 1) [21]. Additionally, an immature variant of HGF can emerge through mRNA alternative splicing, known as NK1, composed of the N-terminal and K1 regions of HGF [31]. The dimeric form of NK1 exhibits the ability to recruit two c-MET receptors [21]. While the activation of c-MET necessitates the presence of just one HGF molecule, stabilizing HGF-*c*-MET interaction mandates the synergy of two HGF molecules along with heparin, which binds to the N-terminus of HGF. Furthermore, extracellular glycosaminoglycans, such as heparin, heparan sulfate, and dermatan sulfate, intensify the affinity of HGF for c-MET [25,26].

## 3. *MET* mutations

### 3.1. *MET-exon-14-skipping*

c-MET downregulation is a critical mechanism in preventing excessive receptor signaling, and identified regulatory mechanisms focus on the JM region of the receptor's cytoplasmic segment, encoded explicitly by exon 14. Within *MET* exon 14, Y1003 is a binding site for casitas B-lineage lymphoma (CBL), an E3 ubiquitin ligase targeting c-MET for ubiquitin-mediated degradation [27]. Skipping exon 14 obstructs CBL-mediated c-MET protein degradation, accumulating c-MET and the potential for oncogenic transformation. Moreover, *MET*Δ14EX has been detected in approximately 3% of lung adenocarcinomas, 2% of other lung neoplasms, 0.5% of brain gliomas, and 0.5% of carcinomas of unknown primary origin [28].

Varied response rates from single-treatment targeted therapies against c-MET alone in METΔ14EX-driven cancers, and the specific molecular mechanisms driving cancer progression and poor prognosis remain less explored [29]. However, recent findings suggest mutual exclusivity between *MET*Δ14EX and mutations in other oncogenes, such as epidermal growth factor receptor (*EGFR*), *KRAS*, and *BRAF* mutations, sparking increased interest in its therapeutic potential [30]. Multivariable analysis indicates that *MET* exon 14 mutation independently correlates with a poor prognosis. Furthermore, *MET*Δ14EX-mutated patients undergoing targeted therapy exhibit poor long-term survival due to acquired drug resistance [31,32].

SMAD2 is a member of the suppressor of mothers against decapentaplegic (SMAD) protein family and acts as a downstream effector in the transforming growth factor (TGF)-β signaling pathway. TGF-β receptor type I (TβRI) phosphorylates SMAD2, inducing a conformational change, allowing it to form a complex with SMAD4 and translocate to the nucleus [33]. Within the nucleus, the SMAD2/SMAD4 complex interacts with other transcription factors, regulating the expression of various target genes involved in cellular processes and contributing to tumor metastasis and recurrence. Studies suggest c-MET interacts with SMAD2, implying that c-METΔ14EX leads to SMAD2 phosphorylation and activation. Further exploration of the mechanisms underlying SMAD2 signaling may offer insights into cancer progression and recurrence in *MET*Δ14EX-altered patients, potentially leading to the development of novel therapeutic strategies [34].

Moreover, c-MET exon 14 skipping alteration is implicated in resistance to targeted therapies and immunotherapy in various cancers, making it a crucial biomarker for predicting treatment response [28,30,32,35,36]. Further research dissecting the molecular signaling steps involved in c-METΔ14EX-driven tumorigenesis and unique mesenchymal differentiation will provide opportunities to highlight potential molecular targets for alternative and combination approaches for more effective therapies. Investigative findings have unveiled significant revelations regarding the mechanisms by which c-METΔ14EX stimulates the receptor kinase's activity, ultimately facilitating cell migration, invasion, metastasis, and recurrence [37,38].

While investigating the tumorigenic role of c-METΔ14EX in tumor invasion, metastasis, and recurrence, researchers successfully generated several homologous cell models across diverse tumors using the CRISPR genome editing system. According to this study, the E3 ligase c-CBL emerges as the primary regulator of c-MET endocytosis, exerting control through interaction with the c-MET JM region. Consequently, the

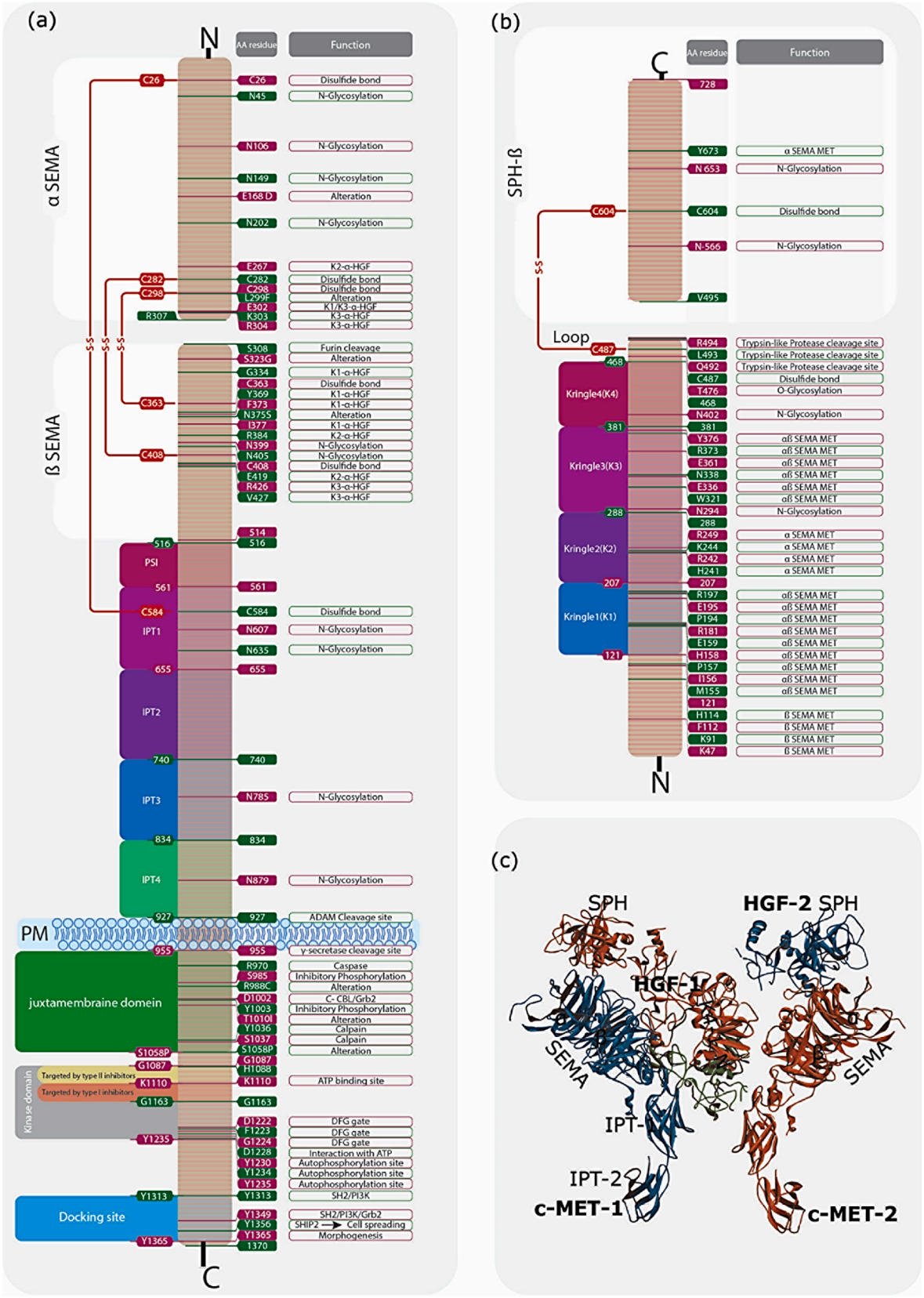


**Fig. 1. Molecular structure of c-MET and HGF. (a)** c-MET domains, important residues, and their functional roles. **(b)** HGF domains, important residues, and their functional roles. **(c)** The 3D structure of two HGF dimers interacted with two c-MET dimers (PDB IDs: 7MO9 and 7MOA). [21].

**Table 1**
**Important amino acid residues of one HGF dimer interacting with two c-MET dimers.** One HGF-αβ dimer interacted with one c-MET-αβ dimer by four interfaces (I-IV). HGF-α (N–K2–K3 domains) has a high affinity for the c-MET SEMA domain. On the other hand, interface IV shows interactions of HGF-β (SPH domain) with the c-MET-α-SEMA domain and has a weaker affinity. Furthermore, the same HGF-α-K1 domain has the potential to interact with the C-terminal of c-MET-α-SEMA of the second c-MET dimer (c-MET II) (Interface V) [21].

| Interface I | | Interface II | | Interface III | | Interface IV | | Interface V | | |
|---|---|---|---|---|---|---|---|---|---|---|
| HGFα N | c-MET I SEMA-β | HGFα K2 | c-MET I SEMA- αβ | HGFα K3 | c-MET I SEMA- αβ | HGFβ SPH | c-MET I SEMA-α | HGFα K1 | | c-MET II SEMA-αβ |
| K47 | N393 | H241 | E267 | W321 | E302 | Y673 | ? | M155 | I156 | E302 |
| K91 | F398 | R242 | R384 | E336 | K303 | | | P157 | H158 | G334 |
| F112 | | K244 | E419 | N338 | R304 | | | E159 | R181 | Y369 |
| H114 | | R249 | | E361 | R426 | | | P194 | E195 | F373 |
| | | | | R373 | V427 | | | R197 | | I377 |
| | | | | Y376 | | | | | | |

absence of the JM region in c-METΔ14EX weakens its interaction with c-CBL, leading to the evasion of c-METΔ14EX endocytosis [34]. As a result, c-METΔ14EX displays heightened and sustained activity due to degradation impairment, fostering cell migration and invasion *in vitro* independently of HGF and promoting metastasis and recurrence *in vivo* [39]. Despite previous associations of c-MET overexpression with metastasis and poor prognosis, experiments reveal that the invasion and metastasis induced by c-METΔ14EX do not necessitate stimulation by HGF, underscoring the autonomy and significance of c-METΔ14EX as a pivotal regulator. Its constant activation propels the malignant process by equipping tumor cells with metastatic potential [34].

### 3.2. *MET fusions*

*MET* fusions act as rare but potent driver genes, instigating downstream signaling pathways and fostering cell growth. Consequently, they are deemed treatable genomic variations, rendering c-MET suppression a potential therapeutic approach for individuals with *MET* fusions. For individuals who develop *MET* fusions after becoming resistant to tyrosine kinase inhibitors (TKIs) that target primary genomic changes, such as EGFR driver mutations, it is recommended to consider using a c-MET-TKI either on its own or in combination with TKIs that address primary genomic alterations, like EGFR-TKIs. This approach is suggested for a rational and effective salvage treatment [40].

*MET* fusions, characterized by *MET* gene rearrangements, yield fusion proteins like echinoderm microtubule-associated protein-like 4 (*EML4*)-*MET*, translocated promoter region (*TPR*)-*MET*, protein tyrosine phosphatase receptor type Z1 (*PTPRZ1*)-*MET*, and CAP-GLY-domain-containing linker protein 2 (*CLIP2*)-*MET*. These fusions signify diverse genetic alterations linked to *MET*, and ongoing research may unveil additional fusion events with distinct partner genes across various malignancies [41–43]. Nevertheless, current knowledge on *MET* fusions is limited, with limited investigations in large tumor cohorts. RNA sequencing of a subset of samples (64%) revealed fusion transcripts involving cancer-associated genes like Fibroblast growth factors 2 (*FGFR2*), neurotrophic tyrosine receptor kinase 2 (*NTRK2*), and phosphatidylinositol 3-kinase regulatory subunit beta (*PIK3R2*), with frequent *MET* involvement, including two previously undescribed *MET* fusions [44,45]. Despite genomic differences, *MET*-fusion-bearing pediatric glioblastomas did not form a distinct cluster, and none expressed the short *MET* variant observed in 6% of high-grade gliomas [43].

Furthermore, in lung cancer patients, a small percentage (0.2–0.3%) had *MET* fusions across various *MET* gene exons, with intragenic *MET* fusions being particularly prevalent (52.6%). Crizotinib effectively treated *MET* fusions, including a newly identified *EML4-MET* fusion, even in patients with multiple treatment failures [46]. These findings suggest that acquired *MET* fusions exhibit regional selectivity, often impacting exons encoding the extracellular region. Notably, primary and acquired *MET*-fused genes differ significantly, indicating distinct functional roles and disease influences [46]. A recent multicenter study in China identified *MET* fusions in solid tumors, with an incidence of 0.34% across various cancer types and 0.07% specifically in lung cancer [47]. This study noted consistency in two *MET* fusions, *COMETT* (*LINC01510*)-*MET* and protein kinase cAMP-dependent type I alpha regulatory subunit 1A (*PRKAR1A*)-*MET*, detected in lung cancer with prior identifications. These consistent findings underscore the imperative for additional investigation into *MET* fusions across diverse tumor populations [47]. Additionally, secondary mutations in the *MET* gene, particularly D1228 H/N and D1246 N variations, may serve as potential resistance mechanisms against c-MET inhibitors in patients with newly diagnosed *MET* fusions [48].

### 3.3. *MET amplification*

*MET* amplification is specifically underscored as a resistance mechanism affecting patients with *EGFR*, *ALK*, *RET*, and *ROS1* alterations in NSCLC. This phenomenon, observed in approximately 1–3% of NSCLC cases, can occur *de novo* or as a secondary resistance mechanism to targeted therapies [49]. Its prevalence ranges from 5 to 21% after first/second-generation EGFR-TKI treatment, 7–15% after first-line osimertinib therapy, and 5–50% in osimertinib resistance after further-line treatment [50]. *MET* amplification leads to EGFR-TKI resistance, potentially associated with ErbB3 (HER3) phosphorylation, activating phosphoinositide 3-kinases (PI3K)/AKT and MEK/MAPK pathways [51,52]. Strategies, including anti-HER3 antibodies and third-generation EGFR-TKIs, have been proposed to counter this resistance. Additionally, c-MET-TKIs and EGFR-TKIs exhibit a synergistic effect in inhibiting cell proliferation [53].

In *ALK*-rearranged NSCLC, around 50% of resistance to second-generation ALK-TKIs is ALK-independent, involving c-MET overactivation [54]. Crizotinib, initially a ALK receptor TKI, can overcome c-MET activation-mediated resistance. However, further evidence is required to clarify *MET* amplification's role in ALK downstream signaling and ALK-TKI resistance [55]. In *RET*-rearranged NSCLC, *MET* amplification acts as a resistance mechanism to RET-specific inhibitors, and combinational therapy with MET/ALK/ROS1-TKIs shows efficacy in resistant tumors [56,57].

Furthermore, acquired *MET* amplification, as a resistance mechanism, can bypass the initial oncogene driver in NSCLC. The hypothesis is that inhibiting c-MET signaling and sustained inhibition of the primary oncogene driver could overcome this resistance. Recent developments include categorizing c-MET-targeting drugs as small molecule inhibitors, antibodies against the c-MET receptor, and antibody-drug conjugates. Preclinical studies suggest that adding a c-MET inhibitor to *MET*-amplified EGFR-mutant-resistant NSCLC cells may effectively counter resistance [58]. In NSCLC, crizotinib demonstrated superior efficacy in immunotherapy and chemotherapy in patients with primary *MET* amplification in first- and second-line treatments [59]. Disease control rates for crizotinib, immunotherapy, and chemotherapy were 81.8%, 72.7%, and 63.6%, respectively. Notably, patients with *MET* amplification and high programmed cell death 1 ligand 1 (PD-L1) expression (>50%) had a median progression-free survival (PFS) time of only 77.5

days after immunotherapy. A meta-analysis revealed that the median PFS durations following crizotinib and immunotherapy were 4.57 and 2.94 months, respectively [59]. Chemotherapy plus bevacizumab exhibited superior efficacy for patients with acquired *MET* amplification compared to c-MET-TKIs ± EGFR-TKIs (310.0 days vs. 73.5 days). Therefore, immunotherapy showed a limited response in patients with *MET* alterations, even those with concurrent high PD-L1 expression. c-MET-TKIs could be considered as an optional treatment with promising efficacy. However, chemotherapy plus bevacizumab might benefit the subpopulation of patients with acquired *MET* amplification after the failure of EGFR-TKIs [59]. Despite various studies identifying *MET* amplification's role in acquired resistance to targeted agents, further elucidation through preclinical and clinical studies is warranted.

## 4. Internalization and degradation of c-MET

Recent studies have shed light on the intricate regulation of c-MET degradation. Notably, c-MET downregulation occurs through diverse mechanisms, encompassing (1) intracellular proteasomal and lysosomal systems, (2) collaborative actions of extracellular and intracellular metalloproteases, and (3) pathways associated with apoptosis and necrosis [60]. The initiation of c-MET internalization is triggered by its binding with HGF at the extracellular domain, with subsequent phosphorylation events at Y1003 orchestrating the termination of canonical c-MET signaling. This termination is achieved by inhibiting auto-phosphorylation and promoting ubiquitination. Once internalized, c-MET faces two fates: recycling to the plasma membrane or degradation within lysosomes, with the latter serving as the primary route for c-MET degradation (Fig. 2) [61].

Furthermore, c-CBL-dependent ubiquitination, contingent on c-MET Y1003 phosphorylation, plays a pivotal role in guiding c-MET toward lysosomal degradation [62]. Conversely, both inside and outside the cell, metalloproteases cleave c-MET independently of HGF binding, offering an alternative regulatory mechanism. Among these, a disintegrin and metalloproteinase (ADAM)-10 emerges as a prominent sheddase for the c-MET receptor, executing cleavage at the extracellular portion of c-MET at the plasma membrane, generating soluble c-MET. Intriguingly, the presence of tissue inhibitor of metalloproteinases (TIMP-1) enhances c-MET phosphorylation, thereby promoting tumorigenic processes. Inhibition of ADAM-10 has been found to instigate metastasis in colorectal, liver, and lung cancer cells [63,64]. ADAM-mediated cleavage results in the generation of two distinct fragments: (1) a 50 kDa α-chain coupled with a C-terminal truncated β-chain, released into the extracellular milieu, and (2) a 55 kDa transmembrane C-terminal fragment that undergoes γ-secretase-mediated release into the cytoplasm, followed by subsequent degradation through the proteasomal complex (Fig. 2) [65,66].

In addition, additional proteolytic processes involving caspase- and calpain-dependent cleavages, primarily within the JM domain, give rise to 40 kDa and 45 kDa c-MET fragments. Remarkably, the p40 MET fragment has been demonstrated to have the ability to induce apoptosis upon overexpression. These 40 kDa fragments also contribute to calcium transfer from the endoplasmic reticulum (ER) to mitochondria, further enhancing apoptotic processes [67,68]. Moreover, specific protein kinase C (PKC) isotypes have been implicated in regulating c-MET trafficking and recycling. Notably, PKCε has been linked to c-MET recycling. In contrast, PKCα plays a pivotal role in mediating perinuclear transportation of c-MET, particularly within membrane structures originating from the ER and Golgi apparatus [69].

On the other hand, full-length c-MET is known to be activated and translocate into the nucleus upon reactive oxygen species (ROS) stimulation [14,70]. Previous studies have shown that RTKs of the EGFR family enter the nucleus via the INTERNET (integral trafficking from the ER to the nuclear envelope transport) pathway [71]. It has been suggested that nuclear transport of c-MET induced by ROS is also carried out through the same mechanism [30]. Interestingly, c-MET has been suggested to bind to DNA damage repair proteins such as PARP and Ku70/80 proteins and promote their functions in the nucleus [14,70].

## 5. The regulation of c-MET downstream signaling

c-MET and HGF undergo specific glycosylation processes. c-MET features N-linked glycosylation at eleven asparagine residues, whereas HGF possesses four N-linked glycosylation sites and an O-linked glycosylation site [72,73]. O-linked glycosylation, impacting HGF-induced dimerization and c-MET activation, has also been detected on c-MET, although its precise location remains unidentified [74]. Previous research has demonstrated that N-glycans within the SEMA domain of c-MET positively regulate its function. In contrast, N-linked glycosylation in regions outside the SEMA domain negatively influences c-MET/HGF signaling [73].

