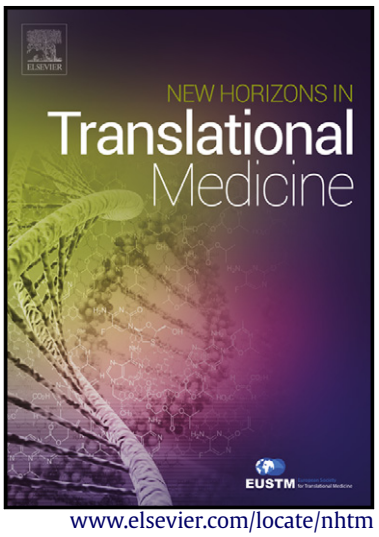

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Emerging Pathways in Treating Human Epidermal Growth Factor Receptor-2-Negative Breast Cancer

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ABSTRACT

Breast cancer remains the leading cause of new cancer cases in women and is responsible for the most cancer-related deaths in women worldwide. The goals of breast cancer treatment are to maintain or improve quality of life, prolong survival, and increase disease-free progression. The majority of breast cancer cases are estrogen receptor (ER)-positive and human epidermal growth factor receptor-2 (HER-2)-negative, and current treatment guidelines recommend multiple lines of endocrine therapy followed by chemotherapy in patients with locally recurrent or metastatic disease. Resistance to current therapies adds to the need for new therapeutic options. Translational research and preclinical data have provided insight into the identification of emerging signaling pathways for novel drug targets, and the development of a growing number of biologic targeted agents is currently underway to identify novel treatments. An alternative approach to improve patient benefit is to boost the efficacy and safety of existing agents by modifying their delivery or pharmacokinetics (ie, adding albumin to paclitaxel) as well as identifying new combination therapies. One combination therapy of interest is the addition of the 130 nm albumin-bound formulation of paclitaxel (*nab*-paclitaxel) to currently approved therapies or targeted agents in development. This review focuses on a number of key agents that are being investigated for the treatment of HER-2-negative breast cancer and the utilization of these agents as combination therapy to achieve prolonged disease control.

Keywords: breast cancer, HER-2-negative, resistance, biologic targeted agents, combination therapies

Abbreviation footnote (abbreviations within main text):

ABC, advanced breast cancer; AE, adverse event; AI, aromatase inhibitor; AKT, protein kinase; BC, breast cancer; CDK, cyclin-dependent kinase; CT, chemotherapy; CTLA, cytotoxic T-lymphocyte antigen; ET, endocrine therapy; HDAC, histone deacetylase; HER-2, human epidermal growth factor receptor-2; HR, hormone receptor; HT, hormone therapy; mAb, monoclonal antibody; MBC, metastatic breast cancer; mTOR, mammalian target of rapamycin; nab-PAC, nab-paclitaxel; OS, overall survival; PARP, poly(adenosine diphosphate [ADP]-ribose) polymerase; PD-1, programmed death-1; PD-L1, programmed death ligand-1; PFS, progression-free survival; PI3K, phosphatidylinositide 3-kinase; TNBC, triple-negative breast cancer; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Focal points:

- Bedside
    - New therapeutic options are necessary for breast cancer patients with HER-2-negative and either hormone receptor positive or negative disease who develop resistance to current therapies. Recent insights into molecular pathways may soon expand the treatment options for all patients with HER-2-negative breast cancer.
- Bench
    - Several rationally designed combinations of biologic targeted agents and next generation chemotherapeutic agents are currently under investigation to prolong disease control and overcome treatment resistance in patients with HER-2-negative breast cancer.

1. Introduction

Breast cancer (BC) is responsible for an estimated 1.67 million new cases of cancer in women worldwide annually, accounting for 25% of the total new cancer cases, making it the most frequently diagnosed cancer in 2012. It is also the leading cause of cancer death in less-developed regions of the world and the second-leading cause of cancer death in more-developed regions [1]. In a review of 15,204 cases of BC, the National Comprehensive Cancer Network noted that 66% of patients were hormone receptor-positive (HR-positive)/human epidermal growth factor receptor-2 (HER-2)-negative, 17% were HER-2-amplified, and the remaining 17% had triple-negative breast cancer (TNBC) [2]. Receptor status is a key covariate as it determines the class/type of systemic therapy provided to BC patients, and this review will focus on HER-2-negative BC, including TNBC.

Although advanced stage/metastatic BC is incurable, it is treatable, and the goals of treatment are to maintain or improve quality of life, prolong survival, and increase disease-free progression. Current treatment guidelines [3-5] recommend the use of endocrine therapy (ET) for all patients with early HR-positive disease, with the choice of agent primarily determined by the patient's menopausal status. Chemotherapy (CT) is recommended after progression or unacceptable toxicity and no clinical benefit after 3 sequential ET regimens. However, for patients with visceral crisis, CT is the recommended initial treatment [5]. Concomitant ET plus CT has shown no benefit for survival and should only be performed in a clinical trial [3, 4]. For TNBC, single-agent CT is preferred, including taxanes and anthracyclines, as there is currently no compelling evidence that combination CT regimens are superior to sequential single agents for these patients [5, 6]. A general schematic for current HER-2-negative BC treatment algorithms is presented in **Fig. 1** [3-5]. Chemotherapy remains an essential component of systemic intervention in patients with HER-2-negative disease, including patients with advanced HR-positive disease who have progressed after multiple lines of endocrine therapy, patients

with TNBC, and patients with symptomatic visceral disease in need of rapid symptomatic control. However, the efficacy of CT options is modest, particularly because second or later lines of therapy and combination CT regimens offer limited efficacy and increases in toxicity [7]. Targeted agents are under investigation for HER-2-negative BC; however, they are less effective in the treatment of advanced disease. Therefore, the combination of CT with a targeted agent is under intense investigation for the treatment of BC, including metastatic disease.

2. Insight from translational research

Traditionally, BC subtypes have been classified based on receptor status; however, the definitions for intrinsic subtypes were recently expanded [8]. Luminal A-like is estrogen receptor (ER)-positive and/or progesterone receptor-positive and HER-2-negative with low expression of Ki-67, a marker for cell proliferation [8, 9]. Luminal B is broken down into 2 types: Luminal B-like (HER-2-negative) is ER-positive and HER-2-negative with either high expression of Ki-67 or low/no expression of progesterone receptor, while Luminal B-like (HER-2-positive) is ER-positive with amplified expression of HER-2 [8]. HER-2-positive (non-luminal) BC is classified as having amplified expression of HER-2 and as absent for HR expression. Finally, TNBC (ductal) is negative for expression of all 3 receptors [8]. The differentiation of traditional clinical subsets into additional categories with varying prognoses suggests that the current treatment paradigm is suboptimal. Furthermore, systemic treatments often impose the selection of resistant phenotypes. In a recent study on the inference of tumor evolution during chemotherapy for BC treatment, phenotypic diversity had been altered before and after treatment, while a pathologic complete response was associated with lower pretreatment genetic diversity [10].

Resistance to treatment is an important aspect of BC therapy, as up to 50% of HR-positive BC patients are refractory to primary treatment, while the remainder will acquire resistance [11]. For example, resistance to tamoxifen can be due to a number of mechanisms

including altered tamoxifen metabolism, and modification of ERα activity due to increased phosphorylation, activation of phosphatidylinositide 3-kinase (PI3K)/protein kinase B (AKT) signaling, aberrant expression of ERα target genes, and even expression of a dominant-negative ERα isoform [12]. Furthermore, it has been demonstrated that ER and HER-2 status can change over time in patients with metastatic BC (MBC), and there is a growing need for repeat tumor biopsies to determine whether a change in therapy is required [13]. Patients with TNBC can experience resistance to chemotherapeutics mainly due to increased efflux of drugs through ABCB1 transporters, thereby lowering the effective intracellular drug concentrations [14]. Many of these resistance pathways have become targets for BC treatment.

