Emerging therapeutic targets in metastatic progression: a focus on breast cancer

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Abstract

Metastasis is the underlying cause of death for the majority of breast cancer patients. Despite significant advances in recent years in basic research and clinical development, therapies that specifically target metastatic breast cancer remain inadequate, and represents the single greatest obstacle to reducing mortality of late-stage breast cancer. Recent efforts have leveraged genomic analysis of breast cancer and molecular dissection of tumor-stromal cross-talk to uncover a number of promising candidates for targeted treatment of metastatic breast cancer. Rational combinations of therapeutic agents targeting tumor-intrinsic properties and microenvironmental components provide a promising strategy to develop precision treatments with higher specificity and less toxicity. In this review, we discuss the emerging therapeutic targets in breast cancer metastasis, from tumor-intrinsic pathways to those that involve the host tissue components, including the immune system.

Keywords

Breast cancer, Metastasis, Targeted therapy, Tumor microenvironment, Immunotherapy

Contents

1. Introduction
2. Status quo in the management of mBC
3. Tumor-intrinsic targeting
4. Stroma-centric targeting
5. Conclusions and future directions

Acknowledgments

References

Abbreviations

ADC, antibody drug conjugate; AR, androgen receptor; CAF, cancer associated fibroblasts; GSI, gamma secretase inhibitor; HR, hormone receptor; mBC, metastatic breast cancer; MSC, mesenchymal stem/stromal cells; TAM, tumor-associated macrophages; TIL, tumor-infiltrating lymphocyte; TME, tumor microenvironment; TNBC, triple-negative breast cancer; T-reg, regulatory T cell.

1. Introduction

The overall 5-year survival rate for breast cancer currently stands at 90% — a dramatic improvement over the 63% survival rate in the early 1960s. When stratified by stage, the 5-year survival rates have increased to 99% for localized disease and 85% for regional advanced disease, a trend that can be attributed to early diagnoses and better treatment regimens. However, for patients with advanced or metastasized breast cancer at the time of diagnosis (abbreviated as mBC in this review), the 5-year survival rate remains at only 26% , reflecting a need for both new therapies and insights into the metastatic process. This disparity in survival between early and late stage breast cancer represents the principle obstacle in breast cancer management.

To date, the FDA has approved over 25 oncology drugs to treat breast cancer (Table 1). These drugs fall into three major categories: 1) Cytotoxic chemotherapies, including mitotic inhibitors, antimetabolites, and various DNA-damaging reagents; 2) Endocrine therapies, including selective estrogen receptor modulators (SERMs), aromatase inhibitors (AIs), and estrogen receptor downregulators (ERDs); and 3) Targeted therapies, which target certain dysregulated pathways in mBC or tumor microenvironment. The majority of these drugs belong to cytotoxic chemotherapies (44%), followed by endocrine therapies (24%) and HER2-targeting therapies (16%). Only 4 drugs (16%) target tumor- and microenvironment-specific molecules beyond the EGFR family, namely mTOR, CDK4/6, RANKL, and bisphosphonates.

The paucity of targeted therapies is further compounded by several critical issues in the management of mBC.

The most crucial of these is the disparity in response rates to systemic chemotherapy, as only 50% of metastatic cancers respond in contrast to 90% of primary tumors . Lower response rate in mBC is also accompanied by a stronger likelihood of acquired therapeutic resistance during the course of treatment .

Finally, the development of targeted agents for the highly metastatic triple-negative (TNBC) subtype has been

largely hindered by a relative lack of understanding into its heterogeneous molecular nature . While targeting tumor-intrinsic factors remains the traditional approach to therapeutic intervention (i.e. targeting aberrant driver events in breast cancer cells), developing research on the tumor microenvironment suggests that a new paradigm of stroma-targeting may yield many novel opportunities. In particular, the use of immunotherapies to target mBC is a potentially promising field .

Here we review the current status of pharmacological management and focus on the landscape of emerging therapeutics for mBC. These include tumor-intrinsic targets such as the PI3K/ATK/mTOR pathway, PARP enzymes, activated growth factor receptors (e.g. EGFRs and FGFRs), cancer stem cell network (e.g. the Notch and Wnt pathways), androgen receptor, as well as therapies targeting communications between the tumor and host (e.g. immunotherapies). We discuss the mechanisms of action and biological implications of these targets with analysis of data from mechanistic and clinical studies. Finally, we address the need for the development of combinatorial therapies, in the context of targeting both the drivers of metastasis as well as the associated stromal components.

2. Status quo in the management of mBC

Clinical management of breast cancer has greatly improved in recent decades through the diagnostic classification of breast cancer into different subtypes, mainly on the basis of the hormone receptors (ER/PR) and the epidermal growth factor receptor HER2. Accordingly, breast cancer treatment is divided into three main classes: 1) hormone receptor-positive (ER+ and/or PR+), 2) ErbB2/HER2/neu-overexpressing (i.e. HER2+), and 3) the remaining TNBC marked by the absence of ER/PR and HER2, which are poorly characterized and the most difficult to manage.

Hormone receptor-positive (HR+) BC patients are primarily treated with endocrine therapy (e.g. letrozole or tamoxifen), either alone or in combination with a cytotoxic chemotherapy drug. These patients generally have a favorable prognosis and are associated with better overall survival compared to the other subtypes.

However, HR+ patients also exhibit a higher risk of late recurrence following 5 years of adjuvant endocrine therapy, likely due to the low proliferation of HR+ tumor cells . Extended adjuvant endocrine therapy beyond 5 years has been shown to significantly reduce risk of recurrence and mortality in HR+ patients, and has been applied in clinical practice . The recent identification of activating mutations in the estrogen receptor (ESR1) demonstrates a central role of acquired endocrine resistance in HR+ mBC, suggesting that second-line ER antagonists may be of substantial therapeutic benefit .

The more aggressive HER2+ BC is characterized by high expression of HER2/neu. These patients are primarily treated with trastuzumab (Herceptin), a landmark success in BC-targeted therapy. However, not all HER2+ tumors respond to anti-HER2 therapy. Although tumors resolve in many patients, others show no response or become resistant . Therefore, a multitude of HER2-targeting drugs exploiting different targeting mechanisms have been developed, such as lapatinib (HER2 and EGFR dual tyrosine kinase inhibitor) and

pertuzumab (HER2 dimerization inhibitor) (see Table 1). Many other HER2-targeting strategies have been proposed and are currently under active investigations .

TNBC represents 15–20% of newly diagnosed breast cancer cases. These patients have a high risk of recurrence, especially in the brain and viscera. This high propensity to metastasize contributes to the worst rates of overall and disease free survival for TNBC patients compared to other subtypes . There are currently no targeted therapies available for these patients, leaving cytotoxic chemotherapies as the only standard of care. Treatment of TNBC remains one of the most pressing challenges in today's clinical practice. Addressing this need, gene expression profiling of over 3000 TNBCs has revealed a deeper stratification of six different TNBC subtype . Both this and other genomics-based studies continue to shed light on the molecular understanding of TNBC heterogeneity and may provide critical insights in developing TNBC-targeted therapies .

