IMPORTANCE The GeparOcto randomized clinical trial compared the efficacy of 2 neoadjuvant breast cancer (BC) treatment regimens: sequential intense dose-dense epirubicin, paclitaxel, and cyclophosphamide (iddEPC) vs weekly paclitaxel and nonpegylated liposomal doxorubicin (PM) in patients with different biological BC subtypes. Patients with triple-negative BC (TNBC) randomized to the PM arm received additional carboplatin (PMCb). Overall, no difference in pathologic complete response (pCR) rates was observed between study arms. It remained elusive whether the germline variant status of BRCA1/2 and further BC predisposition genes are associated with treatment outcome.

OBJECTIVE To determine treatment outcome for BC according to germline variant status.

DESIGN, SETTING, AND PARTICIPANTS This retrospective biomarker study is a secondary analysis of the GeparOcto multicenter prospective randomized clinical trial conducted between December 2014 and June 2016. Genetic analyses assessing for variants in BRCA1/2 and 16 other BC predisposition genes in 914 of 945 women were performed at the Center for Familial Breast and Ovarian Cancer, Cologne, Germany, from August 2017 through December 2018.

MAIN OUTCOMES AND MEASURES Proportion of patients who achieved pCR (ypT0/is ypN0 definition) after neoadjuvant treatment according to germline variant status.

RESULTS In the study sample of 914 women with different BC subtypes with a mean (range) age at BC diagnosis of 48 (21-76) years, overall higher pCR rates were observed in patients with BRCA1/2 variants than in patients without (60.4% vs 46.7%; odds ratio [OR], 1.74; 95% CI, 1.13-2.68; P = .01); variants in non-BRCA1/2 BC predisposition genes were not associated with therapy response. Patients with TNBC with BRCA1/2 variants achieved highest pCR rates. In the TNBC subgroup, a positive BRCA1/2 variant status was associated with therapy response in both the PMCb arm (74.3% vs 47.0% without BRCA1/2 variant; OR, 3.26; 95% CI, 1.44-7.39; P = .005) and the iddEPC arm (64.7% vs 45.0%; OR, 2.24; 95% CI, 1.04-4.84; P = .04). A positive BRCA1/2 variant status was also associated with elevated pCR rates in patients with ERBB2-negative, hormone receptor-positive BC (31.8% vs 11.9%; OR, 3.44; 95% CI, 1.22-9.72; P = .02).

CONCLUSIONS AND RELEVANCE Effective chemotherapy for BRCA1/2-mutated TNBC is commonly suggested to be platinum based. With a pCR rate of 64.7%, iddEPC may also be effective in these patients, though further prospective studies are needed. The elevated pCR rate in BRCA1/2-mutated ERBB2-negative, hormone receptor-positive BC suggests that germline BRCA1/2 testing should be considered prior to treatment start.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02125344
The GeparOcto randomized clinical trial\(^1\) compared the efficacy of treatment with a sequential intense dose-dense epirubicin, paclitaxel, and cyclophosphamide-based chemotherapy regimen (iddEPC) vs a weekly paclitaxel plus nonpegylated liposomal doxorubicin regimen (PM) in 945 patients with different biological subtypes of breast cancer (BC). The study cohort included 403 patients with triple-negative BC (TNBC), 382 patients with ERBB2-positive BC, and 160 patients with ERBB2-negative, estrogen receptor–positive or progesterone receptor-positive (hormone receptor [HR]–positive) BC and histologically verified lymph node involvement. Patients with TNBC randomized to the PM arm received additional carboplatin (PMCb) based on previous results.\(^2\) Patients with ERBB2-positive BC received additional trastuzumab and pertuzumab in both study arms (trial protocol in Supplement 1; eFigure in Supplement 2). No overall difference in pathologic complete response (pCR) rates was observed between study arms (iddEPC arm, 48.3%; PM[Cb] arm, 48.0%; ypT0/is ypNO definition).\(^3\) It was concluded that sequential iddEPC appeared more feasible than PM(Cb) owing to elevated nonhematologic adverse effects and lower adherence to treatment with PM(Cb).\(^1\)

