Hormonal treatment combined with targeted therapies in endocrine-responsive and HER2-positive metastatic breast cancer

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Abstract: Approximately 50% of HER2 positive breast cancer cases are also estrogen receptor (ER) positive. Data supports a role for close cross-talk between the ER and HER2 signaling pathways as an important contributor to the development of *de novo* or acquired resistance to hormone therapies. Therefore a strategy that simultaneously blocks both signaling pathways is a reasonable approach to prevent or overcome either endocrine or anti-HER2 therapy resistance. Moreover, preclinical data support the idea that PI3K inhibitors and CDK4/6 could be an attractive target that functions downstream of both ER and HER2 pathways. We conducted a literature review of the results of phase II and III studies testing targeted therapies in metastatic breast cancer with HER2-positive and hormonal-receptor-positive disease. The analyses included efficacy and toxicity data from earlier studies with a single anti-HER2 drug combined with hormonal therapy up to more recent studies testing new molecules targeting these signaling pathways. The aims of this review are to summarize current knowledge and to discuss research development including the possibility to spare chemotherapy in this subgroup of HER2-positive breast cancer patients.

Keywords: breast cancer, HER2+ breast cancer, hormone-receptor-positive breast cancer, metastasis, molecular oncology

Introduction

The human epidermal growth factor receptor 2 (HER2) is a member of the membrane tyrosine kinase receptor family (i.e. HER1-4), amplified or overexpressed in 20–25% of breast cancers.[1]

Unlike other receptors of the family, HER-2 has unique receptor features: it binds no known specific ligand, but seems to exert its biological activity by serving as a preferential partner for the other HER receptors. Indeed, it forms heterodimers with other members of the erbB family after binding to their specific ligands, thus enhancing and prolonging cell signaling.[2–4] Interestingly, overexpression of HER-2 also induces its spontaneous homodimerization, thereby leading to activation of the tyrosine kinase moiety of the intracytoplasmic domain without the need for a ligand.[5]

HER2 positivity is correlated with aggressive behavior and reduced progression-free survival (PFS) and overall survival (OS).[6–8] HER2 is also a treatment target, predictive of response of anti-HER2 therapy. The efficacy of anti-HER2 drugs has been confirmed in several settings (adjuvant, neoadjuvant and metastatic) and the use of anti HER2 drugs has dramatically modified the course of the disease.[9]

Approximately 50% of HER2-positive breast cancers are also estrogen receptor (ER)-positive, dividing HER2 positive patients into two main subgroups (ER-negative plus HER2-positive, and ER-positive and HER2-positive) with different patterns of growth and response to treatment.[10]

For the nonendocrine-responsive and HER2-positive disease, the treatment strategy includes

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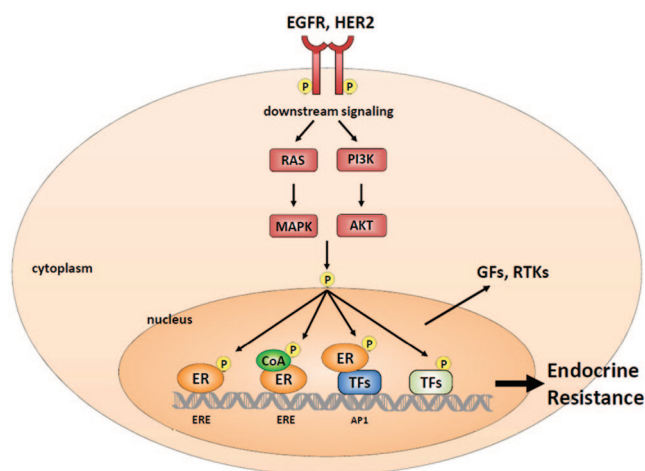
Figure 1. Crosstalk between ER and HER family receptors.
ER, estrogen receptor; HER human epidermal growth factor receptor.

the use of chemotherapy combined with anti-HER2 drugs. In the subgroup of HER2- and ER-positive metastatic breast cancer (MBC), different strategies are being investigated.

