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ORIGINAL REPORT

BRCA1/2 Mutations and Bevacizumab in the Neoadjuvant Treatment of Breast Cancer: Response and Prognosis Results in Patients With Triple-Negative Breast Cancer From the GeparQuinto Study

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ABSTRACT

Purpose

BRCA1/2 mutations are frequent in patients with triple-negative breast cancer (TNBC). These patients are often treated with primary systemic chemotherapy. The aim of this study was to analyze the effects of *BRCA1/2* mutations on pathologic complete response (pCR) and disease-free survival (DFS) in a cohort of patients with TNBC treated with anthracycline and taxane–containing chemotherapy, with or without bevacizumab.

Patients and Methods

Germline DNA was sequenced to identify mutations in *BRCA1* and *BRCA2* in 493 patients with TNBC from the GeparQuinto study. The pCR rates were compared in patients with and without mutation, as well as in patients treated with and without bevacizumab. In addition, the influence of *BRCA1/2* mutation status and pCR status on DFS was evaluated relative to treatment.

Results

BRCA1/2 mutations were detected in 18.3% of patients with TNBC. Overall, patients with mutations had a pCR rate of 50%, compared with 31.5% in patients without a mutation (odds ratio [OR], 2.17; 95% CI, 1.37 to 3.46; $P = .001$). The pCR rate among patients treated with bevacizumab was 61.5% for *BRCA1/2* mutation carriers and 35.6% for those without mutations (OR, 2.90; 95% CI, 1.43 to 5.89; $P = .004$). pCR was a strong predictor of DFS for patients without *BRCA1/2* mutations (hazard ratio, 0.18; 95% CI, 0.11 to 0.31) but not for patients with *BRCA1/2* mutations (hazard ratio, 0.74; 95% CI, 0.32 to 1.69).

Conclusion

The addition of bevacizumab may increase the pCR after standard neoadjuvant chemotherapy for patients with TNBC with *BRCA1/2* mutations. In patients treated with anthracycline and taxane–based chemotherapy (with or without bevacizumab), pCR was a weaker predictor of DFS for *BRCA1/2* mutation carriers than for patients without mutations.

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INTRODUCTION

Treatment for patients with triple-negative breast cancer (TNBC) involves several challenges. The absence of hormone receptors and human epidermal growth factor receptor 2 (HER2) makes the tumors ineligible for antihormonal treatment and trastuzumab or pertuzumab—leaving chemotherapy, with the associated toxicity, as the most effective therapy.

Chemotherapy can achieve a good response and also leads to a favorable long-term prognosis in patients with TNBC. When given as neoadjuvant therapy, the standard chemotherapy regimen including taxane and anthracyclines results in a pathologic complete response (pCR) in 30% to 50% of patients.[1,2] In addition, patients who achieve a pCR have an excellent long-term prognosis in comparison with women who do not achieve a pCR.[1,2]

Mutations in *BRCA1* and *BRCA2* are more common in TNBC than in other molecular

ASSOCIATED CONTENT

Appendix
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Data Supplement
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subtypes, with 11% to 17% of patients with TNBC having germline mutations.[3,4] Patients with TNBC with *BRCA1/2* mutations are reported to have a higher pCR rate than noncarriers in response to standard chemotherapies, with or without platinum agents.[4-9]

A recent report has raised the question of whether patients with *BRCA1/2* germline mutations may represent a subpopulation in which a pCR is not associated with any benefit in terms of the prognosis.[10] As deliberations on whether and how to establish pCR as a surrogate marker for drug approval are ongoing, it will become important to identify subgroups with and without this association between pCR and prognosis.

BRCA1/2 mutations have been reported to result in higher clinical response rates in relation to chemotherapy in patients with breast cancer. However, the influence of antiangiogenic agents such as bevacizumab on clinical response among patients with *BRCA1/2* mutations has not been assessed, despite evidence that tumors with *BRCA1/2* mutations show overexpression of vascular endothelial growth factor, Ang-1, and Ang-2.[11,12] Similarly, hypoxia-associated DNA damage,[13] associated with inhibition of angiogenesis, may contribute to synthetic lethal responses to treatment in tumors with *BRCA1/2* mutations.

The influence of bevacizumab on breast cancer outcome has been tested in two large neoadjuvant chemotherapy trials (NSABP-B40 and GeparQuinto), both of which showed an increased pCR.[14,15] However, only the NSABP-B40 study showed improved disease-free survival (DFS) with the addition of bevacizumab.[16,17] Also, although the benefit of bevacizumab was mainly seen in patients with TNBC in the GeparQuinto study, in the NSABP-B40 study this effect was most prominent in hormone receptor–positive patients.[14,15] These results suggest that additional predictors interacting with the bevacizumab response and treatment-related prognosis are needed.

The aims of this study were to assess the extent to which the pCR rate in patients in the GeparQuinto clinical trial depended on germline *BRCA1/2* mutation status, whether pCR rate interacts with bevacizumab treatment, and how pCR translates into DFS in patients with and without *BRCA1/2* mutations.

PATIENTS AND METHODS

The GeparQuinto phase III trial (ClinicalTrials.gov identifier: NCT00567554) recruited patients into two different treatment settings. Patients with HER2-positive breast cancer were randomly assigned to an anti-HER2 therapy–related study arm,[18] whereas HER2-negative patients were recruited with the aim of testing the efficacy of bevacizumab on neoadjuvant response.[15,17] The current study reports on the patients with TNBC in the HER2-negative arm.

