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Comparison of Neoadjuvant Nab-Paclitaxel+Carboplatin vs Nab-Paclitaxel+Gemcitabine in Triple-Negative Breast Cancer: Randomized WSG-ADAPT-TN Trial Results

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Abstract

Background: Pathological complete response (pCR) is associated with improved prognosis in triple-negative breast cancer (TNBC). The optimal chemotherapy regimen is unclear. Weekly nab-paclitaxel vs conventional paclitaxel or addition of carboplatin to anthracycline-taxane results in higher pCR rates with uncertain survival impact. We evaluated carboplatin vs gemcitabine with a nab-paclitaxel backbone as a short 12-week A-free regimen with a focus on early response.

Methods: Patients with TNBC (estrogen receptor/progesterone receptor $< 1\%$, human epidermal growth factor receptor 2–negative, cT1c-cT4c, cN0/+) were randomly assigned to A: nab-paclitaxel 125 mg/m^2/gemcitabine 1000 mg/m^2 d1,8 three times weekly (q3w); vs B: nab-paclitaxel 125 mg/m^2/carboplatin AUC2 day 1,8 q3w. The trial was powered for a pCR (ypT0/is ypN0) comparison by therapy arm and early response (defined as Ki-67 decrease $>30\%$ or < 500 invasive tumor cells in the three-week serial biopsy). All statistical tests were two-sided.

Results: A total of 336 patients were enrolled (48 centers, arms A/B: n = 182/154). The median age was 50 years. At baseline (A vs B), 62.6% and 62.9% had cT2–4c tumors; 86.8% and 90.9% completed therapy per protocol, respectively. pCR favored arm B (28.7%, 95% CI = 0.22 to 0.36, vs 45.9%, 95% CI = 0.38 to 0.54; 95% CI(d_{BA}) = 6.2% to 27.9%, $P = .002$) and was lower in nonresponders than in early responders (19.5% vs 44.4%, $P < .001$) or in patients with unclassifiable early response (50.0%). The nab-paclitaxel/gemcitabine was associated with more frequent dose reductions (20.6% vs 11.9%, $P = .04$), treatment-related

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serious adverse events (11.1% vs 5.3%, $P = .07$), grade 3–4 infections (7.2% vs 2.6%, $P = .07$), and grade 3–4 ALAT elevations (11.7 vs 3.3%, $P = .01$).

Conclusions: This first large randomized trial suggests high efficacy and excellent tolerability of a neoadjuvant nab-paclitaxel/carboplatin regimen, superior to nab-paclitaxel/gemcitabine in TNBC. De-escalation of further chemotherapy in patients with early pCR after a short anthracycline-free regimen is a promising field of future research. Early necrotic morphological changes and/or proliferation decrease after the first therapy cycle seem to be associated with subsequent pCR.

Triple-negative breast cancer (TNBC) lacks estrogen (ER) and progesterone (PR) receptor expression as well as overexpression/amplification of human epidermal growth factor receptor 2 (HER2). Approximately 15% of patients with early breast cancer (EBC) are diagnosed with TNBC. While pathological complete response (pCR) after neoadjuvant chemotherapy (NACT) implies excellent prognosis in TNBC, chemo-resistant disease remains a clinical challenge (1,2). Standard anthracycline-taxane (A/T) containing NACT leads to pCR in 25% to 40% (3–5) of TNBC patients; however, as chemotherapy remains the only systemic treatment option, there is clinical need for chemotherapy optimization.

In TNBC, adjuvant 12xpaclitaxel weekly is superior (6) to docetaxel every three weeks (q3w). Replacement of standard taxane by dose-intensified nab-paclitaxel provides increased efficacy in the neoadjuvant and metastatic setting (4,7) and appears promising—despite conflicting findings (8,9)—along with other chemotherapy dose-intensification strategies (10,11).

Although A/T-based combination therapy remains the standard of care in EBC (12) compared with non-platinum-containing A-free regimens, there is an increasing body of evidence from clinical trials challenging this perception (13,14). Furthermore, a subgroup of TNBC patients with highly chemosensitive disease (as defined by early response to NACT, eg, after 12 weeks of therapy) may not benefit from extended chemotherapy duration (15); overtreatment might be avoided by early identification of these "responders." Further agents (eg, gemcitabine, carboplatin, eribulin) have been effective in TNBC (16,17), particularly if added to taxanes in the metastatic setting (18–21), but less so if used within polychemotherapy regimens in EBC (22–24).

