



# ***BRCA* mutations and their influence on pathological complete response and prognosis in a clinical cohort of neoadjuvantly treated breast cancer patients**

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## **Abstract**

**Purpose** *BRCA1/2* mutations influence the molecular characteristics and the effects of systemic treatment of breast cancer. This study investigates the impact of germline *BRCA1/2* mutations on pathological complete response and prognosis in patients receiving neoadjuvant systemic chemotherapy.

**Methods** Breast cancer patients were tested for a *BRCA1/2* mutation in clinical routine work and were treated with anthracycline-based or platinum-based neoadjuvant chemotherapy between 1997 and 2015. These patients were identified in the tumor registry of the Breast Center of the University of Erlangen (Germany). Logistic regression and Cox regression analyses were performed to investigate the associations between *BRCA1/2* mutation status, pathological complete response, disease-free survival, and overall survival.

**Results** Among 355 patients, 59 had a mutation in *BRCA1* or in *BRCA2* (16.6%), 43 in *BRCA1* (12.1%), and 16 in *BRCA2* (4.5%). Pathological complete response defined as “ypT0; ypN0” was observed in 54.3% of *BRCA1/2* mutation carriers, but only in 22.6% of non-carriers. The adjusted odds ratio was 2.48 (95% CI 1.26–4.91) for *BRCA1/2* carriers versus non-carriers. Patients who achieved a pathological complete response had better disease-free survival and overall survival rates compared with those who did not achieve a pathological complete response, regardless of *BRCA1/2* mutation status.

**Conclusions** *BRCA1/2* mutation status leads to better responses to neoadjuvant chemotherapy in breast cancer. Pathological complete response is the main predictor of disease-free survival and overall survival, independently of *BRCA1/2* mutation status.

**Keywords** *BRCA1/2* · Neoadjuvant chemotherapy · Pathological complete response · Prognosis · Survival

## **Introduction**

During the last few decades, the connection between the patients' response to neoadjuvant therapy and the prognosis has been investigated in multiple studies. For patients with triple-negative breast cancer (TNBC) and HER2-positive breast cancer, there is a strong association between pathological complete response (pCR) and prognosis, while in hormone receptor-positive patients, the pCR rate is low and

the association between pCR and prognosis is rather weak [1, 2]. Identifying further breast cancer subtypes with a strong or weak correlation between pCR and the prognosis should therefore be helpful for directing future therapies. The present study is concerned with *BRCA1/2* mutations in this context.

The data on *BRCA1/2* mutation status and prognosis are scarce and contradictory. Studies comparing *BRCA1* mutation carriers and non-carriers have reported better [3–6], poorer [7], or similar survival [6, 8, 9]. *BRCA2* mutation carriers appear to have a similar prognosis in comparison with non-carriers [5, 7, 8]. A meta-analysis did not show any major differences in survival, either [10].

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With regard to pCR, reports have demonstrated that a germline mutation in *BRCA1* is associated with excellent pCR rates in breast cancer patients [4, 11–13]. The data for patients with *BRCA2* mutations are not as clear, and the pCR rates in this group were similar to those in patients without a mutation [4, 5].

A recent report questioned whether triple-negative *BRCA1* carriers benefit from pCR at all. Although a clear association was found between pCR and a good prognosis in patients without mutations, no benefit from pCR was noted in patients with a *BRCA1* mutation [14].

The aim of the present study was therefore to investigate pCR in patients with primary breast cancer, with or without *BRCA1/2* mutations. A further aim was to analyze how pCR affects the prognosis in *BRCA1/2* mutation carriers in comparison with non-carriers.

## Methods

### Study design and selection of patients

This analysis was conducted in a group of patients included in the “Erlangen Neoadjuvant Study Breast” (ERNEST-B) study. ERNEST-B represents a consecutive cohort of primary breast cancer patients who were treated with neoadjuvant chemotherapy at the University Breast Center at Erlangen University Hospital between 1997 and 2015. During that time, 6801 patients with primary invasive breast cancer were treated, 1575 of whom received neoadjuvant chemotherapy. *BRCA1/2* testing was performed in 401 of these patients. All patients with primary metastases ( $n = 25$ ) and with bilateral cases ( $n = 21$ ) were excluded. The study population ultimately consisted of 355 breast cancer patients (Fig. 1). The Ethics Committee of the Medical Faculty of Friedrich Alexander University Erlangen–Nuremberg approved this retrospective study.