For breast cancer patients, metastasis to the bone is a common site of recurrence . This type of metastasis is characterized by a vicious cycle of bone resorption and accelerated tumor growth . Osteoclast inhibitors such as the bisphosphonates (e.g. pamidronate, zoledronic acid) and the RANKL-targeting denosumab have been repurposed for breast cancer patients with bone metastases, representing the only organ-tropic anti-metastatic treatment strategy currently available . Bisphosphonates are analogs of pyrophosphate that bind to the bone matrix and are internalized by osteoclast inhibitors. Once inside the cell, they inhibit osteoclast activity through a variety of means, such as acting as farnesyl-transferase inhibitors . Denosumab is a mAb that binds and inhibits receptor activator of nuclear factor kappa-B ligand (RANKL), the principle ligand responsible for the maturation of bone-resorbing osteoclasts . Both classes of drug effectively reduce the risk of skeletal-

related events (SREs) in breast cancer patients with bone metastases, while denosumab has been shown superior to bisphosphonates in terms of both efficacy and tolerability .

Targeted drug delivery to cancer cells, exemplified by the antibody drug conjugate (ADC), has recently emerged as a novel and promising strategy in treating mBC. ADCs link potent chemotherapy drugs with monoclonal antibodies (mAbs) targeting cancer-specific antigens . Administration of ADCs leads to high intratumoral drug concentrations, while non-target tissues are largely spared from chemotherapeutic exposure . Ado-trastuzumab emtansine (Kadcyla, TDM-1), a HER2-targeting mAb trastuzumab conjugated with the microtubule-inhibitory agent DM1, was approved in 2013 for treating HER2+ mBC. Since, multiple ADCs have been developed to target various subtypes of breast cancer and are currently being tested in clinical trials (Table 2).

3. Tumor-intrinsic targeting

Genomics studies have identified numerous genetic and pathway alterations in breast cancer cells, however, only a few have been validated as viable targets in clinical studies. Therapies against ER and HER2 highlight the landmark successes in targeted breast cancer treatment, suggesting that a tumor-intrinsic targeting approach is of significant value. In this section, we discuss several promising therapeutic candidates supported by strong clinical evidence (Figure 1).

3.1. Inhibition of PI3K/AKT/mTOR pathway

The PI3K/AKT/mTOR pathway mediates multiple cellular processes such as proliferation, migration, invasion, survival, metabolism, and angiogenesis . *PIK3CA* is one of the most frequently mutated genes in all subtypes of breast cancer . Its most prevalent activating mutation *PIK3CA*^{H1047R} has recently been shown to play key effects in tumor initiation and cell fate determination in the pre-neoplastic mammary gland . In addition, loss of PTEN and INPP4B are also frequently observed in breast cancer malignancies . Moreover, breast cancers that have constantly active Akt signaling will rely on Akt for survival and are associated with therapeutic resistance . Finally, crosstalk between the PI3K/AKT/mTOR and the Ras-MAPK pathways have been reported, creating a more complex network of signaling .

Disabling the PI3K/AKT/mTOR pathway provides a compelling and rational approach to improve the antitumor effects of existing chemotherapies. Activation of the PI3K/AKT/mTOR pathway is frequently implicated in resistance to endocrine , HER2-targeted and cytotoxic chemotherapies. Everolimus, a rapamycin analog that inhibits mTOR kinase activity, is the first and so far the only FDA-approved compound targeting this pathway. Small molecules designed to specifically target different components in the PI3K/AKT/mTOR pathway have been developed and are under active investigations in clinical trials (Table

3).

Alpelisib (also known as BYL719, PI3K α inhibitor), buparlisib (also known as BKM120, pan-PI3K inhibitor), taselisib (also known as GDC-0032, selective inhibitor of Class I PI3K α,β,γ isoforms) , ipatasertib (also known as GDC-0068, ATP-competitive small molecule inhibitor of all three isoforms of Akt) have emerged as promising drug candidates. Alpelisib, buparlisib and taselisib demonstrate significant antitumor effects when combined with endocrine therapy . Combination of trastuzumab, LJM716 (HER3 mAb) and alpelisib has antitumor activity in pre-treated HER2+, PIK3CA-mutated mBC . The LOTUS (NCT02162719) trial is an ongoing phase II clinical trial to evaluate the efficacy of ipatasertib combined with paclitaxel in treatment of metastatic TNBC.

3.2. Inhibition of PARP

PARP inhibitors represent another emerging class of targeted therapeutics for mBC. PARP1, the first described enzyme of the PARP family, plays a key role in the repair of DNA single-strand breaks via base excision repair (BER); it has also been implicated in other pathways resolving or generating single-strand breaks, such as the nucleotide excision repair (NER) and mismatch repair (MMR) mechanisms . PARP1 inhibitors function by inhibiting the covalent attachment of ADP-ribose to PARP1 substrates, such that DNA repair enzymes cannot be recruited to the site of DNA damage . Studies indicate that PARP1 inhibitors have the most potent antitumor effects in cancers with BRCA-mutations, as double strand break repair via homologous recombination (HR) is not available in BRCA-defective cells . This creates a situation of synthetic lethality in which only the BRCA-mutated tumor cells are affected .

Olaparib is the only PARP inhibitor approved by the FDA, as a single-agent treatment for advanced ovarian

cancer driven by defective BRCA genes. Olaparib has been tested in breast cancer as either a single agent or in combination with other cytotoxic drugs. The current clinical trials involving Olaparib primarily enrolled patients with BRCA-mutated mBC . Second-generation PARP inhibitors have also been developed and are being evaluated in multiple clinical trials (Table 4). Among the agents, veliparib (ABT888) and talazoparib (BMN 673) are the two most promising candidates that have entered phase III clinical trials.

Veliparib is a PARP inhibitor targeting both PARP1 and PARP2. Potential synergistic interactions between veliparib and cisplatin or the EGFR inhibitor lapatinib were reported to suppress TNBC cell lines . A phase III trial (NCT02163694) has been initiated in 2014 to assess efficacy and toxicity of veliparib in BRCA-associated mBC . Talazoparib is a dual-mechanism PARP inhibitor that potently inhibits the PARP enzyme and effectively traps PARP on DNA. It selectively targets tumor cells with BRCA1, BRCA2, or PTEN gene defects with a high potency in cell lines and xenograft models . EMBRACA (NCT01945775) is an ongoing phase III trial evaluating the safety and efficacy of Talazoparib in mBC patients with BRCA mutations.

The use of synthetic lethality has been mostly studied in the context of BRCA1/2-deficient breast and ovarian cancers . Nevertheless, studies suggest that PARP1 inhibitors may also have positive effects in patients that are non-BRCA mutation carriers , possibly due to the less-defined roles of PARP in double strand-break repair, transcriptional regulation, and hormone-dependent cancers .

3.3. Inhibition of activated growth factor receptors

Increased expression of growth factor receptors and activation of their tyrosine kinase activities are frequently observed in breast cancers . Besides HER2, other members of the EGFR family (e.g. EGFR/HER1/ErbB1, HER3/ErbB3) , vascular endothelial growth factor (VEGF) and its receptors (VEGFRs) , fibroblast growth

factor (FGF) and its receptors (FGFRs) , platelet-derived growth factor (PDGF) and its receptors (PDGFRs) , insulin-like growth factor-1 (IGF-1) and its receptor (IGF-1R) , mast/stem cell growth factor receptor (SCFR, also known as c-Kit) , and MET and hepatocyte growth factor receptor (HGFR, also known as c-MET) have been found dysregulated (by amplification, translocations, or mutations) in breast tumors and are associated with poor patient outcomes.