Upon binding to its ligand, c-MET undergoes dimerization and phosphorylation at specific tyrosine residues, initiating downstream signaling. Phosphorylation at positions tyrosine (Y) 1003, 1234, 1235, 1313, 1349, and 1356 on c-MET leads to the recruitment of several Src homology 2 (SH2)-containing proteins, including SH2-containing phosphatidylinositol 3,4,5-trisphosphate 5-phosphatase (SHIP)-2, growth factor receptor-bound protein 2 (GRB2), GRB2-associated-binding protein 1 (GAB1), and PI3K [75]. Following HGF stimulation, c-MET experiences phosphorylation initially at the tyrosine kinase domain (Y1234/1235), followed by the JM domain (Y1003) and the C-terminal docking site (Y1349/1356). Phosphorylation at the JM domain leads to c-MET downregulation in a c-CBL-dependent manner. Conversely, phosphorylation at the docking site recruits various signaling proteins, including GRB2, GAB1, PI3K, SHIP2, PLC-γ1, and Signal transducer and activator of transcription (STAT)-3, culminating in the activation of diverse downstream signaling pathways [22](Fig. 3).

The PI3K/Akt signaling pathway represents one of the key cascades initiated by c-MET activation. Specifically, the p85 PI3K subunit binds to phosphorylated Y1313, Y1349, and Y1356 on c-MET. Notably, both the N-terminal and C-terminal SH2 domains of p85 exhibit the highest affinity for phosphorylated Y1313-*c*-MET [76]. Concerning breast cancer progression and its associations with angiogenesis and metastasis, it has been observed that c-MET protein levels were elevated in HER-2 overexpressing and Luminal B subtypes. Interestingly, downstream signaling pathways linked to c-MET, including RAS-MAPK, PI3K-Akt, and angiogenesis, displayed heightened activity in Luminal B subtype tumors and lymph node metastasis cases [77]. However, in the context of drug-resistant tumor cells, they adapt and sustain proliferation through increased c-MET signaling via STAT3 [78]. Recent research reveals that in contrast to previous models, c-MET and EGFR pathways operate independently, while a STAT3-*c*-MET feed-forward loop fuels sustained cell growth [78].

Moreover, additional receptors, such as G protein-coupled receptors (GPCRs), have been found to activate c-MET in an HGF-independent manner. For instance, in prostate cancer cells, the formyl peptide receptor 2 GPCR induces c-MET phosphorylation at Y1313/1349/1356, activating downstream signaling pathways, including STAT3, PLC-γ1/PKCα, and PI3K/Akt pathways, through upregulation of ROS [79]. Furthermore, studies employing various mutant forms of c-MET, which attenuate the association of downstream adaptor and effector proteins with c-MET, have emphasized the critical role of Gab1 in c-MET-mediated tumor progression (Fig. 3) [80].

In the tumor microenvironment, tumor-associated macrophages (TAMs) are known to play a crucial role. TAMs are categorized into M1 TAMs, recognized for their pro-inflammatory and antitumor characteristics, and M2 TAMs, known for their anti-inflammatory and pro-tumor traits [81]. In gastric cancer, RNA-sequencing analysis revealed an association between macrophage-derived interleukin (IL)-10 and the activation of c-MET/STAT3 signaling pathways [82]. Elevated IL-10 levels in gastric tumor tissues and patients' serum, primarily sourced from TAMs, were linked to the activation of the c-MET/STAT3 pathway,

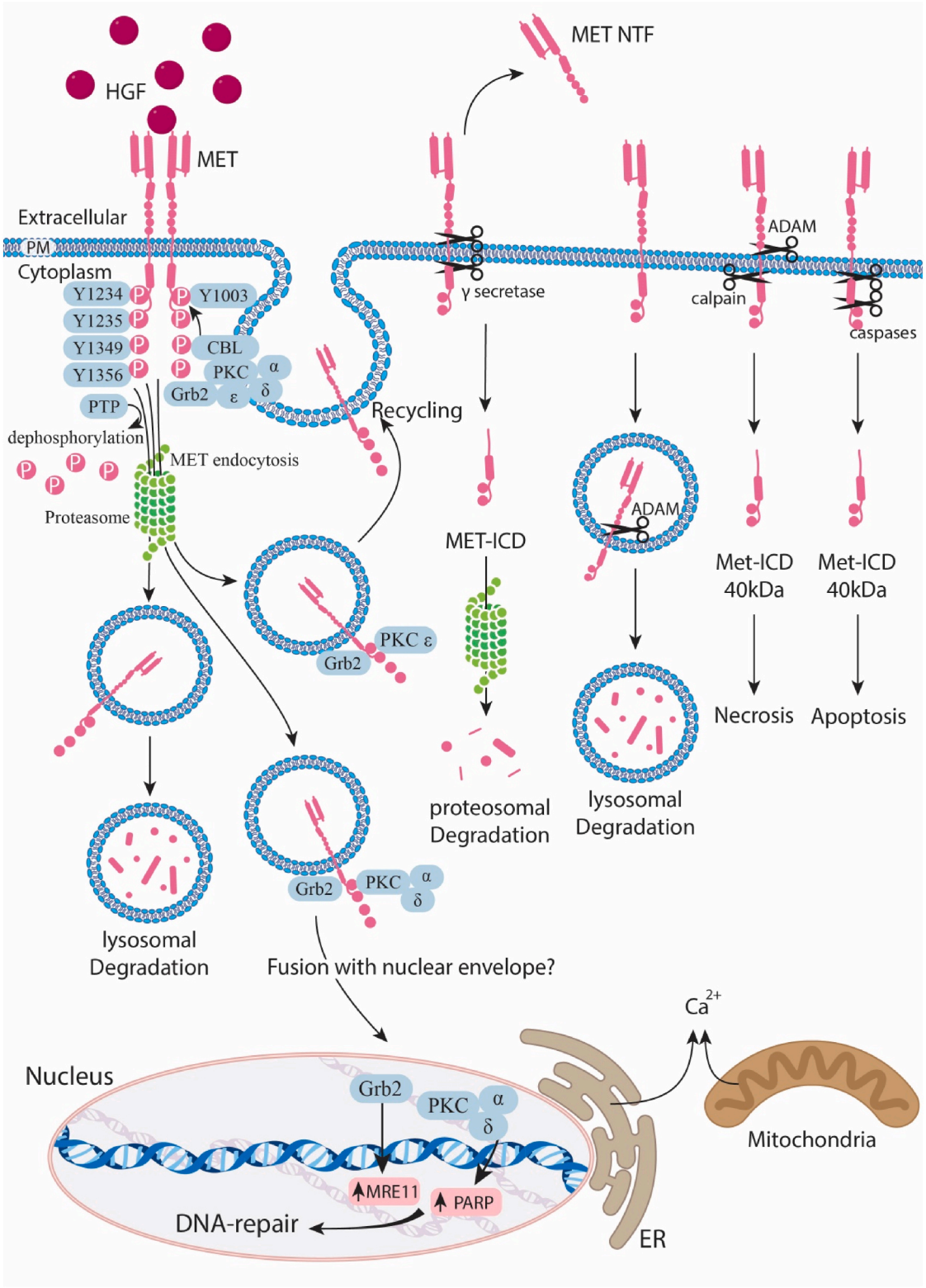


**Fig. 2. Non-canonical c-MET signaling and internalization.** Following dephosphorylation of c-MET kinase and docking domains by protein kinase phosphatases (PTP), inhibitory c-MET phosphorylations at S985 and Y1003 stimulate c-MET internalization and downregulation. Several proteases cleave c-MET at both sides. Sheddase (ADAMs 10 and 17) cleaves the extracellular domain and releases the c-MET N-terminal fragment (NTF); on the other hand, γ-secretase, calpain, and caspases cleave the intracellular domain (ICD), triggering non-canonical c-MET signaling. Further, c-MET internalization leads to proteasomal and lysosomal degradation as well as necrotic and apoptotic deaths, depending on the protease and its cleavage site. Although CBL, targeting Y-1003 c-MET phosphorylation, recruits proteolytic proteins, PKCα, δ, ε, and GRB2, firstly targeting c-MET docking site, are involved in c-MET cellular localization and recycling back to the membrane through further interaction with the juxtamembrane domain. PKCε engages with c-MET recycling, whereas PKCα, δ, and GRB2 direct c-MET toward perinuclear space where it has close contact with mitochondria, Golgi's membranes, endoplasmic reticulum, and nuclear envelope.

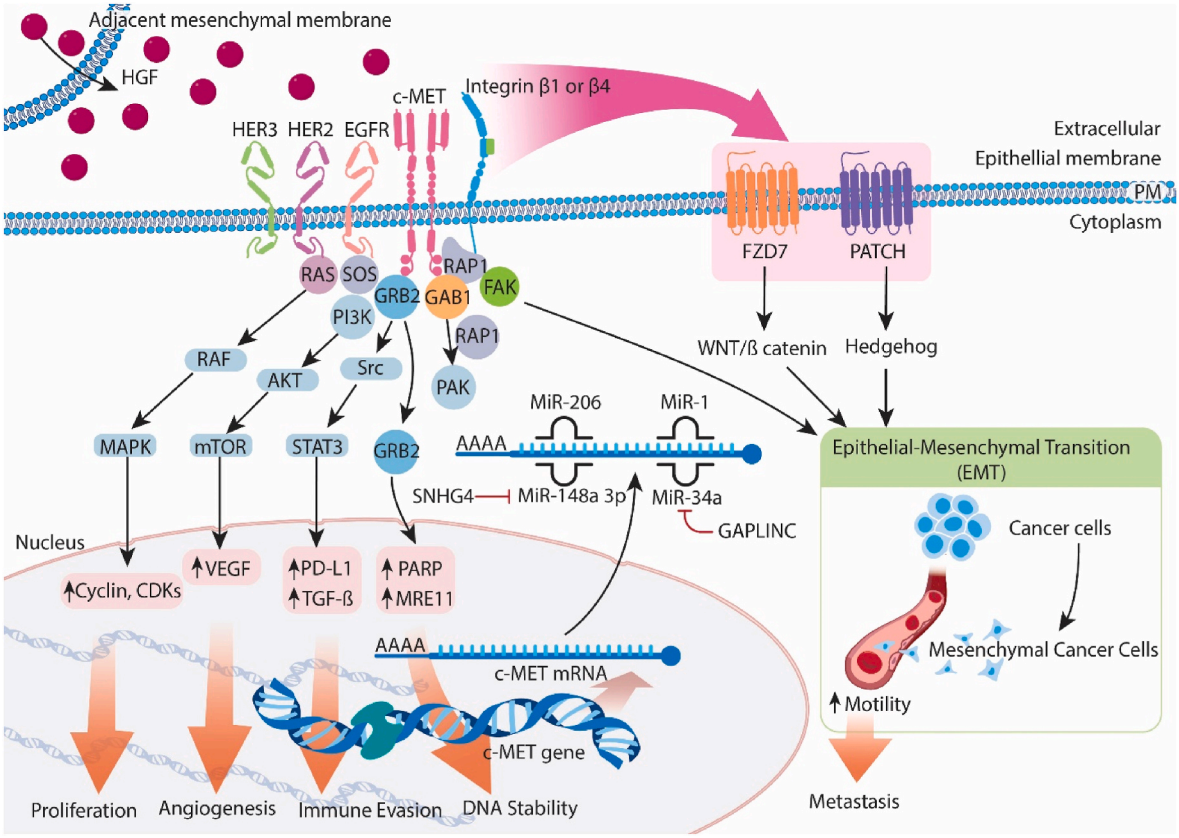


**Fig. 3. Canonical c-MET signaling.** c-MET communicates with HER2/EGFR and activates MAPK and PI3K/Akt pathways, leading to cell proliferation, angiogenesis, and invasion. By stabilizing DNA and upregulating immune checkpoints, c-MET helps cancer cells to be more resistant against targeted and immunotherapy. On the other hand, c-MET interacts with Integrin β, triggering Wnt/β-catenin and hedgehog pathways, which leads to cell migration and epithelial-to-mesenchymal transition (EMT). Furthermore, the c-MET transcript is negatively regulated by miR-1, miR-206, miR-34a, and miR-148a-3p tumor suppressor miRNAs; however, tumor suppressor miRNAs are negatively regulated by SNHG4 and GAPLINC oncogenic lncRNAs. Some c-MET functions, such as c-MET effects on PD-L1 expression and stability, may depend on the cancer type.

promoting gastric cancer progression. These findings suggest that IL-10 is a potential therapeutic target in gastric cancer treatment [82]. However, c-MET signaling significantly influences TAMs-specific cytokines. HGF/c-MET signaling triggered PI3K/Akt activation and concurrent NF-κB signaling inhibition in M1 macrophages, leading to IL-10 and TGF-β release [83]. Interestingly, HGF induced an M1-to-M2 transition in TAMs, decreasing pro-inflammatory markers and promoting an anti-inflammatory phenotype. Conversely, inhibiting HGF/c-MET signaling reversed these effects, maintaining M1 macrophages by elevating IL-1β and iNOS [84–86].

In another aspect of the tumor microenvironment, regulatory T cells (Tregs) critically inhibit various immune cells, including $CD8^+$ and $CD4^+$ T cells, dendritic cells, and natural killer (NK) cells. Targeting markers like CD25, FoxP3, TGF-β receptor, and IDO-1 promise to induce antitumor immunity [87]. In colorectal cancer liver metastasis, $CD4^+FOXP3^+$ Tregs and elevated levels of α-smooth muscle actin, HGF, and c-MET provide potential therapeutic targets. In gastric cancer, HGF and c-MET were also implicated in Treg accumulation in peripheral blood [88]. The expression of c-MET in circulating monocytes of gastric cancer patients was identified, and monocyte-derived dendritic cells exposed to HGF exhibited a regulatory phenotype. Treatment with an anti-HGF antibody reduced circulating Tregs among gastric cancer patients, suggesting potential benefits of HGF/c-MET targeted therapies, including combinations with immune checkpoint inhibitors, in cancer treatment [88,89]. In contrast, in breast cancer brain metastasis, tumor cells with high c-MET expression recruit neutrophils and enhance brain metastasis. c-MET overexpression in tumor cells stimulates cytokine secretion, attracting neutrophils. Therefore, the study offers therapeutic targets for brain metastasis [90].

On the other hand, investigations have unveiled the involvement of two categories of noncoding RNAs in regulating c-MET signaling: microRNAs (miRNAs) and long noncoding RNAs (lncRNAs). Cancer-associated miRNAs can be subdivided into oncogenic miRNAs (oncomiRs) and tumor suppressor miRNAs (tsmiRs). TsmiRs target the mRNAs of specific oncoproteins, opposing cancer progression. Conversely, antagomiRs (miR antagonists) and miRNA sponges, including specific lncRNAs, bind to miRNAs' seed sequences, inhibiting their activity.

Several miRNAs, including miR206, miR-1, miR-34a, and miR-335, have been identified as tsmiRs that directly repress c-MET mRNA. Notably, these miRNAs are downregulated in a multitude of cancers, including lung cancer [91–93], breast cancer [94], ovarian cancer [94–96], cervical cancer [97], prostate cancer [98], colorectal cancer [99–101], GC [102], hepatocellular carcinoma (HCC) [103], esophageal squamous cell carcinoma (ESCC) [104,105], head and neck squamous cell carcinoma (HNSCC) [106], renal cell carcinoma (RCC) [107], osteosarcoma [108–110], and multiple myeloma [111]. Studies across various cancer types have consistently demonstrated that these miRNAs effectively repress *MET* expression, modulating its activity, downstream signaling, and function [91,94,95]. Moreover, these miRNAs have been shown to suppress various cancers through *MET* repression [112,113]. In addition, specific oncogenic lncRNAs have been reported to upregulate c-MET by acting as sponges for miRNAs. Examples include MIAT and GAPLINC, which repress miR-34a, consequently increasing c-MET levels and promoting c-MET signaling [92,99]. Conversely, SNHG4 and NEAT1T have been shown to upregulate c-MET by suppressing miR-148–3p and miR-335, respectively [114,115].

Circular RNAs are a stable, abundant, and conserved non-coding RNAs with the ability to act as a competing endogenous RNAs, sequestering miRNA and modulating mRNA expression. In a study aimed to explore the competing endogenous RNA function of circular RNAs in colorectal cancer (CRC),experimental validation focused on miR-410–3p and its target MET, confirming the competing endogenous RNA regulatory motif of circular MET RNA (*circ-MET*) [116]. Elevated circ-MET levels in CRC cell lines correlated with increased cell proliferation and growth, suggesting a novel regulatory role and potential diagnostic biomarker for CRC [116].

On the other hand, hsa_circ_0080,914 (*circ-HGF*), which encodes a variant of the HGF protein termed C-HGF, are more abundant in glioblastoma (GBM) compared to normal brain tissue [117]. C-HGF activates downstream signaling pathways of c-MET in GBM cell lines, and the modulation of *circ-HGF* expression also impacted tumor growth in intracranial xenografted GBM models. Therefore, *circ-HGF* would be a potential therapeutic target for GBM management [117].

On a parallel note, *circ-MET* was identified as encoding a variant of the MET receptor, MET404, facilitated by the N6-methyladenosine (m6A) reader YTHDF2. The direct interaction of MET404 with the MET-β subunit formed a constitutively activated MET receptor independent of HGF stimulation [118]. Moreover, MET404 is shown to promotes GBM tumorigenesis in a mouse model [118]. Mechanistic insights revealed the role of YTHDC1 in transporting *circ-MET* molecules into the cytosol through an m6A-dependent process. Furthermore, *circ-MET* was found to promote the degradation of *CDKN2A* mRNA by directly interacting with and recruiting YTHDF2. Additionally, circ-MET absorbed miR-1197, preventing its interaction with SMAD3 mRNA [119]. Silencing *circ-MET* led to a significant decrease in pathological angiogenesis and endothelial migration *in vitro*. Acting as a scaffold, *circ-MET* enhanced the interaction between insulin-like growth factor 2 mRNA-binding protein 2 (IGF2BP2) and Notch-regulated Ankyrin repeat protein (NRARP)/endothelial cell-specific molecule 1 (ESM-1), thereby regulating endothelial sprouting and pathological angiogenesis [120].

To harness *circ-MET* as a biomarker, a detection method was developed to assess c-MET activity in patient samples. The study suggests that measuring *circ-MET* levels could be a simple, cost-effective, and non-invasive approach to categorizing patients based on their *MET* expression. Additionally, monitoring *circ-MET* levels in plasma may aid in identifying *MET* amplification as a mechanism of resistance to specific treatments, indicating the potential of *circ-MET* as a valuable biomarker for tracking therapy response and cellular evolution [121].

## 6. Potential of targeting c-MET

Developing c-MET inhibitors is essential in pursuing targeted therapies for different types of cancer. As a crucial RTK, c-MET regulates various cellular processes, including cell growth, survival, migration, and invasion. A diverse range of c-MET inhibitors, such as small molecules, antibodies, and chimeric antigen receptor (CAR)-modified immune cells, have been designed to disrupt aberrant signaling pathways related to this receptor. Although c-MET inhibitors have been successfully applied in multiple cancer types, their use in breast cancer treatment has not been extensively explored. While c-MET inhibitors, particularly antibodies and CAR-immune cells, have succeeded in other cancers, their application in breast cancer remains relatively unexplored. It is essential to examine the potential benefits and challenges of incorporating these diverse c-MET inhibitors in the management of breast cancer.

### 6.1. Small molecule inhibitors

As small molecule inhibitors, three distinct categories of inhibitors have been delineated based on their specificity. Type I c-MET inhibitors, which include subclasses Ia (e.g., crizotinib) and Ib (e.g., capmatinib, MK-2461), bind to Y1230 and the DFG-in active conformation, with Ib inhibitors being more c-MET-specific due to their lack of interaction with G1163 [122]. Conversely, Type II c-MET inhibitors (e.g., BMS-777607, cabozantinib, merestinib, and glesatinib) engage with the ATP binding pocket in the DFG-out conformation (G1087, H1088, and K1110). Type III c-MET inhibitors (e.g., tivantinib) are non-ATP competitive, defying the DFG model [123,124]. The unique type II c-MET inhibitor, glesatinib, employs a distinct target inhibition mechanism and can overcome the resistance observed with type I c-MET inhibitors (Fig. 4) [125].

Moreover, specific c-MET inhibitors such as foretinib, capmatinib, and cabozantinib incorporate a quinoline moiety, endowing them with potent TKI activity against both c-MET and vascular endothelial growth factor receptor-2 (VEGFR)-2 [126]. However, the metabolism of quinoline motifs can lead to nephrotoxicity and clinical setbacks [127]. Multi-kinase inhibitors, including crizotinib, and more selective c-MET inhibitors like capmatinib and tepotinib, have demonstrated clinical efficacy and safety, gaining approval from global regulatory agencies, especially in *MET* exon14 skipping NSCLC patients [122,128].