Based upon a strong link between platinum efficacy and BRCA1 mutation/dysfunction, the use of DNA alkylating agents such as platinum salts is currently of particular interest in TNBC treatment. BRCA1 or 2 mutations are common in young TNBC patients, particularly in patients with a family history of breast/ovarian cancer (25,26). Moreover, molecular similarities occur in sporadic vs BRCA1-mutated TNBC. Given that BRCA1 functions as a DNA-repair gene, substantial efficacy of platinum monotherapy, inducing double-stranded DNA breaks, has been observed, particularly in BRCA1-related BC (less in nonmutated cases) (27–29). The platinum-specific predictive effect of BRCA1 mutation seems to be less pronounced in the context of polychemotherapy (30,31). The observed efficacy of platinum salts in BRCA1-mutated BC has led to extensive investigation of corresponding efficacy in unselected TNBC. Most (if not all) neoadjuvant trials yielded superior pCR (about 50%), but also higher toxicity if carboplatin was added to A/T-based NACT (5,32,33). Early survival results from the phase II trials even suggested a statistically significant (30) positive effect or statistically nonsignificant positive trend (34) of carboplatin-containing NACT on disease-free survival (DFS) in TNBC. Whether increased pCR rates with carboplatin are drug specific or result from chemotherapy intensification remains a matter of debate (35). Based on the available evidence, a direct comparison between anthracycline-free, taxane-based combinations is of substantial clinical interest; in the early responder subgroup, the benefits of extended standard polychemotherapy are questionable.

The ADAPT TN phase II trial is part of the ADAPT umbrella trial, which aims at individualizing therapy in EBC and avoiding over- as well as undertreatment by assessing early response after one cycle of therapy (36). The TN subtrial was designed to investigate the effect of adding carboplatin or gemcitabine to a short, 12-week weekly nab-paclitaxel regimen. In patients without pCR, this regimen was to be followed by standard anthracycline-containing chemotherapy; in patients with pCR, omission of further chemotherapy using Epirubicin/Cyclophopsphamide (EC) was permitted. A key aim of the trial was to identify early responders among TNBC patients (based on proliferation or imaging changes after a first cycle of therapy) and, for these early responders, to establish a short, anthracycline-free, taxane-based NACT regimen with favorable toxicity profile.

Methods

Patient Population

Women with previously untreated, operable, unilateral, primary invasive noninflammatory early TNBC (ER and PR $< 1\%$, HER2-negative, as defined by current guidelines [37], all by central pathology) were eligible if age 18 years or older with good performance status (0/1) and adequate hematologic, cardiac, renal, and hepatic function (see the Supplementary Materials, available online, for further details).

Data were entered into the web-based electronic data capture system. All patients provided written informed consent. The trial was approved by the responsible ethics committee and/or institutional review boards and by the responsible federal authority. An independent data safety monitoring board supervised the conduct of the trial. This trial is registered with ClinicalTrials.gov (NCT01815242).

Trial Design

The treatment allocation list was created for the whole ADAPT trial (including five subprotocols) and stratified by center and nodal status. Randomization was performed centrally at West German Study Group (WSG) in a 1:1 ratio. Treatment allocation was not masked.

Treatment Regimens

Patients were scheduled (Figure 1) to be treated by nab-paclitaxel (Abraxane, Celgene Corporation, Summit, NJ) 125 mg/m^2 d1,8 for four three-week cycles combined with either gemcitabine 1000 mg/m^2 d1,8 (arm A) or with carboplatin (area under curve [AUC]

