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CLINICAL TRIAL

Efficacy of neoadjuvant pertuzumab in addition to chemotherapy and trastuzumab in routine clinical treatment of patients with primary breast cancer: a multicentric analysis

Peter A. Fasching[1] · Andreas D. Hartkopf[2] · Paul Gass[1] · Lothar Häberle[1,3] · Leyla Akpolat-Basci[4] · Alexander Hein[1] · Bernhard Volz[1] · Florin-Andrei Taran[2] · Naiba Nabieva[1] · Birgit Pott[4] · Friedrich Overkamp[5] · Hanna Einarson[2] · Peyman Hadji[6] · Hans Tesch[7] · Johannes Ettl[8] · Diana Lüftner[9] · Markus Wallwiener[10] · Volkmar Müller[11] · Wolfgang Janni[12] · Tanja N. Fehm[13] · Andreas Schneeweiss[14] · Michael Untch[15] · Dirk Pott[16] · Michael P. Lux[1] · Thomas Geyer[1] · Cornelia Liedtke[17] · Harald Seeger[2] · Sarah Wetzig[4] · Arndt Hartmann[18] · Rüdiger Schulz-Wendtland[19] · Erik Belleville[20] · Diethelm Wallwiener[2] · Matthias W. Beckmann[1] · Sara Y. Brucker[2] · Hans-Christian Kolberg[4]

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Abstract

Purpose Neoadjuvant combination treatment with chemotherapy (CTX), trastuzumab (TZM), and pertuzumab (PTZ) has been shown to result in higher pathological complete response rates (pCR) in comparison with treatment with chemotherapy and trastuzumab (CTX/TZM). This analysis was aimed at real-world validation of these results from prospective randomized trials.

Methods In a retrospective analysis conducted in the PRAEGNANT network, patients were eligible for inclusion if they had either received neoadjuvant therapy with CTX/TZM or chemotherapy, trastuzumab, and pertuzumab (CTX/TZM/PTZ) and subsequently underwent surgery for their primary breast cancer. The effect of the two neoadjuvant regimens on pCR in addition to commonly applicable predictors of pCR was analyzed in 300 patients from three study sites, using logistic regression analyses with treatment arm, age, clinical tumor stage, grading, and hormone receptor status as predictors.

Results pCR with complete disappearance of all tumor cells was seen in 30.2% ($n=58$) of patients treated with CTX/TZM and in 52.8% ($n=57$) of those treated with CTX/TZM/PTZ. CTX/TZM/PTZ was positively associated with pCR (adjusted odds ratio 2.44; 95% CI 1.49–4.02). Mastectomy rates were not influenced by the therapy.

Conclusions The results of clinical trials were confirmed in this dataset of patients who were treated outside of clinical trials in everyday routine work. pCR rates can be improved by 20% with pertuzumab in routine clinical use.

Keywords Breast cancer · Neoadjuvant · Trastuzumab · Pertuzumab · pCR · Real-world data · Registry

Introduction

Since the discovery of human epidermal growth factor receptor 2 (HER2) as a prognostic factor in breast cancer patients [1] and the subsequent development of trastuzumab in anti-HER2 therapy, treatment for this group of breast cancer patients has improved immensely [2–8]. In the preoperative neoadjuvant setting, pathological complete response (pCR) rates of around 40% have been reported [9–18]. In the subgroup of HER2-positive patients, moreover, pCR is an established predictor of the prognosis, and improvements in pCR appear to be associated with an improvement in the prognosis to some extent [11, 12, 19].

Peter A. Fasching and Andreas D. Hartkopf have contributed equally to this study.

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✉ Peter A. Fasching
peter.fasching@uk-erlangen.de

Extended author information available on the last page of the article

However, although the prognosis has improved in this subgroup of patients, 20–25% of patients relapse and one in seven patients will die within 10 years after the diagnosis [7, 20, 21]. A strong need to improve anti-HER2 therapies therefore remains.

The combination of trastuzumab and pertuzumab is an established standard therapy for patients with advanced breast cancer [22]. Combining trastuzumab and pertuzumab with neoadjuvant chemotherapy in the NeoSphere trial resulted in a pCR rate of 42% and was significantly superior to neoadjuvant chemotherapy and trastuzumab alone (23%) [23]. A 5 year survival analysis of the NeoSphere trial did not show any significant differences when docetaxel and trastuzumab + pertuzumab were compared with docetaxel (HR 0.69; 95% CI 0.34–1.40) [19].