To overcome the many obstacles of drug resistance and disease progression, a number of emerging pathways are under investigation for the treatment of HER-2-negative BC. Furthermore, the field of genomics is currently playing an important role in our understanding of the genetic differences between normal and malignant tissues. For example, The Cancer Genome Atlas has documented the genetic diversity of luminal/ER-positive, HER-2-positive, and TNBC, and these data have provided the rationale for recently approved and emerging treatments [15]. Inhibition of multiple pathways using combination approaches with CT and targeted agents is also under investigation to improve the duration of response to initial treatment and to provide new options to overcome resistance.

3. Agents in development

Inhibition of a number of physiologic pathways by targeted agents is currently under investigation for the treatment of HER-2-negative BC (**Fig. 2**). These agents include inhibitors of the extracellular receptor tyrosine kinase vascular endothelial growth factor receptor (VEGFR) and its ligand VEGF, the mammalian target of rapamycin (mTOR) and PI3K signaling pathways,

cell cycle progression through cyclin-dependent kinase (CDK) 4 and 6, epigenetic regulation through histone deacetylase (HDAC), and poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP)-mediated DNA repair. Furthermore, the therapeutic potential of novel targets for modulating immune checkpoint regulation, including cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death-1 (PD-1), and programmed death ligand-1 (PD-L1), is also being investigated for patients with BC. Many of these agents are being investigated as combination therapies and are a rational means of achieving prolonged disease control.

3.1. Antiangiogenic agents

Studies have demonstrated that BC is angiogenesis-dependent; elevated expression of VEGF is common in BC and associated with a higher incidence of recurrence or death [16]. Therefore, circulating VEGF and VEGFR, along with other receptor tyrosine kinases such as platelet-derived growth factor receptor, have become important targets for the development of therapeutic agents in BC. Bevacizumab is a fully humanized monoclonal antibody (mAb) VEGF-A inhibitor that was approved by the United States Food and Drug Administration in 2008 for first-line treatment of HER-2-negative metastatic BC in combination with paclitaxel based on results from a phase 3 trial [17] (**Table 1**) [17-47]. Median progression-free survival (PFS) was increased in patients with MBC treated with bevacizumab and paclitaxel compared with paclitaxel alone (11.8 vs 5.9 months; $P < .001$), although there was no significant difference in overall survival (OS) between the 2 groups [17]. Grade 3 or 4 neuropathy, infection, and fatigue were more frequent with bevacizumab combination therapy compared with paclitaxel alone (**Table 1**) [17]. However, the United States Food and Drug Administration recommended the removal of this indication from its label in 2010 based on its interpretation that safety concerns outweighed the improvement in PFS; the use of bevacizumab for the treatment of BC continues in Europe [48]. A number of ongoing clinical trials are evaluating bevacizumab as combination therapy for HER-2-negative BC (**Table 2**). Several small-molecule, multi-targeted tyrosine

kinase inhibitors that block VEGFR and platelet-derived growth factor receptor signaling have also been investigated for first- or second-line treatment of HER-2-negative MBC, including sorafenib and sunitinib. Sorafenib has been evaluated in a handful of phase 2 studies, mostly in combination with chemotherapeutic agents, and has demonstrated efficacy in first- or second-line treatment of MBC (**Table 1**). Of note, increased incidence of grade 3 or 4 hand-foot syndrome is common in most studies of sorafenib (**Table 1**). Sunitinib has failed to show significant efficacy either alone or in combination with CT for the treatment of HER-2-negative BC, including TNBC, and two of four phase 3 studies have been terminated for futility (**Table 1**). Sorafenib is currently being evaluated in a number of ongoing phase 2 trials, and one phase 3 trial as combination therapy for first- or second-line treatment of HER-2-negative MBC, while sunitinib is currently being investigated in combination with CT for neoadjuvant treatment of TNBC in a phase 1/2 trial (**Table 2**).

3.2. PI3K and mTOR inhibitors

Hyperactivation of the PI3K/AKT/mTOR pathway is frequently observed in BC, leading to cancer pathogenesis, progression, and resistance to endocrine treatment [49]. Therefore, the addition of PI3K and mTOR inhibitors to ET or CT may enhance efficacy or delay resistance. A number of PI3K and mTOR inhibitors are being developed for the treatment of HER-2-negative BC, including buparlisib, BEZ235, and everolimus. Buparlisib is a pan-class I PI3K inhibitor that is effective in a number of different cancer types and cellular systems, irrespective of their level of PI3K addiction [50]. BEZ235 is a dual PI3K/mTOR inhibitor that induced downregulation of VEGF, cell cycle arrest, and autophagy in a preclinical study [51]. Clinical activity of either buparlisib or BEZ235 in HER-2-negative BC has yet to be published; however, a number of clinical trials are underway for buparlisib either alone or as combination therapy in HER-2-negative BC and TNBC (**Table 2**). Everolimus (EVE) is an mTOR inhibitor approved in combination with exemestane for the treatment of ER-positive, HER-2-negative advanced BC

(ABC) in patients whose disease has progressed after a nonsteroidal aromatase inhibitor (AI) [52]. In the pivotal phase 3 trial, EVE was evaluated in combination with exemestane (EXE) compared with placebo (PBO) plus EXE in 724 post-menopausal women with ER-positive, HER-2-negative ABC with recurrence or progression following nonsteroidal AI therapy. Median PFS was 7.8 months in the EVE group and 3.2 months in the PBO group (P < .0001) by independent review [52], and the most common grade 3 or 4 adverse events (AEs) were stomatitis (8% for EVE vs 1% for PBO), anemia (6% vs < 1%), dyspnea (4% vs 1%), hyperglycemia (4% vs < 1%), fatigue (4% vs 1%), and pneumonitis (3% vs 0%) (**Table 1**) [40]. Everolimus is also currently being investigated in a number of clinical trials for HER-2-negative BC or TNBC, often as combination therapy with another targeted therapy (**Table 2**).

3.3. CDK4/6 inhibitors

Dysregulated cell cycle progression due to uncontrolled cellular growth is another hallmark of cancer, and disruption of cell cycle progression through inhibition of CDKs is a therapeutic strategy undergoing intense evaluation in multiple cancers [53]. Cyclin-dependent kinase 4 is a key regulator of the transition from G_1 to S phase of the cell cycle, which, when inhibited, causes cell cycle arrest and apoptosis of dividing cells. Furthermore, resistance to ET is often caused by upregulation of signaling pathways that modify cell cycle control [54]. A number of selective CDK4/6 inhibitors are under investigation in HER-2-negative BC, including palbociclib, abemaciclib, and LEE011. Palbociclib has been investigated as single-agent treatment for HR-positive/HER-2-negative ABC, HR-positive/HER-2-positive ABC, and advanced TNBC, and in combination with letrozole as first-line therapy for ER-positive/HER-2-negative MBC. In a phase 2 study in 165 women with ER-positive/HER-2-negative MBC who were treated with first-line palbociclib plus letrozole (LET) or LET alone, median PFS with palbociclib treatment was 20.2 months vs 10.2 months with LET alone (P = .0004) (**Table 1**) [42]. The most common AEs in the palbociclib treatment group were neutropenia, leukopenia,

fatigue, and anemia (**Table 1**). A phase 3 study in the same population is ongoing (NCT01740427; **Table 2**). Another CDK4/6 inhibitor, LEE011, is also under investigation in a number of ongoing clinical trials as combination therapy for HER-2-negative BC (**Table 2**).