In addition, a recent paper suggests that doxazosin (DOXA), a drug used to treat benign prostate hyperplasia, interacts with the tyrosine kinase domains of c-MET and EGFR to suppress them [129]. DOXA inhibits the signals from these RTKs and further suppresses TNBC cell proliferation *in vitro* and *in vivo*. Therefore, it may be an effective therapeutic candidate for TNBC that co-overexpresses c-MET and EGFR [129].

Crizotinib, initially approved as a less specific c-MET inhibitor, gained recognition for targeting ALK in NSCLC. The drug exhibits promise to inhibit c-MET and ALK phosphorylation, restraining tumor growth, displaying antiangiogenic properties, and inducing apoptosis in specific cancer cells. Clinical trials demonstrate effectiveness, especially in NSCLC and other tumors carrying fusion ALK genes or amplified c-MET genes. Crizotinib received accelerated FDA approval on August 26, 2011, for treating $ALK^{+}$ locally advanced or metastatic NSCLC, based on two single-arm trials with objective response rates (ORRs) of 50% and 61% and median response durations of 42 and 48 weeks [130]. However, current efforts focus on developing more specific c-MET inhibitors to overcome resistance to therapies.

In recent advancements in c-MET inhibitors, novel and more specific compounds designed through virtual screening and structural optimization exhibit potent c-MET inhibition with high selectivity among 370 kinases. Their promising anti-proliferative effects against *MET*-amplified HCC cells are further substantiated by significant *in vivo* anti-tumor efficacy, emphasizing their potential for future studies in HCC treatment [135]. Exploration into selenium-containing tepotinib derivatives targeting cellular c-MET and thioredoxin reductase (TrxR) reveals potent dual inhibitory activity. Compound 8b, the most active in this category, triggers G1 phase cell cycle arrest, ROS accumulation, and eventual apoptosis [136]. Another noteworthy compound, LAH-1, exhibiting nanomolar c-MET kinase activity, modulates the HGF/c-MET pathway, induces apoptosis, and hinders colony formation, migration, and invasion. Its favorable *in vitro* ADME properties and acceptable *in vivo* pharmaco-kinetic parameters position it as a promising candidate for cancer intervention [137].

Advancements in EGFR/c-MET dual-target inhibitors, such as the series including TS-41, signify a substantial stride in potential NSCLC treatment. TS-41 exhibits significant inhibitory activity against both EGFR-L858R and c-MET kinases, demonstrating efficacy in inducing apoptosis and cell cycle arrest in NSCLC cells. *In vivo* studies corroborate its strong anticancer efficacy with low toxicity, establishing it as a promising candidate for further exploration in NSCLC treatment [138]. Similarly, the newly developed inhibitor H-22, concurrently targeting the EGFR and c-MET pathways, displays robust anti-tumor properties in NSCLC. *In vitro* experiments underscore its potency in inhibiting EGFR and c-MET kinases, leading to G2/M cell cycle arrest and diminished tumor growth in xenograft models, positioning H-22 as a potential

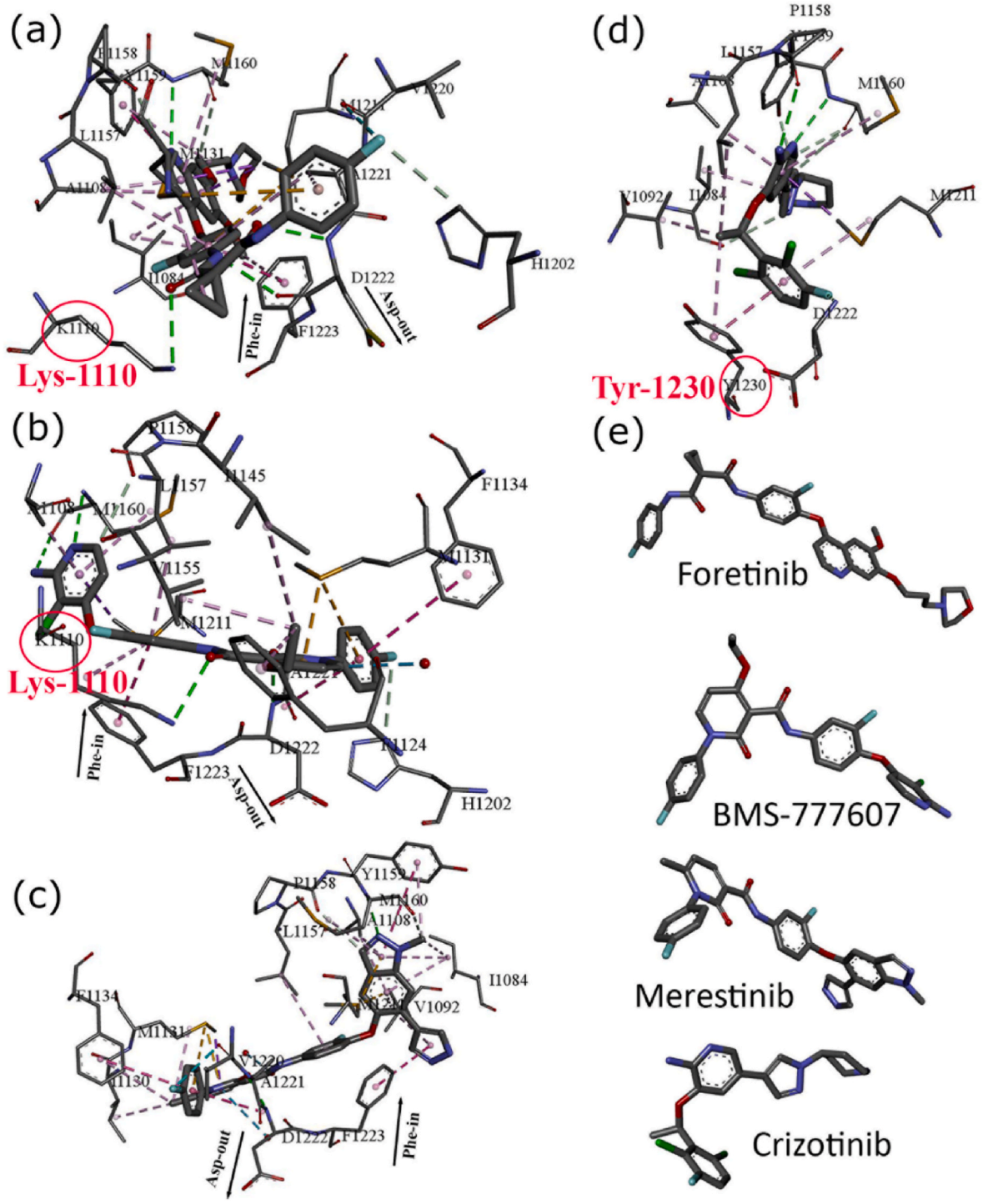


**Fig. 4. Interactions of c-MET inhibitors. (a–c)** Type II inhibitors. DFG gate and K1110 are involved. The Asp (D)-1222 and Phe (F)-1223 side-chain conformations are out and in, respectively, (DFG-out). **(a)** Foretinib (PDB ID: 6SD9) [131]; **(b)** BMS-777607 (PDB ID: 6SDD) [131]; **(c)** Merestinib (PDB ID: 4EEV) [132]; **(d)** Type I inhibitor crizotinib. Tyrosine (Y)-1230 is involved (PDB ID: 2WGJ). [133]; **(e)** Structures of small molecules. This figure was designed using the BIOVIA Discovery Studio Visualizer (v.21.1) [134]. The red circles show the active amino acid residues in the inhibitor interaction.

therapeutic candidate for NSCLC treatment [139].

In radioresistant HNSCC, enhanced c-MET phosphorylation correlates with its increased aggressiveness. Combining the c-MET inhibitor SU11274 with radiation effectively induces tumor shrinkage in a HNSCC mouse model, suggesting a potential therapeutic strategy for overcoming radioresistance in HNSCC [140].

In a clinical trial with advanced NSCLC, the c-MET inhibitor HS-10241 demonstrated tolerability and efficacy, particularly in patients testing positive for c-MET. Encouraging responses in c-MET$^{+}$ patients, with a disease control rate of 80.0%, suggest HS-10241's potential as a therapeutic option for this specific patient population [141].

Moreover, a novel class of ATP-competitive type-III inhibitors specifically designed to target both wild-type and D1228V mutant c-MET kinases have been developed [142]. These inhibitors, employing structure-based drug design and computational analyses, demonstrate nanomolar activities in both biochemical and cellular contexts.

Preliminary pharmacokinetic studies in rats indicate their potential as brain-permeable drugs for treating c-MET-driven cancers [142].

Currently, the safety and effectiveness of vebreltinib enteric-coated capsules in treating patients with glioblastoma, particularly those with the *PTPRZ1-MET* fusion gene, are also being clinically investigated. The *PTPRZ1-MET* fusion gene has been implicated in the progression of gliomas, and the c-MET inhibitor vebreltinib has demonstrated the potential to target it. If the trial proves successful, this targeted intervention protocol could be extended to a larger population of glioma patients, potentially offering significant insights into the safety and effectiveness of c-MET inhibitors [143].

### 6.2. Anti-c-MET antibodies

Alongside small-molecule inhibitors, there is a growing array of anti-*c*-MET antibodies. The METLung study (OAM4971g) explored onartuzumab plus erlotinib in c-MET$^+$ NSCLC patients post-platinum-based chemotherapy, yielding underwhelming results with no significant improvements in overall survival (OS) and potential negative impacts on EGFR-mutated NSCLC patients [144]. Seeking to enhance onartuzumab's efficacy, a novel single-chain variable fragment (scFv) targeting c-MET was developed, demonstrating robust binding affinity and promising anti-cancer properties in preclinical models, such as apoptosis induction, reduced migration and invasion, and suppression of tumor growth and blood supply [145]. Furthermore, a novel therapeutic approach has been developed for cancer treatment by creating anti-*c*-MET antibody Fab fusion proteins with an intracellular epitope peptide chimera [146]. These proteins have been designed to interfere with intracellular signaling pathways, inhibiting tumor cell proliferation and the induction of mitophagy-mediated cell death. In addition, the fusion proteins have effectively inhibited A549 xenograft tumors in mice, providing new avenues for delivering intracellular bio-macromolecules and dual intervention against tumor cell signaling pathways [146].

Amidst resistance to EGFR inhibitors, amivantamab, a bispecific c-MET/EGFR antibody, emerges as a beacon of hope. This innovative therapy engages the immune system through Fc-dependent mechanisms, activating NK cells, monocytes, and macrophages, leading to antibody-dependent cellular cytotoxicity (ADCC), cytokine production, and antibody-dependent cellular trogocytosis (ADCT). This underscores the dual functionality of monoclonal antibodies targeting RTKs like c-MET and EGFR [147,148]. Emibetuzumab (LY2875358), another bivalent anti-*c*-MET antibody, showcases clinical promise by inhibiting both HGF-dependent and HGF-independent c-MET signaling, as observed in a phase I trial [149]. Moreover, in combination with merestinib, emibetuzumab exhibits tumor regression, potentially benefiting *MET* exon 14 skipping patients and suggesting the value of sequential combination therapy for those progressing on single-agent merestinib [38].

Shifting focus to pancreatic ductal adenocarcinoma (PDAC), it is one of the most difficult to treat cancers, and no effective targeted therapy exists. However, SHR-A1403, a novel c-MET antibody-drug conjugate, demonstrates promising preclinical efficacy in PDAC models. By impeding intracellular cholesterol biosynthesis, SHR-A1403 inhibits cancer cell proliferation, migration, and invasion, inducing cell cycle arrest and apoptosis. The robust anti-tumor efficacy in preclinical studies positions SHR-A1403 as a potential therapeutic agent for PDAC treatment [150].

Another innovative approach involves the antibody-drug conjugate, cIRCR201-dPBD, designed to target c-MET for improved antitumor efficacy. Utilizing site-specific drug-conjugate technology, the antibody-drug conjugate consistently binds a prodrug pyrrolobenzodiazepine (PBD) to the cIRCR201 antibody, demonstrating varying sensitivities across 47 cancer cell lines based on c-MET expression levels. Additionally, cIRCR201-dPBD shows significant antitumor activity in *MET*-amplified cancer cells in xenograft models, indicating its potential as a therapeutic strategy for c-MET-expressing tumors [151].

Furthermore, the antibody-drug conjugate P3D12-vc-MMAF is designed to explicitly target c-MET and has shown effective outcomes in preclinical trials without relying on *MET* amplification or mutation. By utilizing the c-MET-specific antibody P3D12, the antibody-drug conjugate induces c-Met degradation while minimizing the activation of c-MET signaling pathways. *In vitro* studies highlight the potent activity of P3D12-vc-MMAF against c-MET-expressing cell lines, surpassing the efficacy of the c-MET-TKI PHA-665752. *In vivo*, the P3D12-vc-MMAF effectively inhibits tumor growth in both *MET* gene-amplified and moderate c-MET-expressing xenograft models, suggesting its potential for clinical superiority [152]. In summary, diverse c-MET inhibitors and antibodies are shaping the landscape of targeted therapy, offering new avenues for cancer treatment.

### 6.3. c-MET-specific CAR-immune cells

CAR-T cells have proven successful in treating hematologic malignancies but encounter challenges when applied to solid tumors. In the domain of solid tumor therapy, CAR-based immunotherapies have traditionally targeted RTKs, except for c-MET. Recent advancements have paved the way for the development of CAR-T and CAR-NK cell therapies directed specifically at c-MET, thereby opening new avenues for clinical research. Although CAR technology, a potential cancer therapy, has demonstrated limited success in treating solid tumors, a notable breakthrough was achieved in the development of a c-MET-specific CAR T cell for breast tumors expressing c-MET [153–156]. This specialized CAR T cell effectively halted tumor growth in mice. A subsequent phase 0 clinical trial (NCT01837602) investigated the safety and feasibility of intratumoral injection of mRNA-transfected c-MET-CAR T cells in patients with metastatic breast cancer. The injections were well-tolerated and induced an inflammatory response, evidenced by tumor necrosis and c-MET loss. This study suggests the potential of mRNA-based c-MET-CAR T cells in treating breast cancer [157].

Furthermore, the development of an anti-*c*-MET-CAR construct involved testing with Jurkat and KHYG-1 cell lines [154]. The c-MET-CAR Jurkat cells, when exposed to c-MET$^+$ GC cells, secreted IL-2, while the c-MET-CAR-KHYG-1 cells exhibited cytotoxicity towards c-MET$^+$ GC cells. Primary T cells transformed into c-MET-CAR-T cells displayed elevated levels of IL-2 and IFN-γ secretion, effectively inhibiting tumor growth in a xenograft assay with NSG mice harboring c-MET$^+$ GC cells [154]. Despite these advancements, CAR-T cell therapy faced challenges in treating solid tumors, mainly attributed to the immunosuppressive effects of PD-1. To overcome this issue, researchers developed a second-generation c-MET CAR and a c-MET-PD1/CD28 CAR with a chimeric-switch receptor (CSR). *In vitro* testing demonstrated that both CAR-T cells exhibited higher cytokine secretion, effectively killed c-MET$^+$ GC cells, and expressed PD-1 upon target cell stimulation. *In vivo* testing revealed that the PD-1/CD28 CSR further improved long-term anti-tumor effects, reduced IL-6 release, and did not cause apparent off-target toxicity. The success of this design strategy suggests promise for enhancing the efficacy of CAR-T cell therapy in GC [158].

Alternatively, to improve the efficacy of CAR-T cells in treating solid tumors, the development of dual-function CAR-T cells targeting c-MET and inhibiting the PD-1/PD-L1 interaction has been pursued. By inhibiting the PD-1/PD-L1 interaction, these CAR-T cells maintained their toxicity towards PD-L1$^+$ tumor cells. These novel dual-function CAR-T cells possess significant potential for robust anti-tumor activity in solid tumors, and produce potent *in vitro* and *in vivo* antitumor effects, accompanied by an increase in immune-signaling molecules (Fig. 5) [159].

On the other hand, researchers explored c-MET-targeted CAR-NK cell immunotherapy for hepatocellular carcinoma. *In vitro* studies revealed that c-MET-CAR-NK cells exhibited specific cytotoxicity against c-MET$^+$ HepG2 cells, indicating that c-MET is a potential and effective target for human liver cancer CAR-NK immunotherapy [156]. The application of c-MET-targeted CAR-NK immunotherapy is a crucial focus of current research. This approach involves a specific CAR construct incorporating

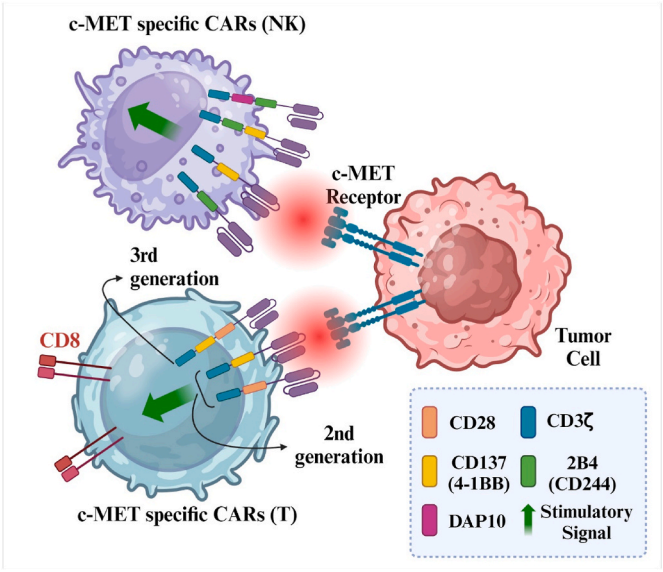


**Fig. 5. Chimeric antigen receptors (CARs) were engineered to target c-MET + tumor cells.** The construction of c-MET-specific CARs has been designed to target c-MET$^+$ cells and activate cytotoxic (CD8$^+$) T cells and natural killer (NK) cells while utilizing distinct transmembrane domains in engineered immune cells.

CD8α-4-1BB-DAP12, which targets c-MET$^+$ cells. By taking advantage of CD8α expression in CD8$^+$ T cells, 4-1BB's presence in both T and NK cells, and DAP12's association with NK cells, this construct has demonstrated efficacy against both *MET*$^{high}$ HepG2 HCC and *MET*$^{low}$ H1299 lung cancer cells, particularly in the context of HepG2 cells [160]. To further enhance the effectiveness of this approach, researchers have tested four distinct c-MET-CARs, denoted as CC1-4, each featuring different NK-specific signaling domains. These CARs have been tested against various lung cancer cell lines *in vitro* and H1299 xenograft tumors *in vivo*. The CCN4 NK cells, fortified with DAP10, emerged as the most potent, exerting significant cytotoxicity on tumor cells both *in vitro* and *in vivo*. This breakthrough study underscores the efficacy of c-MET-specific CARs in fortifying NK cells against c-MET$^+$ lung adenocarcinoma (Fig. 5) [160].

## 7. c-MET-targeted therapy in breast cancer

### 7.1. c-MET, metastasis, and breast cancer

The metastatic role of c-MET predominantly revolves around its interaction with β1 integrin and intricate crosstalk with the Wnt and Hedgehog signaling pathways. Research suggests that c-MET plays a crucial role in orchestrating tissue-specific metastasis in breast cancer by partnering with β1 integrin [161]. β1 integrin forms a binding alliance with c-MET, activating the Wnt and Hedgehog signaling pathways, thereby facilitating metastasis. Specifically, breast cancer cells inclined to metastasize to the bone exhibit heightened levels of the c-MET/β1 integrin complex. This study has also shown that disrupting the interaction between β1 integrin and c-MET significantly reduces invasion and the expression of mesenchymal genes in TNBC cells [161]. Conversely, brain metastasis is a prevalent complication affecting about 30% of metastatic breast cancer patients. Notably, the X-inactive-specific transcript (XIST) lncRNA emerges as a suppressor of breast cancer brain metastasis by downregulating c-MET. In a mouse model of breast cancer, XIST dysfunction promotes brain metastasis, but this detrimental effect can be mitigated by suppressing c-MET expression [162].