### Data collection

As required for certification by the German Cancer Society and German Society of Mastology, each breast cancer case was documented, including patient and tumor characteristics, detailed treatment, and epidemiological data [15]. Follow-up data were collected for up to 10 years after the primary diagnosis, and documentation quality was audited annually.

### Therapies

In the neoadjuvant setting, most patients received the following anthracycline-based therapies: four cycles of epirubicin ( $80\text{--}90\text{ mg/m}^2$ ) and cyclophosphamide ( $600\text{ mg/m}^2$ ) every

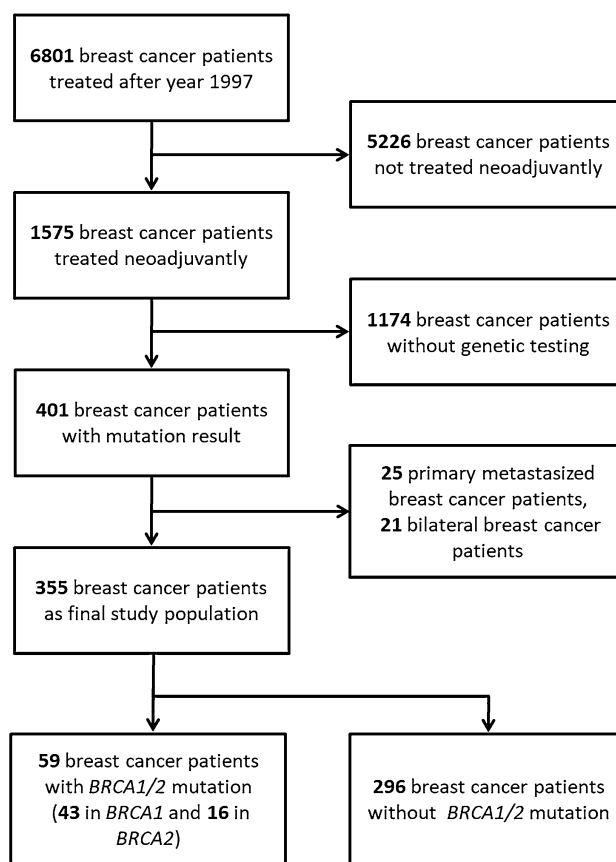


Fig. 1 Patient selection

3 weeks, followed by 12 cycles of paclitaxel ( $80\text{--}90\text{ mg/m}^2$ ) weekly. Platinum-based therapies were administered using the following standard protocol: six cycles of carboplatin AUC5 on day 1 and paclitaxel ( $80\text{--}90\text{ mg/m}^2$ ) on days 1, 8, and 15 every 3 weeks. Platinum-based treatment was not administered before 2007. The documentation only included whether anthracyclines, cyclophosphamide, taxanes, platinum, HER2 therapies, or other treatments were administered. Precise information on the exact treatment scheme for every patient is therefore not available.

### Definition of pCR and molecular subtypes

Data on pathological complete responses were drawn from the original pathology reports. pCR was defined as the complete eradication of invasive tumor cells from the breast and lymph nodes after chemotherapy at the time of surgery (ypT0; ypN0). The tumor’s molecular subtype is defined by hormone receptor status, HER2 status, and cellular proliferation rate (Ki-67). Luminal A-like tumors were estrogen receptor (ER)-positive or progesterone receptor (PR)-positive, HER2-negative, and had low Ki-67 values ( $\leq 14\%$ ). Luminal B-like tumors were ER-positive or PR-positive, and

HER2-negative with high Ki-67 values (> 14%). TNBCs were required to be negative or weakly positive ( $\leq 10\%$ ) for ER and PR, consistent with the guidelines applicable in different treatment years, and constantly negative for HER2 [16, 17]. All HER2-positive tumors were grouped together, regardless of hormone receptor status. ER, PR, and Ki-67 were assessed with immunohistochemistry by individual breast center pathologists, as described previously [18]. HER2 was positive when immunohistochemical staining indicated a 3+ result or the tumor showed HER2 amplification, as determined by chromogene in situ hybridization (CISH; ZytoDot, 2C SPEC HER2/CEN17, Zyto Vision Ltd., Bremerhaven, Germany). The immunohistochemical evaluation was quality-controlled and validated in annual round robin tests.