3.4. HDAC inhibitors

The recent discovery that alterations in histone proteins and DNA can lead to tumorigenesis has led to the evaluation of HDAC inhibitors in solid tumors [55]. Histone deacetylases catalyze the deacetylation of histones, leading to the coiling of chromatin and the blockade of transcription of affected genes [56]. Histone deacetylases are critical in the regulation of expression of numerous genes involved in cell survival, proliferation, and differentiation [57]. A number of HDAC inhibitors have been investigated in various cancers, and 2 agents (entinostat and vorinostat) are under investigation for HER-2-negative BC. Entinostat, a class-specific HDAC inhibitor, has been investigated in combination with EXE in postmenopausal women with ER-positive ABC after they had progressed on a nonsteroidal AI in a phase 2 trial [43]. Entinostat was associated with increased median OS (28.1 months for entinostat plus EXE vs 19.8 months for PBO plus EXE; $P = .036$) and the most common grade 3 or 4 AEs were neutropenia (14% vs 0) and fatigue (13% vs 3%) (**Table 1**) [43]. A second phase 2 trial has evaluated entinostat in combination with 5-azacitidine in women with advanced TNBC or hormone-resistant BC. No responses were observed in the first 13 TNBC subjects and this cohort was closed; 27 patients were enrolled in the hormone-resistant cohort, and median PFS was 1.8 months at a median follow-up of 6.3 months (**Table 1**) [44, 47]. A phase 3 trial is currently underway for entinostat plus EXE in HER-2-negative ABC, while a phase 2 trial is underway for vorinostat, a pan-HDAC inhibitor, in combination with CT for first-line treatment of HER-2-negative BC and TNBC (**Table 2**).

3.5. PARP inhibitors

There is intense interest in DNA repair pathways in oncology. Dysregulation of homologous recombination can be caused by mutations to *BRCA1* or *BRCA2*, which are responsible for 5% to 10% of BCs, most notably TNBC [58]. These tumors may be susceptible to lethality if another DNA repair mechanism, such as base excision repair, is also inhibited. Several groups have demonstrated that BRCA-deficient cells are sensitive to inhibition of PARP [59, 60], which is involved in a variety of cellular processes, including homologous recombination repair of DNA double-strand breaks (reviewed in Calvert et al [61] and Shah et al [62]). The PARP inhibitors veliparib and rucaparib are currently being investigated in TNBC or in BC patients with known *BRCA* mutations. In phase 2 studies, veliparib [45] has demonstrated modest efficacy in MBC patients with *BRCA* mutations, while rucaparib [46] was observed to have similar 1-year OS in patients with TNBC or BC with known *BRCA* mutations receiving rucaparib plus cisplatin compared with cisplatin monotherapy (**Table 1**). Veliparib is currently being investigated in combination with CT in a number of clinical trials, including 2 phase 3 trials (**Table 2**).

3.6. Immunotherapies

The immune system plays an important role in cancer, both in the promotion of tumorigenesis through inflammatory pathways and suppression of adaptive immunity, and in the prevention of tumor formation through immune surveillance [63]. Tumor-infiltrating lymphocytes have been associated with improved outcome in BC and were recently shown to be a predictive marker of response to neoadjuvant CT [64]. An immune response is initiated by antigen recognition, but the magnitude and quality of the response is regulated by additional immune checkpoint molecules [65]. These molecules include PD-1, PD-L1, and CTLA-4, and inhibition of these novel targets is actively being investigated in a number of cancers, including non-small cell lung cancer, renal carcinoma, melanoma, ovarian cancer, and others. Nivolumab,

pembrolizumab, and pidilizumab are mAb inhibitors of PD-1, and MPDL3280A is a mAb inhibitor of PD-L1; ipilimumab is a CTLA-4 inhibitor. No clinical trial data with these agents in BC have been published to date, and none of these agents has progressed to phase 2 trials for the treatment of HER-2-negative BC.

4. Combination regimens with chemotherapeutic agents

Taxanes, such as paclitaxel, are important chemotherapeutic agents for the treatment of HER-2-negative BC. Paclitaxel is indicated for the treatment of MBC after failure of combination CT for metastatic disease or relapse within 6 months of adjuvant CT, with prior therapy including an anthracycline unless clinically contraindicated [66]. It is also being investigated in numerous clinical trials as combination therapy for HER-2-negative and HER-2-positive BC. Due to the hydrophobicity of taxanes, synthetic solvents are used to enable parenteral administration; polyethylated castor oil and ethanol are used as vehicle for paclitaxel [66]. Recently, a 130 nm albumin-bound formulation of paclitaxel (*nab*-paclitaxel) has been developed to improve the chemotherapeutic effects of paclitaxel while avoiding the toxicities associated with polyethylated castor oil [67]. Albumin is a natural carrier of lipophilic molecules allowing *nab*-paclitaxel to be safely infused at higher doses, with shorter infusion times, and with no need for pre-medication [68]. A phase 3 trial comparing paclitaxel with *nab*-paclitaxel in women with MBC demonstrated a significant increase in response rate in the *nab*-paclitaxel group compared with the paclitaxel group (33% vs 19%; $P = .001$), as well as significantly longer time to tumor progression (23.0 weeks vs 16.9 weeks; $P = .006$) [69]. *nab*-Paclitaxel was also associated with a lower incidence of grade 4 neutropenia compared with paclitaxel (9% vs 22%; $P < .001$) [69]. Unlike paclitaxel, *nab*-paclitaxel is being investigated in a limited number of clinical trials in HER-2-negative BC, mostly in combination with bevacizumab. Since their indications are similar [66, 67], *nab*-paclitaxel may replace paclitaxel as combination therapy with targeted agents (bevacizumab,

sorafenib, sunitinib, buparlisib, BEZ235, EVE, and veliparib) because of its improved efficacy and safety.

5. Conclusions

Breast cancer is the leading cause of cancer and cancer death in women worldwide. Although MBC is incurable, it is treatable, with prolonged survival as the ultimate goal of therapy. Many patients with BC progress after multiple lines of therapy or become resistant to treatment; therefore, there is a need for additional treatment strategies for this patient population and repeat biopsies to track change in receptor status to determine treatment modifications. Translational research, including The Cancer Genome Atlas, has generated a wealth of data that provides the rationale for the investigation of novel therapeutic targets, such as the identification of commonly mutated genes in BC. Inhibition of these emerging pathways, either alone or as combination therapy, may provide greater control of disease progression even in patients with resistance to ET. Clinical trial data for a number of these agents have demonstrated promising clinical activity, and further research is underway to develop novel treatment combinations for patients with HER-2-negative BC.

Executive summary

- HER-2-negative breast cancer is incurable, but is treatable. New therapeutic options are needed to manage resistance to current therapies.
- Breast cancer patients acquire resistance to therapy, and these pathways have become targets for treatment. The Cancer Genome Atlas has documented the frequency of common gene mutations in breast cancer subtypes, and a number of agents are under investigation to target these cellular pathways.
- A number of targeted biologic therapies are currently under investigation for HER-2-negative breast cancer, and these include inhibitors of VEGF and VEGFR, mTOR and PI3K signaling pathways, CDK4 and 6, HDAC, PARP, CTLA-4, and PD-1 and PD-L1. Extensive descriptions of clinical efficacy and ongoing trials of key targeted agents from phase 2 or 3 trials for the treatment of HER-2-negative breast cancer are included in this review.
- Combination regimens of a chemotherapeutic agent (such as *nab*-paclitaxel) and a biologic targeted agent are under investigation to achieve prolonged disease control in patients with HER-2-negative breast cancer, including triple-negative breast cancer.
- Continued research is required to demonstrate the efficacy and safety of targeted agents and combination regimens in the treatment of HER-2-negative breast cancer.

