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Beyond HER2: Targeting the ErbB Receptor Family in Breast Cancer

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Abstract

Targeting the HER2 oncogene represents one of the greatest advances in the treatment of breast cancer. HER2 is one member of the ERBB-receptor family, which includes EGFR (HER1), HER3 and HER4. In the presence or absence of underling genomic aberrations such as mutations or amplification events, intricate interactions between these proteins on the cell membrane lead to downstream signaling that encourages cancer growth and proliferation. In this Review, we contextualize efforts to pharmacologically target the ErbB receptor family beyond HER2, with a focus on EGFR and HER3. Preclinical and clinical efforts are synthesized. We discuss successes and failures of this approach to date, summarize lessons learned, and propose a way forward that invokes new therapeutic modalities such as antibody drug conjugates (ADCs), combination strategies, and patient selection through rational biomarkers.

I. Introduction

The ErbB family is comprised of four transmembrane growth factor receptors which are closely related: EGFR (or HER1), HER2, HER3 and HER4 [1]. These proteins are critical for the development of normal cells, but when dysregulated, can promote disordered proliferation, invasion, and unchecked cell survival leading to the development of cancer [2]. Intricate and complex interactions between these receptors, in the presence or absence of extracellular ligands, results in activation of downstream signaling primarily via the PI3K/AKT, MAP kinase, and JAK/STAT pathways [3, 4] (figure 1). Such aberrant signaling is typically caused by mutations or amplification of ErbB family genes, leading to increased homo- or hetero-dimerization and constitutively active kinase activity with resultant downstream signaling [4]. A high-level structural homology exists between members of the ErbB receptor family, with an extracellular ligand binding domain, a transmembrane helix and a cytoplasmic domain which possesses enzymatic activity. However, notable exceptions include the fact that HER2 does not have a direct ligand and HER3 has impaired kinase activity [5]. Interactions between these proteins on the cell surface are highly interrelated,

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forming a complex signaling network where no individual member functions in isolation, and cooperation is the rule rather than the exception [6].

In breast cancer, 15–20% of tumors specifically overexpress HER2 due to ERBB2 gene amplification, resulting in a cancer phenotype that is highly aggressive if left untreated [7]. The capability to pharmacologically target the HER2 oncoprotein represents one of the great triumphs of oncologic science, and has transformed the prognosis of this this disease, resulting in meaningful improvements in overall survival for patients with early or advanced HER2-positive breast cancers, as reviewed elsewhere [8]. Given the intricate relationships between the four ErbB family members in their individual/collective contribution to oncogenesis, renewed interest has arisen in how these interactions can be harnessed to improve upon the tissue specificity and cytotoxicity of existing therapies. In this review, we focus on how targeting ErbB proteins beyond HER2, including epidermal growth factor receptor (EGFR), HER3, and HER4 might improve outcomes for patients with breast cancer. We briefly review historical attempts to target these proteins as well as novel strategies, including monoclonal antibodies (mABs), tyrosine kinase inhibitors (TKIs) and antibody drug conjugates (ADCs).

II. EGFR (HER1)

EGFR, one of the most canonical oncogenes in cancer medicine, is encoded by the *EGFR* gene on chromosome 7p11, and was identified first in the 1970s [9]. Known ligands of EGFR are numerous, and include EGF, TGF-alpha, and amphiregulin, among several others [10]. In the presence or absence of a ligand, the major heterodimerization partner for EGFR is HER2. When paired, EGFR and HER2 form stable activated complexes, which are endocytosed at a slow rate and readily recycled to the cell surface (rather than degraded), resulting in strong and long-lived signaling activation [10]. Targeting EGFR with oral tyrosine kinase inhibitors or mABs has been a successful strategy in many cancer subtypes, including non-small lung cancer [11], colorectal cancer [12], and head and neck cancer [13].

EGFR is overexpressed in up to 66% of basal-like and triple negative breast cancers (TNBC); in the absence of hormone receptor expression, EGFR expression has been used historically as a lineage marker for these subtypes of breast cancer as well as a poor prognostic indicator [14, 15]. For these reasons, efforts to target EGFR in breast cancer have focused largely on TNBC [16]. It has been hypothesized that overexpression of EGFR in TNBC is largely attributable to post-transcriptional changes or gene duplication, since true gene amplifications and activating mutations are relatively rare, occurring in around 2% and 3% of TNBCs respectively [16, 17].