Two further neoadjuvant trials have reported high pCR rates in the range of 57–66% with combinations of different chemotherapies with trastuzumab and pertuzumab [24, 25].

The data from these studies led to the approval of pertuzumab in combination with trastuzumab and chemotherapy as neoadjuvant therapy for patients with primary breast cancer [26, 27]. However, in Germany, where newly approved drugs have to undergo reimbursement assessments by statutory health-insurance providers, the German Federal Joint Committee (G-BA) and the Institute for Quality and Efficiency in Health Care (IQWiG) did not conclude that there is any additional benefit of adding pertuzumab to the neoadjuvant combination treatment of chemotherapy and trastuzumab based on the prognostic benefit, which was at that time unconfirmed [28].

Recently, the adjuvant APHINITY trial reported the effects of the addition of pertuzumab in the adjuvant setting. With a median follow-up of 45 months for 4805 randomized patients, a small but statistically significant difference was seen (3-year invasive disease-free survival rate in the pertuzumab arm 94.1% versus 93.2% in the placebo arm; $P = 0.045$) [29].

With these data from the neoadjuvant setting and a potential benefit in the disease-free survival in the adjuvant setting, real-world data may be helpful for assessing the value of pertuzumab in the neoadjuvant setting in routine clinical use. This paper presents a comparison of two cohorts of patients with HER2-positive primary breast cancer who received neoadjuvant therapy consisting of either chemotherapy and trastuzumab, or chemotherapy and trastuzumab plus pertuzumab.

Patients and methods

The PRAEGNANT research network

The PRAEGNANT study (Prospective Academic Translational Research Network for the Optimization of the Oncological Health Care Quality in the Adjuvant and Advanced/Metastatic Setting; NCT02338167, [30–32]) is an ongoing registry with documentation similar to that used in clinical trial databases. In general, patients can be included at any time point during the course of their disease. For the analysis presented here, the study infrastructure was used for a retrospective analysis of patients from three study sites (Bottrop, Erlangen, and Tübingen). All patients treated in these study sites had been screened for their respective neoadjuvant anti-HER2 treatment. The objective was to identify all patients in these study sites who had received neoadjuvant treatment either with trastuzumab and chemotherapy (CTX/TZM) or with chemotherapy, trastuzumab, and pertuzumab (CTX/TZM/PTZ). Detailed patient referral and recruitment mechanisms for each study site are described in Supplementary Table 1. A total of 402 patients were identified.

Patients were excluded in the following hierarchical order: patients who were participating in a neoadjuvant clinical trial ($n = 85$), patients with metastases at the primary diagnosis ($n = 9$), and patients with metachronous bilateral breast cancer ($n = 8$), resulting in a study population of 300 patients treated in clinical routine. All of the relevant ethics committees approved the study.

Data collection

Patient data were derived from the patients' charts and original pathology reports. The data were collected by trained staff and documented on an electronic case report form [30]. Data for the analysis were monitored and queried remotely, and training and monitoring were carried out on site at the study sites. All participating study sites are certified breast cancer centers which prospectively document treatment and follow-up data. Although the analysis is retrospective, it used prospectively collected follow-up data.

Therapies

All participating study sites were certified breast cancer centers that administer treatment in accordance with the German national guidelines and therapy recommendations. Adherence to guidelines is monitored and audited on an annual basis. A high degree of adherence with the guidelines (> 95%) is therefore assured. Breast-conserving therapy is the aim unless oncological safety is of concern. Adjuvant radiotherapy is performed in all patients with breast-conserving therapy or with mastectomy and additional risk factors. Adjuvant endocrine therapy is performed in all hormone receptor-positive patients.

Definition of pCR, hormone receptor, HER2 status, and grading

Estrogen receptor status, progesterone receptor status, HER2 status, and grading were requested for documentation. There was no central review of biomarkers. The site protocols recommend assessing estrogen receptor and progesterone receptor status as positive if ≥ 1% were stained. A positive HER2 status required an immunohistochemistry score of 3 + or positive fluorescence in situ hybridization/competitive in situ hybridization (FISH/CISH) findings. The pCR assessment was directly documented from the pathology reports. The following definitions of pCR were used. The end point for the primary analysis was $pCR_{complete}$, defined as the complete disappearance of all tumor cells regardless of invasiveness (ypT0 ypN0). For secondary analyses, pCR_{inv} was used, defined as the complete disappearance of invasive tumor cells (ypT0 or ypTis and ypN0).

Statistical analysis

The primary objective was to assess whether the treatment regimen (CTX/TZM versus CTX/TZM/PTZ) was associated with $pCR_{complete}$ and whether the effect of therapy on $pCR_{complete}$ varied between patient subgroups, taking into account predictors for pCR.

For this purpose, a logistic regression model (*basic model*) was fitted with $pCR_{complete}$ ("yes" vs. "no") as the outcome and the following predictors for $pCR_{complete}$: age at diagnosis (continuous), grading (ordinal, G1–G3), clinical tumor size (ordinal; T1–T4), hormone receptor status (categorical; positive, negative). Patients with missing outcomes were excluded from the analyses. Missing predictor values were imputed, and continuous predictors were used as natural cubic spline functions, as done in Salmen et al. [33]. Subsequently, an additional logistic regression model was fitted containing the treatment regimen (categorical; CTX/TZM versus CTX/TZN/PTZ), the predictors from the previous basic model, and the interaction between the treatment regimen and the predictors in the basic model (*interaction model*). The two models were compared using the likelihood ratio test. A significant test result indicates that the treatment regimen influenced $pCR_{complete}$ beyond the other predictors, either across all patients or at least within one of the subgroups defined by the predictors taken into consideration. If the result was not significant, no further analyses were conducted, to avoid false-positive results.

However, if the *P* value was significant, the interaction model was compared with a reduced logistic regression model, the basic model with the treatment regimen added but without the interaction terms (*reduced model*), using the likelihood ratio test again. In case of significance, subgroup-specific odds ratios (ORs) for the treatment regimen adjusted for the other predictors were calculated, using the interaction model. If the result was not significant, an adjusted overall OR for therapy regimen was calculated, using the reduced model.

The performance of the logistic regression models in terms of discrimination and calibration was measured using the area under the receiver operating characteristic curve (AUC) and the Hosmer–Lemeshow statistic χ^2 test comparing predicted and observed $pCR_{complete}$ events, as done recently in [34]. A large *P* value indicates satisfactory calibration. To address overfitting, cross-validated AUC values were also calculated, as described in [35]. The smaller the difference between the cross-validated AUC and the original AUC, the lower the amount of overfitting.

Inter-center heterogeneity was assessed using a likelihood ratio test that compared the reduced model with the reduced model extended by the predictor "study center" and the interaction between treatment regimen and study center. A large *P* value indicates that associations between the treatment regimen and pCR were independent of the individual centers.

Secondary objectives were to explore the effect of therapy on pCR_{inv} and the effect of therapy on mastectomy rates ("yes" vs. "no"). Logistic regression analyses were performed with pCR_{inv} and mastectomy, respectively, as outcomes. For both outcomes, a logistic regression model with the treatment regimen and the predictors from the basic model above was fitted, and adjusted ORs for the treatment regimen were presented. The effect of treatment regimen and pCR on the disease-free survival was estimated using the Kaplan–Meier method. Survival time was censored at 5 years after diagnosis.

All the tests were two-sided, and a *P* value of < 0.05 was regarded as statistically significant. Calculations were carried out using the R system for statistical computing (version 3.0.1; R Core Team, Vienna, Austria, 2013).

Results

Patient, tumor, and study characteristics

A total of 192 patients received treatment with CTX/TZM and 108 were treated with CTX/TZM/PTZ. The patient characteristics relative to the treatment regimen are listed in Table 1. The patient and tumor characteristics appeared to be quite balanced between the two therapy groups. Patient and tumor characteristics relative to the study site are also provided in Supplementary Table 2.

The patients received either anthracycline-based or platinum-based chemotherapy. Platinum-based treatment

Table 1 Patient characteristics relative to treatment regimen

Characteristic	CTX/TZM		CTX/TZM/PTZ	
	n or mean	% or SD	*n* or mean	% or SD
Age at diagnosis	54.3	13.1	54.5	11.6
cT				
cT1	74	38.5	46	42.6
cT2	85	44.3	52	48.1
cT3	10	5.2	5	4.6
cT4	23	12	5	4.6
Hormone receptor				
Negative	64	33.3	40	37.0
Positive	128	66.7	68	63.0
Grading				
1	3	1.6	1	0.9
2	86	44.8	42	38.9
3	103	53.6	65	60.2
Year of diagnosis				
≤ 2010	59	30.7	0	0.0
2011–2014	115	59.9	0	0.0
≥ 2015	18	9.4	108	100.0
$pCR_{complete}$				
No	134	69.8	51	47.2
Yes	58	30.2	57	52.8
Platinum-based CTC				
No	115	59.9	38	35.2
Yes	77	40.1	70	64.8
pCR_{inv}				
No	110	57.3	41	38.0
Yes	82	42.7	67	62.0
Mastectomy				
No	113	58.9	56	52.8
Yes	79	41.1	50	47.2
Number of operations				
1	168	88.9	101	93.5
≥ 2	21	11.1	7	6.5

CTX chemotherapy, $pCR_{complete}$ pathological complete remission (all tumor cells), pCR_{inv} pathological complete remission (all invasive tumor cells), *PTZ* pertuzumab, *SD* standard deviation, *TZM* trastuzumab

was chosen in 147 patients (49%) and anthracycline-based treatment in 153 patients (53%) All but one patient received neoadjuvant taxane therapy. The usage of platinum-based therapies is shown in Supplementary Table 2.

Associations between established predictors of pCR and pCR rates are shown in Supplementary Table 3. The pCR rates were higher in patients with cT1 and cT2 tumors than in those with cT3 and cT4 tumors. Patients with a positive hormone receptor status had a lower pCR rate, and higher grading correlated with higher pCR rates.

Therapy regimen and pCR effect

Comparison of logistic regression models with and without the treatment regimen revealed that the therapy regimen significantly influenced $pCR_{complete}$ in addition to the predictors considered ($P < 0.01$, first likelihood ratio test). The interactions between therapy regimen and the other predictors, however, were not significant ($P = 0.27$, second likelihood ratio test). Thus, it was not shown that the effect of therapy differed between patient subgroups. The adjusted OR for CTX/TZM/PTZ versus CTX/TZM was 2.44 (95% CI 1.49–4.02) (Table 2).

The reduced logistic regression model used to predict risks was well calibrated. The difference between actual and predicted events was quite low ($P = 0.71$, Hosmer–Lemeshow test). The discrimination ability of the final regression model was satisfactory at AUC = 0.662. The cross-validated AUC was 0.632, indicating some overfitting. The cross-validated AUC values for the basic and interaction models were lower (0.588 and 0.614, respectively), confirming the main result that the treatment regimen is predictive without differences between subgroups. The study center did not influence the treatment effect ($P = 0.88$, likelihood ratio test).

The results for pCR_{inv} were similar. The adjusted OR for CTX/TZM/PTZ versus CTX/TZM was 2.04 (95% CI 1.24–3.35) (Table 3). Unadjusted pCR rates are shown in Table 1: patients with CTX/TZM showed a $pCR_{complete}$ in 30.2% ($n = 58$), in comparison with 52.8% ($n = 57$) for patients treated with CTZ/TZM/PTZ. The pCR_{inv} rates were 42.7% ($n = 82$) and 62.0% ($n = 67$), respectively.

Therapy and surgery outcomes

It was not found that the treatment choice influenced the mastectomy rate (OR, 1.45; 95% CI 0.86–2.44; $P = 0.16$). The mastectomy rates were 41.1% ($n = 79$) with CTX/TZM treatment and 47.2% ($n = 50$) with CTX/TZM/PTZ treatment. An analysis of the number of operations needed was not meaningful, as only 28 patients (21 with CTX/TZM/PTZ and seven with CTX/TZM/PTZ) required repeat surgery.

Survival analyses

The Kaplan–Meier curves for disease-free survival are shown in Fig. 1. The statistical power was low, as there were only 34 events and the follow-up period for pertuzumab-treated patients (with drug approval in 2015) was short. Overall-survival analyses were not performed, with only seven events during the observation period.

