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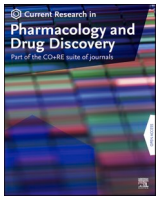

Targeting c-Met in breast cancer: From mechanisms of chemoresistance to novel therapeutic strategies

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ABSTRACT

Breast cancer presents a significant challenge due to its heterogeneity and propensity for developing chemoresistance, particularly in the triple-negative subtype. c-Mesenchymal epithelial transition factor (c-Met), a receptor tyrosine kinase, presents a promising target for breast cancer therapy due to its involvement in disease progression and poor prognosis. However, the heterogeneous expression of c-Met within breast cancer subtypes and individual tumors complicates targeted therapy. Also, cancer cells can develop resistance to c-Met inhibitors through various mechanisms, including bypass signaling pathways and genetic mutations. The off-target effects of c-Met inhibitors further limit their clinical utility, necessitating the development of more selective agents. To overcome these challenges, personalized treatment approaches and combination therapies are being explored to improve treatment efficacy while minimizing adverse effects. Novel c-Met inhibitors with improved selectivity and reduced off-target toxicity show promise in preclinical studies. Additionally, targeted delivery systems aim to enhance drug localization and reduce systemic toxicity. Future directions involve refining inhibitor design and integrating c-Met inhibition into personalized treatment regimens guided by molecular profiling. This review explores the mechanisms by which c-Met contributes to chemoresistance in breast cancer and current challenges in targeting c-Met for breast cancer therapy. It discusses strategies to optimize treatment outcomes, ultimately improving patient prognosis and reducing mortality rates associated with this devastating disease.

1. Introduction

Breast cancer is a complex disease, most widespread, frequently diagnosed, and the second most common cause of cancer death in women globally (Łukasiewicz et al., 2021; Onyia et al., 2023; Dokunmu et al., 2022). Breast cancer has various molecular subtypes with significant diversity among patients, yet the current molecular subtypes fail to accurately predict the progression of disease and relapse (Mitra et al., 2020). Recent studies using "omics" technology, including next-generation sequencing (NGS), have helped to widen the understanding of the heterogeneity of breast cancer by uncovering the cell populace that is involved with chemoresistance (Ogbu et al., 2021). Single-cell sequencing studies have revealed the dynamic nature of treatment response in triple-negative breast cancer (TNBC), which has a high recurrence and a poorer survival rate compared to hormone receptor (HR+) and human epidermal growth factor 2 (HER2) subtypes

Abbreviations: TNBC, triple-negative breast cancer; ADC, antibody-drug conjugate; CAFs, cancer-associated fibroblasts; TAM, tumor-associated macrophage; ORR, objective response rate; PFS, progression-free survival; CSCs, cancer stem cells; EMT, epithelial-mesenchymal transition; HGF, hepatocyte growth factor; VEGFR, vascular endothelial growth factor receptor; EGFR, Epithelial growth factor receptor; NSCLC, non-small-cell lung cancer; TME, tumor microenvironment; FDA, food and drug administration; PARPi, poly-(ADP)-ribose polymerase inhibitors; IHC, immunohistochemistry; HER2, human epidermal growth factor 2; MDR, multidrug resistance; ECM, extracellular matrix; HCC, hepatocellular carcinoma; NAC, neoadjuvant chemotherapy; TIL, tumor-infiltrating lymphocytes; ERα, estrogen receptor alpha; OS, overall survival; mBC, metastatic breast cancer; PDGFRB, platelet-derived growth receptor beta; CML, chronic myeloid leukemia.

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(Bou et al., 2022; Li et al., 2022). The metastatic patient's overall survival is approximately one year, contrasting with five years for the other two subtypes (Grinda et al., 2021). Metastases in breast cancer patients are hardly detectable at diagnosis, complicating treatment. Various therapeutic approaches, including local and systemic therapy, are used in treating both metastatic and non-metastatic breast cancer. However, chemoresistance remains a significant challenge, contributing to treatment failure and unfavorable patient outcomes (Ramos et al., 2021; Pires et al., 2019). This resistance arises from various molecular factors, including drug efflux pumps, selection of chemoresistance cancer-stem-cells (CSCs), tumor microenvironment (TME), activated signaling pathway, and Epithelial-Mesenchymal Transition (EMT) (Sirois et al., 2019). The interaction between tumor cells and nearby stromal cells facilitates breast cancer growth, progression, and chemotherapy through signaling pathways involving paracrine loops, chemokine networks, and direct cell interactions (Muley et al., 2020; Mehraj et al., 2021a). Among the key players, receptor tyrosine kinases (RTKs), crucial for cell processes like growth and survival, play a significant role in cancer progression, with c-Met particularly notable (Uchikawa et al., 2021). c-Met, under normal physiological conditions, binds to its ligand hepatocyte growth factor (HGF), resulting in c-Met activation. c-Met has been reported to interact and form multi-protein complexes with other RTKs, such as epithelial growth factor receptor (EGFR)/HER3, leading to downstream signaling cascade activation (Park and Richardson, 2020). Aberrant c-Met activity promotes survival and proliferation in chemotherapy-resistant cancer cells, making it an attractive therapeutic target (Zhu et al., 2021). Inhibiting aberrant c-Met activity can enhance patient survival, decrease metastatic spread, and prolong the lifespan of patients diagnosed with advanced-stage breast cancer. Thus, targeting c-Met has emerged as a promising method for treating drug-resistant breast cancer, primarily through inhibitors, including tyrosine kinase inhibitors or antibodies (Stanislovas and Kermorgant, 2022). Unfortunately, despite the application of c-Met inhibitors in breast cancer treatment, resistance to treatment persists. This review, therefore, aims to outline the present comprehension of c-Met as a potential treatment target and explore potential clinical approaches to counteract the chemoresistance it induces in breast cancer.

2. Mechanisms of chemoresistance in breast cancer

Over the years, chemotherapy has been the primary systemic treatment for breast cancer; however, the emergence of chemoresistance poses a significant hurdle to its effectiveness (Chen et al., 2020; Prihantono, 2021). Chemoresistance, characterized by the insensitivity of tumor cells to treatment, greatly diminishes the effectiveness of breast cancer chemotherapeutic drugs, contributing to aggressive disease behavior and unfavorable clinical outcomes (Li et al., 2020). This resistance can either be inherent, where malignancies exhibit resistance to chemotherapy drugs before treatment, or acquired, where cancers that initially responded to chemotherapy develop resistance during treatment, notably through de novo multidrug resistance pathways (Emran et al., 2022). Various biochemical changes, influenced by genetic and epigenetic factors, underlie chemoresistance, including overexpression of efflux transporters, activation of survival pathways, non-coding RNAs, TME, and the enrichment of CSCs (Zhang et al., 2020a), as listed in (Fig. 1) and described below. Understanding the mechanisms behind breast cancer chemoresistance is critical to addressing this therapeutic challenge (Kumar et al., 2021).

2.1. Drug efflux transporters

Through the multidrug resistance (MDR) phenomenon, various cancer cells become resistant to different anticancer drugs (Catalano et al., 2022). The MDR uses the ATP binding cassette (ABC) transporters to exert its effect. ABC transporters pump chemotherapeutic drugs out of the cancer cells using ATP, decreasing their intracellular concentration and effectiveness (Giddings et al., 2021), as depicted in (Fig. 2).

ABC transporter expression is highly implicated in the chemoresistance of various cancers, including breast cancer (Kumar et al., 2023). Breast cancer cells can upregulate the expression of efflux transporters such as P-glycoprotein (P-gp), multidrug resistance-associated protein 1 (MRP1), and breast cancer resistance protein (BCRP) (Robinson and Tiriveedhi, 2020). BRCP, located on the cell membrane, is associated with stem cell chemoresistance in TNBC. BRCP mediates the resistance of anti-cancer drugs such as mitoxantrone, doxorubicin, SN-38, and various tyrosine kinase inhibitors (TKIs) (Vaidya et al., 2022). P-gp and MRPI exhibit considerable overlap in their substrate specificity. Taxol, vincristine, etoposide, daunorubicin, and paclitaxel, among other clinically significant chemotherapy agents, are susceptible to P-gp-mediated efflux (Karthika et al., 2022). P-gp acts in tissue cells by removing harmful chemicals from food, thereby protecting them. A recent study revealed that overexpression of the small molecular glycoprotein serglycin (SRGN) increases resistance to chemotherapy both *in vitro* and *in vivo* by interacting with the

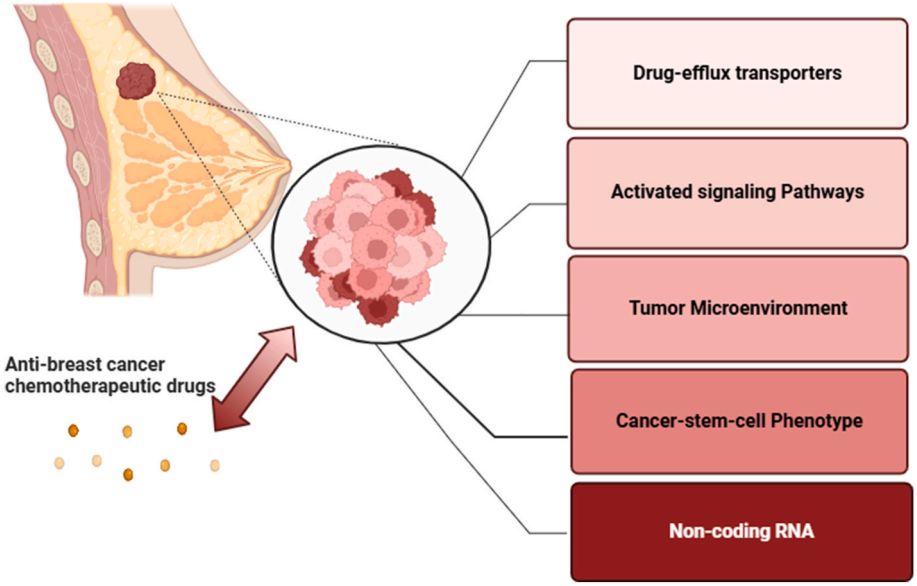


Fig. 1. Schematic representation of mechanisms contributing to breast cancer chemoresistance.