Preclinical studies have shown activity of EGFR antagonists against breast cancer cell lines, as well as potential synergies between EGFR targeted therapies and cytotoxic therapies *in vitro* [18]. However, clinical efforts to target EGFR in TNBC have largely been unsuccessful to date, characterized by increased toxicity, outweighing any additional clinical benefit observed [16]. Despite over a dozen phase I and II clinical trials investigating agents including the EGFR mABs cetuximab, panitumumab, and nimotuzumab, and TKIs such as gefitinib, erlotinib, afatinib, icotinib, no therapies that specifically target EGFR have been

approved for the treatment of breast cancer, as monotherapy or part of a combinatorial strategy [16, 18]. For example, cetuximab has been investigated in metastatic triple negative breast cancer in combination with taxanes [19], platinum agents [20, 21], and irinotecan [22], without any signal for increased activity over single agent chemotherapy. Erlotinib monotherapy had very limited activity in an unselected population of advanced breast cancers [23]. Gefitinib has been investigated as a single agent in advanced breast cancers with very few if any responses [24, 25], with similar results observed with afatinib [26].

The reason for this outcome may be that despite observed overexpression in EGFR, few TNBCs *in vivo* are oncologically addicted to EGFR signaling in such a way that renders them sensitive to EGFR inhibition. Instead, TNBC is a genomically complex disease, characterized by loss of tumor suppressor genes and high mutational burden without single identifiable driver mutations or programs [27]. This stands in contrast to disease entities such as EGFR-mutant lung cancer, which is highly dependent on EGFR signaling, and highly sensitive to EGFR inhibitors [28]. While mABs offer the theoretical additional benefit of immunologic activity over TKIs via engagement of the fragment crystallizable (Fc) component by immune effector cells, any additional activity conferred by these agents has not yet proven to be clinically significant enough to warrant standard use in breast cancer.

Is it possible that the strategy of targeting EGFR in breast cancer is still viable, but the correct tumor subtype, drug combination, or treatment context has not yet been investigated? Perhaps looking past TNBC and/or investigating new drug partners could hold the answer. For example, EGFR alterations including gene amplification are enriched in ER+/HER2− breast cancers that are previously exposed to hormonal therapy; EGFR overexpression conferred resistance to hormonal blockade *in vitro*, which was rescued by EGFR inhibition with TKIs [29]. In the neoadjuvant setting with treatment naïve ER+/HER2− breast cancers, gefitinib did not add any clinical or biochemical benefit (by KI-67 reduction) to anastrozole alone [30], however in the metastatic setting, the addition of gefitinib to hormone therapies in ER+/HER2− breast cancer has exhibited mixed results in small phase 2 studies [31, 32]. It remains to be seen whether refractory ER+/HER2− breast cancer represents a new treatment context in which pharmacologic targeting of EGFR may prove useful in breast cancer. Building on this, EGFR is also frequently overexpressed in inflammatory breast cancer and metaplastic breast cancer, both highly aggressive disease subtypes with poor prognoses and urgent needs for better therapeutic options [15]. Lastly, it is worth noting that few of the targeted studies of EGFR inhibitors in breast cancer utilized a strategic biomarker for patient selection purposes, raising the possibility that a subset of responsive patients exists and have been diluted by existing trial data [15].

Of note, ADCs represent a new and promising strategy to target the ErbB receptors in breast cancer and beyond. ADCs are canonically comprised of a monoclonal antibody targeting a tumor-specific antigen, a highly potent cytotoxic payload, and a linker that connects the two [33]. ADCs accumulate in tumors, where they engage with the target antigen and are internalized, at which point the linker is broken and the payload is released, enacting it’s end-activity on cancer cells. ADCs targeting HER2 have made a profound impact in breast cancer treatment, including ado-trastuzumab emtansine (T-DM1) which is approved

in the adjuvant [34] as well as metastatic [35] setting for HER2-positive breast cancers, and fam-trastuzumab deruxtecan, which is approved in metastatic HER2-positive breast cancer [36] and also recently exhibited substantial activity in HER2-low breast cancers [37].