Therapeutic agents targeting these growth factor-responsive tumors include blockade of individual receptors with mAbs and inhibition of tyrosine kinase activities with small molecule inhibitors. The clinical testing of the long-heralded VEGFR inhibitors failed in Phase II and III clinical trials (see section 4.1.2). Of the myriad growth factors, FGFR is an emerging target of promise. The FGF-FGFR signaling axis plays essential functions in regulating cell proliferation, survival, migration and differentiation in both normal and cancer development . Activation of FGFR signaling may lead to increased tumor angiogenesis and play a role in tumor resistance to antiangiogenic agents and other chemotherapies . In breast cancer, upregulation of the FGFR pathway activity could occur through multiple mechanisms. Amplification of FGFR1 (10% of all BC), FGFR2 (4% of TNBC) and FGFR4 genes (10% of all BC), and germline single nucleotide polymorphisms (SNPs) of FGFR2 and FGFR4 have been reported and are associated with poor prognosis . Therapeutic agents targeting aberrant FGFR activation are now being evaluated in multiple phase II/III clinical trials (Table 5).

3.4. Targeting cancer stem cell signaling

TNBC represents a highly diverse group of cancers , and certain subtypes within this classification show a strong enrichment of cancer stem cell-like features . The cancer stem cell theory hypothesizes that a small fraction of the cells in a tumor have characteristics of somatic stem cells with highly tumorigenic and chemoresistant potential, and could be responsible for the majority of metastatic relapse . As such, the treatment of

specific stem cell features may offer a curative approach to cancer therapy. The Notch and Wnt pathways are the two most extensively studied pathways that have been implicated in both normal and cancer stem cells of the mammary gland, and may be potential targets in TNBC .

3.4.1. Targeting the Notch pathway

Upregulated Notch signaling has been reported in TNBC, and is usually associated with the down-regulation of Numb or activating fusion mutations found in NOTCH1 or NOTCH2 (5-10% of TNBC cases) . Early attempts to target the Notch pathway focused on gamma secretase inhibitors (GSIs) (Table 6). Gamma secretase is a multi-protein integral membrane complex that catalyzes the proteolytic processing of Notch receptors and liberates the Notch intracellular domain (NICD); NICD subsequently translocates to the nucleus and regulates transcription of Notch downstream target genes . Clinical trials involving GSIs demonstrate the feasibility of targeting aberrant Notch signaling in treating mBC (Table 6). However, a low specificity for tumor cells induced high toxicity in GSI-treated patients .

Other Notch-targeting strategies to interfere with Notch signaling show promise in improving therapeutic specificity (Table 6). Antibodies against specific Notch ligands or receptors have been heavily studied in many cancer systems, and will provide an attractive alternative in treating mBC . For example, tumor-derived Jagged1, one of the five Notch ligands, has been shown to promote osteolytic bone metastasis in breast cancer by engaging Notch signaling in the bone cells . It is anticipated that more specific Notch-targeting approaches will rapidly expand as we gain increasing understanding of the Notch signaling network in breast cancer.

3.4.2. Targeting the Wnt pathway

Similar to Notch pathway, activated Wnt signaling has also been implicated in breast cancer tumorigenesis

and recurrence . Canonical β catenin-mediated WNT signaling supports self-renewal of both normal and malignant mammary stem cells . Activated canonical Wnt signaling has been observed in both the primary tumor and lung metastasis of TNBC/basal-like subtype, and is associated with poor clinical outcomes .

Somatic mutations in the Wnt pathway are uncommon in breast cancer; however, dysregulation of proteins in the signaling cascade have been reported. In breast cancer patients, WNT1 protein expression was increased in the tumor tissue compared with non-cancerous adjacent tissue . In this study, Wnt-1 was shown to be markedly elevated in low-grade tumors, but expression levels were reduced as the tumors progressed, suggesting a functional role of Wnt1 at early stages of tumorigenesis. Inhibition of Wnt1 expression reduces the enrichment of cancer stem cells in a mouse model of breast cancer . Receptor-tyrosine-kinase-like orphan receptor 1 (ROR1), a receptor in the non-canonical Wnt pathway, is found to be highly expressed in primary tumors of TNBC patients . ROR1 expression increases in TNBC samples relative to their corresponding normal controls, and correlates with decreased patient survival . ROR1-positive TNBC has been associated with EMT and stem cell-like phenotypes, suggesting that ROR1 might be a potential target for TNBC therapy . Together these studies suggest a potential for Wnt-targeted treatment in breast cancers, but the design of clinical trials should be carefully considered for specific subtypes and/or tumor grades.

3.5. Androgen receptor (AR)

The androgen receptor (AR) is a nuclear receptor activated by the binding of androgenic hormones in the cytoplasm and then translocating into the nucleus . Activated AR regulates gene transcription by binding to specific promoter sequences of target genes . Androgen contributes to the growth of certain types of cancers, most notably prostate cancer . Enzalutamide, an androgen receptor antagonist and potent inhibitor of AR signaling, has been approved for the treatment of metastatic castration-resistant prostate cancer. Although

androgens are often considered to be male sex hormones, they also play important physiologic roles in females .

The prognostic power and clinical relevance of AR expression in breast cancer remains a topic of investigation, and is likely to be subtype-dependent. Some breast cancers express AR, and higher expression is more commonly seen in women with ER+ (67-95%) breast cancer than in women with the HER2+ (63%) or TNBC (10-43%) subtypes . A systematic review and meta-analysis of AR expression and outcomes in early breast cancer concluded that the expression of AR in women with breast cancer is associated with better overall survival (OS) and disease-free survival (DFS) irrespective of ER status . Other studies indicated that AR expression is most significantly associated with a favorable prognosis in ER+ BC patients . While many retrospective histology-based analysis suggest that the presence of AR in breast cancer correlates with better survival outcome , other preclinical and clinical studies implicate that AR antagonists may improve the survival of AR+ TNBC patients . A subclass of TNBC was identified as the luminal androgen receptor (LAR) subtype, as characterized by expression of AR and AR gene targets; LAR cell lines were shown to be uniquely sensitive to AR antagonist bicalutamide .

Investigational trials using AR antagonists, either as monotherapy or combined with other drugs, in patients with AR+ breast cancer are currently ongoing (Table 7). Most of these clinical trials focus on AR+ metastatic TNBC, and a few others target AR+/HR-/HER2+ or AR+/HR+/HER2- mBC subtypes. The discrepancy between the prognostic value of AR and the anti-AR treatment efficacy in clinical trials requires further translational investigations. Such studies will enable a better understanding of the biological functions of androgen and AR, and the mechanisms of action of anti-AR treatment in breast cancer patients.

4. Stroma-centric targeting

Our knowledge of the stroma's contribution to cancer has rapidly grown in the past decade. Stromal cells in the tumor microenvironment (TME) play pivotal roles in facilitating multiple steps during cancer progression and metastasis . Therapeutics targeting tumor-stromal interactions and enhancing host immune response represents an attractive alternative to treat human breast cancer (Figure 2).