Furthermore, brain metastasis remains a leading cause of cancer-related mortality in HER2$^+$ breast cancer patients. The HER2 receptor, often called an orphan receptor, becomes activated through two distinct mechanisms; ligand-independent HER2/HER2 homodimerization and ligand-dependent EGFR/HER2 or HER2/HER3 heterodimerization. Importantly, there is significant crosstalk between HER2 and c-MET, adding complexity to the signaling dynamics in this context [163,164]. To overcome HER2-mediated brain metastasis, a therapeutic strategy involving the combination of the irreversible TKI neratinib with the c-MET inhibitor cabozantinib has been proposed. The combined treatment of neratinib and cabozantinib demonstrated significant reductions in cell proliferation and migration in HER2$^+$ cell lines and organoid growth *in vitro* experiments. These effects were primarily attributed to the inhibition of ERK activation downstream of the c-MET/HER2 axis. Notably, the combination therapy not only hindered primary tumor growth but also effectively prevented the development of brain metastasis [165].

### 7.2. c-MET and resistance to treatment in breast cancer

*BRCA1* (BReast-CAncer susceptibility gene 1) and *BRCA2* are widely recognized as tumor suppressor genes, and mutations in these genes significantly elevate the susceptibility to breast and ovarian cancers. Thorough research has unveiled the multifaceted roles of BRCA proteins, which play in various critical cellular processes. Remarkably, both BRCAs hold pivotal positions in DNA repair mechanisms and the intricate orchestration of gene expression in response to DNA damage. Recent investigations underscore the indispensable role of BRCA proteins in maintaining chromosomal stability, effectively serving as guardians of genomic integrity against potential harm. Importantly, it has been observed that breast cancers carrying *BRCA1* mutations are more likely to fall within the TNBC subtype [166,167]. Furthermore, *BRCA1/2*-mutated breast cancer has exhibited sensitivity to PARP inhibitors, such as olaparib and talazoparib, which are currently harnessed for treating HER2$^-$ cancer with germline *BRCA1/2* mutations [168].

Additionally, c-MET has emerged as a key player in conferring resistance to PARP inhibitors through the direct phosphorylation of PARP on tyrosine 907 in TNBC cells. Consequently, the combination of PARP and c-MET inhibitors has demonstrated a synergistic inhibitory effect on the proliferation of PARP inhibitor-resistant TNBC cells [14,15]. Mechanistically, it has been proposed that ROS contributes to c-MET-mediated PARP inhibitor resistance. The rapid proliferation of cancer cells leads to increased production of ROS, further stimulating receptor tyrosine kinase-associated signaling pathways, including c-MET signaling, by oxidizing cysteine residues of protein tyrosine phosphatases. Moreover, the scavenging of ROS by extracellular superoxide dismutase has been shown to suppress the interaction between breast cancer cells and fibroblasts mediated by HGF [169]. Notably, TNBC cells are characterized by elevated ROS levels, activating c-MET, and translocating to the nucleus, thereby phosphorylating PARP and contributing to inhibitor resistance [14]. Interestingly, in HCC, unlike TNBC, PARP Y907 phosphorylation is regulated by the EGFR/c-MET heterodimer [17]. Therefore, we proposed a treatment method called combination therapy incorporating EGFR, c-MET, and PARP inhibitors to increase the effectiveness against HCC [17]. Beyond its role in PARP inhibitor resistance, c-MET may also be implicated in resistance to EGFR inhibitors and chemotherapy in breast cancer cells. PYK2 has been suggested to contribute to EGFR TKI resistance by acting as a downstream effector of EGFR and c-MET in TNBC [170].

On the other hand, exposing liver and lung cancer cells to c-MET inhibitors has been shown to increase the expression of PD-L1 and induce T cell inactivation [101,102]. Mechanistically, c-MET activates GSK3β by phosphorylating at tyrosine 56, thereby promoting GSK3β-mediated PD-L1 phosphorylation and degradation [171,172]. Therefore, combining c-MET inhibitors with anti-PD-1 antibodies reduces tumor growth and prolonged survival compared to using anti-PD1 or c-MET inhibitors alone [172].

Furthermore, cancer-associated fibroblasts (CAFs) secrete HGF,

activating c-MET signaling in breast cancer, promoting epithelial-to-mesenchymal transition, growth, and radioresistance. Radiation enhances HGF secretion and c-MET expression, activating the pathway. TNFα from irradiated breast cancer cells stimulates CAF proliferation and HGF secretion. High HGF/c-MET expression correlates with poorer recurrence-free survival (RFS) in radiation-treated breast cancer patients. Thus, the potential therapeutic significance of targeting the HGF/c-MET signaling pathway to sensitize breast cancer cells to radiotherapy has been observed [173].

### 7.3. c-MET and breast cancer cell patient survival

The meta-analysis has revealed a robust association between elevated c-MET expression and unfavorable outcomes in RFS and OS across diverse breast cancer cases. Notably, this connection was pronounced in Western patients, while Asian patients did not display a significant link. It's important to highlight that c-MET was correlated with poorer OS in cases lacking lymph node involvement and reduced RFS in $HR^+$ and TNBC, but it didn't notably impact the prognosis in $HER2^+$ breast cancer [8].

In a study encompassing 257 patients across various breast cancer subtypes, both c-MET and phospho-*c*-MET expression levels emerged as significant prognostic indicators for both RFS [c-MET: HR = 2.44; RFS (95% CI) = 1.34–4.44 months, p = 0.003; phospho-*c*-MET: HR = 1.64; RFS (95% CI) = 1.04–2.60 months, p = 0.03] and OS [c-MET: HR = 3.18; OS (95% CI) = 1.43–7.11 months, p = 0.003; phospho-*c*-MET: HR = 1.92; OS (95% CI) = 1.08–3.44 months, p = 0.025]. Moreover, heightened levels of c-MET and phospho-*c*-MET were explicitly associated with poorer RFS in $HR^+$ breast cancer and worse OS in $HER2^+$ breast cancer [174].

In another study comprising 105 women with $ER^+/HER2^-$ breast cancer post-surgery, the influence of c-MET receptor expression on prognosis was investigated. Elevated c-MET levels were linked to larger tumor size, increased Ki67 levels, and decreased progesterone receptor expression. Over a 5-year follow-up, patients with high c-MET levels experienced significantly worse disease-free survival (DFS) and Breast Cancer-Specific Survival (BCSS) rates, and c-MET expression was univariately associated with an elevated risk of recurrence or mortality. Multivariate analysis identified tumor size and high c-MET expression as independent predictors of DFS, with large tumor size also associated with an increased risk of cancer-related death. While a trend suggested a connection between high c-MET levels and poorer survival in basal-like (BL) tumors, statistical significance was not reached [175].

Furthermore, in a multivariate logistic regression analysis, c-MET displayed an independent association with BL status, exhibiting an odds ratio of 6.44 (95% confidence interval = 1.74–23.78, P = 0.005). Additionally, a positive correlation was observed between c-MET and HER2 (P = 0.005), while an inverse correlation was found with tumor size (P < 0.001). Considering cancer subtypes, c-MET emerged as an independent adverse prognostic factor, yielding a hazard ratio of 1.85 (95% confidence interval = 1.07–3.19, P = 0.027). Although there was a tendency towards reduced survival in BL tumors that overexpressed c-MET, this trend did not reach statistical significance [176]. Nonetheless, the importance lies in monitoring *MET* + circulating tumor cells (CTCs) and cell-free DNA (cfDNA) concentration to predict PFS in patients with $HR^+/HER2^-$ metastatic breast cancer. This method differs from assessing c-MET expression in the primary site and serves as an independent predictor, emphasizing the significance of integrated liquid biopsy in predicting disease progression [177].

## 8. Clinical studies of c-MET inhibitors for breast cancer patients

Clinical investigations are currently underway to assess the effectiveness of HGF/c-MET-targeted therapies in various malignancies, including breast cancer. Nevertheless, there are apparent shortcomings in HGF/c-MET-targeted therapy that have yet to be uncovered. Table 2 lists ongoing or concluded clinical trials involving c-MET-targeted medications in breast cancer patients.

### 8.1. Onartuzumab

Onartuzumab (also known as MetMAb), a humanized monovalent monoclonal antibody designed to counteract c-MET, functions by obstructing HGF binding and c-MET phosphorylation through its interaction with the c-MET β Sema-PSI domain. Notably, onartuzumab distinguishes itself from other anti-*c*-MET antibodies by preventing dimerization and hindering the associated signaling pathways when binding to c-MET [178]. An assessment of onartuzumab's clinical

**Table 2**
Clinical studies of c-MET-targeted therapy conducted on breast cancer patients.

| c-MET inhibitor | Duration (Status) | Phase (patients) | BC[a] subtype | Intervention | References |
|---|---|---|---|---|---|
| Onartuzumab | 2011–2016 (completed) | II (158) | TNBC | Combined with bevacizumab and paclitaxel | NCT01186991 |
| Foretinib | 2010–2015 (completed) | I (19) | $HER2^+/ER^+$ | Combined with lapatinib, patients received prior anti-HER2 | NCT01138384 |
| Foretinib | 2010–2015 (completed) | II (47) | TNBC | Foretinib, at a continuous oral daily dose of 60 mg | NCT01147484 |
| Tivantinib | 2009–2013 (completed) | I (87) | Solid tumors, including BC | Combined with sorafenib | NCT00827177 |
| Tivantinib | 2012–2013 (completed) | II (22) | TNBC | Patients received tivantinib 360 mg PO BID on days 1–21. | NCT01575522 |
| Capmatinib | 2019–2023 (active) | I (64) | TNBC | Combined with spartalizumab and LAG525 | NCT03742349 |
| Capmatinib | 2022–2028 (recruiting) | Ib/II (56) | Metastatic | Combined with neratinib | NCT05243641 |
| Sitravatinib | 2022–2023 (recruiting) | II (96) | TNBC | Combined with tislelizumab and nab-paclitaxel | NCT04734262 |
| Cabozantinib | 2013–2015 (completed) | II (35) | TNBC | Cabozantinib at a dose of 60 mg orally once per day for 21-day cycles | NCT01738438 |
| Cabozantinib | 2017–2019 (completed) | II (18) | TNBC | Combined with nivolumab | NCT03316586 |
| Cabozantinib | 2011–2023 (active) | II (68) | $HR^+$ | Combined with fulvestrant | NCT01441947 |
| Cabozantinib | 2014–2020 (completed) | II (36) | $HER2^+$ with brain metastasis | Combined with trastuzumab | NCT02260531 |
| Crizotinib | 2014–2017 (terminated) | I (3) | Metastatic | Combined with sunitinib | NCT02074878 |
| Crizotinib | 2019–2024 (recruiting) | II (58) | Lobular BC Lobular TNBC | Combined with fulvestrant | NCT03620643 |

[a] Breast cancer.

efficacy, either in combination with paclitaxel, with or without the VEGF inhibitor bevacizumab, was conducted in TNBC (NCT01186991). Regrettably, this Phase II clinical trial failed to demonstrate a clinically significant outcome for onartuzumab treatment. The PFS did not improve following onartuzumab/paclitaxel treatment. It is noteworthy that the ORR was higher when onartuzumab/paclitaxel was combined with bevacizumab (median ORR = 42.2%) compared to onartuzumab/paclitaxel without bevacizumab (median ORR = 27.5%). However, it's worth mentioning that 88% of patients in this study were identified as c-MET$^-$ [179], which suggests that the patient selection criteria may not have been optimal for this trial. Moreover, the lack of clinical efficacy of onartuzumab has also been observed in patients with c-MET$^+$ and *EGFR*$^+$ NSCLC [180].

### 8.2. Foretinib

Foretinib (also referred to as GSK1363089 or XL880) represents an oral multikinase inhibitor that primarily targets c-MET and VEGFR, among other receptor proteins. A multicenter Phase II trial (IND197) assessed foretinib's effectiveness in patients with locally recurrent or metastatic TNBC (NCT01147484). According to this Phase II clinical trial, 33% of patients experienced stable disease with a median duration of 5.4 months (2.3–9.7 months). Partial responses to foretinib were observed in 4.7% of patients. Notably, the most frequently reported adverse events included nausea (64%), fatigue (60%), hypertension (58%), and diarrhea (40%). Grade 3 toxicities were observed in 4% of patients for nausea, 4% for fatigue, 49% for hypertension, and 7% for diarrhea [181]. Meanwhile, the same research group conducted a Phase I trial to assess the efficacy and safety of combining foretinib with lapatinib in patients with HER2$^+$ breast cancer (N = 19) (NCT01138384). However, the results reported only a modest PFS of 3.2 months for this combination therapy. Notably, none of the selected patients were c-MET$^+$, suggesting that patient selection criteria may have needed to be revised [182].

### 8.3. Tivantinib

Tivantinib (ARQ197) functions as a non-ATP competitive inhibitor of c-MET. A Phase I trial was carried out to evaluate the safety and determine the suitable dosing of a combination of tivantinib and sorafenib (a VEGFR/PDGFR/RAF kinase inhibitor) in patients with various advanced solid tumors, including breast cancer, melanoma, and HCC (NCT00827177). Interestingly, the breast cancer patients selected for this study (N = 8) exhibited low c-MET expression and showed no objective response to the combination of tivantinib and sorafenib. In contrast, c-MET positivity was observed in 28.6% of melanoma patients (4 out of 14 patients) and 40% of HCC patients (4 out of 10 patients), with corresponding objective response rates of 26% and 10%, respectively. These findings underscore the importance of evaluating c-MET expression before embarking on c-MET-targeted therapy [183].

Additionally, a Phase II trial of tivantinib was conducted in TNBC patients who had previously received 1 to 3 chemotherapy regimens (NCT01575522) [20]. Following tivantinib administration, grade 3 anemia occurred in one patient, grade 3 fatigue in another patient, and grade 3/4 neutropenia in three patients. c-MET expression was assessed using IHC staining and FISH in the 22 patients, revealing that 45.5% had c-MET$^+$ TNBC. However, none of the patients exhibited phospho-*c*-MET$^+$ TNBC. The low response rate observed in this study may be attributed to the specificity of tivantinib. Therefore, it is suggested that the phosphorylated c-MET should also be evaluated prior to initiating c-MET-targeted therapy. Nevertheless, this study highlighted that the benefit of tivantinib treatment was primarily confined to patients with significant total c-MET overexpression [20].

### 8.4. Cabozantinib

Cabozantinib (XL184 or BMS-907351) is a multi-kinase inhibitor targeting c-MET, VEGFR1-3, RET, AXL, FLT3, and KIT receptors. In a single-arm Phase II trial involving TNBC patients, cabozantinib was administered daily (NCT01738438) [184]. Out of the 35 participating patients, three (9%) achieved a partial response, and nine (27%) maintained stable disease, resulting in a clinical benefit rate of 34%. The most frequently reported side effects included fatigue, diarrhea, mucositis, and palmar-plantar erythrodysesthesia. Notably, there were no treatment-related grade 4 adverse events. However, dose reduction was necessary for 30% of patients. Furthermore, the analysis of circulating c-MET revealed that higher baseline plasma concentrations of soluble c-MET were associated with longer PFS, suggesting that cancers with high soluble c-MET levels might be more responsive to c-MET inhibition. Nonetheless, only three patients exhibited c-MET overexpression [185].

Another single-arm Phase II study recruited patients with HR$^+$ breast cancer and bone metastases treated with daily cabozantinib (NCT01441947). In this study, 38% of patients displayed a partial response, while 12% demonstrated stable disease. The median PFS and OS were reported as 4.3 and 19.6 months, respectively, warranting further investigation of cabozantinib in metastatic HR$^+$ breast cancer [186]. The clinical benefits of cabozantinib were also explored in HR$^+$ and HER2$^+$ breast cancer patients with brain metastases (NCT02260531). This Phase II trial comprised three cohorts of breast cancer patients [cohort 1: HER2$^+$ (n = 21), cohort 2: HR$^+$HER2$^-$ (n = 7), and cohort 3: TN (n = 8)], all of whom received cabozantinib daily. Cohort 1 additionally received trastuzumab every three weeks, and participating patients had undergone an average of three prior treatments, including immunotherapy and surgery. Median ORRs of 5%, 14%, and 0% were observed in cohorts 1, 2, and 3, respectively. This study also revealed alterations in soluble c-MET and Tie2 plasma levels, along with decreased VEGFR-2 and TNF-α levels following cabozantinib treatment [187].

### 8.5. Capmatinib

Capmatinib (also known as INC280), an oral small molecule inhibitor targeting c-MET, has gained approval to treat NSCLC [19]. Furthermore, a Phase Ib/II trial has recently commenced investigating the combination of capmatinib and the pan-HER inhibitor neratinib for metastatic breast cancer and metastatic inflammatory breast cancer (NCT05243641). However, the clinical outcomes of capmatinib in breast cancer have yet to be reported.

## 9. Concluding remarks and future direction

In conclusion, this review has comprehensively explored c-MET regulation and downstream signaling in the context of breast cancer. It has illuminated the intricate molecular mechanisms governing c-MET activation downstream pathways, including its new role in the nucleus and its pivotal role in breast cancer metastasis and resistance to treatment. Furthermore, it has highlighted the promising therapeutic potential of targeting c-MET in breast cancer management.

c-MET is highly expressed in various tumors, including breast cancer, and plays critical roles in cancer initiation, progression, drug resistance, and metastasis. While binding to its ligand, HGF, c-MET undergoes autophosphorylation at multiple sites, with distinct molecules recruited to each site, resulting in diverse signals and contributing to c-MET metabolism. However, the relationship between site-specific phosphorylation and c-MET's functions in different cellular locations, cancer types, and disease progression remains elusive. Detailed analyses using various c-MET mutants at specific phosphorylation sites may be essential to unravel these complexities.

The findings presented in this review have shed light on the intricate landscape of c-MET regulation, particularly its glycosylation patterns

and their implications in downstream signaling cascades. Identifying specific glycosylation sites and their impact on c-MET/HGF signaling enhances our understanding of this crucial receptor-ligand system. Moreover, this review has emphasized the diverse signaling pathways initiated by c-MET activation, including the PI3K/Akt and STAT3 pathways, and their relevance in different breast cancer subtypes. The pivotal role of c-MET in promoting angiogenesis, metastasis, and resistance to treatment underscores its significance as a therapeutic target. It has also been implicated in resistance to PARP inhibitors, EGFR inhibitors, and chemotherapy, making it a crucial focus in overcoming these therapeutic challenges. The potential involvement of c-MET in resistance to various other drugs and immunotherapies warrants further exploration in this domain. Apart from the discussed targeted therapies, it is worth noting that there are ongoing phase I clinical trials evaluating the combination of PARP inhibitors with Cabozantinib in advanced urothelial cancer and refractory solid tumors (NCT03425201, NCT05038839).

Moreover, a recent study have attempted to develop a cabozantinib-based proteolysis targeting chimera (PROTACs) utilizing cereblon and Von Hippel-Lindau tumor suppressor as E3-ligases and showed promising results [188]. Obviously, future research is expected to improve the specificity and efficacy of the c-MET-targeted PROTAC, as well as its antitumor activity against c-MET-dependent tumors *in vivo*.

On the other hand, clinical investigations of c-MET inhibitors have exhibited varied outcomes, underscoring the importance of patient stratification based on c-MET expression and phosphorylation status. While numerous c-MET inhibitors have been developed and tested in clinical trials, including those involving breast cancer patients, trials focused solely on c-MET inhibitor monotherapy have yielded disappointing results. While a deficiency in c-MET expression among selected patients has been noted, assessing c-MET phosphorylation levels, indicative of c-MET activity, may hold greater significance. Additionally, studies have indicated that c-MET plays a pivotal role in resistance to EGFR/HER2-targeted therapies and combining pan-HER inhibitors with c-MET inhibitors has shown enhanced efficacy. Consequently, the utility of MET inhibitors may be more promising when combined with other drugs rather than as standalone therapies. Developing novel c-MET inhibitors, such as bispecific antibodies and combination therapies, introduces fresh avenues for improving treatment outcomes. Whether pursued as monotherapy or combination therapy, searching for suitable biomarkers beyond c-MET expression and phosphorylation is poised to be a pivotal research focus in the future. In summary, this review underscores the need for continued research and clinical trials to unlock the therapeutic potential of c-MET inhibition in breast cancer treatment fully.

## CRediT authorship contribution statement

**Parham Jabbarzadeh Kaboli:** Writing – review & editing, Writing – original draft. **Hsiao-Fan Chen:** Writing – review & editing. **Ali Babaeizad:** Visualization. **Kiarash Roustai Geraylow:** Visualization. **Hirohito Yamaguchi:** Writing – review & editing. **Mien-Chie Hung:** Writing – review & editing, Supervision.

## Declaration of competing interest

On behalf of the authors, we declare no conflict of interest in the review manuscript “Unlocking c-MET: A Comprehensive Journey into Targeted Therapies for Breast Cancer” by Jabbarzadeh Kaboli et al.