A total of 1,948 HER2-negative patients were randomly assigned in the main study.[15] Among 663 patients with TNBC who received treatment,[19] 528 provided blood samples for prespecified pharmacogenetics studies. All patients provided written informed consent, and the relevant ethics committees at the participating study sites approved the study protocol (Data Supplement).

Treatment and Assessment of Clinical Data

The assessment of the clinical data from the GeparQuinto study has been described elsewhere.[15] Briefly, HER2-negative patients received epirubicin and cyclophosphamide on day 1 and every 3 weeks for a total of four cycles, followed by docetaxel on day 1 and every 3 weeks for a total of four cycles. Patients were randomly assigned to receive either bevacizumab from the beginning of chemotherapy until surgery or no additional treatment. If there was no sonographic response after four cycles, the patients were taken off treatment and provided with alternative treatment.[20] For the current study, patients were included in analyses if at least one cycle of chemotherapy or bevacizumab was completed. All clinical and

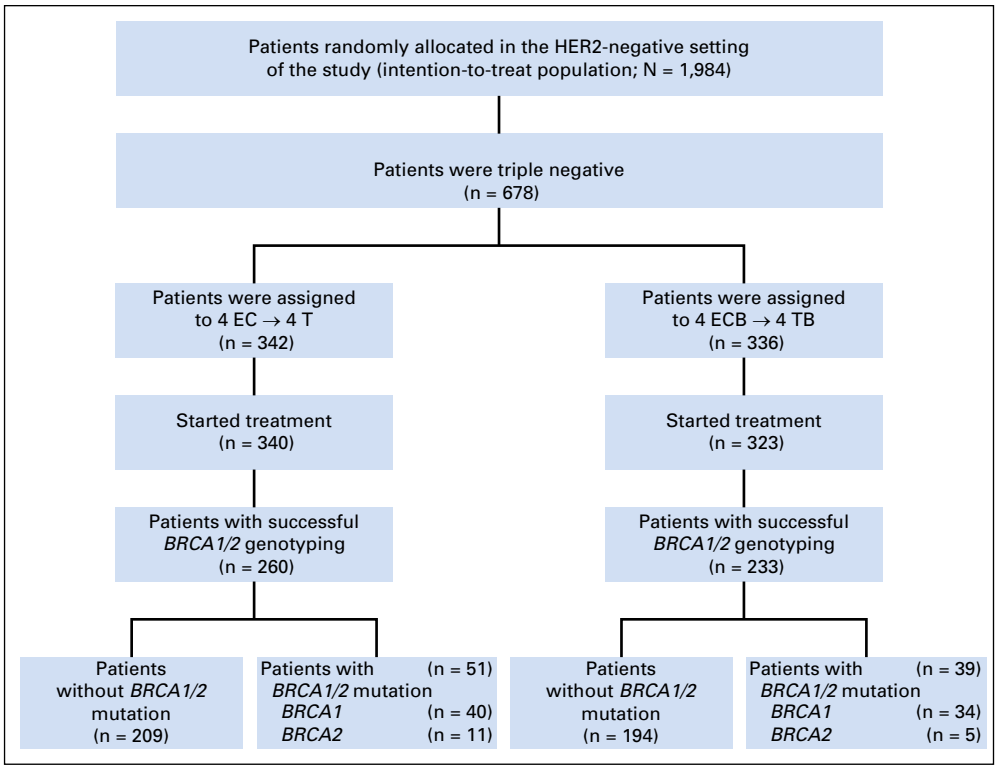

Fig 1. Patient selection. EC, epirubicin/cyclophosphamide; ECB, epirubicin/cyclophosphamide/bevacizumab; T, docetaxel; TB, docetaxel/bevacizumab.

histopathological data were assessed by local pathologists, including tumor stage, HER2 status, estrogen receptor/progesterone receptor status, and grade. Pathology reports were reviewed centrally for pCR.

DNA Extraction and Sequencing

Whole blood samples were collected in citrate-phosphate-dextrose-adenine tubes (Sarstedt AG, Nümbrecht, Germany) from patients at the time of random assignment. Germline DNA was extracted using the automated magnetic bead–based chemagic MSM I method (PerkinElmer chemagen, Baesweiler, Germany) in accordance with the manufacturer's instructions. Quality control identified 35 poor-quality DNA samples among 528 samples available for the sequencing study.

The samples were genotyped as part of a multigene panel–based mutation analysis. The target regions included coding sequences and intron/exon boundaries of coding exons from 643 DNA repair genes, including *BRCA1* and *BRCA2*. Baits for solution-based hybrid selection capture were designed using the Agilent SureSelect design tool. Germline DNA was fragmented and subjected to library preparation using the NEBNext Ultra DNA Library Prep kit with NEB Dual indexed adaptors and enriched for target regions by custom capture (Agilent eArray) using the Agilent SureSelect protocol. Products from each capture reaction were sequenced on a HiSEquation 2000 to 100 times mean coverage of target regions. All likely pathogenic mutations were validated using Sanger sequencing.