4.1. Contributions of stromal cells in creating a favorable tumor microenvironment

Myriad evidence has highlighted the importance of the crosstalk between tumor cells and their surrounding microenvironment . Cancer progression and metastasis are enabled, sustained, and co-evolved through interactions with the stromal cells. While these stromal cells are far from being fully characterized, they include infiltrating immune cells, endothelial cells, cancer-associated fibroblasts (CAFs), and mesenchymal stem/stromal cells (MSCs). . Cytokines and extracellular matrix (ECM) proteins provided by both the stromal and tumor cells facilitate breast cancer progression through a complex network of tumor-stromal communication . Heterogeneous cell types within the TME can also actively influence therapeutic responses and shape resistance .

4.1.1. *Infiltrating immune cells*

Myeloid lineage-derived macrophages can be recruited and educated by tumor cells and the TME to become tumor-associated macrophages (TAMs) or metastasis-associated macrophages (MAMs) . These TAMs and MAMs are immunosuppressive and contribute to tumor progression via numerous macrophage-derived signaling factors, such as cytokines, growth factors, matrix metalloproteinases (MMPs), and hypoxia response proteins . The tumor microenvironment of metastasis (TMEM), characterized by direct interaction between perivascular TAMs, endothelial cells and tumor cells, has been found in human breast cancer specimens . A

high TMEM score is associated with increased risk of distant metastasis . Expression of Mena (INV), an invasive isoform of Mena, correlates with a high TMEM score and enhances transendothelial migration of breast cancer cells . This process has been shown to be mediated through paracrine and autocrine activation of colony-stimulating factor-1 receptor (CSF-1R) .

Preclinical and clinical observations suggest that macrophage-targeting therapies could be a feasible approach to treat breast cancer metastasis. CSF-1/CSF-1R is one of the most important signaling axes during the differentiation of myeloid progenitors to monocytes, macrophages, dendritic cells and bone-resorbing osteoclasts . Blocking macrophage recruitment using CSF-1R inhibitors, in combination with chemotherapy, decreases breast cancer progression and metastasis, and improves survival through CD8⁺ T-cell-dependent mechanisms in tumor-bearing mice . T_H2/M2-type macrophage-derived IL-10 was shown to mediate this CD8⁺ T-cell-dependent responses . Antibodies against CSF-1R reduced TAM numbers and translated into clinical responses in patients with diffuse-type giant cell tumor (Dt-GCT), a type of cancer that overexpresses CSF-1 . Small molecule inhibitors and mAbs against CSF-1R are currently evaluated in patients with advanced solid tumors (Table 8).

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of immune cells from the myeloid lineage. MDSCs possess strong immunosuppressive activities, primarily through suppressing CD8⁺ T-cell cytotoxicity . MDSCs contribute to the establishment of an immunosuppressive pre-metastatic niche via tumor-derived factors such as GM-CSF, [IL-6](#) and lysyl oxidase (LOX) . Inhibition of LOX activity in tumor cells block myeloid cell recruitment to pre-metastatic niche and reduce breast cancer lung and bone metastasis , suggesting a possible strategy for therapeutic intervention.

Regulatory T (T-reg) cell is another class of immunosuppressive cell that primarily functions to inhibit induction and proliferation of effector T cells. A significant increase of T-reg cells was observed in the peripheral blood and TME of invasive breast and pancreas cancer patient . Tumor-infiltrating T-reg cells, recruited by tumor-derived CCL5, could stimulate mammary cancer metastasis through RANKL–RANK signaling . In a breast cancer xenograft model, attenuation of a glycan-binding protein galectin-1 (Gal1) reduced the frequency of T-reg cells within the tumor and reduced lymph node, spleen, and lung metastases, suggesting the possibility of targeting Gal1 in breast cancer metastasis . Understanding the specific roles of T-reg cells in cancer is the key for development of therapeutics against this class of immune cells

4.1.2. Angiogenic vasculature

Vascular endothelial cells and their supporting pericytes together form the angiogenic vasculature . The induction of angiogenesis (also known as angiogenic switch) promotes cancer cell proliferation . The angiogenic vasculature promotes tumor progression not only by supplying nutrients and oxygen, but also through an “angiocrine” mechanism by producing stem and progenitor cell-active factors, ECM components etc. to generate a tumor-favorable microenvironment .

VEGF is one of the most well-known angiogenic factors and has an established role in breast cancer .

VEGFRs are tyrosine kinase receptors primarily expressed on endothelial cells, and are responsible for binding with [VEGF](#) to initiate signal cascades that stimulate angiogenesis and lymphangiogenesis . VEGFRs are up-regulated in multiple cancer types which have a high need for nutrients and oxygen, including breast cancer . Since early in this century, clinical trials involving mAbs or small molecule inhibitors that interrupt VEGF-VEGFR signaling have been conducted extensively in various cancer types. Despite the promising results from other cancer types (e.g. lung cancer, colorectal cancer, renal cell carcinoma (RCC), glioblastoma),

most trials have failed to demonstrate a statistically significant survival advantage in mBC patients . This could be explained by several reasons, for example: drug resistance through activation of alternative angiogenic pathways, and lack of biomarkers to stratify patients that could benefit most from anti-VEGF therapy . Nevertheless, several recent studies shed light on potentially new directions for anti-VEGF therapies. For example, it was demonstrated that blocking lipid synthesis could overcome tumor regrowth and metastasis after antiangiogenic therapy withdrawal . Moreover, PD-L1 was shown to crosstalk with VEGFR2 during angiogenesis, and a combination of anti-VEGF and immunotherapeutic strategies may improve treatment efficacy in mBC .

In addition to the VEGF-VEGFR axis, PDGF-PDGFR signaling has also been implicated in breast cancer tumor-stromal interaction. PDGFRs are expressed on breast cancer stromal cells and tumor-derived PDGFs stimulate the stromal cells to further promote tumorigenesis . PDGFRs are also expressed in invasive breast carcinomas, which correlate with tumor aggressiveness, higher chance of metastasis and shortened survival . Inhibition of PDGFR signaling has proven effective in patients with certain rare tumors , yet it remains to be examined whether this treatment will be beneficial for mBC patients.

4.1.3. *Cancer-associated fibroblasts (CAFs)*

CAFs are a heterogeneous population of fibroblasts residing within the TME and can facilitate malignant transformation and growth of cancer cells . CAFs secrete pro-proliferation signals (e.g. TGF- α), pro-angiogenic signals (e.g. VEGF, FGF and PDGF) and pro-EMT signals (e.g. TGF- β) to facilitate tumor growth, angiogenesis and metastasis . CAFs can also modulate immune polarization in the TME and inhibit the anti-tumor activities of cytotoxic T cells and natural killer (NK) cells . CAFs in the primary breast TME were shown to select for bone specific metastatic traits in tumor cells via CAF-secreted CXCL12 and IGF1 . A

small population of breast cancer stem cells induces periostin (POSTN) expression in resident fibroblasts at the secondary target organ in order to initiate metastasis colonization . Although CAFs are primarily studied as pro-tumorigenic stromal cells, recent studies suggested that tumor-resident fibroblasts could also have tumor-inhibitory effects, suggesting a degree of plasticity in this stromal cell type .