### Mutation screening

Mutations in *BRCA1/2* were analyzed as part of routine clinical testing. Genotyping was performed in patients with a positive family history who met the criteria for *BRCA1/2* diagnostic testing established by the German Consortium for Hereditary Breast and Ovarian Cancer [19] and/or in patients with TNBC, independently of their age. All patients received genetic counseling and provided written informed consent for diagnostic genetic testing and scientific use of their data.

Genomic DNA was extracted with an automated chemagic MSM I system (PerkinElmer, Baesweiler, Germany). Up to 2012, Sanger sequencing was performed, and primers for all coding exons of both genes were designed to cover 100% of coding and flanking sequences. The fragments were sequenced using BigDye version 3.1 (Applied Biosystems, part of Thermo Fisher, Darmstadt, Germany). The polymerase chain reaction products and sequencing reactions were purified automatically with the AMPure and CleanSEQ kits (Agencourt, Beverly, MA, USA) on a Biomek pipetting robot (Beckman Coulter, Fullerton, CA, USA). Purified sequences were separated on an ABI3730 sequencer (Applied Biosystems) and were analyzed using the Sequence Pilot software (JSI Medical Systems, Kippenheim, Germany).

After 2012, the Illumina TruSight Cancer Panel was used as a targeted resequencing kit for library preparation and sequenced on a MiSeq platform (Illumina, San Diego, CA, USA). Library preparation was done using 50 ng of genomic DNA per sample. The prepared libraries were applied to 2 × 150 bp paired-end sequencing, and the reads obtained were mapped to human genome reference GRCh37/hg19 using BWA-MEM version 0.7.7 [20]. *BRCA1/2* and other genes were analyzed using the SeqNext module of the Sequence Pilot software program (JSI Medical Systems). Mutations were classified as deleterious in accordance with

the breast cancer information core [21]. Using both of these methods resulted in 100% of the targets being covered.

### Statistical analysis

A logistic regression model (*basic model*) was fitted with pCR (“yes” vs. “no”) as the outcome and the following predictors for pCR: age at diagnosis (continuous), body mass index (BMI, continuous), clinical tumor size (categorical; T1–T4), molecular tumor type (categorical; TNBC, luminal A-like, luminal B-like, HER2-positive), therapy type (categorical; anthracycline-based therapy, platinum-based therapy). Subsequently, an additional logistic regression model was fitted containing *BRCA1/2* mutation (categorical, “yes” vs. “no”), the predictors from the previous basic model, and the interaction between *BRCA1/2* mutation and therapy type (*interaction model*). The two models were compared using the likelihood ratio test. A significant test result indicates that *BRCA1/2* mutation influenced pCR beyond the other predictors, either across all patients or at least within one of the therapy types. No further analyses were conducted if the test result was not significant, in order to avoid false-positive results. However, if the *p* value was significant, the interaction model was compared with a reduced logistic regression model without the interaction term (*reduced model*), using the likelihood ratio test again. In case of significance, therapy type-specific odds ratios for *BRCA1/2* mutation adjusted for the other predictors were calculated, using the interaction model. If the result was not significant, an adjusted overall odds ratio for *BRCA1/2* mutation was calculated, using the reduced model. No molecular tumor type-specific analyses (e.g., molecular tumor type as an interaction term) were performed, due to the small sample sizes in these subgroups.

The discrimination and calibration achieved by the logistic regression models were assessed using the area under the receiver operating characteristic curve (AUC) and the Hosmer–Lemeshow  $\chi^2$  test comparing predicted and observed pCR events, as done recently in [22]. A large *p* value indicates satisfactory calibration. To address overfitting, cross-validated AUC values were also calculated, as described in [23]. The smaller the difference between the cross-validated AUC and the original AUC, the lower the amount of overfitting.