Several lines of data support a role for close crosstalk between the ER and HER2 signaling pathways (Figure 1). In the preclinical setting, it has been shown that the expression of ER and its downstream targets is increased in cells with acquired resistance to anti-HER2 therapy.[11,12] Reactivation of ER expression and signaling, including a switch from ER-negative to ER-positive status, were observed in clinical HER2-positive tumors after neoadjuvant lapatinib treatment.[12] These results suggest the significance of ER expression and signaling as an alternative survival mechanism in these tumors.

Moreover, this crosstalk contributes to the development of both intrinsic and acquired resistance to hormonal treatment.[12–16] HER2 overexpression or amplification affects endocrine therapy responsiveness both to tamoxifen and to estrogen deprivation by aromatase inhibitors (AI).[17,18] Indeed, in neoadjuvant therapy, ER- and HER2-positive breast cancer patients treated with letrozole or tamoxifen, showed less Ki67 suppression when compared with ER-positive and HER2-negative patients, despite similar short-term clinical efficacy.[19] High levels of HER signaling, working *via* the PI3K and MAPK pathways, can reduce ER levels. Moreover, activation of the pathway by posttranslational modifications (e.g. phosphorylation) of ER, can contribute to the reduction of tumor estrogen-dependency; consequently, the

receptor could be activated in the absence of estrogen.[13]

Understanding of the intrinsic link between the ER and HER2 leads to the development of a strategy that simultaneously blocks both signaling pathways. This is a reasonable approach to prevent or overcome either endocrine or anti-HER2 therapy resistance in some ER- and HER2-positive breast cancer patients.

We conducted a review of the results of phase II and III studies testing targeted therapies in HER2 positive, hormonal-receptor-positive MBC. Studies were identified by a computerized search on PubMed using the following text words: 'breast cancer and (c-erbB-2 or c-erbB2 or Neu or HER2).'

To be included in the analysis, retrieved studies had to fulfill the following simple inclusion criteria: advanced or metastatic breast cancer, endocrine therapy (any line of treatment), and evaluation of HER-2 expression (any method). The analyses included the efficacy and toxicity data of the studies. The future development of this strategy for this subtype of breast cancer are also discussed.

Studies of hormonal therapy with single HER2 blockade in metastatic breast cancer patients

To prevent or overcome either endocrine or anti-HER2 therapy resistance in ER- and HER2-positive metastatic breast cancer patients, some

Table 1. Studies of hormonal therapy with single HER2 blockade in metastatic breast cancer patients.

Trial	No of patients	Phase study	Study end point	Treatment arm	Outcome
TAnDEM	207	Randomized III	PFS	Anastrozole plus trastuzumab or placebo	PFS 4.8 months *versus* 2.4 months *p* 0.0016 median OS 28.5 months *versus* 23.9 months
Study of Marcom.	31	II	ORR	Letrozole and trastuzumab	ORR 26% OS non reported
eLEcTRA	57	Randomized III	TTP	Letrozole alone or letrozole plus trastuzumab	TTP 3.3 months *versus* 14.1 months *p* 0.23 OS non reported
Study of Johnston	219	Randomized III	PFS	Letrozole plus lapatinib or placebo	PFS 8.2 months *versus* 3.0 months *p* 0.019 median OS was 33.3 months *versus* 32.3 months
MINT	359	Randomized II	PFS	anastrozole plus AZD8931 20 mg bid anastrozole plus AZD8931 40 mg bid anastrozole plus placebo	PFS 10.9 months *p* 0.135 13.8 months *p* 0.485 14.0 months 16, 20, and 12 deaths had occurred in the AZD8931 20, 40 mg, and placebo groups, respectively.

ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

studies have valuated the possibility of treating with endocrine therapy (i.e. AI) and a single anti HER2 drug. These studies are summarized in Table 1.

Trastuzumab is a humanized monoclonal antibody that recognizes the extracellular domain of HER2, and was the first anti-HER2 drug developed in a clinical setting. The development of trastuzumab as a HER2-targeting agent represented a paradigm shift in breast cancer from nonspecific chemotherapy to a molecular targeted approach.

In the TAnDEM trial, a randomized phase III study, Kauffman and colleagues compared the PFS in the trastuzumab plus anastrozole arm *versus* the anastrozole alone arm in MBC with HER2-positive and endocrine-responsive disease. Previous treatment with tamoxifen as adjuvant or hormonal therapy for MBC or with anastrozole, if begun up to 4 weeks before random assignment, was permitted. Prior chemotherapy for MBC or adjuvant chemotherapy within 6 months was not permitted.

