# Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial

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## Summary

**Background** Preclinical data suggest that triple-negative breast cancers are sensitive to interstrand crosslinking agents, and that synergy may exist for the combination of a taxane, trastuzumab, and a platinum salt for HER2-positive breast cancer. We therefore aimed to assess the efficacy of the addition of carboplatin to neoadjuvant therapy for triple-negative and HER2-positive breast cancer.

**Methods** Patients with previously untreated, non-metastatic, stage II–III, triple-negative breast cancer and HER2-positive breast cancer were enrolled. Patients were treated for 18 weeks with paclitaxel (80 mg/m² once a week) and non-pegylated liposomal doxorubicin (20 mg/m² once a week). Patients with triple-negative breast cancer received simultaneous bevacizumab (15 mg/kg intravenously every 3 weeks). Patients with HER2-positive disease received simultaneous trastuzumab (8 mg/kg initial dose with subsequent doses of 6 mg/kg intravenously every 3 weeks) and lapatinib (750 mg daily). Patients were randomly assigned in a 1:1 ratio with dynamic allocation and minimisation, stratified by biological subtype and Ki-67 level to receive, at the same time as the backbone regimens, either carboplatin (AUC 1·5 [2·0 for the first 329 patients] once a week) or no carboplatin. The primary endpoint the proportion of patients who achieved a pathological complete response (defined as ypT0 ypN0), analysed for all patients who started treatment; a p value of less than 0·2 was deemed significant for the primary endpoint. This trial is registered with ClinicalTrials.gov, number NCT01426880.

**Findings** 296 patients were randomly assigned to receive carboplatin and 299 to no additional carboplatin, of whom 295 and 293 started treatment, respectively. In this final analysis, 129 patients (43·7%, 95% CI 38·1–49·4) in the carboplatin group achieved a pathological complete response, compared with 108 patients (36·9%, 31·3–42·4) without carboplatin (odds ratio 1·33, 95% CI 0·96–1·85; p=0·107). Of the patients with triple-negative breast cancer, 84 (53·2%, 54·4–60·9) of 158 patients achieved a pathological complete response with carboplatin, compared with 58 (36·9%, 29·4–44·5) of 157 without (p=0·005). Of the patients with HER2-positive tumours, 45 (32·8%, 25·0–40·7) of 137 patients achieved a pathological complete response with carboplatin compared with 50 (36·8%, 28·7–44·9) of 136 without (p=0·581; test for interaction p=0·015). Haematological and non-haematological toxic effects that were significantly more common in the carboplatin group than in the no-carboplatin group included grade 3 or 4 neutropenia (192 [65%] *vs* 79 [27%]), grade 3 or 4 anaemia (45 [15%] *vs* one [<1%]), grade 3 or 4 thrombocytopenia (42 [14%] *vs* one [<1%]), and grade 3 or 4 diarrhoea (51 [17%] *vs* 32 [11%]); carboplatin was more often associated with dose discontinuations (141 [48%] with carboplatin and 114 [39%] without carboplatin; p=0·031). The frequency of grade 3 or 4 haematological events decreased from 82% (n=135) to 70% (n=92) and grade 3 or 4 non-haematological events from 78% (n=128) to 59% (n=77) in the carboplatin arm when the dose of carboplatin was reduced from AUC 2·0 to 1·5.

**Interpretation** The addition of neoadjuvant carboplatin to a regimen of a taxane, an anthracycline, and targeted therapy significantly increases the proportion of patients achieving a pathological complete response. This regimen seems to increase responses in patients with triple-negative breast cancer, but not in those with HER2-positive breast cancer.

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## Introduction

A six to nine times higher risk for relapse has been reported for patients with triple-negative breast cancer or with HER2-positive breast cancer who do not achieve a pathological complete response with neoadjuvant treatment.[1–3] Because of this strong prognostic effect, pathological complete response was proposed as a surrogate for survival in these two breast cancer subtypes, although outcome improvements at surgery did not correlate with improvements of survival.[4,5]

Patients with triple-negative breast cancer, compared with other subtypes, showed high pathological complete

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For the **protocol** see http://www.germanbreastgroup.de/studien/neoadjuvant/geparsixto.html

responses with neoadjuvant treatment with anthracyclines, cyclophosphamide, and taxanes.[6] Recently, an even higher proportion of patients achieving a pathological complete response was reported when bevacizumab was given simultaneously with these cytotoxic agents.[7,8] The introduction of a dual blockade of the HER2 pathway by either two antibodies or by an antibody and a tyrosine-kinase inhibitor, given simultaneously with a taxane-based chemotherapy, induced the highest rates of pathological complete response noted in patients with HER2-positive breast cancer so far.[9–11]

Carboplatin potentially adds further activity to these treatments. Preclinical data suggest that triple-negative breast cancers are more sensitive to interstrand cross-linking agents that damage the DNA such as platinum, because of deficiencies in the *BRCA*-associated DNA repair mechanism.[12] Non-randomised cohort studies suggested higher rates of pathological complete response in triple-negative breast cancer and especially in the subset of *BRCA*-mutation carriers compared with non-triple negative breast cancer in non-*BRCA*-mutation carriers.[11,13–15] A strong synergistic treatment effect was postulated in HER2-positive disease for the combination of a taxane, trastuzumab, and a platinum salt.[16] Subsequently, two phase 2 trials examined carboplatin in HER2-positive metastatic breast cancer. One trial showed superior outcome for patients receiving paclitaxel and trastuzumab in combination with carboplatin compared with patients receiving paclitaxel and trastuzumab alone at the same dose.[17] The other study did not show a similar effect when carboplatin was added to docetaxel and trastuzumab;[18] however, this study used a lower dose of docetaxel (75 mg/m²) in the carboplatin arm.

Several cohort studies reported on the neoadjuvant use of carboplatin in combination with docetaxel and trastuzumab, but until recently no randomised trial has shown the additive effect of platinum to standard type of treatment in the neoadjuvant setting.[19]

The aim of the randomised GeparSixto study was to assess the additional effect of neoadjuvant carboplatin to a regimen containing an anthracycline, a taxane, and targeted therapy (trastuzumab/lapatinib or bevacizumab) on pathological complete response in patients with stage II–III triple-negative breast cancer and HER2-positive breast cancer.