## Acknowledgment

The authors extend their gratitude to China Medical University, Taichung, Taiwan, whose generous financial support has been pivotal in the inception and successful completion of this article. Additionally, we acknowledge the invaluable contributions from the following funding agencies: the National Science and Technology Council (NSTC) Grant 112-2639-B-039-001 –ASP (M.-C.H.) and 111-2314-B-039-007 (H.Y.), the Ministry of Health and Welfare Taiwan Grant MOHW112-TDU-B-222-124016 (M.-C.H.), and The Featured Areas Research Center Program by the Ministry of Education (MOE) in Taiwan.

## Abbreviations

| | |
|---|---|
| **ADAM** | A Disintegrin and Metalloproteinase |
| **BL** | Basal-Like |
| **BRCA** | BReast-CAncer susceptibility gene |
| **c-MET** | Cellular-Mesenchymal Epithelial Transition Factor |
| **CAR** | Chimeric Antigen Receptor |
| **DFS** | Disease-Free Survival |
| **EGFR** | Epidermal Growth Factor Receptor |
| **HER2** | Human Epidermal Growth Factor Receptor 2 |
| **HCC** | Hepatocellular Carcinoma |
| **HGF** | Hepatocyte Growth Factor |
| **IPT** | Immunoglobulin-Plexin-Transcription |
| **lncRNA** | Long Non-Coding RNA |
| **miRNA** | microRNA |
| **NSCLC** | Non-Small Cell Lung Cancer |
| **ORR** | Objective Response Rate |
| **OS** | Overall Survival |
| **PARP** | Poly (ADP-ribose) Polymerase |
| **PDGFR** | Platelet-Derived Growth Factor Receptor |
| **PFS** | Progression-Free Survival |
| **PI3K** | Phosphoinositide 3-Kinase |
| **PKC** | Protein Kinase C |
| **PSI** | Plexin-Semaphorin-Integrin |
| **RFS** | Recurrence-Free Survival |
| **ROS** | Reactive Oxygen Species |
| **RTK** | Receptor Tyrosine Kinase |
| **scFv** | Single-Chain Variable Fragment |
| **SEMA** | Semaphorin |
| **STAT** | Signal Transducer and Activator of Transcription |
| **TKI** | Tyrosine Kinase Inhibitor |
| **TNBC** | Triple-Negative Breast Cancer |
| **VEGF** | Vascular Endothelial Growth Factor |
| **XIST** | X-Inactive-Specific Transcript |

## References

[1] H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, F. Bray, Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA A Cancer J. Clin. 71 (2021) 209–249, https://doi.org/10.3322/caac.21660.

[2] P.J. Kaboli, S. Imani, M. Jomhori, K.-H. Ling, Chemoresistance in breast cancer: PI3K/Akt pathway inhibitors vs the current chemotherapy, Am. J. Cancer Res. 11 (2021) 5155–5183.

[3] P. Jabbarzadeh Kaboli, S. Shabani, S. Sharma, M. Partovi Nasr, H. Yamaguchi, M.-C. Hung, Shedding light on triple-negative breast cancer with Trop2-targeted antibody-drug conjugates, Am. J. Cancer Res. 12 (2022) 1671–1685.

[4] X. Ren, L. Yuan, S. Shen, H. Wu, J. Lu, Z. Liang, c-Met and ERβ expression differences in basal-like and non-basal-like triple-negative breast cancer, Tumour Biol. J. Int. Soc. Oncodevelopmental Biol. Med. 37 (2016) 11385–11395, https://doi.org/10.1007/s13277-016-5010-5.

[5] P. Jabbarzadeh Kaboli, S. Luo, Y. Chen, M. Jomhori, S. Imani, S. Xiang, Z. Wu, M. Li, J. Shen, Y. Zhao, X. Wu, C. Hin Cho, Z. Xiao, Pharmacotranscriptomic profiling of resistant triple-negative breast cancer cells treated with lapatinib and berberine shows upregulation of PI3K/Akt signaling under cytotoxic stress, Gene (2022) 146171, https://doi.org/10.1016/j.gene.2021.146171.

[6] T. Kato, Biological roles of hepatocyte growth factor-Met signaling from genetically modified animals, Biomed. Reports 7 (2017) 495–503, https://doi.org/10.3892/br.2017.1001.

[7] O. Miranda, M. Farooqui, J.M. Siegfried, Status of agents targeting the HGF/c-Met Axis in lung cancer, Cancers 10 (2018), https://doi.org/10.3390/cancers10090280.

[8] S. Yan, X. Jiao, H. Zou, K. Li, Prognostic significance of c-Met in breast cancer: a meta-analysis of 6010 cases, Diagn. Pathol. 10 (2015) 62, https://doi.org/10.1186/s13000-015-0296-y.

[9] M. Inanc, M. Ozkan, H. Karaca, V. Berk, O. Bozkurt, A.O. Duran, E. Ozaslan, H. Akgun, F. Tekelioglu, F. Elmali, Cytokeratin 5/6, c-Met expressions, and PTEN

loss prognostic indicators in triple-negative breast cancer, Med. Oncol. 31 (2014) 801, https://doi.org/10.1007/s12032-013-0801-7.
[10] A.M. Gonzalez-Angulo, H. Chen, M.S. Karuturi, M. Chavez-MacGregor, S. Tsavachidis, F. Meric-Bernstam, K.-A. Do, G.N. Hortobagyi, P.A. Thompson, G. B. Mills, M.L. Bondy, G.R.J. Blumenschein, Frequency of mesenchymal-epithelial transition factor gene (MET) and the catalytic subunit of phosphoinositide-3-kinase (PIK3CA) copy number elevation and correlation with outcome in patients with early stage breast cancer, Cancer 119 (2013) 7–15, https://doi.org/10.1002/cncr.27608.
[11] L. Jia, X. Yang, W. Tian, S. Guo, W. Huang, W. Zhao, Increased expression of c-met is associated with chemotherapy-resistant breast cancer and poor clinical outcome, Med. Sci. Monit. Int. Med. J. Exp. Clin. Res. 24 (2018) 8239–8249, https://doi.org/10.12659/MSM.913514.
[12] Y.-H. Hsu, J. Yao, L.-C. Chan, T.-J. Wu, J.L. Hsu, Y.-F. Fang, Y. Wei, Y. Wu, W.-C. Huang, C.-L. Liu, Y.-C. Chang, M.-Y. Wang, C.-W. Li, J. Shen, M.-K. Chen, A. A. Sahin, A. Sood, G.B. Mills, D. Yu, G.N. Hortobagyi, M.-C. Hung, Definition of PKC-α, CDK6, and MET as therapeutic targets in triple-negative breast cancer, Cancer Res. 74 (2014) 4822–4835, https://doi.org/10.1158/0008-5472.CAN-14-0584.
[13] H.A. El-Attar, M.I. Sheta, Hepatocyte growth factor profile with breast cancer, Indian J. Pathol. Microbiol. 54 (2011) 509–513, https://doi.org/10.4103/0377-4929.85083.
[14] Y. Du, H. Yamaguchi, Y. Wei, J.L. Hsu, H.-L. Wang, Y.-H. Hsu, W.-C. Lin, W.-H. Yu, P.G. Leonard, G.R. Lee, M.-K. Chen, K. Nakai, M.-C. Hsu, C.-T. Chen, Y. Sun, Y. Wu, W.-C. Chang, W.-C. Huang, C.-L. Liu, Y.-C. Chang, C.-H. Chen, M. Park, P. Jones, G.N. Hortobagyi, M.-C. Hung, Blocking c-Met-mediated PARP1 phosphorylation enhances anti-tumor effects of PARP inhibitors, Nat. Med. 22 (2016) 194–201, https://doi.org/10.1038/nm.4032.
[15] Y.-Y. Chu, C. Yam, M.-K. Chen, L.-C. Chan, M. Xiao, Y.-K. Wei, H. Yamaguchi, P.-C. Lee, Y. Han, L. Nie, X. Sun, S.L. Moulder, K.R. Hess, B. Wang, J.L. Hsu, G. N. Hortobagyi, J. Litton, J.T. Chang, M.-C. Hung, Blocking c-Met and EGFR reverses acquired resistance of PARP inhibitors in triple-negative breast cancer, Am. J. Cancer Res. 10 (2020) 648–661.
[16] S. Zhou, Z. Dai, L. Wang, X. Gao, L. Yang, Z. Wang, Q. Wang, Z. Liu, MET inhibition enhances PARP inhibitor efficacy in castration-resistant prostate cancer by suppressing the ATM/ATR and PI3K/AKT pathways, J. Cell Mol. Med. 25 (2021) 11157–11169, https://doi.org/10.1111/jcmm.17037.
[17] Q. Dong, Y. Du, H. Li, C. Liu, Y. Wei, M.-K. Chen, X. Zhao, Y.-Y. Chu, Y. Qiu, L. Qin, H. Yamaguchi, M.-C. Hung, EGFR and c-MET cooperate to enhance resistance to PARP inhibitors in hepatocellular carcinoma, Cancer Res. 79 (2019) 819–829, https://doi.org/10.1158/0008-5472.CAN-18-1273.
[18] C. Mihailidou, M. Vkaramouzis, D. Schizas, A.G. Papavassiliou, Co-targeting c-Met and DNA double-strand breaks (DSBs): therapeutic strategies in BRCA-mutated gastric carcinomas, Biochimie 142 (2017) 135–143, https://doi.org/10.1016/j.biochi.2017.09.001.
[19] S. Dhillon, Capmatinib: first approval, Drugs 80 (2020) 1125–1131, https://doi.org/10.1007/s40265-020-01347-3.
[20] S.M. Tolaney, S. Tan, H. Guo, W. Barry, E. VanAllen, N. Wagle, J. Brock, K. Larrabee, C. Paweletz, E. Ivanova, P. Janne, B. Overmoyer, J.J. Wright, G. I. Shapiro, E.P. Winer, I.E. Krop, Phase II study of tivantinib (ARQ 197) in patients with metastatic triple-negative breast cancer, Invest. N. Drugs 33 (2015) 1108–1114, https://doi.org/10.1007/s10637-015-0269-8.
[21] E. Uchikawa, Z. Chen, G.-Y. Xiao, X. Zhang, X.-C. Bai, Structural basis of the activation of c-MET receptor, Nat. Commun. 12 (2021) 4074, https://doi.org/10.1038/s41467-021-24367-3.
[22] R. Imamura, K. Matsumoto, Hepatocyte growth factor in physiology and infectious diseases, Cytokine 98 (2017) 97–106, https://doi.org/10.1016/j.cyto.2016.12.025.
[23] P.C. Ma, R. Jagadeeswaran, S. Jagadeesh, M.S. Tretiakova, V. Nallasura, E.A. Fox, M. Hansen, E. Schaefer, K. Naoki, A. Lader, W. Richards, D. Sugarbaker, A. N. Husain, J.G. Christensen, R. Salgia, 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. 65 (2005) 1479–1488, https://doi.org/10.1158/0008-5472.CAN-04-2650.
[24] N.A. Lokker, M.R. Mark, E.A. Luis, G.L. Bennett, K.A. Robbins, J.B. Baker, P. J. Godowski, Structure-function analysis of hepatocyte growth factor: identification of variants that lack mitogenic activity yet retain high affinity receptor binding, EMBO J. 11 (1992) 2503–2510, https://doi.org/10.1002/j.1460-2075.1992.tb05315.x.
[25] J.S. Rubin, R.M. Day, D. Breckenridge, N. Atabey, W.G. Taylor, S.J. Stahl, P. T. Wingfield, J.D. Kaufman, R. Schwall, D.P. Bottaro, Dissociation of heparan sulfate and receptor binding domains of hepatocyte growth factor reveals that heparan sulfate-c-met interaction facilitates signaling, J. Biol. Chem. 276 (2001) 32977–32983, https://doi.org/10.1074/jbc.M105486200.
[26] M. Khan, K. Du, M. Ai, B. Wang, J. Lin, A. Ren, C. Chen, Z. Huang, W. Qiu, Y. Yuan, Y. Tian, PD-L1 expression as biomarker of efficacy of PD-1/PD-L1 checkpoint inhibitors in metastatic triple negative breast cancer: a systematic review and meta-analysis, Front. Immunol. 14 (2023) 1060308, https://doi.org/10.3389/fimmu.2023.1060308.
[27] J.M. Lee, B. Kim, S.B. Lee, Y. Jeong, Y.M. Oh, Y.-J. Song, S. Jung, J. Choi, S. Lee, K.H. Cheong, D.U. Kim, H.W. Park, Y.K. Han, G.W. Kim, H. Choi, P.H. Song, K. A. Kim, Cbl-independent degradation of Met: ways to avoid agonism of bivalent Met-targeting antibody, Oncogene 33 (2014) 34–43, https://doi.org/10.1038/onc.2012.551.
[28] G.M. Frampton, S.M. Ali, M. Rosenzweig, J. Chmielecki, X. Lu, T.M. Bauer, M. Akimov, J.A. Bufill, C. Lee, D. Jentz, R. Hoover, S.-H.I. Ou, R. Salgia, T. Brennan, Z.R. Chalmers, S. Jaeger, A. Huang, J.A. Elvin, R. Erlich, A. Fichtenholtz, K.A. Gowen, J. Greenbowe, A. Johnson, D. Khaira, C. McMahon, E.M. Sanford, S. Roels, J. White, J. Greshock, R. Schlegel, D. Lipson, R. Yelensky, D. Morosini, J.S. Ross, E. Collisson, M. Peters, P.J. Stephens, V.A. Miller, Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors, Cancer Discov. 5 (2015) 850–859, https://doi.org/10.1158/2159-8290.CD-15-0285.
[29] A. Drilon, J.W. Clark, J. Weiss, S.-H.I. Ou, D.R. Camidge, B.J. Solomon, G. A. Otterson, L.C. Villaruz, G.J. Riely, R.S. Heist, M.M. Awad, G.I. Shapiro, M. Satouchi, T. Hida, H. Hayashi, D.A. Murphy, S.C. Wang, S. Li, T. Usari, K. D. Wilner, P.K. Paik, Antitumor activity of crizotinib in lung cancers harboring a MET exon 14 alteration, Nat. Med. 26 (2020) 47–51, https://doi.org/10.1038/s41591-019-0716-8.
[30] R.S. Heist, L. Vsequist, D. Borger, J.F. Gainor, R.S. Arellano, L.P. Le, D. Dias-Santagata, J.W. Clark, J.A. Engelman, A.T. Shaw, A.J. Iafrate, Acquired resistance to crizotinib in NSCLC with MET exon 14 skipping, J. Thorac. Oncol. Off. Publ. Int. Assoc. Study Lung Cancer 11 (2016) 1242–1245, https://doi.org/10.1016/j.jtho.2016.06.013.
[31] J.K. Rotow, P. Gui, W. Wu, V.M. Raymond, R.B. Lanman, F.J. Kaye, N. Peled, F. Fece de la Cruz, B. Nadres, R.B. Corcoran, I. Yeh, B.C. Bastian, P. Starostik, K. Newsom, V.R. Olivas, A.M. Wolff, J.S. Fraser, E.A. Collisson, C.E. McCoach, D. R. Camidge, J. Pacheco, L. Bazhenova, T. Li, T.G. Bivona, C.M. Blakely, Co-Occurring alterations in the RAS-MAPK pathway limit response to MET inhibitor treatment in MET exon 14 skipping mutation-positive lung cancer, Clin. Cancer Res. an Off. J. Am. Assoc. Cancer Res. 26 (2020) 439–449, https://doi.org/10.1158/1078-0432.CCR-19-1667.
[32] K. Suzawa, M. Offin, D. Lu, C. Kurzatkowski, M. Vojnic, R.S. Smith, J.K. Sabari, H. Tai, M. Mattar, I. Khodos, E. deStanchina, C.M. Rudin, M.G. Kris, M.E. Arcila, W.W. Lockwood, A. Drilon, M. Ladanyi, R. Somwar, Activation of KRAS mediates resistance to targeted therapy in MET exon 14-mutant non-small cell lung cancer, Clin. Cancer Res. an Off. J. Am. Assoc. Cancer Res. 25 (2019) 1248–1260, https://doi.org/10.1158/1078-0432.CCR-18-1640.
[33] R. French, Y. Feng, S. Pauklin, Targeting TGFβ signalling in cancer: toward context-specific strategies, Trends in Cancer 6 (2020) 538–540, https://doi.org/10.1016/j.trecan.2020.03.010.
[34] Q. Liang, Y. Hu, Q. Yuan, M. Yu, H. Wang, B. Zhao, MET exon 14 skipping mutation drives cancer progression and recurrence via activation of SMAD2 signalling, Br. J. Cancer (2023), https://doi.org/10.1038/s41416-023-02495-5.
[35] S.K. Wong, D. Alex, I. Bosdet, C. Hughesman, A. Karsan, S. Yip, C. Ho, MET exon 14 skipping mutation positive non-small cell lung cancer: response to systemic therapy, Lung Cancer 154 (2021) 142–145, https://doi.org/10.1016/j.lungcan.2021.02.030.
[36] T. Fujino, K. Suda, T. Koga, A. Hamada, S. Ohara, M. Chiba, M. Shimoji, T. Takemoto, J. Soh, T. Mitsudomi, Foretinib can overcome common on-target resistance mutations after capmatinib/tepotinib treatment in NSCLCs with MET exon 14 skipping mutation, J. Hematol. Oncol. 15 (2022) 79, https://doi.org/10.1186/s13045-022-01299-z.
[37] H. Babey, P. Jamme, H. Curcio, J.B. Assié, R. Veillon, H. Doubre, M. Pérol, F. Guisier, E. Huchot, C. Decroisette, L. Falchero, R. Corre, A. Cortot, C. Chouaïd, R. Descourt, Real-World treatment outcomes of MET Exon14 skipping in non-small cell lung cancer: GFPC 03-18 study., target, Oncol. 18 (2023) 585–591, https://doi.org/10.1007/s11523-023-00976-4.
[38] S.B. Yan, S.L. Um, V.L. Peek, J.R. Stephens, W. Zeng, B.W. Konicek, L. Liu, J. R. Manro, V. Wacheck, R.A. Walgren, MET-targeting antibody (emibetuzumab) and kinase inhibitor (merestinib) as single agent or in combination in a cancer model bearing MET exon 14 skipping, Invest. N. Drugs 36 (2018) 536–544, https://doi.org/10.1007/s10637-017-0545-x.
[39] F. Wang, Y. Liu, W. Qiu, E. Shum, M. Feng, D. Zhao, D. Zheng, A. Borczuk, H. Cheng, B. Halmos, Functional analysis of MET exon 14 skipping alteration in cancer invasion and metastatic dissemination, Cancer Res. 82 (2022) 1365–1379, https://doi.org/10.1158/0008-5472.CAN-21-1327.
[40] D. Sun, X. Xing, Y. Wang, H. Hou, MET fusions are targetable genomic variants in the treatment of advanced malignancies, Cell Commun. Signal. 22 (2024) 20, https://doi.org/10.1186/s12964-023-01454-0.
[41] B. Pekova, V. Sykorova, S. Dvorakova, E. Vaclavikova, J. Moravcova, R. Katra, J. Astl, P. Vlcek, D. Kodetova, J. Vcelak, B. Bendlova, RET, NTRK, ALK, BRAF, and MET fusions in a large cohort of pediatric papillary thyroid carcinomas, Thyroid 30 (2020) 1771–1780, https://doi.org/10.1089/thy.2019.0802.
[42] R. Guo, J. Luo, J. Chang, N. Rekhtman, M. Arcila, A. Drilon, MET-dependent solid tumours - molecular diagnosis and targeted therapy, Nat. Rev. Clin. Oncol. 17 (2020) 569–587, https://doi.org/10.1038/s41571-020-0377-z.
[43] Recurrent MET fusion genes represent a drug target in pediatric glioblastoma, Nat. Med. 22 (2016) 1314–1320, https://doi.org/10.1038/nm.4204.
[44] Z.-H. Liu, B.-W. Zhu, M. Shi, Y.-R. Qu, X.-J. He, H.-L. Yuan, J. Ma, W. Li, D.-D. Zhao, Z.-C. Liu, B.-M. Wang, C.-Y. Wang, H.-Q. Tao, T.-H. Ma, Profiling of gene fusion involving targetable genes in Chinese gastric cancer, World J. Gastrointest. Oncol. 14 (2022) 1528–1539, https://doi.org/10.4251/wjgo.v14.i8.1528.
[45] Z. Tao, J. Liu, T. Li, H. Xu, K. Chen, J. Zhang, H. Zhou, J. Sun, J. Han, Z. Guo, H. Yang, W.-M. Cao, X. Hu, Profiling receptor tyrosine kinase fusions in Chinese breast cancers, Front. Oncol. 11 (2021) 741142, https://doi.org/10.3389/fonc.2021.741142.
[46] D. Sun, W. Wu, L. Wang, J. Qu, Q. Han, H. Wang, S. Song, N. Liu, Y. Wang, H. Hou, Identification of MET fusions as novel therapeutic targets sensitive to MET inhibitors in lung cancer, J. Transl. Med. 21 (2023) 150, https://doi.org/10.1186/s12967-023-03999-7.