Bioinformatics Analysis

Paired end sequencing reads (100 bp) were aligned to the hg19 reference human genome using NovoAlign (Novocraft Technologies, Petaling Jaya, Malaysia). Realignment and recalibration were performed using GATK (VN 3.3.0). Samples with a read depth of $<$ 20 times for $>$ 10% of the target regions were excluded. Germline variations were called using GATK HaplotypeCaller. Variants with fewer than alternate allele reads from a minimum read depth of 20 times were excluded. Variants with a heterozygosity ratio of $>$ 70:30 were excluded as possible mosaics. Annotations were defined using the bioR framework[21] for population allele frequencies, 1,000 Genomes[22] and dbSNP (VN 137),[23] known mutation status (Human Gene Mutation database,[24] ClinVar[25]), and protein sequence alterations (Clinical Annotation of Variants, VN 1.0).[26]

Statistical Considerations

In the primary analysis, pathologic response was defined as pathologic stage ypT0 and ypN0 after therapy. Analyses were repeated for pCR defined as ypT0/is and ypN0.[2] DFS was defined as the time from random assignment until any invasive locoregional, invasive contralateral, or distant recurrence of breast cancer or any second primary invasive non-breast cancer, or death as a result of any cause.[17]

Pearson's χ^2 test was used to compare genotyped participants and nonparticipants, as well as for comparisons between patients treated with and without bevacizumab. Fisher's exact test was used to compare pCR rates between groups. Multivariate logistic regression including *BRCA1/2* mutation status and treatment arm, as well as an interaction term, was performed to test for a different effect of *BRCA1/2* mutation status on pCR in patients treated with and without bevacizumab. The Kaplan-Meier product-limit method was used to estimate disease-free survival and distant disease–free survival (DDFS). Univariate Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% CIs. In addition, Cox proportional hazard models including pCR, *BRCA1/2* mutation status, and their interaction term, as well as *BRCA1/2* mutation status, treatment arm, and their interaction term, were performed to test for the influence of differences in pCR and treatment on patient prognosis with and without a *BRCA1/2* mutation.

All statistical tests were two sided, and a *P* value of $<$ .05 was considered significant. No adjustment for multiple testing was performed. The analyses in this report were conducted using the statistical programming language R, version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Table 1. Patient and Tumor Characteristics

Parameter	No BEV Treatment	BEV Treatment	All TNBC	*P*
Age	48 ± 10	48 ± 11	48 ± 11	.955
Ki-67	54 ± 24	57 ± 25	55 ± 25	.374
Tumor size				
T1	54 (20.8)	45 (19.4)	99 (20.2)	.877
T2	152 (58.7)	136 (58.6)	288 (58.7)	
T3-4	53 (20.5)	51 (22.0)	104 (21.2)	
Missing	1	1	2	
Nodal status				
Node negative	133 (52.4)	131 (56.7)	264 (54.4)	.362
Node positive	121 (47.6)	100 (43.3)	221 (45.6)	
Missing	6	2	8	
Grading				
Grade 1-2	72 (28.0)	60 (25.8)	132 (26.9)	.611
Grade 3	185 (72.0)	173 (74.2)	358 (73.1)	
Missing	3	0	3	
Menopausal status				
Premenopausal	164 (63.8)	138 (59.5)	302 (61.8)	.352
Postmenopausal	93 (36.2)	94 (40.5)	187 (38.2)	
Missing	3	1	4	
Type of surgery				
Other	183 (75.9)	157 (71.4)	340 (73.8)	.290
Mastectomy	58 (24.1)	63 (28.6)	121 (26.2)	
Missing	19	13	32	
pCR (ypT0 ypN0)				
No	181 (69.6)	140 (60.1)	321 (65.1)	.030
Yes	79 (30.4)	93 (39.9)	172 (34.9)	
pCR (ypT0/is ypN0)				
No	168 (64.6)	129 (55.4)	297 (60.2)	.043
Yes	92 (35.4)	104 (44.6)	196 (39.8)	
BRCA1/2				
Wild type	209 (80.4)	194 (83.3)	403 (81.7)	.417
Mutated	51 (19.6)	39 (16.7)	90 (18.3)	
BRCA1				
Wild type	220 (84.6)	199 (85.4)	419 (85.0)	.900
Mutated	40 (15.4)	34 (14.6)	74 (15.0)	
BRCA2				
Wild type	249 (95.8)	228 (97.9)	477 (96.8)	.214
Mutated	11 (4.2)	5 (2.1)	16 (3.2)	

NOTE. Data presented as mean ± standard deviation, No., or No. (%).
Abbreviations: BEV, bevacizumab; Ki-67, Kiel 67 antigen; pCR, pathologic complete response; TNBC, triple-negative breast cancer.

RESULTS

Patient Population

Genotype data were obtained for 493 patients from the 528 patients who provided germline DNA for this substudy (Fig 1). Genotyped patients had a more favorable tumor stage than nongenotyped participants (Appendix Table A1, online only). No significant differences in other parameters were observed (Appendix Table A1). In addition, there were no differences between patients treated with bevacizumab (n = 233) or not treated with bevacizumab (n = 260; Table 1). The pCR (ypT0/ypN0) rates were 30.4% (n = 79) and 39.9% (n = 93) for patients not treated and treated with bevacizumab, respectively. These pCR rates were similar to the pCR rates for the complete population (30.9% *v* 41.8%).[19]

Genotyping Results

Deleterious *BRCA1* and *BRCA2* mutations were detected in 90 (18.3%) patients, including 74 (82.2%) with mutations in *BRCA1* and 16 (17.8%) with mutations in *BRCA2*. No patients had

Table 2. Pathologic Complete Response Rates Relative to *BRCA1/2* Mutation Status

Type of Mutation	pCR	Wild Type	Mutation	Overall	Fisher's Exact Test *P*
Definition of pCR: ypT0-ypN0					
BRCA1 or *BRCA2*	No	276 (68.5)	45 (50.0)	321 (65.1)	.001
	Yes	127 (31.5)	45 (50.0)	172 (34.9)	
BRCA1	No	283 (67.5)	38 (51.4)	321 (65.1)	.008
	Yes	136 (32.5)	36 (48.6)	172 (34.9)	
BRCA2	No	314 (65.8)	7 (43.8)	321 (65.1)	.106
	Yes	163 (34.2)	9 (56.3)	172 (34.9)	
Definition of pCR: ypT0/is-ypN0					
BRCA1 or *BRCA2*	No	257 (63.8)	40 (44.4)	297 (60.2)	.001
	Yes	146 (36.2)	50 (55.6)	196 (39.8)	
BRCA1	No	263 (62.8)	34 (45.9)	297 (60.2)	.010
	Yes	156 (37.2)	40 (54.1)	196 (39.8)	
BRCA2	No	291 (61.0)	6 (37.5)	297 (60.2)	.071
	Yes	186 (39.0)	10 (62.5)	196 (39.8)	

NOTE. Data presented as No. (%).
Abbreviation: pCR, pathologic complete response.

mutations in both genes. Deleterious *BRCA1* mutations included 49 frameshift mutations, 16 stop-gain mutations, five consensus splice site mutations, two deletions, one intronic variant, and 17 pathogenic missense mutations. Deleterious *BRCA2* mutations included 10 frameshift, four stop-gain, and two pathogenic missense mutations. Mutations are listed in Appendix Table A2, online only. Among the patients with *BRCA1/2* mutations, 51 (57%) were treated with standard chemotherapy alone and 39 (43%) with chemotherapy and bevacizumab (Fig 1). Similarly, among patients without mutations, 209 (52%) received chemotherapy alone and 194 (48%) were treated with bevacizumab.

Pathologic Complete Response and Prognosis Relative to BRCA *Mutation Status*

Irrespective of the treatment arm, the pCR (ypT0/ypN0) rates were 31.5% and 50.0% for patients without and with *BRCA1/2* mutations, respectively (odds ratio [OR], 2.17; 95% CI, 1.37 to 3.46; $P = .001$). The pCR rates were similar for *BRCA1* (48.6%) and *BRCA2* (56.3%) mutation carriers (Table 2). Although the pCR rates in patients with *BRCA1* mutations and patients with wild-type genotype were significantly different (OR, 1.97; 95% CI, 1.20 to 3.25; $P = .008$), the pCR rate in patients with *BRCA2* mutations was similarly increased relative to the rate in patients with wild-type genotypes (OR, 2.48; 95% CI, 0.91 to 6.77; $P = .106$), although the difference was not statistically significant. The specific pCR rates for groups of *BRCA1* and *BRCA2* mutation carriers and different definitions of pCR are given in Table 2.

With regard to prognosis, patients with *BRCA1/2* mutations had a significantly better DFS (HR, 0.644; 95% CI, 0.415 to 0.998; $P = .047$) than those with no mutations (Fig 2A). However, pCR in patients with *BRCA1/2* mutations was not significantly associated with an improved DFS (HR, 0.74; 95% CI, 0.32 to 1.69; $P = .472$). In contrast, patients without mutations derived substantial benefit from pCR (HR, 0.18; 95% CI, 0.11 to 0.31; $P < .001$). Tests for interaction yielded a *P* value of .005, indicating that patients with *BRCA1/2* mutations had a significantly different DFS after a pCR than patients without mutations. Kaplan-Meier curves are shown in Figure 2B. Analyses were repeated with DDFS as the outcome variable, and results were similar (Appendix Fig A1, online only).

Pathologic Complete Response and Prognosis Relative to BRCA *Mutations and Treatment Arm*

The relationship between pCR rates and both *BRCA* mutation status and treatment was also explored. In patients without bevacizumab treatment, the pCR rates were 27.8% and 41.2% in patients without and with *BRCA1/2* mutations, respectively (OR, 1.82; 95% CI, 0.97 to 3.44; $P = .088$). Patients with bevacizumab treatment had corresponding pCR rates of 35.6% and 61.5%, respectively (OR, 2.90; 95% CI, 1.43 to 5.89; $P = .004$). The test for interaction was not significant ($P = .341$). pCR rates relative to mutation status and treatment arm are shown in Figure 3.

Although substantially different pCR rates were observed, these did not translate into differential effects on DFS. The DFS associated with bevacizumab treatment in patients with *BRCA1/2* mutations had a HR of 1.39 (95% CI, 0.61 to 3.15), whereas the DFS in patients without *BRCA1/2* mutations had a HR of 1.02 (95% CI, 0.74 to 1.40). The test for interaction yielded a *P* value of 0.451 (Fig 2C). Again, analyses were repeated with DDFS as the outcome variable, and results were similar (Appendix Fig A1). In addition, all of the analyses were repeated based on the pCR definition ypT0/is yN0. Similar results were observed (data not shown).

DISCUSSION

This study shows that patients with TNBC and a *BRCA1* or *BRCA2* mutation had higher pCR rates than patients without a mutation (50% *v* 31.5%). In addition, pCR rates of > 60% were observed if patients with mutations were treated with neoadjuvant chemotherapy including anthracyclines and taxanes with the addition of bevacizumab. In contrast, pCR rates of only 40% were achieved in patients with germline *BRCA1/2* mutations but no bevacizumab treatment.