## Methods

### Patients

Women with previously untreated, unilateral or bilateral, non-metastatic primary invasive triple-negative or HER2-positive breast carcinoma were enrolled into our study if they provided written informed consent. Triple-negative status was defined as oestrogen and progesterone receptor levels of less than 1% and HER2-negative (HercepTest [Dako] score 0 or 1+ or gene amplification ratio <2·2 by in-situ hybridisation). Patients older than 18 years, having a Karnofsky performance status index 80 or greater were eligible if they had clinical stage T2–T4a-d tumours or T1c tumours with either clinical or histological stage N+ disease.[6] In patients with multifocal or multicentric breast cancer, the largest lesion was measured. Further relevant criteria for eligibility were normal haematological (absolute neutrophil count ≥2·0×10⁹ cells per L, ≥100×10⁹ platelets per L, haemoglobin ≥100 g/L), renal (creatinine ≤175 μmol/L, urine dipstick for proteinuria <2+), liver (aspartate aminotransferase, alanine aminotransferase, and total bilirubin ≤1·5 times upper normal level), and cardiac function (left ventricular ejection fraction ≥55%); no evidence of distant disease or known or suspected cardiac disease; no previous thromboembolic event; no known haemorrhagic diathesis or coagulopathy; no currently active infection; no active peptic ulcer; no incomplete wound healing or unhealed bone fracture; no pre-existing motor or sensory neuropathy of a severity grade 2 or greater; no disease with a clinically significant effect on gastrointestinal function; no history of abdominal fistula or gastrointestinal perforation of intra-abdominal abscess within 6 months before enrolment; no severe pulmonary condition or illness; no major surgery within the past 28 days or anticipation of the need for major surgery during study treatment; no previous chemotherapy for any malignancy; no previous radiation therapy for breast cancer; and no concurrent treatment with other anticancer or investigational agents.

The protocol was reviewed by the responsible ethics committee at each participating site. The conduct of the trial was supervised by an independent data and safety monitoring committee.

### Randomisation

The treatment allocation list was created and randomisation was done centrally at the German Breast Group headquarters in a 1:1 ratio to receive carboplatin or

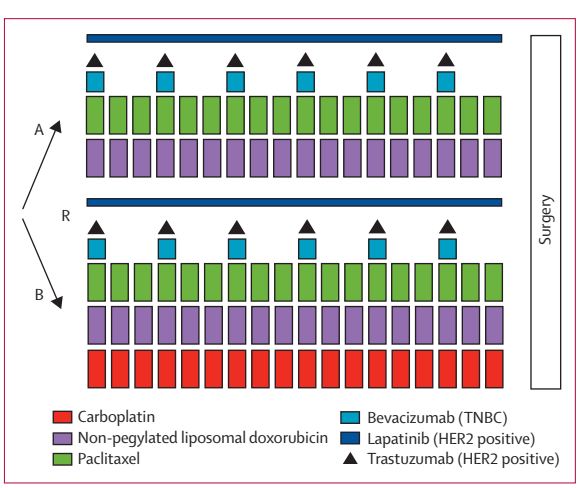


***Figure 1:*** **Trial design**
Regimens were without (A) and with (B) carboplatin. TNBC=triple-negative breast cancer.

not, according to dynamic allocation, and was stratified according to biological subtype (triple-negative or HER2-positive/hormone-receptor-negative or HER2-positive/hormone-receptor-positive), and Ki-67 level (≤20% or >20%). The minimisation method of Pocock and Simon[20] was used for randomisation. Treatment allocation was not masked.

## Procedures

The treatment regimen is shown in figure 1. All patients were scheduled to receive paclitaxel 80 mg/m² plus non-pegylated liposomal doxorubicin 20 mg/m², both given once a week for 18 weeks. The less cardiotoxic non-pegylated liposomal encapsuled form of doxorubicin[21] was chosen because patients with triple-negative breast cancer received bevacizumab 15 mg/kg intravenously every 3 weeks simultaneously with all cycles; patients with HER2-positive disease received trastuzumab as an 8 mg/kg initial dose with subsequent 6 mg/kg doses intravenously every 3 weeks and oral lapatinib 750 mg daily simultaneously with all cycles.

Patients who were randomly assigned to receive simultaneous carboplatin received the drug at a dose of 2·0 area under curve (AUC), once every week for 18 weeks. The dose was reduced to AUC 1·5 after an interim safety analysis; 329 patients had been accrued by this point. The dose of carboplatin could be reduced to AUC 1·1 in case of intolerable toxic effects.

Permitted supportive treatments were dexamethasone (2–4 mg), 5HT3 inhibitors, clemastine, ranitidine, and loperamide as standby medication for patients receiving lapatinib, but no primary prophylaxis with G-CSF was

