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Clinical Implementation of Novel Targeted Therapeutics in Advanced Breast Cancer

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Abstract

The majority of advanced breast cancers have genetic alterations that are potentially targetable with drugs. Through initiatives such as The Cancer Genome Atlas (TCGA) and the International Cancer Genome Consortium (ICGC), data can be mined to provide context for next-generation sequencing (NGS) results in the landscape of advanced breast cancer. Therapies for targets other than estrogen receptor alpha (ER) and HER2, such as cyclin-dependent kinases CDK4 and CDK6, were recently approved based on efficacy in patient subpopulations, but no predictive biomarkers have been found, leaving clinicians to continue a trial-and-error approach with each patient. Next-generation sequencing identifies potentially actionable alterations in genes thought to be drivers in the cancerous process including phosphatidylinositol 3-kinase (PI3K), AKT, fibroblast growth factor receptors (FGFRs), and mutant HER2. Epigenetically directed and immunologic therapies have also shown promise for the treatment of breast cancer via histone deacetylases (HDAC) 1 and 3, programmed T cell death 1 (PD-1), and programmed T cell death ligand 1 (PD-L1). Identifying biomarkers to predict primary resistance in breast cancer will ultimately affect clinical decisions regarding adjuvant therapy in the first-line setting. However, the bulk of medical decision-making is currently made in the secondary resistance setting. Herein, we review the clinical potential of PI3K, AKT, FGFRs, mutant HER2, HDAC1/3, PD-1, and PD-L1 as therapeutic targets in breast cancer, focusing on the rationale for therapeutic development and the status of clinical testing.

Keywords

PI3K; HER2; FGFR1; AKT; IMMUNOTHERAPY

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Potentially actionable genetic alterations can be found in the majority of tumors in patients with metastatic breast cancer via next-generation sequencing [Vasan et al., 2014] and many have been associated with resistance to adjuvant therapies [Yang et al., 2016]. Increasingly, the clinician is challenged with combining clinical and molecular criteria in an effort to create a more personalized approach to the treatment of the advanced cancer patient [De Abreu et al., 2014]. Differentiating between primary and secondary resistance and identifying driver mutational events are important components of current research, and will be critical to identify the optimal sequence of treatments for molecularly defined cancer subtypes. In the meantime, clinicians are confronted with increasing amounts of molecular data on individual patients' cancers with little clinical response data to inform treatment recommendations. Many institutions are establishing Molecular Tumor Boards to aid clinicians in applying patient-specific genetic information to their clinical decisions [Schwaederle et al., 2014; Tafe et al., 2015]. With this goal in mind, herein we review the clinical potential of phosphatidylinositol 3-kinase (PI3K), AKT, fibroblast growth factor receptors (FGFRs), mutant HER2, histone deacetylases (HDAC) 1 and 3, programmed T cell death 1 (PD-1), and programmed T cell death ligand 1 (PD-L1) as therapeutic targets in breast cancer against genetic alterations identified by next-generation sequencing with a focus on the rationale for therapeutic development, and the status of clinical testing.

Approximately 75% of primary breast cancers express estrogen receptor alpha (ER) and/or progesterone receptor (PR), 20% of cancers overexpress HER2, and 20% are ER-/PR-/HER2- (triple-negative). The presence of ER/PR or HER2 in the early-stage disease setting generally indicate a degree of dependence on estrogens or HER2 for cancer cell growth, respectively. Through the development of anti-estrogens (e.g., tamoxifen and aromatase inhibitors) and HER2-targeted agents (e.g., trastuzumab, pertuzumab), targeted therapies have changed the natural-history of 80% of breast cancers, yet many cancers still relapse [EBCTCG, 2005; Forbes et al., 2008; Slamon et al., 2011]. The triple-negative subtype has yet to have a clear target identified, and relapses are commonly seen within 5–8 years of diagnosis. Therefore, the first clinical step in a patient with newly diagnosed advanced/metastatic breast cancer is determining whether she/he has progressed to metastatic disease due to primary or secondary drug resistance. Primary resistance is generally defined as the development of metastatic disease during or within one year of initiating adjuvant therapy. If a biomarker were identified to predict resistance to endocrine agents in advanced ER+ disease, the development of resistance may be preventable through alternative adjuvant therapy. Depending on the results of ongoing trials with patients with high-risk ER+ breast cancer combining endocrine agents with mTOR inhibitors or CDK inhibitors, it may become routine to genotype early-stage breast cancer to inform treatment decisions for ER+ cases.