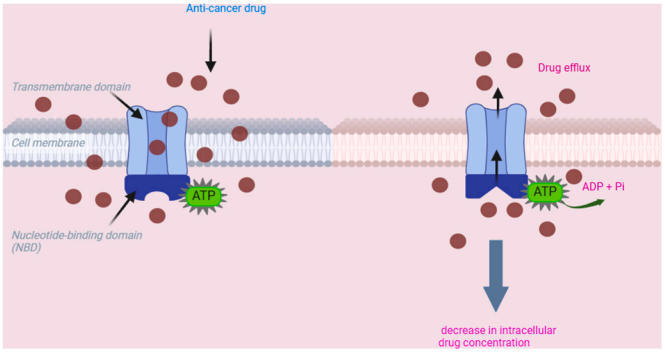


Fig. 2. Schematic representation of the ABC transporter-mediated efflux of anti-cancer drugs in cancer cells. The anti-cancer drug enters the cell through passive diffusion and encounters the ABC transporter embedded in the cell membrane. The transporter consists of two main domains: the transmembrane domain (TMD) and the nucleotide-binding domain (NBD). The NBD binds and hydrolyzes ATP, providing the energy required for the transporter to function. Upon binding of ATP to the NBD, the transporter undergoes a conformational change that facilitates the efflux of the anti-cancer drug from the intracellular environment to the extracellular space. The hydrolysis of ATP to ADP and inorganic phosphate (Pi) releases energy, driving this conformational shift. As a result, the intracellular concentration of the drug decreases, leading to reduced efficacy of the anti-cancer therapy.

transcriptional coactivator YES-associated protein (YAP) to sustain stem cell-like properties in breast cancer cells (Zhang et al., 2020a). Overexpression of the MDR gene increases P-gp capacity, which leads to higher efflux pump activity and chemoresistance. Overexpression of the MDR1 gene has been associated with tumor responses to chemotherapy treatments (Haque et al., 2020). Previous research has demonstrated that overexpression of the MDR1 gene results in a 17% tumor response, whereas in the absence of overexpression, the tumor response might reach 68% (Prihantono, 2021). MRPI transports numerous neutral and anionic compounds and metabolites of phase II drug metabolism. In TNBC, multidrug-resistant protein-8 (ABCC11/MRP8) overexpression leads to resistance against chemotherapeutic drugs like 5-Fluorouracil and methotrexate (Cao et al., 2021).

2.2. Signaling pathways

A complex interplay of signaling pathways governs survival, proliferation, and invasiveness in breast cancer. Signaling pathways such as PTEN/PI3K/AKT/mTOR, NF-kB, and JAK/STAT have been identified as contributors to chemoresistance to breast cancer (Kaboli et al., 2021). The PI3K-AKT-mTOR pathway is particularly crucial for regulating cell survival, growth, and migration. Activated AKT indirectly impacts mTOR phosphorylation, resulting in enhanced protein synthesis and cell proliferation, which is beneficial to malignant cells (Peng et al., 2022). PTEN, a tumor suppressor, inhibits the PI3K-AKT-mTOR activity (Hashemi et al., 2023). However, when PTEN is impaired and AKT is overexpressed, this signaling pathway is frequently linked to tumor aggressiveness, unfavorable prognosis, and chemoresistance in breast cancer (Cao et al., 2021; Aquila et al., 2020). The NF-kB, a proinflammatory transcription factor, is frequently activated in breast cancer. The NF-kB signaling pathway plays a significant role in TNBC and has been implicated in the development of chemoresistance and metastasis in breast cancer (Leung et al., 2020). The JAK/STAT signaling pathway is critical for tumor development and progression. Furthermore, STAT3 and STAT5 have been demonstrated to enhance breast cancer growth and progression, and the JAK/STAT pathway is a possible therapeutic target in breast cancer patients (De Araujo et al., 2020). Moreover, the Wnt/β-catenin pathways, important for cancer stem cells (CSCs) self-renewal and regulating normal breast development and abnormal tumorigenesis, have garnered attention. In recent times, findings indicate elevated expression of the Wnt pathway in various cancers, including breast cancer, where it contributes to tumor recurrence (Xu et al., 2020a). Hence, inhibiting the Wnt signaling pathway has been suggested as a promising therapeutic approach for breast cancer (Castagnoli et al., 2020). The Notch signaling pathway plays a crucial role in preserving the normal functions of stem cells, such as self-renewal and differentiation (Zhou et al., 2022). In breast cancer, dysregulated Notch signaling has been linked to tumor initiation, advancement, and metastasis. Previous research has indicated that notch signaling is connected with resistance to chemotherapy in breast cancer and that notch inhibitors can enhance the sensitivity of breast cancer cells to cytotoxic drugs (Kumar et al., 2021). In addition, the Hedgehog (Hh) signaling pathway is critical for embryogenesis, tissue regeneration, and stem cell renewal (Cierpikowski et al., 2023). An *in vivo* experiment revealed that neoplastic cells' hedgehog ligand alters cancer-associated fibroblasts (CAFs), providing a conducive environment for the development of chemoresistance in TNBC (Chandra et al., 2021; Cazet et al., 2018).

2.3. Tumor microenvironment

On the one hand, the tumor cells are harbored by both cellular and non-cellular components of the TME, including stromal cells, extracellular matrix (ECM), CAF, and tumor-associated macrophages (TAMs) (Zhao et al., 2023; Cleanclay et al., 2023). The tumor cells co-opt these components to further their progression, as depicted in (Fig. 3) below. TME, on the other hand, is a complex ecosystem composed of a variety of malignant and noncancerous cells enclosed in a glycoprotein-rich ECM (Cazet et al., 2018). In the breast cancer tumor microenvironment, CAFs represent the predominant non-malignant cell population and are important in the cancer progression, metastasis, and resistance to chemotherapy (Wright et al., 2023). Studies have shown that CAFs play a crucial role in facilitating tumor resistance to various forms of treatments, including chemotherapy, endocrine therapy, and targeted

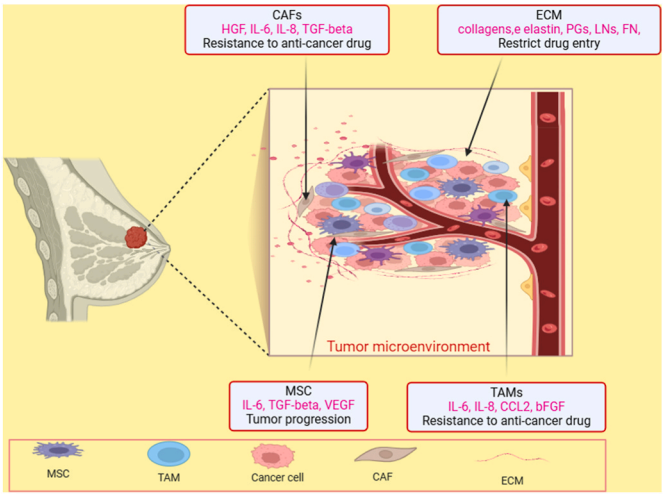


Fig. 3. Schematic illustration of the effect of the tumor microenvironment on chemoresistance in breast cancer. TAMs release various soluble factors, such as interleukin-6 (IL-6), interleukin-8 (IL-8), chemokine C-C motif ligand 2 (CCL2), and Basic fibroblast growth factor (bFGF), which contribute to drug resistance. Additionally, CAFs release HGF, transforming growth factor-beta (TGF-beta), IL-6, and IL-8, further promoting chemoresistance. Mesenchymal stem cells (MSCs) facilitate tumor development by secreting cytokines and growth factors such as IL-6, TGF-beta, and vascular endothelial growth factor (VEGF), leading to tumorigenesis, metastasis, and stemness maintenance. The ECM within the TME, comprising collagens, proteoglycans (PGs), laminins (LNs), elastin, and fibronectin (FN), undergoes continuous degradation and deposition due to cytokines and growth factors from tumor and stromal cells. This process increases ECM stiffness, hindering the entry of chemotherapeutic drugs into tumor cells.

therapies (Rizzolio et al., 2022). HGF secreted by CAFs in tumor microenvironment induces resistance to tyrosine kinase and EGFR inhibitors (Ham et al., 2021). However, preclinical studies on multi-drug resistant breast cancer revealed that targeting the CAFs and tumor cells increased drug penetration within tumors, reducing proliferation and metastasis in tumor cells (Zhang et al., 2023; Feng et al., 2022a). Furthermore, TAMs are pivotal in cancer growth, metastasis, and treatment responses.

TAMs produce survival factors in tumor cells and trigger anti-apoptotic signaling pathways (Yang et al., 2020). Increased expression of TAMs has been linked to poor clinical outcomes and chemoresistance in breast cancer (Zhan et al., 2023). According to research, paclitaxel-treated tumor cells express colony-stimulating factor 1(CSF1), which stimulates the recruitment of TAM to block paclitaxel-induced growth arrest of breast tumor cells (Qiu et al., 2018). In a breast tumor environment, ECM proteins are involved in chemoresistance (Henke et al., 2020). Studies have shown that the binding of tumor cells to collagen type 1 (COL1), a TME component, lowers tumor cells' susceptibility to cytotoxic drugs such as cisplatin, mitoxantrone, and docetaxel (Mehraj et al., 2021b).

