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ORIGINAL ARTICLE

# De-escalation strategies in HER2-positive early breast cancer (EBC): final analysis of the WSG-ADAPT HER2+/HR− phase II trial: efficacy, safety, and predictive markers for 12 weeks of neoadjuvant dual blockade with trastuzumab and pertuzumab ± weekly paclitaxel

U. A. Nitz[1,2], O. Gluz[1,2,3]*, M. Christgen[4], E.-M. Grischke[5], D. Augustin[6], S. Kuemmel[7], M. Braun[8], J. Potenberg[9], A. Kohls[10], K. Krauss[11], A. Stefek[12], C. Schumacher[13], H. Forstbauer[14], T. Reimer[15], H. Fischer[16], C. Liedtke[17,18], R. Wuerstlein[19], J. Schumacher[20], R. Kates[1], H. Kreipe[3] & N. Harbeck[1,19], on behalf of the West-German Study Group (WSG)-ADAPT Investigators

[1]West German Study Group GmbH, Moenchengladabach; [2]Evangelical Hospital Johanniter Bethesda, Breast Center Niederrhein, Moenchengladbach; [3]University of Cologne, Cologne; [4]Institute of Pathology, Medical School Hannover, Hannover; [5]Department of Gynecology and Obstetrics, University Clinics Tuebingen, Tuebingen; [6]Breast Center Ostbayern, Deggendorf; [7]Breast Center, Clinics Essen-Mitte, Essen; [8]Rotkreuz Clinics Munich Breast Center, Munich; [9]Department of Oncology Evangelical Waldkrankenhaus Berlin, Berlin; [10]Department of Gynecology and Obstetrics, Evangelical Hospital, Ludwigsfelde; [11]Department of Gynecology and Obstetrics, University Clinics RWTH, Aachen; [12]Breast Center, Evangelical Hospital Johanniter, Stendal; [13]Breast Center, St. Elisabeth Hospital Cologne, Cologne; [14]Oncology Practice Network, Troisdorf; [15]Department of Gynecology and Obstetrics, University Clinics Rostock, Suedstadt; [16]Breast Center, Evangelical Hospital Gelsenkirchen, Gelsenkirchen; [17]Department of Gynecology and Obstetrics, University Clinics Schleswig-Holstein/Campus Luebeck, Luebeck; [18]Charite Berlin; [19]Breast Center, Department of Gynecology and Obstetrics, University of Munich (LMU) and CCCLMU, Munich; [20]Palleos Healthcare, Statistics, Wiesbaden, Germany

*Correspondence to*: Dr Oleg Gluz, West German Study Group and Evangelical Hospital Johanniter Bethesda, Breast Center Niederrhein, Ludwig-Weber-Str. 15, 41061 Moenchengladbach, and University of Cologne, Germany. Tel: +49-2161-9812330; Fax: +49-2161-5662319; E-mail: oleg.gluz@wsg-online.com

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**Background:** Response rates in HER2-overexpressing EBC treated with neoadjuvant chemotherapy and trastuzumab (T) have been improved by addition of pertuzumab (P). The prospective, phase II, neoadjuvant WSG-ADAPT HER2+/HR− trial assessed whether patients with strong early response to dual blockade alone might achieve pathological complete response (pCR) comparable to that of patients receiving dual blockade and chemotherapy.

**Patients and methods:** Female patients with HER2+/HR− EBC (M0) were randomized (5:2) to 12 weeks of T + P ± weekly paclitaxel (pac) at 80 mg/m$^2$. Early response was defined as proliferation decrease ≥30% of Ki-67 (versus baseline) or low cellularity (<500 invasive tumor cells) in the 3-week biopsy. The trial was designed to test non-inferiority for pCR in early responding patients of the T + P arm versus all chemotherapy-treated patients.

