Breast Cancer Treatments

Subjects: Oncology

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Breast cancer (BC) is the most frequent cancer diagnosed in women worldwide. This heterogeneous disease can be classified into four molecular subtypes (luminal A, luminal B, HER2 and triple-negative breast cancer (TNBC)) according to the expression of the estrogen receptor (ER) and the progesterone receptor (PR), and the overexpression of the human epidermal growth factor receptor 2 (HER2). Current BC treatments target these receptors (endocrine and anti-HER2 therapies) as a personalized treatment. Along with chemotherapy and radiotherapy, these therapies can have severe adverse effects and patients can develop resistance to these agents. Moreover, TNBC do not have standardized treatments. Hence it is essential to develop new treatments to target more effectively each BC subgroup.

breast cancer personalized therapies molecular subtypes breast cancer treatment luminal HER2 TNBC

1. Introduction

Breast cancer (BC) is the most frequent cancer and the second cause of death by cancer in women worldwide. According to Cancer Statistics 2020, BC represents 30% of female cancers with 276,480 estimated new cases and more than 42,000 estimated deaths in 2020 [1].

Invasive BC can be divided into four principal molecular subtypes by immunohistological technique based on the expression of the estrogen receptor (ER), the progesterone receptor (PR), and the human epidermal growth factor receptor 2 (HER2) [2]. Luminal A BC (ER+ and/or PR+, and HER2-) represents around 60% of BC and is associated with a good prognosis [3]. Luminal B BC (ER+ and/or PR+, and HER2+) represents 30% of BC and is associated with high ki67 (>14%), a proliferation marker, and a poor prognosis [4]. HER2 BC (ER-, PR-, and HER2+) represents 10% of BC and is also associated with a poor prognosis [5]. Lastly, triple-negative BC (TNBC) (ER-, PR-, and HER2-) represents 15–20% of BC and is associated with more aggressivity and worse prognosis compared to other BC molecular subtypes and often occurs in younger women [6]. Characteristics of BC by molecular subtypes are described in **Figure 1**.

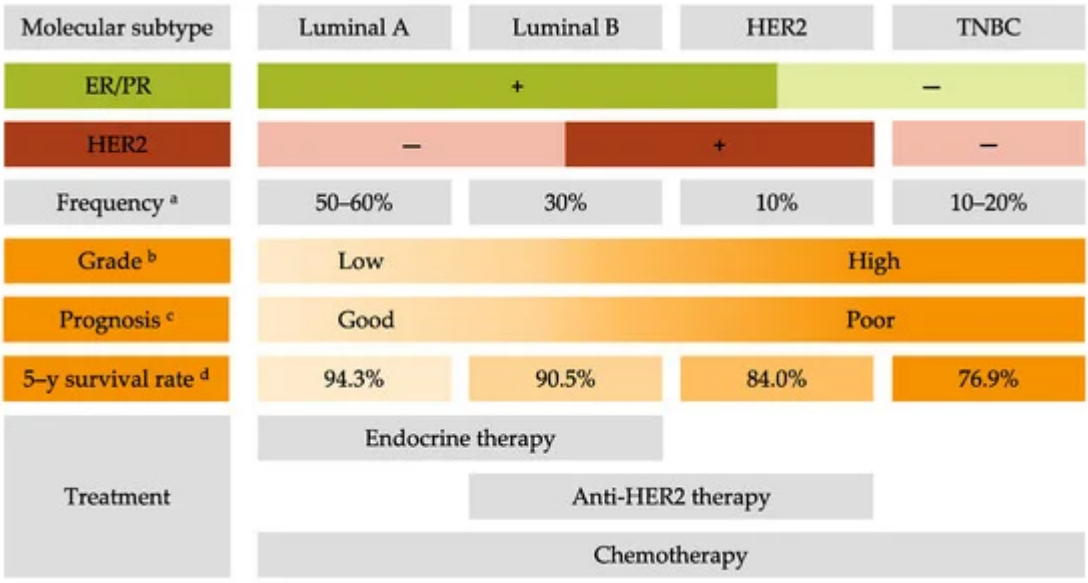

Figure 1. Characteristics of breast cancer molecular subtypes. ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; TNBC: triple-negative breast cancer. [a]. Frequency derived from Al-thoubaity et al. [7] and Hergueta-Redondo et al. [8]. [b]. Grade derived from Engstrom et al. [9]. [c]. Prognosis derived from Hennigs et al. [10] and Fragomeni et al. [11]. [d]. The 5–year survival rate derived from the latest survival statistics of SEER [12].

The 5-year relative BC-specific survival rate of BC is encouraging with 90.3% for all subtypes and stages. However, for metastatic BC the 5-year relative cancer-specific survival rate is still low: 29% regardless of subtype and can drop to 12% for metastatic TNBC [12]. This clearly indicates that strategies of treatment for metastatic BC patients are not effective enough to ensure a good survival rate. Thus, it is crucial to find new solutions for the treatment of metastatic BC and especially TNBC.

Treatment choice is based on the grade, stage, and BC molecular subtype to have the most personalized, safe, and efficient therapy. The grade describes the appearance of tumor cells compared to normal cells. It includes tubule differentiation, nuclear pleomorphism, and the mitotic count [13]. The stage is used to classify the extent of cancer in the body and is defined using the TNM system comprising tumor size, lymph node status, and the presence of metastases [14]. For non-metastatic BC, the strategic therapy involves removing the tumor by complete or breast-conserving surgery with preoperative (neoadjuvant) or postoperative (adjuvant) radiotherapy and systemic therapy including chemotherapy, and targeted therapy. Targeted therapy comprises endocrine therapy for hormone receptor-positive (HR+) BC and anti-HER2 therapy for HER2+ BC. Unfortunately, there is no available targeted therapy for the TNBC subtype. For metastatic BC the priority is to contain tumor spread as this type of BC remains incurable. The same systemic therapies are used to treat metastatic BC [15].

Challenges in the treatment of BC including dealing with treatment resistance and recurrence. Indeed, 30% of early-stage BC have recurrent disease, mostly metastases [16]. Thus, it is crucial to develop new strategic therapies to treat each BC subgroup effectively.

2. Common Treatments for All Breast Cancer Subtypes

In addition to surgery, radiotherapy and chemotherapy are used routinely to treat all BC subtypes [17].