A Cox regression model was fitted with disease-free survival as outcome and with the following predictors: age at diagnosis, BMI, clinical tumor size, molecular tumor type, *BRCA1/2* mutation status, and pCR. This Cox model was compared with an extended Cox model additionally including the interaction between *BRCA1/2* mutation status and pCR, using a likelihood ratio test. In case of significance, *BRCA1/2* mutation-specific hazard ratios for pCR were calculated using the interaction model. Otherwise, an overall hazard ratio for pCR was calculated using the model without

the interaction term. The proportional hazards assumptions were checked using the Grambsch–Therneau method. The results of the survival analyses are also illustrated using Kaplan–Meier curves for patient groups defined by pCR status, *BRCA1/2* mutation status, and therapy type. A similar analysis was performed for overall survival. Sensitivity analyses with time from genetic testing to event, instead of time from diagnosis to event, were performed to address a possible bias due to immortal time between the date of diagnosis and the date of genetic testing.

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 [24]. All of 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.

## Results

### Patient and tumor characteristics relative to *BRCA1/2* mutation status

Fifty-nine patients had a mutation in either *BRCA1* or *BRCA2* (16.6%). Forty-three mutations were detected in *BRCA1* (12.1%) and 16 in *BRCA2* (4.5%). The *BRCA1/2* mutation rates were 24.6% in all tested patients with TNBC, 10.3% in HER2-positive patients, 16.5% in patients with luminal B-like tumors, and 0.0% in patients with luminal A-like tumors.

Patient characteristics relative to *BRCA1/2* mutation status are shown in Table 1. *BRCA1/2* mutation carriers were on average 8 years younger than non-carriers. Among mutation carriers, 49.0% had at least one first-degree relative with breast and/or ovarian cancer, while this rate was 20.0% in non-mutation patients. Among the *BRCA1/2* mutation carriers, 57.6% of the tumors were triple-negative, 10.2% were HER2-positive, 32.2% were luminal B-like, and none was luminal A-like. *BRCA1/2*-related breast cancer was also more likely to have a histological grading of 3 (91.5 vs. 58.1%) and a higher Ki-67 level (57.7 vs. 41.4%).

### Therapies

In the total study population, 24.5% of the patients received carboplatin. Relative to molecular subtype, 49.3% of patients with TNBC, 8.6% of those with HER2-positive breast cancer, 12.2% of those with luminal B-like breast cancer, and none with luminal A-like breast cancer received carboplatin-based therapy, regardless of mutation status. All patients with HER2-positive breast cancer were treated with trastuzumab.

**Table 1** Patient demographics and clinical characteristics

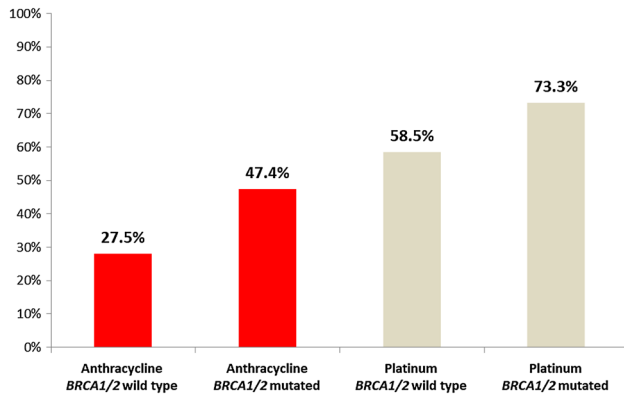
Patient characteristics	<i>BRCA1/2</i> mutation carriers ( <i>n</i> = 59)		<i>Non-BRCA1/2</i> mutation carriers ( <i>n</i> = 296)	
	<i>n</i> or mean	% or SD	<i>n</i> or mean	% or SD
Age at diagnosis	41.4	10.7	49.4	12.2
BMI (kg/m <sup>2</sup> )	24.7	4.4	25.3	5.0
First-degree relative with either breast or ovarian cancer				
Yes	24	49.0	50	20.0
No	25	51.0	200	80.0
Clinical tumor size				
cT1	23	39.0	69	23.3
cT2	33	55.9	181	61.1
cT3	1	1.7	17	5.7
cT4	2	3.4	29	9.8
Clinical nodal status				
cN-negative	34	57.6	137	46.3
cN-positive	25	42.4	159	53.7
Grading				
G1	0	0	13	4.4
G2	5	8.5	111	37.5
G3	54	91.5	172	58.1
ER status				
Positive	20	33.9	166	56.1
Negative	39	66.1	130	43.9
PR status				
Positive	12	20.3	134	45.3
Negative	47	79.7	162	54.7
HER2 status				
Positive	6	10.2	52	17.6
Negative	53	89.8	244	82.4
Proliferation index (Ki-67)				
High (> 14%)	56	94.9	240	81.1
Low (≤ 14%)	3	5.1	56	18.9
Molecular subtype				
Luminal A-like	0	0.0	44	14.9
Luminal B-like	19	32.2	96	32.4
HER2-positive	6	10.2	52	17.6
TNBC	34	57.6	104	35.1