[47] H. Xia, J. Zhang, T. Chen, M. Wang, D. Chen, T. Si, Y. Liu, Molecular characterization of MET fusions from a large real-world Chinese population: a multicenter study, Cancer Med. 12 (2023) 14015–14024, https://doi.org/10.1002/cam4.6047.

[48] J. Kang, Q.-M. Deng, W. Feng, Z.-H. Chen, J.-W. Su, H.-J. Chen, W.-X. Wang, S. Zhang, Q. Wang, Z. Chen, W.-Z. Zhong, C.-W. Xu, J.-J. Yang, Response and acquired resistance to MET inhibitors in de novo MET fusion-positive advanced non-small cell lung cancer, Lung Cancer 178 (2023) 66–74, https://doi.org/10.1016/j.lungcan.2023.01.017.

[49] M. Lee, P. Jain, F. Wang, P.C. Ma, A. Borczuk, B. Halmos, MET alterations and their impact on the future of non-small cell lung cancer (NSCLC) targeted therapies, Expert Opin. Ther. Targets 25 (2021) 249–268, https://doi.org/10.1080/14728222.2021.1925648.

[50] K. Qin, L. Hong, J. Zhang, X. Le, MET amplification as a resistance driver to TKI therapies in lung cancer: clinical challenges and opportunities, Cancers 15 (2023), https://doi.org/10.3390/cancers15030612.

[51] R. Yoshida, M. Saigi, T. Tani, B.F. Springer, H. Shibata, S. Kitajima, N. R. Mahadevan, M. Campisi, W. Kim, Y. Kobayashi, T.C. Thai, K. Haratani, Y. Yamamoto, S.K. Sundararaman, E.H. Knelson, A. Vajdi, I. Canadas, R. Uppaluri, C.P. Paweletz, J.J. Miret, P.H. Lizotte, P.C. Gokhale, P.A. Jänne, D. A. Barbie, MET-induced CD73 restrains STING-mediated immunogenicity of EGFR-mutant lung cancer, Cancer Res. 82 (2022) 4079–4092, https://doi.org/10.1158/0008-5472.CAN-22-0770.

[52] Y. Wang, P. Tian, L. Xia, L. Li, R. Han, M. Zhu, A. Lizaso, T. Qin, M. Li, B. Yu, X. Mao, H. Han-Zhang, Y. He, The clinical efficacy of combinatorial therapy of EGFR-TKI and crizotinib in overcoming MET amplification-mediated resistance from prior EGFR-TKI therapy, Lung Cancer 146 (2020) 165–173, https://doi.org/10.1016/j.lungcan.2020.06.003.

[53] P. Shi, Y.-T. Oh, G. Zhang, W. Yao, P. Yue, Y. Li, R. Kanteti, J. Riehm, R. Salgia, T. K. Owonikoko, S.S. Ramalingam, M. Chen, S.-Y. Sun, Met gene amplification and protein hyperactivation is a mechanism of resistance to both first and third generation EGFR inhibitors in lung cancer treatment, Cancer Lett. 380 (2016) 494–504, https://doi.org/10.1016/j.canlet.2016.07.021.

[54] T. Sakashita, N. Yanagitani, S. Koike, S.-K. Low, S. Takagi, S. Baba, K. Takeuchi, M. Nishio, N. Fujita, R. Katayama, Fibroblast growth factor receptor 3 overexpression mediates ALK inhibitor resistance in ALK-rearranged non-small cell lung cancer, Cancer Sci. 113 (2022) 3888–3900, https://doi.org/10.1111/cas.15529.

[55] A. Kogita, Y. Togashi, H. Hayashi, E. Banno, M. Terashima, M.A. DeVelasco, K. Sakai, Y. Fujita, S. Tomida, Y. Takeyama, K. Okuno, K. Nakagawa, K. Nishio, Activated MET acts as a salvage signal after treatment with alectinib, a selective ALK inhibitor, in ALK-positive non-small cell lung cancer, Int. J. Oncol. 46 (2015) 1025–1030, https://doi.org/10.3892/ijo.2014.2797.

[56] E.Y. Rosen, M.L. Johnson, S.E. Clifford, R. Somwar, J.F. Kherani, J. Son, A. A. Bertram, M.A. Davare, E. Gladstone, E. Vivanova, D.N. Henry, E.M. Kelley, M. Lin, M.S.D. Milan, B.C. Nair, E.A. Olek, J.E. Scanlon, M. Vojnic, K. Ebata, J. F. Hechtman, B.T. Li, L.M. Sholl, B.S. Taylor, M. Ladanyi, P.A. Jänne, S. M. Rothenberg, A. Drilon, G.R. Oxnard, Overcoming MET-dependent resistance to selective RET inhibition in patients with RET fusion-positive lung cancer by combining selpercatinib with crizotinib, Clin. Cancer Res. an Off. J. Am. Assoc. Cancer Res. 27 (2021) 34–42, https://doi.org/10.1158/1078-0432.CCR-20-2278.

[57] J.J. Lin, S. Vliu, C.E. McCoach, V.W. Zhu, A.C. Tan, S. Yoda, J. Peterson, A. Do, K. Prutisto-Chang, I. Dagogo-Jack, L. Vsequist, L.J. Wirth, J.K. Lennerz, A. N. Hata, M. Mino-Kenudson, V. Nardi, S.-H.I. Ou, D.S.-W. Tan, J.F. Gainor, Mechanisms of resistance to selective RET tyrosine kinase inhibitors in RET fusion-positive non-small-cell lung cancer, Ann. Oncol. Off. J. Eur. Soc. Med. Oncol. 31 (2020) 1725–1733, https://doi.org/10.1016/j.annonc.2020.09.015.

[58] X. Le, S. Puri, M. Vnegrao, M.B. Nilsson, J. Robichaux, T. Boyle, J.K. Hicks, K. L. Lovinger, E. Roarty, W. Rinsurongkawong, M. Tang, H. Sun, Y. Elamin, L. C. Lacerda, J. Lewis, J.A. Roth, S.G. Swisher, J.J. Lee, W.N.J. William, B. S. Glisson, J. Zhang, V.A. Papadimitrakopoulou, J.E. Gray, J. Vheymach, Landscape of EGFR-dependent and -independent resistance mechanisms to osimertinib and continuation therapy beyond progression in EGFR-mutant NSCLC, Clin. Cancer Res. an Off. J. Am. Assoc. Cancer Res. 24 (2018) 6195–6203, https://doi.org/10.1158/1078-0432.CCR-18-1542.

[59] D. Sun, J. Tao, W. Yan, J. Zhu, H. Zhou, Y. Sheng, C. Xue, H. Li, H. Hou, Optimal treatments for NSCLC patients harboring primary or acquired MET amplification, Technol. Cancer Res. Treat. 21 (2022) 15330338221128414, https://doi.org/10.1177/15330338221128414.

[60] K.C. Park, D.R. Richardson, The c-MET oncoprotein: function, mechanisms of degradation and its targeting by novel anti-cancer agents, Biochim. Biophys. Acta Gen. Subj. 1864 (2020) 129650, https://doi.org/10.1016/j.bbagen.2020.129650.

[61] J. Lefebvre, F. Ancot, C. Leroy, G. Muharram, A. Lemière, D. Tulasne, Met degradation: more than one stone to shoot a receptor down, FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol. 26 (2012) 1387–1399, https://doi.org/10.1096/fj.11-197723.

[62] J. Vabella, P. Peschard, M.A. Naujokas, T. Lin, C. Saucier, S. Urbé, M. Park, Met/Hepatocyte growth factor receptor ubiquitination suppresses transformation and is required for Hrs phosphorylation, Mol. Cell Biol. 25 (2005) 9632–9645, https://doi.org/10.1128/MCB.25.21.9632-9645.2005.

[63] F. Schelter, J. Kobuch, M.L. Moss, J.D. Becherer, P.M. Comoglio, C. Boccaccio, A. Krüger, A disintegrin and metalloproteinase-10 (ADAM-10) mediates DN30 antibody-induced shedding of the met surface receptor, J. Biol. Chem. 285 (2010) 26335–26340, https://doi.org/10.1074/jbc.M110.106435.

[64] F. Schelter, M. Grandl, B. Seubert, S. Schaten, S. Hauser, M. Gerg, C. Boccaccio, P. Comoglio, A. Krüger, Tumor cell-derived Timp-1 is necessary for maintaining metastasis-promoting Met-signaling via inhibition of Adam-10, Clin. Exp. Metastasis 28 (2011) 793–802, https://doi.org/10.1007/s10585-011-9410-z.

[65] B. Foveau, F. Ancot, C. Leroy, A. Petrelli, K. Reiss, V. Vingtdeux, S. Giordano, V. Fafeur, D. Tulasne, Down-regulation of the met receptor tyrosine kinase by presenilin-dependent regulated intramembrane proteolysis, Mol. Biol. Cell 20 (2009) 2495–2507, https://doi.org/10.1091/mbc.e08-09-0969.

[66] F. Ancot, C. Leroy, G. Muharram, J. Lefebvre, J. Vicogne, A. Lemiere, Z. Kherrouche, B. Foveau, A. Pourtier, O. Melnyk, S. Giordano, A. Chotteau-Lelievre, D. Tulasne, Shedding-generated Met receptor fragments can be routed to either the proteasomal or the lysosomal degradation pathway, Traffic 13 (2012) 1261–1272, https://doi.org/10.1111/j.1600-0854.2012.01384.x.

[67] D. Tulasne, J. Deheuninck, F.C. Lourenco, F. Lamballe, Z. Ji, C. Leroy, E. Puchois, A. Moumen, F. Maina, P. Mehlen, V. Fafeur, Proapoptotic function of the MET tyrosine kinase receptor through caspase cleavage, Mol. Cell Biol. 24 (2004) 10328–10339, https://doi.org/10.1128/MCB.24.23.10328-10339.2004.

[68] L. Duplaquet, C. Leroy, A. Vinchent, S. Paget, J. Lefebvre, F. VandenAbeele, S. Lancel, F. Giffard, R. Paumelle, G. Bidaux, L. Heliot, L. Poulain, A. Furlan, D. Tulasne, Control of cell death/survival balance by the MET dependence receptor, Elife 9 (2020), https://doi.org/10.7554/eLife.50041.

[69] C.-T. Hu, C.-C. Cheng, J.-R. Wu, S.-M. Pan, W.-S. Wu, PKCε-mediated c-Met endosomal processing directs fluctuant c-Met-JNK-paxillin signaling for tumor progression of HepG2, Cell. Signal. 27 (2015) 1544–1555, https://doi.org/10.1016/j.cellsig.2015.02.031.

[70] M.-K. Chen, Y. Du, L. Sun, J.L. Hsu, Y.-H. Wang, Y. Gao, J. Huang, M.-C. Hung, H (2)O(2) induces nuclear transport of the receptor tyrosine kinase c-MET in breast cancer cells via a membrane-bound retrograde trafficking mechanism, J. Biol. Chem. 294 (2019) 8516–8528, https://doi.org/10.1074/jbc.RA118.005953.

[71] Y.-N. Wang, H.-H. Lee, H.-J. Lee, Y. Du, H. Yamaguchi, M.-C. Hung, Membrane-bound trafficking regulates nuclear transport of integral epidermal growth factor receptor (EGFR) and ErbB-2, J. Biol. Chem. 287 (2012) 16869–16879, https://doi.org/10.1074/jbc.M111.314799.

[72] X. Hu, F. Tang, P. Liu, T. Zhong, F. Yuan, Q. He, M. vonItzstein, H. Li, L. Weng, X. Yu, Structural and functional insight into the glycosylation impact upon the HGF/c-Met signaling pathway, Front. Cell Dev. Biol. 8 (2020) 490, https://doi.org/10.3389/fcell.2020.00490.

[73] A. Saitou, Y. Hasegawa, N. Fujitani, S. Ariki, Y. Uehara, U. Hashimoto, A. Saito, K. Kuronuma, K. Matsumoto, H. Chiba, M. Takahashi, N-glycosylation regulates MET processing and signaling, Cancer Sci. 113 (2022) 1292–1304, https://doi.org/10.1111/cas.15278.

[74] W.L. Lv, Y.Y. Hu, Z.N. Li, W. Zhang, Q. Pan, PAX3 silencing suppresses gastric cancer proliferation and angiogenesis via MET/PI3K signaling, Neoplasma 67 (2020) 304–311, https://doi.org/10.4149/neo_2019_190429N378.

[75] Z. Wang, Y. Nie, K. Zhang, H. Xu, T.A. Ramelot, M.A. Kennedy, M. Liu, J. Zhu, Y. Yang, Solution structure of SHIP2 SH2 domain and its interaction with a phosphotyrosine peptide from c-MET, Arch. Biochem. Biophys. 656 (2018) 31–37, https://doi.org/10.1016/j.abb.2018.08.012.

[76] C. Ponzetto, A. Bardelli, F. Maina, P. Longati, G. Panayotou, R. Dhand, M. D. Waterfield, P.M. Comoglio, A novel recognition motif for phosphatidylinositol 3-kinase binding mediates its association with the hepatocyte growth factor/scatter factor receptor, Mol. Cell Biol. 13 (1993) 4600–4608, https://doi.org/10.1128/mcb.13.8.4600-4608.1993.

[77] S. Mitra, A. Bal, D. Kashyap, S. Kumar, S. Shrivastav, A. Das, G. Singh, Tumour angiogenesis and c-Met pathway activation - implications in breast cancer, APMIS 128 (2020) 316–325, https://doi.org/10.1111/apm.13031.

[78] Y. Zhu, H. Zhang, X. Han, Z. Wang, Y. Cui, R. Tian, Z. Wang, B. Han, J. Tian, F. Zhang, R. Niu, STAT3 mediated upregulation of C-MET signaling acts as a compensatory survival mechanism upon EGFR family inhibition in chemoresistant breast cancer cells, Cancer Lett. 519 (2021) 328–342, https://doi.org/10.1016/j.canlet.2021.07.048.

[79] F. Cattaneo, M. Parisi, R. Ammendola, WKYMVm-induced cross-talk between FPR2 and HGF receptor in human prostate epithelial cell line PNT1A, FEBS Lett. 587 (2013) 1536–1542, https://doi.org/10.1016/j.febslet.2013.03.036.

[80] I. Seiden-Long, R. Navab, W. Shih, M. Li, J. Chow, C.Q. Zhu, N. Radulovich, C. Saucier, M.-S. Tsao, Gab1 but not Grb2 mediates tumor progression in Met overexpressing colorectal cancer cells, Carcinogenesis 29 (2008) 647–655, https://doi.org/10.1093/carcin/bgn009.

[81] Z. He, S. Zhang, Tumor-associated macrophages and their functional transformation in the hypoxic tumor microenvironment, Front. Immunol. 12 (2021) 741305, https://doi.org/10.3389/fimmu.2021.741305.

[82] L. Chen, Y. Shi, X. Zhu, W. Guo, M. Zhang, Y. Che, L. Tang, X. Yang, Q. You, Z. Liu, IL-10 secreted by cancer-associated macrophages regulates proliferation and invasion in gastric cancer cells via c-Met/STAT3 signaling, Oncol. Rep. 42 (2019) 595–604, https://doi.org/10.3892/or.2019.7206.

[83] H. Wang, Y.-F. Yang, L. Zhao, F.-J. Xiao, Q.-W. Zhang, M.-L. Wen, C.-T. Wu, R.-Y. Peng, L.-S. Wang, Hepatocyte growth factor gene-modified mesenchymal stem cells reduce radiation-induced lung injury, Hum. Gene Ther. 24 (2013) 343–353, https://doi.org/10.1089/hum.2012.177.

[84] M. Cutolo, R. Campitiello, E. Gotelli, S. Soldano, The role of M1/M2 macrophage polarization in rheumatoid arthritis synovitis, Front. Immunol. 13 (2022) 867260, https://doi.org/10.3389/fimmu.2022.867260.

[85] N. Nishikoba, K. Kumagai, S. Kanmura, Y. Nakamura, M. Ono, H. Eguchi, T. Kamibayashiyama, K. Oda, S. Mawatari, S. Tanoue, S. Hashimoto, H. Tsubouchi, A. Ido, HGF-MET signaling shifts M1 macrophages toward an M2-like phenotype through PI3K-mediated induction of arginase-1 expression, Front. Immunol. 11 (2020) 2135, https://doi.org/10.3389/fimmu.2020.02135.

[86] W. Choi, J. Lee, J. Lee, S.H. Lee, S. Kim, Hepatocyte growth factor regulates macrophage transition to the M2 phenotype and promotes murine skeletal muscle regeneration, Front. Physiol. 10 (2019) 914, https://doi.org/10.3389/fphys.2019.00914.

[87] P.J. Kaboli, L. Zhang, S. Xiang, J. Shen, M. Li, Y. Zhao, X. Wu, Q. Zhao, H. Zhang, L. Lin, J. Yin, Y. Wu, L. Wan, T. Yi, X. Li, C.H. Cho, J. Li, Z. Xiao, Q. Wen, Molecular markers of regulatory T cells in cancer immunotherapy with special focus on acute myeloid leukemia (aml) - a systematic review, Curr. Med. Chem. 27 (2020) 4673–4698, https://doi.org/10.2174/0929867326666191004164041.

[88] X. Huang, Z. Chen, N. Zhang, C. Zhu, X. Lin, J. Yu, Z. Chen, P. Lan, Y. Wan, Increase in CD4(+)FOXP3(+) regulatory T cell number and upregulation of the HGF/c-Met signaling pathway during the liver metastasis of colorectal cancer, Oncol. Lett. 20 (2020) 2113–2118, https://doi.org/10.3892/ol.2020.11785.

[89] J. Palle, L. Hirsch, A. Lapeyre-Prost, D. Malka, M. Bourhis, S. Pernot, E. Marcheteau, T. Voron, F. Castan, A. Lacotte, N. Benhamouda, C. Tanchot, E. François, F. Ghiringhelli, C. dela Fouchardière, A. Zaanan, E. Tartour, J. Taieb, M. Terme, Targeting HGF/c-Met Axis decreases circulating regulatory T cells accumulation in gastric cancer patients, Cancers 13 (2021), https://doi.org/10.3390/cancers13215562.

[90] Y. Liu, M.R. Smith, Y. Wang, R.J. D'Agostino, J. Ruiz, T. Lycan, G.L. Kucera, L. D. Miller, W. Li, M.D. Chan, M. Farris, J. Su, Q. Song, D. Zhao, A. Chandrasekaran, F. Xing, c-Met mediated cytokine network promotes brain metastasis of breast cancer by remodeling neutrophil activities, Cancers 15 (2023), https://doi.org/10.3390/cancers15092626.

[91] D. Jiao, J. Chen, Y. Li, X. Tang, J. Wang, W. Xu, J. Song, Y. Li, H. Tao, Q. Chen, miR-1-3p and miR-206 sensitizes HGF-induced gefitinib-resistant human lung cancer cells through inhibition of c-Met signalling and EMT, J. Cell Mol. Med. 22 (2018) 3526–3536, https://doi.org/10.1111/jcmm.13629.

[92] Y. Fu, C. Li, Y. Luo, L. Li, J. Liu, R. Gui, Silencing of long non-coding RNA MIAT sensitizes lung cancer cells to gefitinib by epigenetically regulating miR-34a, Front. Pharmacol. 9 (2018) 82, https://doi.org/10.3389/fphar.2018.00082.

[93] Q. Chen, D. Jiao, Y. Wu, J. Chen, J. Wang, X. Tang, H. Mou, H. Hu, J. Song, J. Yan, L. Wu, J. Chen, Z. Wang, MiR-206 inhibits HGF-induced epithelial-mesenchymal transition and angiogenesis in non-small cell lung cancer via c-Met/PI3k/Akt/mTOR pathway, Oncotarget 7 (2016) 18247–18261, https://doi.org/10.18632/oncotarget.7570.