ADCs targeting EGFR have been tested clinically in various settings [38–40], and early phase studies are underway in solid tumors with initial results expected in the coming months and years. While no EGFR-targeted ADC is currently approved for treatment, three main experimental candidates have emerged: MRG1003 (delivering MMAE with a cleavable linker), M1231 (a bispecific mAB targeting MUC1 and EGFR, delivering a hemiasterlin payload), and depatuxizumab mafodotin (delivering MMAF via a non-cleavable linker) [41]. Although many of the early trial efforts in these drugs are focusing on other EGFR-expressing cancers such as glioblastoma, gastrointestinal, and head/neck malignancies, preclinical efforts are underway to develop such ADCs alone or in combination therapy regimens specifically for use in TNBC [42, 43]. Of special note, this ADC approach may take advantage of EGFR as a ‘docking station’ for ADC internalization and ultimately payload delivery, and may be effective regardless of whether tumors are driven by downstream activity of the ADC target [33]. As discussed further below, the potential for on-target off-tumor toxicity of EGFR-targeted agents is another hurdle to be overcome by these agents, given the role that EGFR plays in normal tissue.

III. HER3

HER3 is encoded by the *ERBB3* gene, located on chromosome 12q13; known ligands for this receptor include NRG-1 and NRG-2 [44]. Of special note, HER3 does not possess kinase activity on its own, however it is capable of forming heterodimers with HER2 (and/or EGFR), which dramatically increases transphosphorylation and activation of downstream signaling cascades, in perhaps the most mitogenic stimulus in human breast cancer [44, 45]. Moreover HER3 stands out among ErbB family members as a potent inducer of PI3K activity, due to direct binding with the PI3K p85 subunit [46]. Preclinically, HER3 expression is necessary for HER2-mediated signaling in HER2-overexpressing breast cancer cell lines, underlining the importance of heterodimerization for the ErbB receptor family in oncogenesis [47]. Overexpression of HER3 occurs in approximately 10–30% of primary breast carcinomas and is associated with worse outcomes in some studies [48]; however unified and consistent measurement of HER3 expression, which is often highly variable over time, has not been agreed upon in the research community, which qualifies the results of such studies.

Mechanistically, overexpression of HER3 is hypothesized to lead to de-novo and acquired resistance to HER2-targeted therapies in HER2-positive breast cancer [49, 50]. Indeed, pertuzumab, a HER2-targeted mAB which substantially prolongs overall survival in HER2-positive advanced breast cancer and increases rates of pathologic complete response in early HER2-positive breast cancer, is thought to add to the antiproliferative effects of the HER2-targeted mAB trastuzumab specifically by interfering with the heterodimerization of HER2 and HER3 [51]. HER3 overexpression has also been observed as a mechanism of feedback upregulation and therapy escape when PI3K is inhibited in HER2-positive breast cancers,

showing how targeting downstream effectors of ErbB family genes can have unexpected consequences [52, 53].

Efforts to target HER3 in cancer have historically fallen into three categories: blocking the kinase activity of its relevant dimerization partners, blocking the dimerization process, or directly targeting the HER3 protein itself [46]. Because of its lack of intrinsic kinase activity, TKIs which target the ATP binding site should not effectively inhibit HER3, which likely undercuts the benefits of this approach [54]. Of note, mutations in *ERBB3* occur in breast cancer, albeit relatively rarely with a prevalence of 1–2% [55]. Such mutations can be oncogenic in preclinical models, and can occur in the extracellular or kinase domains [56]. HER2 kinase inhibition with neratinib has been attempted in patients with HER3 mutant cancers in the SUMMIT basket trial, however no clinical responses were observed in this small subpopulation [57].

For these reasons, many efforts to target this protein have relied on mABs as a therapeutic strategy [58]. Example agents include seribantumab, lumretuzumab, elgemtumab, and patritumab, which have highly limited activity as single agents, and have thus far not demonstrated meaningful benefit when used in combination strategies [59]. Additionally, toxicities may emerge when these agents are employed in combinations. For example, the triplet of elgemtumab along with trastuzumab and alpelisib led to significant gastrointestinal toxicity in patients with PI3K-mutated HER2-positive advanced breast cancer, suggesting that care must be taken when combining multiple agents targeting this pathway, as on-target off-tumor side effects can occur [60].

