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Hormone Receptor/Human Epidermal Growth Factor Receptor 2-positive breast cancer: Where we are now and where we are going

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ABSTRACT

Near 75% of all breast cancers (BC) express estrogen receptors (ER) and/or progesterone receptors (PgR), while up to 20% of BC show an overexpression/amplification of Human Epidermal Growth Factor Receptor 2 (HER2). Around 50% of all HER2-overexpressing BC show the coexistence of both HER2 overexpression/amplification and ER and/or PgR overexpression. Numerous *in vitro* and *in vivo* studies suggest the existence of a cross-talk between their downstream pathways, which seem to affect the natural history, response to therapy and outcome of patients affected by this subset of BC. Meta-analyses or subgroup analysis of numerous neo-/adjuvant trials demonstrated significant clinical implications deriving from ER/HER2 co-existence, consisting in a different pattern of relapse and dissimilar outcome in response to anti-HER2 therapy. However, only two randomized trials in early disease and three in advanced disease specifically addressed the issue whether a combined approach with both hormonal and anti-HER2 therapy would have a better therapeutic impact in this subset of BC compared to the lone anti-HER2 or hormonal therapies (HT). None of these trials demonstrated improvements in overall survival, even though several efficacy end-points such as progression free survival, in advanced setting, or pCR rates in neoadjuvant setting, often favored the combined hormonal and anti-HER2 therapeutic approach. In the next few years, a certain number of ongoing randomized trials, both in neoadjuvant and advanced setting, will evaluate the efficacy of new anti-HER2 drugs, T-DM1 and pertuzumab, in combination with HT, helping to improve the therapeutic strategy for this specific subtype of breast tumors.

Introduction

Approximately 75% of all breast cancers (BC) express estrogen receptors (ER) and/or progesterone receptors (PgR) [1], while up to 20% of BC show an overexpression/amplification of Human Epidermal Growth Factor Receptor 2 (HER2). In nearly 50% of HER2 positive (+) BC, there is the coexistence of both expression of ER/PgR and iperexpression/amplification of HER2 [2,3]. *In vitro* and *in vivo* models suggested the existence of a cross-talk between the two downstream pathways (Fig. 1) which affects the natural history, response to therapy and outcome of patients affected by this subset of BC. In this paper we will discuss the current preclinical and clinical evidence concerning the bidirectional cross-talk between ER and HER2 pathways and the potential clinical implications of this intriguing coexistence.

An overview of HER2 and ER pathways

HER2 is a member of the HER family, which consists in 4 transmembrane tyrosine kinase receptors: EGFR/HER1, c-erbB2/HER2, HER3 and HER4. HER2 functions as universal co-receptor for the other HER family members and, when overexpressed or amplified, constitutively stimulates tumor growth, invasiveness and survival via activation of several signaling cascades, mostly MAPK and PI3K/Akt pathways [4–6]. More specifically, HER2-EGFR dimers induce proliferation and improve invasive functions, HER2 homodimers alter cell polarity and HER2-HER3 dimers increase tumor cell metabolic functions, favor cell survival, induce proliferation and increase invasiveness [1–3]. Finally, HER2 overexpression also results in an increased production of the rare ΔHER2 isoform with