Table 2 Prediction of pathological complete response ($pCR_{complete}$) with therapy regimen in addition to known predictors

Predictor		Coefficient (SE)	OR (95% CI)	*P* value
Intercept		– 0.9653 (0.8872)	–	
Age at diagnosis[a]	Per year	0.0014 (0.0099)	1.00 (0.98, 1.02)	0.89
Grading	Per grade	0.3283 (0.2417)	1.39 (0.86, 2.23)	0.17
cT	Per stage	– 0.2056 (0.1467)	0.81 (0.61, 1.09)	0.16
Hormone receptor	Negative[b]	0	1	–
	Positive	– 0.6164 (0.2575)	0.54 (0.33, 0.89)	0.02
Treatment regimen	CTX/TZM[b]	0	1	–
	CTX/TZM/PTZ	0.8934 (0.2540)	2.44 (1.49, 4.02)	< 0.001

Coefficients of logistic regression model with $pCR_{complete}$ as outcome, odds ratios adjusted for the other predictors, and *P* values from Wald tests are shown

CI confidence intervals, *cT* clinical tumor stage, *CTX* chemotherapy, *OR* odds ratio, *PTZ* pertuzumab, *SE* standard error, *TZM* trastuzumab

[a]The continuous predictor age fitted best as linear function

[b]Reference category

Table 3 Prediction of complete disappearance of invasive tumor cells (pCR_{inv}) with treatment regimen in addition to known predictors

Predictor		Coefficient (SE)	OR (95% CI)	*P* value
Intercept		– 0.0882 (0.8502)	–	–
Age at diagnosis[a]	Per year	– 0.0044 (0.0096)	1.00 (0.98, 1.01)	0.65
Grading	Per grade	0.4101 (0.2329)	1.51 (0.95, 2.38)	0.08
cT	Per stage	– 0.2953 (0.1403)	0.74 (0.57, 0.98)	0.04
Hormone receptor	Negative[b]	0	1	–
	Positive	– 0.6785 (0.2554)	0.51 (0.31, 0.84)	< 0.01
Treatment regimen	CTX + TZM[b]	0	1	–
	CTX + TZM + PTZ	0.7121 (0.253)	2.04 (1.24, 3.35)	< 0.01

Coefficients of logistic regression model with pCR_{inv} as outcome, odds ratios adjusted for the other predictors, and *P* values from Wald tests are shown

CI confidence intervals, *cT* clinical tumor stage, *CTX* chemotherapy, *OR* odds ratio, *PTZ* pertuzumab, *SE* standard error, *TZM* trastuzumab