Regarding secondary resistance emerging data suggests that ER (*ESR1*) mutations may be such a biomarker, as they appear to predict poor outcome [Schiavon et al., 2015]. Preclinical studies have demonstrated that *ESR1* mutations that induce production of the constitutively active receptor, are observed in 10–30% of tumors previously treated with aromatase inhibitors, may be a marker of secondary resistance, and may therefore identify tumors better treated with endocrine therapies that target ER directly (e.g., selective ER downregulators such as fulvestrant) rather than moving directly to chemotherapy [Arnedos et al., 2015].

Secondary resistance is progressive disease that occurs greater than 1 year after adjuvant therapy or in the metastatic setting after multiple lines of therapy that affect the same target. In the ER+ and HER2+ settings, most clinicians would choose second-line targeted therapies that are FDA-approved. However, discordance in ER, PR, and HER2 status between primary tumors and metastases have been reported in 16%, 40%, and 10% of patients, respectively [Amir et al., 2012]. Thus, a first step in managing disease progression should be to confirm the presence or absence of conventional targets, and if a new target is found, it is reasonable to use FDA-approved regimens for these targets first. As recommended by a recent expert panel, when discordance of results between primary and metastatic tissues exists, the consensus is to preferentially use the ER, PR, and HER2 status from the metastasis to direct therapy if supported by the clinical scenario and the patient's goals of care [Van Poznak et al., 2015].

In the setting of advanced triple-negative breast cancer, one may be more inclined to consider molecular profiling and clinical trials in the first-line setting due to the aggressive nature of this subtype and the lack of approved targeted agents. It is in these settings of ER+ and HER2+ secondary resistance, and in triple-negative breast cancer, that molecular profiling is making the most significant impact and will be the focus of this review. We will discuss the clinical potential of drug targets encoded by genes containing alterations common in breast cancer: HER2, PI3K, AKT, and FGFRs. We will also address potential epigenetic and immune targets.

MUTANT HER2 (*ERBB2*)

Therapeutic targeting of HER2 has resulted in multiple drugs, including trastuzumab, lapatinib, pertuzumab, and the antibody-drug conjugate trastuzumab emtansine, thereby changing the natural history of a previously aggressive cancer type to one that is increasingly curable or at least manageable in the metastatic setting for years to decades. Despite huge successes in this subtype of breast cancer, some patients are constitutively resistant or even in those who respond, many eventually develop resistance [Wang et al., 2011]. The Cancer Genome Atlas (TCGA) project has identified HER2 mutations in 2–5% of a wide range of solid tumors [TCGA, 2012], and the most common mutations are either in the kinase domain or at residues 309–310 of the extracellular domain. HER2-activating mutations cause oncogenic transformation of cultured breast epithelial cells, and increase growth in xenograft models [Bose et al., 2013]. Such mutations are associated with resistance to the EGFR/HER2 inhibitor lapatinib. Conversely, the irreversible pan-HER inhibitor neratinib that showed clinical benefit in trastuzumab-resistant HER2+ breast cancer in Phase I trials [Gandhi et al., 2014] and case reports does have efficacy and inhibits mutant HER2, illustrating the importance of careful analysis of molecular results prior to off-label use of drugs [Trowe et al., 2008; D'Amato et al., 2015]. Phase I trials have demonstrated the safety of neratinib in combination with chemotherapy in unselected HER2+ cancers [Gandhi et al., 2014]. On-going trials and the NCI MATCH Trial platform are evaluating the efficacy of neratinib in patients with HER2-mutant cancers (NCT01670877, NCT02465060). Finally, the EGFR/HER2/vascular endothelial growth factor receptor (VEGFR) inhibitor EXEL-7647 (tesevatinib) is also active against most of the HER2 mutations associated with lapatinib resistance [Gendreau et al., 2007]. This drug binds both the active and inactive

conformations of HER2 and inhibits a large spectrum of HER2 mutations in preclinical studies, in particular the EGFR T790M and HER2 T798I mutations, making it a promising intervention for resistance in advanced HER2 positive disease [Gendreau et al., 2007]. A summary of studies evaluation mutant HER2 targets in breast cancer can be found in Table I.

