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# Genetic Alterations, Therapy Response, and Survival Among Patients With Triple-Negative Breast Cancer

## A Secondary Analysis of a Randomized Clinical Trial

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## Abstract

**IMPORTANCE** Subgroup definitions for possible deescalation of neoadjuvant cancer treatment are urgently needed in clinical practice.

**OBJECTIVE** To investigate the effect of *BRCA1* and/or *BRCA2* tumor pathogenic variants (tPVs) by comparing 2 deescalated neoadjuvant regimens (nab-paclitaxel plus either carboplatin or gemcitabine) on pathologic complete response (pCR), invasive disease–free survival (IDFS), and overall survival (OS) of patients with early-stage triple-negative breast cancer (TNBC).

**DESIGN, SETTING, AND PARTICIPANTS** This was a preplanned secondary analysis of a phase 2 prospective randomized clinical trial (ADAPT-TN) conducted by the West German Study Group (WSG) at 45 sites in Germany between June 2013 and February 2015. The trial enrolled patients with noninflammatory early-stage TNBC (clinical tumor size ≥1 cm; estrogen receptor and progesterone receptor expression <1%; and *ERBB2* negative). DNA samples from pretreatment biopsies were obtained. Genetic analysis was performed between January 2018 and March 2020. Final data analyses took place in September 2023.

**EXPOSURE** Patients were randomized to 12 weeks of treatment with nab-paclitaxel plus either carboplatin or gemcitabine; omission of otherwise mandatory anthracycline-containing chemotherapy was allowed in the case of pCR. tPVs in 20 cancer-associated genes, including *BRCA1* and *BRCA2*, were analyzed using a customized gene panel.

**MAIN OUTCOMES AND MEASURES** The prevalence of *BRCA1* and/or *BRCA2* tPVs and their effect on pCR rate, IDFS, and OS were evaluated using logistic and Cox proportional hazards regression.

**RESULTS** Of the 307 patients with DNA samples from pretreatment biopsies available, tumor next-generation sequencing analyses were successful for 266 patients. The 266 patients included in this analysis were female, with a median age of 51 years (range, 26-76 years). A total of 162 patients (60.9%) had a clinical tumor size of 2 cm or greater, and 70 (26.3%) had clinical node-positive disease. *BRCA1* and/or *BRCA2* tPVs were detected in 42 patients (15.8%). The highest pCR rate among patients with *BRCA1* and/or *BRCA2* tPVs was seen in the nab-paclitaxel plus carboplatin group (9 of 14 patients [64.3%]) compared with the nab-paclitaxel plus gemcitabine group (10 of 28 [35.7%]) (odds ratio, 3.24 [95% CI, 0.85-12.36]; $P = .08$); the highest numeric 5-year IDFS and OS rates (84.4% and 92.9%, respectively) were seen in the nab-paclitaxel plus carboplatin group.

*(continued)*

## Key Points

**Question** Are tumor pathogenic variants (tPVs) in *BRCA1* and/or *BRCA2* associated with the response to deescalated neoadjuvant nab-paclitaxel plus either carboplatin or gemcitabine among patients with early-stage triple-negative breast cancer (TNBC)?

**Findings** This secondary analysis of a randomized clinical trial investigated tumor next-generation sequencing data of 266 patients with early-stage TNBC who received a deescalated neoadjuvant anthracycline-free approach of nab-paclitaxel plus either gemcitabine or carboplatin. The numerically highest pathologic complete response rate of 64% was observed among patients with *BRCA1* and/or *BRCA2* tPVs who received carboplatin.

**Meaning** These findings suggest that *BRCA1*-tPV and/or *BRCA2*-tPV status might be a promising stratification marker for chemotherapy deescalation in early-stage TNBC.

+ Visual Abstract

+ Supplemental content

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*Abstract (continued)*

**CONCLUSIONS AND RELEVANCE** In this secondary analysis of the WSG-ADAPT-TN randomized clinical trial on tPVs, deescalated nab-paclitaxel plus carboplatin was superior to nab-paclitaxel plus gemcitabine, particularly in patients with *BRCA1* and/or *BRCA2* tPVs. These findings suggest that *BRCA1* and/or *BRCA2* tPV status could be a candidate marker for a deescalation strategy in early-stage TNBC; however, prospective validation of survival outcomes in larger cohorts with differentiation between germline and somatic pathogenic variants is necessary.