[94] B.-H. Choi, D.Y. Ryu, I.-G. Ryoo, M.-K. Kwak, NFE2L2/NRF2 silencing-inducible miR-206 targets c-MET/EGFR and suppresses BCRP/ABCG2 in cancer cells, Oncotarget 8 (2017) 107188–107205, https://doi.org/10.18632/oncotarget.22513.

[95] C. Dai, Y. Xie, X. Zhuang, Z. Yuan, MiR-206 inhibits epithelial ovarian cancer cells growth and invasion via blocking c-Met/AKT/mTOR signaling pathway, Biomed. Pharmacother. 104 (2018) 763–770, https://doi.org/10.1016/j.biopha.2018.05.077.

[96] W. Qu, X. Chen, J. Wang, J. Lv, D. Yan, MicroRNA-1 inhibits ovarian cancer cell proliferation and migration through c-Met pathway, Clin. Chim. Acta 473 (2017) 237–244, https://doi.org/10.1016/j.cca.2017.07.008.

[97] A.-H. Chen, Y.-E. Qin, W.-F. Tang, J. Tao, H.-M. Song, M. Zuo, MiR-34a and miR-206 act as novel prognostic and therapy biomarkers in cervical cancer, Cancer Cell Int. 17 (2017) 63, https://doi.org/10.1186/s12935-017-0431-9.

[98] S. Gao, Z. Zhao, R. Wu, L. Wu, X. Tian, Z. Zhang, MiR-1 inhibits prostate cancer PC3 cells proliferation through the Akt/mTOR signaling pathway by binding to c-Met, Biomed. Pharmacother. 109 (2019) 1406–1410, https://doi.org/10.1016/j.biopha.2018.10.098.

[99] Y. Luo, J. Ouyang, D. Zhou, S. Zhong, M. Wen, W. Ou, H. Yu, L. Jia, Y. Huang, Long noncoding RNA GAPLINC promotes cells migration and invasion in colorectal cancer cell by regulating miR-34a/c-MET signal pathway, Dig. Dis. Sci. 63 (2018) 890–899, https://doi.org/10.1007/s10620-018-4915-9.

[100] J. Lyu, Y. Sun, X. Li, H. Ma, MicroRNA-206 inhibits the proliferation, migration and invasion of colorectal cancer cells by regulating the c-Met/AKT/GSK-3β pathway, Oncol. Lett. 21 (2021) 147, https://doi.org/10.3892/ol.2020.12408.

[101] X.L. Ren, G.Y. He, X.M. Li, H. Men, L.Z. Yi, G.F. Lu, S.N. Xin, P.X. Wu, Y.L. Li, W. T. Liao, Y.Q. Ding, L. Liang, MicroRNA-206 functions as a tumor suppressor in colorectal cancer by targeting FMNL2, J. Cancer Res. Clin. Oncol. 142 (2016) 581–592, https://doi.org/10.1007/s00432-015-2053-8.

[102] Z. Zheng, D. Yan, X. Chen, H. Huang, K. Chen, G. Li, L. Zhou, D. Zheng, L. Tu, X. DaDong, MicroRNA-206: effective inhibition of gastric cancer progression through the c-met pathway, PLoS One 10 (2015) e0128751, https://doi.org/10.1371/journal.pone.0128751.

[103] Y. Dang, D. Luo, M. Rong, G. Chen, Underexpression of miR-34a in hepatocellular carcinoma and its contribution towards enhancement of proliferating inhibitory effects of agents targeting c-MET, PLoS One 8 (2013) e61054, https://doi.org/10.1371/journal.pone.0061054.

[104] J. Zhang, X. Fa, Q. Zhang, MicroRNA-206 exerts anti-oncogenic functions in esophageal squamous cell carcinoma by suppressing the c-Met/AKT/mTOR pathway, Mol. Med. Rep. 19 (2019) 1491–1500, https://doi.org/10.3892/mmr.2018.9775.

[105] J. Chu, J. Jia, L. Yang, Y. Qu, H. Yin, J. Wan, F. He, LncRNA MIR31HG functions as a ceRNA to regulate c-Met function by sponging miR-34a in esophageal squamous cell carcinoma, Biomed. Pharmacother. 128 (2020) 110313, https://doi.org/10.1016/j.biopha.2020.110313.

[106] K. Koshizuka, T. Hanazawa, I. Fukumoto, N. Kikkawa, R. Matsushita, H. Mataki, K. Mizuno, Y. Okamoto, N. Seki, Dual-receptor (EGFR and c-MET) inhibition by tumor-suppressive miR-1 and miR-206 in head and neck squamous cell carcinoma, J. Hum. Genet. 62 (2017) 113–121, https://doi.org/10.1038/jhg.2016.47.

[107] F. Liu, N. Chen, Y. Gong, R. Xiao, W. Wang, Z. Pan, The long non-coding RNA NEAT1 enhances epithelial-to-mesenchymal transition and chemoresistance via the miR-34a/c-Met axis in renal cell carcinoma, Oncotarget 8 (2017) 62927–62938, https://doi.org/10.18632/oncotarget.17757.

[108] F.B. Zhan, X.W. Zhang, S.L. Feng, J. Cheng, Y. Zhang, B. Li, L.Z. Xie, Q.R. Deng, MicroRNA-206 reduces osteosarcoma cell malignancy in vitro by targeting the PAX3-MET Axis, Yonsei Med. J. 60 (2019) 163–173, https://doi.org/10.3349/ymj.2019.60.2.163.

[109] K. Zhu, W. Wang, Green tea polyphenol EGCG suppresses osteosarcoma cell growth through upregulating miR-1, Tumour Biol. J. Int. Soc. Oncodevelopmental Biol. Med. 37 (2016) 4373–4382, https://doi.org/10.1007/s13277-015-4187-3.

[110] Z. Sun, T. Zhang, B. Chen, Long non-coding RNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) promotes proliferation and metastasis of osteosarcoma cells by targeting c-met and SOX4 via miR-34a/c-5p and miR-449a/b, Med. Sci. Monit. Int. Med. J. Exp. Clin. Res. 25 (2019) 1410–1422, https://doi.org/10.12659/MSM.912703.

[111] L. Li, Y. Zheng, W. Zhang, L. Hou, Y. Gao, Scutellarin circumvents chemoresistance, promotes apoptosis, and represses tumor growth by HDAC/miR-34a-mediated down-modulation of Akt/mTOR and NF-κB-orchestrated signaling pathways in multiple myeloma, Int. J. Clin. Exp. Pathol. 13 (2020) 212–219.

[112] S. Georges, L.R. Calleja, C. Jacques, M. Lavaud, B. Moukengue, F. Lecanda, T. Quillard, M.T. Gabriel, P.-F. Cartron, M. Baud'huin, F. Lamoureux, D. Heymann, B. Ory, Loss of miR-198 and -206 during primary tumor progression enables metastatic dissemination in human osteosarcoma, Oncotarget 9 (2018) 35726–35741, https://doi.org/10.18632/oncotarget.26284.

[113] R. ElBezawy, M. DeCesare, M. Pennati, M. Deraco, P. Gandellini, V. Zuco, N. Zaffaroni, Antitumor activity of miR-34a in peritoneal mesothelioma relies on c-MET and AXL inhibition: persistent activation of ERK and AKT signaling as a possible cytoprotective mechanism, J. Hematol. Oncol. 10 (2017) 19, https://doi.org/10.1186/s13045-016-0387-6.

[114] L. Mu, H. Zhao, Y. Yang, R. Song, Long noncoding RNA NEAT1 aggravates sorafenib-resistance in non-small cell lung cancer via regulating miRNA-335/c-Met, J. BUON. 26 (2021) 345–352.

[115] Y. Liu, X. Huang, D. Lu, Y. Feng, R. Xu, X. Li, C. Yin, B. Xue, H. Zhao, S. Wang, Y. Ma, C. Jia, LncRNA SNHG4 promotes the increased growth of endometrial tissue outside the uterine cavity via regulating c-Met mediated by miR-148a-3p, Mol. Cell. Endocrinol. 514 (2020) 110887, https://doi.org/10.1016/j.mce.2020.110887.

[116] Y. Liu, L. Chen, T. Liu, X. Su, L. Peng, J. Chen, F. Tan, P. Xing, Z. Wang, J. Di, B. Jiang, H. Qu, Genome-wide circular RNA (circRNA) and mRNA profiling identify a circMET-miR-410-3p regulatory motif for cell growth in colorectal cancer, Genomics 114 (2022) 351–360, https://doi.org/10.1016/j.ygeno.2021.11.038.

[117] J.T. Saunders, S. Kumar, A. Benavides-Serrato, B. Holmes, K.E. Benavides, M. T. Bashir, R.N. Nishimura, J. Gera, Translation of circHGF RNA encodes an HGF protein variant promoting glioblastoma growth through stimulation of c-MET, J. Neuro Oncol. 163 (2023) 207–218, https://doi.org/10.1007/s11060-023-04331-5.

[118] J. Zhong, X. Wu, Y. Gao, J. Chen, M. Zhang, H. Zhou, J. Yang, F. Xiao, X. Yang, N. Huang, H. Qi, X. Wang, F. Bai, Y. Shi, N. Zhang, Circular RNA encoded MET variant promotes glioblastoma tumorigenesis, Nat. Commun. 14 (2023) 4467, https://doi.org/10.1038/s41467-023-40212-1.

[119] L. Yang, Y. Chen, N. Liu, Y. Lu, W. Ma, Z. Yang, W. Gan, D. Li, CircMET promotes tumor proliferation by enhancing CDKN2A mRNA decay and upregulating SMAD3, Mol. Cancer 21 (2022) 23, https://doi.org/10.1186/s12943-022-01497-w.

[120] M.-D. Yao, Q. Jiang, Y. Ma, Y. Zhu, Q.-Y. Zhang, Z.-H. Shi, C. Zhao, B. Yan, Targeting circular RNA-MET for anti-angiogenesis treatment via inhibiting endothelial tip cell specialization, Mol. Ther. 30 (2022) 1252–1264, https://doi.org/10.1016/j.ymthe.2022.01.012.

[121] F. Bersani, F. Picca, D. Morena, L. Righi, F. Napoli, M. Russo, D. Oddo, G. Rospo, C. Negrino, B. Castella, M. Volante, A. Listì, V. Zambelli, F. Benso, F. Tabbò, P. Bironzo, E. Monteleone, V. Poli, F. Pietrantonio, F. DiNicolantonio, A. Bardelli, C. Ponzetto, S. Novello, G. Vscagliotti, R. Taulli, Exploring circular MET RNA as a potential biomarker in tumors exhibiting high MET activity, J. Exp. Clin. Cancer Res. 42 (2023) 120, https://doi.org/10.1186/s13046-023-02690-5.

[122] L. Hong, J. Zhang, J. Vheymach, X. Le, Current and future treatment options for MET exon 14 skipping alterations in non-small cell lung cancer, Ther. Adv. Med. Oncol. 13 (2021) 1758835921992976, https://doi.org/10.1177/1758835921992976.

[123] E. Gherardi, W. Birchmeier, C. Birchmeier, G. VandeWoude, Targeting MET in cancer: rationale and progress, Nat. Rev. Cancer 12 (2012) 89–103, https://doi.org/10.1038/nrc3205.

[124] R.J. Roskoski, Classification of small molecule protein kinase inhibitors based upon the structures of their drug-enzyme complexes, Pharmacol. Res. 103 (2016) 26–48, https://doi.org/10.1016/j.phrs.2015.10.021.

[125] L.D. Engstrom, R. Aranda, M. Lee, E.A. Tovar, C.J. Essenburg, Z. Madaj, H. Chiang, D. Briere, J. Hallin, P.P. Lopez-Casas, N. Baños, C. Menendez, M. Hidalgo, V. Tassell, R. Chao, D.I. Chudova, R.B. Lanman, P. Olson, L. Bazhenova, S.P. Patel, C. Graveel, M. Nishino, G.I. Shapiro, N. Peled, M. M. Awad, P.A. Jänne, J.G. Christensen, 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. an Off. J. Am. Assoc. Cancer Res. 23 (2017) 6661–6672, https://doi.org/10.1158/1078-0432.CCR-17-1192.

[126] A. Martorana, G. LaMonica, A. Lauria, Quinoline-based molecules targeting c-met, EGF, and VEGF receptors and the proteins involved in related carcinogenic pathways, Molecules 25 (2020), https://doi.org/10.3390/molecules25184279.
[127] J.W. Zhang, W. Xiao, Z.T. Gao, Z.T. Yu, J.Y.J. Zhang, Metabolism of c-met kinase inhibitors containing quinoline by aldehyde oxidase, electron donating, and steric hindrance effect, Drug Metab. Dispos. 46 (2018) 1847–1855, https://doi.org/10.1124/dmd.118.081919.
[128] A. Desai, S. Cuellar, The current landscape for METex14 skipping mutations in non-small cell lung cancer, J. Adv. Pract. Oncol. 13 (2022) 539–544, https://doi.org/10.6004/jadpro.2022.13.5.8.
[129] S. Kim, J.M. Park, S. Park, E. Jung, D. Ko, M. Park, J. Seo, K.D. Nam, Y.K. Kang, K. Lee, L. Farrand, Y.-J. Kim, J.Y. Kim, J.H. Seo, Suppression of TNBC metastasis by doxazosin, a novel dual inhibitor of c-MET/EGFR, J. Exp. Clin. Cancer Res. 42 (2023) 292, https://doi.org/10.1186/s13046-023-02866-z.
[130] Hannaneh Parvaresh, Ghazaal Roozitalab, Fatemeh Golandam, Payam Behzadi, Jabbarzadeh Kaboli Parham, Unraveling the potential of ALK-targeted therapies in, Biomedicines 12 (2024) 297, https://doi.org/10.3390/biomedicines12020297.
[131] G.W. Collie, C.M. Koh, D.J. O'Neill, C.J. Stubbs, P. Khurana, A. Eddershaw, A. Snijder, F. Mauritzson, L. Barlind, I.L. Dale, J. Shaw, C. Phillips, E.J. Hennessy, T. Cheung, A.J. Narvaez, Structural and molecular insight into resistance mechanisms of first generation cMET inhibitors, ACS Med. Chem. Lett. 10 (2019) 1322–1327, https://doi.org/10.1021/acsmedchemlett.9b00276.
[132] S.B. Yan, V.L. Peek, R. Ajamie, S.G. Buchanan, J.R. Graff, S.A. Heidler, Y.-H. Hui, K.L. Huss, B.W. Konicek, J.R. Manro, C. Shih, J.A. Stewart, T.R. Stewart, S. L. Stout, M.T. Uhlik, S.L. Um, Y. Wang, W. Wu, L. Yan, W.J. Yang, B. Zhong, R. A. Walgren, LY2801653 is an orally bioavailable multi-kinase inhibitor with potent activity against MET, MST1R, and other oncoproteins, and displays anti-tumor activities in mouse xenograft models, Invest. N. Drugs 31 (2013) 833–844, https://doi.org/10.1007/s10637-012-9912-9.
[133] J.J. Cui, M. Tran-Dubé, H. Shen, M. Nambu, P.-P. Kung, M. Pairish, L. Jia, J. Meng, L. Funk, I. Botrous, M. McTigue, N. Grodsky, K. Ryan, E. Padrique, G. Alton, S. Timofeevski, S. Yamazaki, Q. Li, H. Zou, J. Christensen, B. Mroczkowski, S. Bender, R.S. Kania, M.P. Edwards, Structure based drug design of crizotinib (PF-02341066), a potent and selective dual inhibitor of mesenchymal-epithelial transition factor (c-MET) kinase and anaplastic lymphoma kinase (ALK), J. Med. Chem. 54 (2011) 6342–6363, https://doi.org/10.1021/jm2007613.
[134] BIOVIA, Dassault Systèmes, Discovery Studio Visualizer,v.21.1.0.20298. San Diego, 2020.
[135] W. Min, Y. Wang, H. Shen, M. Zheng, C. Tong, H. Shen, D. Wang, Y. Zhu, X. Wang, Y. Xiao, X.-Y. Zhang, P. Yang, Discovery of potent and selective c-Met inhibitors for MET-amplified hepatocellular carcinoma treatment, Eur. J. Med. Chem. 264 (2024) 116025, https://doi.org/10.1016/j.ejmech.2023.116025.
[136] J. Hu, L. Chen, Z. Lu, H. Yao, Y. Hu, L. Feng, Y. Pang, J.-Q. Wu, Z. Yu, W.-H. Chen, Design, synthesis and antitumor activity of novel selenium-containing tepotinib derivatives as dual inhibitors of c-met and TrxR, Molecules 28 (2023), https://doi.org/10.3390/molecules28031304.
[137] L. Sima, Z. Wang, L. Yu, Y. Hou, D. Zhao, B. Luo, W. Liao, X. Liu, Discovery of LAH-1 as potent c-Met inhibitor for the treatment of non-small cell lung cancer, J. Enzym. Inhib. Med. Chem. 39 (2024) 2286435, https://doi.org/10.1080/14756366.2023.2286435.
[138] S. Tang, C. Sun, X. He, W. Gan, L. Wang, D. Qiao, X. Guan, S. Xu, P. Zheng, W. Zhu, Design, synthesis, and biological evaluation of 4-(2-fluorophenoxy)-7-methoxyquinazoline derivatives as dual EGFR/c-Met inhibitors for the treatment of NSCLC, Eur. J. Med. Chem. 263 (2024) 115939, https://doi.org/10.1016/j.ejmech.2023.115939.
[139] H. Zhang, W. Gan, D. Fan, P. Zheng, Q. Lv, Q. Pan, W. Zhu, Novel quinazoline-based dual EGFR/c-Met inhibitors overcoming drug resistance for the treatment of NSCLC: design, synthesis and anti-tumor activity, Bioorg. Chem. 142 (2024) 106938, https://doi.org/10.1016/j.bioorg.2023.106938.
[140] L. Lang, F. Chen, Y. Li, C. Shay, F. Yang, H. Dan, Z.G. Chen, N.F. Saba, Y. Teng, Adaptive c-met-PLXDC2 signaling Axis mediates cancer stem cell plasticity to confer radioresistance-associated aggressiveness in head and neck cancer, Cancer Res. Commun 3 (2023) 659–671, https://doi.org/10.1158/2767-9764.CRC-22-0289.
[141] X. Dong, X. Li, J. Chen, S. Ma, D. Mu, J. Hu, S. Lu, Phase 1 study of the selective c-MET inhibitor, HS-10241, in patients with advanced solid tumors, JTO Clin. Res. Reports. 4 (2023) 100449, https://doi.org/10.1016/j.jtocrr.2022.100449.
[142] I.N. Michaelides, G.W. Collie, U. Börjesson, C. Vasalou, O. Alkhatib, L. Barlind, T. Cheung, I.L. Dale, K.J. Embrey, E.J. Hennessy, P. Khurana, C.M. Koh, M. L. Lamb, J. Liu, T.A. Moss, D.J. O'Neill, C. Phillips, J. Shaw, A. Snijder, R.I. Storer, C.J. Stubbs, F. Han, C. Li, J. Qiao, D.-Q. Sun, J. Wang, P. Wang, W. Yang, Discovery and optimization of the first ATP competitive type-III c-MET inhibitor, J. Med. Chem. 66 (2023) 8782–8807, https://doi.org/10.1021/acs.jmedchem.3c00401.
[143] Z. Bao, S. Li, L. Wang, B. Zhang, P. Zhang, H. Shi, X. Qiu, T. Jiang, PTPRZ1-METFUsion GENe (ZM-FUGEN) trial: study protocol for a multicentric, randomized, open-label phase II/III trial, Chinese Neurosurg. J. 9 (2023) 21, https://doi.org/10.1186/s41016-023-00329-0.
[144] D.R. Spigel, M.J. Edelman, K. O'Byrne, L. Paz-Ares, S. Mocci, S. Phan, D. S. Shames, D. Smith, W. Yu, V.E. Paton, T. Mok, 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. Off. J. Am. Soc. Clin. Oncol. 35 (2017) 412–420, https://doi.org/10.1200/JCO.2016.69.2160.
[145] R. Vafaei, Z. Khaki, M. Salehi, N. Jalili, M.R. Esmailinejad, A. Muhammadnajad, S.M. Nassiri, A. Vajhi, S.M. Kalbolandi, R. Mirzaei, L. Farahmand, Development of a MET-targeted single-chain antibody fragment as an anti-oncogene targeted therapy for breast cancer, Invest. N. Drugs 41 (2023) 226–239, https://doi.org/10.1007/s10637-023-01354-7.
[146] X. Dou, Q. Xu, B. Dong, G. Xu, N. Qian, C. Yang, H. Li, L. Chen, X. Gao, H. Song, Anti-c-MET fab-grb2-gab1 fusion protein-mediated interference of c-MET signaling pathway induces methuosis in tumor cells, Int. J. Mol. Sci. 23 (2022), https://doi.org/10.3390/ijms231912018.
[147] S. Vijayaraghavan, L. Lipfert, K. Chevalier, B.S. Bushey, B. Henley, R. Lenhart, J. Sendecki, M. Beqiri, H.J. Millar, K. Packman, M. Vlorenzi, S. Laquerre, S. L. Moores, Amivantamab (JNJ-61186372), an Fc enhanced EGFR/cMet bispecific antibody, induces receptor downmodulation and antitumor activity by monocyte/macrophage trogocytosis, Mol. Cancer Therapeut. 19 (2020) 2044–2056, https://doi.org/10.1158/1535-7163.MCT-20-0071.
[148] R.P. Taylor, M.A. Lindorfer, Fcγ-receptor-mediated trogocytosis impacts mAb-based therapies: historical precedence and recent developments, Blood 125 (2015) 762–766, https://doi.org/10.1182/blood-2014-10-569244.
[149] L.S. Rosen, J.W. Goldman, A.P. Algazi, P.K. Turner, B. Moser, T. Hu, X.A. Wang, J. Tuttle, V. Wacheck, J.E. Wooldridge, M. Banck, 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. an Off. J. Am. Assoc. Cancer Res. 23 (2017) 1910–1919, https://doi.org/10.1158/1078-0432.CCR-16-1418.
[150] Y. Jin, Z. Zhang, S. Zou, F. Li, H. Chen, C. Peng, X. Deng, C. Wen, B. Shen, Q. Zhan, A novel c-MET-targeting antibody-drug conjugate for pancreatic cancer, Front. Oncol. 11 (2021) 634881, https://doi.org/10.3389/fonc.2021.634881.
[151] B. Min, J. Jin, H. Kim, N.-G. Her, C. Park, D. Kim, J. Yang, J. Hwang, E. Kim, M. Choi, H.Y. Song, D.-H. Nam, Y. Yoon, cIRCR201-dPBD, a novel pyrrolobenzodiazepine dimer-containing site-specific antibody-drug conjugate targeting c-met overexpression tumors, ACS Omega 5 (2020) 25798–25809, https://doi.org/10.1021/acsomega.0c03102.
[152] R. Fujita, V. Blot, E. Wong, C. Stewart, V. Lieuw, R. Richardson, A. Banah, J. Villicana, A. Timmer, J. Coronella, R. Newman, M. Gymnopoulos, A novel non-agonist c-Met antibody drug conjugate with superior potency over a c-Met tyrosine kinase inhibitor in c-Met amplified and non-amplified cancers, Cancer Biol. Ther. 21 (2020) 549–559, https://doi.org/10.1080/15384047.2020.1737490.
[153] J. Min, C. Long, L. Zhang, J. Duan, H. Fan, F. Chu, Z. Li, c-Met specific CAR-T cells as a targeted therapy for non-small cell lung cancer cell A549, Bioengineered 13 (2022) 9216–9232, https://doi.org/10.1080/21655979.2022.2058149.
[154] C.H. Kang, Y. Kim, D.Y. Lee, S.U. Choi, H.K. Lee, C.H. Park, c-Met-Specific chimeric antigen receptor T cells demonstrate anti-tumor effect in c-met positive gastric cancer, Cancers 13 (2021), https://doi.org/10.3390/cancers13225738.
[155] X. Huang, J. Guo, T. Li, L. Jia, X. Tang, J. Zhu, Q. Tang, Z. Feng, c-Met-targeted chimeric antigen receptor T cells inhibit hepatocellular carcinoma cells in vitro and in vivo, J. Biomed. Res. 36 (2021) 10–21, https://doi.org/10.7555/JBR.35.20200207.
[156] B. Liu, Z.-Z. Liu, M.-L. Zhou, J.-W. Lin, X.-M. Chen, Z. Li, W.-B. Gao, Z.-D. Yu, T. Liu, Development of c-MET-specific chimeric antigen receptor-engineered natural killer cells with cytotoxic effects on human liver cancer HepG2 cells, Mol. Med. Rep. 20 (2019) 2823–2831, https://doi.org/10.3892/mmr.2019.10529.
[157] J. Tchou, Y. Zhao, B.L. Levine, P.J. Zhang, M.M. Davis, J.J. Melenhorst, I. Kulikovskaya, A.L. Brennan, X. Liu, S.F. Lacey, A.D.J. Posey, A.D. Williams, A. So, J.R. Conejo-Garcia, G. Plesa, R.M. Young, S. McGettigan, J. Campbell, R. H. Pierce, J.M. Matro, A.M. DeMichele, A.S. Clark, L.J. Cooper, L.M. Schuchter, R. H. Vonderheide, C.H. June, Safety and efficacy of intratumoral injections of chimeric antigen receptor (CAR) T cells in metastatic breast cancer, Cancer Immunol. Res. 5 (2017) 1152–1161, https://doi.org/10.1158/2326-6066.CIR-17-0189.
[158] C. Chen, Y.-M. Gu, F. Zhang, Z.-C. Zhang, Y.-T. Zhang, Y.-D. He, L. Wang, N. Zhou, F.-T. Tang, H.-J. Liu, Y.-M. Li, Construction of PD1/CD28 chimeric-switch receptor enhances anti-tumor ability of c-Met CAR-T in gastric cancer, OncoImmunology 10 (2021) 1901434, https://doi.org/10.1080/2162402X.2021.1901434.
[159] X. Yuan, Z. Sun, Q. Yuan, W. Hou, Q. Liang, Y. Wang, W. Mo, H. Wang, M. Yu, Dual-function chimeric antigen receptor T cells targeting c-Met and PD-1 exhibit potent anti-tumor efficacy in solid tumors, Invest. N. Drugs 39 (2021) 34–51, https://doi.org/10.1007/s10637-020-00978-3.
[160] Y. Peng, W. Zhang, Y. Chen, L. Zhang, H. Shen, Z. Wang, S. Tian, X. Yang, D. Cui, Y. He, X. Chang, Z. Feng, Q. Tang, Y. Mao, Engineering c-Met-CAR NK-92 cells as a promising therapeutic candidate for lung adenocarcinoma, Pharmacol. Res. 188 (2023) 106656, https://doi.org/10.1016/j.phrs.2023.106656.
[161] D. Lau, H. Wadhwa, S. Sudhir, A.C.-C. Chang, S. Jain, A. Chandra, A.T. Nguyen, J. M. Spatz, A. Pappu, S.S. Shah, J. Cheng, M.M. Safaee, G. Yagnik, A. Jahangiri, M. K. Aghi, Role of c-Met/β1 integrin complex in the metastatic cascade in breast cancer, JCI Insight 6 (2021), https://doi.org/10.1172/jci.insight.138928.
[162] F. Xing, Y. Liu, S.-Y. Wu, K. Wu, S. Sharma, Y.-Y. Mo, J. Feng, S. Sanders, G. Jin, R. Singh, P.-A. Vidi, A. Tyagi, M.D. Chan, J. Ruiz, W. Debinski, B.C. Pasche, H.-W. Lo, L.J. Metheny-Barlow, R.B.J. D'Agostino, K. Watabe, Loss of XIST in breast cancer activates MSN-c-met and reprograms microglia via exosomal miRNA to promote brain metastasis, Cancer Res. 78 (2018) 4316–4330, https://doi.org/10.1158/0008-5472.CAN-18-1102.
[163] R. Roskoski, The ErbB/HER family of protein-tyrosine kinases and cancer, Pharmacol. Res. 79 (2014) 34–74, https://doi.org/10.1016/j.phrs.2013.11.002.