2.4. Cancer stem cell phenotypes

Evidence indicates that a specific subset of cells with stem cell characteristics drives breast cancer progression. These cells, termed CSCs, are pivotal in tumor initiation, advancement, metastasis, and resistance to therapy (Zhang et al., 2020b), illustrated in (Fig. 4). Tumor microenvironment components and non-cellular factors increase tumor cell stemness by interacting bidirectionally with tumor cells and secreted proteins. Additionally, numerous stromal cells, including immune cells, have been shown to control breast cancer stemness and self-renewal of breast cancer stem cells (BCSCs) via a cytokine network (Guha et al., 2023). BCSCs frequently exhibit hyperactivation of the PI3K and NRF2 signaling pathways. BCSCs are more resistant to chemotherapy than non-CSCs due to the hyperactivation of these anti-apoptotic pathways (Saha and Lukong, 2022). Moreover, breast cancer cell lines and tumor tissues obtained from patients resistant to chemotherapy revealed a larger frequency of BCSCs (Mehraj et al., 2021a). Studies have highlighted the heightened expression of various ABC transporters in BCSCs, aiding the expulsion of chemotherapy drugs and facilitating key processes associated with cancer advancement. Moreover, several biomarkers of breast cancer stem cells, such as CD10, CD24, CD44, ALDH1, EpCAM, and ABCG2, have been identified, with their upregulation linked to chemoresistance (Li et al., 2021; Zeng et al., 2021). Earlier investigations have underscored the roles of CD10 and GPR77 in promoting tumor growth and resistance to chemotherapy (Su et al., 2018), while the high ratio of CD44/CD24 and the presence of ALDH1+ cells have been consistently observed during metastasis (Escudero Mendez et al., 2022), highlighting the promise of BCSC markers in monitoring tumor advancement, metastasis, and guiding cancer treatment strategies.

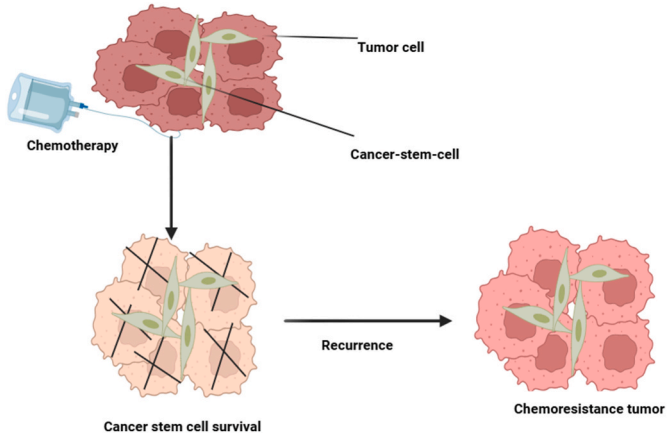


Fig. 4. Schematic representation illustrating the function of cancer stem cells in chemotherapeutic resistance. After chemotherapy, while most tumor cells are eliminated, CSCs survive, leading to resistance and facilitating tumor recurrence and progression.

2.5. Non-coding RNAs

Non-Coding RNAs (ncRNAs) serve as key regulators in intracellular and intercellular signaling pathways implicated in breast cancer progression, particularly in the development of chemoresistance (Ahmadi et al., 2024). These include various classes, such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) (Singh et al., 2023). miRNAs, characterized by their small size (18–25 nucleotides), play a pivotal role in breast cancer metastasis and chemoresistance (Singh et al., 2023; Ratti et al., 2020). Dysregulation of specific miRNAs has been linked to resistance against endocrine therapy, notably tamoxifen, by down-regulating the expression of estrogen receptor alpha (ERα) (Ji et al., 2019). For instance, miR-221/222, miR-342-3p, and miR-873 have been found to confer tamoxifen resistance by targeting ERα and p27Kip (Alizadeh et al., 2019; Muluhngwi and Klinge, 2015). Additionally, miRNAs like miR-451 and miR-326 downregulate MDR-related genes, enhancing sensitivity to doxorubicin (Drá et al., 2020), while miR-200c restores sensitivity to paclitaxel by suppressing genes associated with drug resistance (Chen et al., 2018).

In contrast, lncRNAs, with lengths exceeding 200 nucleotides, have also been implicated in breast cancer chemoresistance (Ahmadpour et al., 2023). For example, lncRNA-SNHG14 mediates trastuzumab responses through tumor cell-extracellular exosomes, with its overexpression associated with trastuzumab resistance (Ye et al., 2022). Similarly, Linc00839 overexpression promotes cell proliferation, invasion, and chemoresistance, whereas knockdown sensitizes cells to paclitaxel and suppresses tumor development (Chen et al., 2020). Another lncRNA, SNHG7, which is elevated in chemoresistant breast cancer, contributes to tumorigenesis by acting as a sponge for miR-34a, activating the EMT and Notch-1 pathways (Li et al., 2020). In summary, ncRNAs, including miRNAs and lncRNAs, play intricate roles in breast cancer chemoresistance, highlighting their potential as therapeutic targets in combating this disease.

3. Role of c-Met in breast cancer progression and chemoresistance

3.1. c-Met signaling and breast cancer progression

The dysregulation of c-Met in cancer, including breast cancer, stems from various activation mechanisms such as mutation, overexpression, autocrine signaling, and gene amplification (Faiella et al., 2022; Wood et al., 2021). This aberrant c-Met signaling pathway activation plays a crucial role in breast cancer progression and resistance to chemotherapy by controlling key cellular processes like proliferation, survival, metastasis, and EMT (Park and Richardson, 2020). Overexpression of c-Met, particularly prevalent in TNBC, has garnered significant therapeutic attention as it correlates with invasion and metastatic spread (Chaudhary et al., 2020). High expression of c-Met is linked to a poorer prognosis in breast cancer, especially in TNBC cases, with studies indicating overexpression in more than 20% of breast cancer cases and exceeding 50% in TNBC (Fu et al., 2021). The expression pattern of c-Met varies across different stages of breast cancer, with minimal levels in normal breast tissue, increasing levels in ductal carcinoma *in situ* (DCIS), and reaching peak expression in invasive cancer (Ayoub et al., 2020). Notably, a significant proportion (about 14–54%) of invasive breast cancers exhibit highly expressed c-Met, contributing to unfavorable survival outcomes (Iovino et al., 2022; Abouelfadl et al., 2022). A

study on c-Met and β1 integrins (c-met/β1) complex involvement in metastases revealed that this complex promotes the expression of mesenchymal genes and pathways, including Wnt and hedgehog pathway, involved in breast cancer progression, particularly in basal and luminal A subtypes (Lau et al., 2021; Barzaman et al., 2022). The c-Met/β1 integrin complex seems to promote metastasis via activating the Wnt and hedgehog signaling pathways. This complex increased intravasation in TNBC, resulting in metastasis in specific organs and a preference for bone colonization by TNBC. This is likely due to the complex's affinity for collagen type I, thus making the c-met/β1 complex a therapeutic target (Stanislovas and Kermorgant, 2022; Lau et al., 2021). More so, OS2966, a therapeutic antibody that disrupts the binding between c-Met and β1, has been used to inhibit invasion and mesenchymal expression in breast cancer (Lau et al., 2021; Jahangiri et al., 2017).

3.2. c-Met and chemoresistance in breast cancer

In advanced breast cancer, chemoresistance is a significant challenge. In the quest for chemoresistance acquisition, the signaling pathways responsible for cell proliferation and survival undergo adaptive evolution and become redundant (Lim and Ma, 2019). As a result, chemoresistance breast cancers are more likely to proliferate, even under stressful environments. Recent studies have linked high expression and amplification of c-Met to chemoresistance in breast cancer.

c-Met plays a universal role in promoting drug resistance by upregulating efflux transporters in the cell membrane, thereby reducing the intracellular concentration of chemotherapeutic agents (Wood et al., 2021). A study by Jung et al. demonstrated that in doxorubicin-resistant ovarian cancer cells (A2780DR), c-Met overexpression leads to activating the drug transporter BCRP/ABCG2. Among the 50 ABC transporters sampled, BCRP/ABCG2 expression was elevated by more than 50% in A2780DR cells, with transcript levels 45-fold higher and similar protein increases compared to A2780 cells. Further investigation revealed higher expression of the proto-oncogene c-Met in A2780DR cells. c-Met activates the PI3K/AKT pathway, enhancing tumor growth, migration, and survival. Transcript levels of c-Met were 3.6-fold higher in A2780DR cells, with increased c-Met protein levels (145 kDa) and marginally elevated p85 PI3K subunit levels. Elevated phosphorylated AKT levels confirmed the activation of c-Met/PI3K/AKT signaling in these cells (Jung et al., 2015). Another study showed that c-Met and ABCB1/MDR1 were overexpressed in multidrug-resistant uterine sarcoma and breast cancer cell lines compared to their parental lines (Hung et al., 2015). c-Met overexpression in several human tumors leads to acquiring stem cell-like phenotypes. For instance, *in vitro* studies on pancreatic cancer cells revealed that cells with overexpressed c-Met formed tumor spheres, indicating self-renewal capability, while cells with low or negative c-Met did not. Inhibition of c-Met with XL184 significantly reduced tumor sphere formation, showing that c-Met activity is necessary to maintain the cancer stem cell population, contributing to chemoresistance (Li et al., 2011). Furthermore, inhibition of c-Met with SU11274 and silencing *MET* by shRNA repressed BCRP/ABCG2 (Jung et al., 2015) and ABCB1/MDR1, enhancing chemosensitivity (Hung et al., 2015).