*BMI* body mass index, *ER* estrogen receptor, *PR* progesterone receptor, *TNBC* triple-negative breast cancer

Across all breast cancer types, 35.6% of patients with a *BRCA1/2* mutation received carboplatin, while the rest received anthracycline-based treatments. Carboplatin treatments relative to molecular subtype in the group of mutation carriers represented 44.1% of treatments for patients with TNBC, 16.7% for HER2-positive patients, and 26.3% for patients with luminal B-like tumors.

**Table 2** Pathological complete response (pCR, defined as ypT0; ypN0) relative to *BRCA1/2* mutation status

pCR	<i>BRCA1/2</i> wild type		<i>BRCA1/2</i> mutated		<i>BRCA1</i> mutated		<i>BRCA2</i> mutated	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
No	229	77.4	27	45.7	18	41.9	9	56.3
Yes	67	22.6	32	54.3	25	58.1	7	43.7
Total	296	100.0	59	100.0	43	100.0	16	100.0

**Fig. 2** Rates of pathological complete response (pCR, defined as ypT0; ypN0) relative to *BRCA1/2* mutation status and treatment regimen in the subpopulation of patients with triple-negative breast cancer

### pCR relative to *BRCA1/2* mutation status

In patients without a mutation, the pCR rate was 22.6% ( $n=67$ ). In mutation carriers, the pCR rate was 54.3% ( $n=32$ ). With regard to subgroups of patients with either *BRCA1* or *BRCA2* mutations, the pCR rates were 58.1% in *BRCA1* carriers and 43.7% in *BRCA2* carriers (Table 2).

The pCR rates were further analyzed in relation to mutation status and treatment administered in the subsets of luminal A/B-like tumors, in HER2-positive tumors, in triple-negative tumors, and in overall breast cancer. Among TNBC patients ( $n=138$ ) who received anthracycline-based treatment, the pCR rate was 27.5% in non-carriers and 47.4% in *BRCA1/2* mutation carriers, while for patients who received platinum-based treatments, the rates were 58.5% and 73.3% (Fig. 2). In addition, for *BRCA1/2* mutation carriers, the pCR rates were higher across all breast cancer subtypes if carboplatin was administered. The responses to neoadjuvant chemotherapy for non-mutation carriers, for *BRCA1* mutation carriers, and for *BRCA1/2* mutation carriers are shown in Table 3. However, sample sizes in patients with luminal A/B-like tumors and HER2-positive tumors were too low for further conclusions to be drawn.