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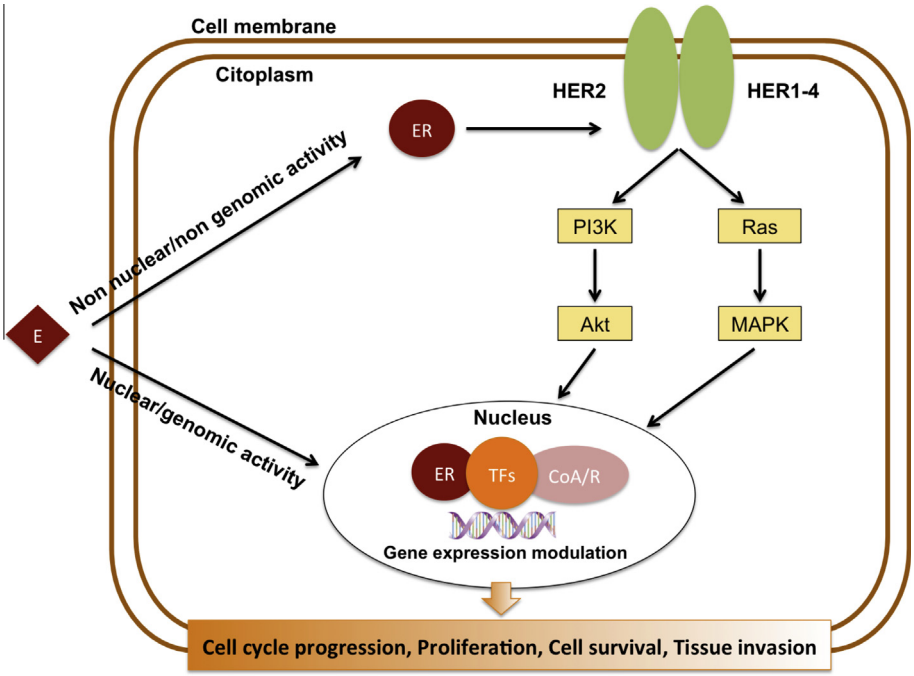

Fig. 1. Simplified ER and HER2 signalings' cross-talk. Estrogens (E) act via a non nuclear/non genomic activity and a nuclear/genomic activity. Non nuclear estrogen receptor (ER) interacts directly or indirectly (e.g. via G proteins) with human epidermal growth factor receptor (HER)2/HER1-4 dimers activating their downstream kinase pathways (e.g. Ras-MAPK and PI3K-Akt pathways), which in turn phosphorylate ER and other transcription factors (TFs) and coactivators/corepressors (CoA/R), modulating gene expression. HER2 signaling pathways also reduce ER expression at both mRNA and protein levels. ER also promotes HER2, other tyrosine chinese receptors (TKR) and TKR ligands' gene expression. This bidirectional cross-talk leads to cancer cell cycle progression, proliferation, survival and invasiveness.

more potent signaling characteristics [6]. Apart from being a driver gene for breast tumors, HER2 is also a relevant negative prognostic factor [7] associated with decreased disease/event free survival (DFS/EFS) and overall survival (OS) [8], however it is also the molecular target of HER2-targeted agents such as trastuzumab, pertuzumab, lapatinib and T-DM1. ER modulates the expression of numerous genes. The binding of estrogen determines a receptor dimerization, which regulates gene expression. ER can also function as a co-regulator for other transcriptional factors. Several tyrosine kinase receptors such as EGFR, IGF1 and HER2 may activate ER in a ligand independent manner, via phosphorylation, determining an important cross-talk between ER and tyrosin receptor kinase pathways [1]. Some studies also suggest a non-transcriptional mechanism of action for ER, which can alter the expression of several growth factors-dependent genes [1]. The majority of BCs are driven in growth and survival by constitutively activated ER, expressed in nearly 75% of all breast tumors [1]. HER2+ BC is a heterogeneous disease. In nearly 50% of them there is also the ER and/or PgR expression (HR+) [2,3]. A study from the Cancer Genome Atlas Network [9], based on genomic DNA copy number arrays, DNA methylation, exome sequencing, mRNA arrays, microRNA sequencing and reverse phase protein arrays, confirmed, on a molecular basis, the existence of at least two subtypes of HER2+ BC, as follows:

- HER2E-mRNA-subtype/HER2-clinically positive tumors, which showed a significantly higher expression of a number of tyrosin kinase receptors (RTKs), including HER2 itself and genes within the HER2-amplicon.
- Luminal-mRNA-subtype/HER2-clinically positive tumors, which showed higher expression of the typical Luminal genes, including GATA3, BCL2 and estrogen receptor gene ESR1.