In a recent study, overexpression of HER-2 was observed to upregulate c-Met, resulting in resistance to trastuzumab, a commonly used therapy targeting HER2/neu. This observation is crucial because targeting c-Met with therapy could benefit cases resistant to trastuzumab (Mitra et al., 2020; Faiella et al., 2022). Another investigation revealed that c-Met promotes STAT3, which then binds to and stimulates the Met promoter, increasing c-Met expression and sustaining proliferation in chemoresistant breast cancer—evidence for the emergence of a new STAT-c-Met feed-forward loop in chemoresistant breast cancer (Zhu et al., 2021). However, capmatinib, a c-Met specific inhibitor, has been proven in preclinical studies to suppress chemoresistant breast cancer, indicating increased sensitivity to this treatment. Overexpression of c-Met has been associated with resistance to anti-EGFR TKI monotherapy, where c-Met TKI monotherapy causes upregulation and activation of EGFR, which acts as a compensatory RTK signaling in TNBC, leading to metastasis. However, a preclinical investigation found that dual-blocking c-Met/EGFR inhibitor doxazosin (DOXA) significantly reduced tumor growth and metastasis in TNBC cells (Kim et al., 2023). Furthermore, the c-Met and Epidermal growth factor receptor 1/2 (ERBB1/2) pathway is crucial in the spread of many cancer types, including breast cancer. Overexpression of ERBB1 was seen in both brain metastatic breast cancer cells and trastuzumab-resistant ones, with modest expression of ERBB2. However, c-Met overexpression was only seen in brain metastatic breast cell lines. As a result, the c-Met and ERBB1 pathways have been identified as potential therapeutic targets. However, the combination of neratinib, a TKI, and cabozantinib, a c-Met inhibitor, was shown to inhibit brain metastatic breast cancer (Gautam et al., 2020). Thus, High c-Met in breast cancer, especially TNBC, promotes chemoresistance, but targeting c-Met with inhibitors or combinations offers promise for overcoming this resistance.

4. Challenges in targeting c-Met for breast cancer therapy

4.1. Tumor heterogeneity and differential c-met expression

A key obstacle in developing targeted therapy for breast cancer is its heterogeneity, particularly in the TNBC subtype (Chapdelaine and Sun, 2023). Treatment is primarily based on surgery, radiation therapy, and chemotherapy due to the diverse molecular and phenotypic characteristics observed in breast cancer. Malignant cancers exhibit significant intertumor and intratumor heterogeneity, leading to variations in therapeutic response and treatment outcomes (Chapdelaine and Sun, 2023; Ramó et al., 2020). Most importantly, differential c-Met expression and tumor heterogeneity are interconnected, complicating diagnosis and treatment strategies. Studies have shown that tumors often have higher c-Met levels than healthy tissue. However, c-Met expression is not always uniform throughout a tumor (Abboud et al., 2021; Zhu et al., 2015). Research indicates that tumors can have areas with high, low, or even absent c-Met expression compared to the average of the tumor. This variation, known as intratumor heterogeneity, arises from genetic heterogeneity within the tumor, with different subclones harboring distinct mutations in the *MET* gene. This leads to varying levels of c-Met expression and activity, resulting in differential responses to c-Met inhibitors. A study involving 66 Brazilian patients with esophageal squamous cell carcinoma (ESCC) evaluated c-Met expression and intratumor heterogeneity. In 37 ESCC samples, c-Met was significantly overexpressed in tumors ($P < 0.0001$), with a median fold-change of 5.0 and 83.78% of cases showing at least a two-fold increase in c-Met expression. Among samples from different tumor regions (superficial and profound biopsies) of five patients, two showed consistent c-Met overexpression, while three exhibited heterogeneous patterns, with some areas showing reduced expression compared to non-tumor surrounding tissue (NTST) (Abboud et al., 2021). Another study reported that while half the tumors showed high c-Met expression, the staining intensity varied within the tumor samples, indicating intratumor heterogeneity. This variability in staining intensity highlights the challenges in targeting c-Met, as different regions within the same tumor may respond differently to c-Met inhibitors. These studies underscore the variability of c-Met expression within different tumor regions, highlighting the need for comprehensive profiling and functional studies to understand its role in tumor heterogeneity better and to design effective interventions targeting diverse cancer cell populations.

Intratumoral heterogeneity, characterized by differences in cancer cell populations within the same tumor specimen, is a major predictor of therapeutic resistance and treatment failure, as shown in (Fig. 5). Genetic instability contributes to high levels of intercellular heterogeneity, influencing epigenetic factors and the cell cycle (Sadida et al., 2024). Changes in these parameters can influence the gene expression involved

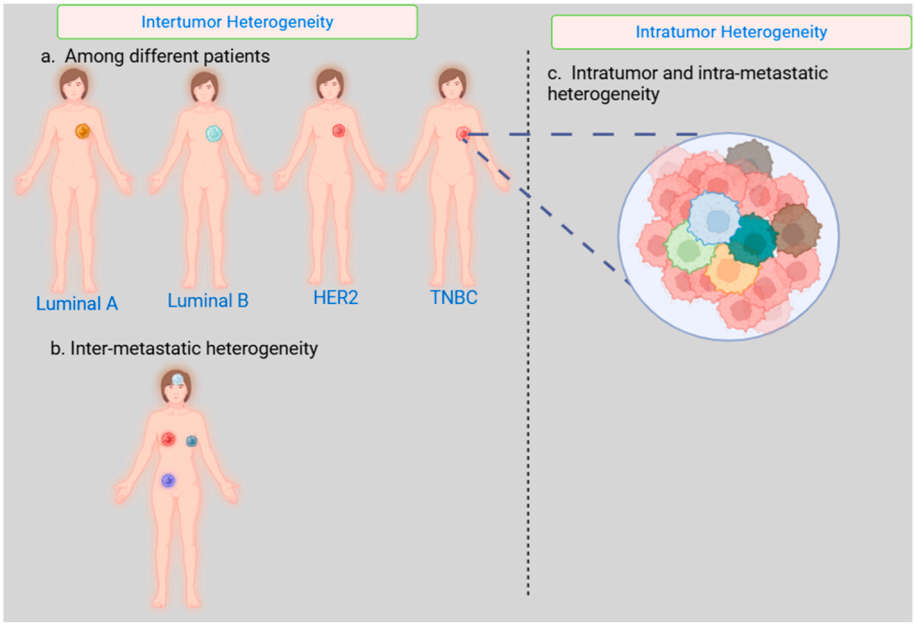


Fig. 5. A schematic representation of breast cancer heterogeneity, illustrating: a) Inter-tumor heterogeneity: differences observed among breast cancer patients, reflecting distinct histological subtypes. b) Intra-metastatic heterogeneity: variability between primary breast cancer and metastatic lesions. c) Intratumor heterogeneity: variation in cell types within a single tumor, highlighting the diverse cellular composition.

in chemoresistance, leading to treatment failure and recurrence (Guo et al., 2023). BCSCs, which are highly heterogeneous, have been implicated in cancer recurrence even after surgery. Additionally, different breast cancer subtypes show distinct risks of recurrence, with TNBC having a higher recurrence rate compared to other subtypes. The lack of effective targeting approaches, especially within the first five years, contributes to the higher recurrence rates observed in TNBC (Hossain et al., 2021; Zagami and Carey, 2022). Furthermore, the role of tumor-infiltrating lymphocytes (TILs) varies among breast cancer subtypes, with high TILs associated with survival benefits in HER2-positive cancers but poorer survival in luminal or HER2-negative tumors (Guo et al., 2023; Zagami and Carey, 2022). Breast cancer heterogeneity poses challenges in determining treatment prognosis and recurrence risk. Individual patients and lesions should be thoroughly characterized at various intervals to tailor treatment strategies effectively. However, this heterogeneity complicates matching patients with appropriate treatments, hindering personalized medication. Additionally, druggable targets for which the FDA has approved treatments, such as estrogen and progesterone, are not uniformly expressed in breast cancer. For example, a change in estrogen status, such as a lack of estrogen expression in tumors, can prevent patients from benefiting from endocrine therapies like tamoxifen and aromatase inhibitors. While expression of c-Met has been detected in different breast cancer subtypes, such as luminal, HER2-positive, and TNBC, the level of expression differs among subtypes and individual tumors. Consequently, targeted therapies may cause modest regression and selective expansion of resistant populations, leading to future relapse (Ramó et al., 2020). A study was conducted on 20 patients diagnosed with TNBC who underwent neoadjuvant chemotherapy (NAC). Within this cohort, 10 patients were found to harbor persistent chemoresistant clones following treatment. Subsequent investigation utilizing single-cell DNA and RNA sequencing revealed that these resistant clones were pre-existing and had been adaptively selected by NAC (El-Sayes et al., 2021; Kim et al., 2018). This multifaceted heterogeneity underscores the need for comprehensive molecular profiling and personalized treatment approaches to effectively target c-Met and other potential therapeutic targets in breast cancer.

4.2. Acquisition of resistance to c-met inhibitors

Cancer cells can develop resistance to targeted therapies, including those that target c-Met. This means that the drug may initially be effective, but the cancer cells will eventually find a way to bypass the effects of the drug, either by turning on alternative signaling pathways or acquiring mutations that confer resistance to the treatment. However, resistance, whether de novo or acquired, always exists, leading to treatment failure and cancer progression. Small molecule kinase inhibitors have produced many impressive responses, but selective pressure frequently results in de novo mutations in the target protein (c-Met), leading to chemoresistance (Marrocco and Yarden, 2023).