In particular, TNBC is associated with a hereditary cause, and germline variant screening of unselected patients with TNBC revealed a high BRCA1/2 variant prevalence.\(^2,3\) BRCA1/2 genes are critical in the homologous recombination repair of DNA double-strand breaks. Many of the other genes involved in homologous recombination repair are now recognized to also contribute to hereditary BC risk. Heterozygous germline inactivation of these genes may be accompanied by a somatic inactivation of the second allele, resulting in a homologous recombination deficiency and limited DNA repair capacity of the tumor cell.\(^4\) This functional role in DNA repair may be exploited in the treatment of homologous recombination-deficient cancers with drugs that challenge the DNA repair machinery, such as epirubicin, cyclophosphamide, doxorubicin, and carboplatin, which were used in the GeparOcto trial.\(^1\) These data prompted us to conduct this retrospective biomarker study of patients enrolled in the GeparOcto trial to determine treatment efficacies according to germline variant status overall, by treatment arm, and by tumor subtype.

### Methods

Of the 945 patients enrolled in the original GeparOcto investigation, 914 (96.7%) were successfully analyzed for germline (g) variants in BRCA1/2 and 16 further BC predisposition genes (Figure 1; eMethods in Supplement 2). All patients provided written informed consent for trial participation and translational research. The Ethics Committee of the University of Cologne (07-048) granted ethical approval for genetic analyses. Pearson χ\(^2\) test was used to compare pCR rates between groups. Univariate logistic regression analyses were performed to estimate odds ratio (OR) and 95% CIs. Interaction was assessed using the Breslow-Day test; P-values less than .05 were considered statistically significant. Analyses were performed with SPSS statistical software version 25 (IBM Corp). This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

### Results

In the subgroup of 914 patients included in this investigation, the mean (range) age at BC diagnosis was 48 (21-76) years. Overall pCR rates were similar to those observed in the original in-
Of the 914 patients, 96 (10.5%) carried pathogenic gBRCA1/2 variants (Figure 2A; eTable 2 in Supplement 2). Irrespective of the treatment arm and subtype, patients with gBRCA1/2 variants had higher pCR rates compared with patients without gBRCA1/2 variants (60.4% vs 46.7%; OR, 1.74; 95% CI, 1.13-2.68; P = .01; eTable 1 in Supplement 2); interaction between gBRCA1/2 variant and study arm was not significant (P = .11).

The gBRCA1/2 variant prevalence as well as the pCR rates were highly different when analyzed by biological tumor subtypes. As expected from the GeparSixto trial,2 a high gBRCA1/2 variant prevalence was observed in patients with TNBC (69 of...
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BRCA1/2

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therapy response. Among the 818 patients without non-

not significant (74.3% vs 64.7%; OR, 1.58; 95% CI, 0.56-4.43; P = .39; Figure 2C). Interaction between gBRCA1/2 variant and study arm was not significant (P = .51).

In ERBB2-positive BC, a low gBRCA1/2 variant prevalence was suggested. Five gBRCA1/2 variant carriers (5 of 365 [1.4%]; Figure 2A; eTable 2 in Supplement 2) were present in this subgroup; therefore, we refrained from calculating ORs according to gBRCA1/2 variant status. Overall, pCR rates of approximately 60% were observed in ERBB2-positive BC (eTable 1 in Supplement 2).

In ERBB2-negative, HR-positive BC, a high gBRCA1/2 variant prevalence was observed (22 of 156 [14.1%]; Figure 2A; eTable 2 in Supplement 2). Irrespective of the treatment arm, a positive gBRCA1/2 variant status was associated with a higher pCR rate (31.8% vs 11.9%; OR, 3.44; 95% CI, 1.22-9.72; P = .02; Figure 2D, eTable 1 in Supplement 2); interaction between gBRCA1/2 variant and study arm was not significant (P = .44).

It is currently unknown whether variants in additional, non-BRCA1/2 BC predisposition genes are associated with chemotherapy response. Among the 818 patients without gBRCA1/2 variants, 76 patients (9.3%) carried at least 1 variant in the 16 non-BRCA1/2 genes (Figure 2B; eTable 2 in Supplement 2). The overall variant prevalence was mainly driven by the ATM, CHEK2, FANCN, and PALB2 BC predisposition genes,5,7 and a high variant prevalence was found in all 3 biological subgroups (Figure 2B). In accordance with previous studies, variants in the FANCN and PALB2 genes are associated with TNBC, while variants in the ATM and CHEK2 genes are associated with ERBB2-positive and ERBB2-negative, HR-positive BC14 (eTable 2 in Supplement 2). Patients without pathogenic gBRCA1/2 variants but germline variants in non-BRCA1/2 genes achieved pCR rates comparable to patients without any variant (eTable 1 in Supplement 2); however, gene-specific effects cannot be excluded.