The coexistence of both HR and HER2 overactivated pathways influences the natural history of disease and patients' outcome. In fact, data from prospective cohorts have demonstrated different outcome between the HR+/HER2+ and HR negative (−)/HER2+ population with a distinct pattern of recurrence. The latter experienced more relapses in the first five years, with brain rather than bones as first site of recurrence [10,11]. A retrospective analysis from the HERA trial of adjuvant trastuzumab also demonstrated for the HR− cohort a very high risk of early recurrence, in contrast with HR+ disease, characterized by a relatively consistent risk of relapse over time [12].

Therapeutic implications of HER2 and ER pathways cross-talk: preclinical evidences

The presence of both HR and HER2 amplified pathways seem to impact on therapy efficacy. It is well known that patients with higher levels of HER-2 had statistically significant lower levels of HR than patients with lower levels of HER-2 [3]. Since levels of expression of HR are directly correlated with response to hormone therapy (HT) [3,13,14], the reduced effectiveness of hormonal treatments usually experienced in this subset of patients compared to HR+ HER2 negative breast cancers is not surprising at all. Moreover, several studies have provided numerous evidences that HER2 pathways may directly or indirectly contribute to the development of resistance to HT. The currently identified mechanisms of resistance are summarized below [15]:

- A HER-mediated activation of the PI3K/Akt/mTOR and p42/44 MAPK pathways induces a down-regulation of both ER and PgR expression.
- The PAX2 transcriptional factor loss or deregulation seems to be associated with the acquisition of a HER2-driven phenotype by preventing the HER2 transcriptional repression by estrogen-ER and tamoxifen-ER complexes.
- In BC cell lines some studies have shown a possible role for the membrane ER in promoting an antiapoptotic effect through EGFR, HER2, IGFR1 and their transduction pathways.

It is clearly established that HER2 pathways are involved in the development of several cases of HT resistance. Moreover, the ER expression in HER2+ tumors may suggest the existence of a cross-talk between ER and HER2 signaling pathways involved in the development of resistance to anti-HER2 therapies [3], as indicated by preclinical studies. In HR+/HER2+ cell lines a sustained inhibition of HER2 with lapatinib or the combination of lapatinib and trastuzumab was suddenly overcome by ER stimulation, which become the primary controller of cancer survival and proliferation [16,17].

Other preclinical data in HR+/HER2+ BC cell lines showed a restoration of lapatinib or trastuzumab responsiveness with estrogen deprivation or by using fulvestrant [18].

Furthermore, in metastatic patients chronically exposed to trastuzumab, HR− tumors showed a sudden up-regulation of ER followed by a decrease of response to anti-HER2 therapies [19]. Similar findings during anti-HER2 therapy were reported also in other studies [20,21]. The increasing in HR signaling in HR+/HER2+ tumors treated with lapatinib monotherapy in preclinical models may suggest that HR positivity could be a marker of HER2 target therapies sensitivity. Preclinical studies showed that double blocking HER2 and ER by various combinations of lapatinib, trastuzumab, pertuzumab and gefitinib with tamoxifen or ED (a substance which mimics the effect aromatase inhibitors) induced the best tumor response in mice carrying xenograft tumors with amplification/overexpression of HER2 [22,23].

In a recent preclinical study, in HER2+ clinical BC specimens collected in a lapatinib neoadjuvant trial, HER2 inhibition enhanced or restored ER expression with parallel upregulation of PgR and the antiapoptotic protein Bcl2, representing a potential mechanism of survival and anti-HER2 resistance. Interestingly, the effective inhibition of ER signaling with fulvestrant completely reverted lapatinib resistance *in vitro*. Finally, in a xenograft model, in presence of restored ER expression, adding HT to anti-HER2 treatment significantly delayed tumor progression [21]. These preclinical data strongly suggest that a bi-directional cross-talk between ER and HER2 signaling pathways may determine a reduced effectiveness for both anti-HER2 targeted and HT.