FIBROBLAST GROWTH FACTOR RECEPTORS (FGFRs)

Cancer epidemiological and molecular studies have reported a variety of genetic alterations involving fibroblast growth factors and receptors including gene amplifications, chromosomal translocations, and mutations as well as aberrant protein overexpression [Turner et al., 2010]. Several lines of evidence indicate that these alterations lead to constitutive receptor activation and upregulation of downstream oncogenic signaling pathways, indicating potential targets for both solid and hematologic malignancies. For example, *FGFR1* amplification that correlates with protein overexpression has been described in 8.5% of breast cancers, and *FGFR2* amplification in 4% of triple-negative breast cancers [Turner et al., 2010]. The FGFRs are a family of four transmembrane growth factor receptor tyrosine kinases which bind FGF ligands. There are four FGFR genes in mammals and 22 different ligands have been identified which collectively elicit a broad spectrum of biological activities including cell growth, differentiation, morphogenesis and patterning, wound healing and angiogenesis. This binding interaction stimulates both normal cell development as well as pathological growth in many cancers. Upon ligand binding, FGFR activation drives canonical intracellular signaling cascades, including RAS/RAF/MEK/ERK, PI3K/AKT/mTOR, PLC γ /PKC, STAT, Wnt, hedgehog, and bone morphogenic proteins (BMPs) [Jin et al., 2012]. Although FGFR1/2/3/4 aberrations have been reported in breast cancer, *FGFR1* amplification is most common in Luminal B, ER+ breast cancers, occurring in 16–27 % of cases [Turner et al., 2010]. Although ER+ tumors have a good prognosis when treated with adjuvant endocrine therapy, *FGFR1* amplification is a marker of poor prognosis and a mechanism of endocrine resistance [Paik et al., 2004; Smith et al., 2005; Dowsett et al., 2007].

Interestingly, *FGFR1* amplification is uncommon in HER2+ breast cancers, leading some to suggest that aberrations in these receptors may be mutually exclusive ways of activating similar downstream growth signaling, and/or that there is no selective pressure to acquire redundant aberrations [Elsheikh et al., 2007]. In vitro studies suggest that, similar to EGFR targeting in lung and colon cancers, *KRAS* mutations drive resistance to FGFR inhibitors [Turner et al., 2010]. Eight FGFR inhibitors have been studied for the treatment of breast cancer (Table II), and early data are promising. A phase II multicenter study with dovitinib showed partial response or stable disease in five (25%) patients with metastatic *FGFR1*-amplified ER+ breast cancer. Of those patients with *FGFR1*-non-amplified ER+ disease, only 1 (3%) exhibited stable disease. When amplifications in *FGFR1*, *FGFR2*, or *FGFR3* were grouped to define “FGF pathway-amplified” breast cancer, mean tumor size in such cases was reduced by 21%. In patients who did not present with FGF pathway-amplified breast cancer, mean tumor size increased by 12% [Andre et al., 2013a].

An obstacle in the study of FGFR inhibitors includes the indiscriminate nature of their targets. Many of these drugs inhibit multiple TKIs including vascular endothelial growth

factor receptor (VEGFR), and platelet derived growth factor receptor (PDGFR), and have a spectrum of affinities for FGFR1-2/3/4. A second issue includes short-lived response rates, attributed to gatekeeper mutations that confer resistance to first-generation FGFR inhibitors. Second-generation FGFR inhibitors are currently under development to overcome this resistance [Tan et al., 2014].

PI3K, AKT, AND MTOR

A large body of experimental and clinical evidence suggests that hyperactivation of the phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR pathway, the most frequently mutated pathway in breast cancer, promotes anti-estrogen as well as trastuzumab resistance. PI3K is commonly activated by growth factor receptor tyrosine kinases and G-protein-coupled receptors in breast cancer cells. The signaling cascades triggered by PI3K, including PDK1, AKT, SGK, and mTOR, promote cell growth, survival, and metastasis. For detailed information, we refer the reader to a previously published, comprehensive review of this material [Miller et al., 2011].

