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REVIEW ARTICLE

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Dual HER2 blockade in adjuvant and neoadjuvant treatment of HER2-positive breast cancer: the role of pertuzumab

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ABSTRACT

Trastuzumab and pertuzumab belong to the group of humanised IgG1 monoclonal antibodies produced using recombinant DNA technology. The synergism of action of both antibodies results from their different targets: trastuzumab binds to the IV subdomain of the HER2 receptor and blocks signals independent of the ligand, while pertuzumab binds to subdomain II of this receptor and blocks ligand-dependent signals. Adding pertuzumab to trastuzumab and chemotherapy in pre-operative (neoadjuvant) treatment of HER2-positive breast cancer patients increases complete pathological response rates without enhancing adverse reactions. It was also shown in patients with breast cancer that pCR resulting from pre-operative treatment may translate into improved survival parameters.

Key words: trastuzumab, pertuzumab, perioperative therapy, breast cancer, HER2

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Introduction

The epidermal growth factor receptor (HER, ErbB) family consists of four membrane receptors with tyrosine kinase activity: ErbB1 (HER1), ErbB2 (HER2), ErbB3 (HER3), and ErbB4 (HER4) [1, 2]. As a result of interaction between them, homo- and heterodimers are formed. In breast cancer patients overexpressing HER2, the presence of HER2:HER3 heterodimers is associated with increased cell proliferation and worse prognosis. Preclinical studies have shown that the combination of two monoclonal antibodies — trastuzumab and pertuzumab — provides better control of HER2-positive breast cancer cell growth in comparison with trastuzumab alone [3–6]. Trastuzumab and pertuzumab belong to the group of humanised growth IgG1 monoclonal antibodies produced using recombinant DNA technology in Chinese hamster ovary (CHO) cell lines. The synergism of action of both antibodies results from their different targets — trastuzumab binds to the IV subdomain of the HER2 receptor and blocks signals independent of the ligand, while pertuzumab binds to the subdomain II of this receptor and blocks ligand-dependent signals [3–6].

Evaluation of response to neoadjuvant (preoperative) treatment

In 2012 the US Food and Drug Administration (FDA) set up the Collaborative Trials in Neoadjuvant Breast Cancer (CTneoBC) working group to properly plan the research and interpret their results during the process of accelerated registration. The first effect of CTneoBC's work was a meta-analysis, which showed that the pathological complete response (pCR) is associated with event-free survival (EFS) or overall survival (OS). This association applies especially to the so-called aggressive phenotypes of breast cancer: triple-negative, HER2-positive without expression of oestrogen (ER) and/or progesterone receptors (PgR), and luminal carcinomas with low grade of histological differentiation [7]. For this reason, the FDA and EMA (European Medicines Agency) can register new drugs used prior to surgery based on pCR as a surrogate for survival parameters [8, 9]. Hence, in the best interest of the patients, it was assumed that many years of waiting for the results of the trails evaluating ESF and OS could deprive many patients of the possibility of receiving potentially effective treatment. Moreover, the aim of induction

Table 1. Clinical studies with trastuzumab in the pre-operative setting

Study	N	Regimen	pCR (%)	3-year DFS/EFS (%)
MDACC [13]	45 *vs.* 19	H+(P→FEC) *vs.* P→FEC	60 *vs.* 26	100 *vs.* 85
NOAH [14]	117 *vs.* 118	H+(AP→P→CMF) *vs.* AP→P→CMF	43 *vs.* 22; p < 0.0007	71 *vs.* 59; p = 0.001
GeparQuattro [15]	146 *vs.* 144 *vs.* 136	H+(EC→D *vs.* EC→DX *vs.* EC→D→X)	33 *vs.* 31 *vs.* 35	BD
Hannah [16]	260 *vs.* 263	H_{SC}+D→H_{SC}+FEC *vs.* H_{IV}+D→H_{IV}+FEC	45 *vs.* 41	BD

pCR — pathologic complete response; DFS — disease free survival; EFS — event-free survival; H — trastuzumab; P — paclitaxel; E — epirubicin; C — cyclophosphamide; F — fluorouracil; M — methotrexate; D — docetaxel; X — capecitabine; BD — lack of data