The authors reported that the 103 patients in the trastuzumab plus anastrozole arm experienced significantly improved PFS, with a median PFS of 4.8 months (95% CI, 3.7–7.0 months) *versus* 2.4 months (95% CI, 2.0–4.6 months) in the anastrozole alone arm (104 patients).[20] The results of TAnDEM trial are consistent with those from a phase II study assessing letrozole plus trastuzumab in 31 evaluable postmenopausal women with HER2- and ER-positive advanced breast cancer. This trial showed an objective response rate of 26% and a clinical benefit rate (CBR) of 52%. The median time to progression (TTP) was 5.8 months and the median duration of response was 20.6 months, suggesting that durable responses can be seen with combined hormonal and anti-HER2 therapy.[21]

The phase III eLEcTRA trial investigated the efficacy and safety of trastuzumab plus letrozole as first-line treatment in 57 HER2-positive and hormone-receptor-positive MBC. Median TTP increased from 3.3 months with letrozole to 14.1 months with trastuzumab plus letrozole;

however, this was not statistically significant (HR, 0.67; 95% CI, 0.35–1.29; $p = 0.23$).[22]

The combination of trastuzumab and AI improved the outcome compared with hormonal therapy alone, suggesting that the use of HER2-targeted therapy with an AI can substantially delay chemotherapy in some patients who experience clinical benefit.

A different therapeutic approach to inhibiting HER2-mediated signaling is to use lapatinib, a reversible small molecule tyrosine kinase inhibitor targeting the HER2 and EGFR intracellular kinase domain.[23,24] In fact, the endocrine resistance development could also be involved the EGFR pathway. Two randomized trials in ER-positive MBC suggested that gefitinib, a EGFR tyrosine kinase inhibitor, may improve PFS when added to endocrine therapy with either tamoxifen or anastrozole.[25,26]

In a phase III trial, the combination of letrozole plus lapatinib with letrozole plus placebo was compared as first-line treatment in patients with ER-positive MBC.[27]

In the HER2-positive population, the median PFS increased from 3.0 months for letrozole-placebo to 8.2 months for letrozole-lapatinib, with a significant reduction in the risk of progression for the combination (HR 0.71; 95% CI, 0.53–0.96; $p = 0.019$); however, of the 60 patients (10%) who had grade 3 or 4 diarrhea in the combination arm, 15% required discontinuation.

AZD8931 is an orally active, reversible, equipotent tyrosine kinase inhibitor of EGFR, HER2, and HER3 signaling that has shown anticancer activity in a range of *in vitro* and *in vivo* preclinical models.[28] In the phase II MINT study, 359 MBC patients were randomized 1:1:1 to receive daily anastrozole (1 mg) in combination with AZD8931 20 mg twice daily, AZD8931 40 mg bid, or placebo. Median PFS in the AZD8931 20, 40 mg, and placebo arms was 10.9 (1.37; 0.91–2.06, $p = 0.135$), 13.8 (1.16; 0.77–1.75, $p = 0.485$), and 14.0 months, respectively. Safety findings showed a greater incidence of diarrhea, rash, dry skin in patients treated with AZD8931 *versus* placebo.[29] Consequently, the use of AZD8931 does not enhance endocrine responsiveness and is associated with greater skin and gastrointestinal toxicity.

The results of the above-mentioned studies showed that the combination of hormonal and single HER2 (trastuzumab or lapatinib) blockade leads to a mild improvement in PFS. This suggest that interruption of the crosstalk between HER2 and ER-α might be effective only in a few cases or for a short duration This strategy could be relegated either to patients who could not tolerate chemotherapy or to postchemotherapy empirical maintenance strategies

Studies of hormonal therapy with dual anti HER2 blockade in metastatic breast cancer patients

Pertuzumab is a monoclonal antibody that binds to different epitopes on HER2 compared with trastuzumab.