Resistance to c-Met inhibitors can be categorized into on-target and off-target mechanisms (Meador and Hata, 2020). On-target resistance involves alterations in the c-Met protein that hinder the drug's ability to bind or function effectively. Key examples include mutations in the c-Met kinase domain and *MET* amplification. Specific mutations, such as those in codons H1094, G1163, L1195, D1228, and Y1230, have been observed to confer resistance to various c-Met inhibitors depending on the specific drug and mutation. For instance, Ergstorm et al. investigated resistance mechanisms to three c-Met inhibitors, capmatinib, crizotinib, and glesatinib, in cancer cell lines. They discovered secondary MET mutations contributing to resistance. In the capmatinib-resistant (Cap-res) model, an A to G mutation (c.3689A > G) results in a Y1230C mutation in the c-Met protein. In the crizotinib-resistant (Criz-res) model, a T to C mutation (c.3688T > C) leads to a Y1230H mutation, and another T to C mutation (c.3598T > C) results in an F1200L mutation. Further investigation revealed significant cross-resistance between capmatinib and crizotinib. In the Cap-res cell line, crizotinib's potency decreased approximately 50-fold (IC50). Conversely, in the Criz-res cell line, capmatinib was largely ineffective (IC50 > 3 μM) (Engstrom et al., 2017). These findings suggest that the Y1230C, Y1230H, and F1200L mutations confer resistance to both inhibitors, likely by altering the c-Met binding sites or structural conformation. Two case reports involving male non-smokers with lung adenocarcinoma demonstrated the clinical relevance of these findings. A 71-year-old man with a *MET* exon 14 splice site alteration began crizotinib therapy, but after six months of disease progression, a newly

acquired MET Y1230H mutation was identified, conferring resistance to crizotinib (Schrock et al., 2017). Similarly, a 64-year-old man with the same MET alteration initially responded to crizotinib but showed disease progression after eight months. Comprehensive genomic profiling revealed *MET* gene amplification, three MET A-loop mutations (D1228N, Y1230H, Y1230S), and a G1163R solvent front mutation, all contributing to crizotinib resistance (Engstrom et al., 2017).

Off-target resistance involves activating alternative signaling pathways that allow cancer cells to bypass c-Met inhibition. Examples include mutations or amplifications in other genes, such as KRAS, EGFR, HER2, or BRAF, which can activate alternative growth pathways. In a study involving 20 patients, on-target resistance mechanisms, including single and polyclonal MET kinase domain mutations in codons H1094, G1163, L1195, D1228, and Y1230, as well as high levels of amplification of the *MET* exon 14–mutant allele, were observed in seven patients. Off-target resistance mechanisms were detected in nine patients, including KRAS mutations and amplifications in KRAS, EGFR, HER3, and BRAF. One case displayed both on-target and off-target resistance mechanisms. In two patients with on-target resistance mutations, switching between type I (crizotinib and capmatinib) and type II (glesatinib) c-Met TKIs resulted in second partial responses (Recondo et al., 2020). These findings highlight the complexity of resistance mechanisms to c-Met inhibitors and underscore the need for comprehensive genomic profiling to tailor treatment strategies effectively. A study on a rare metastatic TNBC case with *MET* amplification reported an initial good response to crizotinib treatment. However, after 37 weeks, the patient experienced progression despite continued crizotinib therapy. Analysis revealed a newly acquired MET mutation conferring resistance to crizotinib but sensitivity to cabozantinib, another c-Met inhibitor (Parsons et al., 2020). This case emphasizes the challenge of managing resistance in targeted therapy for breast cancer with specific genomic alterations like *MET* amplification. Also, a study has linked the hyperactivation of c-Met to PARP inhibitors (PARPi) resistant in TNBC (Chu et al., 2020).

4.3. Off-target effects and toxicity of c-met inhibitors

c-Met is involved in normal cellular processes in the body. Drugs that target c-Met may also have off-target effects on healthy tissues, which can lead to side effects (Bansal et al., 2023). Many c-Met inhibitors have been developed to treat breast cancer. However, a few drugs have been successful in clinical applications, while most are flawed due to their effectiveness and negative effects. For example, the FDA revoked the approval of bevacizumab due to the heightened risk of severe side effects, such as hemorrhagic tumor necrosis and suicidal ideation, when used in conjunction with paclitaxel. This decision was made because the potential risks of treatment outweighed the minimal benefits observed. Also, the clinical trial of tivantinib for hepatocellular carcinoma treatment revealed adverse effects such as hematologic toxicity and neutropenia (Zhang et al., 2022). Additionally, palmar-plantar erythrodysesthesia (PPE), Lethargy, increased aspartate aminotransferase, hypertension, stomach discomfort, asthenia, dyspnea, anorexia, diarrhea, and respiratory failure have all been reported as side effects of cabozantinib in breast cancer treatment (Bruchbacher et al., 2024).

5. Strategies to overcome the challenges in targeting c-Met

Strategies to overcome the challenges in targeting c-Met for breast cancer therapy involve a multifaceted approach aimed at improving treatment effectiveness and reducing adverse effects. One crucial aspect is the development of predictive biomarkers to pinpoint patients most apt to benefit from c-Met targeted therapy. While the expression of c-Met protein alone may not reliably predict sensitivity, ongoing research aims to discover robust biomarkers that can accurately select patients for personalized treatment, thus avoiding unnecessary side effects.

Combination therapies offer another avenue to improve treatment outcomes, particularly in heterogeneous tumors with diverse driver mutations. Combining c-Met targeted drugs with therapies that address different signaling pathways or mechanisms within the tumor can enhance treatment efficacy, potentially overcoming resistance mechanisms and improving patient outcomes. This approach has spanned combining chemotherapy and immunotherapy with promising results in preclinical and clinical trials. A typical example is seen in a phase III clinical trial whereby atezolizumab (immunotherapy agent) and nab-paclitaxel (chemotherapy) combined revealed an improved progression-free survival (PFS) in metastatic TNBC patients (El-Sayes et al., 2021). In another study, the researchers discovered that c-Met is highly active in TNBC cells that have developed resistance to PARPi. They found that combining talazoparib with crizotinib, which inhibits c-Met, effectively suppressed cell proliferation in these resistant cells. Surprisingly, directly targeting c-Met had minimal impact on talazoparib sensitivity in PARPi-resistant cells. However, they observed increased activation of EGFR and interaction between EGFR and c-Met in these cells. Combining EGFR and PARPi showed enhanced inhibition of proliferation in TNBC cells with reduced c-Met. Moreover, simultaneous inhibition of c-Met and EGFR improved sensitivity to talazoparib in TNBC cells resistant to PARPi. These results imply that concurrent inhibition of both c-Met and EGFR might restore sensitivity to PARPi in TNBC (Chu et al., 2020).

Next-generation c-Met inhibitors are also under development to address the limitations of current drugs (Attili et al., 2023). These inhibitors aim to be more selective for c-Met and less susceptible to resistance mutations, thereby improving treatment efficacy while reducing off-target effects on healthy tissues. Refining the design of c-Met inhibitors is crucial to reducing the risk of adverse reactions and improving patient safety. Additionally, targeted delivery systems are being investigated to deliver c-Met targeted drugs specifically to cancer cells, minimizing their effect on healthy tissues. Methods such as nanoparticles or ADCs enhance drug localization and reduce systemic toxicity, enhancing treatment efficacy while minimizing side effects associated with off-target drug exposure (Liu et al., 2021).

6. Therapeutic approaches targeting c-Met

6.1. Small molecule inhibitors of c-met

A viable therapeutic approach for treating cancer is inhibiting aberrant activation of c-Met activity. In recent times, most identified small molecule inhibitors targeting the kinase domain's active site are ATP competitive inhibitors, which prevent c-Met signaling transduction by blocking tyrosine phosphorylation. Small molecule inhibitors are categorized into type I or type II depending on their structures and affinity for binding with the c-Met kinase domain, with type I (e.g., tivantinib and capmatinib) being more sensitive and type II (e.g., foretinib and cabozantinib) being more effective because they inhibit several kinases (Zhang et al., 2020c). Type II inhibitors are characterized by their ability to bind to the inactive form of the target kinase, usually in the DFG-out conformation. Also, the structural characteristic known as '5-atom regulation' is notably present in type II c-Met inhibitors. Therefore, the c-Met is a critical focal point for identifying small-molecule anticancer inhibitors. Numerous small molecule inhibitors of c-Met, such as cabozantinib, fortinib, and capmatinib, are derived from quinazoline, rendering them potent for targeting and inhibiting c-Met/VEGFR-2 kinases (Martorana et al., 2020). Additionally, various multi-kinase inhibitors have been discovered and employed in cancer therapy. These compounds can target multiple receptors with potent cytotoxic effects and high selectivity towards kinases. Many of these inhibitors have undergone clinical trials, where their pharmacodynamic and pharmacokinetic properties, mechanism of action, efficacy, toxicities, and drug resistance have been studied. Some are currently in ongoing trials, while others are yet to enter clinical testing. For instance, tepotinib (a selective c-Met inhibitor) has shown clinical efficacy and safety and has obtained approval from the US Food and

Drug Administration (FDA), particularly for *MET* exon14 skipping non-small cell lung cancer (NSCLC) patients (Zhong et al., 2021; Liang and Wang, 2020). However, it has not yet entered clinical trials for the treatment of breast cancer. Crizotinib inhibited the proliferation of breast cancer cell lines moderately, according to an *in vitro* study. When crizotinib was combined with HER2 inhibitors, the response across breast cancer cell lines varied from synergistic to antagonistic and then mixed. However, the study also discovered that crizotinib treatment altered breast cancer cell lines' cell cycle, resulting in increased DNA replication and cell division (S and G2/M phases) and enhanced apoptosis (sub-G0 phase). This suggests that crizotinib affects cell growth and survival pathways in breast cancer cells (Stanley et al., 2017). Given c-Met's elevated expression in a significant portion of breast cancers and its association with anti-EGFR resistance in NSCLC, an *in vitro* study hypothesized c-Met's involvement in anti-EGFR resistance in TNBC cell lines, specifically MDA-MB-468. Results demonstrated that combining an EGFR inhibitor (gefitinib or cetuximab) with tepotinib exhibited synergistic anti-proliferative effects, suggesting a potential therapeutic strategy targeting both EGFR and c-Met in TNBC (Sohn et al., 2014; Albers et al., 2023). Furthermore, in an *in vivo* experiment that made use of the HCC1954-xenograft model, a combination of neratinib and tepotinib significantly reduced tumor size, highlighting their potential in treating tumors with cooperating pan-HER and c-Met dysregulation (Laing et al., 2019; MacNeil et al., 2022). A preclinical study showed that dubbed compound A (Cpd A) c-met inhibitor also has an anti-proliferative effect on TNBC when used with neratinib (Breen et al., 2020). The study demonstrated that Cpd A inhibited the growth of TNBC to a greater extent, especially in the Cpd A-sensitive cells.