AKT, a serine/threonine kinase with 3 isoforms (AKT1, AKT2, and AKT3) is an important downstream target of the PI3K pathway and increased AKT activity which signals activated PI3K, is detected in 20–55% of breast cancer specimens [Altomare and Testa, 2005; Ma et al., 2016b]. Pre-clinical studies of an allosteric pan-AKT inhibitor (MK-2206) induced apoptosis of estrogen receptor positive cell lines under estrogen deprived conditions or in combination with ER down-regulator fulvestrant [Ma et al., 2016b]. A follow-up phase I trial of MK-2206 in combination with either anastrozole or fulvestrant or both, in a heterogeneous population of patients with metastatic ER+ HER2 negative breast cancer resulted in 42% clinical benefit without disease progression for at least 6 months. Due to these promising results, a neoadjuvant Phase II trial is now underway [Ma et al., 2016b].

mTOR is found in two protein complexes, TORC1 and TORC2, which typically lie downstream and upstream of AKT, respectively. While the addition of a the TORC1 inhibitor everolimus prevents disease progression in patients with anti-estrogen-resistant breast cancer, inhibition of TORC1 relieves negative feedback on activators of PI3K [O'Reilly et al., 2006; Carracedo et al., 2008; Miller et al., 2009]. These data suggest that inhibitors of PI3K, AKT, or mTOR (to block both TORC1 and TORC2) may be more effective in combination with anti-estrogens. Clinical testing of PI3K inhibitors in combination with anti-estrogens suggests that this strategy is feasible. Among 46 patients with metastatic disease treated with the PI3K inhibitor buparlisib (BKM120) and the anti-estrogen (aromatase inhibitor) letrozole, 39% experienced clinical benefit [Mayer et al., 2014b]. Among 24 patients with anti-estrogen-resistant metastatic disease treated with the anti-estrogen fulvestrant and buparlisib, 50% had clinical benefit [Ma et al., 2015]. In 116 patients with advanced ER+ breast cancer, randomization to treatment with fulvestrant plus the PI3K inhibitor pictilisib (GDC-0941) doubled median progression-free survival versus fulvestrant/placebo [Krop et al., 2014]. In the ongoing BELLE-2 trial [Baselga et al., 2015], early results show that the combination of fulvestrant/buparlisib increases PFS from 5 to 6.9 months in unselected patients after progression on an AI. Interestingly, PI3K (*PIK3CA*)

mutations in circulating tumor DNA may predict response to fulvestrant/BKM120, but mutations in tumors may not [Baselga et al., 2015].

Since pan-PI3K inhibitors such as buparlisib and pictilisib elicit toxicities that frequently necessitate changes in treatment, isoform-specific inhibitors of Class IA PI3K are being developed. Expression of the p110 δ isoform of PI3K is limited to immune and hematopoietic cells, while p110 α and p110 β expression are ubiquitous. p110 α inhibitors are effective against cancers that harbor activating mutations in *PIK3CA* (encodes p110 α) [Fritsch et al., 2014; Mayer et al., 2014a; Shah et al., 2014]. PTEN loss promotes p110 β signaling [Jia et al., 2009; Rabinovsky et al., 2009; Edgar et al., 2010; Ni et al., 2012]. However, combined targeting of p110 α/β may be more effective than single-isoform inhibition in ER+ BC [Crowder et al., 2009; Schwartz et al., 2015], and testing of p110 β -selective inhibitors in patients with breast cancer has not yet been reported.

This pathway also has promise in HER2 positive breast cancer since the PI3K/AKT pathway lies downstream of growth factor receptor kinases receptors such as EGFR and HER2 and HER2 growth factor receptor signaling is mainly transduced by the phosphatidylinositol 3-kinase (PI3K)/AKT/mechanistic target of rapamycin (mTOR) and ERK1/2 oncogenic pathways.

Downregulation of PTEN phosphatase or constitutive PI3K activation are demonstrated resistance mechanisms for anti-HER2 therapies and decreased PTEN expression and activating mutations of PI3K are present in between 13–52% and 13–30% of her2 positive breast cancer, respectively [Wisinski et al., 2016]. Treatment with AKT-inhibitors alone can lead to upregulation of HER3 and as a key co-receptor for HER2 may be an important pathway to target simultaneously [Wisinski et al., 2016].

Similarly, it is known that rapalogs can suppress trastuzumab-resistance in PTEN deficient tumors and restore sensitivity to trastuzumab [Acevedo-Gadea et al., 2015]. Safety of the combination has been established in Phase I trials and in the Bolero-3 Phase III trial the addition of everolimus to the combination of trastuzumab plus vinorelbine showed improvement in progression free survival in patients previously treated with trastuzumab and paclitaxel [Andre et al., 2014b].