**Results:** From February 2014 to December 2015, 160 patients were screened, 92 were randomized to T + P and 42 to T + P+pac. Baseline characteristics were well balanced (median age 54 versus 51.5 years, cT2 51.1 versus 52.4%, cN0 54.3 versus 61.9%); 91.3% of patients completed T + P per protocol and 92.9% T + P+pac. The pCR rate in the T + P+pac arm was 90.5%, compared with 36.3% in the T + P arm as a whole. In the T + P arm, 24/92 were classified as non-responders, and their pCR rate was only 8.3% compared with 44.7% in responders (38/92) and 42.9% in patients with unclassified early response (30/92). No new safety signals were observed in the study population.

**Conclusion:** Addition of taxane monotherapy to dual HER2 blockade in a 12-week neoadjuvant setting substantially increases pCR rates in HER2+/HR− EBC compared with dual blockade alone, even within early responders to dual blockade. Early non-response under dual blockade strongly predicts failure to achieve pCR.

**Key words:** pertuzumab/trastuzumab with paclitaxel weekly in HER2+/HR− EBC

## Introduction

HER2-overexpressing BC is a biologically aggressive subtype occurring in about 15%–25% of newly diagnosed cases [1]. Adjuvant standard of 1 year of trastuzumab (T)+chemotherapy reduces distant recurrence risk by 40%–50%[2]. Pathological complete response (pCR) after neoadjuvant therapy has strong prognostic impact [hazard ratio for event-free survival (EFS) of 0.39] in HER2 disease; pCR rates in HR−/HER2+ exceed those in HR+/HER2+ disease and correlate more strongly with EFS (hazard ratio of 0.15) [3–5].

Neoadjuvant anti-HER2 dual blockade trastuzumab and pertuzumab (T + P) with chemotherapy were approved by the Food and Drug Administration and the European Medical Agency in patients with high-risk EBC, based primarily on the neoadjuvant phase II NeoSphere trial in advanced HER2+ EBC [6–8], and supported by positive survival results in the metastatic CLEOPATRA trial [9]. NeoSphere demonstrated superior pCR (and suggested reduced invasive 5-year recurrence risk, in exploratory analysis) for 12 weeks P + T+Docetaxel (Doc)—versus the former standard, T + Doc—followed by anthracycline-containing chemotherapy and trastuzumab in all patients. NeoSphere patients with HR−/HER2+ tumors treated by (very well tolerated) T + P alone experienced promising pCR of 27%; however no predictive markers for this or other CHT-free combinations [9] have yet been identified [10]

West German Study Group - Adjuvant Dynamic marker-Adjusted Personalized Therapy trial (WSG-ADAPT) is the first randomized trial concept utilizing predictive information from early response to therapy (documented by tumor proliferation drop after 3-week induction treatment) for de-escalation in EBC [11]. The de-escalation strategies are specific to the sub-type: In HR+/HER2- disease, emphasis was placed on avoiding chemotherapy in patients at intermediate risk of recurrence with good early response to endocrine therapy. In HER2-positive disease, the WSG-ADAPT trials have evaluated new anti-HER2 therapies in a randomized, neoadjuvant phase II design.

As HER2+/HR− and HER2+/HR+ BC appear to be biologically distinct [12], with more aggressive but also more chemosensitive characteristics of HER2+/HR− subgroup, as evidenced by response to neoadjuvant therapy and subsequent survival rates, separate ADAPT-WSG neo-adjuvant trials were designed for these HER2+ entities [13]. The HER2+/HR+ trial assessed the predictive impact of early response on pCR,the potential added value of endocrine therapy + T or T-DM1, and omission of polychemotherapy in the neo-adjuvant setting. The final analysis of the randomized, phase II WSG-ADAPT HER2+/HR− trial reported here has evaluated the added value of chemotherapy in the presence of optimized anti-HER2 therapy (trastuzumab + pertuzumab), by comparing 12 weeks of dual anti-HER2-blockade alone to their combination with weekly paclitaxel. A particular aim was to identify an early-responder population with regard to pCR after T + P alone treatment, which is strongly associated with lomg-term prognosis particularly in HER2+/HR− BC and assess whether this population might be spared neo-adjuvant chemotherapy.