A recent report evaluated *BRCA1/2* mutations, pCR, and prognosis in the GeparSixto Study.[4] The study compared the addition of carboplatin to treatment with weekly paclitaxel plus weekly liposome-encapsulated doxorubicin plus weekly bevacizumab. Although only 50% of the patients in GeparQuinto received bevacizumab, the drug was given to all patients with TNBC in the GeparSixto trial. pCR rates of 33.1% (n = 40) in

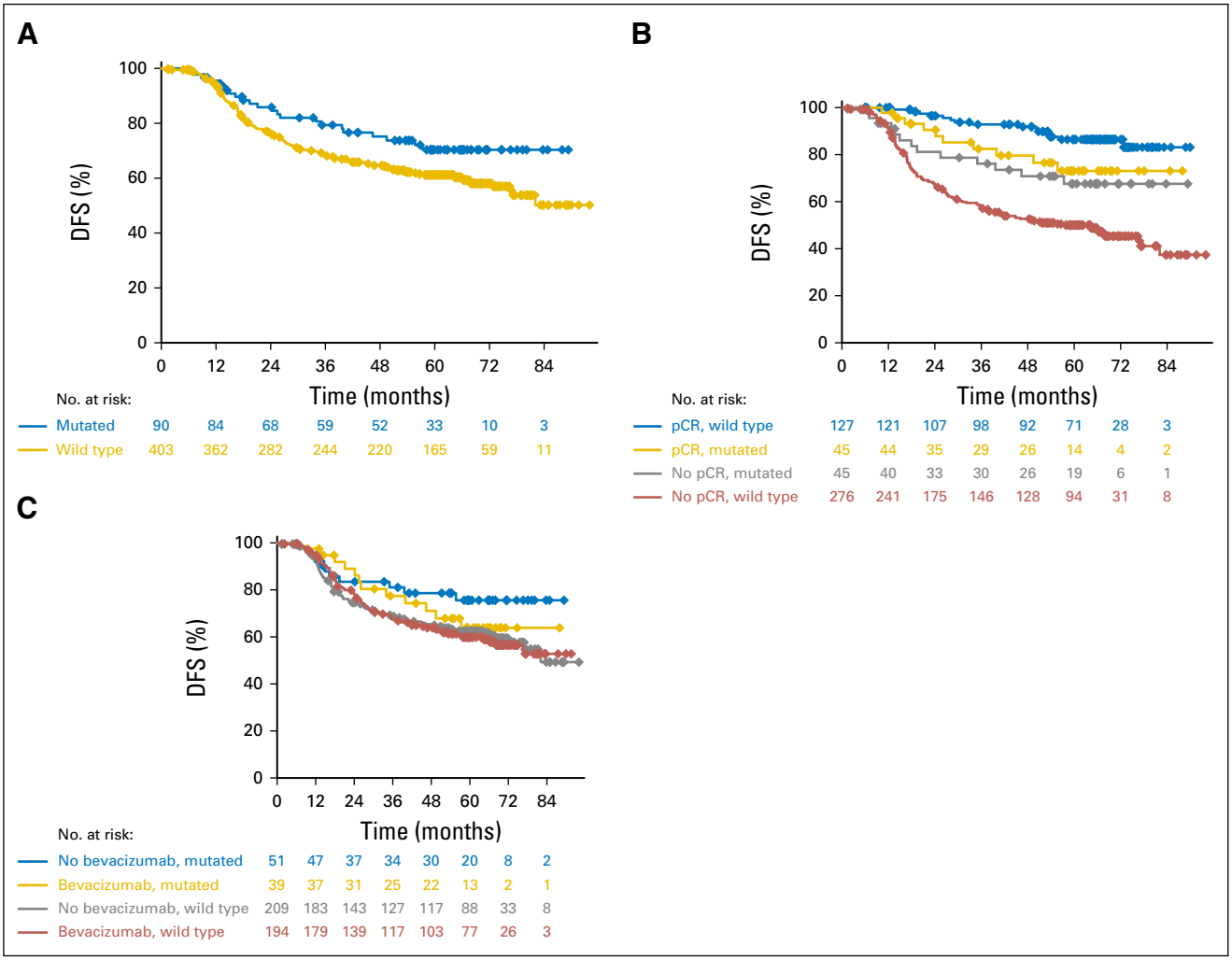

Fig 2. Kaplan-Meier curves for disease-free survival (DFS). (A) Comparison of DFS in all patients (hazard ratio [HR], 0.644; 95% CI, 0.415 to 0.998; $P = .047$). (B) Comparison of the effects of pathologic complete response (pCR) on the DFS. The HR for pCR in mutation carriers was 0.74 (95% CI, 0.32 to 1.69; $P = .472$); the HR for pCR in patients without mutations was 0.18 (95% CI, 0.11 to 0.31; $P < .001$). The interaction test showed a P value of .005. (C) Comparison of DFS relative to the treatment arm and mutation status. The HRs for bevacizumab treatment were 1.39 (95% CI, 0.61 to 3.15; $P = .428$) in patients with a *BRCA1/2* mutation and 1.02 (95% CI, 0.74 to 1.40; $P = .903$) in patients without a *BRCA1/2* mutation. $P_{(interaction)} = .451$.