Table 2. Clinical studies involving dual blockade in the pre-operative setting — "2 generation"

Study	Phase	Regimen	pCR (%)	p-value
NeoALTTO [18]	3	$L_{6\ wks.}$→$L/P_{12\ wks.}$ *vs.* $H_{6\ wks.}$→$H/P_{12\ wks.}$ *vs.* $L/H_{6\ wks.}$→$L/H/P1_{2\ wks.}$	51 *vs.* 20 *vs.* 29	0.0001
CALGB 40601 [19]	3	P/H/L *vs.* P/H *vs.* P/L→ ddAC→34×H	51 *vs.* 40 *vs.* 32	0.11
NSABP-B41 [20]	3	AC→P/H/L *vs.* AC→P/H *vs.* AC→P/L	62 *vs.* 52 *vs.* 53	0.095
CHER-LOB [21]	3	P/H/L→FEC/H/L *vs.* P/H→FEC/H *vs.* P/L→FEC/L	47 *vs.* 25 *vs.* 26	0.019

pCR — pathologic complete response; D — docetaxel; P — paclitaxel weekly; H — trastuzumab; L — lapatinib; dd — dose dense; F — 5-fluorouracil, A — doxorubicin; C — cyclophosphamide; E — epirubicin

treatment in breast cancer is to increase the proportion of sparing surgeries and to avoid the need to remove axillary lymph nodes, which is directly related to regression of the primary tumour and metastases in regional lymph nodes, respectively. The de-escalation of local treatment in breast cancer patients was reflected in guidelines of the St. Gallen Consensus Conference 2017 [10].

The definition of pCR adopted by FDA in the process of accelerated drug registration is the absence of invasive and pre-invasive cancer in the breast and lymph nodes (ypT0/pN0) or the absence of an invasive component only (ypT0/TisypN0) [8]. This is in line with the definition used in the studies conducted by the German Breast Group and MD Anderson Cancer Centre as well as with the TNM American Joint Committee on Cancer/International Union Against Cancer classification. In turn, the definition of pCR used in the National Surgical Adjuvant Breast and Bowel Project (NSABP) allows the presence of tumour cells in the lymph nodes, and in the criteria accepted by Sataloff et al. — also microinvasions up to 1 mm within the primary tumour [8, 11, 12].

Neoadjuvant (pre-operative) treatment

Chemotherapy regimens with trastuzumab

Several studies have shown that the addition of trastuzumab to chemotherapy in pre-operative treatment of HER2-positive, locally advanced and early breast cancer (tumour size over 2 cm) may increase the pCR rate (Table 1) [13–16]. In the phase 3 NOAH study, during longer follow-up (median over five years), it was also shown that the combination of trastuzumab with chemotherapy prolongs EFS, albeit without significant effect on OS [17]. A later phase 3 trial comparing the subcutaneous and intravenous forms of trastuzumab confirmed a high pCR rate (approximately 45%), with ER expression being the only factor influencing pCR rate in both arms (ER– *vs.* ER+), HR = 2.68, 95% CI 1.85–3.87, p < 0.0001) [16]. Currently, in pre-operative treatment, trastuzumab is combined with chemotherapy regimens that do not differ from those used after surgery in an adjuvant setting. In order to reduce the risk of cardiac complications, the simultaneous use of trastuzumab and anthracyclines is not recommended in both cases [10].

Chemotherapy regimens with dual HER2 blockade

Lapatinib and trastuzumab

Adding lapatinib, reversible EGFR, and HER2 receptor tyrosine kinase inhibitor to trastuzumab and chemotherapy allowed an increase in the pCR rate (Table 2) [18–21]. However, this benefit was achieved at the expense of the severity of adverse effects, mainly grade 3 diarrhoea and hepatic toxicity (increase in transaminase levels). As a result, despite the fact that in the NeoALTTO trial obtaining pCR was associated with

Table 3. Clinical studies involving dual blockade in the pre-operative and post-operative setting

Study	Phase	Regimen
NeoALTTO [18]	3	$L_{6\ wks.}$→L/$P_{12\ wks.}$→OP→3×FEC→$L_{34\ wks.}$ *vs.* H_6→H/P_{12}→OP→3×FEC→H_{34} *vs.* L/H_6→L/H/P_{12}→OP→3×FEC→L/H_{34}
ALTTO [30]	3	$CHT_{12–18\ wks.}$ or $ANT_{9–12}$ →T_{12} or DK_{18} in combination with anti-$HER2_{52\ wks.}$: T *vs.* L *vs.* T_{12}→L_{34} *vs.* T/L_{52}
NeoSphere [23]	2	4×D/H→OP→3×$FE_{90}C/H_{cycles\ 5–17}$ *vs.* 4×D/H/PE→OP→ 3×$FE_{90}C/H_{5–17}$ *vs.* 4×D/PE→OP→3×$FE_{90}C/H_{5–21}$ *vs.* 4×H/PE→OP→4×D→3×$FE_{90}C/H_{5–17}$
APHINITY [31]	3	3–4×FAC/FEC→3–4×D//PE/$H_{18\ cycles}$ or 12×P/PE/H_{18} *vs.* 4×AC/$EC_{every\ 3\ or\ 2\ wks.}$→4×D//PE/$H_{18}$ or 12×P/PE/H_{18} *vs.* 6×DK//PE/H_{18}

D — docetaxel (75→100 mg/m^2 every 3 weeks IV); PE — pertuzumab (840→420 mg every 3 weeks IV); P — paclitaxel (80 mg/m^2 weekly IV); H — trastuzumab (8→6 mg/kg every 3 weeks IV); L — lapatinib; dd — dose dense; F — 5-fluorouracil, A — doxorubicin; C — cyclophosphamide; E — epirubicin; K — carboplatin; OP — surgical operation; CHT — chemotherapy; ANT — anthracyclines; T — taxoids

longer three-year EFS (HR = 0.38, 95% CI 0.22–0.63, p = 0.0003) and OS (HR = 0.35; 95% CI 0.15–0.70; p = 0.005) [22], the combination of lapatinib and trastuzumab is currently not recommended in pre-operative treatment [10].

Trastuzumab and pertuzumab

The phase 2 NeoSphere study compared four regimens of pre-operative treatment in patients with locally advanced and operable breast cancer: docetaxel (D) and trastuzumab (H), D, H, and pertuzumab (P), D and P, and H and P, all at intervals of three weeks [23]. After four cycles of induction treatment the patient underwent surgery, which, depending on previous treatment, was followed either by trastuzumab in a total of 17 applications without pertuzumab, with complementary chemotherapy $FE_{90}C$ (three cycles of fluorouracil 600 mg/m^2, epirubicin 90 mg/m^2, cyclophosphamide 600 mg/m^2) or, in the case of arm H and P — four docetaxel cycles and three $FE_{90}C$ cycles administered successively [23]. The highest pCR rate (45.8%) was achieved in arm D, H, and P, including 63.2% of patients without ER expression. Importantly, pertuzumab did not increase the severity of adverse reactions, including cardiological complications. During extended observation in the NeoSphere study (median five years), the proportion of patients without tumour recurrence was slightly higher in the group receiving regimen D, T, and P (84%, 95% CI 72–91%) than in the group receiving D/T (81%; 95% CI 72–88%) [24]. The phase 2 study with low statistical power of comparisons including survival parameters, makes the interpretation of the results on DFS difficult. Analysis of biomarkers in this study showed a positive relationship between the level of HER2 expression and pCR rate and worse response in patients with mutation in exon 9 of *PIK3CA* gene [25]. The aim of another phase 2 trial (TRYPHAENA) was to assess the cardiac safety of short-term (18 weeks) pre-operative treatment with pertuzumab and trastuzumab in combination with concurrent or sequential chemotherapy with or without anthracyclines (1–3 × $FE_{100}C$/PH→4–6 × $D_{75–100}$/PH; 1–3 × $FE_{100}C$/→4–6 × $D_{75–100}$/PH; 6 × D_{75}/carboplatin$_{AUC6}$/PH) [26]. In this study, there were no differences in cardiac tolerance, including asymptomatic lowering of the left ventricular ejection fraction (LVEF) and symptomatic heart failure. Regardless of the adopted definition (ypT0/is or ypT0ypN0), the percentage of obtained pCR was within the range 50–66% [26]. Similarly to the NeoSphere study, a higher pCR rate was obtained in patients without expression of steroid receptors [23, 26].