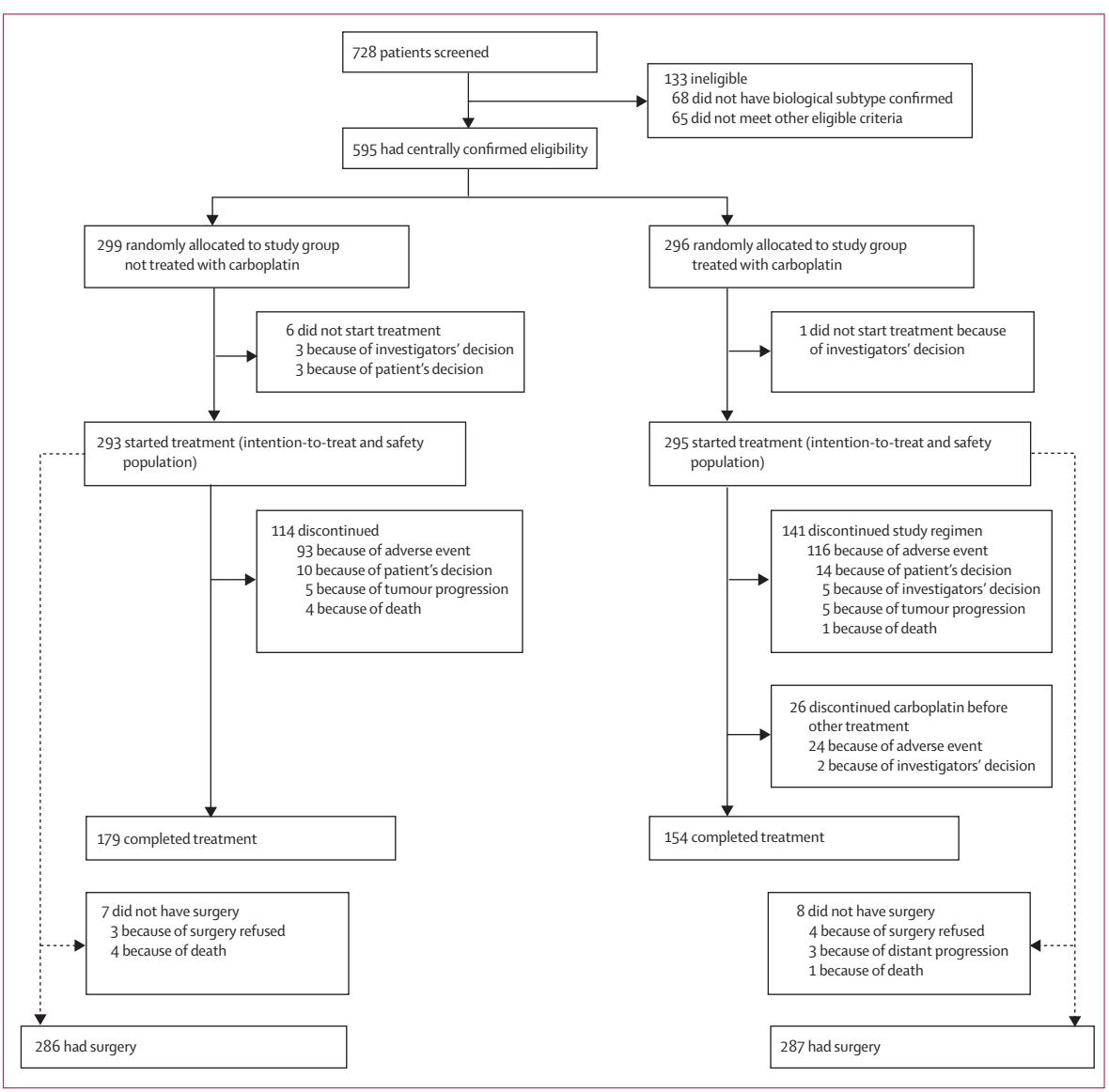


*Figure 2:* **Trial profile**

recommended. In cases of tumour progression, the study treatment was discontinued and further local or systemic treatment was permitted at the discretion of the investigator. Patients were scheduled for surgery within 21 days after last receipt of chemotherapy or after at least 28 days after the last bevacizumab infusion.

Haematological measures were assessed weekly and biochemical measures, the target lesion, and regional lymph nodes were examined by palpation every 3 weeks. Breast ultrasound was repeated every sixth week and breast ultrasound and mammography were repeated before breast surgery. Assessment of left ventricular ejection fraction by echocardiography was repeated after 9 weeks of therapy and before surgery.

| | Treatment without carboplatin (n=293) | Treatment with carboplatin (n=295) |
|---|---|---|
| **Age (years)** | | |
| <30 | 12 (4%) | 12 (4%) |
| 30 to <40 | 48 (16%) | 57 (19%) |
| 40 to <50 | 109 (37%) | 103 (35%) |
| 50 to <60 | 84 (29%) | 79 (27%) |
| 60 to <70 | 32 (11%) | 35 (12%) |
| ≥70 | 8 (3%) | 9 (3%) |
| Median (range) | 47 (21–78) | 48 (21–75) |
| **Clinical tumour stage by palpation** | | |
| cT1 | 67 (27%) | 61 (24%) |
| cT2 | 138 (55%) | 154 (61%) |
| cT3 | 26 (10%) | 25 (10%) |
| cT4a-c | 5 (2%) | 3 (1%) |
| cT4d | 15 (6%) | 11 (4%) |
| Not measurable | 42 | 41 |
| Median size, mm (range) | 30 (3–200) | 30 (10–230) |
| **Tumour stage by sonography** | | |
| cT1 | 77 (27%) | 75 (26%) |
| cT2 | 187 (64%) | 186 (65%) |
| cT3 | 7 (2%) | 12 (4%) |
| cT4a-d | 5 (2%) | 3 (1%) |
| cT4d | 15 (5%) | 11 (4%) |
| Missing | 2 | 8 |
| Median size, mm (range) | 25 (3–129) | 25 (7–180) |
| **Nodal stage by palpation** | | |
| cN0 | 160 (57%) | 171 (61%) |
| cN1 | 98 (35%) | 94 (34%) |
| cN2 | 19 (7%) | 12 (4%) |
| cN3 | 3 (1%) | 4 (1%) |
| Missing | 13 | 14 |
| **Nodal status by sonography** | | |
| cN0 | 148 (52%) | 154 (54%) |
| cN1 | 113 (40%) | 109 (38%) |
| cN2 | 19 (7%) | 18 (6%) |
| cN3 | 6 (2%) | 4 (1%) |
| Missing | 7 | 10 |

(Table 1 continues in next column)

Pathological response of the breast tumour and axillary lymph nodes were assessed by local pathologists. Pathological reports were reviewed by one independent board certified pathologist (KE) from whom treatment assignments were masked, and response was staged in accordance with the Union for International Cancer Control TNM system.[22]

Clinical complete response was defined as the absence of evidence of disease in the breast on physical and ultrasound examination, mammogram, and, if done, on MRI. A partial response was defined as a reduction in the product of the two largest perpendicular diameters of the primary tumour by 50% or more; progressive disease was defined as an increase in tumour size by 25% or more or the presence of a new lesion. All remaining scenarios were categorised as no change. Patients were deemed to have had breast-conserving surgery if the final surgical procedure was tumourectomy, segmentectomy, or quadrantectomy and to have had axillary conserving sentinel-node surgery in case no complete dissection of axillary nodes was done. Toxic effects were graded in accordance with the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0. We

| | Treatment without carboplatin (n=293) | Treatment with carboplatin (n=295) |
|---|---|---|
| (Table continued from previous column) | | |
| **Sentinel node biopsy performed before registration** | | |
| No | 165 (56%) | 132 (45%) |
| Yes, negative | 91 (31%) | 107 (36%) |
| Yes, positive | 37 (13%) | 56 (19%) |
| Tumour type | | |
| Ductal invasive | 274 (94%) | 280 (95%) |
| Lobular invasive | 6 (2%) | 4 (2%) |
| Other | 13 (4%) | 11 (4%) |
| **Tumour grade** | | |
| 1 | 6 (2%) | 8 (3%) |
| 2 | 98 (33%) | 95 (32%) |
| 3 | 189 (65%) | 192 (65%) |
| **Oestrogen and progesterone status by central pathology** | | |
| Oestrogen and progesterone negative | 212 (72%) | 212 (72%) |
| Oestrogen or progesterone positive | 81 (28%) | 83 (28%) |
| **HER2 status by central pathology** | | |
| HER2 negative | 157 (54%) | 158 (54%) |
| HER2 positive | 136 (46%) | 137 (46%) |
| **Ki-67 by central pathology** | | |
| ≤20% | 63 (22%) | 63 (21%) |
| >20% | 230 (79%) | 232 (79%) |
| Median number (range) | 40 (3–95) | 40 (2–95) |

Data are n (%) unless stated otherwise.