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TABLES

Table 1. Clinical Activity of Key Targeted Agents From Phase 2 or 3 Trials for the Treatment of HER-2-Negative BC

Agent	Phase	Regimen	Patients, N (demographics)	Efficacy	Safety
Anti-angiogenics					
Bevacizumab [17]	3	BEV+PAC vs PAC alone	722 Initial treatment for MBC	Median PFS for BEV+PAC vs PAC alone was 11.8 mo vs 5.9 mo (P < .001); OS rate was 26.7 mo vs 25.2 mo (P = .16)	Most common grade 3/4 AEs for BEV+PAC vs PAC alone were neuropathy (23.6% vs 17.6%), infection (9.3% vs 2.9%), and fatigue (8.5% vs 4.9%)
Bevacizumab [18]	2	BEV+PAC (PB) vs BEV+PAC+SUN (PBS)	46 HER-2-negative MBC	Median PFS was not reached due to premature study termination	Most common grade 3/4 AEs for PBS vs PB were neutropenia (44% vs 9%), leukopenia (30% vs 0), fatigue (26% vs 9%), diarrhea (17% vs 0), and febrile neutropenia (13% vs 4%)

Bevacizumab [19]	3	BEV+DOC vs PBO+DOC	736 First-line treatment of HER-2-negative LRBC or MBC	Median PFS was 8.2 mo for PBO+DOC vs 10.1 mo for BEV (15 mg/kg) + DOC (P = .006)	Most common grade ≥3 AEs for BEV+DOC vs PBO+DOC were neutropenia (19.8% vs 17.3%) and febrile neutropenia (16.2% vs 11.3%)
Bevacizumab [20]	3	BEV+CT vs PBO+CT	1,237 First-line treatment of HER-2-negative MBC	Median PFS was significantly longer for each BEV+CT combination vs PBO+CT (P < .001); no statistically significant OS difference between groups	Hypertension and proteinuria were consistently increased in the BEV-containing arms regardless of CT combination
Bevacizumab [21]	Registry	BEV+CT	2,264 First-line treatment for HER-2-negative LRBC or MBC	Median OS was 30.0 mo in patients who continued BEV after discontinuation of CT and 18.4 mo in patients who discontinued BEV before/same time as discontinuation of CT	Slightly higher incidence of grade ≥3 AEs in patients treated for ≥12 mo (65.8%) vs the overall population (57.6%)

Bevacizumab [22]	2	BEV+GEM	52 First-line treatment for LRBC or MBC after neoadjuvant and/or adjuvant taxane therapy with a ≥12-mo disease-free interval	Median PFS was 4.8 mo (95% CI, 3.4-7.6); 1-yr OS rate was 68.7% (95% CI, 54.1%-79.5%)	Most common AEs were nausea (51.9%), fatigue (46.2%), decreased appetite (25.0%), and anemia (25.0%); most common grade 3/4 AEs were neutropenia (13.5%), leukopenia (11.5%), and hypertension (7.7%)
Bevacizumab [23]	3	BEV+PAC vs BEV+CAP	533 (per protocol population) HER-2-negative, MBC without previous CT	Median PFS for BEV+PAC vs BEV+CAP was 11.0 mo (95% CI, 10.4-12.9) vs 8.1 mo (95% CI, 7.1-9.2) (*P* = .0052)	Most common grade ≥3 AEs were neutropenia (18%), peripheral neuropathy (14%), and leukopenia (7%) with BEV+PAC, and hand-foot syndrome (16%), hypertension (6%), and diarrhea (5%) with BEV+CAP
Sorafenib [24]	2	SOR+BEV	18 MBC with ≤2 prior CT regimens	Median PFS was 2.8 mo; accrual was terminated due to lack of clear efficacy and increased toxicity	50% of patients reported grade 3 toxicity

Sorafenib [25]	2b	SOR+CAP vs PBO+CAP	229 First- or second-line treatment of HER-2-negative, locally advanced BC or MBC	Median PFS for SOR+CAP vs PBO+CAP was 6.4 mo vs 4.1 mo (P = .001); median OS was 22.2 mo vs 20.9 mo (P = .42)	Most common grade 3 AE for SOR+CAP vs PBO+CAP was hand-foot syndrome (44% vs 14%)
Sorafenib [26]	2b	SOR+PAC vs PBO+PAC	237 First-line treatment of HER-2-negative, LRBC or MBC	Median PFS for SOR+PAC vs PBO+PAC was 6.9 mo vs 5.6 mo (P = .0857); median OS was 16.8 mo vs 17.4 mo (P = .904)	Most common grade 3/4 toxicities for SOR+PAC vs PBO+PAC were hand-foot syndrome (31% vs 3%), neutropenia (13% vs 7%), and anemia (11% vs 6%)
Sorafenib [27]	2b	SOR+CT vs PBO+CT	160 Locally advanced BC or HER-2-negative MBC with prior BEV therapy	Median PFS for SOR+CT vs PBO+CT was 3.4 mo vs 2.7 mo (P = .02); median survival was 13.4 mo vs 11.4 mo (P = .95)	Most common grade 3/4 AEs for SOR+CT vs PBO+CT were hand-foot syndrome (39% vs 5%), stomatitis (10% vs 0), and fatigue (18% vs 9%)

Sunitinib [28]	2	SUN	64 MBC after taxane and anthracycline treatment	ORR was 11%; median time to progression was 10 wk; median OS was 38 wk	Most common grade 3 AEs were fatigue (14%), dyspnea (9%), hand-foot syndrome (9%), and nausea (8%)
Sunitinib [29]	2	SUN vs no therapy	36 HER-2-negative, MBC who achieved an objective response with taxane-based therapy	PFS ≥5 mo for SUN vs no therapy was 28% vs 21%; median PFS was 2.8 mo vs 3.1 mo	Grade 3/4 toxicities occurred in 69% with SUN and 11% with no therapy
Sunitinib [30]	2	SUN alone	83 LRBC or MBC	ORR was 8%; median PFS was 3.6 mo; median OS was 15.6 mo	Most common AEs were fatigue (60%), diarrhea (54%), and nausea (49%); most common grade 3/4 AEs were fatigue (17%), neutropenia (16%), and thrombocytopenia (11%)

Sunitinib [31]	2	SUN vs SOC CT	217 Advanced TNBC, relapsed after anthracycline- and taxane-based CT	Median PFS was 2.0 mo for SUN vs 2.7 mo for SOC CT (*P* = .888); median OS was 9.4 mo vs 10.5 mo (*P* = .839)	Most common grade 3 AEs for SUN vs SOC CT were neutropenia (20% vs 5%), leukopenia (10% vs 3%), and asthenia (10% vs 1%); most common grade 4 AE was neutropenia (1% vs 6%)
Sunitinib [32]	3	SUN+DOC vs DOC alone	593 First-line treatment for HER-2-negative, ABC	Median PFS was 8.6 mo for SUN+DOC vs 8.3 mo for DOC alone (*P* = .265); median OS was 24.8 mo vs 25.5 mo (*P* = .904)	Most common grade 3 AEs were neutropenia (17% for SUN+DOC vs 10% for DOC alone), hand-foot syndrome (17% vs 1%), leukopenia (10% vs 13%), and diarrhea (10% vs 4%); most common grade 4 AEs were neutropenia (29% vs 33%), and leukopenia (5% vs 9%)

Sunitinib [33]	3	SUN+PAC vs BEV+PAC	485 First-line treatment of HER-2-negative ABC	Median PFS for BEV+PAC vs SUN+PAC was 9.2 mo vs 7.4 mo (*P* = .999); early termination due to futility of reaching primary endpoint	Most common grade 3 AEs for SUN+PAC vs BEV+PAC were neutropenia (39% vs 15%), fatigue (12% vs 8%), and leukopenia (10% vs 6%); most common grade 4 AE was neutropenia (14% vs 5%)
Sunitinib [34]	3	SUN+CAP vs CAP alone	442 MBC after multiple lines of CT	Median PFS for SUN+CAP vs CAP alone was 5.5 mo vs 5.9 mo (*P* = .941)	Except for hand-foot syndrome, toxicity was more severe with SUN+CAP; grade 3 AEs were reported by 59% of SUN+CAP patients vs 47% of CAP-alone patients, and grade 4 AEs were reported by 4% vs 17%