Therapeutic implications of HER2 and ER pathways cross-talk: clinical evidences

Studies in the neoadjuvant setting showed a correlation between anti-HER2 therapies activity and HR status. The CTneoBC pooled analysis including 12 international neoadjuvant trials clearly demonstrated an association between pCR and long-term outcome in HER2+ BC, irrespective of HR status (EFS Hazard Ratio/HR: 0.39; 95% CI: 0.31–0.50; OS HR: 0.34; 95% CI: 0.24–0.47), even though the strength of the association was higher for the HR− subgroup (EFS HR: 0.25; 95% CI: 0.18–0.34; OS HR: 0.19; 95% CI: 0.12–0.31). HR-/HER2+ tumors receiving trastuzumab (trast+) were the subgroup with a more favorable outcomes after achieving pCR (EFS HR: 0.15; 95% CI: 0.09–0.27; OS HR: 0.08, 95% CI: 0.03–0.22) compared to HR+/HER2+ trastuzumab untreated (trast−) or trast+(trast+ OS HR: 0.56; 95% CI: 0.23–1.37; trast− OS HR: 0.57; 95% CI: 0.31–1.04) and HR−/HER2+ not receiving trastuzumab (OS HR: 0.29; 95% CI: 0.17–0.50). Additionally, HR−/HER2+ trast+ disease was the one with the highest percentage of pCR achieved, compared to all BC subtypes and, more specifically among all of the HER2+ BC subgroups (HR−HER2 + trast + 50.3% pCR vs HR + HER2 + trast+ 30.9% pCR vs HR−HER2 + trast− 30.2% pCR vs HR + HER2 + trast− 18.3% pCR) [24].

A recent meta-analysis from Von Minckwitz and colleagues [25] including 7 randomized neoadjuvant trials reported a statistically significant impact on prognosis for pCR in HR−/HER2+, as opposite pCR did not correlate with prognosis in HR+/HER2+ tumors (referred as Luminal B HER2+, in the paper), irrespective of trastuzumab treatment. Additionally, HER2+ non-luminal tumors achieved pCR more frequently than luminal B HER2+ both treated with chemotherapy plus trastuzumab (32.9% vs 22.2%, respectively) and experienced better DFS than patients with luminal B HER2+ disease ($p < 0.02$).

Recent neoadjuvant clinical trials in HER2+ disease (NeoALTTO, NeoSphere, CALGB40601) also showed a different response rates to anti-HER2 drugs in HR+ vs HR− tumors. In NeoALTTO (lapatinib vs trastuzumab vs lapatinib-trastuzumab), in-breast pCR were consistently higher in HR− than in HR+ disease treated with trastuzumab (36.5% vs 22.7%), lapatinib (33.7% vs 16.1%) or with their combination (61.3% vs 41.6%) [26]. These results may be of prognostic relevance, since achievement of pCR was associated with improved EFS [27]. In NeoSphere trial (docetaxel-pertuzumab or trastuzumab or both vs pertuzumab-trastuzumab) in-breast pCR was, again, higher in HR− (63.2%) disease rather than HR+ (26%) in the docetaxel-trastuzumab-pertuzumab arm but also in the chemo-free dual HER2 blockade arm (27.3% vs 5.9%) [28]. The CALGB 40601 trial (lapatinib vs trastuzumab vs their combination, all followed by weekly paclitaxel) failed to demonstrate a statistically significant difference in pCR rates among the experimental arms. Anyway a molecular subtyping analysis was performed before and after systemic therapy on tumor samples, allowing to divide the clinical HER2+ tumors into all of the four major intrinsic subtypes. Interestingly the in-breast pCR rates (overall result 46%) was higher in the HER2-enriched/clinical HER2+ subtype (69% of the responses) [29]. Results from these trials are summarized in Table 1.