**TRIAL REGISTRATION** ClinicalTrials.gov Identifier: NCT01815242

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## Introduction

Triple-negative breast cancer (TNBC) is an aggressive disease defined by the lack of estrogen receptor (ER) and progesterone receptor (PR) expression, as well as the absence of *ERBB2* (formerly *HER2*) amplification, accounting for 10% to 20% of all breast cancer cases.[1,2] Due to the lack of therapeutic targets, antihormonal and *ERBB2*-directed approaches are ineffective. Therefore, early-stage TNBC is usually treated with chemotherapy, preferably in the neoadjuvant setting (NACT).[3,4] Pathologic complete response (pCR) after NACT is associated with a favorable survival outcome in TNBC[5,6] and represents an important stratification factor in the selection of further post-neoadjuvant therapies.[7,8] Despite the promising introduction of poly(ADP-ribose) polymerase (PARP) inhibitors[8] and immune checkpoint inhibitors,[9] chemotherapy, especially as NACT, remains a therapeutic key component in the treatment of early-stage TNBC. Beyond the immunohistochemical conformity, TNBC is a highly heterogeneous disease[10] and shows a correlation with hereditary cause.[2,11] In unselected TNBC, the prevalence of germline pathogenic variants (gPVs) in *BRCA1* and/or *BRCA2* (hereinafter *BRCA1/2*), which are crucial in homologous recombination and DNA double-strand repair, is in the range of 9% to 18%.[12-17] As DNA-intercalating substances inducing double-strand breaks, platinum derivates have been the focus of ongoing research in TNBC. Previous clinical trials demonstrated a superior pCR rate when platinum is combined with current standard components (anthracyclines, usually combined with cyclophosphamide, and taxanes).[18-20] In the GeparSixto and BrighTNess trials, the addition of carboplatin also lead to increased disease–free survival (DFS) and event-free survival (EFS) rates in early-stage TNBC[21-23]; however, the CALGB 40603 trial could not confirm the EFS benefit of carboplatin,[24] and none of the aforementioned trials could prove a benefit for overall survival (OS).[25] Regarding *BRCA1/2*-associated breast cancer, carboplatin did not improve pCR rate in subgroup analyses of the GeparSixto,[26] BrighTNess,[18,27] and GeparOLA[28] trials.

Currently, anthracycline-cyclophosphamide followed by carboplatin combined with taxane is the preferred regimen in stage 2 to 3 TNBC.[29] Because the potential clinical benefit comes with a risk of higher toxicity,[25,30,31] the short-term and long-term adverse effects of these potent agents cannot be overlooked. To avoid overtreatment, the identification of predictive biomarkers for possible deescalation, as well as the optimal regimen for patients with stage 1 TNBC, should be further investigated.

The ADAPT-TN prospective randomized clinical trial, conducted by the West German Study Group (WSG), compared 4 cycles of nab-paclitaxel plus carboplatin (n = 154) with nab-paclitaxel plus gemcitabine (n = 182) for early-stage TNBC, investigating pCR as the primary end point.[32] This deescalated, anthracycline-free neoadjuvant approach allowed the omission of standard anthracycline-cyclophosphamide–containing adjuvant chemotherapy if pCR was achieved. A statistically significant improvement in pCR was observed in the carboplatin group (45.9% vs 28.7%).[32] Although pCR was associated with superior survival,[33] the beneficial effect of carboplatin on pCR did not translate into 5-year invasive DFS (IDFS) and OS.[34] This preplanned secondary analysis of the WSG-ADAPT-TN trial aimed to determine whether detecting pathogenic variants (PVs)

in *BRCA1/2* within tumor tissue could identify a subgroup of patients benefitting from carboplatin. This is of special interest because the design of the WSG-ADAPT-TN trial offers important insights into the effect of carboplatin without simultaneous or prior use of anthracycline-cyclophosphamide.

## Methods

The WSG-ADAPT-TN phase 2 randomized clinical trial enrolled 336 patients with operable early-stage TNBC (clinical tumor size ≥1 cm without inflammatory cancer [cT1c-cT4c]; clinical node positive [cN+] or negative [cN0]; ER/PR expression <1%; and *ERBB2* negative; confirmed by central pathology) at 45 study sites in Germany between June 2013 and February 2015.[32-34] The trial protocol is presented in Supplement 1. The responsible ethics committees or institutional review boards and federal authorities approved the study, including all procedures and translational research. Written informed consent was obtained from every study participant. This secondary analysis followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

### Primary Outcomes

Patients in the WSG-ADAPT-TN trial were randomized to 12 weeks of NACT with nab-paclitaxel (125 mg/m$^2$ given on days 1 and 8 every 3 weeks) combined with either gemcitabine (1000 mg/m$^2$ given on days 1 and 8 every 3 weeks; n = 182) or carboplatin (area under the curve AUC2 dosing given on days 1 and 8 every 3 weeks; n = 154). For 324 participants, pCR status was assessed (eFigure 1 in Supplement 2). The primary end point was pCR (ypT0/is, ypN0) rate, evaluated after surgery according to local standards or, in the case of expected residual tumor, by confirmational biopsy (non-pCR; n = 30). If pCR was achieved, the mandatory adjuvant anthracycline-cyclophosphamide–containing chemotherapy could be omitted. Secondary end points were IDFS (defined as time from randomization until any invasive cancer–related event or death), OS, and translational parameters, including *BRCA1/2*–tumor pathogenic variant (tPV) status. Pseudonymized clinical data were collected by the WSG and centrally stored.

### DNA Isolation and Next-Generation Sequencing

The isolation of DNA derived from entire formalin-fixed paraffin-embedded (FFPE) pretreatment tumor biopsies was performed using the Maxwell RSC DNA FFPE Kit (Promega) at the WSG central pathology laboratory (Institute of Pathology, University Hospital Hannover, Hannover, Germany). DNA samples were centrally analyzed at the Center for Familial Breast and Ovarian Cancer, University Hospital Cologne, Cologne, Germany, using the customized TruRisk V2 gene panel (Agilent). Target enrichment was performed applying the SureSelect XT low-input FFPE-optimized protocol according to manufacturer recommendations. The input DNA was sheared using a Bioruptor Pico device (Diagenode). For next-generation sequencing (NGS), a HiSeq4000 sequencing device (Illumina) was used.