## Patients and methods

Eligible patients were female, aged >18, centrally confirmed HER2-positive [14], ER and PR-negative (immunostaining in <1% of tumor nuclei), with histologically confirmed, unilateral primary BC, no evidence of distant metastasis, good Performance Status (East Cooperative Oncology Group (ECOG) status ≤1 or Karnofsky Index ≥ 80%), normal organ and heart function. Clinical tumor stages included cT1-4c, and any clinical nodal status (cN) was permitted; participation was strongly recommended in patients with cT2+ (or cT1 with cN+). Written informed consent was obtained before patient enrollment.

Exclusion criteria were previously known hypersensitivity to the study substances; prior malignancy with DFS < 10 years (except curatively treated basalioma of the skin or pTis of the cervix uteri), non-operable (including inflammatory) BC; previous or concurrent treatment with cytotoxic agents, concurrent treatment with other experimental drugs; participation in another trial; known polyneuropathy ≥ grade 2; severe and relevant co-morbidities.

Eligible patients were randomized (supplementary Figure S1, available at *Annals of Oncology* online) to pertuzumab (loading dose 840 mg, then 420 mg three weekly) plus trastuzumab (loading dose of 8 mg/kg, then 6 mg/kg three weekly) (T + P) for four cycles versus T + P 3 weekly + pac 80 mg/m$^2$ every three weeks. Randomization was carried out locally, stratified by center and nodal status, with intended 5 : 2 ratio of T + P arm to T + P+pac arm. After neoadjuvant experimental treatment, surgery or histological confirmation of non-pCR by core needle biopsy was obligatory within three weeks; pCR at surgery was defined as no invasive tumor residuals in breast and lymph nodes.

Trial eligibility verification, baseline assessment, and early-response assessment of the on-treatment, 3-week biopsy were carried out by central pathology. Ki-67 was assessed using the rabbit monoclonal Ki-67-antibody 30-9 (Ventana Medical System, Inc.); measurement required at least 500 invasive tumor cells.

The early-response criterion after one therapy cycle was subject to evaluation and adaptation in pre-planned interim analysis; the resulting criterion for early response was either relative Ki-67 decrease ≥30% versus baseline ('proliferation response' [15]) or—as in the WSG ADAPT HER2+/HR+ sub-trial—<500 invasive tumor cells in the 3-week biopsy ("cellularity response") [13].

After surgery, treatment according to national standards was recommended: 4× epirubicin/cyclophophamide (→12xPac weekly in the T + P-arm), 40 weeks trastuzumab and radiotherapy. At investigator discretion, further chemotherapy could be omitted for patients achieving pCR after 12-week neoadjuvant therapy.

The WSG-ADAPT HER2+/HR− trial was approved by national authorities and all responsible local ethics committees. Trial conduct was supervised by an independent DSMB; trial registration number (clinicaltrials.gov) is NCT01779206.

### Statistical considerations

The trial was designed to test non-inferiority of pCR in early responders receiving T + P vs. all patients receiving T + P+pac. With the aim of comparing approximately equal numbers of early responders of the T + P arm with the entire T + P+pac arm, the randomization ratio was targeted at 5:2, in view of the pre-trial estimate of 60% non-responders in the T + P arm (i.e. two-fifths responders).

For the primary hypothesis, 'non-inferiority' was defined as pCR no worse than 23% lower in the early-responder fraction of the T + P arm than in the entire T + P+pac arm. Planning assumed a high pCR rate of 60% in the T + P+pac arm; the pre-trial estimate of pCR for the T + P arm as a whole was 30%, with a hypothesized 'enhanced' pCR of 60% among early responders (equal to that of the T + P+pac arm).

Recruitment of n = 220 patients was planned (allowing for 10% drop-outs). Under these assumptions, the trial had 80% power to reject the null hypothesis (inferiority).

Secondary end points were toxicity and safety, EFS, and overall survival. Toxicity was reported according to Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.

In safety analysis, *P* values were computed by Fisher's exact test as flagging devices to highlight potential AE differences between treatment arms without multiple-testing corrections; these are not intended as robust measures of statistical significance.