This has paved the way for new platforms, which include bispecific antibodies as well as ADCs. For example, the HER3-targeted ADC patritumab deruxtecan (U3–1402) has shown signs of activity in advanced, heavily-pretreated breast cancers [61]. Most recent results at the time of this publication showed an ORR of 30.1% in hormone receptor positive (HR+)/HER2− breast cancer (n=113), 22.6% in TNBC (n=53), and 42.9% in HER2+ disease (n=14) in phase I/II studies [62]. Duration of response ranged from 5.9 to 8.3 months. In this study, HER3 expression on pre-treatment specimens did not seem to correlate well with response and temporal variation in HER3 expression may compromise its use as a biomarker. Of note, the SOLTI-TOT HER3 window of opportunity trial investigated the use of a single pre-operative dose of patritumab deruxtecan in HR+/HER2− breast cancer, finding an ORR of 45%, with increased tumor cellularity and tumor-infiltrating lymphocyte (CelTIL) score, and no apparent correlation between response and pre-treatment ERBB3 mRNA [63]. Several other HER3-targeted ADCs are in preclinical development [59]. Of note, while activation in parallel pathways and lack of oncogenic dependence are standard means of resistance to classical targeted therapies such as mABs and TKIs, ADCs may be able to overcome these mechanisms by using the target protein as a means of delivering a cytotoxic payload [64]. In this way, ADCs represent a promising strategy to overcome the compensatory signaling changes and oncologic complexity that have allowed cancers to evade therapies targeting the ErbB receptor family.

A few bispecific antibodies have been investigated which target HER3 in addition to other targets, though experience in breast cancer is limited. For example, duligotuzumab

bispecifically targets EGFR and HER3, with the hope of overcoming acquired resistance to EGFR inhibition, and showed preclinical activity in TNBC [65]. This agent was investigated in metastatic colon cancer but unfortunately had increased toxicity without any improvement in efficacy compared to cetuximab, and no studies in breast cancer have been reported [66]. M-111 is a bispecific antibody-fusion protein targeting HER2 and HER3, which was investigated clinically in breast cancer over a decade ago in a phase 1 study [67]; MM-141 (istiratumab) targets HER3 and IGF-1R and advanced to phase 2 studies in pancreatic cancer [68], but has not been developed clinically in breast cancer. Of special note, HER2/3 bispecific antibodies have found a promising niche in a mechanistically distinct clinical setting: *NRG1* gene rearrangements encoding for NRG1, the predominant ligand of HER3 and HER4, which can potently activate ERBB signaling [69]. Preclinical and preliminary clinical data strongly support further investigation of this strategy in the subset of patients with breast cancer harboring *NRG1* rearrangements, demonstrating the importance of biomarker selection in therapy deployment.

IV. HER4

The *ERBB4* gene is located on chromosome 22q33; known ligands of HER4 include neuregulins and epiregulin, among others [44, 70]. The role of HER4 in cancer development and signaling is a complex one, with many unanswered questions. HER4 is capable of homodimerization or heterodimerization, which may have contrasting effects on cell proliferation and survival. Some studies have shown a positive correlation between *ERBB4* expression and breast cancer related outcomes [18, 71, 72], in that HER4 promotes differentiation and growth suppression [73]. However other studies have suggested that this relationship is highly context-dependent, and differs with membranous vs. nuclear staining, as well as homo- vs. heterodimerization [18, 74, 75]. These mixed results can be attributed to the complexity of HER4 biology, which involves at least four different receptor isoforms, some of which can be cleaved, forming soluble intracellular domain that can localize to the nucleus or cytoplasm and has numerous and diverse activities [44].

Accordingly, some have hypothesized that inhibiting HER4 could be deleterious and lift the brakes on the pro-apoptotic signals mediated by the protein [44, 76]. However, the cleaved intracellular domain, when localized in the nucleus, specifically appears to co-activate estrogen receptor activity, suggesting a potential role for HER4 biology in ER+ breast cancers [77]. Beyond this, structural differences between HER4 isoforms poses another challenge in drug design—target engagement must be carefully controlled to avoid unwanted downstream effects [78]. While HER4-targeted mABs have been investigated preclinically, none have entered clinical trials as of yet [78, 79].