Comparison of prediction models with and without *BRCA1/2* mutation status showed that *BRCA1/2* mutation status significantly influenced pCR additionally to

**Table 3** Pathological complete response (pCR, defined as ypT0; ypN0) of anthracycline and platinum treatment relative to molecular subtype and *BRCA1/2* mutation status

	Anthracycline		Platinum	
	No pCR ( $n=223$ )	pCR ( $n=45$ )	No pCR ( $n=33$ )	pCR ( $n=54$ )
<i>BRCA1/2</i> wild type ( $n=296$ )				
Luminal A/B-like	122	9	5	4
HER2-positive	41	7	2	2
TNBC	37	14	22	31
Total	200	30	29	37
<i>BRCA1</i> mutated ( $n=43$ )				
Luminal A/B-like	5	3	0	3
HER2-positive	2	2	0	1
TNBC	7	6	4	10
Total	14	11	4	14
<i>BRCA2</i> mutated ( $n=16$ )				
Luminal A/B-like	6	0	0	2
HER2-positive	0	1	0	0
TNBC	3	3	0	1
Total	9	4	0	3

TNBC triple-negative breast cancer

the predictors considered ( $p=0.03$ , first likelihood ratio test). The interaction between *BRCA1/2* mutation and therapy type, however, was not significant ( $p=0.84$ , second likelihood ratio test). Thus, it was not demonstrated that the effect of *BRCA1/2* differed between patients who received anthracycline-based treatments and those who received platinum-based treatments. The adjusted odds ratio for *BRCA1/2* carriers versus non-carriers was 2.48 (95% CI 1.26–4.91).

The reduced logistic regression model used to estimate the odds ratio was well calibrated. The difference between actual and predicted events was very low ( $p=0.71$ , Hosmer–Lemeshow test). Discrimination was also satisfactory, at AUC = 0.828. The cross-validated AUC was 0.811, indicating some overfitting. The cross-validated AUC values for the basic model and the interaction model were lower (0.807 and 0.806, respectively), confirming the main result that *BRCA1/2* mutation status is predictive without differences between therapy types.

## Influence of pCR and BRCA1/2 mutation status on prognosis

The prognostic effect of pCR on the disease-free survival did not differ between patients with or without *BRCA1/2* mutations ( $p=0.55$ , likelihood ratio test). The adjusted hazard ratio for pCR status in the overall patient population was 0.30 (95% CI 0.15–0.60). Kaplan–Meier curves relative to pCR and mutation status are shown in Fig. 3a. Disease-free survival did not differ relative to mutation status and type of therapy (Fig. 3b).

The overall survival analysis yielded similar results. It was not shown that overall survival depended on *BRCA1/2* mutation status ( $p=0.13$ , likelihood ratio test). Again, patients benefited from pCR (hazard ratio 0.20; 95% CI 0.07–0.60).

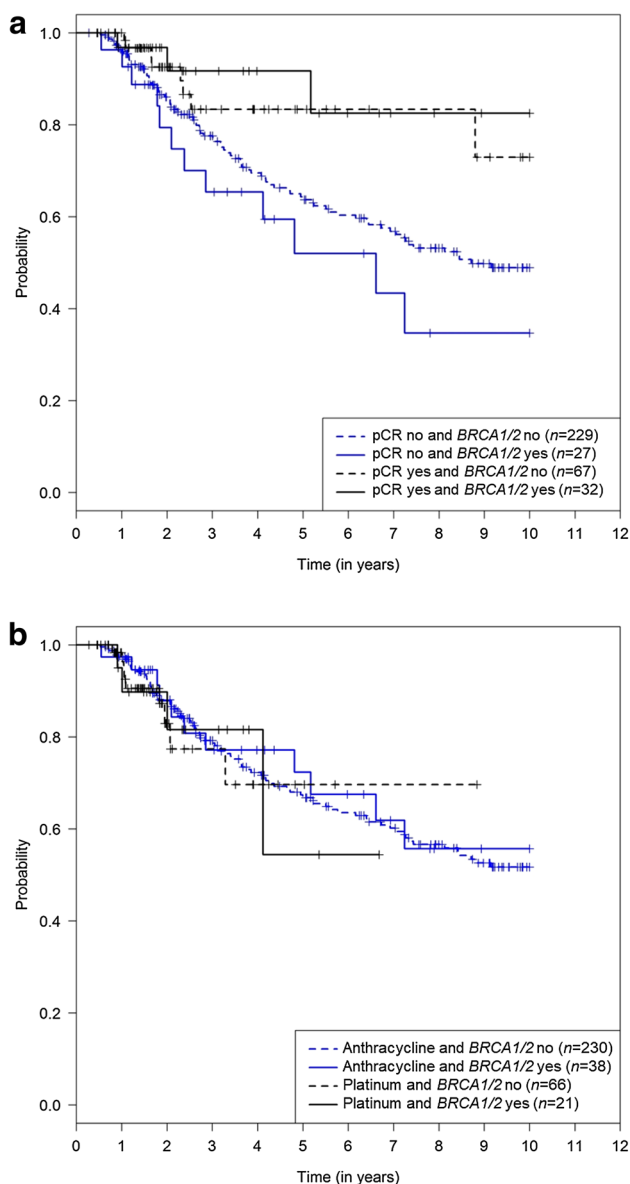
## Time interval between breast cancer diagnosis and genetic test results