An overview of the analyzed genes and a description of the bioinformatic analyses and variant classification are presented in the eMethods in Supplement 2. NGS analysis and variant classification was performed from January 2018 through February 2020.

### Statistical Analysis

Categorical data were compared using the $\chi^2$ or Fisher exact test as appropriate. Continuous data were compared using the 2-sample Wilcoxon test with continuity correction. IDFS and OS are displayed using Kaplan-Meier plots and compared using the log-rank test. $P < .05$ (2-tailed) indicated statistical significance without adjusting for multiple comparisons.

tPVs were assessed for their association with pCR, IDFS, and OS using logistic and Cox proportional hazards regression, respectively, for all patients combined and for both treatment groups separately. The clinical model for multivariable analysis is described in the eMethods in

Supplement 2. Data analysis was performed using SAS, version 9.4 (SAS Institute). Final data analyses took place in September 2023.

## Results

### Study Sample

Due to low DNA amounts (<10 ng), 24 of the 307 available DNA samples of pretreatment biopsies were not sequenced (baseline characteristics of all 307 patients are presented in eTable 1 in Supplement 2). In 17 samples, the sequencing output failed quality control (eFigure 1 in Supplement 2). NGS analyses of tumor samples from 266 patients with early-stage TNBC were successful, and these patients were included in this secondary analysis. All 266 patients were female, with a median age of 51 years (range, 26-76 years) (**Table 1** and eTable 1 in Supplement 2). A total of 158 patients (59.4%) were treated with nab-paclitaxel plus gemcitabine and 108 (40.6%) were treated with nab-paclitaxel plus carboplatin (hereinafter referred to as the gemcitabine and carboplatin groups). Of the 266 patients, 162 (60.9%) had a clinical tumor size of 2 cm or greater, and 70 (26.3%) had cN-positive disease.

Compared with patients without available tPV assessment (eTable 1 in Supplement 2), the analyzed subcohort had significantly more frequent basal-like TNBC according to PAM50 (prediction analysis of microarray 50) subtype[33] (225 of 264 [85.2%] vs 25 of 36 [69.4%]; $P = .04$), with higher Ki67 levels (mean [SD], 68.4% [21.4] vs 58.1% [22.2]; $P < .001$). In addition, these patients more often were treated with gemcitabine (158 of 266 [59.4%] vs 24 of 70 [34.3%]; $P < .001$).

### Prevalence and Genotype-Phenotype Correlation of *BRCA1/2* tPVs

*BRCA1/2* tPVs were present in 42 of 266 patients (15.8%) with TNBC (**Table 2** and eTable 2 in Supplement 2). Compared with patients with *BRCA1/2* wild type (WT), patients with *BRCA1/2* tPV were significantly younger (median age, 46.5 [range, 29-67] vs 53.0 [range, 26-76] years; $P = .001$) and more often were premenopausal (28 of 42 [66.7%] vs 97 of 224 [43.3%]; $P = .02$). All other characteristics were well balanced (Table 1).

### pCR Rate According to *BRCA1/2*-tPV Status

Overall, 19 of 42 patients (45.2%) with *BRCA1/2* tPV had a pCR, compared with 77 of 224 patients (34.4%) without *BRCA1/2* tPV (odds ratio [OR], 1.58 [95% CI, 0.81-3.07]; $P = .18$). The *BRCA1/2*-tPV carboplatin group had a significantly higher pCR rate (9 of 14 [64.3%]) than all others pooled together (*BRCA1/2*-tPV gemcitabine and *BRCA1/2* WT in both groups; 87 of 252 [34.5%]; OR, 3.41 [95% CI, 1.11-10.50]; $P = .02$). The direct comparison with *BRCA1/2*-tPV gemcitabine (10 of 28 [35.7%]; OR, 3.24 [95% CI, 0.85-12.36]; $P = .08$) and *BRCA1/2*-WT carboplatin (45 of 94 [47.9%]; OR, 1.96 [95% CI, [0.61-6.29]; $P = .26$) showed a numeric benefit but was not statistically significant (**Figure 1**).

Multivariable analyses identified clinical tumor size, Ki67, and treatment group as relevant factors for the clinical model. Within the gemcitabine group, age was selected additionally; within the carboplatin group, only Ki67 remained relevant (eTable 4 in Supplement 2). The model confirmed the aforementioned findings, showing an OR greater than 1 for *BRCA1/2* tPVs in favor of achieving pCR after gemcitabine, with wide CIs (OR, 2.34 [95% CI, 0.88-6.19]; $P = .09$). The results were attenuated for the entire cohort (OR, 1.87 [95% CI, 0.87-4.00]; $P = .11$) and for the carboplatin group (OR, 1.47 [95% CI, 0.41-5.21]; $P = .55$) (eTable 5 in Supplement 2).