patients without a *BRCA1/2* mutation and 50% (n = 12) in patients with a *BRCA1/2* mutation in the nonplatinum arm were observed in GeparSixto.[4] These results were slightly attenuated compared with the findings in the GeparQuinto study. In addition, a smaller study of pCR in patients with TNBC treated mainly with dose-dense doxorubicin/cyclophosphamide and dose-dense paclitaxel or weekly paclitaxel without bevacizumab treatment recently suggested that *BRCA1* mutations may represent a subgroup of patients with TNBC who do not benefit from a pCR.[10] The GeparQuinto results also showed that pCR had a smaller influence on DFS in patients with mutations (HR, 0.74; $P = .472$). In contrast, a statistically significant influence of pCR on DFS (HR, 0.18; $P < .001$) was observed for patients with wild-type tumors. The test for interaction yielded a P value of .005, indicating that the effect of pCR on DFS was smaller in *BRCA1/2* mutation carriers than in patients with wild-type tumors. However, these comparisons should be interpreted with caution because of small sample sizes.

One possible explanation for the absence of an influence of increased pCR on prognosis in patients with *BRCA1/2* mutations is the inclusion of subsequent contralateral breast cancers in the DFS analyses. Patients with a *BRCA1/2* mutation have a 5-year risk for contralateral breast cancer of 10% to 15%, compared with 3% in patients without mutations.[27] To address this possibility, we repeated the analysis using DDFS as the outcome variable. Similar results were observed, suggesting that the finding is independent of contralateral breast cancer events. Interestingly, the GeparSixto study did not show a differential effect of pCR on prognosis in patients with and without *BRCA1/2* mutations.[4] Whether the effect of pCR on prognosis in GeparSixto was driven by the platinum treatment, possibly in combination with bevacizumab, remains to be determined.

At the molecular level, several preclinical studies and clinical data imply a connection between DNA repair, hypoxia, and vascular endothelial growth factor signaling pathways. Indeed, antiangiogenic therapy may contribute to synthetic lethality[28,29] in patients with *BRCA1/2* mutations. Treatment with antiangiogenic drugs has been shown to induce hypoxia in tumors,[30] and hypoxia has been shown to downregulate different mechanisms of DNA repair.[13] Treatment with chemotherapy and with bevacizumab as an agent that potentially

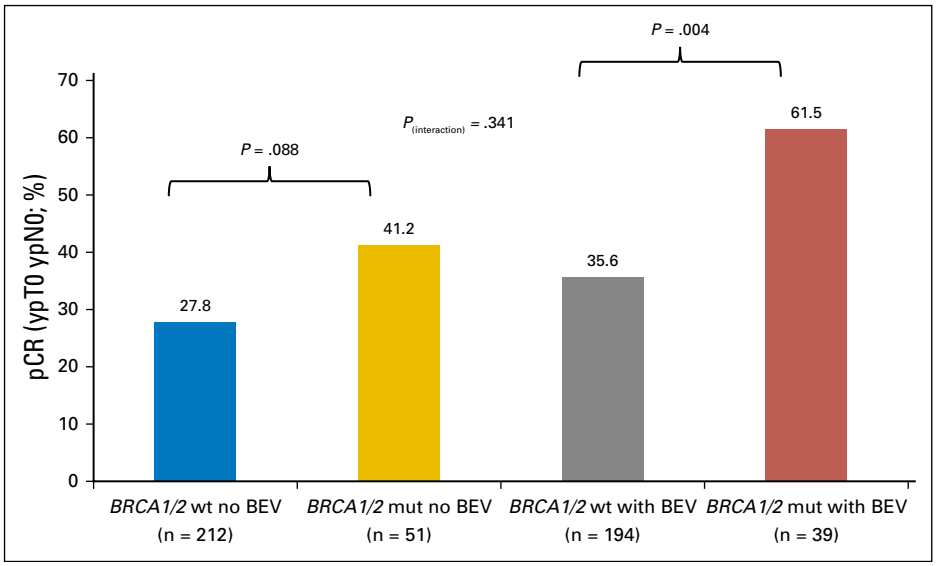

Fig 3. Pathologic complete response (pCR) rates relative to *BRCA1/2* mutation status and treatment arm. BEV, bevacizumab; mut, mutation; wt, wild type.

catalyzes additional genetic instability and downregulation of DNA repair response pathways may synergistically result in high response rates. Thus, bevacizumab-induced hypoxia and the resulting impairment of several DNA repair pathways may be one component of synthetic lethality in the context of DNA repair and cell death.

The main limitation of this study is the low sample size and the small number of *BRCA1/2* mutation carriers. Although almost 500 patients with TNBC breast cancer were genotyped, there were only 90 mutation carriers. Therefore, an analysis incorporating mutation status, treatment arm, pCR, and prognosis and addressing whether pCR relative to the treatment arm has an effect on prognosis could not be undertaken. However, combining data from GeparSixto, GeparQuinto, NSABP-B40 and CALGB 40603 could provide additional insight into this question. Another limitation is that not every patient included in GeparQuinto provided blood for this analysis. However, samples were collected at the time of random assignment, and there were no differences in patient or tumor characteristics with regard to treatment arm.