6.2. Monoclonal antibodies targeting c-met

Monoclonal antibodies (mAbs) are an immunotherapy drug designed to target specific proteins in cancer cells. In the case of c-Met targeted therapy, the mAbs target the c-Met protein. Monoclonal antibodies targeting c-Met work by binding to the c-Met protein on the surface of cancer cells. This binding can block the signals that c-Met usually sends to the cell, which can help slow or inhibit cancer cell growth. Various therapeutic strategies involving antibodies have been investigated in preclinical research and clinical trials to block c-Met in cancers. Some of these mAbs are effective in treating some cancer types, including NSCLC, gastric cancer, and liver cancer (Shah et al., 2021). Conventional bivalent monoclonal antibodies frequently trigger the auto-activation of c-Met by promoting its dimerization (Huang et al., 2020a). For instance, Onartuzumab, a monovalent antibody directed at c-Met, hinders the interaction between HGF and c-Met without inducing c-Met activation, attributed to its monovalent characteristic. However, this antibody failed to advance past the phase III clinical trial stage due to inadequate patient selection. To circumvent this, different strategies, such as single-chain variable fragments (scFvs) and fragment antigen-binding antibodies (Fabs), which are small derivatives of whole antibodies, were developed, and they are cost-effective with improved tissue penetration and rapid blood clearance (Zarei et al., 2020). These proteins have shown strong binding affinity and potential anti-cancer properties. The result of a study that aimed at identifying a specific Fab antibody targeting c-Met, particularly for potential therapeutic applications against c-Met-positive tumor cells, revealed that, among the tested Fabs, clone C16 exhibited the highest affinity for c-Met and significantly binds to MKN45 cells, a human gastric adenocarcinoma cell line known to express high levels of c-Met, in contrast to c-Met negative T47D cell (Zarei et al., 2020). However, further research and development would be expedient in exploring the therapeutic potential of C16 and its efficacy in preclinical and clinical settings. Furthermore, a study evaluated the anti-tumor effects of BS001, a bispecific antibody binding both c-Met and CD3 on lung, ovarian, and breast cancer. The findings indicated that BS001 exhibited robust killing of tumor cells mediated by T-cells *in vivo* and *in vitro*. When combined with atezolizumab, an anti-PD-L1 antibody, BS001 demonstrated even stronger tumor growth inhibition than individual treatments. However, combining BS001 with Pembrolizumab led to heightened inhibition of tumor growth and decreased tumor recurrence in a xenograft model (Huang et al., 2020b).

In response to resistance against EGFR inhibitors, there has been a rise in diverse bispecific antibodies targeting c-Met. These therapies offer various mechanisms of action, such as inhibiting c-Met signaling and promoting antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) (De Gorter et al., 2022). In a preclinical xenograft study, MCLA-129, a bispecific antibody targeting EGFR and c-Met, showed promising activity against NSCLC cells through ADCC and ADCP mechanisms, indicating its potential as a therapeutic agent for NSCLC treatment (Bossi et al., 2023). Similarly, amivantamab (JNJ-61186372), another novel bispecific antibody targeting both EGFR and c-Met in NSCLC, exhibited enhanced antitumor efficacy compared to small molecule inhibitors targeting EGFR and c-Met in preclinical studies using an *in vivo* model (HCC827-HGF) (Neijssen et al., 2021). This highlights the dual capability of monoclonal antibodies targeting RTKs such as c-Met and EGFR, potentially overcoming resistance observed with single-agent therapies. Furthermore, a humanized bivalent monoclonal antibody targeting c-Met inhibits c-Met activity by facilitating its internalization and degradation. During a phase I clinical trial, emibetuzumab demonstrates clinical potential by effectively blocking both HGF-dependent and HGF-independent c-Met signaling (Rosen et al., 2017; Kim and Kim, 2017).

Another pioneering approach involves the use of antibody-drug conjugate (ADC). For example, BYON3521, a new ADC specifically engineered to target c-Met, combines a humanized antibody with a cell-killing drug and boasts a high affinity for human and cynomolgus c-Met. Leveraging site-specific drug-conjugate technology, the ADC demonstrates potent efficacy in cancer cell lines where c-Met is amplified or overexpressed. BYON3521 also showed significant anti-tumor activity in diverse tumor types upon a single dose administration in patient-derived xenograft models, and it was well tolerated (Groothuis et al., 2021). Additionally, the ADC ABBV-400 consisting of the c-Met–targeting antibody telisotuzumab conjugated to a potent topoisomerase 1 inhibitor (Top1i) payload has undergone phase I clinical trial (NCT05029882) for the investigation of safety, pharmacokinetics, and tolerability in patients with advanced solid tumors including NSCLC, gastroesophageal adenocarcinoma (GEA), and colorectal cancer (CRC). The results showed that ABBV-400 demonstrated promising antitumor activity across various tumor types. The objective response rate (ORR) was 24.4% (11/45; 95% CI: 12.9, 39.5), and the common adverse events observed were anemia, neutropenia, thrombocytopenia, and nausea (Sharma et al., 2023). Additionally, a recent study examined the anti-tumor effects of P3D12-vc-MMAF, an ADC targeting c-Met with minimal signaling activation, and compared it to the c-Met TKI, PHA665752. P3D12-vc-MMAF demonstrated potent *in vitro* activity across a spectrum of c-Met expression levels, while PHA665752 showed limited efficacy. Additionally, P3D12-vc-MMAF exhibited robust tumor growth inhibition *in vivo*, suggesting its potential as a promising therapeutic option for c-Met-driven cancers (Fujita et al., 2020).

6.3. c-Met RNAi therapeutics

The development of innovative therapeutic strategies leveraging RNA interference is rapidly expanding, offering promising avenues for cancer treatment through the precise targeting of specific genes sequentially (Barresi et al., 2022). RNA interference (RNAi) involves converting double-stranded RNA (dsRNA) into short interfering RNAs (siRNAs), which subsequently reduce gene expression by specifically targeting mRNA molecules (Barresi et al., 2022; Brü et al., 2020). This approach employs both naturally occurring miRNAs and externally introduced siRNAs (Lin et al., 2020). Research indicates that c-Met is a target gene for various miRNAs regulating its activity. It has been

observed that the majority of miRNAs involved in c-Met signaling exhibit anti-oncogenic properties. For instance, miRNA-206, a c-Met and Bcl-2 inhibitor, promotes cell death while inhibiting tumor development and metastasis in NSCLC (Zhan et al., 2020).

In bladder cancer, miR-433 acts as a tumor suppressor by directly targeting c-Met and CREB1, which inhibits cell proliferation, motility, and EMT when highly expressed (Xu et al., 2016). This suggests that miR-433 initiates the degradation or translation inhibition of c-Met and CREB1, thus reducing their activity or expression levels. Additionally, miR-323a-3p, another potential tumor suppressor in bladder cancer, targets both c-Met and SMAD3 (Li et al., 2017; Bhavsar et al., 2023). Its overexpression reduces cell motility by regulating EMT progression, primarily through its effect on SNAIL, a key regulator of EMT. By binding to the mRNA of c-Met and SMAD3, miR-323a-3p downregulates their expression levels, thereby inhibiting downstream signaling pathways associated with EMT progression (Feng et al., 2022b). Therefore, miRNAs targeting c-Met offer a promising therapeutic strategy for overcoming drug resistance in diverse cancers by disrupting the c-Met signaling pathway and improving the effectiveness of anticancer treatments.

7. Advantages of targeting c-met over other TKIs

The landscape of TKIs spans various targets and therapeutic agents developed to inhibit pathways crucial in cancer progression. Among these, c-Met inhibitors have garnered significant interest due to their unique role in oncogenic signaling. Targeting c-Met offers several distinct advantages over other TKIs. Firstly, c-Met inhibitors are designed to specifically target the c-Met receptor tyrosine kinase, which is frequently dysregulated in various cancers. This targeted approach results in fewer off-target effects compared to nonselective TKIs that inhibit multiple kinases, potentially reducing the incidence of adverse effects (Fogli et al., 2022). The specificity of c-Met inhibitors is particularly advantageous in tumors where c-Met plays a central role in driving oncogenesis (Zhang et al., 2022). Disrupting c-Met signaling pathways crucial for cell proliferation, survival, motility, and invasion can significantly reduce tumor growth and metastasis. This targeted mechanism underscores the therapeutic potential of c-Met inhibitors in precision oncology.

Additional critical advantage of c-Met inhibitors is their ability to overcome resistance mechanisms observed with other TKIs. Resistance to conventional EGFR inhibitors (e.g., erlotinib, gefitinib) often arises through secondary mutations or activation of alternative pathways, including c-Met (Friese-Hamim et al., 2017). Incorporating c-Met inhibitors into treatment regimens can effectively counteract this resistance, offering a strategic advantage in managing resistant cancers (Friese-Hamim et al., 2017). Similarly, while VEGFR inhibitors (e.g., sunitinib, sorafenib) effectively target angiogenesis (Ranieri et al., 2017), they may induce significant side effects due to their broader impact on vascular function. In contrast, c-Met inhibitors, with their more targeted approach, may present a better safety profile while maintaining therapeutic efficacy. Unlike some TKIs highly effective in specific cancer types (e.g., BCR-ABL inhibitors in CML) (Leonetti et al., 2011), c-Met inhibitors demonstrate broad applicability across various solid tumors (Dong et al., 2022). This versatility enhances their clinical utility and positions them as potential candidates for combination therapies. Combinatorial approaches involving c-Met inhibitors with other targeted agents, chemotherapy, or immunotherapy have shown promise in enhancing treatment outcomes by addressing multiple oncogenic pathways simultaneously. The development of selective c-Met inhibitors such as tepotinib and capmatinib represents a significant advancement in optimizing therapeutic benefits. These inhibitors achieve complete c-Met inhibition with acceptable safety profiles, contrasting with nonselective inhibitors that may exhibit increased toxicity due to off-target effects (Bouattour et al., 2018). Selective c-Met inhibitors can be used at optimal doses to maximize therapeutic efficacy while minimizing adverse effects, thus improving patient outcomes (Bouattour et al., 2018).