### Survival According to *BRCA1/2*-tPV Status

The median follow-up time was 60 months (IQR, 54-62 months). Within the analyzed subcohort, an event in terms of IDFS was observed in 64 patients; 44 patients died. Five-year IDFS rates were similar in both the gemcitabine and carboplatin groups (75.4% vs 76.3%; unadjusted hazard ratio [HR], 0.95 [95% CI, 0.57-1.56]; $P = .83$) and comparable with those of the entire study cohort.[34]

The *BRCA1/2*-tPV and *BRCA1/2*-WT subgroups showed similar 5-year IDFS rates (77.1% vs 75.4%; unadjusted HR, 0.91 [95% CI, 0.45-1.83]; *P* = .78). When separated by regimen (**Figure 2**A), patients with *BRCA1/2* tPV showed the numerically highest IDFS rate after carboplatin treatment compared with gemcitabine treatment (84.4% vs 74.1%; unadjusted HR, 0.54 [95% CI, 0.11-2.60]; *P* = .44). No difference between carboplatin vs gemcitabine treatment occurred in the *BRCA1/2*-WT cohort (75.2% vs 75.7%; unadjusted HR, 1.02 [95% CI, 0.60-1.74]; *P* = .94).

Patients with *BRCA1/2*-tPV treated with carboplatin had the highest 5-year OS rate (Figure 2B) compared with the *BRCA1/2*-tPV gemcitabine group (92.9% vs 81.0%; unadjusted HR, 0.41 [95% CI,

**Table 1. Baseline Characteristics of Patients According to *BRCA1/2*-tPV Status**

| Characteristic[a] | Patient group | | | *P* value |
|---|---|---|---|---|
| | Total (N = 266) | *BRCA1/2*-WT (n = 224) | *BRCA1/2*-tPV (n = 42) | |
| Age at registration, y | | | | |
| Median (IQR) | 51.0 (43-61) | 53.0 (44-62) | 46.5 (37-53) | .001[b] |
| Mean (SD) | 51.5 (11.8) | 52.5 (11.8) | 46.0 (10.3) | |
| Menopausal status | | | | |
| Postmenopausal | 127 (47.7) | 115 (51.3) | 12 (28.6) | .02[c] |
| Premenopausal | 125 (47.0) | 97 (43.3) | 28 (66.7) | |
| Unknown or unclear | 14 (5.3) | 12 (5.4) | 2 (4.8) | |
| Clinical tumor size | | | | |
| 1 | 104 (39.1) | 89 (39.7) | 15 (35.7) | .75[c] |
| 2 | 145 (54.5) | 120 (53.6) | 25 (59.5) | |
| 3-4 | 17 (6.4) | 15 (6.7) | 2 (4.8) | |
| Clinical nodal status | | | | |
| 0 | 196 (73.7) | 161 (71.9) | 35 (83.3) | .30[c] |
| 1 | 61 (22.9) | 55 (24.6) | 6 (14.3) | |
| 2-3 | 9 (3.4) | 8 (3.6) | 1 (2.4) | |
| Grade (central) | | | | |
| 2 | 15 (5.6) | 14 (6.3) | 1 (2.4) | .48[d] |
| 3 | 251 (94.4) | 210 (93.8) | 41 (97.6) | |
| Ki67 (primary, central), %[e] | | | | |
| Median (IQR) | 75 (55-85) | 75 (55-85) | 75 (60-80) | .96[b] |
| Mean (SD) | 68.4 (21.4) | 68.2 (21.9) | 69.4 (18.5) | |
| Histology (central) | | | | |
| NST | 262 (98.9) | 220 (98.7) | 42 (100) | >.99[d] |
| Medullary | 1 (0.4) | 1 (0.4) | 0 | |
| Invasive-lobular | 2 (0.8) | 2 (0.9) | 0 | |
| Metaplastic | 1 (0.4) | 1 (0.4) | 0 | |
| PAM50 subtype[f] | | | | |
| Basal | 225 (85.2) | 185 (83.3) | 40 (95.2) | .38[d] |
| ERBB2 (formerly *HER2*) enriched | 15 (5.7) | 14 (6.3) | 1 (2.4) | |
| Luminal A | 3 (1.1) | 3 (1.4) | 0 | |
| Normal | 21 (8.0) | 20 (9.0) | 1 (2.4) | |
| Treatment group[g] | | | | |
| Gemcitabine | 158 (59.4) | 130 (58.0) | 28 (66.7) | .30[c] |
| Carboplatin | 108 (40.6) | 94 (42.0) | 14 (33.3) | |
| pCR | | | | |
| ypT0/ypN0 | | | | |
| No | 178 (66.9) | 155 (69.2) | 23 (54.8) | .07[c] |
| Yes | 88 (33.1) | 69 (30.8) | 19 (45.2) | |
| ypT0is/ypN0 | | | | |
| No | 170 (63.9) | 147 (65.6) | 23 (54.8) | .18[c] |
| Yes | 96 (36.1) | 77 (34.4) | 19 (45.2) | |

Abbreviations: NST, invasive carcinoma of no special type; pCR, pathologic complete response; tPV, tumor pathogenic variant; WT, wild type.

[a] Data are presented as No. (%) of patients unless otherwise indicated. Statistical tests were applied according to sample size and variable category.

[b] Wilcoxon test.

[c] Pearson $\chi^2$ test.

[d] Fisher exact test.

[e] Data were missing for 5 patients in the *BRCA1/2*-WT group and 1 patient in the *BRCA1/2*-tPV group.

[f] Data were missing for 2 patients in the *BRCA1/2*-WT group.

[g] Patients were treated with nab-paclitaxel plus either carboplatin or gemcitabine.

0.05-3.54]; *P* = .42). The *BRCA1/2*-WT carboplatin group showed a numerically worse outcome than the *BRCA1/2*-WT gemcitabine group (77.8% vs 82.8%; unadjusted HR, 1.18 [95% CI, 0.62-2.23]; *P* = .62).