The combination of pertuzumab and trastuzumab is more active than a single anti HER2 drug because of a more comprehensive signaling blockade.[30,31] Moreover, several studies have demonstrated that dual block of HER2 combined with chemotherapy is superior in both the metastatic, neoadjuvant and adjuvant settings compared with a single HER2 blockade.[32–34]

The studies evaluating the efficacy of dual block anti HER2 and hormonal therapy in MBC HER2-positive and endocrine-responsive disease are summarized in Table 2. In all studies, the hormonal therapy was an AI.

In the PERTAIN study, 129 patients were randomly assigned to dual block with trastuzumab and pertuzumab and AI or trastuzumab and AI.[35] The patients could receive induction chemotherapy with taxane according to physician choice. An interesting observation about PERTAIN was the fact that investigators opted not to include taxanes in nearly 50% of cases, even though it was permitted by the protocol. The median PFS was 18.89 months (95% CI, 14.09–27.66 months) in the anti-HER2 dual block arm and 15.80 months (95% CI, 11.04–18.56 months) in the trastuzumab arm (stratified hazard ratio, 0.65; 95% CI, 0.48–0.89; $p = 0.0070$). Among patients who did not receive induction chemotherapy, the median PFS was 21.72 months (95% CI, 12.42–32.95 months) in the pertuzumab plus trastuzumab arm and 12.45 months (95% CI, 6.21–18.53 months) in the trastuzumab arm. The safety profile was

Table 2. Studies of hormonal therapy with double HER2 blockade in metastatic breast cancer patients.

Trial	No of patients	Phase study	Study end Point	Treatment arm	Outcome
PERTAIN	258	Randomized II	PFS	Trastuzumab AI +/– pertuzumab	PFS 18.8 months and 15.8 months p 0.0070 OS not reported
ALTERNATIVE	355	Randomized III	PFS	Trastuzumab and lapatinib and AI Trastuzumab and AI Lapatinib and AI	PFS 11 *versus* 5.7 months p 0.0064 (lapatinib + trastuzumab + AI *versus* trastuzumab + AI) median OS, 46.0 *versus* 40.0 months

AI, aromatase inhibitor; OS, overall survival; PFS, progression-free survival.

consistent with previous trials of pertuzumab plus trastuzumab.

Consequently, the dual block combination with pertuzumab and trastuzumab significantly improved PFS compared with trastuzumab plus an AI.

The combination of trastuzumab and lapatinib is based on the different mechanisms of action of these drugs that simultaneously target the intracellular and extracellular HER2 domains.

In the phase III study of Blackwell and colleagues, patients with HER2-positive MBC whose disease progressed during prior trastuzumab-based therapies were randomly assigned to receive lapatinib monotherapy or lapatinib in combination with trastuzumab. Of the 128 patients with both HER2-positive and ER-positive breast cancer, no differences were observed in OS between the combination arm compared with the monotherapy arm (12 *versus* 11.2 months, respectively; HR, 0.85; 95% CI, 0.57–1.26).[36] Further new data comes from a phase III trial, ALTERNATIVE. The eligible patients, in second line or further, were randomly assigned (1:1:1) to treatment with lapatinib plus trastuzumab and AI, trastuzumab plus AI or lapatinib and AI. Investigators' choice of AI included letrozole, anastrozole, or exemestane.[37] Median PFS was 11.0 months in the combination with dual HER2 block plus AI group *versus* 5.7 months in the trastuzumab group (hazard ratio = 0.62, p = 0.0064). Median PFS in the lapatinib group was 8.3 months (hazard ratio *versus* trastuzumab group = 0.71, p = 0.0361). The incidence of grade 3 or 4 serious adverse events (SAEs) was similar in the three treatment groups,

with the exception of grade 3 diarrhea, which was higher in the lapatinib plus trastuzumab arm (13%).

All these trials in the MBC setting confirmed that hormonal therapy, including an AI and dual anti-HER2 therapy, can be safely and effectively combined.

New strategies in metastatic HER2-positive, endocrine-responsive disease

CDK4/6 pathway activation is a well-known mechanism of resistance to endocrine therapy, consequently CDK4/6 inhibitors have shown activity in cellular models of acquired resistance to endocrine therapies.[38,39]

Moreover, preclinical studies have demonstrated that ER-positive or HER2-positive cell lines are the most sensitive to inhibition by CDK4/6 inhibitors, and that the combination of CDK4/6 inhibitors and hormonal therapy or CDK4/6 inhibitors and anti-HER2 agents have synergistic effects.[40]

These data collectively indicate that CDK4/6 could be a therapeutic target that functions downstream of both ER and HER2 pathways. The potential efficacy of multiple blocks including CDK4-5 inhibitor in HER positive disease were recently confirmed in the neoadjuvant setting while results in the metastatic setting are not yet available.