***Table 1:*** **Patients characteristics at baseline (intention-to-treat population)**

used a standard definition for serious adverse events, except that uncomplicated neutropenia grade IV was not regarded as such an event.

### Outcomes

The primary outcome for this study was the proportion of patients who achieved a pathological complete response (ypT0 ypN0) after neoadjuvant treatment. Secondary outcomes were: tolerability; treatment adherence; response rates as assessed by physical examination and imaging tests before surgery; the pathological stages ypT0/is ypN0, ypT0/is ypN0/+, and ypN0 after neoadjuvant therapy; the regression grade; and the rate of breast and axilla conservation. Efficacy was assessed in predefined subgroups according to centrally assessed triple-negative or HER2-positive subtype, and according to Ki-67 levels (≤20% or >20%).

### Statistical analysis

Based on the findings of the GeparQuattro (NCT00288002)[23,24] and GeparQuinto (NCT00567554)[7,25] studies, we assumed that 40% of patients would achieve a pathological complete response with the regimen without carboplatin (with bevacizumab or with trastuzumab and lapatinib); we expected that this would increase to 49% with the addition of carboplatin (odds ratio [OR] 1·44). With these assumptions, we estimated that we would need to enrol 592 patients, according to a two-sided continuity-corrected Pearson's $\chi^2$ test with an $\alpha$ level of 0·20 and a $\beta$ level of 0·20. The significance level was set to a two-sided $\alpha$ of 0·20 for the primary endpoint only, for all other tests the $\alpha$ was set to 0·05.

All patients who received at least one treatment were included in the efficacy and safety analyses. A predefined interim safety analysis was done after 60 patients had received at least two cycles of treatment. The results of this analysis did not allow a clear conclusion on the feasibility of the regimen (no specific pattern of toxic effects were identified that were attributable to one of the drugs and a low number of patients reached the end of treatment). The independent data monitoring committee therefore recommended the continuation of the study without changes, but requested a second unplanned safety interim analysis. This second analysis included 242 patients who had received at least one cycle and a total of 904 cycles. Based on this second analysis, it was recommended that the dose of carboplatin was reduced to AUC 1·5.

Treatment groups were compared with the use of a continuity-corrected two-sided Pearson's $\chi^2$ test and Fisher's exact test, and 95% CIs are provided for the efficacy endpoints. 15 patients had no surgery and were counted as having had no response. Multivariate logistic regression was used to adjust for the baseline factors: triple-negative tumours versus HER2 positive and oestrogen or progesterone positive versus HER2 positive and oestrogen and progesterone negative tumours as stratified; Ki67 (≤20% *vs* >20%); age (<40 years *vs* ≥40 years); tumour size by sonography (cut at median); cT1–3 versus cT4 and nodal status (cN0 *vs* cN+; defined as cN+ by palpation or sonography *vs* cN0 in all available assessments). Univariate logistic regression was done in subgroups; a Breslow–Day test[26] was used for testing the homogeneity of ORs across subgroups. A preplanned subpopulation treatment effect pattern plot (STEPP) analysis[27] was done to explore the effect of mean relative total dose intensity overall (mRTDI)[28] for all treatments and mRTDI of carboplatin (with AUC 2·0 as planned dose) for patients with triple-negative and HER2-positive tumours, separately.

| | Treatment without carboplatin (n=293) | Treatment with carboplatin (n=295) | p value |
|---|---|---|---|
| **ypT0 ypN0** | | | |
| No | 185 (63·1%) | 166 (56·3%) | 0·107 |
| Yes | 108 (36·9%, 31·3–42·4) | 129 (43·7%, 38·1–49·4) | |
| **ypT0/is ypN0** | | | |
| No | 154 (52·6%) | 138 (46·8%) | 0·187 |
| Yes | 139 (47·4%, 41·7–53·2) | 157 (53·2%, 47·5–58·9) | |
| **ypT0/is ypN0/+** | | | |
| No | 138 (47·1%) | 120 (40·7%) | 0·137 |
| Yes | 155 (52·9%, 47·2–58·6) | 175 (59·3%, 53·7–64·9) | |
| **ypN0** | | | |
| No | 74 (25·3%) | 70 (23·7%) | 0·738 |
| Yes | 219 (74·7%, 69·8–79·7) | 225 (76·3%, 71·4–81·1) | |
| **Regression grade** | | | |
| RG 0 | 6 (2·1%) | 6 (2·1%) | 0·541 |
| RG 1 | 87 (30·4%) | 72 (25·2%) | |
| RG 2 | 38 (13·3%) | 33 (11·5%) | |
| RG 3 | 35 (12·2%) | 30 (10·5%) | |
| RG 4 | 12 (4·2%) | 16 (5·6%) | |
| RG 5 | 108 (37·8%) | 129 (45·1%) | |
| Missing | 7 | 9 | |
| **Clinical response** | | | |
| Complete response | 115 (39·2%) | 136 (46·1%) | |
| Partial response | 147 (50·2%) | 129 (43·7%) | |
| Overall response | 262 (89·4%, 85·3–92·7) | 265 (89·8%, 85·8–93·0) | 0·978 |
| No change | 20 (6·8%) | 17 (5·8%) | |
| Progressive disease | 5 (1·7%) | 2 (0·7%) | |
| Missing | 6 (2·0%) | 11 (3·7%) | |
| **Breast conserving surgery** | | | |
| No | 69 (24·1%) | 80 (27·9%) | 0·354 |
| Yes | 217 (75·9%, 70·9–80·8) | 207 (72·1%, 66·9–77·3) | |
| No surgery | 7 | 8 | |
| **Axillary conserving surgery** | | | |
| No | 156 (56·7%) | 134 (48·6%) | 0·066 |
| Yes | 119 (43·3%, 37·4–49·1) | 142 (51·4%, 45·6–57·3) | |
| Missing | 18 | 19 | |

Data are n (%) or n (%, 95% CI).