Interim analysis was planned after $n = 75$ treated patients for evaluation of study assumptions and early-response criteria. A second interim analysis was recommended by the DSMB that examined early response and pCR: The probability of demonstrating the primary non-inferiority hypothesis was assessed by Bayesian analysis of data from $N = 120$ patients. The resulting low probability (<1%) led to recommended stoppage of the trial. Confidence intervals (exact, based on F-distribution) for pCR in each trial arm as a whole and for their relative differences (based on normal approximation) are reported here, as well as pCR rates (and classification percentages) by responder category in the T + P arm.

Python 2.7.12 (Python Software Foundation, Beaverton, OR) was used for statistical analysis.

## Results

Between February 2014 and December 2015, 160 patients from 40 centers were screened and 134 randomized. The ITT set consisted of 92 patients allocated to T + P and 42 patients allocated to T + P+pac. 91.3% completed T + P and 90.5% T + P+pac. Patient flow and study conduct are shown in the CONSORT diagram (supplementary Figure S2, available at *Annals of Oncology* online).

Patient characteristics (supplementary Table S1, available at *Annals of Oncology online*) were balanced between the two arms (T + P versus T + P+pac): median age 54 versus 51.5 years; cT1 tumors in 41.3% versus 40.5%; cT2 tumors in 51.1% versus 52.4%; cN0 in 54.4% versus 61.9% of patients.

The observed pCR (ypT0/is, ypN0) rate in the T + P arm was $p_A$=34.4% ($CI_{95\%}$, 24.7% to 45.2%), quite close to the pre-trial estimate. However, at $p_B$=90.5% ($CI_{95\%}$, 77.4% to 97.3%]) the observed pCR rate after 12 weeks of T + P+pac was far higher than the pre-trial estimate. The corresponding relative difference attributable to chemotherapy was ($p_B$-$p_A$)=56.1% ($CI_{95\%}$, 42.8% to 69.3%]).

Rates of 'total' pCR (ypT0, ypN0) were 24.4% (T + P) and 78.6% (T + P+pac) (Figure 1). No further chemotherapy was documented in 49/69 patients with pCR (71%).

Regarding early response and pCR: In the T + P arm, 24/92 (26.1%) were classified as non-responders, meaning that adequate cells for Ki-67 determination were available and proliferation response failed to occur; non-responding patients had 8.3% pCR. Early response occurred in 38/92 (41.3%), while in 30/92 (32.6%), neither early-response criterion (proliferation, cellularity) could be determined, usually because the tumor lesion was not identifiable in ultrasound; pCR in responders and indeterminate cases were 44.7% and 42.9%, respectively.

In the T + P+pac arm, neither of the two non-responders achieved 'total' pCR, though one achieved ypT0/is, ypN0.

### Safety

Ten patients experienced SAEs (n = 5 T + P; n = 5 T + P+pac); six SAEs were reportedly therapy-related ($n = 4$ T + P, $n = 2$ T + P+pac). All patients recovered without sequelae. AEs of any grade were reported so far in 68.9% of T + P-treated patients and 97.6% of T + P+pac-treated patients (supplementary Table S1, available at *Annals of Oncology* online). Further details are given in the supplement, available at *Annals of Oncology* online.