4.1.4. Mesenchymal stem/stromal cells (MSCs)

MSCs are [multipotent stromal cells](#) that can [differentiate](#) into a variety of cell types such as osteoblasts, chondrocytes, adipocytes, myocytes, and cardiomyocytes . They are traditionally found in the bone marrow, but can also be isolated from cord and peripheral blood . Bone-marrow-derived MSCs have been shown to enhance breast cancer cell motility, invasion and metastasis, dependent on CCL5-CCR5 signaling between cancer cells and MSCs . Other studies also confirm that MSCs are able to supply contextual signals (e.g. CCL5, IL6, CXCL7, CXCL10, TGF β 1) to the tumor-associated stroma, creating an immunosuppressive microenvironment and promoting metastatic progression . These signaling events have been observed between MSCs and breast cancer cells as well as between MSCs and other stromal cell types. Recent studies also highlighted the roles of MSC-associated microRNAs in regulating breast cancer progression . The therapeutic potential of targeting MSCs in mBC warrants further investigations as MSCs could be either tumor-promoting or tumor-suppressing depending on different environmental inflammatory conditions .

4.2. Immunotherapies

Historically, breast cancer has been considered poorly immunogenic, thus less responsive to immunotherapies. A few mechanisms may contribute to this. First, the percentages of both type1 (IL-2, IFN γ or TNF α) and type 2 (IL-4) cytokines produced by T lymphocytes were found significantly lower in the peripheral blood of patients with breast cancer compared to healthy controls, suggesting a general immune dysfunction in these

patients . Second, myeloid suppressor cells, Th2 CD4+T cells and T-reg cells function together to create an immune-suppressive TME and suppress CD8+ cytotoxicity via cytokine signaling (e.g. IL-4, IL-13, IL-10, IL-6 and TGF β) . Third, many cancer cells, including breast cancer, downregulate MHC molecules and/or co-stimulatory molecules and upregulate immunosuppressive factors such as PD-L1, resulting in immune escape .

Despite the less immunogenic nature, a small population of breast cancer do induce stronger cytotoxic T- and NK-cell responses, and tend to have a more favorable prognosis with a better response to chemotherapy . Recent studies suggest that significant immune cell infiltration via tumor-infiltrating lymphocytes (TIL) in early breast cancer predicts higher responses to chemotherapy, reduced risk of distant metastasis, and better overall survival, particularly in the TN and HER2+ subtypes . These observations suggest that immunotherapies could have potential to elicit strong immune response in at least a subset of mBC.

4.2.1. *Therapeutic vaccine*

Therapeutic vaccines are designed to elicit an immune response against tumor-associated antigens (TAAs) and enhance the host immune system to attack TTA-bearing cancer cells. Vaccination usually takes a relatively a long time (i.e. weeks to months) to produce enough antigen-specific cytotoxic T cell for an effective immune response , thus may not be the most appropriate treatment for patients in an advanced-disease setting. Most breast cancer vaccine clinical trials are studied in an adjuvant setting in early stage patients with minimal residual tumor cells. Vaccination in combination with other targeted therapies or immunotherapies in patients with high risk of recurrence provide an opportunity to boost and maintain the host immune response in order to eradicate the fewer number of isolated tumor cells before they have a chance to establish larger metastases (Table 8).

4.2.2. Immune checkpoint blockade

After decades of incremental progresses, researchers have started to appreciate the therapeutic power of modulating activities of immune checkpoints, such as cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) . Both CTLA-4 and PD1 belong to the CD28 family receptors and they transmit inhibitory signals to prevent T-cell activation . Blocking the functions of these checkpoint proteins liberates tumor-specific T cells to exert their effector function against tumor cells and subsequently induces a strong immune response . Immune checkpoint blockade have demonstrated promising activities in a variety of malignancies, including melanoma, RCC, head and neck, lung, bladder and prostate cancers . To date, the FDA has approved three such drugs for the treatment of metastatic melanoma and squamous non-small cell lung cancer: ipilimumab (Yervoy), pembrolizumab (Keytruda), and nivolumab (Opdivo). The first targets the CTLA-4 pathway and the latter two target PD-1.

PD-1 ligand (PD-L1) expression was observed in 30% of breast cancer patients, and positively associated with HR-negative and triple-negative (TN) status and high levels of TILs . Clinical studies indicate that immune checkpoint blockade, in combination with cytotoxic drugs, have the potential to improve clinical outcomes for patients with mBC, especially metastatic TN and HER2+ breast cancer with lymphocytic tumor infiltrates at diagnosis . mAb targeting PD-1 (Pembrolizumab/MK-3475) or PD-L1 (MPDL3280A) demonstrated promising therapeutic activities in heavily pretreated metastatic TNBC . Multiple clinical trials, including a phase III trial of MPDL3280A, have been recently initiated in patients with mBC (Table 8).

Several other [immunomodulatory](#) agents which have the potential to enhance anti-tumor immune response were also reported. For example, indoleamine-pyrrole 2, 3-dioxygenase (IDO) is an immune checkpoint

molecule expressed on various stromal cells such as macrophages . IDO is also expressed by a number of tumor types that possess an immune-escape strategy, and is correlated with poor prognosis . Another example is OX40, a potent TNF receptor family co-stimulatory receptor that can potentiate T cell receptor signaling. Ligation of OX40 with an agonistic anti-OX40 mAb has been shown to enhance anti-tumor immunity . Phase II trials of IDO inhibitor and anti-OX40 mAb are currently being tested in mBC patients (Table 8). Additional therapeutic targets involved in anti-cancer immune response include T-cell immunoglobulin and mucin domain-containing protein 3 (TIM-3) , lymphocyte-activation gene 3 (LAG-3) , and the costimulatory receptor of the TNF receptor family CD137 .

A small subset of HER2+ and TNBC patients that have relatively high levels of TILs might benefit most from current immune checkpoint inhibitors. Those patients that have no or relatively low TILs would require additional strategies to increase TILs prior to immune checkpoint blockade . Cancer vaccine can activate and expand tumor-specific CD8+ T cells but itself usually yields limited success in controlling cancer progression . Vaccine priming before or concurrent with one or several immune checkpoint blockade may potentiate the effector T-cell functions and finally translate into long-term disease control of mBC.

5. Conclusions and future directions

Advances in cancer genomics have identified a large number of potential therapeutic targets, many of which have been studied extensively in preclinical and clinical models. Better classification of breast cancer subtypes and in depth characterization of druggable signaling pathways using new biotechnologies like next-generation sequencing (NGS) will enable selection of the most appropriate drugs to target specific genomic alterations. Mutations of BRCA, PIK3CA, AKT1, etc., as well as deregulated signaling such as the FGF and AR pathways, provide promising targets to individualize therapy in metastatic breast cancer. Tumor-intrinsic targeted therapies are likely to yield higher specificity and less toxicity, but may develop drug resistance as the treatment continues. This could be due to secondary mutations that abrogate contact points for drug binding, and/or activation of alternative compensatory signaling mechanisms . On the other hand, the stroma-centric targeting approach could elicit a broader impact against cancerous cells. This strategy has been proved successful in other tumor types such as melanoma, and has also demonstrated promising preliminary results in a subset of mBC patients. Targeting the tumor-promoting elements of the TME and harnessing host immune mechanisms to eradicate cancer cells represent an emerging treatment paradigm. However, while the signaling molecules between the tumor and immune-suppressive stromal cells are potential drug targets, the similarities between tumor-associated stroma and normal stromal cells may potentially cause severe adverse effects .