[164] Y.E. Stern, A. Al-Ghabkari, A. Monast, B. Fiset, F. Aboualizadeh, Z. Yao, I. Stagljar, L.A. Walsh, S. Duhamel, M. Park, Met-HER3 crosstalk supports proliferation via MPZL3 in MET-amplified cancer cells, Cell. Mol. Life Sci. 79 (2022) 178, https://doi.org/10.1007/s00018-022-04149-w.

[165] S.K. Gautam, R.K. Kanchan, J.A. Siddiqui, S.K. Maurya, S. Rauth, N. Perumal, P. Atri, R.C. Venkata, K. Mallya, S. Mirza, M.P. Ponnusamy, V. Band, S. Mahapatra, M. Jain, S.K. Batra, M.W. Nasser, Blocking c-MET/ERBB1 Axis prevents brain metastasis in ERBB2+ breast cancer, Cancers 12 (2020), https://doi.org/10.3390/cancers12102838.

[166] C. Denkert, C. Liedtke, A. Tutt, G. vonMinckwitz, Molecular alterations in triple-negative breast cancer-the road to new treatment strategies, Lancet (London, England) 389 (2017) 2430–2442, https://doi.org/10.1016/S0140-6736(16)32454-0.

[167] H. Chen, J. Wu, Z. Zhang, Y. Tang, X. Li, S. Liu, S. Cao, X. Li, Association between BRCA status and triple-negative breast cancer: a meta-analysis, Front. Pharmacol. 9 (2018) 909, https://doi.org/10.3389/fphar.2018.00909.

[168] A.N.J. Tutt, J.E. Garber, B. Kaufman, G. Viale, D. Fumagalli, P. Rastogi, R. D. Gelber, E. deAzambuja, A. Fielding, J. Balmaña, S.M. Domchek, K.A. Gelmon, S.J. Hollingsworth, L.A. Korde, B. Linderholm, H. Bandos, E. Senkus, J.M. Suga, Z. Shao, A.W. Pippas, Z. Nowecki, T. Huzarski, P.A. Ganz, P.C. Lucas, N. Baker, S. Loibl, R. McConnell, M. Piccart, R. Schmutzler, G.G. Steger, J.P. Costantino, A. Arahmani, N. Wolmark, E. McFadden, V. Karantza, S.R. Lakhani, G. Yothers, C. Campbell, C.E.J. Geyer, Adjuvant olaparib for patients with BRCA1- or BRCA2-mutated breast cancer, N. Engl. J. Med. 384 (2021) 2394–2405, https://doi.org/10.1056/NEJMoa2105215.

[169] B.O. Golden, B. Griess, S. Mir, M. Fitzgerald, C. Kuperwasser, F. Domann, M. Teoh-Fitzgerald, Extracellular superoxide dismutase inhibits hepatocyte growth factor-mediated breast cancer-fibroblast interactions, Oncotarget 8 (2017), https://doi.org/10.18632/oncotarget.22379, 107390–107408.

[170] S.-Y. Shin, A.-K. Müller, N. Verma, S. Lev, L.K. Nguyen, Systems modelling of the EGFR-PYK2-c-Met interaction network predicts and prioritizes synergistic drug combinations for triple-negative breast cancer, PLoS Comput. Biol. 14 (2018) e1006192, https://doi.org/10.1371/journal.pcbi.1006192.

[171] X. Sun, C.-W. Li, W.-J. Wang, M.-K. Chen, H. Li, Y.-J. Lai, J.L. Hsu, P.B. Koller, L.-C. Chan, P.-C. Lee, F.-J. Cheng, C. Yam, G.-Y. Chen, M.-C. Hung, Inhibition of c-MET upregulates PD-L1 expression in lung adenocarcinoma, Am. J. Cancer Res. 10 (2020) 564–571.

[172] H. Li, C.-W. Li, X. Li, Q. Ding, L. Guo, S. Liu, C. Liu, C.-C. Lai, J.-M. Hsu, Q. Dong, W. Xia, J.L. Hsu, H. Yamaguchi, Y. Du, Y.-J. Lai, X. Sun, P.B. Koller, Q. Ye, M.-C. Hung, MET inhibitors promote liver tumor evasion of the immune response by stabilizing PDL1, Gastroenterology 156 (2019), https://doi.org/10.1053/j.gastro.2019.01.252, 1849-1861.e13.

[173] B. Wang, W. Liu, C. Liu, K. Du, Z. Guo, G. Zhang, Z. Huang, S. Lin, B. Cen, Y. Tian, Y. Yuan, J. Bu, Cancer-associated fibroblasts promote radioresistance of breast cancer cells via the HGF/c-Met signaling pathway, Int. J. Radiat. Oncol. Biol. Phys. 116 (2023) 640–654, https://doi.org/10.1016/j.ijrobp.2022.12.029.

[174] K.P. Raghav, W. Wang, S. Liu, M. Chavez-MacGregor, X. Meng, G.N. Hortobagyi, G.B. Mills, F. Meric-Bernstam, G.R.J. Blumenschein, A.M. Gonzalez-Angulo, cMET and phospho-cMET protein levels in breast cancers and survival outcomes, Clin. Cancer Res. an Off. J. Am. Assoc. Cancer Res. 18 (2012) 2269–2277, https://doi.org/10.1158/1078-0432.CCR-11-2830.

[175] F. Iovino, A. Diana, F. Carlino, F. Ferraraccio, G. Antoniol, F. Fisone, A. Perrone, F. Zito Marino, I. Panarese, M.S. Tathode, M. Caraglia, G. Gatta, R. Ruggiero, S. Parisi, F. DeVita, F. Ciardiello, L. Docimo, M. Orditura, Expression of c-MET in estrogen receptor positive and HER2 negative resected breast cancer correlated with a poor prognosis, J. Clin. Med. 11 (2022), https://doi.org/10.3390/jcm11236987.

[176] C.M. Ho-Yen, A.R. Green, E.A. Rakha, A.R. Brentnall, I.O. Ellis, S. Kermorgant, J. L. Jones, C-Met in invasive breast cancer: is there a relationship with the basal-like subtype? Cancer 120 (2014) 163–171, https://doi.org/10.1002/cncr.28386.

[177] J. Park, E.S. Chang, J.-Y. Kim, C. Chelakkot, M. Sung, J.-Y. Song, K. Jung, J. H. Lee, J.Y. Choi, N.Y. Kim, H. Lee, M.-R. Kang, M.J. Kwon, Y.K. Shin, Y.H. Park, Y.-L. Choi, c-MET-positive circulating tumor cells and cell-free DNA as independent prognostic factors in hormone receptor-positive/HER2-negative metastatic breast cancer, Breast Cancer Res. 26 (2024) 13, https://doi.org/10.1186/s13058-024-01768-y.

[178] M. Merchant, X. Ma, H.R. Maun, Z. Zheng, J. Peng, M. Romero, A. Huang, N. Yang, M. Nishimura, J. Greve, L. Santell, Y.-W. Zhang, Y. Su, D.W. Kaufman, K. L. Billeci, E. Mai, B. Moffat, A. Lim, E.T. Duenas, H.S. Phillips, H. Xiang, J. C. Young, G.F. VandeWoude, M.S. Dennis, D.E. Reilly, R.H. Schwall, M. A. Starovasnik, R.A. Lazarus, D.G. Yansura, Monovalent antibody design and mechanism of action of onartuzumab, a MET antagonist with anti-tumor activity as a therapeutic agent, Proc. Natl. Acad. Sci. U.S.A. 110 (2013) E2987–E2996, https://doi.org/10.1073/pnas.1302725110.

[179] V. Diéras, M. Campone, D.A. Yardley, G. Romieu, V. Valero, S.J. Isakoff, H. Koeppen, T.R. Wilson, Y. Xiao, D.S. Shames, S. Mocci, M. Chen, P. Schmid, Randomized, phase II, placebo-controlled trial of onartuzumab and/or bevacizumab in combination with weekly paclitaxel in patients with metastatic triple-negative breast cancer, Ann. Oncol. Off. J. Eur. Soc. Med. Oncol. 26 (2015) 1904–1910, https://doi.org/10.1093/annonc/mdv263.

[180] K. Kishi, H. Sakai, T. Seto, T. Kozuki, M. Nishio, F. Imamura, H. Nokihara, M. Satouchi, S. Nakagawa, T. Tahata, K. Nakagawa, First-line onartuzumab plus erlotinib treatment for patients with MET-positive and EGFR mutation-positive non-small-cell lung cancer, Cancer Treat. Res. Commun. 18 (2019) 100113, https://doi.org/10.1016/j.ctarc.2018.10.004.

[181] D. Rayson, S. Lupichuk, K. Potvin, S. Dent, T. Shenkier, S. Dhesy-Thind, S. L. Ellard, C. Prady, M. Salim, P. Farmer, G. Allo, M.-S. Tsao, A. Allan, O. Ludkovski, M. Bonomi, D. Tu, L. Hagerman, R. Goodwin, E. Eisenhauer, P. Bradbury, Canadian Cancer Trials Group IND197: a phase II study of foretinib in patients with estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2-negative recurrent or metastatic breast cancer, Breast Cancer Res. Treat. 157 (2016) 109–116, https://doi.org/10.1007/s10549-016-3812-1.

[182] S.K. Chia, S.L. Ellard, M. Mates, S. Welch, C. Mihalcioiu, W.H.J. Miller, K. Gelmon, C. Lohrisch, V. Kumar, S. Taylor, L. Hagerman, R. Goodwin, T. Wang, S. Sakashita, M.S. Tsao, E. Eisenhauer, P. Bradbury, A phase-I study of lapatinib in combination with foretinib, a c-MET, AXL and vascular endothelial growth factor receptor inhibitor, in human epidermal growth factor receptor 2 (HER-2)-positive metastatic breast cancer, Breast Cancer Res. 19 (2017) 54, https://doi.org/10.1186/s13058-017-0836-3.

[183] I. Puzanov, J. Sosman, A. Santoro, M.W. Saif, L. Goff, G.K. Dy, P. Zucali, J. A. Means-Powell, W.W. Ma, M. Simonelli, R. Martell, F. Chai, M. Lamar, R. E. Savage, B. Schwartz, A.A. Adjei, Phase 1 trial of tivantinib in combination with sorafenib in adult patients with advanced solid tumors, Invest. N. Drugs 33 (2015) 159–168, https://doi.org/10.1007/s10637-014-0167-5.

[184] S.M. Tolaney, D.R. Ziehr, H. Guo, M.R. Ng, W.T. Barry, M.J. Higgins, S.J. Isakoff, J.E. Brock, E. Vivanova, C.P. Paweletz, M.K. Demeo, N.H. Ramaiya, B. A. Overmoyer, R.K. Jain, E.P. Winer, D.G. Duda, Phase II and biomarker study of cabozantinib in metastatic triple-negative breast cancer patients, Oncol. 26 (2021) e1483, https://doi.org/10.1002/onco.13809.

[185] S.M. Tolaney, D.R. Ziehr, H. Guo, M.R. Ng, W.T. Barry, M.J. Higgins, S.J. Isakoff, J.E. Brock, E. Vivanova, C.P. Paweletz, M.K. Demeo, N.H. Ramaiya, B. A. Overmoyer, R.K. Jain, E.P. Winer, D.G. Duda, Phase II and biomarker study of cabozantinib in metastatic triple-negative breast cancer patients, Oncol. 22 (2017) 25–32, https://doi.org/10.1634/theoncologist.2016-0229.

[186] J. Xu, M.J. Higgins, S.M. Tolaney, S.E. Come, M.R. Smith, M. Fornier, U. Mahmood, J. Baselga, B.Y. Yeap, B.A. Chabner, S.J. Isakoff, A phase II trial of cabozantinib in hormone receptor-positive breast cancer with bone metastases, Oncol. 25 (2020) 652–660, https://doi.org/10.1634/theoncologist.2020-0127.

[187] J.P. Leone, D.G. Duda, J. Hu, W.T. Barry, L. Trippa, E.R. Gerstner, R.K. Jain, S. Tan, E. Lawler, E.P. Winer, N.U. Lin, S.M. Tolaney, A phase II study of cabozantinib alone or in combination with trastuzumab in breast cancer patients with brain metastases, Breast Cancer Res. Treat. 179 (2020) 113–123, https://doi.org/10.1007/s10549-019-05445-z.

[188] A.A. Sachkova, D. Vandreeva, A.S. Tikhomirov, A.M. Scherbakov, D.I. Salnikova, D. Vsorokin, F.B. Bogdanov, Y.D. Rysina, A.E. Shchekotikhin, E.S. Shchegravina, A.Y. Fedorov, Design, synthesis and in vitro investigation of cabozantinib-based PROTACs to target c-met kinase, Pharmaceutics 14 (2022), https://doi.org/10.3390/pharmaceutics14122829.