In adjuvant setting several studies demonstrated poorer outcome for HR+/HER2+ BC patients compared to HR+/HER2− patients undergone HT. Anyway some studies indicate no benefit or a potentially detrimental effect in tamoxifen-treated patients, while other failed to show similar results [30–35].

Retrospective analyses for the ATAC and BIG1-98 adjuvant aromatase inhibitors (AI) trials reported a worse clinical outcome in HER2+ BCs, regardless of treatment type but failed to demonstrate a clear interaction between HER2 status and type of HT on long-term efficacy outcomes [36,37].

In a retrospective subgroup analysis of the HERA trial, in patients with HR+/HER2+ tumors a slightly lower magnitude of effect for adjuvant trastuzumab was observed between experimental arm vs observational arm (% DFS events: 10.1% vs 14.4%; HR 0.68; 95% CI:0.51–0.89) compared to what happened in HR−/HER2+ tumors (% DFS events: 15.5% vs 23.5%; HR 0.62; 95% CI:0.5–0.77). Additionally, considering a different pattern of relapse (earlier recurrences for HR−, relatively higher risk of recurrence over time for HR+), the efficacy of trastuzumab treatment appeared to be more pronounced in first years of follow-up for the HR− cohort, and more consistent through time for HR+ cohort [12]. Also in a very recent retrospective study concerning early HR+/HER2+ BC, adjuvant Trastuzumab improved both relapse free survival (RFS) and breast cancer specific survival (BCSS) ($p < 0.0001$ and $p = 0.001$, respectively), when added to chemotherapy. However, the effect on BCSS in tumors expressing both ER and PgR in more than 30% of cells failed to reach the statistic significance ($p = 0.26$). Additionally, adjuvant Trastuzumab failed to add a statistically significant improvement for both endpoints (RFS and BCSS) in tumors with ER and PgR overexpressed in more than 50% of cells ($p = 0.09$ and $p = 0.16$, respectively). Furthermore, distinct patterns of relapse were also observed between lower overexpressing and higher overexpressing HR tumors, with the latter showing low and constant risk in the first 5 years and a late increase beyond 5 years, with modest trastuzumab effect [38].

Table 1
Neoadjuvant trials of anti-HER2 therapies in HR−/HER2+ vs HR+ HER2+ breast cancer.

Trial	Phase	Scheme	Results
NeoALTTO	III	Trastuzumab vs Lapatinib vs Trastuzumab + Lapatinib	In-breast pCR in HR-/HER2 + vs HR+/HER2+: • Trastuzumab arm: 36.5% vs 22.7% • Lapatinib arm: 33.7% vs 16.1% • Trast. + Lap. arm: 61.3% vs 41.6%
NeoSphere	II	Docetaxel ± Trastuzumab ± Pertuzumab vs Trastuzumab + Pertuzumab	In-breast pCR in HR−/HER2 + vs HR+/HER2+: • Doc. ± Trast. ± Pert. arm: 63.2% vs 26% • Trast.+Pert. arm: 27.3% vs 5.9%
CALGB40601	III	Trastuzumab vs Lapatinib vs Trastuzumab + Lapatinib followed by weekly paclitaxel	In-breast pCR: • Overall result: 46% • HER2-E/HER2clinically + subtype: 69%

pCR: pathologic complete response; HER2-E: HER2-enriched; HER2-clinically+: HER2 clinically positive.

Table 2
Clinical trials exploring the role of combined anti-HER2 with hormonal therapies.