Sunitinib [35]	3	SUN vs CAP	482 HER-2-negative BC that recurred after anthracycline and taxane therapy	Median PFS for SUN vs CAP was 2.8 mo vs 4.2 mo; median OS was 15.3 mo vs 24.6 mo; study was terminated for failure to reach primary endpoint	Grade 3 AEs were observed in 46% with SUN vs 30% with CAP; most common grade 3 AEs were neutropenia (10% vs 3%) and hand-foot syndrome (8% vs 16%); grade 4 AEs were observed in 7% vs 3%
PI3K/mTOR Inhibitors					
Buparlisib	No published data available that met the inclusion criteria				
BEZ235	No published data available that met the inclusion criteria				
Everolimus [36]	2	EVE+LET vs PBO+LET	270 Neoadjuvant treatment of postmenopausal women with ER-positive BC	Response rate by clinician palpation for EVE vs PBO was 68.1% vs 59.1% (*P* = .0616)	Common grade 3/4 AEs for EVE group included hyperglycemia (5.1%), stomatitis, and pneumonitis (2.2% each), thrombocytopenia, fatigue, increased ALT, and hypokalemia (1.5% each); no significant grade 3/4 AEs were reported for PBO group

Everolimus [37]	2	EVE+LET	65 (interim report on 24) Postmenopausal MBC after recurrence or progression on TAM or AI	22% PR, 28% SD, 50% PD	Most common toxicities were mucositis and weight loss; grade 3 bone marrow toxicity was observed in ~5% of patients
Everolimus [38]	2	EVE+TAM vs TAM	111 Postmenopausal HR-positive/HER-2-negative, AI-resistant MBC	6 mo CBR for EVE+TAM vs TAM alone was 61% vs 42%; TTP was 8.6 mo vs 4.5 mo	Nonhematologic grade 3/4 AEs were similar in EVE+TAM vs TAM alone groups (P = .2)
Everolimus [39]	2	EVE+FUL	33 Postmenopausal ER-positive BC with disease relapse/progression within 6 mo of AI use	Median TTP is 7.4 mo (4 patients remaining on therapy at the time of publication)	Most common AEs: elevated AST (81%) or ALT (68%), hyperglycemia (61%), anemia (61%), elevated cholesterol (60%), hypokalemia (52%), mucositis (48%), and weight loss (48%)

Everolimus [40]	3	EVE+EXE vs PBO+EXE	724 HR-positive ABC after recurrence or progression with AI	Median PFS for EVE+EXE vs PBO+EXE was 6.9 mo vs 2.8 mo (hazard ratio = 0.43; 95% CI, 0.35-0.54; *P* < .001) by investigator assessment (interim analysis)	Most common grade 3/4 AEs for EVE+EXE vs PBO+EXE were stomatitis (8% vs 1%), anemia (6% vs <1%), dyspnea (4% vs 1%, hyperglycemia (4% vs <1%) fatigue (4% vs 1%), and pneumonitis (3% vs 0)
CDK4/6 Inhibitors					
Palbociclib [41]	2	PAL alone	36 (interim report on 28) 18 [64%] HR-positive/ HER-2-negative ABC; 2 [7%] HR-positive/ HER-2-positive ABC; 8 [29%] TNBC	Clinical benefit (PR + SD >6 mo) observed in 6 (21%) patients total (4 [23%] of HR-positive/HER-2-negative and 1 [13%] TNBC patients)	Grade 3/4 toxicities were transient neutropenia (50%) and thrombocytopenia (21%)
Palbociclib [42]	2	PAL+LET vs LET alone	165 Front-line therapy for ER-positive/HER-2-negative MBC	PFS for PAL+LET vs LET alone was 20.2 mo vs 10.2 mo (hazard ratio = 0.488; 95% CI, 0.319-0.748; *P* = .0004)	Most common AEs with PAL+LET were neutropenia, leukopenia, fatigue, and anemia

Abemaciclib	No published data available that met the inclusion criteria				
LEE011	No published data available that met the inclusion criteria				
HDAC Inhibitors					
[43]	2	ENT+EXE vs PBO+EXE	130 Postmenopausal with ER-positive ABC after progression on a nonsteroidal AI	Median PFS for ENT+EXE vs PBO+EXE was 4.3 mo vs 2.3 mo (*P* = .055); median OS was 28.1 mo vs 19.8 mo (*P* = .036)	Most common grade 3/4 AEs for ENT+EXE vs PBO+EXE were neutropenia (14% vs 0) and fatigue (13% vs 3%)
Entinostat [44]	2	ENT+5-AZA	27 Hormone-resistant ABC	Median PFS was 1.8 mo and median OS was 11.5 mo at a median FU of 6.3 mo	Therapy was well tolerated; few grade 3/4 AEs were observed
Entinostat [47]	2	ENT+5-AZA	13 Advanced TNBC	No responses observed following first stage of 2-stage design; cohort was closed	Most common grade 3/4 AEs were leukopenia and neutropenia (23% each)

Vorinostat	No published data available that met the inclusion criteria				
PARP Inhibitors					
Veliparib [45]	2	VEL, then VEL+CARB after progression	41 MBC with *BRCA1* or *BRCA2* mutations (50% are HR-positive)	PR (>4 cycles of FU): 2/12 (17%) for *BRCA1* and 3/13 (23%) for *BRCA2*	3 patients withdrew due to grade 2 seizures, grade 3 thrombocytopenia, or grade 2 thrombocytopenia and neutropenia
Rucaparib [46]	2	Cisplatin±RUC	128 TNBC or known *BRCA* mutations with invasive disease after anthracycline or taxane neoadjuvant therapy	1-yr DFS was similar (~76%) in both treatment groups	Toxicity required cisplatin dose reduction (20%) or delay (~43%) in both arms; RUC dose reduction was uncommon (6%)
Immunotherapies					
PD-1/PD-L1 Inhibitors					
Nivolumab	No published data available that met the inclusion criteria				
Pembrolizumab	No published data available that met the inclusion criteria				
Pidilizumab	No published data available that met the inclusion criteria				
MPDL3280A	No published data available that met the inclusion criteria				

CTLA-4 Inhibitor

Ipilimumab	No published data available that met the inclusion criteria

5-AZA, 5-azacitidine; ABC, advanced breast cancer; AE, adverse event; AI, aromatase inhibitor; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BC, breast cancer; BEV, bevacizumab; CAP, capecitabine; CARB, carboplatin; CBR, clinical benefit rate; CDK, cyclin-dependent kinase; CI, confidence interval; CT, chemotherapy; CTLA, cytotoxic T-lymphocyte antigen; DFS, disease-free survival; DOC, docetaxel; ENT, entinostat; ER, estrogen receptor; EVE, everolimus; EXE, exemestane; FU, follow-up; FUL, fulvestrant; GEM, gemcitabine; HDAC, histone deacetylase; HER-2, human epidermal growth factor receptor-2; HR, hormone receptor; LET, letrozole; LRBC, locally recurrent breast cancer; MBC, metastatic breast cancer; mo, month; mTOR, mammalian target of rapamycin; ORR, objective response rate; OS, overall survival; PAC, paclitaxel; PAL, palbociclib; PARP, poly(adenosine diphosphate [ADP]-ribose) polymerase; PB, paclitaxel plus bevacizumab; PBO, placebo; PBS, paclitaxel plus bevacizumab plus sunitinib; PD, progressive disease; PD-1, programmed death-1; PD-L1, programmed death ligand-1; PFS, progression-free survival; PI3K, phosphatidylinositide 3-kinase; PR, partial response; RUC, rucaparib; SD, stable disease; SOC, standard of care; SOR, sorafenib; SUN, sunitinib; TAM, tamoxifen; TNBC, triple-negative breast cancer; TTP, time to progression; VEL, veliparib; wk, week; yr, year.