V. A note on toxicity

EGFR, HER2, HER3 and HER4 are expressed widely in normal tissues, and play a major role in physiologic cell processes. Specifically, EGFR is expressed in the skin, gastrointestinal system, and kidney [80]; HER2 is expressed in the gastrointestinal, respiratory, reproductive tract, skin, breast, placenta, and heart [81]; HER3 is found at high levels in the gastrointestinal tract and central nervous system [82], and HER4 is found in

skeletal muscle, heart, and central nervous system [70]. Inhibition of these proteins and their downstream activities can have significant consequences in normal tissue, as reflected in the toxicity patterns seen across ErbB-family targeted therapies. This has direct effects on the therapeutic window of drugs that that inhibit these proteins and is a critical consideration in the pharmacologic development of such agents.

Across tumor types, EGFR targeted therapies are known to cause skin toxicity, manifesting as an acneiform rash most commonly seen on the face; such a rash occurs in >80% of patients treated with cetuximab [83]. Gastrointestinal toxicity such as diarrhea and nausea, as well as hepatotoxicity are also relatively common, all due to normal tissue expression and function of the wild type EGFR protein [83]. Drugs that have a higher affinity for mutant EGFR, such as osimertinib, have a better therapeutic index in patients with EGFR-mutant cancers [84], however activating EGFR mutations are rare in breast cancer. The toxicity patterns of HER3-targeted agents may depend on the therapeutic modality and also combination therapy partners [85].

Turning to newer therapy modalities, toxicity patterns seen with ADCs are complex, and are influenced by payload and linker-specific factors, in addition to function of the target protein [33]. Patritumab deruxtecan, for example, appears to be associated primarily with payload-related hematologic toxicity, however drug-induced pneumonitis occurs as well [61]. Similar pneumonitis has also been observed with the HER2-targeted ADC trastuzumab deruxtecan in breast cancer [86], as well as the trop-2 targeted ADC datopotamab DXd in lung cancer (though curiously less so in breast cancer) [87, 88]. It remains to be seen whether this is due to target expression in or around lung tissue, or off-target payload effects.

VI. Future directions

To date, targeting EGFR, HER3 or HER4 in breast cancer with monoclonal antibodies or small molecule inhibitors has unfortunately born little fruit. This is most likely due to the complexity of interactions between the ErbB receptor family members as well as their downstream signaling cascades, which, besides HER2, function largely in a network fashion rather than as singular oncogenes in breast cancer. With some examples discussed above, it is quite possible that biomarkers can select the patients who would benefit from molecular inhibition of EGFR, HER3 or HER4, and preclinical studies should strive to elucidate the role of these players in resistance to existing therapies.

Moreover, the ability to target these proteins with ADCs has opened up a new pathway with real potential to improve patient outcomes. Because ADCs capitalize on the presence of a cell surface marker which may or may not be a functional oncogenic driver, they can overcome the mechanisms of intrinsic resistance to small molecular inhibitors, including parallel pathway signaling and feedback upregulation. The ultimate cytotoxicity of ADCs is largely due to the delivery of a chemotherapeutic payload, which can kill cells regardless of these complexities and the resilience of cell signaling interactions. Further, the bystander effect can overcome spatial heterogeneity of target expression, which may be of particular utility in EGFR and HER3, which may not be homogeneously or stably expressed in breast cancer. Perhaps the most promising example of this strategy, as discussed above, is

patritumab deruxtecan, which is currently being investigated clinically in phase 2 studies in breast cancer.

VII. Conclusion

Despite many setbacks, strategies targeting ErbB proteins beyond HER2 still hold promise, particularly those which take advantage of new drug delivery platforms and biomarker selection. Herein, we highlight the progress and pitfalls of these efforts to date. Promising strategies include the use of ADCs and monoclonal or bispecific antibodies, and future studies would likely benefit from using biomarker selection in order to better balance the benefits of these drugs against their known toxicity. Further, translational work is required to identify synergistic partners to overcome primary and acquired resistance seen in breast cancers driven by ErbB family signaling. Ultimately, a comprehensive understanding of the intrinsic and extrinsic features of the ErbB ecosystem is critical to personalizing treatments and securing clinical benefit for patients with breast cancer.