[a]The continuous predictor age fitted best as linear function

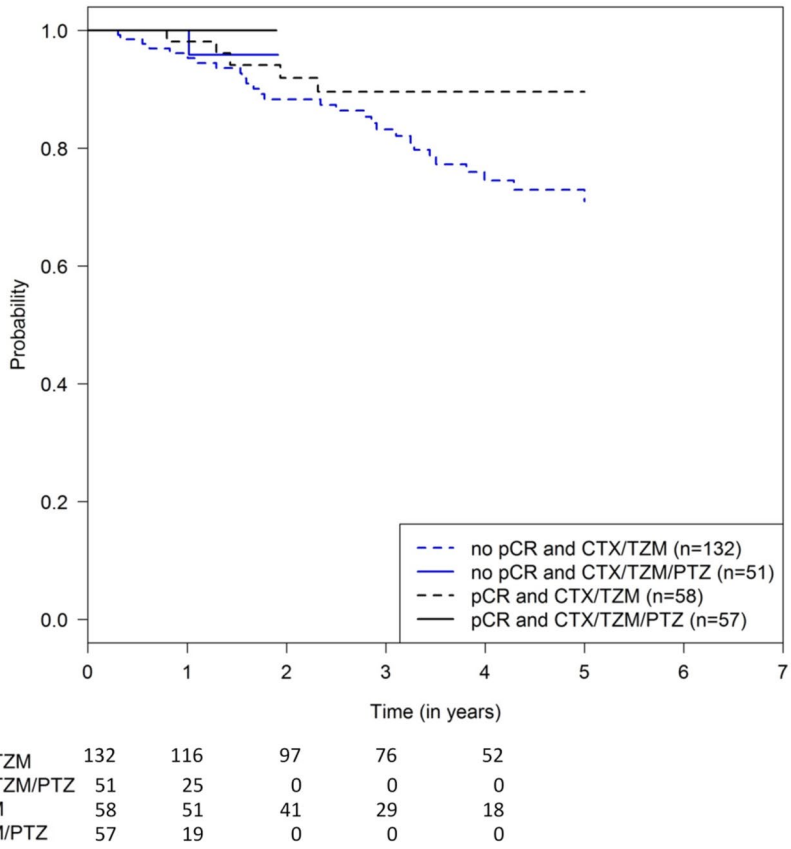
[b]Reference category

Discussion

This study shows that outside of clinical trials, patients treated with CTX/TZM/PTZ in everyday neoadjuvant clinical routine had an approximately 20% higher pCR rate in comparison with patients treated with CTX/TZM alone. This effect was consistent among all of the subgroups. The choice of neoadjuvant treatment did not have any influence on the mastectomy rate. The number of events and the median follow-up period did not allow any conclusions to be drawn at present regarding the prognosis.

This real-world analysis shows pCR rates similar to those reported in clinical trials using the triple combination of CTX/TZM/PTZ. Initially, the NeoSphere trial showed a pCR rate (pT0/is pN0) of 42% [23]. In the TRYPHAENA trial, two anthracycline-containing regimens (5-fluorouracil, epirubicin, and cyclophosphamide [FEC] + pertuzumab + trastuzumab followed by docetaxel + pertuzumab + trastuzumab and FEC followed by docetaxel + pertuzumab + trastuzumab) were compared with the anthracycline-free regimen of docetaxel + carboplatin + pertuzumab + trastuzumab [24]. The rates of pCR (pT0/pTis pN0/pN1) in that study were 61.3%, 57.3%, and 66.2%, respectively [24]. The BERENICE trial recently achieved pCR rates (pT0/pTis pN0) of 61.8% in patients treated with dose-dense chemotherapy followed by paclitaxel + TZM/PTZ and 60.7% in those treated with FEC followed by docetaxel + TZM/PTZ [25]. A U.S.-based registry reported pCR rates (pT0/pTis pN0) of 40% in patients treated with CTX/TZM and 57% in those treated with CTX/TZM/PTZ (calculated from [36]).

The present data, with 62.0% for pT0/is pN0 and 52.8% for pT0 pN0, confirm these published findings. With regard



At Risk					
no pCR and CTX/TZM	132	116	97	76	52
no pCR and CTX/TZM/PTZ	51	25	0	0	0
pCR and CTX/TZM	58	51	41	29	18
pCR and CTX/TZM/PTZ	57	19	0	0	0

Fig. 1 Kaplan–Meier curves for disease-free survival relative to pathological complete response ($pCR_{complete}$) and treatment regimen. The numbers of events were 28 (no pCR and CTX/TZM), 1 (no pCR and CTX/TZM/PTZ), 5 (pCR and CTX/TZM), and 0 (pCR and CTX/TZM/PTZ)

to the low pCR rates in the NeoSphere trial, it should be borne in mind that the NeoSphere patients were only treated with docetaxel, while anthracycline or platinum were not permitted in the trial protocol. The length of neoadjuvant chemotherapy was therefore shorter than is usually the case in everyday clinical practice and in other studies.

The results of this report and earlier registry and clinical trials data [23, 24, 36, 37] show that the improvement in pCR rates is reproducible in clinical practice; instead of three out of ten women achieving a pCR, the figure is five out of ten with complete disappearance of all tumor cells from the breast and axillary lymph nodes. In Germany, about 7300 HER2-positive patients receive neoadjuvant treatment per year. Adding pertuzumab to the neoadjuvant treatment regimen could allow approximately 1500 additional women to achieve complete disappearance of tumor cells.

Despite these clear differences and the impact on a relevant number of patients, the German Federal Joint Committee (G-BA) and the Institute for Quality and Efficiency in Health Care (IQWiG) have not taken the view that there is any additional benefit from the addition of pertuzumab to neoadjuvant chemotherapy and trastuzumab, which is because of the unreported effect on the prognosis [28]. Even with the recently published data from the APHINITY study, there was only a small absolute difference of 0.9% between the treatment arms (3-year disease-free survival rates) [29], with overall-survival data still pending.

In clinical practice, this might not in fact be the most relevant argument from the patients' standpoint. Assuming that 7300 patients with HER2-positive early breast cancer are treated with neoadjuvant therapy in Germany, potentially an additional 1760 patients per year would achieve a pCR if pertuzumab were to be used in combination with trastuzumab. In addition to this argument, an independent review of the available data regarding pertuzumab in neoadjuvant treatment performed by the School of Health and Related Research Technology Appraisal Group at the University of Sheffield found that the therapy was cost-effective. The reviewers recommended providing access to neoadjuvant pertuzumab for patients with early-stage HER2-positive breast cancer [38]. Additionally, it must be borne in mind that several trastuzumab biosimilars are being introduced into health care in late 2017 and early 2018, which may reduce the total costs of this combination neoadjuvant anti-HER2 treatment.