Trial	Phase	Scheme	Results	*p*
TAnDEM	III	Anastrozole vs Anastrozole + Trastuzumab	• median PFS/TTP: 2.4 vs 4.8 mts • ORR: 7% vs 20% • CBR: 28% vs 43%	0.0016 – –
EGF30008	III	Letrozole vs Letrozole + Lapatinib	• Median PFS: 3.0 vs 8.2 mts • ORR: 15% vs 28% • CBR: 29% vs 48%	0.019 – –
eLEcTRA	III	Letrozole vs Letrozole + Trastuzumab	• Median PFS: 3.3 vs 14.1 mts • ORR: 13% vs 27% • CBR: 39% vs 65%	0.23 – –

mts: months; PFS: progression free survival; TTP: time to progression; ORR: overall response rate; CBR: clinical benefit rate.

In advanced setting a retrospective analysis showed a better sensitivity to chemotherapy plus anti-HER2 therapy in HR− tumors, with significant benefit in PFS when a maintenance HT was added to trastuzumab after chemotherapy in HR + HER2+ BC [39]. In contrast, a retrospective observational study including 164 women affected by HER2+ tumors treated with trastuzumab-based first line therapy, showed that patients with long-term clinical benefit had a higher likelihood of having HR+ tumors. Anyway, it may be relevant that the subgroup of HR+ patients had received maintenance trastuzumab and/or HT after first-line, which could have positively affected the outcome [40]. In another retrospective study concerning metastatic BC, a cohort of all BC subtypes treated with up to four lines of systemic therapy showed a better PFS, OS and post progression survival (PPS) beyond first line treatment for HER2+ tumors compared to the other BC subtypes ($p < 0.0001$ for all measures of outcome). These results seemed to be driven mostly by the HR + HER2+ cohort performance (median PFS of 17.5 vs 8.1 months, median OS of 55.3 vs 26 c of 27.8 vs 14 months, for HR+ HER2+ and HR−HER2+ subset, respectively) [41].

A prospective observational study on a cohort of more than 1000 HER2+ BC patients showed that in HR+/HER2+ tumors, the dual targeting of HR and HER2, with or without chemotherapy, was clearly associated with more prolonged PFS and OS compared to anti-HER2 treatment alone [42]. All of the above mentioned data consistently showed a different response to anti-HER2 or HT in patients with a HER2+ BC according to HR status, hinting that ER may constitute an escape pathway for tumors treated with anti-HER2 agents and vice versa. Therefore, combining HT with anti-HER2 therapy may represent a promising strategy to overcome both endocrine and anti-HER2 resistance.

Combining HT with anti-HER2 therapies: current clinical evidence

Only two trials in early disease and three trials in advanced disease addressed the issue whether a combined approach with both HT and anti-HER2 therapy would have a better therapeutic impact in HR+/HER2+ BC compared to the conventional combination of chemotherapy with anti-HER2 targeted agents. The three advanced-setting trials compared a first-line therapy with an AI to an experimental arm with a combination of the AI and lapatinib or trastuzumab (table 2). The TAnDEM trial showed a median PFS/time-to-progression (TTP) of 2.4 months for the AI (anastrozole) arm compared to the experimental arm (anastrozole/trastuzumab) 4.8 months ($p = 0.0016$), with an overall response rate (ORR) of 7% vs 20% and a clinical benefit rate (CBR) of 28% vs 43%, respectively [43]. Interestingly, nearly 15% of patients who received trastuzumab plus anastrozole did not experience disease progression for at least 2 years, suggesting that this combination is highly effective at least in a subgroup of patients. The EGF 30008 trial showed a median PFS of 3.0 months for the letrozole arm vs 8.2 months for the letrozole-lapatinib arm ($p = 0.019$). The ORR was 15% and 28%, and the CBR was 29% and 48%, for letrozole arm compared to letrozole-lapatinib arm [44]. The eLEcTRA trial showed a median PFS of 3.3 months for the letrozole arm vs 14.1 months for the letrozole-trastuzumab arm ($p = 0.23$); the ORR was 13% vs 27% and the CBR was 39% vs 65%, respectively [45]. None of these trials demonstrated a clear benefit in terms of OS [43–45]. On the basis of these results, several guidelines [46–48] recommended the use of a combination of trastuzumab or lapatinib in combination with an AI as a first-line option treatment for postmenopausal women with HR+ HER+ BC, if chemotherapy is not clearly indicated. However, the standard clinical practice has been dramatically influenced by the recent CLEOPATRA [49] and EMILIA [50] trials. The first one demonstrated a significant increase in both PFS (18.7 vs 12.4 months, HR 0.68, 95% CI: 0.58–0.80; $p < 0.001$) and OS (56.5 vs 40.8 months, HR 0.68, 95% CI: 0.56–0.84; $p < 0.001$) with the combination of trastuzumab, pertuzumab and docetaxel as compared to trastuzumab and docetaxel in first-line therapy of advanced HER2+ BC. Subgroup analysis failed to show a differential impact based on HR status. The EMILIA compared the novel trastuzumab conjugated with the chemotherapic DM1 to lapatinib combined to capecitabine for the treatment of advanced HER2+ BC in second line or more. The experimental arm was superior in both