Our knowledge of breast cancer metastasis has advanced significantly in recent years, with particular emphasis on an integrated understanding of the tumor and its associated microenvironment. Most of current clinical studies are still at early stages of evaluating single or double agent toxicity and efficacy. As a step forward, it is important to start combining drugs using biologically informed translational studies to guide trial design and improve patient outcomes. Although most current approaches of precision medicine aim at

targeting driver events, additional applications such as identification of DNA repair deficiencies and mechanisms of immune suppression could be developed in the future. The ultimate goal is to attack the tumor cells as well as the TME, and at the same time preserve the normal function of organs not involved. Rational combinations of surgery/ radiotherapy/ cytotoxic chemotherapy, with tumor-intrinsic and/or stroma-centric targeted therapies, are likely to improve the treatment efficacy without causing severe toxic effects.

Figure legends:

Figure 1. Therapeutic candidates targeting tumor-intrinsic pathways of mBC. This schematic diagram highlights several tumor-intrinsic pathways and the therapeutic agents currently available or being developed to target them.

Figure 2. Therapeutic candidates targeting tumor-stromal interactions and enhancing host immune response of mBC. This schematic diagram illustrates several key stromal cell populations important for regulating the growth of mBC, as well as therapeutic agents available or being developed to target the molecular pathways that mediate tumor-stromal interactions.

Table 1. FDA approved oncology drugs suitable for treatment of mBC.

Category	Generic name	Brand name	Class	Company	Patient population	Approval date
Cytotoxic chemotherapy	Capecitabine	Xeloda	Antimetabolite	Roche	mBC	1998
	Cyclophosphamide	Cytoxan	DNA-damaging reagent	Roxane, Baxter Healthcare	mBC	1959
	Docetaxel	Taxotere	Mitotic inhibitor	Rhone Poulenc Rorer	mBC	1996
	Eribulin mesylate	Halaven	Mitotic inhibitor	Eisai	mBC	2010
	Fluorouracil	Adrucil	Antimetabolite	N/A	N/A	N/A
	Gemcitabine hydrochloride	Gemzar	Antimetabolite	Eli Lilly	mBC	2004
	Ixabepilone	Ixempra	Mitotic inhibitor	Bristol-Meyers Squibb	mBC	2007
	Paclitaxel	Taxol	Mitotic inhibitor	Bristol-Myers Squibb	BC	1994
	Protein-bound paclitaxel	Abraxane	Mitotic inhibitor	Celgene	mBC	2005
	Thiotepa	Thiotepa	DNA-damaging reagent	American Cyanamid	mBC	1950s
Endocrine therapy	Vinblastine Sulfate	Velban	Mitotic inhibitor	N/A	N/A	N/A
	Anastrozole	Arimidex	Aromatase inhibitor	AstraZeneca	HR+ mBC	1996
	Exemestane	Aromasin	Aromatase inhibitor	Pharmacia & Upjohn	HR+ mBC	1999
	Fulvestrant	Faslodex	Estrogen receptor antagonist	AstraZeneca	HR+ mBC	2002
	Letrozole	Femara	Aromatase inhibitor	Novartis	HR+ mBC	2001
	Tamoxifen	Nolvadex	Selective estrogen receptor modulator	AstraZeneca	HR+ mBC	1998
	Toremifene	Fareston	Selective estrogen receptor modulator	GTx	HR+ mBC	2009
	Lapatinib	Tykerb	Dual HER1/HER2 inhibitor	GlaxoSmithKline	HER2+ mBC	2007
	Pertuzumab	Perjeta	HER2 inhibitor	Genentech	HER2+ mBC	2012
	Trastuzumab	Herceptin	HER2 inhibitor	Genentech	HER2+ mBC	1998
HER2-targeted therapy	Trastuzumab emtansine (TDM-1)	Kadcyla	HER2- antibody-drug conjugate	Genentech	HER2+ mBC	2013
	Other targeted therapy	Denosumab	Xgeva	Amgen	Bone mBC	2010
		Everolimus	Afinitor	Novartis	HR+, HER2- mBC	2012
		Palbociclib	Ibrance	Pfizer	HR+, HER2- mBC	2015
		Pamidronate, Zoledronic acid	Aredia, Zometa	Chiron, Novartis	Bone mBC	1996, 2002

Table 2. Breast cancer-targeting ADCs in clinical development

Target antigen	ADC designation	Application	Patient population	Development Stage	Main results	Representative clinical trials (ClinicalTrials.gov Identifier) *	Reference
HER2	MM-302	Combo	HER2+ mBC	Phase I, II, III	Manageable safety profile, evidence of antitumor activity	NCT02213744 , NCT01304797	
	SYD985	Mono	mBC	Phase I	Preclinical antitumor activity	NCT02277717	
	XMT-1522	N/A	mBC	Preclinical	Preclinical antitumor activity	N/A	
gpNMB	CDX-011	Mono	gpNMB+ mBC	Phase I, II	Acceptable safety profile, evidence of antitumor activity	NCT01997333 , NCT01156753 , NCT00704158	
Top-2	IMMU-132	Mono	mBC	Phase I, II	Acceptable safety profile,	NCT01631552	

					evidence of antitumor activity		
Mesothelin (MSLN)	BMS-986148	Mono	Advanced solid tumor	Phase I, II	Preclinical antitumor activity	NCT02341625	
	BAY94-9343	Mono	Advanced solid tumor	Phase I	Preclinical antitumor activity	NCT01439152, NCT02485119	
CA6	SAR566658	Mono	CA6+ breast cancers	Phase I	Favorable safety profile, evidence of antitumor activity	NCT01156870	
Ephrin-A4 (EFNA4)	PF-06647263	Mono	Advanced solid tumor	Phase I	Preclinical antitumor activity	NCT02078752	
LIV-1 (SLC39A6)	SGN-LIV1A	Mono	LIV-1-Positive mBC	Phase I	Preclinical antitumor activity	NCT01969643	
Ly6E	DIYE5953A	Mono	Advanced solid tumor	Phase I	Preclinical antitumor activity	NCT02092792	
c-RET	Y078-DM1/DM4	N/A	HER2+ and basal breast cancer	Preclinical	Preclinical antitumor activity	N/A	
B7-H4	Anti-B7-H4 ADC	N/A	B7-H4+ breast cancer	Preclinical	Preclinical antitumor activity	N/A	
CD138	BT-062	N/A	mBC	Preclinical	Preclinical antitumor activity	N/A	

*Phase III, II and I trials are highlighted in red, blue and black respectively

Table 3. mBC-targeting PI3K/AKT/mTOR pathway inhibitors in clinical development.