*Table 2:* **Comparison of treatment efficacy by various endpoint**

The database was locked on Nov 11, 2013, and all statistical analyses were done with SAS software, version 9.2. This study is registered with ClinicalTrials.gov, number NCT01426880.

### Role of the funding source

The funders had no role in the collection, analysis, or interpretation of the data. The study statistician (VN) had access to the raw data. The report was first drafted by GvM and reviewed by all authors and the funders. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

Between Aug 29, 2011, and Dec 12, 2012, we screened 728 patients at 54 centres in Germany for eligibility. 68 patients did not have their biological subtype centrally confirmed and 65 patients did not meet other eligibility criteria. Of the remaining 595 patients, seven did not start treatment (four because of investigator decisions and three because of patient's decision) and were not included in the intention-to-treat analysis. Thus, 588 patients (295 with carboplatin, 293 without) were included in the intention-to-treat and safety populations (figure 2).

Baseline characteristics were balanced between the two groups except for pretreatment sentinel node biopsy (table 1). 315 patients had triple-negative (157 treated without and 158 with carboplatin) and 273 had HER2-positive (136 treated without and 137 with carboplatin) tumours. 329 patients were treated before the dose-reduction amendment and 259 thereafter (for AUC 2·0, 165 treated without and 164 treated with carboplatin; for AUC 1·5, 128 treated without and 131 treated with carboplatin). There was no difference in baseline characteristics between those who entered the study before the protocol amendment and those who entered after the amendment (data not shown).

108 (36·9%; 95% CI 31·3–42·4) of 293 patients who received treatment without carboplatin and 129 (43·7%, 38·1–49·4) of 295 patients treated with carboplatin had a pathological complete response (ypT0 ypN0; OR 1·33; 95% CI 0·96–1·85; p=0·107; table 2). After adjustment for age, clinical tumour and nodal stage, sonographical tumour size, grade, and biological subtype as covariates, the OR was 1·39 (95% CI 0·98–1·98; p=0·068). The proportion of patients achieving a pathological complete response using the ypT0/is ypN0 definition and ypT0/is ypN0/+ definition are shown in table 2; there was no difference between rates with and without carboplatin (p=0·187 and p=0·137, respectively). No differences between treatment groups were noted for secondary efficacy endpoints (table 2).

Figure 3 shows the effect of carboplatin on the proportion of patients achieving a pathological complete response within prospectively stratified and clinically relevant subgroups. Of the 315 patients with triple-negative breast cancer, 58 (36·9%, 95% CI 29·4–44·5) of 157 patients treated without the addition of carboplatin and 84 (53·2%, 54·4–60·9) of 158 patients treated with the addition of carboplatin achieved a pathological complete response (p=0·005); using the ypT0/is ypN0 definition, 67 (42·7%, 34·9–50·4) of 157 patients and 90 (53·2%, 49·2–64·7) of 158 patients achieved a pathological complete response (p=0·015). Among the 273 patients with HER2-positive tumours, 50 (36·8%, 28·7–44·9) of 136 patients achieved a pathological complete response without carboplatin as did 45 (32·8%, 25·0–40·7) of 137 patients treated with carboplatin (p=0·581). Using the ypT0/is ypN0 definition, pathological complete responses were achieved in 72 (52·9%, 44·6–61·3) with carboplatin and 67 (48·9%, 40·5–57·3) without (p=0·585). The test for interaction for the effect of carboplatin in patients with triple-negative breast cancer versus patients with HER2-positive disease was significant (p=0·015). Before the dose amendment, 69 (41·8%, 34·3–49·3) of 165 patients treated without carboplatin and 69 (42·1%, 34·5–49·6) of 164 patients treated with carboplatin achieved a pathological complete response (p>0·999). After the dose amendment, 39 (30·5%, 22·5–38·4) of 128 patients treated without carboplatin and 60 (45·8%, 37·3–54·3) of 131 patients treated with carboplatin achieved a pathological complete response (p=0·016; test for interaction p=0·059).

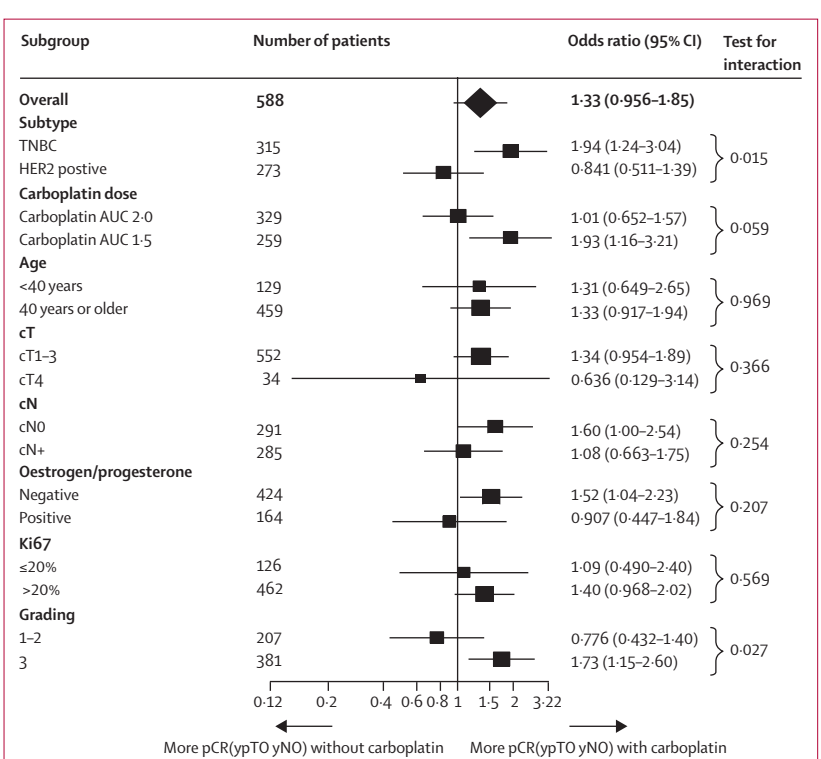


*Figure 3*: **Effect of treatment with and without the addition of carboplatin overall and in subgroups**

STEPP analyses showed different dose-response relations in patients with triple-negative disease and with HER2-positive disease. Whereas in patients with HER2-positive tumours a continuous increase in the proportion of patients achieving a pathological complete response was noted with higher mRTDI up to 100%, patients with triple-negative disease did not seem to benefit further once a mRTDI of 50% was reached. Pathological complete responses decreased with mRTDIs greater than 80% (figure 4).