This study is the largest so far that has examined the effect of *BRCA1/2* mutations in the neoadjuvant treatment of TNBC. pCR rates are clearly higher in patients with *BRCA1/2* mutations. High pathologic complete response rates in patients treated with chemotherapy and bevacizumab imply a role of antiangiogenic-induced hypoxia in the synthetic lethality of tumor cells with *BRCA1/2* mutations. In this study, with standard treatment with anthracyclines, cyclophosphamide, and taxanes (with or without bevacizumab), the data suggest that *BRCA1/2* mutation carriers do not benefit as much from a pCR in comparison with patients with a *BRCA1/2* wild-type genotype. Additional studies and analyses need to be conducted to clarify the population in which *BRCA1/2* mutation status uncouples pCR from a favorable prognosis.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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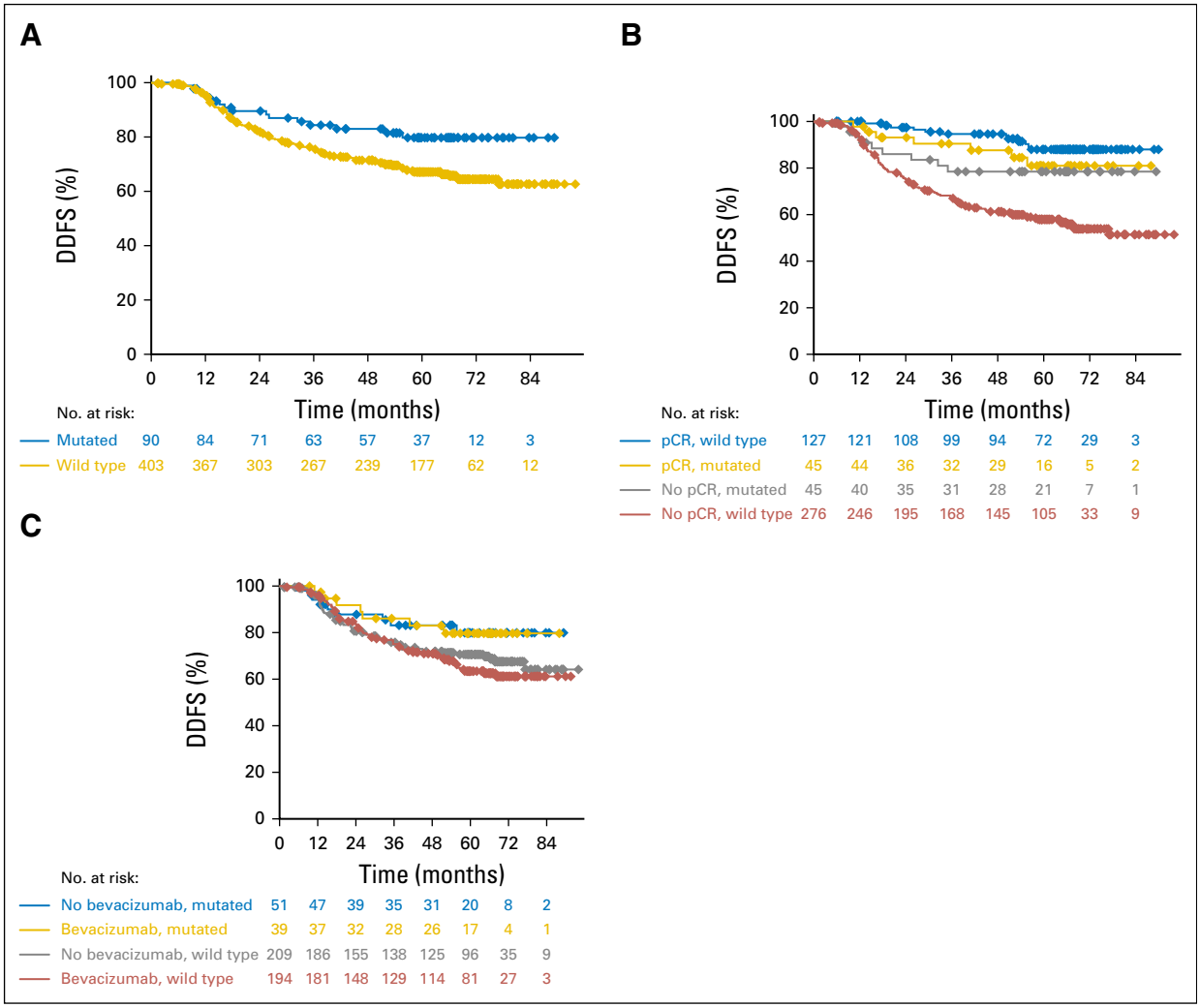

Fig A1. Kaplan-Meier curves for distant disease-free survival (DDFS). (A) Comparison of DDFS in all patients. Hazard ratio (HR), 0.554 (95% CI, 0.329 to 0.933; $P = .024$). (B) Comparison of the effects of pathologic complete response (pCR) on the DDFS. The HR for pCR in mutation carriers was 0.74 (95% CI, 0.27 to 1.98; $P = .541$); the HR for pCR in patients without mutations was 0.19 (95% CI, 0.10 to 0.34; $P < .001$). The interaction test showed a P value of 0.0195. (C) Comparison of DDFS relative to the treatment arm and mutation status. The HRs for bevacizumab treatment were 0.97 (95% CI, 0.36 to 2.60; $P = .947$) in patients with a *BRCA1/2* mutation and 1.15 (95% CI, 0.81 to 1.64; $P = .432$) in patients without a *BRCA1/2* mutation. $P_{(interaction)} = .756$.