2.1. Surgery

The most standard breast surgery approaches are either total excision of the breast (mastectomy), usually followed by breast reconstruction, or breast-conserving surgery (lumpectomy). Lumpectomy entails the excision of the breast tumor with a margin of surrounding normal tissue. The recommended margins status is defined as “no ink on tumor”, meaning no remaining tumor cells at the tissue edge [18]. Studies show that total mastectomy and lumpectomy plus irradiation are equivalent regarding relapse-free and overall survival (OS) [19]. Contraindications for breast-conserving surgery include the presence of diffuse microcalcifications (suspicious or malignant-appearing), disease that cannot be incorporated by local excision with satisfactory cosmetic result, and *ATM* (ataxia-telangiesctasia mutated) mutation (biallelic inactivation) [18].

2.2. Radiotherapy

Radiation therapy has been used to treat cancer since Röngten discovered the X-ray in 1895 [20]. High-energy radiations are applied to the whole breast or a portion of the breast (after breast-conservative surgery), chest wall (after mastectomy), and regional lymph nodes [21]. Postmastectomy radiation to the chest wall in patients with positive lymph nodes is associated with decreased recurrence risk and BC mortality compared to patients with negative lymph nodes [22]. A radiation boost to the regional node radiation treatment can be incorporated after mastectomy for patients at higher risk for recurrence [23]. Radiotherapy can be administered concurrently with personalized therapy (anti-HER2 therapy or endocrine therapy).

Radiation therapy is used to treat all BC subtypes, but its implication is more important for TNBC, as there is no personalized therapy for this subtype. It has been shown that radiotherapy benefits TNBC patients both after conserving surgery and mastectomy [24].

2.3. Chemotherapy

BC chemotherapy comprises several families of cytotoxic drugs, including alkylating agents, antimetabolites and tubulin inhibitors [25]. Cyclophosphamide is a nitrogen mustard alkylating agent causing breakage of the DNA strands [26]. The mechanism of action for anthracyclines (doxorubicin, daunorubicin, epirubicin, and idarubicin) includes DNA intercalation, thereby inhibiting macromolecular biosynthesis [27]. Taxanes, including docetaxel and paclitaxel, bind to microtubules and prevent their disassembly, leading to cell cycle arrest and apoptosis [28].

Chemotherapy can be administered in the neoadjuvant or adjuvant setting and for metastatic BC treatment.

3. Current Personalized Treatments for Breast Cancer: Strengths and Weaknesses

The current strategies of treatment are principally based on the tumor progression and BC molecular subtypes in order to offer the most personalized treatment for BC patients. The algorithm of BC treatment is represented in **Figure 2**.

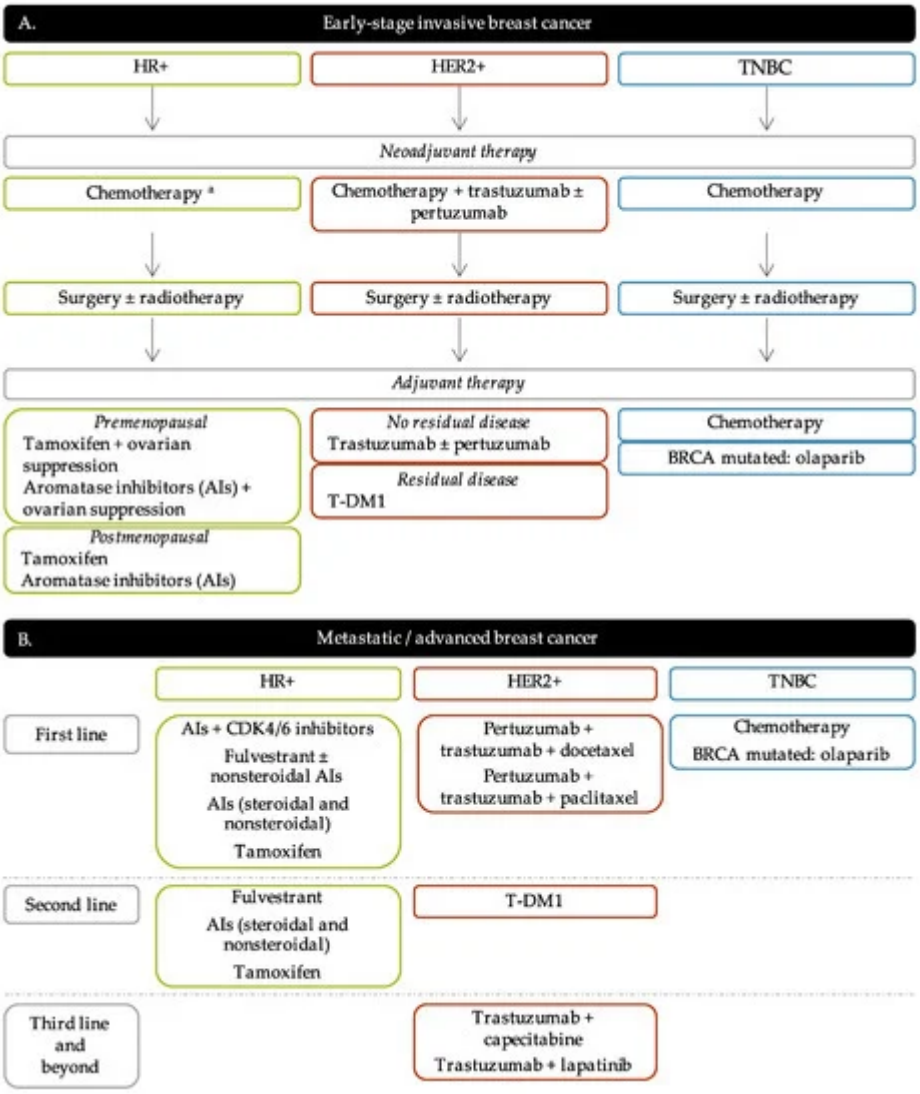

Figure 2. Breast cancer treatment flow diagram. (**A**). Early-stage breast cancer. (**B**). Metastatic/advanced breast cancer. [a] Neoadjuvant chemotherapy for HR+ BC patients is not systematic. It is mainly administered to luminal B BC patients and/or elder BC patients. HR+: hormone receptors positive; HER2+: human epidermal growth factor receptor 2 positive; TNBC: triple-negative breast cancer; AIs: aromatase inhibitors; T-DM1: trastuzumab-emtansine.