NA-PHER2 (NCT 02530424) is a multicohort, open-label, exploratory, phase II study. In this study, the eligible patients received as neoadjuvant therapy a combination of dual anti HER

therapy (trastuzumab and pertuzumab) for six cycles plus a CDK4/6 inhibitor (palbociclib) and a hormonal therapy [fulvestrant (500 mg) every 4 weeks for five cycles].[41] The coprimary endpoints were change from the baseline in Ki67 expression at 2 weeks of treatment and at surgery, and changes in apoptosis from baseline to surgery. A total of 30 patients were assessed for primary and secondary endpoints. At surgery, eight (27%; 95% CI 12–46) patients had a pathological complete response in breast and axillary nodes. The most frequent grade 3 adverse events were neutropenia [10 (29%)] and diarrhoea [5 (14%)].

In the MBC setting, several studies are ongoing with CDK 4-6 inhibitors, anti HER2 therapy, and hormonal therapy. These studies are summarized in Table 3 and include a phase I/II trial assessing the side effects and best dose of anastrozole, palbociclib, trastuzumab, and pertuzumab in treating participants with ER- and HER2-positive MBC.

There is a phase Ib/II trial that studies the side effects and best dose of ribociclib (a CDK4/6 inhibitor) with trastuzumab or trastuzumab emtansine in MBC.

MonarcHER (NCT02675231) is a phase II, open-label, study in postmenopausal women with hormonal-receptor-positive and HER2-positive locally advanced or MBC previously treated with ≥2 HER2-directed therapies in the advanced disease setting, with T-DM1 and a taxane in any disease setting.

This trial aims to evaluate the effectiveness of abemaciclib (a selective inhibitor of CDK4 and CDK6) plus trastuzumab with or without fulvestrant or chemotherapy.

The results of these studies will contribute to clarifying the role of target treatment in a subgroup of HER2-positive breast cancer.

A resistance to anti-HER2 therapy may arise through PI3K/Akt/mTOR pathway activation.[42] The PI3K/AKT pathway is downstream from the site of action of HER2-targeted drugs, making its activation an important resistance pathway.

A pooled analysis of a large number (>950) of HER2-positive patients from five neoadjuvant trials that tested the efficacy of single or dual anti-HER2 therapy with chemotherapy reported that PIK3CA mutant tumors are associated with lower pCR rates compared with wild-type tumors, especially within the ER-positive subgroup.[43]

The BOLERO 1 and 3 trials evaluated the mTOR inhibitor everolimus in HER2-MBC, but showed only a small benefit at the cost of significant toxicity.[44,45]

Conversely, treatment with alpelisib (an orally bioavailable, small-molecule, α-specific PI3K inhibitor) and fulvestrant prolonged PFS among patients with PIK3-mutated, ER-positive, HER2-negative advanced breast cancer who had received endocrine therapy previously.[46]

Recently, a small study reported that the combination of alpelisib and T-DM1 is tolerable and demonstrates activity in trastuzumab-resistant HER2-positive MBC. Furthermore, activity was observed in T-DM1-resistant disease.[47] These data suggest that PIK3CA inhibition targets an important resistance pathway to anti-HER2 therapy and provides the rationale for further studies of PI3K inhibition in refractory HER2-positive MBC to validate these results.

Discussion

The currently recommended first-line treatment for HER2-positive MBC is trastuzumab, pertuzumab, and a taxane. If the cancer progresses during or after first-line therapy, T-DM1 is recommended for 2nd-line treatment.[48] However, these guidelines do not propose distinct management strategies for ER+ and ER− HER2+ BC.

HER2-positive, hormonal-receptor-positive breast cancer represents a heterogeneous disease that has a unique feature, namely the presence of three targets.