Genetic test results were available at a median of 5.8 months (interquartile range 1.7–29.8 months; mean 23.1 months) after breast cancer diagnosis. In patients with a *BRCA1/2*-negative test result, the median time from diagnosis to genetic testing was 6.0 months (interquartile range 1.6–33.5 months; mean 24.3 months). In patients with a *BRCA1/2*-positive test result, the median time from diagnosis to genetic testing was 4.8 months (interquartile range 2.1–20.8 months; mean 17.3 months). Sensitivity analyses with date of genetic testing as the start of the observation time showed results similar to the main analyses. It was not shown that disease-free and overall survival were influenced by *BRCA1/2* test results, and patients with pCR had a better prognosis than patients without pCR (data not shown).

## Discussion

This study shows that patients with *BRCA1/2* mutations have higher pCR rates than patients without mutations, and that pCR is associated with a better prognosis regardless of *BRCA1/2* mutation status. Although it was not shown that *BRCA1/2* status had a different effect on the pCR rate in patients treated with anthracyclines and those receiving carboplatin, the highest pCR rates were observed in *BRCA1/2* mutation carriers with TNBC who received platinum-based therapy.

With pCR having an influence on the prognosis regardless of *BRCA1/2* mutation status, the present study is in line with findings from the GeparSixto study [25]. In that study, pCR was clearly associated with a favorable 3-year disease-free survival (96.1% for patients with wild-type mutations and 95.5% for patients with *BRCA1/2*



**Fig. 3** **a** Kaplan–Meier curves showing disease-free survival relative to pathological complete response (pCR, defined as ypT0; ypN0) and *BRCA1/2* mutation status. **b** Kaplan–Meier curves showing disease-free survival relative to treatment type and *BRCA1/2* mutation status

mutations). After chemotherapy without pCR, the 3-year disease-free survival rates were 65.4% for patients with wild-type mutations and 62.7% for *BRCA1/2* mutation carriers [25]. The GeparSixto study had a different chemotherapy regimen, with pegylated doxorubicin and bevacizumab for all TNBCs [25], but the present study is very similar to the one by Paluch-Shimon et al. [14]. In that study, neoadjuvant chemotherapy with doxorubicin and cyclophosphamide followed by paclitaxel yielded a similar survival after a median follow-up of 44 months, although the pCR rate for *BRCA1* mutation carriers versus

non-carriers was nearly as twice as high (68 vs. 37%;  $p = 0.01$ ) [14]. It remains unclear what the population effects were that led to the results of the study by Paluch-Shimon et al. The results could be due to chance, but an analysis of the GeparQuinto study also reported that in patients with *BRCA1/2* mutations, the effect of pCR on the prognosis may be weaker than in patients with wild-type mutations [26].

Identifying patient subgroups with a clear association, or lacking an association, between pCR and the prognosis is of great importance for understanding how neoadjuvant study results can be translated into the adjuvant setting. While a clear association between pCR and prognosis has been established in patients with TNBC and HER2-positive breast cancer, this effect appears to be weaker in patients with hormone receptor-positive breast cancer [1, 2]. With regard to *BRCA1/2*, this might be an important piece of information in the near future as genetic testing becomes increasingly integrated into clinical practice [27], and neoadjuvant poly(adenosine diphosphate ribose) polymerase (PARP) inhibitor studies are under way [28]. However, there is one more aspect that needs to be taken into consideration: With regard to therapies, there have also been a few examples from randomized trials suggesting that the randomization did not result in any difference in pCR, although the patients still benefited from one of the therapies more than the other [29, 30]. Whether *BRCA1/2* mutation status may be helpful, probably as one of the many factors that are of importance in this context, will require further research.