Discussion

Patients with gBRCA1/2 variants benefited most from both treatment regimens, while variants in non-BRCA1/2 BC predisposition genes were not associated with therapy response. Especially following the studies by Byrski et al9 and most recently the Triple Negative Trial by Tutt et al,10 effective chemotherapy of gBRCA1/2-mutated TNBC is suggested to be platinum based, a result that was also confirmed in our investigation. In gBRCA1/2-mutated TNBC, we demonstrate that iddEPC appears to be also effective, though with a pCR rate approximately 10 percentage points lower than that observed in the PMCb arm. It remains elusive whether this difference is associated with survival outcome. However, our study was not powered to compare PM(Cb) vs iddEPC treatment efficacies specifically in patients with gBRCA1/2-mutated BC; larger prospective studies are required to address this question. Of further interest is the high gBRCA1/2 variant prevalence in ERBB2-negative, HR-positive BC along with the elevated pCR rate of gBRCA1/2 variant carriers compared to noncarriers. Although the subgroup of patients with ERBB2-negative, HR-positive BC was small in our study (n = 156), we suggest that patients with ERBB2-negative, HR-positive BC may benefit from BRCA1/2 testing prior to treatment start.

Limitations

The study did have a limitation. It was not powered to compare PM(Cb) vs iddEPC treatment efficacies in patients with gBRCA1/2-mutated BC.

Conclusions

Effective chemotherapy for gBRCA1/2-mutated TNBC is commonly suggested to be platinum based. With a pCR rate of 64.7%, we demonstrate that iddEPC appears to be also effective in these patients and may be considered in future prospective studies. The elevated pCR rate in gBRCA1/2-mutated ERBB2-negative, HR-positive BC suggests that germline BRCA1/2 testing should be considered prior to treatment start.

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Author Contributions: Drs Lederer and Nekljudova had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of Interest Disclosures: Dr Loibl reported receiving grants for the GeparOcto Study from Roche, Amgen, and Teva Pharmaceutical Industries during the conduct of the study; grants and honoraria for lectures and advisory boards paid to institution from AbbVie, Amgen, AstraZeneca, Celgene, Novartis, Pfizer, and Roche; honoraria for lectures and advisory boards paid to institution from Seattle Genetics and Samsung; honoraria for lectures and advisory boards paid to institution from Roche; grants and honoraria paid to institution from Daiichi Sankyo; honoraria for advisory boards paid to institution from Lilly; and advisor fees paid to institution from Eirgenix outside the submitted work; in addition, Dr Loibl reported receiving payment for documentation of patient data from the German Breast Group during the conduct of the study; receiving grants for advisory or consultancy roles from Roche and Novartis; receiving honoraria from Pfizer, Lilly, and Genomic Health outside the submitted work. Dr Lübke reported receiving payment for documentation of patient data from the German Breast Group during the conduct of the study; receiving grants for advisory or consultancy roles from Roche and Novartis; receiving honoraria from Pfizer, Lilly, and Genomic Health outside the submitted work. Dr Rhiem reported receiving travel from Pfizer, Lilly, Genentech, and Roche during the conduct of the study; receiving grants for advisory or consultancy roles from Roche and Novartis; receiving honoraria from Pfizer, Lilly, and Genomic Health outside the submitted work. Dr Tesch reported receiving travel grants from Bristol-Myers Squibb and Amgen and personal fees from Roche and AstraZeneca outside the submitted work. Dr Jakisch reported receiving travel grants from Bristol-Myers Squibb and Amgen and personal fees from Roche and AstraZeneca outside the submitted work. Drs Schmutzler and Hahnen reported receiving honoraria from AstraZeneca outside the submitted work. Dr Schneeweiss reported receiving research grants from Roche and Celgene; honoraria from Amgen, AstraZeneca, Celgene, Lilly, Merck Sharp & Dohme, Novartis, Pfizer, and Tesaro; and medical writing grants from Roche outside the submitted work. No other disclosures were reported.

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