Table 3
Ongoing clinical trials evaluating the combination of new anti-HER2 treatments combined with hormone therapy.

Trial	Phase	Scheme	Primary End-point
ADAPT HER2+/HR+	II	TDM1 + TAM/AI vs TDM1 vs Trastuzumab + TAM/AI	pCR
PER-ELISA	II	Trastuzumab + Pertuzumab + Letrozole	pCR
PERTAIN	II	Trastuzumab + Pertuzumab + AI vs Trastuzumab + AI	PFS
DETECT V	III	Trastuzumab + Pertuzumab + CT vs Trastuzumab + Pertuzumab + HT	Number of participants with adverse events
3GCC	II	Trastuzumab + Pertuzumab vs Trastuzumab + Pertuzumab + Eribulin vs Trastuzumab + Pertuzumab + HT	ORR

HT: hormonal therapy; CT: chemotherapy; TAM: Tamoxifen; AI: aromatase inhibitor.

PFS (9.6 vs 6.4 months, HR 0.65; 95% CI: 0.55–0.77; $p < 0.001$), OS (30.9 vs 25.1 months, HR 0.68, 95% CI: 0.55–0.85; $p < 0.001$) and ORR (43.6% vs 30.8%; $p < 0.001$). Significantly, none of the two trials tested the novel anti-HER2 therapy combined with HT, therefore the current standard of care for metastatic HER2+ BC consists of trastuzumab combined with pertuzumab and a taxane for first line and TDM1 alone, starting from second line or as possible first-line option in patients who experienced a disease relapse within six months of adjuvant therapy.

In early disease two small phase II neoadjuvant trials provided some evidences that double blocking HER2 and HR pathways, without adding chemotherapy, may result in an effective strategy. The TBCRC023 compared lapatinib plus trastuzumab, adding letrozole ± GnRH analoge in ER+ patients, for 12 weeks vs 24 weeks. pCR rates were higher in the 24 weeks arm (24.2% vs 12.2%) mostly thanks to the results in the ER+ subgroup (33.2% vs 8.7%), while pCR rates were quite similar for the ER− patients, suggesting a more potent effect for the association of HT and anti-HER2 therapy [51]. The TBCRC006 compared lapatinib vs trastuzumab, adding letrozole ± GnRH in HR+ patients, for 12 weeks. The overall pCR was 27% (21% in ER+ and 36% in ER− patients) [52].

Ongoing trials and future perspectives

The overall clinical evidences concerning the efficacy of a combined Hormonal/anti-HER2 therapy approach are interesting and definitely worthy of further study. In this perspective, several recent clinical trials have been studying the combination of the novel anti-HER2 drugs TDM1 and pertuzumab with HT both in neoadjuvant and advanced setting (Table 3).