Pre-operative *vs.* post-operative treatment in the anti-HER2 therapy era

In the studies conducted prior to implementation of anti-HER2 therapy, it was shown that the survival time of patients with early breast cancer is not dependent on whether systemic treatment is used before or after surgery. However, pre-operative hormone therapy or/and chemotherapy increases the applicability of sparing surgeries, and achieving pCR translates into an improvement in DFS and OS [27, 28]. After the introduction of anti-HER2 treatment, it was shown that the combination of molecularly targeted drugs and chemotherapy before surgery allows an increase in pCR rate (Table 1 and 2) [13–16, 18–21]. A meta-analysis of more than 5000 patients with HER2-positive breast cancer and 38 studies — published in 2016 — additionally showed that achieving pCR is also associated with longer ESF and OS [29].

Single (trastuzumab) and dual HER2 blockade (lapatinib/trastuzumab or pertuzumab/trastuzumab) added to chemotherapy were compared in the NeoALTTO (pre-operative treatment) and ALTTO (post-operative treatment), as well as [18, 30] the NeoSphere (pre-operative treatment) and APHINITY (postoperative treatment) studies, respectively (Table 3) [23, 31]. In the NeoALTTO study, EFS and OS prolongation was only obtained in patients with pCR [22], and in the phase 3 ALTTO trial relative improvement in DFS was 16% in

favour of lapatinib plus trastuzumab, but this difference was not significant (HR = 0.84; 97.5% CI 0.70–1.02, p = 0.048), and patients receiving lapatinib had more adverse reactions [30].

A combination of dual (pertuzumab/trastuzumab) HER2 blockade and chemotherapy in NeoSphere allowed a higher pCR rate and a trend toward improvement of DFS as compared to single blockade with trastuzumab [23, 24]. In the phase 3 APHINITY study, the addition of pertuzumab to chemotherapy and 12-month treatment with trastuzumab (hormone therapy also allowed) increased the percentage of three-year survivors without invasive relapse from 90 to 92% (HR = 0.77; 95% CI 0.62–0.96, p = 0.02), without increasing the rate of adverse reactions. The magnitude of DFS benefit was higher in the subgroup of patients with metastases in axillary lymph nodes (HR = 0.77, 95% CI 0.62–0.96, p = 0.02) [31].

In 2013, the FDA registered pertuzumab in combination with trastuzumab and docetaxel in patients with HER2-positive, locally advanced (including inflammatory) and early breast cancer (diameter of primary tumour above 2 cm or metastases in axillary lymph nodes). In 2015 this regimen was registered by EMA and also included in the St. Gallen Consensus Conference Guidelines [8, 9, 32]. In 2016, the British NICE (National Institute for Health and Care Excellence) recognised the use of pre-operative treatment with pertuzumab and trastuzumab in combination with chemotherapy, stressing however the need to negotiate with the manufacturer the treatment costs [33]. According to the St. Gallen guidelines from 2017, the use of this regimen could be considered in patients with HER2-positive cancer treated with a radical intention in the case of lymph node involvement and/or absence of steroid receptor expression [10].

Summary

In pre-operative treatment, the dual anti-HER2 blockade involving trastuzumab and pertuzumab in combination with chemotherapy increases the pCR rate and at the same time does not increase the toxicity of treatment. In patients with breast cancer, obtaining pCR as a result of preoperative treatment may translate into improvement of survival parameters, especially in relation to aggressive phenotypes (triple-negative and HER2-positive cancers). International recommendations recommend a dual blockade with trastuzumab and pertuzumab as one of the pre-operative options for treatment of HER2-positive breast cancer patients. This particularly applies to patients with unfavourable prognostic factors, such as the presence of metastases in lymph nodes and/or negative expression of steroid receptors.

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Conflict of interest: lectures, participation in congresses, advisory boards membership: AstraZeneca, Pfizer, Roche, GSK, Novartis, Teva, Amgen, Egis.

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