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Table 2. Ongoing Trials of Key Targeted Agents From Phase 2 or 3 Trials for the Treatment of HER-2-Negative BC*

Agent (Trial Name)	Treatment	Trial Phase (NCT)	Study Population	Primary Endpoint
Anti-angiogenics				
Bevacizumab	BEV+*nab*-PAC+CAR	2 (NCT00618657)	HER-2-negative or HER-2-positive BC[b]	PFS
Bevacizumab	Pre-Op: BEV+CIS Post-Op: BEV+DOX+CYC+PAC	2 (NCT00580333)	TNBC	PCR
Bevacizumab	BEV+DOC+CYC vs DOC+DOX+CYC+PEG vs DOC+CYC	3 (NCT00887536)	Node-positive, high-risk node-negative, HER-2-negative, HR-positive or HR-negative BC	Invasive DFS
Bevacizumab	BEV+AMG386+PAC vs BEV+PBO+PAC vs AMG386+PAC	2 (NCT00511459)	HER-2-negative MBC or RBC	PFS
Bevacizumab (Stop&Go)	BEV+PAC (1^{st}); L-DOX or CAP (2^{nd})	3 (NCT01935492)	HER-2-negative MBC or LABC	PFS

Bevacizumab (Beverly1)	BEV+FLU+EPI+CYC, followed by BEV+DOC (neo), then BEV (adj)	2 (NCT00820547)	Pre- or postmenopausal, inflammatory, HER-2-negative BC, no metastatic disease	CHRR
Bevacizumab	BEV+FLU+EPI+CYC, followed by BEV+DOC	2 (NCT01985841)	HER-2-negative BC	CR
Bevacizumab (BEVPAC)	BEV+PAC vs PAC	2 (NCT01722968)	HER-2-negative MBC	Biomarker identification
Bevacizumab	BEV+ET or CT vs PBO+ET or CT	2 (NCT00773695)	HER-2-negative BC	PCR
Bevacizumab	BEV+PAC vs PLA+PAC	3 (NCT01663727)	HER-2-negative MBC or LRBC	PFS
Bevacizumab	BEV+DOX+CYC+PAC	2 (NCT01959490)	HER-2-negative or HER-2-positive BC[c]	Predicted PCR
Bevacizumab	BEV+CAR+DOX	2 (NCT00608972)	Metastatic TNBC	PFS
Bevacizumab	DOX+CYC+GM-CSF, followed by CAR+*nab*-PAC+BEV	2 (NCT00254592)	HER-2-negative or HER-2-positive BC[d]	OCR
Bevacizumab	BEV+PAC vs BEV+CYC+CAP	3 (NCT01131195)	Pre- or postmenopausal, HER-2-negative MBC, RBC, or LABC	Incidence of grade 3-5 AEs
Bevacizumab	BEV+*nab*-PAC+CAR	2 (NCT00479674)	Metastatic TNBC	Safety

Bevacizumab	BEV+PAC vs BEV+CAP	3 (NCT00600340)	HER-2-negative LRBC or MBC	OS
Bevacizumab	BEV+*nab*-PAC, followed by DOX+CYC+PEG vs *nab*-PAC, followed by DOX+CYC+PEG vs DOX+CYC+PEG, followed by *nab*-PAC	2 (NCT00856492)	Pre- or postmenopausal, HER-2-negative, inflammatory or LABC	PCR
Bevacizumab	BEV+*nab*-PAC, followed by BEV+ERL	2 (NCT00733408)	Advanced TNBC	PFS
Bevacizumab (CARIN)	BEV+CAP vs BEV+CAP+VIN	2 (NCT00868634)	HER-2-negative MBC or LABC	PFS
Bevacizumab	BEV+CAR+PAC	1/2 (NCT00691379)	Metastatic TNBC	ORR
Bevacizumab (ESMERALDA)	BEV+ERI	2 (NCT01941407)	HR-positive or HR-negative, HER-2-negative MBC	DCR
Bevacizumab	BEV+*nab*-PAC+CAR, followed by BEV+DOX+CYC, followed by surgery, then BEV	2 (NCT00777673)	TNBC	PCR
Bevacizumab	BEV+PAC or DOC	4 (NCT01094184)	Metastatic TNBC	Safety, Tolerability

Bevacizumab	BEV+ET (LET or FUL) vs ET (LET or FUL)	3 (NCT00545077)	Postmenopausal, HER-2-negative MBC or LABC	PFS
Sorafenib	SOR+IXA	1/2 (NCT00825734)	HER-2-negative MBC	PFS
Sorafenib	SOR+CAP vs PBO+CAP	3 (NCT01234337)	HER-2-negative LABC or MBC	PFS, Safety
Sorafenib	SOR, followed by SOR+CIS, followed by PAC	2 (NCT01194869)	Early-stage TNBC	PCR
Sorafenib	SOR+PAC	2 (NCT00622466)	Pre- or postmenopausal, HR-positive or HR-negative, HER-2-negative MBC	ORR
Sorafenib (PASO)	SOR+PAC vs PAC	2 (NCT01320111)	HER-2-negative BC	PFS
Sorafenib	SOR+PAC vs PBO+PAC	2b (NCT00499525)	Pre- or postmenopausal, HER-2-negative LRBC or MBC	PFS
Sunitinib	SUN+PAC+CAR	1/2 (NCT00887575)	Locally advanced TNBC	MTD (P1) PCR (P2)

PI3K/mTOR Inhibitors

Buparlisib (BELLE-2)	BKM120+FUL vs PBO+FUL	3 (NCT01610284)	Postmenopausal, HR-positive/HER-2-negative LABC or MBC; prior treatment with AIs	PFS
Buparlisib (BELLE-3)	BKM120+FUL vs PBO+FUL	3 (NCT01633060)	Postmenopausal, HR-positive/HER-2-negative LABC or MBC; prior treatment with AIs and mTOR inhibitors	PFS
Buparlisib (BELLE-4)	BKM120+PAC vs PBO+PAC	2/3 (NCT01572727)	HER-2-negative LABC or MBC patients with or without PI3K activation	PFS
Buparlisib (B-YOND)	BKM120+TAM+GOS vs BYL719+TAM+GOS vs PBO+TAM+GOS	2 (NCT02058381)	Premenopausal, HR-positive/HER-2-negative LABC or MBC	PFS
Buparlisib	BKM120+PAC	2 (NCT01953445)	Pre- or postmenopausal, stage 2 or 3, ER-positive/HER-2-negative BC	PCR
Buparlisib	BKM120+CAP	2 (NCT02000882)	TNBC patients with brain metastases	CBR
Buparlisib	BKM120	2 (NCT01629615)	Metastatic TNBC	CBR

Buparlisib	BKM120	2 (NCT01790932)	TNBC	CBR
Buparlisib	BKM120+LET vs BYL719+LET vs PBO+LET	2 (NCT01923168)	Postmenopausal, HR-positive/HER-2-negative BC	PCR
BEZ235	BEZ235+PAC	1b/2 (NCT01495247)	HER-2-negative LABC or MBC	DLT, MTD (P1b)
Everolimus (DETECT IV)	EVE+ET	2 (NCT02035813)	Postmenopausal, HR-positive/HER-2-negative MBC; HER-2-negative CTCs	PFS
Everolimus	EVE+ET vs PBO+ET	3 (NCT01805271)	ER-positive/HER-2-negative BC; received 3 years of AHT	DFS
Everolimus	EVE+PAC+BEV vs PBO+PAC+BEV	2 (NCT00915603)	HER-2-negative MBC	PFS
Everolimus (BOLERO-4)	EVE+LET	2 (NCT01698918)	Postmenopausal, ER-positive/HER-2-negative MBC or LABC	PFS
Everolimus	EVE+LEE011+EXE vs EVE+EXE vs LEE011+EXE	1b/2 (NCT01857193)	Postmenopausal, ER-positive/HER-2-negative LABC	DLT/MTD (P1b) PFS (P2)