The ADAPT trial for HER2+/HR+ BC is the first one to explore in neoadjuvant setting the efficacy of dual targeting HER2 and HR with one of the two novel anti-HER2 drugs recently approved in advanced BC. Three-hundred-eighty patients received neoadjuvant therapy with T-DM1 + tamoxifen (TAM) or AI (arm A) vs T-DM1 alone (arm B) vs trastuzumab + TAM or AI (arm C). After surgery, patients were to receive standard adjuvant treatment with anthracycline, taxane and trastuzumab. The interim analysis on 130 patients showed an overall pCR rate of 30.8% (pCR arm A 40.5% vs 45.8% arm B vs 6.7% arm C). The difference between either arm A or B vs C was statistically significant ($p < 0.001$), despite no significant difference between arm A vs B. Interestingly, exploratory analysis suggests benefit of adding HT to T-DM1 only in premenopausal (pCR: 28.6% for T-DM1 vs 47.6% for T-DM1 + HT) rather than postmenopausal setting (pCR: 64.3% vs 50%) [53]. However, an impact on these findings may be the result of both different HT options (Tam vs AI) and prematurity of results. In fact, most recent data presented at San Antonio Breast Cancer Symposium 2015 failed to show a sustained difference between the pCR achieved in T-DM1 vs T-DM1 + HT arms (overall pCR 41% vs 41.5%, respectively; 44.1% vs 45.0% pCR in postmenopausal subset; 37.9% vs 38.1% pCR in premenopausal subset) [54]. Final data set is required to further validate these results. Noteworthy, another phase II neoadjuvant trial (PER-ELISA) is currently recruiting participants and will test the efficacy of the combination of trastuzumab, pertuzumab and letrozole [55]. Rimawi and colleagues have been conducting since 2012 the randomized phase II trial PERTAIN, exploring the combination of an AI with trastuzumab and pertuzumab vs an AI with trastuzumab in first line treatment of HR+/HER2+ metastatic BC (MBC) in postmenopausal setting [56]. The DETECT V/CHEVENDO trial is a randomized phase III study which aims to compare the combination of trastuzumab, pertuzumab and a chemotherapy drug (docetaxel, paclitaxel, capecitabine or vinorelbine) with the combination of trastuzumab, pertuzumab and HT (tamoxifen, fulvestrant, letrozole or anastrozole). It is an ongoing trial currently recruiting participants [57]. Finally, the phase II 1303GCC trial will compare trastuzumab in combination with pertuzumab alone vs trastuzumab, pertuzumab and eribuline vs trastuzumab, pertuzumab and HT (anastrozole or fulvestrant) in locally advanced or metastatic BC affecting patients aged 60 or more [58]. Definitive results from all of these trials will provide fundamental data concerning the efficacy and tolerability of the combination of HT with novel anti-HER2 drugs T-DM1 and pertuzumab which, if positive, although not exhaustive, may help redefining the standard therapeutic approaches in HR+/HER2+ BC.

Conclusions

Since compelling evidence concerning activity for hormonal/anti-HER2 combination therapy has partially arisen in the setting of both early and advanced HR+/HER2+ BC, future research should be focused on comparing the current standard of care for HER2+ BC, which usually contains also chemotherapic drugs, to the association of hormonal and HER2 blockade therapy. In this perspective, the ongoing trials are crucial, but further phase III randomized controlled trials using T-DM1 as control arm or adjuvant/neoadjuvant trials experimenting both pertuzumab-trastuzumab combination or T-DM1 as control arm are needed to help addressing the issue. In fact, the shift to a more complex targeted therapy strategy, oriented to contrast both estrogen and HER2 pathways, may help obtaining adequate results with a convenient lower toxicity, compared to standard chemotherapy drugs-containing regimens, helping to delay their use.

Authors' contributions

All authors conceived the study. FS, GB, CC and ID searched for the literature results. FS, GB and CC wrote the article. ID, SDP and LDM revised the manuscript. All authors approved the final paper.

Conflict of interests

The authors financed this study and declare no conflict of interests.

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