Multivariable modeling identified cN status as a relevant factor for the clinical model of IDFS and OS (eTable 4 in Supplement 2). After adjustment, effect sizes decreased, but the trend remained consistent (eTable 5 in Supplement 2).

## Association of pCR With Survival

The association of pCR with IDFS, described in the entire study cohort,[33,34] was observed in the *BRCA1/2*-WT group (5-year IDFS non-pCR vs pCR: 65.4% [95% CI, 56.7%-72.8%] vs 94.4% [95% CI, 85.7%-97.9%]; *P* < .001) and in the *BRCA1/2*-tPV group (non-pCR vs pCR: 68.5% [95 CI, 45.0%-83.6%] vs 87.2% [95% CI, 57.2%-96.7%]; *P* = .11) in a similar magnitude. Regarding OS, pCR rate was associated with improved outcome in the cohort without *BRCA1/2* tPVs (5-year OS non-pCR vs pCR: 71.9% [95% CI, 63.2%-79.0%] vs 97.0% [95% CI, 88.5%-99.3%]; *P* < .001) and with *BRCA1/2* tPVs (non-pCR vs pCR: 72.6% [95% CI, 48.8%-86.7%] vs 100% [95% CI, 100%-100%]; *P* = .02) (**Figure 3**).

## Prevalence and Genotype-Phenotype Correlation of Non-*BRCA1/2* tPVs

Among the 266 patients, a high prevalence of *TP53* tPVs was observed (233 [87.6%]), followed by *PIK3CA* (22 [8.3%]) and *PTEN* (15 [5.6%]). tPVs in other breast cancer–associated genes were rare and no tPV was detected in 22 samples (8.3%). For an overview, see Table 2. eTable 2 in Supplement 2 provides comprehensive tPV information.

The 2 samples displaying a *CDH1* tPV were the only ones derived from invasive-lobular cancer (eFigure 2 in Supplement 2), and tPVs in *PIK3CA*, *PTEN*, or both were associated with a nonbasal-like PAM50 subtype, compared with TNBCs without these alterations (18 of 32 [56.3%] vs 21 of 232 [9.1%]; *P* < .001).

## pCR Rate According to Non-*BRCA1/2* tPVs

An overview of the pCR rate according to tPVs in non-*BRCA1/2* genes is given in eTable 3 in Supplement 2 (multivariable analyses are detailed in eTable 5 in Supplement 2). *TP53* tPVs did not have a substantial effect on pCR in our cohort. There was an indication for a deleterious effect of *PIK3CA* tPVs; however, the results were not statistically significant (n = 22; all: pCR rate, 18.2%; OR, 0.28 [95% CI, 0.07-1.08]; *P* = .06).

**Table 2. Prevalence of tPVs in Breast Cancer Risk Genes**

| Gene | No. (%) of samples (N = 266)[a] |
|---|---|
| *BRCA1/2* tPVs | |
| *BRCA1*[b] | 37 (13.9) |
| *BRCA1* and *BRCA2* | 2 (0.8) |
| *BRCA2* | 3 (1.1) |
| All *BRCA1/2* | 42 (15.8) |
| tPVs in non-*BRCA1/2* genes | |
| *TP53*[c] | 233 (87.6) |
| *PIK3CA*[d] | 22 (8.3) |
| *PTEN* | 15 (5.6) |
| *PALB2*[e] | 5 (1.9) |
| *BARD1* | 3 (1.1) |
| *FANCM* | 3 (1.1) |
| *CDH1* | 2 (0.8) |
| *CHEK2* | 2 (0.8) |
| *RAD50* | 1 (0.4) |
| *RAD51C* | 1 (0.4) |
| *RAD51D* | 1 (0.4) |
| *STK11* | 1 (0.4) |
| *XRCC2* | 1 (0.4) |
| *MAP3K1* | 1 (0.4) |

Abbreviation: tPV, tumor pathogenic variant.

[a] Because several samples harbored multiple tPVs, these samples are counted for each respective gene and therefore multiple referenced. No tPVs were identified in *ATM*, *BRIP1*, *MRE11A*, and *NBN*.

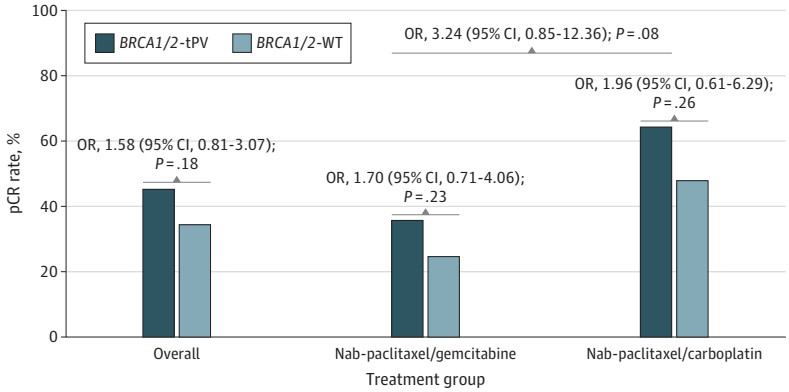
[b] One patient carried 2 distinct *BRCA1* tPVs.

[c] One sample displayed 2 distinct *TP53* tPVs.