Everolimus (VicTORia)	EVE+VIN vs VIN	2 (NCT01520103)	HER-2-negative MBC or LABC	PFS
Everolimus	EVE+HT vs PBO+HT	3 (NCT01674140)	HR-positive/ HER-2-negative BC	Invasive DFS
Everolimus	EVE+ET vs PBO+ET	3 (NCT01773460)	HR-positive/HER-2-negative MBC patients who showed progression after EVE+EXE therapy	PFS
Everolimus (S1222 Trial)	EVE+FUL+ANA vs EVE+FUL+PBO vs PBO+FUL+PBO	3 (NCT02137837)	Postmenopausal, HR-positive/HER-2-negative BC	PFS
Everolimus	EVE+*nab*-PAC	1/2 (NCT00934895)	HER-2-negative LABC or MBC	MTD (P1) ORR (P2)
Everolimus	EVE+GEM+CIS vs GEM+CIS	1b/2 (NCT01939418)	Metastatic TNBC	RP2D (P1b) PFS (P2)
Everolimus (BOLERO-6)	EVE vs CAP vs EVE+EXE	2 (NCT01783444)	ER-positive/HER-2-negative LABC or MBC	PFS
Everolimus	EVE vs TRA vs EVE+TRA	2 (NCT00912340)	Hormone-refractory, HER-2-negative MBC	ORR

Everolimus (NECTAR)	EVE+CIS	2 (NCT01931163)	TNBC	ORR
CDK4/6 Inhibitors				
Palbociclib (PALOMA-3)	PAL+FUL vs PBO+FUL	3 (NCT01942135)	Pre- or postmenopausal, HR-positive/HER-2-negative LABC or MBC	PFS
Palbociclib (PALOMA-2)	PAL+LET vs PBO+LET	3 (NCT01740427)	Postmenopausal, ER-positive/HER-2-negative LABC	PFS
Palbociclib (PEARL)	PAL+EXE vs CAP	3 (NCT02028507)	Pre- or postmenopausal, HR-positive/HER-2-negative MBC with prior AI therapy	PFS
Palbociclib	PAL+LET	1/2 (NCT01684215)	Postmenopausal, ER-positive/HER-2-negative LABC	DLT (P1) PFS (P2)
Palbociclib	PAL+ET	2 (NCT02040857)	Pre- or postmenopausal, HR-positive/HER-2-negative, stage 2 or stage 3 BC	TDR
Palbociclib	PAL+LET vs LET	1/2 (NCT00721409)	Postmenopausal, ER-positive/HER-2-negative LABC	Safety (P1) PFS (P2)

Palbociclib	PAL+ANA+GOS[a]	2 (NCT01723774)	Pre- or postmenopausal; ER-positive/HER-2-negative, stage 2 or stage 3 BC	Complete cell cycle arrest
Palbociclib (POP)	PAL vs NI	2 (NCT02008734)	Pre- or postmenopausal; HR-positive/HER-2-negative BC	Antiproliferative response
Palbociclib	PAL+LET	2 (NCT01709370)	Postmenopausal; ER-positive/HER-2-negative BC	ORR
Palbociclib (PENELOPE-B)	PAL vs PBO	3 (NCT01864746)	Pre- and postmenopausal; HR-positive/HER-2-negative, high-risk, early BC	Invasive DFS
Abemaciclib	No clinical trial information available that met the inclusion criteria			
LEE011	LEE011+LET vs BYL719+LET vs LEE011+BYL719+LET	1b/2 (NCT01872260)	Postmenopausal; ER-positive/HER-2-negative LABC	DLT (P1b) PFS (P2)
LEE011	LEE011+BKM120+FUL vs LEE011+BYL719+FUL vs LEE011+FUL	1b/2 (NCT02088684)	Postmenopausal; HR-positive/HER-2-negative metastatic ABC	DLT (P1b) PFS (P2)
LEE011 (MONALEESA-1)	LEE011+LET vs LET	2 (NCT01919229)	Postmenopausal; HR-positive/HER-2-negative, grade 2 or grade 3, early BC	CCRR

LEE011 (MONALEESA-2)	LEE011+LET vs PBO+LET	3 (NCT01958021)	Postmenopausal; HR-positive/HER-2-negative LABC	PFS
HDAC Inhibitors				
Entinostat	ENT+AZA	2 (NCT01349959)	HR-positive/HER-2-negative or TNBC with LABC or MBC	ORR
Entinostat	ENT+EXE vs PBO+EXE	3 (NCT02115282)	Postmenopausal, HR-positive/HER-2-negative ABC	PFS, OS
Entinostat (ENCORE 305)	ENT+FUL vs PBO+FUL	2 (NCT02115594)	Postmenopausal, ER-positive/HER-2-negative ABC	PFS
Vorinostat	VOR+CAR+*nab*-PAC vs PBO+CAR+*nab*-PAC	2 (NCT00616967)	HR-positive/HER-2-negative BC or TNBC	PCR
PARP Inhibitors				
Veliparib	VEL+CAR+PAC vs PBO+CAR+PAC	3 (NCT02163694)	HER-2-negative LABC or MBC, *BRCA*-associated BC patients	PFS
Veliparib	VEL+CYC vs PBO+CYC	1/2 (NCT01351909)	HR-positive/HER-2-negative MBC	RP2D (P1) PFS (P2)
Veliparib	VEL+PAC+CAR vs PAC+CAR	2 (NCT01818063)	Stage 2A/B or Stage 2A/B/C TNBC patients	PCR

Veliparib (Brightness)	VEL+CAR+PAC, followed by DOX/CYC vs PBO+CAR+PAC, followed by DOX/CYC vs PBO+PLA+PAC, followed by DOX/CYC	3 (NCT02032277)	Early-stage TNBC; *BRCA* tested	PCR
Rucaparib	RUC+CIS vs CIS	2 (NCT01074970)	TNBC or HR-positive/HER-2-negative BC patients with known *BRCA1/2* mutations	DFS
Immunotherapies				
PD-1/PD-L1 Inhibitors				
Nivolumab	No clinical trial information available			
Pembrolizumab (MK-3475)	No clinical trial information available			
Pidilizumab	No clinical trial information available			
MPDL3280A	No clinical trial information available			
CTLA-4				
Ipilimumab	No clinical trial information available			

ABC, advanced breast cancer; adj, adjuvant; AE, adverse event; AHT, adjuvant hormone therapy; AI, aromatase inhibitor; ANA, anastrozole; AZA, azacitidine; BC, breast cancer; BEV, bevacizumab; CAP, capecitabine; CAR, carboplatin; CBR, clinical benefit rate; CCRR, cell cycle response rate; CHRR, complete histologic response rate; CIS, cisplatin; CR, complete response; CT, chemotherapy; CTC, circulating tumor cells; CTLA, cytotoxic T-lymphocyte antigen; CYC, cyclophosphamide; DCR, disease control rate; DFS, disease-free survival; DLT, dose limiting toxicity; DOC, docetaxel; DOX, doxorubicin; ENT, entinostat; EPI, epirubicin hydrochloride; ER, estrogen receptor; ERI, eribulin; ERL, erlotinib hydrochloride; ET, endocrine therapy; EVE, everolimus; EXE, exemestane; FLU, fluorouracil; FUL, fulvestrant; GEM, gemcitabine; GM-CSF, granulocyte–macrophage colony-stimulating factor; GOS, goserelin; HDAC, histone deacetylase; HER-2, human epidermal growth factor receptor-2; HR, hormone receptor; HT, hormone therapy; IXA, ixabepilone; LABC, locally advanced breast cancer; L-DOX, liposomal doxorubicin; LET, letrozole; LRBC, locally recurrent breast cancer; MBC, metastatic breast cancer; MTD, maximum tolerated dose; mTOR, mammalian target of rapamycin; *nab*-PAC, *nab*-paclitaxel; neo, neoadjuvant; NI, no intervention; OCR, overall clinical response; ORR, overall response rate; OS, overall survival; P1, phase 1; P2, phase 2; PAC, paclitaxel; PAL, palbociclib; PARP, poly(adenosine diphosphate [ADP]-ribose) polymerase; PBO, placebo; PCR, pathologic complete response; PD-1, programmed death-1; PD-L1, programmed death ligand-1; PEG, pegfilgrastim; PFS, progression-free survival; PI3K, phosphatidylinositide 3-kinase; Post-Op, Postoperative; Pre-Op; Preoperative; RBC, recurrent breast cancer; RP2D, recommended phase 2 dose; RUC, rucaparib; SOR, sorafenib; SUN, sunitinib; TAM, tamoxifen; TDR, treatment discontinuation rate; TNBC, triple-negative breast cancer; TRA, trastuzumab; VEL, veliparib; VIN, vinorelbine; VOR, vorinostat.