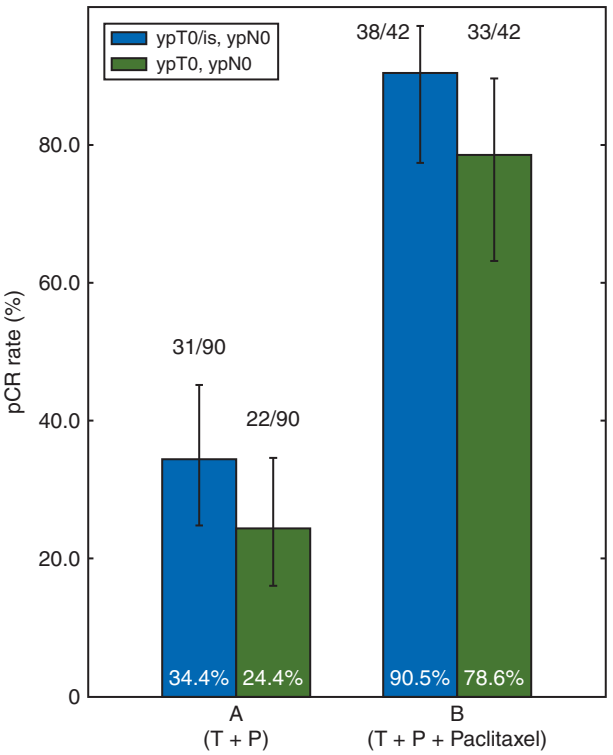


**Figure 1.** Pathological complete response (pCR) rates in the treatment arms.

## Discussion

Addition of mono-chemotherapy to dual blockade in the WSG-ADAPT HER2+/HR− neoadjuvant trial reduced the number of patients failing to achieve pCR from about two-thirds to about one-tenth. The pCR rate of 34.4% in the chemotherapy-free arm is consistent with other trials: 27% after 12 weeks of T + P [6], 36% (ypT0/any ypN) after tratuzumab-lapatinib (T + L) [16]; 43% after 18 weeks of T + L [17]. However, 90.5% pCR in the chemotherapy-containing arm was considerably higher than anticipated and so far superior to T + P that no clinically relevant sub-population of early responders in this chemotherapy-free arm could have exhibited comparable (non-inferior) pCR in this 12-week neoadjuvant setting.

Nonetheless, the T + P arm of the WSG-ADAPT HER2+/HR− phase II trial provides striking – though explorative – results suggesting poor pCR (8.3%) in patients failing to achieve response after one cycle of dual blockade; much lower than in others (early responders: 44.7%, unclassifiable: 42.9%).

Identification of early responders by measurement of pre- and post-therapeutic Ki-67 requires a minimum number of tumor cells in a second tumor biopsy. This technique appears quite promising after three weeks of neoadjuvant therapy in HR+/HER2-negative EBC [18]. However, tumors responding to dual

HER2 blockade in HR−/HER2-positive EBC often exhibit rapid necrosis after one cycle. Inclusion of low cellularity (besides Ki-67 drop) in early-response classification corresponds biologically to observed increases in "normal subtype "in responding patients after one cycle of neoadjuvant anti-HER2 therapy, as described by Prat et al. [17]. Further analyses from the ADAPT trial will evaluate the role of imaging (e.g. ultrasound, magnetic resonance imaging, mammography) and/or further predictive factors (e.g. molecular subtypes, immune markers [10, 17]) in this setting.

Notwithstanding these technical issues in *positive* response identification, our results suggest that Ki-67 drop (by standard histopathology) already has good *negative* predictive value for pCR in HR−/HER2-positive EBC: i.e. non-response is a clearly identifiable signal, and there is little doubt that early non-response to neoadjuvant dual blockade is a strong predictor of poor pCR. Future neoadjuvant trials with dual anti-HER2 blockade alone, an early-response assessment should be further evaluated: early non-responders require another neoadjuvant therapy approach. The very high pCR rate in the T + P+pac arm suggests that non-responders would likely have benefitted from neoadjuvant chemotherapy. Potential approaches include chemotherapy plus dual blockade or (considering safety and cost-effectiveness [19]) chemotherapy with a different anti-HER2 compound.

As for early responders to T + P, the pCR rate of about 40-45% in the WSG-ADAPT HER2+/HR− trial was still less than half that of patients receiving chemotherapy plus dual blockade (as recommended by all international guidelines). The well-established correlation of pCR with survival—particularly in the HER2+/HR− setting—would tend to argue against forgoing neoadjuvant chemotherapy (in addition to dual blockade). To resolve these issues, a sequential approach, adding chemotherapy at later stage of therapy in early responders (currently under investigation in the metastatic setting [20]), should be examined in further prospective EBC trials. Determination of an optimal chemotherapy strategy in early responders should be based on a holistic, comprehensive health economic assessment including safety and long-term survival in an era of increasingly potent anti-HER2 therapies.