In the triple negative subtype, results have been mixed. In metastatic disease, combining everolimus with carboplatin demonstrated a clinical benefit rate (complete remission + partial remission + stable disease for greater than or equal to 6 months) of 36% [Singh et al., 2014] but in the neoadjuvant setting the addition of everolimus to 12 weeks of paclitaxel followed by four cycles of 5-fluorouracil, epirubicin and cyclophosphamide showed no significant difference despite evidence of mTOR downregulation. [Gonzalez-Angulo et al., 2014].

For a summary of studies evaluating PI3K/AKT targets in breast cancer see Table III.

HDAC1/3

Epigenetic modifiers are emerging as a promising group of drug targets, including histone deacetylases (HDACs). Compared to normal cells, tumor cells have different patterns of DNA methylation and histone modification which alter nucleosome and chromatic structure. Drugs that inhibit HDACs can cause transcriptional reactivation of dormant tumor-suppressor genes, including PTEN [Hollander et al., 2011; Nguyen et al., 2011], and may also have differentiating, cell-cycle arresting, and apoptotic effects. Phase I trials indicate that HDAC inhibitors are well-tolerated and could be combined with conventional chemotherapy or DNA demethylating agents (Table IV).

HDAC inhibitors can induce hyperacetylation of nuclear HSP90 chaperone proteins, causing depletion of proteins involved in DNA damage response and homologous recombination. Inhibitors of poly-ADP-ribose polymerase (PARP) are synthetically lethal with defective homologous recombination [Bryant et al., 2005; Farmer et al., 2005]. Thus, co-treatment using HDAC inhibitors with PARP inhibitors or cisplatin exerts synthetic lethality in TNBC cells. HDAC inhibitors are well documented to induce inactivation of AKT and ERK, which appears to enhance the activity of PARP inhibition in TNBC cells [Ha et al., 2014].

IMMUNOTHERAPY: PD-1 AND PD-L1

Most of the attention for immunotherapies such as the checkpoint inhibitor pembrolizumab in breast cancer is as a single agent or in combination with cytotoxic chemotherapy for TNBC due to Phase Ib results indicating significant single agent activity with impressive durations of response [Nanda, 2015].

Based on the recent interim analysis of the ongoing MOSCATO-01 trial [Massard, 2015], molecular screening of 700 patients with advanced-stage cancer, including 70 patients with metastatic breast cancer, alterations of the PTEN/PI3K/AKT and FGFR/FGF pathways are the two most frequently detected actionable pathways observed across all tumor types. Molecular profiling can identify alterations in these genes, but molecular tools to measure pathway activation through RNA or protein expression are needed to better predict which mutations are driving metastasis. Until response rates for drugs targeting these pathways are defined, the next best step for metastatic TNBC is anti-PD1 treatments that have shown 18% objective response rates in unselected patients as monotherapy [Nanda, 2015]. Potential predictive biomarkers are under investigation based on studies of patients with melanoma and lung cancer, which have shown that the presence of neoantigens and mutational load may predict response to immune checkpoint modulators [Snyder et al., 2014]. Until reliable predictive tests are identified, a reasonable approach for metastatic TNBC with primary resistance to adjuvant chemotherapy is a clinical trial that either evaluates efficacy of anti-PD1 treatments on PD-L1- or PD-1-overexpressing cancers, or a combination of immune therapy with standard cytotoxic therapy known to have efficacy in the first-line setting.

The predictive value of PD-L1 expression in ER + disease is emerging based on preliminary data from KEYNOTE 028, a Phase Ib study of pembrolizumab in participants with advanced solid tumors (NCT02054806). Within the ER+/HER2- breast cancer cohort, 19% of tumors

were PD-L1+ and this appears to inversely correlate with ER expression. PD-L1 expression may be more common in Luminal B tumors [Rugo, 2015] and may be a prognostic indicator [Muenst et al., 2014; Schalper et al., 2014]. Of the 25 tumors that tested positive for PD-L1 and were treated with at least one dose of pembrolizumab, the overall response rate with 7 months of followup was 12%, clinical benefit rate was 20%, and three patients had a response lasting longer than 24 weeks [Rugo, 2015]. These results have prompted larger phase II trials for PD-L1+/ER+ metastatic breast cancer (Table V).