* Clinical trials were limited to phase 2 or 3 in patients with HER-2-negative BC in clinicaltrials.gov.

[a] GOS administered to premenopausal patients.

[b] The HER-2-positive patient subpopulation will receive TRA+*nab*-PAC+CAR therapy.

[c] The HER-2-positive patient subpopulation will receive TRA+DOC+CAR therapy.

[d] The HER-2-positive subpopulation will receive DOX+CYC+GM-CSF, followed by CAR+*nab*-PAC+TRA therapy.

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FIGURE LEGENDS

Fig. 1. Current recommendations for the treatment of HER-2-negative breast cancer.

For patients who have completed surgical resection of breast tumors, general systemic intervention is determined by receptor status. Patients who are HR-positive and HER-2-negative are treated with multiple lines of endocrine therapy; if a rapid response is required, chemotherapy is the recommended treatment. After progression on endocrine therapy, patients can be treated with exemestane plus everolimus; otherwise, chemotherapy is recommended. Patients who are HR-negative and HER-2-negative (TNBC) are treated with sequential lines of single-agent chemotherapy. Combination chemotherapy regimens are only recommended if patients require a rapid response or in the case of rapid disease progression. If patients progress after chemotherapy, palliative care is provided. AI, aromatase inhibitor; HER-2, human epidermal growth factor receptor-2; HR, hormone receptor; TNBC, triple-negative breast cancer.

[a] Cardoso F, et al [3].

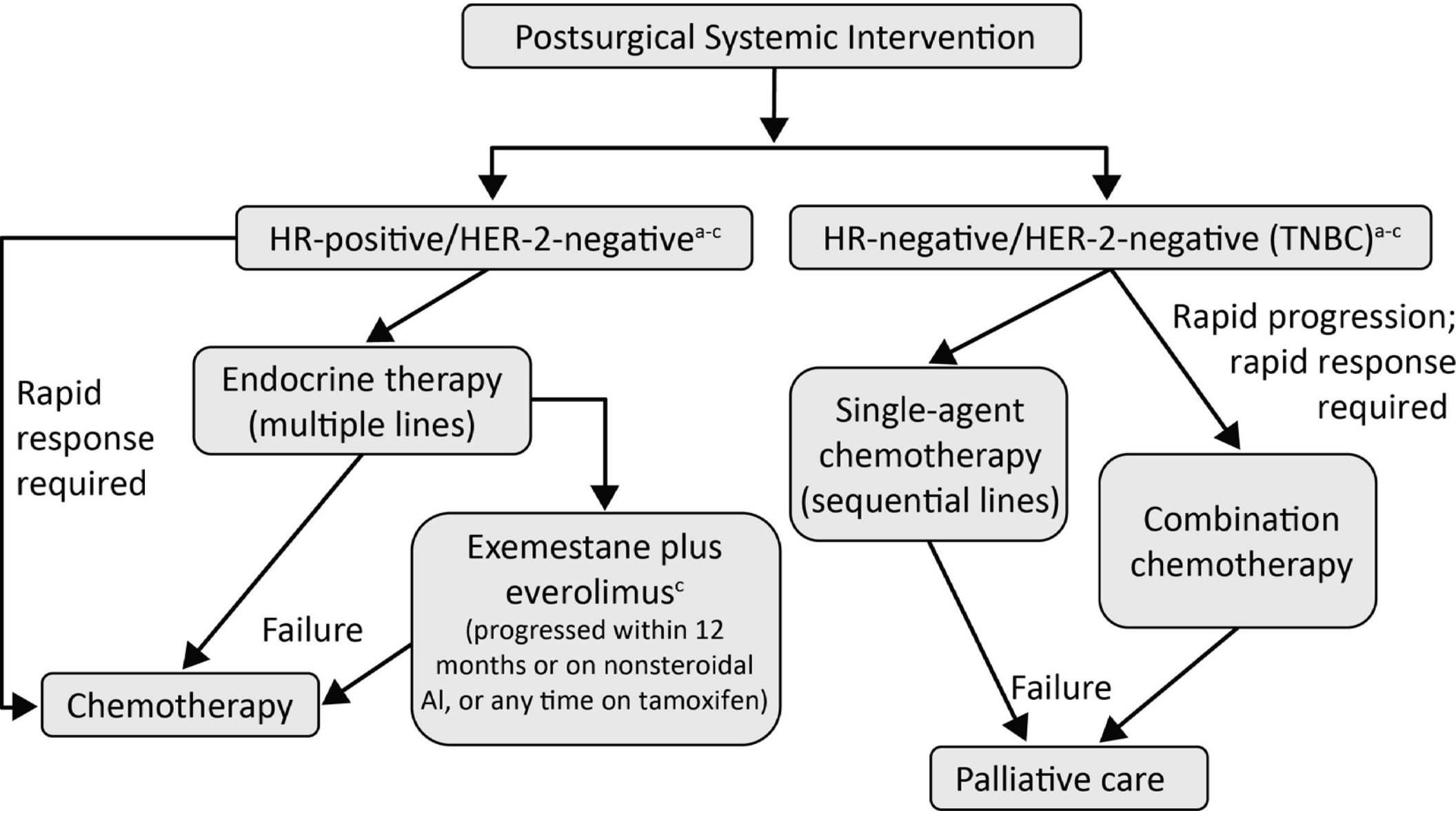
[b] Senkus E, et al [4].

[c] National Comprehensive Cancer Network [5].

Fig. 2. Emerging targets for the treatment of HER-2-negative breast cancer.

Multiple emerging pathways are currently under investigation for the treatment of HER-2-negative breast cancer. Inhibition of these physiologic pathways with targeted agents as combination therapy with chemotherapeutic agents, notably with *nab*-paclitaxel, is a rational means of prolonged disease control. CDK, cyclin dependent kinase; CTLA-4, cytotoxic T-lymphocyte antigen-4; HDAC, histone deacetylase; HER-2, human epidermal growth factor receptor-2; mTOR, mammalian target of rapamycin; PARP, poly(adenosine diphosphate [ADP]-ribose) polymerase; PD-1, programmed death-1; PDGFR, platelet-derived growth factor

receptor; PD-L1, programmed death ligand-1; PI3K, phosphatidylinositide 3-kinase; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.


Postsurgical Systemic Intervention
HR-positive/HER-2-negative[a-c]
HR-negative/HER-2-negative (TNBC)[a-c]
Rapid response required
Endocrine therapy (multiple lines)
Rapid progression; rapid response required
Single-agent chemotherapy (sequential lines)
Combination chemotherapy
Exemestane plus everolimus[c] (progressed within 12 months or on nonsteroidal AI, or any time on tamoxifen)
Failure
Chemotherapy
Failure
Palliative care