[d] One sample displayed 2 distinct *PIK3CA* tPVs.

[e] One sample displayed 2 distinct *PALB2* tPVs.

**Figure 1. Pathologic Complete Response (pCR) Rate According to *BRCA1/2*–Tumor Pathogenic Variant (tPV) Status Overall and in Both Treatment Groups**




OR indicates odds ratio; WT, wild type.

### Survival According to Non-*BRCA1/2* tPVs

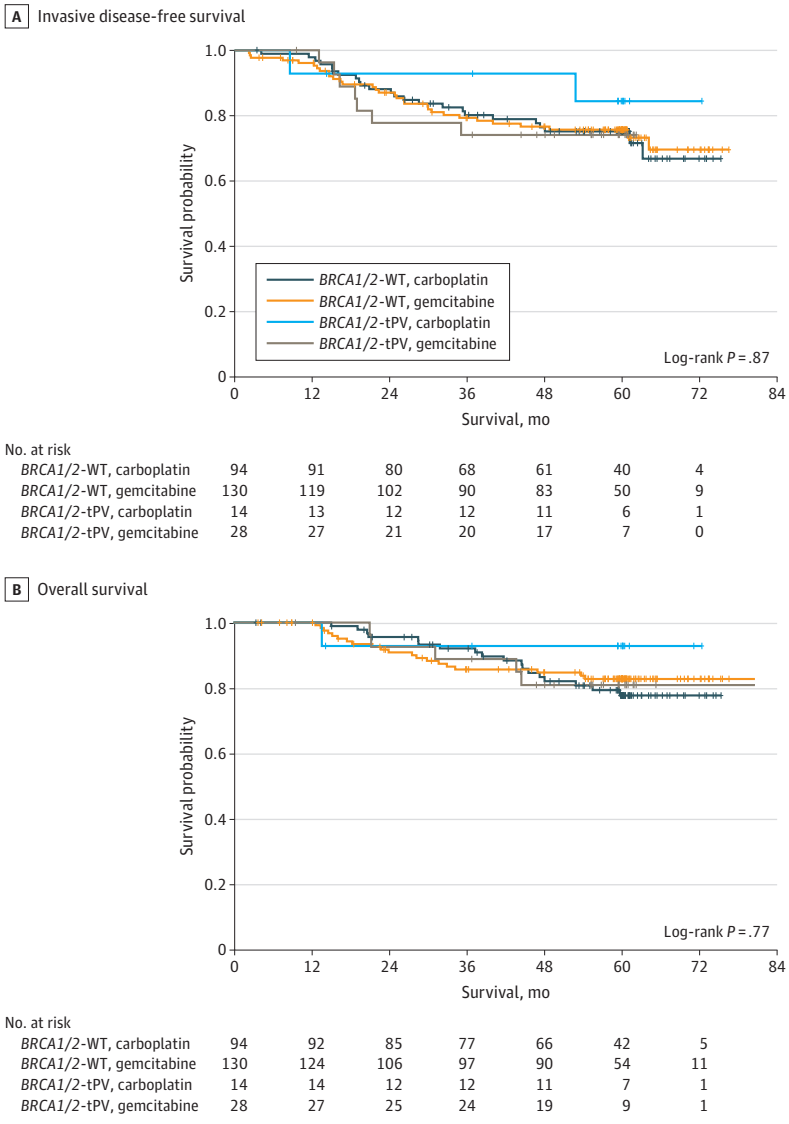
*TP53* tPVs were associated with worse 5-year IDFS compared with *TP53* WT (74.0% vs 87.4%; HR, 2.81 [95% CI, 1.02-7.78]; *P* = .046). There was no statistically significant effect for *PIK3CA* tPVs (56.1% vs 77.6%; HR, 1.61 [95% CI, 079-3.28]; *P* = .19). For OS, the associations were similar but less distinct. More detailed information is presented in the eResults and eTable 5 in Supplement 2.

## Discussion

The WSG-ADAPT-TN trial assessed the effect of nab-paclitaxel plus either carboplatin or gemcitabine as deescalated NACT in early-stage TNBC. pCR was the primary end point, which provided the opportunity to examine the effect of carboplatin without the simultaneous or previous use of anthracyclines. In this preplanned exploratory substudy, we investigated the prevalence of tPVs in *BRCA1/2* and other breast cancer–associated genes and their effect on pCR and survival outcomes.

The highest pCR rate (9 of 14 patients [64.3%]) was seen in the *BRCA1/2*-tPV carboplatin group. This finding was statistically significant when compared with all others of the analyzed cohort, but