PERSPECTIVES

There are many perspectives on the value of targeted therapies, and it is unlikely that we will ever have a Phase III trial that definitively proves that the concept of genetic profiling and use of genetically directed targeted agents improves survival. As with many approaches to oncology, results can be viewed from a half-full versus half-empty perspective. The recently published SHIVA trial [Le et al., 2015] was a randomized controlled Phase II study that restricted its population to alterations in only three molecular pathways. SHIVA did not show an improvement in PFS compared to physician's choice of chemotherapy in a heavily pre-treated population. Does this mean the concept doesn't work? In most cases, there is clinical benefit at least in terms of stable disease or preserved quality of life and it remains to be seen whether applying this approach earlier in the course of a patient's disease through better predictive biomarkers may yield more convincing results. In some subgroups with significant benefit, cancer histology is critical (i.e., BRAF inhibitors in BRAF^{V600E}-mutant non-melanoma cancers [Hyman et al., 2015]). The challenge is to identify biomarkers to predict response, and to identify potential benefit earlier in the disease process.

Developments on the horizon will likely change the playing field: larger gene panels, software for interpretation of individual genetic profiles and vaccine trials. Many institutions are already finding it difficult to justify the cost of next generation sequencing for large numbers of patients when only a fraction benefit and this approach is clearly not sustainable in the long term. Until and unless reliable, predictive biomarkers are identified, the only way to streamline this process is to systematically link genetic alterations with histology and drugs to identify which subsets benefit most, and then create a more efficient screening process. This will require international collaboration to create databases and registries as well as cooperation from pharmaceutical companies to provide affordable access to drugs. The Breast Cancer Research Foundation, ASCO's TAPUR trial and NCI's MATCH platform are all examples of ambitious multi-disciplinary collaborative efforts to better characterize metastatic breast cancer and identify more effective therapies. In the present moment, molecular profiling and clinical trials to identify metastatic breast cancer patients most likely to benefit from novel therapies, are essential steps that cannot be omitted. This approach is most important for the triple negative, hormone refractory and her2 refractory subgroups our most challenging patients, for whom the potential benefit will be worth the cost and effort.

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TABLE I

Summary of Studies Evaluating Mutant HER2 (ERBB2) Targets in Metastatic Breast Cancer

Kinase target	Drug	Breast cancer sub-type	Phase of development	Reference
Pan-ErbB	Neratinib	ErbB2 + metastatic	Phase I/II neratinib + trastuzumab	Swaby et al. [2009]
			Phase II	Hyman et al. [2016]
			Phase II	Burstein et al. [2009]
			Phase I/II neratinib plus vinorelbine	Awada et al. [2013]
			Phase I neratinib plus paclitaxel and trastuzumab	Chow et al. [2013]
			Phase I/II neratinib plus Paclitaxel + trastuzumab	Jankowitz et al. [2013]
			Phase I/II neratinib + capecitabine	Saura et al. [2011]
ERbb1/2	Lapatinib	ErbB2+	Phase III lapatinib alone versus with trastuzumab	Blackwell et al. [2010]
			Phase III lapatinib plus capecitabine versus capecitabine	Cameron et al. [2008]
		HER2 neg/unknown	Phase III lapatinib plus paclitaxel versus paclitaxel	Di Leo et al. [2008]
		ER/PR positive	Phase III lapatinib plus Letrozole versus letrozole	Johnston et al. [2009]
		ErbB2 + metastatic	Phase II	Gomez et al. [2008]
		ErbB2 + with brain metastases	Phase II	Lin et al. [2009]

TABLE II

Summary of Studies Evaluating FGFR Targets in Metastatic Breast Cancer

Kinase target	Drug	Breast cancer sub-type	Phase of development	Reference
VEGFR ½, FGFR1	Brivanib	Any	Phase I brivanib plus chemotherapy	Jonker et al. [2011]
Multi-targeted	Dovitinib	Her2 neg	Phase II metastatic	Andre et al. [2011]
		HER2+ ER+	Phase II dovitinib plus fulvestrant versus fulvestrant	Andre et al. [2013a]
		HER2 neg, FGFR amplified	Phase II	Andre et al. [2010]
		Her2 neg inflammatory y	Phase II	NCT01202591
FGFR1-3	AZD4547	All	Phase II	Andre et al. [2013b]
		ER+	Phase I/II AZD4547 + fulvestrant versus fulvestrant	NCT01202591
		ER+ after progression on AI	Phase I/II AZD4547 + letrozole OR anastrozole after progression on NSAI	NCT01791985
Multi-targeted	Lucitanib	All	Phase I/II	Soria et al. [2014]
		ER+	Phase II	Andre et al. [2014a]
FGFR1-4, VEGFR2	BGJ398	All	Phase I	Sequist et al. [2014]
		All	Phase I	Wolf et al. [2012]
FGFR 1-4	JNJ-42756493	All	Phase I	Bahleda et al. [2014]
Multi-targeted	Orantinib	All	Phase I	NCT00024063
Multi-targeted	Nintedanib	Her2 neg	Phase I/II nintedanib plus paclitaxel	Quintela-Fandino et al. [2014]