3.1. Endocrine Therapy

Endocrine therapy is the main strategy to treat HR positive invasive BC. The purpose of this therapy is to target the ER directly (selective estrogen receptors modulators and degraders) or the estrogen synthesis (aromatase inhibitors) [29]. The most common types of endocrine therapy are selective estrogen receptor modulators (SERMs), selective modulators estrogen receptor degraders (SERDs), and aromatase inhibitors (AIs) [30]. Endocrine therapy mechanism of action and resistance are described in **Figure 3**.

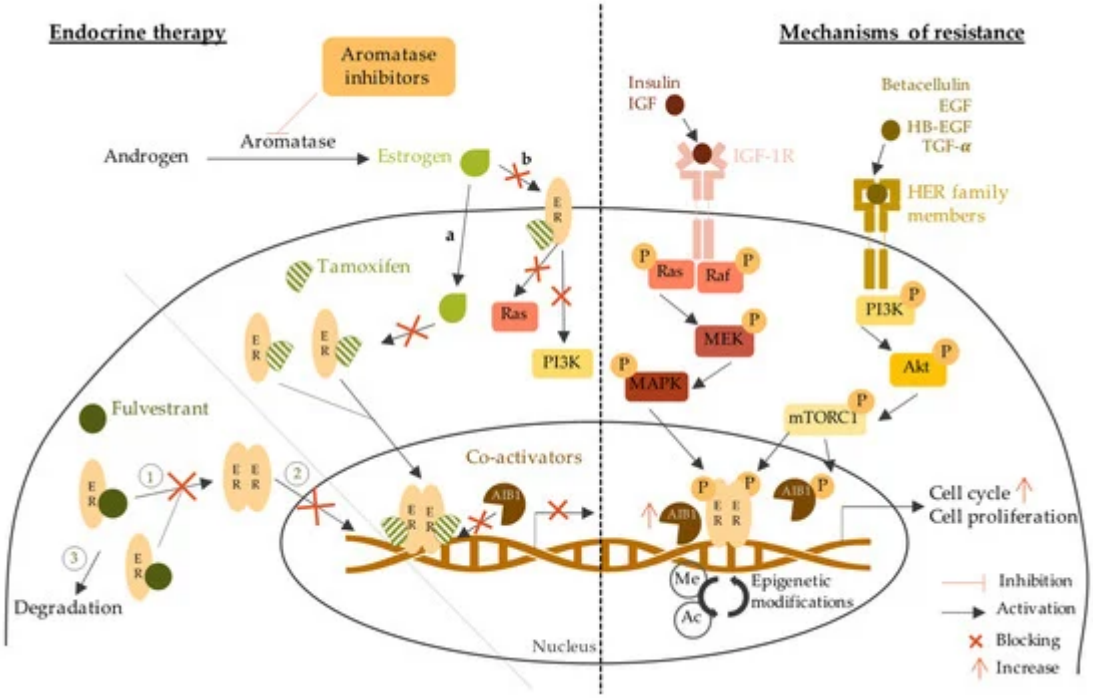

Figure 3. Endocrine therapy mechanisms of action and resistance. The left part of the figure shows the mechanism of endocrine therapy through aromatase inhibitors, tamoxifen, and fulvestrant. The right part of the figure describes the mechanisms of resistance to endocrine therapy through the epigenetic modifications, the increase of coactivators and cell cycle actors, and the activation of other signaling pathways. Estrogens can go through the plasma membrane by a. diffusion as they are small non-polar lipid soluble molecules; b. binding to membrane ER initiating the activation of Ras/Raf/MAPK and PI3K/Akt signaling pathways which are blocked by tamoxifen. 1: inhibition of ER dimerization; 2: blockage of nucleus access; 3: ER degradation. ER: estrogen receptor; AIB1: amplified in breast cancer 1; IGF-1R: insulin growth factor receptor 1; IGF: insulin growth factor; HER: human epidermal receptors; EGF: epidermal growth factor; HB-EGF: heparin-binding EGF-like growth factor; TGF-α: transforming growth factor alpha; MEK/MAPK: mitogen activated protein kinase; PI3K: phosphoinositide 3-kinase; mTOR: mammalian target of rapamycin; Me: methylation; Ac: acetylation.

3.2. Anti-HER2 Therapy

The overexpression of HER2 is associated with worse survival outcome compared to HR-positive/HER2-negative BC [31][32]. Hence, therapies targeting HER2 are essential to treat HER2-positive BC. The current anti-HER2 therapies comprise antibodies that target specific HER2 epitopes, tyrosine kinase inhibitors (TKIs) and, more recently, antibody-drug conjugates (ADCs) [33]. Anti-HER2 mechanisms of action and resistance are described in **Figure 4**.