Of the 588 patients who started treatment, 114 (39%) in the group not given carboplatin and 141 (48%) in the group given carboplatin did not complete six cycles of treatment, mainly because of adverse events (p=0·031; figure 2). Treatment discontinuations were most common in patients with triple-negative disease receiving carboplatin (77 [49%] patients given carboplatin *vs* 56 [36%] not given carboplatin; p=0·023), whereas in patients with HER2-positive tumours, no difference between the groups was noted (64 [47%] patients given carboplatin *vs* 58 [43%] not given carboplatin; p=0·543). Treatment discontinuation in the carboplatin group was necessary in 87 (53%) patients starting with a carboplatin dose of AUC 2·0 and in 54 (41%) starting with a carboplatin dose of AUC 1·5. Dose reduction of any chemotherapy agent was reported in 162 (55%) patients not given carboplatin and 204 (69%) who did receive carboplatin. mRTDI for all treatments was 78·5% without carboplatin and 70% with carboplatin (p<0·0001), and 65·8% specifically for carboplatin. mRTDI was 80·2% without carboplatin and 71·3% with carboplatin (p<0·0001) for patients with triple-negative breast cancer and 76·6% without carboplatin and 67·8% with carboplatin (p<0·0001) for patients with HER2-positive tumours. mRTDI in the carboplatin group increased from 67·7% to 72·1% when the dose of carboplatin was reduced from AUC 2·0 to AUC 1·5.

Carboplatin-specific toxic effects, such as anaemia, neutropenia, thrombocytopenia, and nausea, occurred more commonly in the group given carboplatin (table 3; appendix). The addition of carboplatin was also associated with a higher rate of diarrhoea and anorexia, whereas hand-foot syndrome, skin rash, nail changes, pneumonitis, and other cardiac disorders were more common in the group not treated with carboplatin, which accords with the higher mRTDI in this group. Cardiac toxic effects were low in both groups. The frequency of grade 3 or 4 haematological events decreased from 82% (n=135) to 70% (n=92) and grade 3 or 4 non-haematological events from 78% (n=128) to 59% (n=77) in the group given carboplatin when the dose was reduced from AUC 2·0 to AUC 1·5. During treatment there were four deaths in the group not given carboplatin (two related to cardiac and two related to neutropenic events) and one death due to sepsis related to port infection in the group given carboplatin. 115 serious adverse events occurred in the group not given carboplatin and 130 such events occurred in the group given carboplatin. The most common serious adverse events were fever without infection (34 [12%] in the group not given carboplatin and 26 [9%] in the group given carboplatin), infection (32 [11%] and 26 [9%]), and neutropenia (seven [2%] and 12 [4%]).

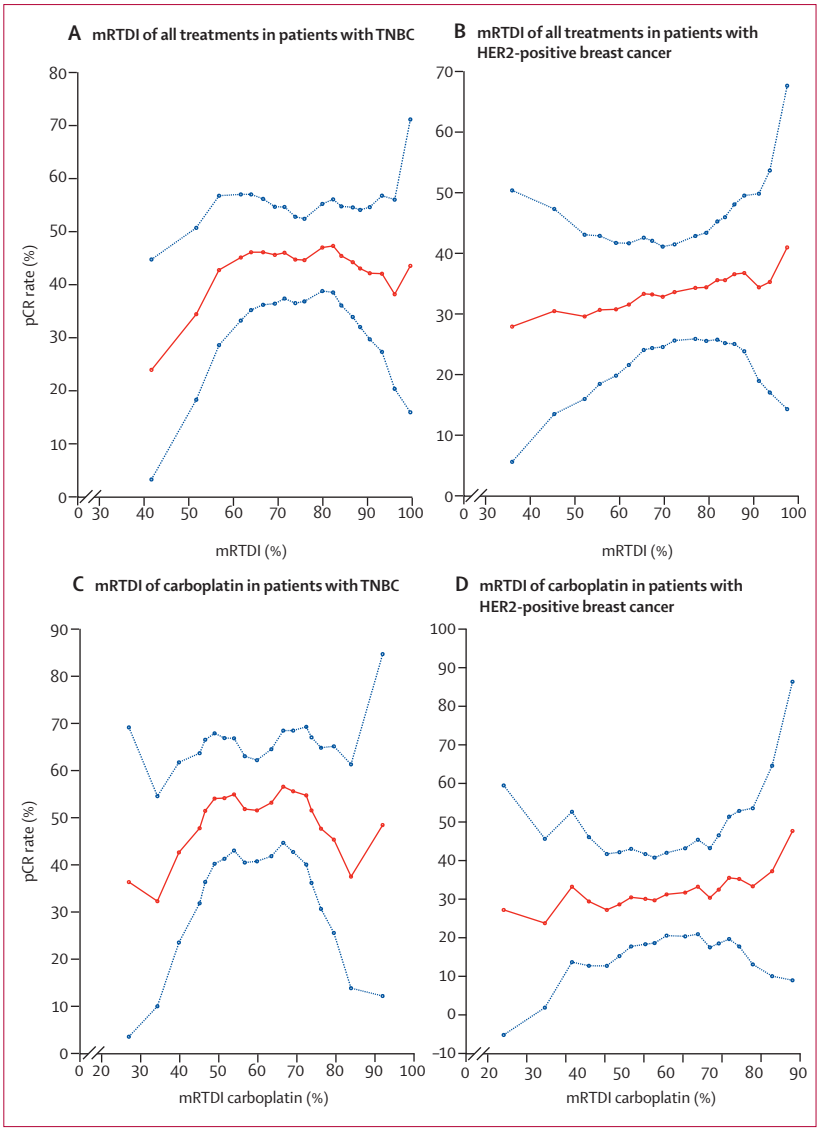


***Figure 4:*** **Subpopulation treatment effect pattern plot analysis**
Analysis of the correlation of mRTDI with pathological complete response in patients with triple-negative breast cancer (A+C) or HER2-positive (B+D) tumours. mRTDI was calculated for all treatments (A+B) or for carboplatin alone (C+D). Mean proportion of patients with a pathological complete response (middle line) and 95% CIs (upper and lower line) are plotted. mRTDI=mean relative total dose intensity. TNBC=triple-negative breast cancer. pCR=pathological complete response.