The results of early studies that focused on the HER2-positive and hormonal-receptor-positive disease (triple-positive), showed that the combination of hormonal therapy plus an anti-HER2 drug is more effective compared with hormonal therapy alone. However, the improvement in PFS is moderate, suggesting that interruption of the crosstalk between HER2 and ER-α might be effective only in a few cases or for a short duration. These trials did not have a trastuzumab alone arm, thus it is not known whether the addition of endocrine therapy to HER2-targeted therapy actually improves PFS; however, trastuzumab

Table 3. Ongoing trials with CDK 4/6 inhibitors and anti HER2 blockade and hormonal therapy in metastatic breast cancer.

CDK 4/6 inhibitor	Phase study	Population	Study end point	Treatment arm	ClinicalTrials.gov number
Palbociclib	I/II	Up to 1 previous line of anti HER2 therapy	The number of patients in the phase Ib part of the study with any adverse events (AE). PFS (phase II part)	Tucatinib + Palbociclib + letrozole	NCT 3054363
Palbociclib	II	2–4 previous lines of HER2 therapy	PFS at 6 months	Palbociclib + trastuzumab +/– letrozole	NCT 02448420
Palbociclib	I/II	First line advanced HER2 positive	DLT MTD CBR	Palbociclib + trastuzumab + pertuzumab + anastrozole	NCT 03304080
Ribociclib	Ib/II	Cohort A: at least one previous line of anti HER2 therapy B at least trastuzumab, pertuzumab, TDM1	MTD or Recommended phase II Dose (RP2D) CBR	A Ribociclib + TDM1 B Ribociclib + trastuzumab	NCT 02657343
Abemaciclib	II	At least 2 lines anti HER2 therapy	PFS	Abemaciclib + trastuzumab + fulvestrant *versus* Abemaciclib + trastuzumab *versus* trastuzumab + chemotherapy	NCT 02675231

CBR, clinical benefit rate; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; PFS, progression free survival.

by itself, with no chemotherapy, is much less effective, probably due to the incomplete inhibition of the HER receptor.[49]

The subsequent step was to evaluate whether the dual HER2 blockade combined with hormonal therapy (AI) was superior to a single block in interfering with crosstalk between the ER and HER2. These data suggest that maintenance strategies after taxane in first-line therapy are safe; although no randomized studies prove the strategy is superior to dual blockade alone, it remains valid in ER-positive patients following induction chemotherapy. Moreover, the use of dual anti-HER2 inhibition represents a promising strategy to further improve the clinical outcomes of these patients. This suggests that a niche of patients with HER2-positive and hormone-receptor-positive disease may be treated only with endocrine and anti HER 2 therapies, therefore sparing chemotherapy. The possibility of avoiding chemotherapy leads to more manageable treatment with the possibility of prolonging it for a long period. This is a relevant aspect because, although advanced breast cancer is a treatable disease, it is still generally incurable and the goals of care are to optimize both length and quality of life.[48]

Taken together, these data suggest that, among highly selected patients with ER-positive and HER2-positive breast cancer, it is possible to avoid chemotherapy using only targeted therapies that include the dual anti-HER2 blockade (with either pertuzumab and trastuzumab or lapatinib and trastuzumab) with hormonal therapy or anti-HER2 monotherapy. The dual blockade can be used since it provides a benefit in PFS. However, the greater side effects, higher costs, and lack of OS benefit so far, when compared with monotherapy, should be discussed with the patient weighing the pros and cons of each treatment.

In endocrine-responsive disease and HER2-negative MBC, all currently available CDK4, six inhibitors combined with hormonal therapy (AI or fulvestrant) radically modified the course of disease, showing large improvement in PFS compared with hormonal therapy alone.[50–52] It is possible that the CDK 4/6 inhibitor will play a role

also in HER-positive disease. Indeed, the possibility of revert the resistance of trastuzumab using CDK4/6 inhibition will lead to the development of CDK4/6 inhibition in HER2-positive disease.

The toxicity profile of CDK4/6 inhibition limits its use in combination with chemotherapy, thereby rendering it a good candidate for the combination with endocrine therapy plus biological agents.

In conclusion, better knowledge of the mechanism of anti-HER2 resistance could permit the development of new drugs and treatment. Current research fields include the role of the microenviroment (e.g. immune-system) or the use of CDK4/6 and PI3K inhibitors.

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