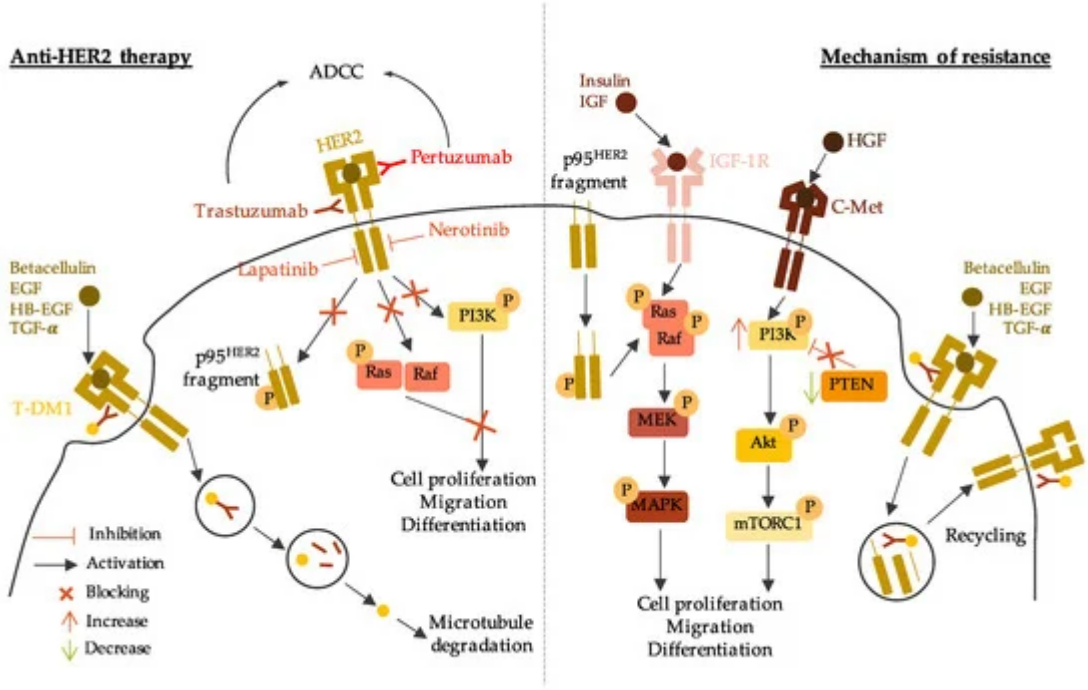

Figure 4. Anti-HER2 therapy mechanisms of action and resistance. The left part of the figure describes the mechanism of action of anti-HER2 therapy through anti-HER2 antibody (trastuzumab and pertuzumab), tyrosine kinase inhibitors (lapatinib and nerotinib), and the antibody-drug conjugate trastuzumab-emtansine (T-DM1). The right part of the figure describes the mechanism of resistance to anti-HER2 therapy through constitutive active $p95^{HER2}$ fragment, activation of other signaling pathways, and rapid recycling of HER2-T-DM1. ADCC: antibody-dependent cellular cytotoxicity; HER2: human epidermal growth factor receptor 2; EGF: epidermal growth factor, HB-EGF: heparin-binding EGF-like growth factor; TGF-α: transforming growth factor alpha; T-DM1: trastuzumab-emtansine; IGF-1R: insulin growth factor receptor 1; IGF: insulin growth factor; HGF: hepatocyte growth factor; MEK/MAPK: mitogen activated protein kinase; PI3K: phosphoinositide 3-kinase; mTOR: mammalian target of rapamycin; PTEN: phosphatase and tensin homolog.

3.3. PARP Inhibitors

The prevalence of *BRCA* (Breast Cancer genes) mutations in TNBC patients is approximately 20% [34]. BRCA1 and BRCA2 are proteins involved in the DNA damage response to repair DNA lesions [35]. Mutations in *BRCA 1/2* genes are associated with an increased risk of breast and ovarian cancers [36]. PARP (poly-(ADP-ribose) polymerase protein) proteins are also involved in the DNA damage response as they recruit DNA repair proteins, such as BRCA1 and BRCA2, to the damage site [37]. PARP inhibitors (PARPi) were developed to inhibit DNA repair in BRCA-mutated BC since cells defective in BRCA functions cannot repair DNA damage when PARP is inhibited [38]. The principal PARPis currently in clinical development are olaparib, talazoparib, veliparib, and rucaparib [39]. PARP inhibitors mechanisms of action and resistance are described in **Figure 5**.

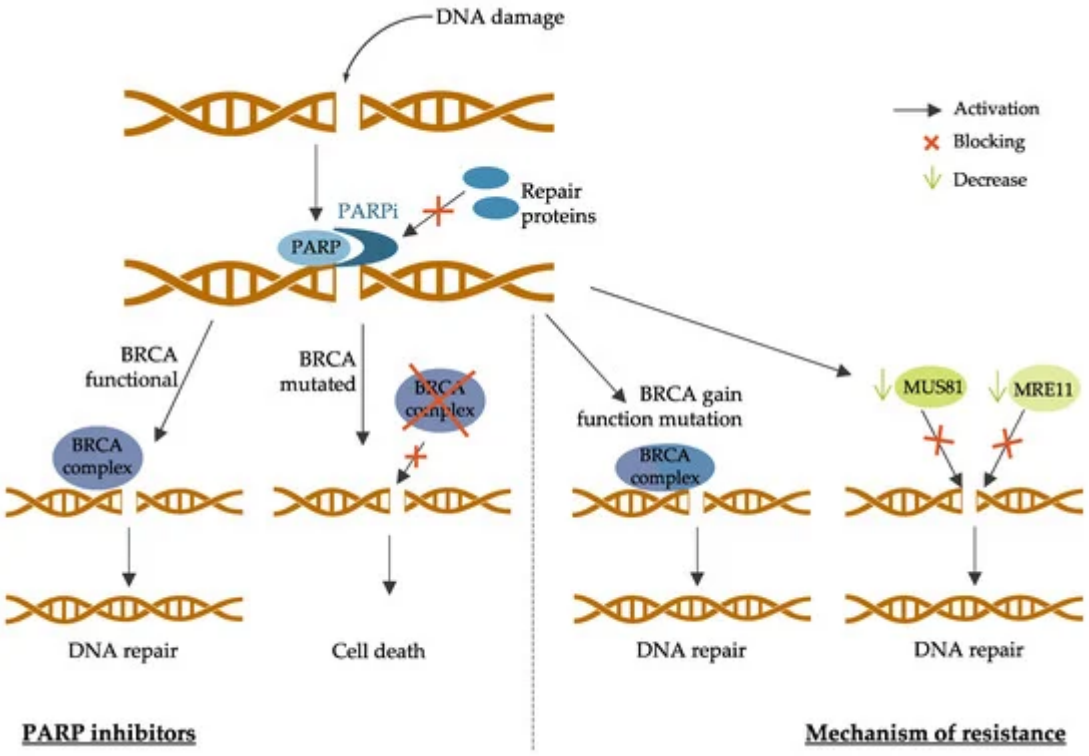

Figure 5. PARP inhibitors mechanisms of action and resistance. The left part of the figure describes the mechanism of PARP inhibitors in the context of BRCA mutated breast cancer. The right part of the figure describes the mechanism of resistance to PARP inhibitors through secondary intragenic mutations restoring BRCA proteins functions and the decrease of the recruitment of nucleases (MUS81 or MRE11) to protect the replication fork. PARP: poly-(ADP-ribose) polymerase protein; PARPi: PARP inhibitors; BRCA: breast cancer protein; MUS81: methyl methanesulfonate ultraviolet sensitive gene clone 81; MRE11: meiotic recombination 11.

4. New Strategies and Challenges for Breast Cancer Treatment

4.1. Emerging Therapies for HR-Positive Breast Cancer

The major mechanisms of action of current endocrine therapy resistance occur via (1) the mTOR/PI3K/Akt signaling pathway and (2) the actors of the cell cycle progression CDK4/6. Therefore, emerging therapies for HR+ BC mainly target the actors of these pathways to bypass estrogen-independent cell survival [40]. The most recent completed clinical trials on emerging therapies for HR+ BC are presented in **Table 1**.

Table 1. Most recent completed clinical trial on emerging therapies for HR-positive breast cancer.

Targeted Therapy	Drug Name	Trial Number	Patient Population	Trial Arms	Outcomes
Pan-PI3K inhibitors	Buparlisib	BELLE-2 Phase III NCT01610284 [41]	HR+/HER2- Postmenopausal Locally advanced or MBC Prior AI treatment	Buparlisib + fulvestrant vs. placebo + fulvestrant	PFS 6.9 months vs. 5.0 months (HR 0.78; $p = 0.00021$) PFS 6.8 months vs. 4.0 months in PI3K mutated (HR 0.76; $p = 0.014$)
		BELLE-3 Phase III NCT01633060 [42]	HR+/HER2- Postmenopausal Locally advanced or MBC Prior endocrine therapy or mTOR inhibitors	Buparlisib + fulvestrant vs. placebo + fulvestrant	PFS 3.9 months vs. 1.8 months (HR 0.67; $p = 0.0003$)
		BELLE-4 Phase II/III NCT01572727 [43]	HER2- Locally advanced or MBC No prior chemotherapy	Buparlisib + pacliatxel vs. placebo + paclitaxel	PFS 8.0 months vs. 9.2 months (HR 1.18, 95% CI 0.82–1.68) PFS 9.1 months vs. 9.2 months in PI3K mutated (HR 1.17, 95% 0.63–2.17)
	Pictilisib	FERGI Phase II NCT01437566	HR+/HER2- Postmenopausal Prior AI treatment	Pictilisib + fulvestrant vs. placebo + fulvestrant	PFS 6.6 months vs. 5.1 months (HR 0.74; $p = 0.096$)

Targeted Therapy	Drug Name	Trial Number	Patient Population	Trial Arms	Outcomes
		[44]			PFS 6.5 months vs. 5.1 months in PI3K mutated (HR 0.74; $p = 0.268$) PFS 5.8 months vs. 3.6 months in non-PI3K mutated (HR 0.72; $p = 0.23$)
		PEGGY Phase II NCT01740336 [45]	HR+/HER2- Locally recurrent or MBC	Pictilisib + paclitaxel vs. placebo + paclitaxel	PFS 8.2 months vs. 7.8 months (HR 0.95; $p = 0.83$) PFS 7.3 months vs. 5.8 months in PI3K mutated (HR 1.06; $p = 0.88$)
Isoform-specific inhibitors	Alpelisib	Phase Ib NCT01791478 [46]	HR+/HER2- Postmenopausal MBC Prior endocrine therapy	Alpelisib + letrozole	CBR 35% (44% in patients with *PIK3CA* mutated and 20% in *PIK3CA* wild-type tumors; 95% CI [17%; 56%])
		SOLAR-1 Phase III NCT02437318 [47]	HR+/HER2- Advanced BC Prior endocrine therapy	Alpelisib + fulvestrant vs. placebo + fulvestrant	PFS 7.4 months vs. 5.6 months in non-PI3K mutated (HR 0.85, 95% CI 0.58–1.25)

Targeted Therapy	Drug Name	Trial Number	Patient Population	Trial Arms	Outcomes
					PFS 11.0 months vs. 5.7 months in PI3K mutated (HR 0.65; $p = 0.00065$)
		NEO-ORB Phase II NCT01923168 [48]	HR+/HER2- Postmenopausal Early-stage BC Neoadjuvant setting	Alpelisib + letrozole vs. placebo + letrozole	ORR 43% vs. 45% (*PIK3CA* mutant), 63% vs. 61% (*PIK3CA* wildtype) pCR rates low in all groups
	Taselisib	SANDPIPER Phase III NCT02340221 [49]	HR+/HER2- Postmenopausal Locally advanced or MBC PIK3CA-mutant Prior AI treatment	Taselisib + fulvestrant vs. placebo + fulvestrant	PFS 7.4 months vs. 5.4 months (HR 0.70; $p = 0.0037$)
		LORELEI Phase II NCT02273973 [50]	HR+/HER2- Postmenopausal Early-stage BC Neoadjuvant setting	Taselisib + letrozole vs. placebo + letrozole	ORR 50% vs. 39.3% (OR 1.55; $p = 0.049$) ORR 56.2% vs. 38% in PI3K mutated (OR 2.03; $p = 0.033$) No significant difference in pCR

Targeted Therapy	Drug Name	Trial Number	Patient Population	Trial Arms	Outcomes
mTOR inhibitors	Everolimus	BOLERO-2 Phase III NCT00863655 [51]	HR+/HER2- Advanced BC Prior AI treatment	Everolimus + exemestane vs. placebo + exemestane	PFS 6.9 months vs. 2.8 months (HR 0.43; $p < 0.001$)
		TAMRAD Phase II NCT01298713 [52]	HR+/HER2- Postmenopausal MBC Prior AI treatment	Everolimus + tamoxifen vs. tamoxifen alone	CBR 61% vs. 42% TTP 8.6 months vs. 4.5 months (HR 0.54)
		PrE0102 Phase II NCT01797120 [53]	HR+/HER2- Postmenopausal MBC Prior AI treatment	Everolimus + fulvestrant vs. placebo + fulvestrant	PFS 10.3 months vs. 5.1 months (HR 0.61; $p = 0.02$) CBR 63.6% vs. 41.5% ($p = 0.01$)
Akt inhibitors	Capivasertib	FAKTION Phase II NCT01992952 [54]	HR+/HER2- Postmenopausal Locally advanced or MBC Prior AI treatment	Capivasertib + fulvestrant vs. placebo + fulvestrant	PFS 10.3 months vs. 4.8 months (HR 0.57; $p = 0.0035$)
		Phase I	ER+	Capivasertib + fulvestrant vs.	CBR 50% vs. 47%

Targeted Therapy	Drug Name	Trial Number	Patient Population	Trial Arms	Outcomes
		NCT01226316 [55]	AKT1^{E17K}-mutant MBC Prior endocrine treatment	Capivasertib alone	ORR 6% (fulvestrant-pretreated) and 20% (fulvestrant-naïve) vs. 20%
CDK4/6 inhibitors	Palcociclib	PALOMA-1 Phase II NCT00721409 [56]	HR+/HER2- Postmenopausal Advanced BC No prior systemic treatment	Palbocilib + letrozole vs. letrozole alone	PFS 20.2 months vs. 10.2 months (HR 0.488; p = 0.0004) PFS 26.1 months vs. 5.7 months (HR 0.299; $p < 0.0001$) in non-Cyclin D1 amplified PFS 18.1 months vs. 11.1 months (HR 0.508; p = 0.0046) in Cyclin D1 amplified
		PALOMA-2 Phase III NCT01740427 [57]	HR+/HER2- Postmenopausal Advanced BC No prior systemic treatment	Palbocilib + letrozole vs. placebo + letrozole	PFS 24.8 months vs. 14.5 months (HR 0.58; $p <$ 0.001)
		PALOMA-3 Phase III	HR+/HER2- MBC	Palbociclib + fulvestrant	PFS 9.5 months vs. 4.6 months (HR 0.46; $p < 0.0001$)

Targeted Therapy	Drug Name	Trial Number	Patient Population	Trial Arms	Outcomes
		NCT01942135 [58]	Prior endocrine therapy	vs. placebo + fulvestrant	
	Ribociclib	MONALEESA-2 Phase III NCT01958021 [59]	HR+/HER2- Postmenopausal Advanced or MBC	Ribociclib + letrozole vs. placebo + letrozole	PFS 25.3 months vs. 16.0 months (HR 0.568; $p < 0.0001$)
		MONALEESA-3 Phase III NCT02422615 [60]	HR+/HER2- Advanced BC No prior treatment or prior endocrine therapy	Ribociclib + fulvestrant vs. placebo + fulvestrant	PFS 20.5 months vs. 12.8 months (HR 0.593; $p < 0.001$)
	Abemaciclib	MONARCH-2 Phase III NCT02107703 [61]	HR+/HER2- Advanced or MBC Prior endocrine treatment	Abemaciclib + fulvestrant vs. fulvestrant alone	PFS 16.4 months vs. 9.3 months (HR 0.553; $p < 0.001$)
		MONARCH-3 Phase III NCT02246621 [62]	HR+/HER2- Advanced or MBC Prior endocrine treatment	Abemaciclib + anastrozole or letrozole vs. placebo + anastrozole or letrozole	PFS 28.18 months vs. 14.76 months (HR 0.546; $p < 0.0001$)

Breast Cancer. Surg. Oncol. Clin. N. Am. 2018, 27, 95–120.

Targeted Therapy	Drug Name	Trial Number	Patient Population	Trial Arms	Outcomes
Antibodies drug conjugate (ADC)	Trastuzumab-deruxtcan (DS-8201a)	DESTINY-Breast01 Phase II NCT03248492 [64]	HER2+ MBC Prior trastuzumab-emtansine treatment	Trastuzumab-deruxtcan monotherapy	PFS 16.4 months
	Trastuzumab-duocarmycin (SYD985)	Phase I dose-escalation and dose-expansion NCT02277717 [65]	HER2+ Locally advanced or metastatic solid tumors	Trastuzumab-duocarmycin monotherapy	ORR 33%

HR+: hormone receptors positive; HER2-: human epidermal growth factor receptor 2 negative; MBC: metastatic breast cancer; BC: breast cancer; PFS: progression free survival; CBR: clinical benefit rate; ORR: objective response rate; pCR: pathologic complete response; HR: hazard ratio.

4.2. New Strategic Therapies for HER2-Positive Breast Cancer

HER2+ BC is currently treated with specific HER2 targeting antibodies or tyrosine kinase inhibitors (TKIs), and more recently, with T-DM-1, an antibody-drug conjugate. These treatments have greatly improved HER2+ BC survival. However, 25% of HER2+ BC patients will still develop resistance to anti-HER2 treatment. Hence, new therapeutic strategies are emerging, such as new antibodies targeting HER2, new TKIs, vaccines, and PI3K/mTOR and CDK4/6 inhibitors [63]. The most recent completed clinical trials on new strategies for HER2+ BC treatment are gathered in **Table 2**.

Table 2. Most recent completed clinical trials on emerging therapies for HER2+ breast cancer.

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Targeted Therapy	Drug Name	Trial Number	Patient Population	Trial Arms	Outcomes
Modified antibodies	Margetuxumab (MGAH22)	SOPHIA Phase III NCT02492711 [66]	HER2+ Advanced or MBC Prior anti-HER2 therapies	Margetuximab + chemotherapy vs. trastuzumab + chemotherapy	PFS 5.8 months vs. 4.9 months (HR 0.76; $p = 0.03$) OS 21.6 months vs. 19.8 months (HR 0.89; $p = 0.33$) ORR 25% vs. 14% ($p < 0.001$)
Tyrosine kinase inhibitors	Tucatinib	HER2CLIMB Phase II NCT02614794 [67]	HER2+ Locally advanced or MBC Prior anti-HER2 therapies	Tucatinib + trastuzumab and capecitabine vs. placebo + trastuzumab and capecitabine	PFS 33.1% (7.8 months) vs. 12.3% (5.6 months) (HR 0.54; $p < 0.001$) PFS 24.9% vs. 0% (HR 0.48; $p < 0.001$) in brain metastases patients OS 44.9% vs. 26.6% (HR 0.66; $p = 0.005$)

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Targeted Therapy	Drug Name	Trial Number	Patient Population	Trial Arms	Outcomes
	Poziotinib	NOV120101-203 Phase II NCT02418689 [68]	HER2+ MBC Prior chemotherapy and trastuzumab	Poziotinib monotherapy	PFS 4.04 months
HER2-derived peptide vaccine	E75 (NeuVax)	Phase I/II NCT00841399 NCT00854789 [69]	HER2+ Node-positive or high-risk node-negative BC HLA2/3+	E75 vaccination vs. non-vaccination	DFS 89.7% vs. 80.2% (p = 0.008) DFS 94.6% in optimal dosed patients (p = 0.005 vs. non-vaccination)
	GP2	Phase II NCT00524277 [70]	HER2 (IHC 1-3+) Disease free Node-positive or high-risk node-negative BC HLA2+	GP2 + GM-CSF vs. GM-CSF alone	DFS 94% vs. 85% (p = 0.17) DFS 100% vs. 89% in HER2-IHC3+ (p = 0.08)
	AE37	Phase II NCT00524277 [71]	HER2 (IHC 1-3+) Node-positive or high-risk node-negative BC	AE37 + GM-CSF vs. GM-CSF alone	DFS 80.8% vs. 79.5% (p = 0.70) DFS 77.2% vs. 65.7% (p =

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Targeted Therapy	Drug Name	Trial Number	Patient Population	Trial Arms	Outcomes
					0.21) HER2-low DFS 77.7% vs. 49.0% (p = 0.12) TNBC
	Alpelisib	Phase I NCT02167854 [72]	HER2+ MBC with a *PIK3CA* mutation Prior ado-trastuzumab emtansine and pertuzumab	Alpelisib + Trastuzumab + LJM716	Toxicities limited drug delivery 72% for alpelisib 83% for LJM716
PI3K inhibitors		Phase I NCT02038010 [73]	HER2+ MBC Prior trastuzumab-based therapy	Alpelisib + T-DM1	PFS 8.1 months ORR 43% CBR 71% and 60% in prior T-DM1 patients
	Copanlisib	PantHER Phase Ib NCT02705859 [74]	HER2+ Advanced BC Prior anti-HER2 therapies	Copanlisib + trastuzumab	Stable disease 50%
mTOR inhibitors	Everolimus	BOLERO-1	HER2+	Everolimus + trastuzumab vs.	PFS 14.95 months vs.

progression on an aromatase inhibitor in metastatic, oestrogen receptor-positive breast cancer (FAKTION): A multicentre, randomised, controlled, phase 2 trial. Lancet Oncol. 2020, 21, 345–357.

Targeted Therapy	Drug Name	Trial Number	Patient Population	Trial Arms	Outcomes
		Phase III NCT00876395 [75]	Locally advanced BC No prior treatment	placebo + trastuzumab	14.49 months (HR 0.89; p = 0.1166) PFS 20.27 months vs. 13.03 months (HR 0.66; p = 0.0049)
		BOLERO-3 Phase III NCT01007942 [76]	HER2+ Advanced BC Trastuzumab-resistant Prior taxane therapy	Everolimus + trastuzumab and vinorelbine vs. placebo + trastuzumab and vinorelbine	PFS 7.00 months vs. 5.78 months (HR 0.78; p = 0.0067)
CDK4/6 inhibitors	Palbociclib	SOLTI-1303 PATRICIA Phase II NCT02448420 [77]	HER2+ ER+ or ER- MBC Prior standard therapy including trastuzumab	Palbociclib + trastuzumab	PFS 10.6 months (luminal) vs. 4.2 months (non-luminal) (HR 0.40; p = 0.003)
	Ribociclib	Phase Ib/II NCT02657343 [78]	HER2+ Advanced BC Prior treatment with	Ribociclib + trastuzumab	PFS 1.33 months No dose-limiting toxicities

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Targeted Therapy	Drug Name	Trial Number	Patient Population	Trial Arms	Outcomes
			trastuzumab, pertuzumab, and trastuzumab emtansine		
	Abemaciclib	MonarcHER Phase II NCT02675231 [79]	HER2+ Locally advanced or MBC Prior anti-HER2 therapies	Abemaciclib + trastuzumab and fulvestrant (A) vs. abemaciclib + trastuzumab (B) vs. standard-of-care chemotherapy + trastuzumab (C)	PFS 8.3 months (A) vs. 5.7 months (C) (HR 0.67; $p = 0.051$) PFS 5.7 months (B) vs. 5.7 months (C) (HR 0.97; $p = 0.77$)

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HER2+ human epidermal growth factor receptor 2 positive; ER+: estrogen receptor positive; HLA-A2+: human leukocyte antigen 2; EBCT: breast cancer; BC: breast cancer; PFS: progression free survival; CBR: clinical benefit rate; ORR: objective response rate; DFS: disease-free survival OS: overall survival GM-CSF: granulocyte macrophage colony-stimulated factor; HR: hazard ratio.

4.3. Emerging Therapies for Triple Negative Breast Cancer (TNBC)

TNBC is the most aggressive BC subtype. The fact that TNBC lacks ER and PR expression and does not overexpress HER2, combined with its high heterogeneity, has contributed to the difficulties in developing efficient therapies [80]. Thus, multiple strategic therapies have been developed to treat all TNBC subtypes. These include conjugated antibodies, targeted therapy, and immunotherapy. An overview of the most recent and completed clinical trials on emerging therapies for TNBC is presented in **Table 3**.

Table 3. Most recent completed clinical trials on emerging therapies for TNBC.

Targeted Therapy	Drug Name	Trial Number	Patient Population	Trial Arms	Outcomes
Antibodies Drug Conjugate	Sacituzumab govitecan	ASCENT Phase III NCT02574455 [81]	TNBC MBC Prior standard treatment	Sacituzumab govitecan vs. single-agent chemotherapy	PFS 5.6 months vs. 1.7 months (HR 0.41; $p < 0.001$) PFS 12.1 months vs. 6.7 months (HR 0.48; $p < 0.001$)
VEGF inhibitors	Bevacizumab	BEATRICE Phase III NCT00528567 [82]	Early TNBC Surgery	Bevacizumab + chemotherapy vs. chemotherapy alone	IDFS 80% vs. 77% OS 88% vs. 88%
		CALGB 40603 Phase II NCT00861705 [83]	TNBC Stage II to III	Bevacizumab + chemotherapy vs. chemotherapy alone or Carboplatin + chemotherapy vs. chemotherapy alone	pCR 59% vs. 48% (p = 0.0089) (Bevacizumab) pCR 60% vs. 44% (p = 0.0018) (Carboplatin)
EGFR inhibitors	Cetuximab	TBCRC 001 Phase II NCT00232505 [84]	TNBC MBC	Cetuximab + carboplatin	Response < 20% TTP 2.1 months

8[illegible] [illegible]nar, M.; Toi, M.; Suter, T.; Steger, G.G.; Pivot, X.; Mackey, J.; Jackisch, C.; Dent, R.; et al. Final efficacy and updated safety results of the randomized phase III BEATRICE trial evaluating adjuvant bevacizumab-containing therapy in triple-negative early breast cancer. Ann. Oncol. 2017, 28, 754–760.

Targeted Therapy	Drug Name	Trial Number	Patient Population	Trial Arms	Outcomes
		Phase II NCT00463788 [85]	TNBC MBC Prior chemotherapy treatment	Cetuximab + cisplatin vs. cisplatin alone	ORR 20% vs. 10% (p = 0.11) PFS 3.7 months vs. 1.7 months (HR 0.67; p = 0.032) OS 12.9 months vs. 9.4 months (HR 0.82; p = 0.31)
Receptor Monoclonal A					
mTORC1 inhibitors	Everolimus	Phase II NCT00930930 [86]	TNBC Stage II or III Neoadjuvant treatment	Everolimus + cisplatin and paclitaxel vs. placebo + cisplatin and paclitaxel	pCR 36% vs. 49%
Akt inhibitors	Ipatasertib	LOTUS Phase II NCT02162719 [87]	TNBC Locally advanced or MBC No prior sytemic therapy	Ipatasertib + paclitaxel vs. placebo + paclitaxel	PFS 6.2 months vs. 4.9 months (HR 0.60; p = 0.037) PFS 6.2 months vs. 3.7 moths (HR 0.58; p = 0.18) in PTEN-low patients
		FAIRLANE Phase II NCT02301988 [88]	Early TNBC Neoadjuvant treatment	Ipatasertib + paclitaxel vs. placebo + paclitaxel	pCR 17% vs. 13% pCR 16% vs. 13% PTEN-low patients pCR 18% vs. 12% PIK3CA/AKT1/PTEN-

Positive, Estrogen Receptor–Negative Metastatic Breast Cancer. Clin. Cancer Res. 2013, 19, 5505–5512.

Targeted Therapy	Drug Name	Trial Number	Patient Population	Trial Arms	Outcomes
					altered patients
	Capivasertib	PAKT Phase II NCT02423603 [89]	TNBC MBC No prior chemotherapy treatment	Capivasertib + paclitaxel vs. placebo + paclitaxel	PFS 5.9 months vs. 12.6 months (HR 0.61; p = 0.04)
Androgen receptor inhibitors	Bicalutamide	Phase II NCT00468715 [90]	HR- AR+ or AR- MBC	Bicalutamide monotherapy	CBR 19% PFS 12 weeks
	Enzalutamide	Phase II NCT01889238 [91]	TNBC AR+ Locally advanced or MBC	Enzalutamide monotherapy	CBR 25% OS 12.7 months
CYP17 inhibitors	Abiraterone acetate	UCBG 12-1 Phase II NCT01842321 [92]	TNBC AR+ Locally advanced or MBC Centrally reviewed	Abiraterone acetate + prednisone	CBR 20% ORR 6.7% PFS 2.8 months

Cancer Res. Treat. 2018, 107, 671–680.

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Targeted Therapy	Drug Name	Trial Number	Patient Population	Trial Arms	Outcomes
			Prior chemotherapy		
Anti-PDL1 antibodies	Atezolizumab	Impassion 130 Phase III NCT02425891 [93]	TNBC Locally advanced or MBC No prior treatment	Atezolizumab + nab-paclitaxel vs. placebo + nab-paclitaxel	OS 21.0 months vs. 18.7 months (HR 0.86; $p = 0.078$) OS 25.0 months vs. 18.0 months (HR 0.71, 95% CI 0.54–0.94)) in PDL-1+ patients
		Impassion 031 Phase III NCT03197935 [94]	TNBC Stage II to III No prior treatment	Atezolizumab + chemotherapy vs. placebo + chemotherapy	pCR 95% vs. 69% $p = 0.0044$
	Durvalumab	GeparNuevo Phase II NCT02685059 [95]	TNBC MBC Stromal tumor-infiltrating lymphocyte (sTILs)	Durvalumab vs. placebo	pCR 53.4% vs. 44.2% pCR 61.0% vs. 41.4% in window cohort
		SAFIRO BREAST-IMMUNO	HER2- MBC	Durvalumab vs. maintenance chemotherapy	HR of death 0.37 for PDL-1+ patients

Targeted Therapy	Drug Name	Trial Number	Patient Population	Trial Arms	Outcomes
		Phase II NCT02299999 [96]	Prior chemotherapy		HR of death 0.49 for PDL-1- patients
		Phase I NCT02484404 [97]	Recurrent women's cancers including TNBC	Durvalumab + cediranib + olaparib	Partial response 44% CBR 67%
	Avelumab	JAVELIN Phase Ib NCT01772004 [98]	MBC Prior standard-of-care therapy	Avelumab monotherapy	ORR 3.0% overall ORR 5.2% in TNBC ORR 16.7% in PDL-1+ vs. 1.6% in PDL-1- overall ORR 22.2.% in PDL-1+ vs. 2.6% in PDL-1- in TNBC
Anti-PD1 antibodies	Pembrolizumab	KEYNOTE-086 Phase II NCT02447003 [99]	TNBC MBC Prior or no prior systemic therapy	Pembrolizumab monotherapy	Previously treated patients: ORR 5.3% overall ORR 5.7% PDL-1+ patients PFS 2.0 months OS 9.0 months

Targeted Therapy	Drug Name	Trial Number	Patient Population	Trial Arms	Outcomes
					Non-previously pretreated: ORR 21.4% PFS 2.1 months OS 18.0 months
		KEYNOTE-119 Phase III NCT02555657 [100]	TNBC MBC Prior systemic therapy	Pembrolizumab vs. chemotherapy	OS 12.7 months vs. 11.6 months (HR 0.78; $p = 0.057$) in PDL1+ patients OS 9.9 months vs. 10.8 months (HR 0.97, 95% CI 0.81–1.15)
		KEYNOTE-355 Phase III NCT02819518 [101]	TNBC MBC No prior systemic therapy	Pembrolizumab + chemotherapy vs. placebo + chemotherapy	PFS 9.7 months vs. 5.6 months (HR 0.65; $p = 0.0012$) in PDL-1+ patients PFS 7.6 months vs. 5.6 months (HR 0.74; $p = 0.0014$)
		KEYNOTE-522 Phase III NCT03036488 [102]	Early TNBC Stage II to III No prior treatment	Pembrolizumab + paclitaxel and carboplatin vs. placebo + paclitaxel and carboplatin	pCR 64.8% vs. 51.2 % ($p < 0.001$)

Targeted Therapy	Drug Name	Trial Number	Patient Population	Trial Arms	Outcomes
Anti-CDL4 antibodies	Tremelimumab	Phase I [103]	Incurable MBC	Tremelimumab + radiotherapy	OS 50.8 months
Vaccines	PPV	Phase II UMIN000001844 [104]	TNBC MBC Prior systemic therapy	PPV vaccine	PFS 7.5 months OS 11.1 months
	STn-KLH	Phase III NCT00003638 [105]	MBC Prior chemotherapy Partial or complete response	STn-KLH vaccine vs. non-vaccine	TTP 3.4 months vs. 3.0 months

TNBC: triple negative breast cancer; HER2: human epidermal growth factor receptor; HR: hormonal receptor; MBC: metastatic breast cancer; BC: breast cancer; AR: androgen receptor; PPV: personalized peptide vaccine; PFS: progression free survival; CBR: clinical benefit rate; ORR: objective response rate; IDFS: invasive disease-free survival; OS: overall survival; TTP: time to progression; pCR: pathologic complete response; HR: hazard ratio.