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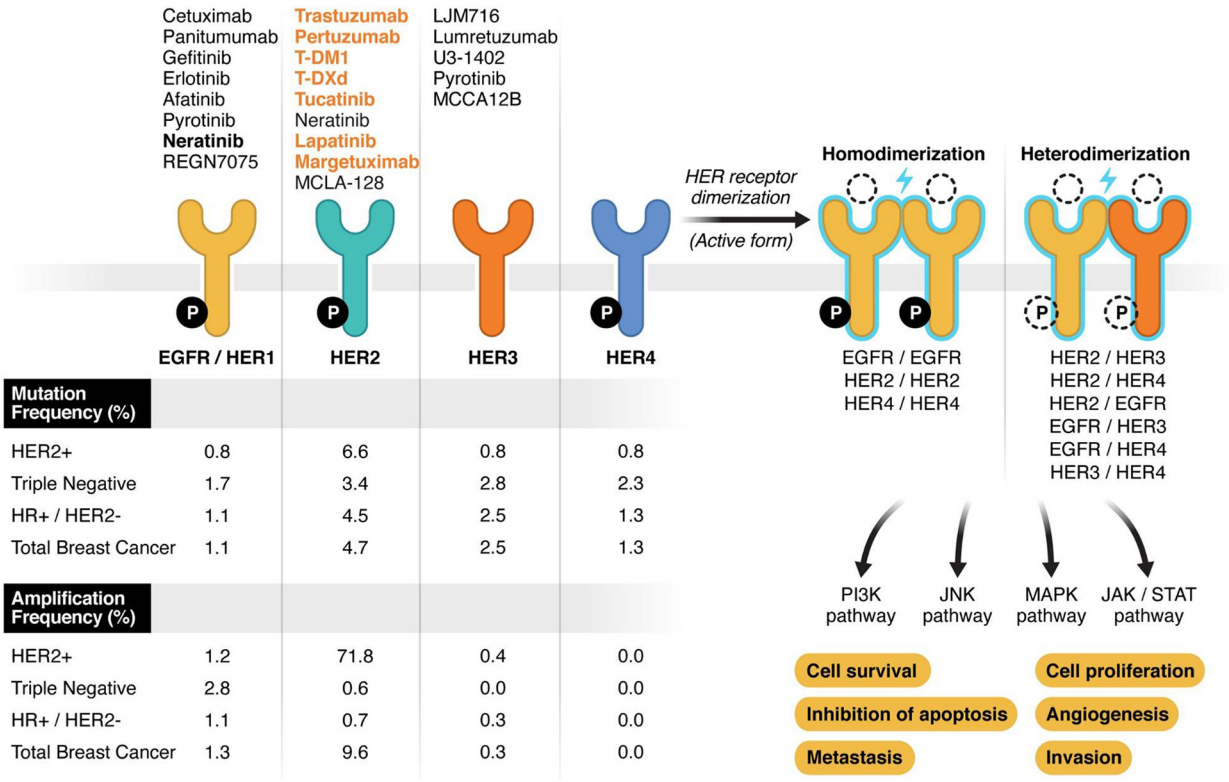
- Prior efforts to target the ErbB receptor family beyond HER2 have been inadequate
- Novel therapeutic approaches such as antibody-drug conjugates hold promise
- Better patient selection can improve the potential of these agents in breast cancer



Mutation Frequency (%)				
HER2+	0.8	6.6	0.8	0.8
Triple Negative	1.7	3.4	2.8	2.3
HR+ / HER2-	1.1	4.5	2.5	1.3
Total Breast Cancer	1.1	4.7	2.5	1.3
Amplification Frequency (%)				
HER2+	1.2	71.8	0.4	0.0
Triple Negative	2.8	0.6	0.0	0.0
HR+ / HER2-	1.1	0.7	0.3	0.0
Total Breast Cancer	1.3	9.6	0.3	0.0

Figure 1.