TABLE III

Summary of Studies Evaluating PI3K Targets in Metastatic Breast Cancer

Kinase target	Drug	Breast cancer sub-type	Phase of development	Reference
Pan-PI3K	Buparlisib	All	Phase I	Bendell et al. [2012]
		ER+/Her2 neg	Phase IB buparlisib + letrozole	Mayer et al. [2014b]
		ER +	Phase I buparlisib + fulvestrant	Ma et al. [2016a]
		Her2 neg	Phase II buparlisib + paclitaxel versus placebo + paclitaxel	Martin et al. [2013]
		ER+ Her2 neg, after AI	Phase III buparlisib + fulvestrant	Iwata et al. [2013]
		HER2+, PI3K activated after progression on trastuzumab	Phase Ib/II Buparlisib+ lapatinib	Goncalves [2013]
		All	Phase IB	Saura et al. [2014]
		Her2+	Phase II neoadjuvant buparlisib + trastuzumab + paclitaxel	Loi et al. [2013]
PI3K α / β	Pictilisib	All	Phase I	Sarker et al. [2015]
		ER+, AI resistant	Phase II pictilisib + fulvestrant versus placebo + fulvestrant	Krop et al. [2014]
Pan-PI3K	PX-866	All	Phase I	Hong et al. [2012]
PI3K/p110 α	BYL719	All	Phase I	Juric et al. [2012]
		PIK3CA + mutation	Phase I	Gonzalez-Angulo et al. [2013]
PI3K/p110 α	INK1117	All	Phase I	Jessen et al. [2011]
Pan-PI3K	GDC-0941	ER/PR/Her2 negative	Phase Ib/II GDC-0941 + cisplatin	Abramson et al. [2014]
PI3K/mTOR	GDC-0980	All	Phase I	Wagner et al. [2011]

TABLE IV

Summary of Studies Evaluating HDAC Targets in Metastatic Breast Cancer

Kinase target	Drug	Breast cancer sub-type	Phase of development	Reference
HDCA1-3,6	Vorinostat	ER+ after progression	Phase II vorinostat + tamoxifen	Munster et al. [2011]
		All	Phase I/II vorinostat + paclitaxel + bevacizumab	Ramaswamy et al. [2012]
		All	Phase II	Vansteenkiste et al. [2008]
		All	Phase II	Luu et al. [2008]
		All	Phase I vorinostat + doxorubicin	Munster et al. [2009]
HDAC1,3	Entinostat	ER+ after AI	Phase II exemestane ± entinostat	Yardley et al. [2013]
		ER + after AI	Phase II entinostat + AI	Wardley et al. [2010]
		Triple-negative	Phase I entinostat + nivolumab + ipilimumab	NCT02453620
Pan-HDAC	Panobinostat	HER2+	Phase I panobinostat +trastuzumab	Conte et al. [2009]
		Triple-negative	Phase I/II panobinostat + letrozole	

TABLE V

Summary of Studies Evaluating PD1 Targets in Metastatic Breast Cancer

Kinase target	Drug	Breast cancer sub-type	Phase of development	Reference
Anti-PD1	Pembrolizumab	Triple negative	Phase IB	Nanda [2015]
			Phase II pembrolizumab + chemotherapy	NCT02622074
		Triple-neg/inflammatory	Phase III pembrolizumab+ chemotherapy	NCT02555657
		HER2 pos	Phase I/II	NCT02129556
	Nivolumab	Triple neg OR ER+	Phase II pembrolizumab + doxorubicin OR anti-estrogen	NCT02648477
		Triple-neg	Phase II nivolumab after chemotherapy	NCT02499367
		Any	Phase I/II nivolumab + ipilimumab	NCT01928394
		Any	Phase I nivolumab + nab-paclitaxel	NCT02309177
		Triple neg	Phase I entinostat +nivolumab ipilimumab	NCT02453620
Anti-PDL1	Atezolizumab	All	Phase I	NCT01375842