Category	Agent	Application	Patient population	Development stage	Main results	Representative clinical trials (ClinicalTrials.gov Identifier)*	Reference
Pan-PI3K inhibitor	Buparlisib (BKM120)	Mono, combo	mBC	Phase I, II, III	Acceptable safety profile, evidence of antitumor activity	NCT01633060 , NCT01610284 , NCT01572727 , NCT02000882 , NCT02404844 , NCT01629615 , NCT01923168 , NCT02088684	
	Picitilisib (GDC-0941)	Combo	mBC	Phase I, II	Well tolerated, evidence of antitumor activity	NCT01740336 , NCT01437566 , NCT01740336 , NCT01918306 , NCT01042925 , NCT01082068	
	Platralisib (SAR245408, XL147)	Combo	mBC	Phase I, II	Acceptable safety profile, evidence of antitumor activity	NCT01042925 , NCT01082068	
Dual PI3K/mTOR inhibitor	BEZ235 (NVP-BEZ235)	Combo	mBC	Phase I, II	Poorly tolerated, evidence of antitumor activity	NCT01495247	
	XL765 (SAR245409)	Combo	HR+ BC refractory to AI	Phase I, II	Manageable safety profile, associated with clinically relevant stable disease	NCT01082068	
	Apitolisib (GDC-0980, RG7422)	Combo	mBC	Phase I, II	Acceptable safety profile, preclinical antitumor activity	NCT01437566	
Selective p110α inhibitor	Alpelisib (BYL719)	Mono, combo	mBC	Phase I, II, III	Acceptable safety profile, evidence of antitumor activity	NCT02437318 , NCT02506556 , NCT01872260 , NCT02379247 , NCT02088684 , NCT01923168	
	Taselisib (GDC-0032)	Combo	mBC	Phase I, II, III	Well tolerated, promising preliminary activity in HR+ mBC, especially in patients with PIK3CA mutant tumors	NCT02340221 , NCT02457910 , NCT02390427	
	MLN1117 (INK1117)	Mono	Advanced solid tumors	Phase I	Acceptable safety profile, evidence of antitumor activity	NCT01449370	
Akt inhibitor	MK2206	Mono, combo	mBC	Phase I, II	Well tolerated, evidence of antitumor activity	NCT01923168 , NCT01277757 , NCT01042379 , NCT02162719 , NCT01362374	
	Ipatasertib (GDC-0068)	Combo	mBC	Phase I, II	Well tolerated, evidence of antitumor activity		
	Temsirolimus (CCI-779) **	Mono, combo	mBC	Phase I, II, III	Minimal activity as monotherapy or combined with letrozole in mBC	NCT00083993 , NCT02456857 , NCT01111825 , NCT00376688	
mTOR inhibitor	Ridaforolimus (Deforolimus, MK-8669, AP23573)	Combo	mBC	Phase I, II	Well tolerated, evidence of antitumor activity	NCT01605396 , NCT00736970 , NCT01234857	
	MLN0128 (INK128)	Combo	mBC	Phase I, II	Preclinical antitumor activity	NCT02049957 , NCT01058707 , NCT02142803 , NCT02159989 , NCT02327169	

* Phase III, II and I trials are highlighted in red, blue and black respectively ** Approved for advanced renal cell carcinoma (RCC), Phase I, II in mBC

Table 4. mBC-targeting PARP inhibitors in clinical development.

Agent	Application	Patient population	Development stage	Main results	Representative clinical trials (ClinicalTrials.gov Identifier)*	Reference
Olaparib (AZD-2281)	Mono, combo	mBC with BRCA1/2 mutations	Phase I, II, III	Acceptable safety profile, durable response in mBC treated with olaparib monotherapy after combination with carboplatin and paclitaxel	NCT02000622 , NCT00494234 , NCT01078662 , NCT02208375 , NCT01116648 , NCT02498613 , NCT02299999 , NCT00679783 , NCT00516724	
Velparib (ABT886)	Combo		Phase I, II, III	Acceptable safety profile, promising antitumor activity	NCT02163694 , NCT01009788 , NCT01306032 , NCT01042379 , NCT01149083 , NCT01827384 , NCT01506609 , NCT02158507	
Talazoparib (BMN 673)	Mono		Phase I, II, III	Well tolerated, promising antitumor activity	NCT01945775 , NCT02034916 , NCT02282345 , NCT01989546 , NCT02286687 , NCT02401347 , NCT02358200	
Niraparib (MK-4827)	Mono		Phase I, II, III	Well tolerated, promising antitumor activity	NCT01905592	
Rucaparib (CO-338)	Mono		Phase I, II	Acceptable safety profile, efficacy warrants further investigation	NCT01482715 , NCT00664781 , NCT01074970	

* Phase III, II and I trials are highlighted in red, blue and black respectively

Table 5. mBC-targeting FGFR inhibitors in clinical development.

Category	Agent	Application	Patient population	Development stage	Main results	Representative clinical trials (ClinicalTrials.gov Identifier)*	Reference
Non-selective FGFR TKI	Dovitinib (TKI258)	Mono, combo	mBC, solid tumors	Phase I, II, III	Acceptable safety profile, evidence of antitumor activity	NCT02116803 , NCT01484041 , NCT01262027 , NCT01528345 , NCT00958971	
	JNJ-42756493	Mono	Advanced solid tumors	Phase I	Manageable safety profile, evidence of antitumor activity	NCT01962532 , NCT01703481	
	Lucitanib (E-3810)	Mono	mBC (FGF-FGFR aberrant)	Phase I, II	Manageable safety profile, evidence of antitumor activity	NCT02202746 , NCT02053636 , NCT01283945	
Selective FGFR TKI	Nintedanib (BIBF1120)	Mono, combo	mBC	Phase I, II	Well tolerated, evidence of antitumor activity	NCT02389764 , NCT01658462	
	AZD4547	Mono, combo	mBC	Phase I, II	Acceptable safety profile, evidence of antitumor activity	NCT01791985 , NCT01202591 , NCT02299999	
	BAY1163877	Mono	Advanced solid tumors	Phase I	Preclinical antitumor activity	NCT01976741	
	BGI398	Mono	Advanced solid tumors	Phase I, II	Acceptable safety profile, single-agent activity in patients with FGFR-genetically altered solid tumors	NCT02160041 , NCT01928459 , NCT01004224	
	FGF ligand trap and FGFR mAb	Combo	Solid malignancies with deregulated FGF signaling	Phase I	Preclinical antitumor activity	NCT01868022	
	MGFR1877S (RG744)	Mono	Advanced solid tumors	Phase I	N/A	NCT01363024	N/A

* Phase III, II and I trials are highlighted in red, blue and black respectively

Table 6. mBC-targeting Notch pathway inhibitors in clinical development.

Category	Agent	Application	Patient population	Development stage	Main results	Representative clinical trials (ClinicalTrials.gov Identifier)*	Reference
Pan-Notch inhibitor	BMS-906024	Mono, combo	Advanced solid tumors	Phase I	Preclinical antitumor activity	NCT01653470, NCT01292655	
DLI4-specific antibody	Dencizumab (OMP-21M18)	Mono	Advanced solid tumors	Phase I	Well tolerated with encouraging early clinical activity in pancreatic cancer and metastatic NSCLC; clinical trial in mBC ongoing	NCT00744562	
	MED10639	Mono	Advanced solid tumors	Phase I	Manageable safety profile, evidence of antitumor activity	NCT01577745	
Anti-Notch 1	OMP-52M51	Mono	Advanced solid tumors	Phase I	Acceptable toxicity profile, evidence of antitumor activity	NCT01778439	
Anti-Notch2/3	OMP-59R5 (tarextumab)	Mono	Advanced solid tumors	Phase I	Acceptable toxicity profile, evidence of antitumor activity	NCT01277146	
Notch inhibitor	Not stated	Mono	Advanced cancer	Phase I	N/A	NCT01158404	N/A
Gamma secretase inhibitors	MK0752	Combo	mBC	Phase I, II	Acceptable toxicity profile, evidence of antitumor activity	NCT00645333, NCT00106145, NCT01295632	
	PF-03084014	Mono	Advanced solid tumors	Phase I, II	Acceptable toxicity profile, efficacy warrants further investigation	NCT02338531, NCT02299635	
	RO4929097	Mono	mBC	Phase I, II	Acceptable toxicity profile, evidence of antitumor activity	NCT01151449, NCT01217411	

* Phase III, II and I trials are highlighted in red, blue and black respectively

Table 7. mBC-targeting AR inhibitors in clinical development.