In summary, targeting c-Met offers unique advantages over other TKIs, including greater specificity, overcoming resistance mechanisms, and potential synergy in combination therapies. As ongoing research and clinical trials unravel the optimal applications of c-Met inhibitors in cancer therapy, their evolving role in precision oncology underscores their transformative potential in reshaping treatment paradigms.

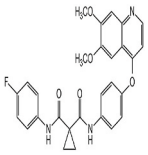
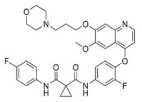
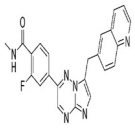
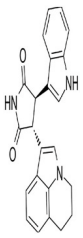
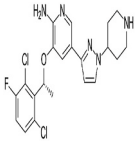
8. Clinical trials of inhibitors that target c-Met in breast cancer patients

Over recent years, numerous c-Met inhibitors have been created for therapeutic tumor investigations, demonstrating notable antitumor efficacy in preclinical breast cancer studies. Some of these inhibitors, alongside antibodies directed against c-Met, have been employed in clinical trials for breast cancer treatment, yielding specific efficacy (Park and Richardson, 2020; Kim, 2022), and are summarized below in (Table 1). Furthermore, ongoing efforts are directed towards developing novel c-Met inhibitors and drug therapy approaches for breast cancer. The results of ongoing and upcoming clinical trials investigating anti-c-Met therapy are highly anticipated. However, challenges, including receptor cross-talk and the development of resistance, need to be tackled to optimize treatment effectiveness. Also, there are some discrepancies in the effectiveness of c-Met inhibitors in preclinical studies versus clinical trials, and this has been attributed to the selection of patients for clinical trials, which often overlooks the status of *MET* amplification and fails to utilize suitable biomarkers that could indicate the dependency of tumors on c-Met (Park and Richardson, 2020; Hughes and Siemann, 2019).

8.1. Cabozantinib (XL184, BMS-907351)

Cabozantinib is an orally bioavailable multi-kinase that inhibits c-Met, VEGFR2, and other RTKs, including RET, Fms-like tyrosine kinase 3 (FLT3), and KIT (Hagege et al., 2022; O' et al., 2022). It suppresses c-Met and VEGFR2 signaling *in vivo* and *in vitro*, causing tumor growth inhibition and tumor regression (Turk et al., 2020; Choy et al., 2022; Lefebvre and Allan, 2021). Cabozantinib can permeate the blood-brain barrier (BBB), and it has been approved by the FDA for the treatment of metastatic medullary thyroid cancer, advanced renal cell carcinoma, and hepatocellular carcinoma (Choy et al., 2022). In the literature, several studies evaluated cabozantinib in breast cancer, either as a standalone treatment or in combination with another drug. The initial study was a Phase II randomized discontinuation trial (RDT) of patients with metastatic breast cancer (ClinicalTrials.gov NCT00940225). showing an objective response rate (ORR) of 13.6% (95 % CI: 6–25.7 %), with a disease control rate at 12 weeks of 46.7% (Tolaney et al., 2016). This was followed by a single-arm phase II trial that involved patients with metastatic TNBC (ClinicalTrials.gov NCT01738438), resulting in an ORR of 9% (95% CI: 2–26) (Tolaney et al., 2017). Also, a phase II study investigated the efficacy and safety of cabozantinib combined with nivolumab (anti-PD-1 antibody) in metastatic TNBC (ClinicalTrials.gov NCT03316586). The results showed that in mTNBC patients (n = 18), the ORR was 6% (95% CI: 0–27), and the median PFS was 3.6 months (95% CI: 1.9–6.9), with no unexpected adverse events (Barroso-Sousa et al., 2021). An alternate study evaluated the antitumor activity of cabozantinib monotherapy in HER2-positive breast cancer patients with bone metastases. Results revealed that the bone scan response rate was 38.5% (90% CI, 27.1%–51.0%), median PFS was 4.3 months (90% CI, 2.8–5.5), and median overall survival (OS) was 19.6 months (90% CI, 18.0–26.8), with no patients achieving ORR either complete response (CR) or partial response (PR) per RECIST, (ClinicalTrials.gov identifier. NCT01441947) (Xu et al., 2020b). Additionally, a phase II randomized trial assessed the effectiveness and tolerability of cabozantinib either as a standalone treatment or in combination with

Table 1
c-Met inhibitors structural properties and their clinical studies conducted on breast cancer patients.

c-Met inhibitors and mechanism	Structural formula	Clinical trial	Phase	No of patients	Breast cancer subtypes	Design	Status
Cabozantinib Multi- TKI		NCT01738438	2	35	TNBC	Cabozantinib	Completed
		NCT03316586	2	18	TNBC	Cabozantinib + nivolumab	Completed
		NCT01441947	2	68	HR+	Cabozantinib + fulvestrant	Active not recruiting
		NCT02260531	2	36	HER2+ with brain metastasis	Cabozantinib + trastuzumab	Completed
Foretinib Multi- TKI		NCT01147484	2	47	TNBC	Foretinib	Completed
		NCT01138384	1	19	HER2+	Foretinib + lapatinib	Completed
Capmatinib Selective-TKI		NCT05243641	1b/2	56	Metastatic	Capmatinib + neratinib	Recruiting
		NCT03742349	1	64	TNBC	Capmatinib + partalizumab + LAG525	Terminated
Tivantinib Selective-TKI		NCT01575522	2	22	TNBC	Tivantinib	Completed
		NCT00827177	1	87	Solid tumors, including Breast cancer	Tivantinib + sorafenib	Completed
Crizotinib Multi- TKI		NCT03620643	2	58	Lobular breast cancer, Lobular TNBC	Crizotinib + fulvestrant	Active not recruiting
		NCT02074878	1	3	Metastatic	Crizotinib + sunitinib	Terminated
Onartuzumab		NCT01186991	2	185	TNBC	Onartuzumab + bevacizumab + paclitaxel	Completed

trastuzumab in breast cancer patients with brain metastases (ClinicalTrials.gov NCT02260531). A total of 36 patients were enrolled in the study (cohort 1, n = 21; cohort 2, n = 7; cohort 3, n = 8). For cohort 1 (HER2-positive patients), the results showed that the central nervous system (CNS) ORR was 5% (95% CI 0.2%–23%), the median PFS was 4.1 months, and the median OS was 13.8 months. For cohort 2 (HR-positive patients), the results should be that CNS ORR was 14% (95% CI 1%–51%), median PFS was 2.4 months, and median OS was 5.1 months. And CNS ORR was 0% in cohort 3 (triple-negative patients). However, the median PFS for all patients in the trial was 3.0 months (95% CI 2.0 months–4.2 months) (Leone et al., 2020).

8.2. Foretinib (GSK1363089, XL88)

Foretinib is an oral multi-kinase inhibitor that targets c-Met, RON, VEGFR2, AXL, angiopoietin receptor (TIE2), and platelet-derived growth factor receptor beta (PDGFRB) (Nazari et al., 2024). Foretinib is an ATP-competitive inhibitor of c-Met that binds strongly to the c-Met ATP pocket tyrosine kinase domain. It has undergone phase I/II clinical studies, demonstrated anti-proliferative properties, and induced tumor death. A phase II trial, conducted without blinding and utilizing a single-arm design, aimed to assess the effectiveness of foretinib monotherapy in patients with recurrent or metastatic TNBC (ClinicalTrials.gov number, NCT01147484). Findings showed that in TNBC patients, the ORR was 4.7% in the intent-to-treat (ITT) population and 5.4% in the response evaluable cTNBC population, and the median PFS was 1.9 months (95% CI: 1.8–3.2) in the ITT population (Rayson et al., 2016). A phase Ib clinical trial assessed the efficacy, safety, and recommended phase II doses (RP2D) of foretinib in combination with lapatinib in HER-2-positive metastatic breast cancer (mBC) (ClinicalTrials.gov number, NCT01138384). The results revealed that in HER-2-positive mBC patients (n = 19), the ORR was 0%, and the median PFS was 3.2 months (95% CI 1.61–4.34). Furthermore, the findings revealed that at dose level 4 (DL 4) (foretinib 45 mg/lapatinib 1250 mg), there was grade 3 of both fatigue and diarrhea, indicating the need for dose reductions. Then, no dose-limiting toxicities were seen at dose level 3 (DL3). As a result, the RP2D of the combination was determined to be foretinib 45 mg orally once a day and lapatinib 1000 mg once a day (Chia et al., 2017).

8.3. Capmatinib (INC280)

Capmatinib is an extremely selective ATP-competitive c-Met inhibitor, demonstrating a 10,000-fold greater selectivity for c-Met than other kinases. It can inhibit c-Met activity at picomolar doses (Liang and Wang, 2020). The FDA has approved capmatinib to treat metastatic NSCLC (Dhillon, 2020). A Phase Ib/II clinical trial has started exploring the potential of combining capmatinib with the pan-HER inhibitor neratinib for treating metastatic breast cancer and metastatic inflammatory breast cancer (ClinicalTrials.gov number, NCT05243641). However, the clinical outcomes of capmatinib in breast cancer have not yet been documented (Jabbarzadeh Kaboli et al., 2024).