See Online for appendix

## Discussion

The findings of the GeparSixto phase 2 study show that, at a prespecified α level of 0·2, a significantly greater proportion of patients achieved a pathological complete response with the addition of carboplatin to a combination regimen including a taxane, non-pegylated

| | Treatment without carboplatin (n=293) | | | | Treatment with carboplatin (n=295) | | | | p value* |
|---|---|---|---|---|---|---|---|---|---|
| | Grades 1–2 | Grade 3 | Grade 4 | Grade 5 | Grades 1–2 | Grade 3 | Grade 4 | Grade 5 | |
| Anaemia | 258 (88%) | 1 (<1%) | 0 | 0 | 242 (82%) | 42 (14%) | 3 (1%) | 0 | <0·0001 |
| Neutropenia | 135 (46%) | 63 (22%) | 16 (6%) | 0 | 84 (29%) | 126 (43%) | 66 (22%) | 0 | <0·0001 |
| Febrile neutropenia | 0 | 12 (4%) | 2 (<1%) | 1 (<1%) | 0 | 19 (6%) | 6 (2%) | 0 | 0·140 |
| Thrombocytopenia | 28 (10%) | 1 (<1%) | 0 | 0 | 155 (53%) | 38 (13%) | 4 (1%) | 0 | <0·0001 |
| Nausea | 155 (53%) | 12 (4%) | 0 | 0 | 184 (62%) | 29 (10%) | 0 | 0 | 0·009 |
| Vomiting | 75 (26%) | 6 (2%) | 1 (<1%) | 0 | 102 (35%) | 16 (5%) | 0 | 0 | 0·087 |
| Diarrhoea | 153 (52%) | 32 (11%) | 0 | 0 | 156 (53%) | 49 (17%) | 2 (<1%) | 0 | 0·033 |
| Mucositis | 212 (72%) | 44 (15%) | 1 (<1%) | 0 | 193 (65%) | 45 (15%) | 5 (2%) | 0 | 0·654 |
| Anorexia | 88 (30%) | 8 (3%) | 1 (<1%) | 0 | 99 (34%) | 22 (8%) | 0 | 0 | 0·025 |
| Fatigue | 211 (72%) | 40 (14%) | 0 | 0 | 205 (70%) | 48 (16%) | 1 (<1%) | 0 | 0·358 |
| Hand-foot syndrome | 146 (50%) | 48 (16%) | 0 | 0 | 135 (46%) | 27 (9%) | 0 | 0 | 0·009 |
| Skin rash (acneiform) | 31 (11%) | 6 (2%) | 0 | 0 | 25 (9%) | 0 | 0 | 0 | 0·015 |
| Nail changes | 98 (33%) | 11 (4%) | 0 | 0 | 81 (28%) | 2 (1%) | 0 | 0 | 0·012 |
| Peripheral sensory neuropathy | 190 (65%) | 21 (7%) | 0 | 0 | 173 (59%) | 19 (6%) | 0 | 0 | 0·746 |
| Fever | 85 (29%) | 17 (6%) | 3 (1%) | 0 | 67 (23%) | 11 (4%) | 0 | 0 | 0·100 |
| Infection | 119 (41%) | 37 (13%) | 7 (2%) | 1 (<1%) | 126 (43%) | 37 (13%) | 3 (1%) | 1 (<1%) | 0·642 |
| Thromboembolic events | 12 (4%) | 7 (2%) | 3 (1%) | 0 | 14 (5%) | 7 (2%) | 3 (1%) | 0 | 1·000 |
| Pneumonitis | 6 (2%) | 6 (2%) | 3 (1%) | 0 | 0 | 1 (<1%) | 0 | 0 | 0·011 |
| Arterial hypertension | 33 (11%) | 9 (3%) | 0 | 0 | 29 (10%) | 5 (2%) | 0 | 0 | 0·295 |
| LVEF decrease, congestive heart failure (NYHA), and myocardial infarction | 6 (2%) | 0 | 0 | 1 (<1%) | 5 (2%) | 2 (<1%) | 0 | 0 | 1·000 |
| Other cardiac disorders | 24 (8%) | 3 (1%) | 1 (<1%) | 1 (<1%) | 20 (7%) | 0 | 0 | 0 | 0·030 |
| Surgical complications | 3 (1%) | 2 (<1%) | 0 | 0 | 5 (2%) | 4 (1%) | 0 | 0 | 0·450 |
| Other non-haematological adverse events | 219 (75%) | 67 (23%) | 6 (2%) | 0 | 212 (72%) | 76 (26%) | 1 (<1%) | 0 | 0·777 |

Data are n (absolute percentage—ie, excluding patients with missing information). The grades of maximal serverity per patient are based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTC) Version 3.0, except congestive heart failure, which was based on New York Heart Association (NYHA) classification. *Compares incidence of grades 3–5 between groups. LVEF=left ventricular ejection fraction. NYHA=New York Heart Association.

***Table 3:*** **Haematological and non-haematological toxic effects**

liposomal doxorubicin, and dual HER2-receptor blockade in patients with HER2-positive breast cancer or inhibition of neoangiogenesis in patients with triple-negative disease. An absolute increase in the proportion of patients achieving a pathological complete response of 16% with the addition of carboplatin was noted in patients with triple-negative breast cancer, but no effect was seen in patients with HER2-positive breast cancer.

These results contrast with a previous randomised study (panel) that assessed the addition of carboplatin, given at a dose of AUC 6 every 3 weeks together with docetaxel at a dose of 75 mg/m², by comparison with docetaxel alone at a dose of 100 mg/m² for four cycles after pretreatment with epirubicin and cyclophosphamide in 96 patients with basal-like breast cancer, which showed a similar pathological complete response (pT0/is ypN0) of 30% of patients in both treatment groups.[30] The CALGB study 40603 (NCT00861705) of 446 patients with triple-negative breast cancer who received bevacizumab, carboplatin, or both at a dose of AUC 6 every 3 weeks together with weekly paclitaxel and subsequent doxorubicin/cyclophosphamide in a two by two factorial design.[8] Both the addition of carboplatin and of bevacizumab increased the rate of pathological complete response (ypT0/is ypN0) from 41% to 54% (OR 1·71; p=0·0029) and from 44% to 52% (OR 1·36; p=0·057), respectively. Although 24% of patients in the arm with both carboplatin and bevacizumab had febrile neutropenia, treatment discontinuations due to toxic effects were necessary in only 12% of patients.