Otherwise, the results of the present study are very similar to the published data, with patients with a *BRCA1/2* mutation having clearly higher pCR rates than patients without a mutation [4, 11–14, 25, 26, 31]. The greater efficacy of chemotherapy in these tumors is apparently related to a reduced capacity for DNA repair and/or higher tumor proliferation [32–35].

The present study also investigated whether the type of treatment administered influences pCR in *BRCA1/2* mutation carriers differently from non-carriers. Although it was not shown in this retrospective study that the type of chemotherapy has a different influence on pCR rates in patients with or without *BRCA1/2* mutation, the highest pCR rates were achieved in triple-negative *BRCA1/2* mutation carriers who were treated with carboplatin. The comparable pCR rate in the GeparSixto trial was 61.5% in TNBC patients receiving platinum-containing chemotherapy [25]. Another recent study by Narod et al. investigated 10-year all-cause survival in 372 Polish women with breast cancer and a *BRCA1* mutation. The best survival rates were observed if women received cisplatin and an oophorectomy, in comparison with those who had neither of these two treatments (10-year survival, 94.4 vs. 65.4%;  $p < 0.01$ ) [36]. These data and the present study therefore

support the use of platinum-containing chemotherapies for patients with TNBC and a *BRCA1/2* mutation, based on extraordinarily high pCR rates that appear to translate into a favorable prognosis.

Emerging data on the efficacy of platinum in TNBC and *BRCA1/2* mutation carriers encouraged the implementation of platinum treatment in the present study population after 2007. Platinum treatment has shown very promising efficacy in several trials [11, 25, 26, 31, 36–42] and has been under discussion for certain subgroups of TNBC as an alternative to anthracycline-based treatment [43]. Irrespective of *BRCA1/2* mutation status, subgroup analyses from the GeparSixto trial demonstrated higher pCR rates in TNBC patients with G3 tumors in comparison with G1/G2 tumors [41]. In addition, platinum has been successfully used in several trials in patients with HER2-positive breast cancer [41, 42, 44]. Early results from these studies prompted us subsequently to include platinum in the treatment of patients with TNBC and/or *BRCA1/2* mutation carriers.

Major limitations of this retrospective study are the small sample size for *BRCA1/2* carriers and the heterogeneity of tumor types and different treatments, sometimes with different dosages. Moreover, carboplatin was not administered before 2007. The subgroups become too small for subgroup analyses to be performed in relation to mutation status, molecular subtype, treatment, and pCR. These questions cannot be adequately answered in this study and require further investigation in larger trials. Due to the study's retrospective nature, the analyses of disease-free survival and overall survival are limited. However, no unexpected associations and no immortal time bias were noted.

In conclusion, this study shows higher pCR rates after neoadjuvant chemotherapy in patients with *BRCA1/2* mutations than in patients without mutations. It also shows that pCR in *BRCA1/2* mutation carriers has similar effects on the prognosis to those seen in patients with a wild-type genotype. High pCR rates in mutation carriers with TNBC after platinum-containing chemotherapy support the use of this chemotherapy regimen in this patient population.

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## Compliance with ethical standards

**Conflict of interest** PAF has received honoraria from Amgen, Celgene, Roche, Pfizer, and Novartis. MPL has received honoraria from MSD and AstraZeneca. PG has received honoraria from Novartis and financial support for symposia from Roche, Novartis, and PharmaMar. All other authors declare that they do not have any conflicts of interest.

**Ethical approval** This retrospective study and the anonymized scientific use of the data were approved by the Ethics Committee of the Medical Faculty of Friedrich Alexander University Erlangen–Nuremberg.

**Informed consent** Informed consent was obtained from each individual participant included in the study.

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