Table A1. Tumor and Patient Characteristics

Parameter	Not Genotyped	Genotyped	All TNBC	*P*
Age	48 ± 10	48 ± 11	48 ± 11	.758*
Ki-67	54 ± 29	55 ± 25	55 ± 26	.786*
Tumor size				
T1	21 (12.0)	100 (20.2)	121 (18.1)	.003†
T2	97 (55.4)	289 (58.5)	386 (57.7)	
T3-4	57 (32.6)	105 (21.3)	162 (24.2)	
Missing	0	2	2	
Nodal status				
Node negative	77 (44.8)	266 (54.5)	343 (52.0)	.033†
Node positive	95 (55.2)	222 (45.5)	317 (48.0)	
Missing	3	8	11	
Grading				
Grade 1-2	58 (33.1)	134 (27.2)	192 (28.7)	.145†
Grade 3	117 (66.9)	359 (72.8)	476 (71.3)	
Missing	0	3	3	
Menopausal status				
Premenopausal	106 (62.0)	303 (61.6)	409 (61.7)	1.00†
Postmenopausal	65 (38.0)	189 (38.4)	254 (38.3)	
Missing	4	4	8	
Type of surgery				
Other	115 (71.9)	342 (73.7)	457 (73.2)	.679†
Mastectomy	45 (28.1)	122 (26.3)	167 (26.8)	
Missing	15	32	47	
Bevacizumab				
No	85 (48.6)	263 (53.0)	348 (51.9)	.334†
Yes	90 (51.4)	233 (47.0)	323 (48.1)	
pCR (ypT0 ypN0)				
No	117 (66.9)	324 (65.3)	441 (65.7)	.781†
Yes	58 (33.1)	172 (34.7)	230 (34.3)	
pCR (ypT0/is ypN0)				
No	110 (62.9)	300 (60.5)	410 (61.1)	.590†
Yes	65 (37.1)	196 (39.5)	261 (38.9)	

NOTE. Data presented as mean ± standard deviation, No., or No. (%).
Abbreviations: Ki-67, Kiel 67 antigen; pCR, pathologic complete response; TNBC, triple-negative breast cancer.
*Student *t*-test.
†χ^2 test.

Table A2. List of Likely Deleterious Mutations

Gene	HGVS Mutation Nomenclature	No. for This Mutation
BRCA1	c.5266dupC	14
BRCA1	c.181T>G_p.Cys61Gly	12
BRCA1	c.3700_3704del5	2
BRCA1	c.3661G>T_p.Glu1221X	2
BRCA1	c.3481_3491del11	2
BRCA1	Ex8-12 del	1
BRCA1	Ex21 del	1
BRCA1	c.893delA	1
BRCA1	c.843_846delCTCA	1
BRCA1	c.798_799delTT	1
BRCA1	c.68_69delAG	1
BRCA1	c.5560delC	1
BRCA1	c.5509T>C_p.Trp1837Arg	1
BRCA1	c.5503C>T_p.Arg1835X	1
BRCA1	c.5444G>A_p.Trp1815X	1
BRCA1	c.53T>C_p.Met18Thr	1
BRCA1	c.5177_5180delGAAA	1
BRCA1	c.5152+1G>C	1
BRCA1	c.5096G>A_p.Arg1699Gln	1
BRCA1	c.5080G>T_p.Glu1694X	1
BRCA1	c.5074G>C_p.Asp1692His	1
BRCA1	c.5074+1G>A	1
BRCA1	c.4690delC	1
BRCA1	c.4689C>G_p.Tyr1563X	1
BRCA1	c.4675+1G>A	1
BRCA1	c.4533_4534delCA	1
BRCA1	c.4389C>A_p.Tyr1463X	1
BRCA1	c.4183C>T_p.Gln1395X	1
BRCA1	c.4071delA	1
BRCA1	c.4065_4068delTCAA	1
BRCA1	c.4035delA	1
BRCA1	c.3770_3771delAG	1
BRCA1	c.3756_3759delGTCT	1
BRCA1	c.3485delA	1
BRCA1	c.3477_3480delAAAG	1
BRCA1	c.3247_3251del5	1
BRCA1	c.3193dupG	1
BRCA1	c.3062delG	1
BRCA1	c.2923C>T_p.Gln975X	1
BRCA1	c.2411_2412delAG	1
BRCA1	c.2263G>T_p.Glu755X	1
BRCA1	c.213-12A>G	1
BRCA1	c.1729G>T_p.Glu577X	1
BRCA1	c.1687C>T_p.Gln563X	1
BRCA1	c.1673_1674delAA	1
BRCA1	c.1252G>T_p.Glu418X	1
BRCA1	c.1127delA	1
BRCA2	c.9097dupA	2
BRCA2	c.3847_3848delGT	2
BRCA2	c.961C>T_p.Gln321X	1
BRCA2	c.9371A>T_p.Asn3124Ile	1
BRCA2	c.8363G>A_p.Trp2788X	1
BRCA2	c.7879A>T_p.Ile2627Phe	1
BRCA2	c.7180A>T_p.Arg2394X	1
BRCA2	c.5946delT	1
BRCA2	c.5238dupT	1
BRCA2	c.4449delA	1
BRCA2	c.2606C>G_p.Ser869X	1
BRCA2	c.2100delA	1
BRCA2	c.1310_1313delAAGA	1
BRCA2	c.1029delA	1
Total		90

NOTE. Position annotations are relative to transcripts ENST00000357654 and ENST00000544455 for *BRCA1* and *BRCA2*, respectively.
Abbreviation: HGVS, Human Gene Variation Society.