The extremely high observed pCR (ypT0/is/ypN0) of 90.5% in the taxane monochemotherapy-containing arm of the WSG-ADAPT HER2+/HR− trial may reflect the specific characteristics of the 'non-luminal' (HER2+/HR−) population among HER2+ patients. In the NeoSphere trial, Gianni et al. [6] reported pCR rates of 39.3% and 45.8% (ypT0, any ypN) after twelve weeks T + P+Doc in unselected HER2+ EBC and 63.2% (ypT0, any ypN) in the HER2+/HR− subset. Whereas the rates for dual blockade alone were comparable, the reported pCR in NeoSphere HR− patients receiving T + P+Doc was about 14% below the lower 95%-confidence interval for ypT0/is/ypN0 in patients receiving T + P+pac in the WSG-ADAPT HER2+/HR− trial which might be explained rather by more advanced tumors compared with the ADAPT trial than by taxane type used [21].

Given our substantial pCR rate after only 12 weeks of T + P+pac, the optimal chemotherapy backbone for the dual HER2 blockade with T + P needs to be defined. The TRYPHANEA trial reported for HER2+/HR− disease breast-only-pCR rates of 79.4% and 65% for 3xFEC+/-P + T followed by 3xDoc + P+T, 83.8% for 6xdocetaxel/carboplatin + P+T (TCbHP). About one-fifth of the patients in TRYPHANEA, where cardiotoxicity was the primary end point, had locally advanced BC [22]. GeparSepto has shown pCR rates of 81.4% and 72.9% in patients treated by 12xnab-paclitaxel + P+T versus 12xpaclitaxel + P+T followed by 4xEC, respectively [23], in a comparable cohort. In the adjuvant setting, a 12xpaclitaxel weekly + T backbone as in WSG-ADAPT HER2+/HR− has become a standard treatment option in N0 patients with tumor size up to 30 mm [24]. In the first-line metastatic therapy, addition of carboplatin to a taxane plus trastuzumab did not result in better efficacy [25]. The excellent efficacy observed in WSG-ADAPT HER2+/HR− with 12xPac + P+T renders questionable an intensification of the chemotherapy backbone in HER2+/HR− disease beyond taxane monotherapy, particularly in patients with pCR. Nevertheless, long-term outcome data in patients with pCR omitted further chemotherapy need to be awaited before the WSG-ADAPT HER2+/HR− regimen can be considered standard-of-care.

Several meta-analyses support a strong correlation of pCR with outcome in HER2+/HR− disease [4, 5]; direct conclusions on the survival impact of neoadjuvant and adjuvant dual anti-HER2 blockade with P + T in EBC will soon be available from the APHINITY trial. In the meantime, neoadjuvant treatment seems to be a reliable setting for a selective use of dual blockade as a promising tool for future de-escalation strategies.

The WSG-ADAPT HER2+/HR− trial has demonstrated that chemotherapy is a key component in the treatment of HER2+/HR− disease; our pCR rates compare favorably with those reported for longer and more aggressive chemotherapy, again posing the question of de-escalation of toxicity as already reported for the adjuvant setting [24]. The strong correlation between pCR and outcome in non-luminal HER2+ EBC suggests that patients achieving pCR after 12 weeks of P + T+pac may be sufficiently treated by adding adjuvant trastuzumab alone and no more aggressive chemotherapy. The ADAPT results are particularly important in view of the statistically significant, but moderate absolute 3-year invasive-DFS improvement (from 93.2% to 94.1%) by adjuvant 1-year P + T therapy compared with trastuzumab alone with anthracycline and/or taxane-based polychemotherapy which suggest that this adjuvant therapy option is not appropriate for unselected patient cohorts with HER2-positive EBC [26]. Future outcome data for our trial will demonstrate for which patients in particular such de-escalation approaches using dual blockade are best suited, also in view of the APHINITY results. Nevertheless, with respect to cost-effectiveness discussions and resource-limitation worldwide as well as the intent to avoid late toxicities, the ADAPT strategy of de-escalation should be further explored. Determining neoadjuvant early response could also support adjuvant de-escalation strategies as piloted by FinHER [27], PHARE [28], and most recently by the ShortHER trial [29].

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