**Figure 2. Survival According to *BRCA1/2*–Tumor Pathogenic Variant (tPV) Status and Treatment Group**

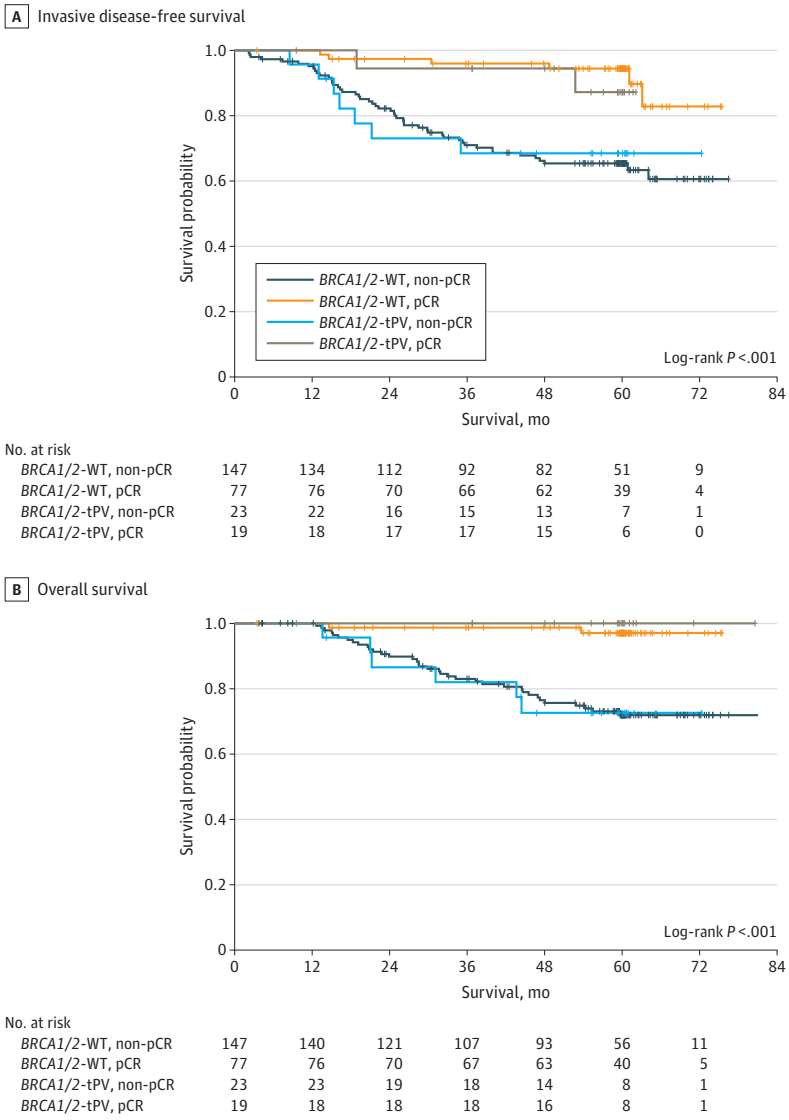



WT indicates wild type.

not when compared with the *BRCA1/2*-tPV gemcitabine group (10 of 28 [35.7%]) or the *BRCA1/2*-WT carboplatin group (45 of 94 [47.9%]) directly. The *BRCA1/2*-tPV gemcitabine-treated group tended to have a higher pCR rate compared with the *BRCA1/2*-WT group (24.6%), which might be explained by higher chemosensitivity of *BRCA1/2*-associated TNBCs in general.[35,36] Whether this effect was based on nab-paclitaxel or gemcitabine remains unclear. Likewise, 5-year IDFS and OS rates were highest in the *BRCA1/2*-tPV carboplatin-treated group, although they were not statistically significant.

Previous clinical trials provide insights on the effect of *BRCA1/2* PVs on carboplatin response. Within the GeparSixto trial, the addition of carboplatin to a dose-dense anthracycline-taxane/bevacizumab regimen improved pCR rate (43% vs 53%) in early-stage TNBC[19] and led to significantly superior DFS (76% vs 86%).[21] Patients carrying a *BRCA1/2* gPV had comparable pCR rates in both treatment groups (67% vs 65%), which was explained by saturation due to the DNA-damaging effect of anthracycline.[37] No notable benefit of carboplatin regarding 3-year survival was observed in the *BRCA1/2*-gPV group.

**Figure 3. Effect of Pathologic Complete Response (pCR) on Survival in the *BRCA1/2*–Wild Type (WT) and *BRCA1/2*–Tumor Pathogenic Variant (tPV) Cohorts**



In the BrighTNess trial,[18] the addition of carboplatin with veliparib (treatment arm A) or without veliparib (treatment arm B) to a standard anthracycline-cyclophosphamide-taxane–containing regimen (treatment arm C) led to a beneficial pCR rate (57% [arm A] and 50% [arm B] vs 41% [arm C] in *BRCA1/2*-gPV subgroups), which was independent of *BRCA1/2* gPV status.[27] pCR was associated with improved DFS in patients with *BRCA1/2* gPV and *BRCA1/2* WT.[23] Within the GeparOLA study, patients with *BRCA1/2*-gPV or homologous recombination deficient, *ERBB2*-negative breast cancer received standard or dose-dense taxane combined with carboplatin vs PARP inhibitors, followed by anthracycline-cyclophosphamide.[28] This resulted in a pCR rate of 60% in both groups for patients with *BRCA1/2* tPV.[28]

Even in the absence of anthracycline, the pCR rate we observed in the small *BRCA1/2*-tPV group treated with deescalated nab-paclitaxel plus carboplatin was similarly high in this study compared with that in *BRCA1/2*-associated breast cancers treated with carboplatin added to standard or dose-dense anthracycline-taxane treatment (with or without cyclophosphamide) in the aforementioned trials. Although the GeparOLA baseline characteristics were similar,[28] patients with locally more advanced disease were included in the BrighTNess and GeparSixto trials.[19,21] Therefore, this cross-trial comparison should be interpreted with caution.