8.4. Tivantinib (ARQ197)

Tivantinib is an orally administered c-Met inhibitor that operates through a non-ATP competitive mechanism. It is highly selective for c-Met, 10–100 times more selective than 229 other kinases tested, with an inhibitory constant (Ki) of 355 nmol (Zhao et al., 2021). A single-arm phase II trial evaluated the response of metastatic TNBC patients who received 1 to 3 courses of chemotherapy to tivantinib monotherapy (ClinicalTrials.gov number, NCT01575522). The findings revealed that in mTNBC (patients = 22), the ORR was 4.5 % (95 % CI 0–22.8 %), and the median PFS was six months (95 % CI 0.2–24.7 %). Also, immunohistochemistry (IHC) staining and fluorescence *in situ* hybridization (FISH) were used to evaluate the c-Met expression, and it was revealed that 45.5% of the patients had c-Met positive TNBC. The study's absence of phospho-c-Met + TNBC patients suggests that the limited response rate observed may be due to the specificity of tivantinib. Hence, it is recommended that phosphorylated c-Met levels be assessed before starting c-Met-targeted therapy. Nonetheless, the study emphasizes that the advantages of tivantinib treatment were mainly seen in patients with substantial total c-Met overexpression. (Jabbarzadeh Kaboli et al., 2024; Tolaney et al., 2015). Additionally, a phase 1 clinical trial evaluated the dose escalation of tivantinib in combination with sorafenib, a kinase inhibitor targeting VEGFR, PDGFR, and RAF, in patients with different advanced solid tumors, including breast cancer, HCC, and melanoma (ClinicalTrials.gov number, NCT00827177). Interestingly, the results showed that the breast cancer patients included in this study (totaling 8) had low expression of c-Met and did not exhibit any objective response (0%) to the tivantinib and sorafenib combination. Conversely, 28.6% of melanoma patients (4 out of 14 patients) and 40% of HCC patients (4 out of 10 patients) were positive for c-Met. The response rates in these groups were 26% and 10%, respectively. These results emphasize the necessity of assessing the expression of c-Met before initiating therapy targeting this molecule (Jabbarzadeh Kaboli et al., 2024; Puzanov et al., 2015).

8.5. Onartuzumab (MetMAb)

Onartuzumab is a fully-humanized monoclonal antibody that targets c-Met by preventing HGF's alpha chain binding to the c-Met ligand binding region (β Sema-PSI domain) (Liang and Wang, 2020). Onartuzumab differs from other anti-c-Met antibodies in that it prevents dimerization and inhibits subsequent downstream signaling pathways when it binds to c-Met. Onartuzumab has been subjected to clinical trials in patients diagnosed with metastatic TNBC. The study was a randomized phase II experiment that looked into the efficacy, safety, and tolerability of onartuzumab in combination with paclitaxel, with or without bevacizumab, a VEGF inhibitor (ClinicalTrials.gov, NCT01186991). The main objective was PFS, while the secondary objectives included overall survival, ORR, and safety. Unfortunately, this study did not show a clinically significant outcome of onartuzumab treatment. The study results showed that adding onartuzumab to paclitaxel did not enhance PFS. The ORR was 42.2% (95% CI 28.6−57.1) when onartuzumab, bevacizumab, and paclitaxel were combined, compared to 27.5% (95% CI 15.9−40.6) with onartuzumab and paclitaxel alone. It is also worth noting that the small number of detected positive patients limited the assessment of the impact of the c-Met IHC (Dié et al., 2015).

9. Role of c-Met signaling in homeostasis

c-Met signaling is critical not only in pathological states such as cancer but also in normal physiological processes and maintaining cellular homeostasis (Organ and Tsao, 2011). The c-Met receptor, activated by its ligand HGF, orchestrates many cellular responses essential for tissue development, repair, and regeneration (You et al., 2015). During embryonic development, c-Met and HGF are crucial for the growth and survival of hepatocytes and placental trophoblast cells (You et al., 2015). Knockout studies have shown that embryos lacking c-Met or HGF exhibit significantly impaired liver and placental development, leading to in-utero death due to compromised nutrient exchange (Zhao et al., 2022). Moreover, c-Met signaling facilitates the migration and differentiation of myogenic precursors essential for developing skeletal muscles and other tissues (Organ and Tsao, 2011). Activation of c-Met signaling induces cell scattering, disrupting cadherin-based cell-cell contacts and promoting cell motility (Organ and Tsao, 2011). This process is critical during embryogenesis and wound repair, facilitating tissue reorganization and regeneration. The c-Met/HGF axis is pivotal in cellular growth and regeneration across various organs. For instance, HGF-induced c-Met activation in the liver stimulates hepatocyte proliferation and tissue repair mechanisms following injury (Zhao et al., 2022). Similarly, c-Met signaling supports organ growth and repair in the kidneys through enhanced cell proliferation and tissue remodeling (Trusolino et al., 2010).

In wound healing, c-Met signaling on keratinocytes promotes epithelial cell migration and proliferation, accelerating wound closure and tissue regeneration (Trusolino et al., 2010). This process underscores the trophic role of HGF in facilitating tissue repair. c-Met signaling contributes to tubulogenesis, a critical process in organ regeneration involving partial epithelial-mesenchymal transition (EMT), cell chain formation, and redifferentiation into mature tubules. The activation of STAT3, MAPK, and PI3K/Akt pathways supports cell survival, proliferation, and structural organization during tubule formation (Zhao et al., 2022; Trusolino et al., 2010). In angiogenesis, c-Met signaling promotes endothelial cell proliferation, migration, and tube formation, which are essential for establishing new blood vessel networks and maintaining vascular integrity (Liu et al., 2023). This process ensures adequate oxygen and nutrient supply to tissues, supporting overall physiological balance. In summary, c-Met signaling is indispensable for maintaining physiological homeostasis through its roles in embryonic development, organ regeneration, wound healing, and vascular homeostasis. These functions underscore the broad significance of the c-Met pathway beyond disease context, highlighting its critical role in normal cellular functions and tissue maintenance.

10. Future perspectives and directions

Advancements in understanding the biology of c-Met and its role in breast cancer are pivotal for developing more targeted therapeutic interventions. Recent studies have elucidated the complex signaling pathways regulated by c-Met, shedding light on its involvement in tumor growth, metastasis, and resistance to conventional treatments. Several studies have shown the importance of c-Met in promoting breast cancer metastasis through its interaction with various downstream effectors, highlighting its potential as a therapeutic target (Faiella et al., 2022; Ho-Yen et al., 2015; Zhang et al., 2018). Innovative strategies are being explored to improve the efficacy of c-Met-targeted therapies. This involves the creation of novel small molecule inhibitors with improved pharmacokinetic properties and reduced off-target effects. Additionally, combination therapies that target multiple signaling pathways concurrently are being investigated to overcome resistance mechanisms. Studies have shown that the combination of c-Met inhibitors with inhibitors of other receptor tyrosine kinases enhanced anti-tumor efficacy in preclinical models (Dulak et al., 2011; Hassan et al., 2016). Integrating c-Met inhibition into personalized treatment strategies is promising for optimizing patient outcomes. By profiling individual tumors for c-Met expression and other molecular characteristics, clinicians can tailor treatment regimens to target specific vulnerabilities (ingrid garajova, 2015). This approach has been supported by various studies that demonstrated the feasibility of molecular profiling to guide personalized therapy selection in breast cancer patients. Furthermore, the role of biomarkers in patient selection and response prediction is crucial for optimizing treatment outcomes and minimizing adverse

effects. Biomarker-guided approaches enable clinicians to pinpoint individuals most apt to respond positively to c-Met-targeted treatment, maximizing treatment efficacy and minimizing unnecessary exposure to potentially toxic agents. Previous studies have identified *MET* amplification as a predictive indicator for the effectiveness of c-Met inhibitors in breast cancer patients, underscoring the importance of biomarker-driven treatment approaches (Abouelfadl et al., 2022; Wang et al., 2023).

11. Conclusion

Breast cancer remains a formidable challenge worldwide, underscoring the critical need for innovative therapeutic strategies. Diagnostic and prognostic biomarkers are pivotal in guiding treatment decisions and improving patient outcomes. Among these biomarkers, c-Met has emerged as a promising candidate for targeted therapy in breast cancer because of its involvement in disease progression and poor prognosis. While existing small molecule inhibitors have shown effectiveness in targeting aberrant c-Met signaling pathways, their limitations, including bypass secretion and mutagenesis effects, underscore the necessity for further refinement. Future efforts should prioritize the development of novel c-Met inhibitors characterized by enhanced safety profiles, efficacy and selective targeting of c-Met pathways, and reduced off-target toxicity. Moreover, there is a pressing need for innovative inhibitor designs capable of overcoming resistance mechanisms, including bypass secretion and alterations in the c-Met protein. These advancements hold the potential to significantly enhance the effectiveness of breast cancer chemotherapy and ultimately reduce mortality rates associated with this devastating disease.

CRediT authorship contribution statement

Emeka Eze Joshua Iweala: Conceptualization, Supervision, Writing – review & editing. **Doris Nnenna Amuji:** Conceptualization, Writing – original draft, Visualization. **Abimbola Mary Oluwajembola:** Writing – review & editing, Visualization. **Eziuche Amadike Ugbogu:** Writing – review & editing.

Authors contributions

D.N.Amuji wrote the main manuscript; and generated Figs. 1–5; E.E.J.Iweala and D.N.Amuji were responsible for the conceptualization of the study; E.E.J.Iweala, E.A. Ugbogu, and A.M.Oluwajembola reviewed and edited; A.M.Olujembola designed the graphical abstract. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

The data that has been used is confidential.

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