Agent	Application	Patient population	Development stage	Main results	Representative clinical trials (ClinicalTrials.gov Identifier)*	Reference
Enzalutamide (MDV3100)	Mono, combo	AR+ mBC	Phase I, II	Acceptable toxicity profile, preliminary activity observed in AR+ TNBC	NCT02007512 , NCT02457910 , NCT02091960 , NCT01889238 , NCT01597193 , NCT01362374	
Oteronel (TAK-700)	Mono	AR+ mBC	Phase I, II	Well tolerated, clinical benefit observed in heavily pretreated HR+ mBC	NCT01990209 , NCT01808040	
DHEA (Dehydroepiandrosterone)	Mono	AR+ mBC	Phase I, II	N/A	NCT02000375 , NCT01990209	N/A
AZD5312 (ISIS-ARRx)	Mono	AR+ advanced solid tumors	Phase I	Preclinical pharmacology reported	NCT02144051	
Enobosarm (GTx-024)	Mono	AR+ mBC	Phase I, II	Well tolerated, evidence of antitumor activity	NCT02368691 , NCT02463032 , NCT01616758	
Bicalutamide	Mono	AR+ mBC	Phase I, II	Well tolerated, evidence of antitumor activity	NCT02348281 , NCT00468715 , NCT02299999	
CR1447 (4-OH-testosterone)	Mono	AR+ mBC	Phase I/II	N/A	NCT02067741	N/A
Abitarone Acetate (CB/630)	Mono, combo	AR+/ER+ mBC	Phase I, II, III	Manageable toxicity profile, efficacy warrants further investigation	NCT01517802 , NCT01381874 , NCT01842321 , NCT00755885	

* Phase III, II, and I trials are highlighted in red, blue and black respectively

Table 8. Stroma and immune targeting agents in clinical development.

Category	Agent	Application	Patient population	Development stage	Main results	Representative clinical trials (ClinicalTrials.gov Identifier)*	Reference
CSF1R inhibitor	AMG 820	Mono	Advanced solid tumors	Phase I	N/A	NCT01444404	N/A
	ARRY-382	Mono	Advanced cancer	Phase I	Well tolerated, CSF1R significantly inhibited, efficacy not revealed	NCT01316822	
	IMC-CS4 (LY3022855)	Mono	mBC	Phase I	N/A	NCT02265536, NCT01346358	N/A
	PLX3397 (PLX108-01)	Combo	Advanced solid tumors	Phase I, II	N/A	NCT02452424 , NCT01596751 , NCT01042379 , NCT01004861, NCT01525602	N/A
anti-PD-1	MEDI0680 (AMP-514)	Mono, combo	Advanced solid tumors	Phase I	N/A	NCT02118337, NCT02013804	N/A
	Nivolumab	Combo	mBC	Phase I	N/A	NCT02309177	N/A
	Pembrolizumab (MK-3475)	Mono, combo	mBC	Phase I, II	Acceptable safety profile, promising antitumor activity including durable responses in PD-L1 metastatic TNBC	NCT02129556 , NCT02395627 , NCT02331251 , NCT02318901, NCT02178722 , NCT02447003 , NCT02411656 , NCT02513472 , NCT02452424 , NCT02331251 , NCT01772004, NCT01943461	
anti-PD-L1	Avelumab (MSB0010718C)	Mono	Advanced solid tumors	Phase I	Acceptable safety profile, activity not revealed	NCT02484404 , NCT02318277 , NCT01693562 , NCT02403271 , NCT02221960, NCT01938612, NCT02261220, NCT02301130, NCT01975831, NCT02141347	
	MEDI4736	Mono, combo	Advanced solid tumors	Phase I, II	Acceptable safety profile, efficacy warrants further investigation	NCT02484404 , NCT02318277 , NCT01693562 , NCT02403271 , NCT02221960, NCT01938612, NCT02261220, NCT02301130, NCT01975831, NCT02141347	
	MPDL3280A (atezolizumab)	Mono, combo	Advanced solid tumors	Phase I, II, III	Well tolerated, promising efficacy in pretreated metastatic PD-L1 IHC 2 or 3 TNBC patients	NCT02425891 , NCT02530489 , NCT02543645 , NCT02458638 , NCT02478099 , NCT02174172, NCT02471846, NCT02350673, NCT02304393, NCT02410512, NCT01988896, NCT02323191	
anti-CTLA-4	Tremelimumab	Combo	Advanced solid tumors	Phase I, II	Acceptable safety profile, efficacy warrants further investigation	NCT02205333 , NCT02301130, NCT02261220, NCT02141347, NCT01975831	
OX40 agonist	anti-OX40	Mono, combo	mBC	Phase I	N/A	NCT02221960	N/A
	MEDI0562	Mono	Advanced solid tumors	Phase I	N/A	NCT02318394	N/A
	MEDI6469	Mono, combo	Advanced solid tumors	Phase I, II	N/A	NCT02205333 , NCT01862900	N/A

IDO pathway inhibitor	Indoximod (1-methyl-d-tryptophan)	Combo	mBC	Phase I, II	Acceptable safety profile, evidence of antitumor activity	NCT01792050 , NCT01042535	
Agonist anti-CD27 antibody	Varilumab (CDX-1127)	Combo	Advanced solid tumors	Phase I, II	Well tolerated, promising signs of clinical activity	NCT02543645 , NCT02270372	
Therapeutic vaccine	Multiple	Mono, combo	mBC	Phase I, II	ONT-10, a MUC1 liposomal vaccine: acceptable safety profile with evidence of antitumor activity	NCT00266110 , NCT02018458 , NCT00971737 , NCT02479230 , NCT01730118 , NCT01837602 , NCT01061840 , NCT01660529 , NCT01376505 , NCT01526473 , NCT02157051 , NCT02270372 , NCT01556789	

* Phase III, II and I trials are highlighted in red, blue and black respectively

Acknowledgement

We thank the members of our laboratories for helpful discussions and M. Esposito, W. Lu, Y. Wei, and H.A. Smith for critical reading of the manuscript. We also apologize to the many investigators whose important studies could not be cited directly here owing to space limitations. The work was supported by Howard Hughes Medical Institute International Student Research Fellowship to Z.L. and grants from the Brewster Foundation, the Breast Cancer Research Foundation and the U. S. Department of Defense (BC123187) to Y.K.

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Inhibitors of activated

GFRs:

- EGFRs (HER1/2/3)
- VEGFRs
- FGFRs
- PDGFRs,
- IGF-1R
- SCFR (c-Kit)
- HGFR (c-MET)

GFRs

CSC signals

Inhibitors of CSC signals:

- GSIs and other Notch inhibitors
- Ligand or receptor-specific Abs

PI3K/AKT/mTOR

inhibitors:

- Pan-PI3K
- Dual PI3K/mTOR
- Selective p110α
- Akt
- mTOR

AR inhibitors:

- Enzalutamide
- Orteronel
- DHEA
- Enobosarm
- Bicalutamide
- Abiraterone acetate

PARP inhibitors:

- Olaparib
- Veliparib
- Talazoparib
- Niraparib
- Rucaparib

Figure 2