Schematic representation of ERBB-family receptors. On the right part of the figure, the 4 receptors have been represented: on upper side, FDA-approved (orange) and experimental (black) targeted agents for each receptor; on the lower side amplification and mutation frequency is reported. The genomic alterations frequency has been extracted from MSKCC sequencing data by MSK-IMPACT including 1918 breast cancer samples (published data, Razavi et al. Cancer Cell 2018 https://doi.org/10.1016/j.ccell.2018.08.008). ER/PR and HER2 status have been defined as the last status determined per SOC that guided the therapeutic choice at the time of the data collection. The right part of the figure represents all possible combinations of dimerization (active form) of ERBB-receptors along with the downstream molecular pathway and the effect of their activation on breast cancer cells. Ligand and intracellular phosphorylation (P) are represented with dotted lined because their status vary across the receptors/dimers. Specifically: all the receptors are active with the phosphorylation of the intracellular domain except HER3. In normal conditions, all receptors have a ligand-dependent activity except HER2.

Table 1:

Efficacy and safety of anti- ErbB family drugs (excluding HER2− selective therapies) in breast cancer

Drug	Class	Target	Phase	Subtype/Setting	N	Combination Partners	Activity	Tox. of special Interest
Cetuximab	mAb	Amplified EGFR	II II II	mTNBC [89] MBC [22] Early TNBC Neoadj setting[90]	102 19 25	Alone Cet/Tax/carbo Cet/Docetaxel	ORR: 6–16% pCR rate: 24%	Rash ≥ G3: 3%
Panitumumab	mAb	Amplified EGFR	II	mTNBC[91] Early TNBC (neoadj) setting[92]	71 60	Panitumumab/Carbo/Gem Panitumumab/FEC100→ docetaxel	ORR:42% PFS: 4.4 mo pCR rate: 46.8%	Skin tox ≥ G3: 43.3–70%
Gefinitib	TKI	Mutant EGFR	II	HR+/Her2+/− MBC[93] HR+/HER2− MBC (TAM-resistant)[94] HR+ HER2+/−MBC (TAM-naïve) [95] Early BC (neoadj) [96] Early HR+ BC (neoadj)[97]	40 71 290 206	Monotherapy ANA + Gef or plac TAM + Gef/plac EP→ Gef/Plac ANA+Gef vs ANA	ORR: 0% ORR: 22% vs 28% mPFS: 10.9 vs 8.8 pCR rate: 5% ki67 change 0–16w: mean 1.37 (p=.26)	Diarrhea G≥3: 10–13% Rash: G≥3: 16.1–30%
Erlotinib	TKI	Mutant EGFR	II	MBC[23]	69	Monotherapy	ORR: 3%	Rash: G≥2: 6–13%
Afatinib	TKI	Mutant EGFR	II III	HER2−MBC[26] HER2+ MBC[98]	50 208	Monotherapy Afatinib+ Vino vs Trastuzumab+Vino	ORR: 0% mPFS: 5.6 vs 5.5 mo	Diarrhea G≥3:40% Diarrhea G≥3: 24% Rash: G≥3:11%
Pyrotinib	TKI	panErbB	III	HER2+ MBC[99]	266	Pyrotinib + Cape vs Lapatinib + Cape	mPFS: 12.5 vs 6.8 mo HR: 0.39 CI: 0.25–0.56	Diarrhea G3: 31%
LJM716	mAb	HER3	I	HER2+ /PIK3CA mutant MBC[85]	10	LJM716 Trastuzumab and alpelisib	ORR: 1/21 (4.8%); CBR > 30 weeks: 4/21	G ≥3 diarrhea (n = 6), hypokalemia (n = 3), abnormal liver enzymes (n = 3)
Lumretuzumab	mAb	HER3	I I	Highly pretreated HER3 amplified solid tumors [100] HER3 +, HER2-Low Breast Cancer [101]	25 35	Pertuzumab + paclitaxel	CBR: 21.3% ORR: 38% - 55% (untreated pts)	No DLT, diarrhea 46.8% G3 Diarrhea 50%
Patritumab deruxtecan	ADC	HER3	I/II	HER3-high or low TNBC or HR+/ HER2−[102]	172		HER3-high: ORR:10–30% HER3-low: 29–33%	ILD: 5%