Differences in the trial designs (weekly *vs* 3-weekly dosing of carboplatin, cyclophosphamide as another DNA-damaging agent in both arms, identical *vs* different taxane dose) might explain this variation of results. Nevertheless, we do not provide baseline characteristics of patients with triple-negative disease separately in this report because we did not want to create the impression that the same trial was done separately in two populations; also, available conventional baseline information will not help to identify different types of triple-negative disease. Information on the germline BRCA mutation status as well as on corresponding genetic changes of the tumour (so-called BRCAness) are not available at present, but this work is in progress.

Similar to previous studies of our group,[7,24] higher proportions of patients achieving a pathological complete response was not associated with higher rates of breast-conserving surgery.

The GeparSixto study has several weaknesses and strengths. As a phase 2 study with a level of significance of 0·2 it cannot provide confirmative evidence of the activity of carboplatin. Furthermore, activity was only identified in the subgroup of patients with triple-negative breast cancer. Nevertheless, this prospectively defined subgroup has a reasonable size to allow for survival analyses similar to that of the NOAH study,[32] where an absolute difference in pathological complete response of 19% with the addition of trastuzumab to polychemotherapy translated into a survival benefit for the 235 patients with HER2-positive breast cancer. In addition, the regimen used in this study is far from other standard regimens; however, it was designed in accordance with previous findings from our neoadjuvant studies identifying characteristics of treatment correlated with high rates of pathological complete response.[33] A high relative dose-intensity of both taxane and anthracycline seems to be associated with high proportion of patients achieving pathological complete response, especially for triple-negative disease. This is why we chose a weekly anthracycline/taxane combination, still allowing us to have similar doses in both treatment groups.

The observed pathological complete response is the highest ever noted in neoadjuvant studies of the German Breast Group for these two breast cancer subtypes. Nonetheless, the gain in efficacy of GeparSixto has to be weighed against a high proportion of treatment discontinuations (39% for in the group without carboplatin and 48% in the group with carboplatin) and low mRTDI. It seems that the dose reduction of carboplatin to AUC 1·5 did not only reduce the incidence of haematological and non-haematological adverse events but also had no detrimental effect on efficacy in patients with triple-negative disease. However, we could not identify a significant difference in baseline characteristics of patients entering the study before and after the amendment and therefore believe that the difference in pathological complete response in the control group before and after the amendment is probably a chance finding. The optimum dose and schedule of carboplatin needs to be established in future studies. The STEPP analysis showed that maintaining mRTDI for carboplatin at the highest level possible is less relevant in patients with triple-negative breast cancer, so a dose of carboplatin at AUC 1·5 could achieve a better risk–benefit profile.

One strength of the study is the central confirmation of receptor status and Ki-67. Furthermore, a large set of biomaterials was collected that will allow the investigation of predictive markers, such as germline mutations of *BRCA*, somatic *BRCA* mutations, and other markers potentially related to the effect of carboplatin.

### *Panel:* Research in context

#### Systematic review

A systematic search of the Medline as part of the planning for this trials was done using the terms "cisplatin", "carboplatin", "breast cancer", "neoadjuvant", and "clinical trial". No date or language limits were applied to the search. Only one retrospective and one phase 1 study was identified, making it appropriate to run a randomised trial.[12,29]

#### Interpretation

Three randomised trials (reported since the start of GeparSixto),[8,30,31] in addition to GeparSixto, have assessed the use of a platinum salt as part of neoadjuvant treatment for patients with triple-negative breast cancer. Three, including the GeparSixto study, reported a significantly greater proportion of pathological complete responses for the carboplatin containing arms. However, one of them added carboplatin and veliparib, an inhibitor of PARP, simultaneously to standard treatment, so the efficacy of carboplatin alone cannot be described.[31] One study did not show a benefit for carboplatin; however, the design was imbalanced regarding backbone treatment intensity.[30] Carboplatin could be a promising new treatment option for patients with triple-negative breast cancer. However, phase 3 trial results, survival analyses, and analyses of the subgroup of patients carrying a *BRCA* mutation are needed to fully assess clinical value.

In conclusion, the results of GeparSixto show that adding neoadjuvant carboplatin to a regimen consisting of taxane-anthracycline chemotherapy and targeted therapy substantially increased pathological complete responses in patients with stage II–III triple negative breast cancer, but not for patients with HER2-positive disease. However, the addition of carboplatin significantly increases haematological and non-haematological side-effects. A subsequent phase 3 study, GeparOcto is now planned to be open in the second quarter of 2014 to explore the study regimen, with and without carboplatin, with pertuzumab instead of lapatinib for HER2-postive disease and without bevacizumab for triple-negative disease. We believe that with better tolerated targeted treatment components and carboplatin used at an AUC 1·5, as well as a learning curve on better dealing with this intense regimen, the feasibility of the regimen will become more acceptable.

#### Contributors

The study was designed and the protocol was written by the GvM and by members of the neoadjuvant subcommittee of the German Breast Group (AS, SL, CD, JUB, CJ, SP, BG, SK, HE, JeH, SC, CH, JöH, and MU). GvM, AS, SL, CS, CD, MR, JUB, CJ, SP, BG, DMZ, SK, HE, PK, JeH, SC, HT, CH, JöH, FK, PAF, BVS, KM, and MU contributed to data collection that was located at GBG headquarter, Neu-Isenburg, Germany. VN and KM analysed the data. GvM and VN had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors interpreted the data. The first draft of the report was written by GvM. The decision to submit the manuscript for publication was made by all authors. All authors contributed to the review of the manuscript. No persons other than the listed authors contributed to the writing of the report.

#### Declaration of interests

GvM received research grants from GlaxoSmithKline, Roche, and Teva and speaker and consultancy honoraria from Roche and Teva. AS received research grants from and honoraria from Roche. HE received honoraria from Roche and GSK. PAF received research grants from Novartis and Amgen, and honoraria from Roche and Novartis.

HT received honoraria from Roche, Novartis, and Amgen. CD received grants from German Breast Group. JeH received honoraria from TEVA, GSK, and Roche. All remaining authors declare that they have no competing interests.

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