With regard to other predictors of pCR our study showed that in this HER2 positive population hormone receptor status was a clear predictor for both outcome variables of pCR with odds ratios between 0.51 and 0.54. Other variables did not have such a stable effect on pCR

indicating the prominent role of hormone receptor status on the pCR as seen in many other neoadjuvant studies [12–15, 18].

The present study has several limitations. First, the distribution of treatment choices over the years shows that after 2014, mainly PTZ-containing therapy was administered and almost no trastuzumab any more. There is evidence showing that pCR rates are increasing over the years [39]. A cohort effect can therefore not be excluded. In addition, although the sample size is comparable to that in the NeoSphere study, some of the subgroups are rather small for adequately powered subgroup analysis. One other limitation is the lack of information about the duration of the chemotherapy and antibody therapy. Patients were considered to be treated with the drugs, if at least one cycle was documented. Also as this is real-world data, there was a variety of chemotherapy regimens including platinum. However sample sizes were to low to assess the influence of these different kinds of chemotherapies. With only three study sites, it may be difficult to generalize the data to the whole of Germany, but no differences were found between the study sites with regard to the effect of the treatment regimen on pCR.

Conclusions

This study shows that the rates of pathological complete remission in neoadjuvant treatment regimens containing trastuzumab and pertuzumab are about 20% higher than in regimens that use trastuzumab alone. This analysis of real-world data, not including any patients who were participating in clinical trials, thus supports the published data showing increases in the pCR rate through the addition of PTZ. In everyday clinical practice, it is challenging to deliberately choose a treatment regimen that has a 20% lower pCR rate. However, data regarding the prognosis need to be taken into account when the risks and benefits of this form of treatment are being assessed. With clear and measurable effects outside of clinical trials, patient-care/health-care research may be able to answer questions that have not yet been addressed or cannot be addressed in clinical studies.

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Compliance with ethical standards

Conflict of interest P.G. has received honoraria from Novartis and financial support for symposia from Novartis, Roche, and PharmaMar. A.D.H. has received honoraria from Teva, GenomicHealth, Celgene, AstraZeneca, Novartis, Pfizer, and Roche. F.A.T. has received honoraria from AstraZeneca, GenomicHealth, Novartis, and Roche. N.N. has received consultancy honoraria from Janssen-Cilag and travel support from Novartis. F.O. has received speaker and consultancy honoraria from Amgen, Celgene, AstraZeneca, Novartis, Roche, and MSD. P.H. has received honoraria, unrestricted educational grants, and research funding from Amgen, AstraZeneca, Eli Lilly, MSD, Novartis, Pfizer, and Roche. H.T. has received honoraria from Novartis, Roche, Celgene, TEVA, and Pfizer, and travel support from Roche, Celgene, and Pfizer. J.E. has received honoraria from Roche, Celgene, Novartis, Pfizer, Pierre Fabre, and TEVA, and travel support from Celgene, Pfizer, TEVA, and Pierre Fabre. D.L. has received honoraria from Aurikamed, Roche, Pfizer, Novartis, Celgene, AstraZeneca, Eli Lilly, and L'Oreal. M.W. has received speaker honoraria from AstraZeneca, Celgene, and Novartis. V.M. has received speaker honoraria from Amgen, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, Pfizer, Pierre-Fabre, Novartis, Roche, Teva, and Janssen-Cilag, and consultancy honoraria from Genomic Health, Roche, Pierre Fabre, Amgen, Daiichi-Sankyo, and Eisai. W.J. has received honoraria and research grants from Novartis. A.S. has received honoraria from Roche, Celgene, AstraZeneca, Novartis, Pfizer, Zuckschwerdt Verlag GmbH, Georg Thieme Verlag, Aurikamed GmbH, MCI Deutschland GmbH, bsh medical communications GmbH, and promedicis GmbH. M.P.L. has received honoraria from Pfizer, Roche, MSD, Hexal, Novartis, AstraZeneca, TEVA, Celgene, Eisai, medac, and Thieme for advisory boards, lectures, and travel support. C.L. reports personal fees from Celgene, from TEVA, from Pierre Fabre, from Novartis, from Amgen, from Eisai, from GSK, from Roche, from Puma, from Hexal, from Daiichi Sankyo, and from Genomic Health, outside of the submitted research. E.B. received honoraria from Novartis for consulting and clinical research management activities. P.A.F. has received honoraria from Roche, Pfizer, Novartis, and Celgene. His institution conducts research for Novartis. H.-C.K. has received honoraria from Carl Zeiss meditec, TEVA, Theraclion, Novartis, Amgen, AstraZeneca, Pfizer, Janssen-Cilag, GSK, LIV Pharma, and Genomic Health. All of the remaining authors have declared no conflicts of interest.