Notes: TKI: tyrosine kinase inhibitor; N: number; Tax: ; MBC: metastatic breast cancer; BC: breast cancer; mTNBC: metastatic triple negative breast cancer; HR+: hormone receptor positive; mPFS: median progression free survival; ORR: overall response rate; ANA: anastrozole; TAM: tamoxifen; pCR: pathological complete response; CBR: clinical benefit rate; DLT: dose-limiting toxicity; Plac: placebo; G: grade; mo: months; EP: epirubicin and paclitaxel; vino: vinorelbine; neoadj: neoadjuvant: tox: toxicities; cape: capecitabine; ILD: interstitial lung disease; pts: patients; Lapa: lapatinib; Pyro: pyrotinib

Table 2:

Ongoing trials of anti- ErbB family drugs (excluding HER2− selective therapies) in breast cancer

NCT Identifier	Phase	Drug	Target	Combination therapy	Drug class	Population	Primary endpoint
NCT02980341	I/II	U3–1402	HER3	-	ADC	HER3+	Safety
NCT04699630	II	U3–1402	HER3	-	ADC	MBC	ORR and PFS6
NCT04965766	II	U3–1402	HER3	-	ADC	MBC	ORR
NCT04610528	I Pre-surgery (WoO)	U3–1402	HER3	-	ADC	mRNA-ERBB3 expressed eBC	CelTIL score
NCT04460430	II	Neratinib	EGFR/HER3/ HER4	Fulv/TAM/EXE	TKI	HR+/HER2− /HER2 mutant MBC	PFS
NCT05154396	II	Neratinib escalating dose	EGFR/HER3/ HER4	-	TKI	HR+/HER2−/HER4+ eBC (neadj)	Safety
NCT04965064	II	Neratinib	EGFR/HER3/ HER4	Capecitabine	TKI	BM HER2− with HER2 CELsignia +	OS
NCT03065387	II	Neratinib	HER2/EGFR	Palbociclib or Trametinib or everolimus	TKI	HER2 mutant	Safety of the combination
NCT04872985	II	Pyrotinib	panErbB	-	TKI	HR+/HER2−/HER4+ eBC (neadj)	tpCR
NCT04582968	II	Pyrotinib	panErbB	+ RT	TKI	HER2+ MBC with BM	Safety CNS
NCT04001621	II	Pyrotinib	panErbB	-	TKI	HER2+ MBC	PFS
NCT04681911	II	Pyrotinib	panErbB	Inetetamab (ADC) + Chemo	TKI	HER2+ MBC	ORR
NCT04481932	II	Pyrotinib	panErbB	TCbH	TKI	HER2+ early BC (neadj)	tpCR
NCT04255056	II	Pyrotinib		AC			
NCT04646759	III	Pyrotinib	panErbB	Fulvestrant	TKI	HR+/HER2+ MBC	PFS
NCT05255523	II	Pyrotinib	panErbB	Trastuzumab	TKI	2L HER2+ MBC	Incidence of first BM event
NCT04973319	III	Pyrotinib	panErbB	Sequentially after HP	TKI	Non-pCR patient (post-neoad)	IDFS
NCT03321981	II	MCLA-128	HER3	ET or H/Chemotherapy	TKI	HR+ or HER2+	CBR 24w

Note: ORR: overall response rate; ET: endocrine therapy; CBR 24w: clinical benefit rate at 24 weeks; CNS: central nervous system; TKI: tyrosine kinase inhibitor; ADC: antibody drug conjugate; tpCR: total pathological complete response; CNS: central nervous system; FULV: fulvestrant; TAM: tamoxifen; eBC: early breast; WoO: window of opportunity; CelTIL: tumor cellularity and TILS; BM: brain metastasis; HR: hormone receptor; EXE: exemestane; TCbH: Taxotere, Carboplatin, Herceptin; AC: adriamycin and cyclophosphamide; mTNBC: metastatic triple negative breast cancer; IDFS: invasive disease-free survival; HP: trastuzumab and pertuzumab

https://clinicaltrials.gov/ (last update on 4/05/2022)