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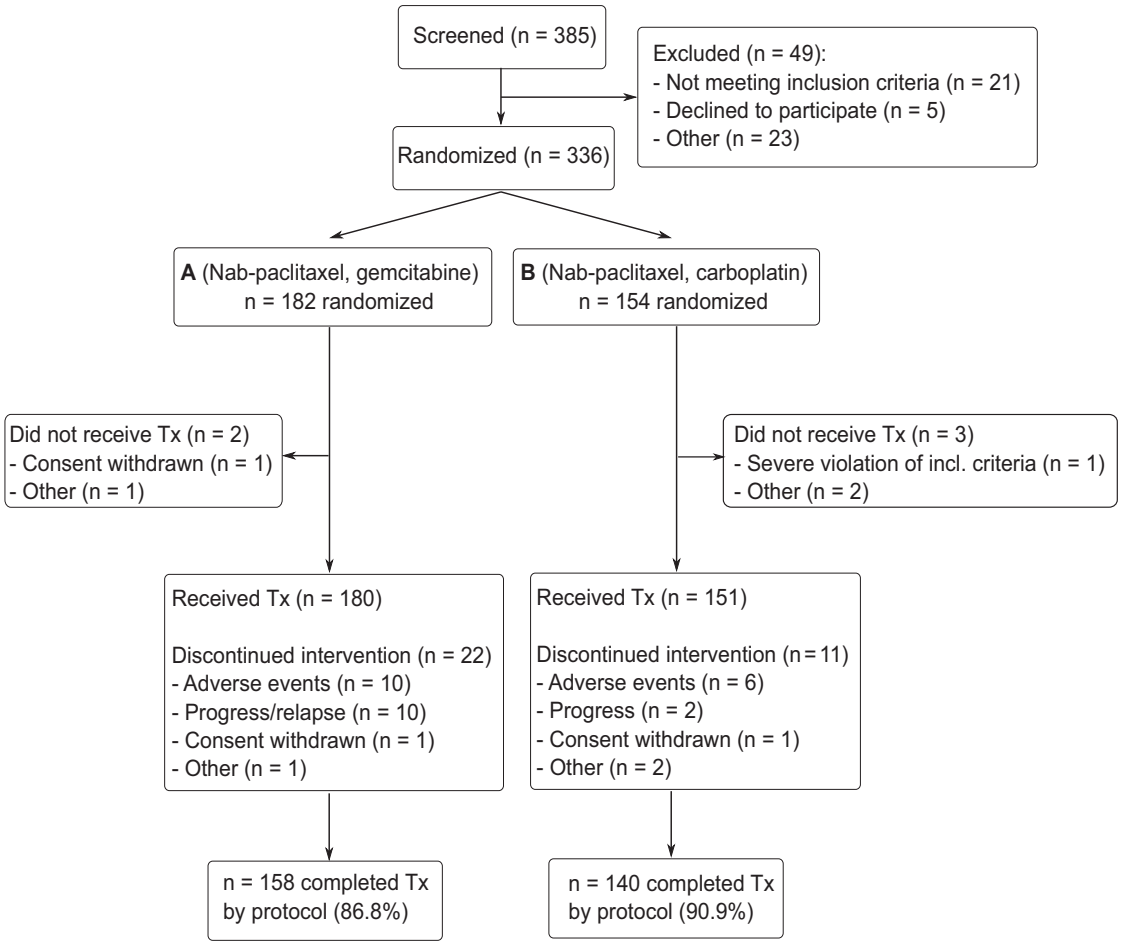

Figure 1. Consort diagram. The most frequent reasons for screening failure were detection of metastatic disease during the screening phase and nonconfirmation of triple-negative status by the central lab across all sites.

= 2) d1,8 (arm B) (for details see the Supplementary Materials, available online).

Evaluation of the primary tumor (by ultrasound and, if appropriate, by MRI with core biopsy) was performed prior to the second therapy cycle. In case of residual clinical tumor burden after 12 weeks, continuation of NACT as poststudy treatment was permitted in the case of histological confirmation of residual invasive tumor (coded as non-pCR). All patients were to be treated by standard anthracycline-containing chemotherapy after trial medication. Omission of further chemotherapy in case of pCR (ypT0/is/ypN0) was allowed.

Trial End Points

pCR—defined as absence of invasive tumor cells in the breast and lymph nodes (ypT0/is ypN0), assessed by local pathologists—constituted the primary end point of the trial (in all patients and by "early response status"). