Emerging Targeted Therapies for HER2-Positive Breast Cancer

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HER2-positive (HER2+) breast cancer, which accounts for ~20% of breast cancer, is one of the more aggressive and has the worst overall survival rate among them. These patients are treated with trastuzumab, a monoclonal antibody targeting the HER2 molecule. Even though trastuzumab is an effective therapy, resistance events hamper its clinical benefit, making the development of new therapies a constantly growing area of interest.

breast cancer HER2 therapies

1. Monoclonal and Bispecific Antibodies

In this section researchers summarized the different therapies directed to HER2 that are currently part of the therapeutic landscape of HER2+ breast cancer such as monoclonal and bispecific antibodies, tyrosine kinase inhibitors (TKI), antibody-drug conjugates (ADC) and their combination with anti-immune checkpoint inhibitors (ICIs). Researchers described the current first line of the standard of care treatment which is the combination of trastuzumab, pertuzumab and taxanes, and the novel HER2-targeted antibodies directed to the same binding epitopes as the already approved monoclonal antibodies or different ones to achieve therapeutic effectiveness (margetuximab and 1E11).

Bispecific antibodies (BsAb) are antibodies that can bind two different antigens on the same or different molecule and are classified into two groups: the ones that have two Fabs and a Fc region (trifunctional antibodies) and the ones that do not have the latter. They exert their function through antibody-dependent cell phagocytosis (ADCP) and antibody-dependent cell cytotoxicity (ADCC), complement dependent cytotoxicity, inhibition of signaling pathways through interaction with membrane receptors and induction of apoptosis. The current state-of-the-art on BsAbs has been extensively reviewed [1]. Since several BsAbs have been developed and tested throughout the years, in this section researchers will summarize those that target the HER2 molecule and have promising results in preclinical or clinical trials (**Table 1**). Regarding the BsAbs, researchers mentioned HER2/HER2, HER2/HER3, HER2/CD3 and HER2/CD16 BsAbs. Lastly, the main adverse events for bispecific antibodies consist of cytokine release syndrome (CRS) of grades 3 and 4 [2][3], which has been suggested to be avoided by retention of the Fc portion of the antibodies. The development of BsAb is a rapidly growing field, which is reflected in the plethora of antibodies being generated and tested in clinical and preclinical models. In the next few years, the ongoing clinical trials will be completed and could change the management of HER2+ breast cancer patients in the clinic.

Table 1. Bispecific antibodies for HER2+ breast cancer in clinical trials.

Drug	Clinical Trial Identifier	In Combination with	Population	Reference
Trastuzumab/pertuzumab				
MBS301	NCT03842085		Malignant HER2-expressing solid tumors	[4]
Zanidatamab (ZW25)	NCT02892123	Chemotherapy	HER2-expressing solid tumors	[5][6]
	NCT05035836		Early HER2+ breast cancer	
	NCT04224272	Palbociclib and fulvestrant	Advanced HER2+ breast cancer	
	NCT05027139	Anti-CD47	Solid HER2+ tumors including the HER2-low breast cancer	
	NCT04881929	Chemotherapy	HER2+ breast cancer	
KN026	NCT04521179 NCT04040699	KN046 (bispecific antibody against PD-1 and CTLA-4)	Locally advanced HER2+ solid tumors and HER2+ solid tumor	[7]
	NCT04778982	Palbociclib and fulvestrant	Advanced breast cancer	
HER2/HER3				

Zenocutuzumab (MCLA-128)	NCT03321981	Trastuzumab and chemotherapy or trastuzumab and vinorelbine	HER2-low breast cancer and metastatic HER2+ breast cancer that progressed to T-DM1 treatment	[8]
MM-111	NCT01097460	Trastuzumab	Advanced HER2 amplified and heregulin-positive breast cancer	
	NCT00911898		Advanced, refractory HER2 A\amplified and heregulin-positive cancers	

2. Antibody-Drug Conjugates

Another striking approach for the treatment of cancer in the last few years are the antibody-drug conjugates (ADC), which take advantage of the specific targeting of monoclonal antibodies and combines it with drugs with potent cytotoxic effects, achieving targeted drug delivery [9]. The ADCs as a whole have a synergistic effect when compared to their parts alone; this is mainly due to the bystander killing effect, in which the drug payload can exert its effect not only on the target cells but also in the TME [10]. In addition, the ADCs have demonstrated that they are effective even when the target protein is expressed in small amounts. In HER2+ breast cancer, trastuzumab-emtansine (T-DM1) made its debut to revolutionize the field [11], and ADCs are being developed in hopes of better treatment options. In this sense, ADCs have shown promising results against brain metastases [12] and in HER2-low breast cancer [13]. There are currently 14 FDA-approved ADCs for various cancers, with the target molecule, conjugated drugs, and/or the linkers varying. Adverse events of ADCs account for 10–15% [14][15], and the most common are fatigue, neuropathies, leukopenia, thrombocytopenia, pneumonitis, interstitial lung disease, and nausea [16][17][18]. The preeminent trastuzumab-based ADCs used in the clinical setting and those that have shown promising results in preclinical models are shown in **Table 2**.

Table 2. Current clinical trials of ADCs in HER2+ breast cancer.

Drug	Payload	Drug-to-Antibody	Clinical Trial Identifyer	In Combination	Population	Reference

		Ratio	with		
			NCT04784715	Pertuzumab	HER2+ metastatic breast cancer	
			NCT04538742	Durvalumab (anti-PD-L1,)	HER2+ metastatic breast cancer	
T-DXd	Deruxtecan (topoisomerase I inhibitor)	~8	NCT04538742, NCT04539938	Tucatinib	HER2+ breast cancer or HER2+ metastatic breast cancer	
			NCT04556773	Durvalumab, paclitaxel, capivasertib, anastrozole, fulvestrant, or capecitabine	HER2-low advanced or metastatic breast cancer	[19]
Trastuzumab-duocarmycine (SYD985)	Duocarmycine (DNA alkylating agent)	2.8	NCT03262935		HER2+ locally advanced or metastatic breast cancer	[20]
			NCT01042379 (I-SPY)	Chemotherapy	Breast cancer	
			NCT04602117 (ISPY-P1.01)	Paclitaxel	Metastatic cancer	

			NCT04235101	Niraparib (PARP inhibitor)	Solid tumors	
ARX788	Amberstatin 269 (microtubule inhibitor)	2	NCT01042379		HER2+ breast cancer	
			NCT04829604, NCT02512237		HER2+ metastatic breast cancer	
			NCT05041972		HER2-mutated or HER2-amplified tumors	
			NCT05018676		HER2-low breast cancer	
			NCT05018702		Breast cancer patients with brain metastasis	
Disitamab vedotin (RC48)	Monomethyl auristatin E (microtubule inhibitor)	4	NCT03255070		HER2+ solid tumors	[21]
			NCT02881190		Advanced or metastatic HER2+ tumors	
			NCT05134519		HER2+ breast cancer	
			NCT04400695		Locally advanced or metastatic	

					HER2-low breast cancer	
			NCT05331326		HER2-expression metastatic breast cancer with abnormal activation of PAM pathway	
			NCT03052634		Advanced breast cancer	
			NCT05726175	Penpulimab (AK105)	HER2-low breast cancer	
			NCT03500380		HER2+ metastatic breast cancer with or without liver metastases	
A166	Duo-5 (microtubule inhibitor)	2.8	NCT03602079		Relapsed/refractory cancers wxpressing HER2 antigen or amplified HER2 gene	[22][23][24]
MRG002	Monomethyl auristatin E (microtubule inhibitor)	~3.8	NCT05263869		HER2+ advanced breast cancer	
			NCT04924699		HER2+ metastatic tumors	
			NCT04742153		HER2-low locally advanced	

					metastatic breast cancer	
Zanidatamab zovodotin (ZW49)	Auristatin based (microtubule inhibitor)	2	NCT03821233		Metastatic HER2+ tumors	
BDC-1001	TLR7/8 agonist	Not reported	NCT04278144	Nivolumab	Advanced HER2-expressing solid tumors	[25]
ALT-P7	Monomethyl auristatin E (microtubule inhibitor)	2	NCT03281824		HER2+ breast cancer	[26]
XMT-1522	Auristatin derivative (AF-HPA)	12	NCT02952729		Advanced HER2+ breast cancer patients	[27]
PF-06804103	Derivative of auristatin	4	NCT03284723		HER2+ breast cancer	[28]
Targeted thorium-227 conjugates (TTCs)/BAY2701439	Thorium-227 (cytotoxic alpha radiation)	Not reported	NCT04147819		Advanced HER2-expressing cancer	

3. Tyrosine Kinase Inhibitors

TKIs are a family of small molecules that inhibit protein tyrosine kinases, which are responsible for signal transduction to regulate cellular, physiological, and biochemical processes. TKIs compete with ATP in tyrosine kinase receptors' ATP binding domain, inhibiting downstream signaling [29]. In this sense, TKIs can inhibit cell proliferation, migration, and invasion and induce apoptosis. Due to their size, TKIs can cross the blood-brain barrier

more easily than other HER2-targeted therapies such as monoclonal antibodies or ADCs [30]. Several TKIs that target the HER2 family are currently approved for the treatment of cancer in combination with other therapies, and this area is still being researched due to resistance events that impair their effectiveness and off-target toxicity which usually implies diarrhea, rash, infections, and hepatic toxicity [31][32].

Lapatinib was the first FDA-approved TKI for the treatment of HER2+ and HER2-low breast cancer [33]. Is a reversible small molecule inhibitor of EGFR/HER1 and HER2 that blocks the phosphorylation of the receptors, which inhibits the activation of the MAPK and PI3-K pathways and consequently inhibits cell proliferation [34]. Lapatinib showed penetration of the blood-brain barrier and exhibited a reduction in brain metastases, as it was reported in the EGF105084 [35], LANDSCAPE [36], and CEREBEL [37] clinical trials. In this regard, Khan et al. reported intracranial activity of lapatinib and increased survival for HER2+ breast cancer patients with brain metastases in a meta-analysis [38]. Currently, lapatinib is FDA-approved for breast cancer treatment in combination with letrozole or capecitabine in hormone receptor positive and HER2+ breast cancer, or with capecitabine or with trastuzumab for receptor positive and HER2+ postmenopausal patients, in which case an increase in PFS was observed but no benefit in overall survival [39]. Lapatinib is not currently approved for its use in the neoadjuvant setting.

Neratinib is an irreversible pan-HER inhibitor that not only has a greater effect than lapatinib but also can increase trastuzumab-mediated ADCC [40][41][42][43]. Preclinical studies showed that neratinib induces cell cycle arrest and proliferation inhibition in HER2-expressing cells [44]. In the exteNET clinical trial, neratinib showed a 73% rate of response in patients with HER2+ metastatic breast cancer previously treated with adjuvant or neoadjuvant trastuzumab, but on the other hand, it exhibited high toxicity, which led to dose reduction and treatment of the adverse events diarrhea [45][46][47][48]. When tested in patients with early HER2+ breast cancer, the results were as promising as for the advanced cases, since neratinib showed an improvement in disease-free survival [49]. Neratinib in combination with lapatinib showed better tolerability and effectiveness than lapatinib alone [50]. Neratinib is currently being tested in combination with other therapies such as T-DM1 (NCT02236000) [51] and fulvestrant (NCT03289039) [52][53]. Regarding brain metastases, neratinib showed a reduced incidence of central nervous system events [54][55][56]. Given these clinical trial results, adjuvant neratinib was FDA-approved in 2017 for patients with HER2+ breast cancer who were previously treated with adjuvant trastuzumab for one year, and it is also administered in combination with capecitabine since 2020 for patients who received at least two previous anti-HER2 treatments [57].

Tucatinib is a selective HER2 TKI with reduced inhibition on EGFR that exhibited antitumor activity in breast and gastric tumors in preclinical models administered as a monotherapy [58] or in combination with trastuzumab in HER2+ breast cancer xenograft models [59]. These results led to the development of a phase 1 clinical trial (HER2CLIMB and NCT02614794) to test tucatinib in combination with trastuzumab and capecitabine, which showed great antitumor effect in metastatic breast cancer with the only adverse events being diarrhea, nausea, and palmo-plantar erythrodysesthesia [60]. Given the results of the phase 3 HER2CLIMB [61] trial, tucatinib was approved by the FDA in 2020 to treat patients with metastatic HER+ breast cancer. Tucatinib also showed improved efficacy in reducing brain metastasis [62][63]. Considering these results, tucatinib is the first TKI that was

approved by the FDA for the treatment of brain metastases. Due to the promising results of tucatinib, there are several clinical trials exploring the effect of the combination of tucatinib with T-DM1 (NCT04457596, NCT03975647, NCT01983501, and NCT05323955), with T-DXd (NCT04539938 and NCT04538742), and with CDK4/6 inhibitors (NCT03054363) in HER2+ breast cancer patients.

The TKIs that are currently being used in the clinic and those that have been successful in preclinical or clinical trials and could offer therapeutic alternatives are shown in **Table 3**.

Table 3. Current clinical trials of selected TKIs in HER2+ breast cancer.

Drug	Description	In Combination with	Clinical Trial Identifyer	Population	Reference
Tucatinib	Selective and reversible HER2 inhibitor with minimal inhibition of EGFR/HER1	T-DM1	NCT04457596, NCT03975647, NCT01983501, NCT05323955	HER2+ breast cancer	
		T-DXd	NCT04539938, NCT04538742	HER2+ breast cancer	
Pyrotinib	Irreversible pan-HER inhibitor		NCT01937689	HER2+ metastatic breast cancer	[64]
		Capecitabine	NCT02361112	HER2+ metastatic breast cancer	[65]
Poziotinib	Irreversible pan-HER inhibitor	T-DM1	NCT03429101	HER2+ breast cancer	
Epertinib (S-222611)	Reversible pan-HER inhibitor		2013-003894-87	HER2+ tumors	[66][67][68]

DZD1516	Selective HER2 inhibitor	Trastuzumab and capecitabine or T-DM1	NCT04509596	Metastatic HER2+ breast cancer	[69]

4. HER2-Targeted Therapies in Combination with Immunotherapy

Despite the efforts for developing new strategies against the HER2 molecule, there are still a 20% of the patients with local disease who experience de novo or acquired resistance to the HER2-targeted therapies [70]. In particular, the in vivo mechanism of action of trastuzumab and trastuzumab-based therapies relies on the innate and adaptive immune response. ADCC and ADCP, mainly performed by NK cells and macrophages, respectively, trigger an innate immune response that promotes antigen presentation and the subsequent adaptive immune response [71][72][73][74]. This evidence and preclinical data point out that using ICI enhances the trastuzumab antitumor effect, providing the rational basis for the combination of ICI with HER2-targeted therapies to overcome therapy resistance [75]. The combination of ICIs and HER2-targeted therapies that were or are being tested in the clinical setting are listed in **Table 4**.

Table 4. Clinical trials combining immunotherapies with HER2-targeted therapies.

ID	Type of Study	Status	No. Patients	Population	Treatment
Pembrolizumab (anti PD-1 antibody)					
NCT02129556 PANACEA	Phase 1/2 Single arm	Completed	58	Metastatic HER2+ breast cancer, trastuzumab-resistant	Pembrolizumab with trastuzumab [76]
NCT03747120	Phase 2 open-label, randomized	Recruiting	174	Naive patients with invasive human HER2+ breast cancer whose primary tumors are >	Neoadjuvant trastuzumab, pertuzumab, and paclitaxel Arm A: trastuzumab + pertuzumab +

				2 cm and/or clinically lymph node-positive	paclitaxel, Arm B: trastuzumab + pertuzumab + paclitaxel+ pembrolizumab or Arm C: trastuzumab + pembrolizumab + paclitaxel [77].
NCT03032107	Phase 1b	Active, not recruiting	27	Metastatic HER2+ breast cancer	Pembrolizumab + T-DM1
NCT04789096 TUGETHER	Two arms, phase 2	Not yet recruiting	50	Women or men with HER2+, metastatic breast cancer, who have progressed since previous treatment	Pembrolizumab + tucatinib + trastuzumab (PD-L1+) or Pembrolizumab + tucatinib + trastuzumab + capecitabine (PD-L1-)
NCT04660929	Phase 1, open label	Recruiting	48	HER2+ recurrent or metastatic solid tumors	Anti-HER2 CAR macrophages + pembrolizumab
NCT05020860 I-SPY trial	Phase 2, open label	Not yet recruiting	185	Early HER2+ breast cancer	Neoadjuvant paclitaxel + trastuzumab + pertuzumab in combination with pembrolizumab
NCT03272334 Breast-47	Phase 1/2	Recruiting	33	Metastatic HER2+ breast cancer	Pembrolizumab administered in

					combination with HER2 and CD3 bispecific antibody armed activated T cell (BATs) infusions
Atezolizumab (anti-PD-L1 antibody)					
NCT02924883 KATE2	Phase 2, double blind	Completed	133	Locally advaced or metastatic HER2+ breast cancer	Atezolizumab and trastuzumab-emtansine (T-DM1) Arm 1: T-DM1 + atezolizumab, Arm 2: T-DM1 + placebo [78]
NCT04740918 KATE3	Phase 3, doble blind	Recruiting	320	Locally advanced or metastatic HER2+ and PD-L1+ breast cancer who have received prior trastuzumab- (+/− pertuzumab) and taxane-based therapies	Atezolizumab and T-DM1 Arm A: T-DM1 + placebo, Arm B: T-DM1 + atezolizumab
NCT03726879 IMpassion050	Phase 3, doble blind	Active, not recruiting	454	High-risk early HER2+ breast cancer	Atezolizumab or placebo in combination with neoadjuvant doxorubicin + cyclophosphamide followed by paclitaxel + trastuzumab +

					pertuzumab (ddAC-PacHP) Arm 1: Atezolizumab + ddAC-PacHP. Arm 2: placebo + ddAC-PacHP [79]
NCT04873362 Astefania	Phase 3, doble blind	Recruiting	1700	High risk HER2+ breast cancer following preoperative therapy	Adjuvant atezolizumab or placebo and T-DM1. Arm A: placebo + T-DM1. Arm B: Atezolizumab + T-DM1 [80]
NCT02605915	Phase 1, open label	Completed	98	HER2+ and HER2− breast cancer	Atezolizumab + T-DM1 or with trastuzumab and pertuzumab (with and without docetaxel) in patients with HER2+ breast cancer and atezolizumab + doxorubicin and cyclophosphamide in HER2− breast cancer
NCT03417544	Phase 2	Active, not recruiting	33	Central nervous system metastases in patients with	Atezolizumab + pertuzumab + high-dose trastuzumab

				HER2+ breast cancer	
NCT03199885	Phase 3, doble blind	Active, not recruiting	600	First-line metastatic HER2+ breast cancer	Arm I: pertuzumab + trastuzumab + taxane therapy + atezolizumab. Arm II: pertuzumab + trastuzumab + taxane therapy + placebo
NCT04759248 ATREZZO	Phase 2, open label	Recruiting	110	Advanced/metastatic HER2+ breast cancer	Atezolizumab + trastuzumab + vinorelbine
NCT03595592 APTneo	Phase 3, open label	Active, not recruiting	650	Early high-risk and locally advanced HER2+ breast cancer	Arm 1:Trastuzumab + pertuzumab + carboplatin + paclitaxel (HPCT). Arm 2: Doxorubicin + cyclophosphamide (AC) followed by HPCT + atezolizumab, Arm 3: HPCT + atezolizumab
			Durvalumab (anti PD-L1 antibody)		
NCT02649686 CCTG IND.229	Phase 1, open label	Completed	15	Metastatic HER2+ breast cancer	Durvalumab + trastuzumab [81]

				receiving trastuzumab	
NCT04538742 DB-07	Phase 1b/2, open label	Recruiting	450	Metastatic HER2+ breast cancer	Trastuzumab Deruxtecan (T-DXd) in Combination With Other Anti-cancer Agents
Avelumab (anti PD-L1 antibody)					
NCT01772004 JAVELIN solid tumor	Phase 1, open label	Completed	1756	Metastatic or locally advaced solid tumors	Avelumab monotherapy to 26 HER2+ breast cancer [82]
NCT03414658 AVIATOR	Phase 2, open label	Recruiting	100	Advanced HER2+ breast cancer	Trastuzumab + vinorelbine with avelumab or avelumab + utomilumab (anti CD137)
Monalizumab (anti-NKG2A antibody)					
NCT04307329 MIMOSA	Phase 2, open label	Active, not recruiting	38	Metastatic HER2+ breast cancer	Molalizumab + trastuzumab in cohort of low TILS (< 5%) or cohort of high TILS (≥ 5%) [83]
IMM2902 (HER2/SIRPα Bispecific mAb-Trap Antibody-receptor Fusion Protein)					

NCT05076591	Phase 1, open label	Recruiting	135	Advanced solid tumors HER2+	IMM2902, dose escalation
Utomilumab (anti-CD137 antibody)					
NCT03414658 AVIATOR	Phase 2, open label	Recruiting	100	Advanced HER2+ breast cancer	Trastuzumab + vinorelbine with avelumab or avelumab + utomilumab (anti CD137)
NCT03364348	Phase 1, open label	Completed	18	Advanced HER2+ breast cancer	Utomilumab + T-DM1 or trastuzumab

The full research also addresses the combination of ICIs and BsAb, the enhancement of ADCP, ADCC or the adaptive immune response through immunotherapy in combination with HER2-targeted therapies, cell therapies (such as CAR-T, CAR-M or CAR-NK), anti-cancer vaccines and exosome-based therapies for the treatment of HER2+ or HER2-low breast cancer.

5. Conclusions

Since the description of the HER2 receptor as a biomarker and an attractive therapeutic target for HER2+ breast cancer, several drugs have been developed, with trastuzumab dominating the treatment landscape for this breast cancer subtype. However, resistance events impair the clinical benefit, indicating that the development of novel HER2-targeted therapies is not only desirable but also required. In this sense, there are more than 2000 clinical trials registered to date to evaluate new HER2-targeted therapies. Along with drug development, new tools, such as single-cell sequencing, theranostics, spatial transcriptomics, and proteomics, have been developed in tandem with the technological advances. The HER2+ landscape treatment can count on multiple HER2-targeting monoclonal antibodies, HER2-targeted ADCs, which have proven to be promising in the clinical setting; for example, T-DXd became the second line of treatment for HER2+ breast cancer patients. Several new TKIs have been developed and tested, among others, that have improved the management of HER2+ breast cancer patients and will change clinical practice. One of the main complications in cancer is the establishment of metastasis, and in this sense, some of the therapies mentioned in this research have shown to be effective in the metastatic setting. All the above-mentioned initiatives encourage the scientific community to collaborate on the development of new

HER2-targeted therapies and clinical trials testing different treatment combinations that could overcome tumor progression or even metastasis. The importance of discovering new biomarkers that can predict therapy response must be emphasized in this regard, as this will allow researchers to determine which patients will benefit from which therapies or combination treatments offer them the best treatment option.

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