Ethical approval All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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Affiliations

Peter A. Fasching[1] · Andreas D. Hartkopf[2] · Paul Gass[1] · Lothar Häberle[1,3] · Leyla Akpolat-Basci[4] · Alexander Hein[1] · Bernhard Volz[1] · Florin-Andrei Taran[2] · Naiba Nabieva[1] · Birgit Pott[4] · Friedrich Overkamp[5] · Hanna Einarson[2] · Peyman Hadji[6] · Hans Tesch[7] · Johannes Ettl[8] · Diana Lüftner[9] · Markus Wallwiener[10] · Volkmar Müller[11] · Wolfgang Janni[12] · Tanja N. Fehm[13] · Andreas Schneeweiss[14] · Michael Untch[15] · Dirk Pott[16] · Michael P. Lux[1] · Thomas Geyer[1] · Cornelia Liedtke[17] · Harald Seeger[2] · Sarah Wetzig[4] · Arndt Hartmann[18] · Rüdiger Schulz-Wendtland[19] · Erik Belleville[20] · Diethelm Wallwiener[2] · Matthias W. Beckmann[1] · Sara Y. Brucker[2] · Hans-Christian Kolberg[4]

1 Department of Gynecology and Obstetrics, Erlangen University Hospital, Comprehensive Cancer Center Erlangen-EMN, Friedrich Alexander University of Erlangen–Nuremberg, Universitätsstrasse 21–23, 91054 Erlangen, Germany

2 Department of Obstetrics and Gynecology, University of Tübingen, Tübingen, Germany

3 Biostatistics Unit, Department of Gynecology and Obstetrics, Erlangen University Hospital, Erlangen, Germany

4 Marienhospital Bottrop, Bottrop, Germany

5 Oncologianova GmbH, Recklinghausen, Germany

6 Frankfurter Hormon und Osteoporosezentrum Goethestrasse, Goethestr.23, Frankfurt, Germany

7 Oncology Practice, Bethanien Hospital, Frankfurt am Main, Germany

8 Department of Obstetrics and Gynecology, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany

[9] Department of Hematology, Oncology and Tumor Immunology, Charité University Hospital, Campus Benjamin Franklin, Berlin, Germany

[10] Department of Obstetrics and Gynecology, University of Heidelberg, Heidelberg, Germany

[11] Department of Gynecology, Hamburg-Eppendorf University Medical Center, Hamburg, Germany

[12] Department of Gynecology and Obstetrics, Ulm University Hospital, Ulm, Germany

[13] Department of Gynecology and Obstetrics, Düsseldorf University Hospital, Düsseldorf, Germany

[14] National Center for Tumor Diseases and Department of Gynecology and Obstetrics, Heidelberg University Hospital, Heidelberg, Germany

[15] Department of Gynecology and Obstetrics, Helios Clinics Berlin-Buch, Berlin, Germany

[16] Onkologische Schwerpunktpraxis Bottrop, Bottrop, Germany

[17] Department of Gynecology and Breast Center, Charité University Hospital, Campus Mitte, Berlin, Germany

[18] Institute of Pathology, Erlangen University Hospital, Comprehensive Cancer Center Erlangen-EMN, Friedrich Alexander University of Erlangen–Nuremberg, Erlangen, Germany

[19] Institute of Diagnostic Radiology, Erlangen University Hospital, Comprehensive Cancer Center Erlangen-EMN, Friedrich Alexander University of Erlangen–Nuremberg, Erlangen, Germany

[20] ClinSol GmbH & Co KG, Würzburg, Germany