In escalated treatment of high-risk early-stage TNBC, carboplatin has become a standard combination agent for anthracycline-cyclophosphamide-taxane and pembrolizumab, according to the pivotal KEYNOTE-522 trial.[9,38] This is of special interest because the PARP inhibitor olaparib can be a relevant option in (post-neo)adjuvant treatment of *BRCA1/2*-gPV–associated breast cancer, whereas its effect on survival was attenuated after platinum within the OlympiA trial.[8] However, when comparing the results of our trial and other trials, it remains unclear whether a completion of a 24-week regimen is necessary in case a pCR is achieved after 12 weeks of taxane treatment combined with carboplatin. Our results allow the presumption that *BRCA1/2* tPV status might be a stratification factor for deescalated, shorter treatment regimens in case of favorable prognostic conditions (eg, cN0 and pCR).

In concordance with the results of the BrighTNess trial,[23] our findings can support the hypothesis that pCR is a surrogate marker for survival in patients with *BRCA1/2* tPVs. However, the association was only observed for OS, and survival outcomes were only secondary end points.

Because adjuvant anthracycline-cyclophosphamide was mandatory in case of non-pCR but optional after pCR, this analysis cannot clarify whether anthracycline-cyclophosphamide can be omitted in the *BRCA1/2*-tPV group treated with carboplatin despite the high survival rate. In the main WSG-ADAPT-TN trial, anthracycline-cyclophosphamide after pCR did not alter IDFS risk,[34] which was in line with the small phase 2 NEOCART trial showing superior pCR (61% vs 39%) and equivalent EFS and OS rates after 37 months when comparing 6 cycles of carboplatin-docetaxel with an anthracycline-cyclophosphamide-taxane regimen in early-stage TNBC.[39] Because IDFS events in this subset in our analysis were rare (8 of 96 patients with pCR), this aspect needs to be addressed in future investigations.

In an exploratory, hypothesis-generating approach, we assessed the effects of tPVs in non-*BRCA1/2* genes on clinical outcome. The numerically worse outcome of patients with a *PIK3CA* tPV is in line with previous reports of chemotherapy resistance and low response rates to NACT in early-stage TNBC harboring somatic *PIK3CA* PVs.[40,41] Because targeted approaches might be promising, several clinical trials with *PIK3CA*-directed agents are ongoing in advanced TNBC.[42]

In this analysis, patients without *TP53* tPVs showed a favorable survival. In a secondary analysis of the GeparSixto trial,[43] no effect of *TP53* tPVs on survival in the early-stage TNBC subgroup was observed, whereas earlier data showed a superior outcome of basal-like BCs with *TP53* tPVs when treated with dose-dense anthracycline-cyclophosphamide.[44,45]

### Limitations

This study has some limitations. Because the overall study was not powered for this exploratory approach with small genetic subgroups, the findings often were not statistically significant even when large effects were observed.

Due to the retrospective explorative character of the analysis, moderate imbalances were observed in baseline characteristics regarding higher rates of basal-like TNBC, higher Ki67 levels, and a greater proportion of patients treated with gemcitabine in the analyzed subcohort compared with those not analyzed. Whereas the pCR and IDFS rates were comparable with those of the whole study cohort, a more balanced ratio of treatment groups would have strengthened the statistical power to estimate the effect of carboplatin.

Also, survival was a secondary end point, not the focus of the trial design, and the unclear role of adjuvant anthracycline-cyclophosphamide treatment allows only a vague interpretation of survival data. The events in the *BRCA1/2*-tPV group were rare (OS: n = 6; and IDFS: n = 9), limiting the statistical power.

Furthermore, we did not perform mutual genetic germline testing, which made the differentiation of gPVs from somatic PVs impossible. Approximately 1% of patients with familial breast cancer carry germline large genomic rearrangements in *BRCA1/2*,[46] which were not detected by the method applied in this study. The DNA amount of the samples was limited and in several cases was below or close to 10 ng, leading to a high dropout rate. Because entire biopsies were processed, the tumor cell count was unclear, whereas the prevalence of tPVs in *BRCA1/2* and *TP53* was in line with previous findings,[47-51] indicating that the detection of tPVs was generally sufficient.

## Conclusions

In this secondary analysis of a randomized clinical trial of patients with early-stage TNBC, deescalated neoadjuvant nab-paclitaxel plus carboplatin was highly effective and superior to nab-paclitaxel plus gemcitabine. Although a beneficial pCR rate was observed in both the *BRCA1/2*-WT and *BRCA1/2*-tPV subgroups, the effect was more distinct in the latter and possibly translated into improved survival. To prevent overtreatment, *BRCA1/2* tPV status may thus be a useful stratification factor for chemotherapy deescalation. Larger prospective randomized trials, designed for survival end points, are necessary. Possible combinations with PARP inhibitors and immune checkpoint inhibitors in deescalation, as well as the comparison of these potent agents alone[52,53] vs deescalated NACT in *BRCA1/2*-associated early-stage TNBC, should be evaluated. Moreover, the effect of germline vs somatic PVs in *BRCA1/2* as predictive factors and the relevance of PVs in other breast cancer–associated genes should be further investigated.

### ARTICLE INFORMATION

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**Author Contributions:** Drs Richters and Haverkamp 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. Dr Hahnen and Prof Harbeck contributed equally to this work.

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**SUPPLEMENT 1.**
**Trial Protocol**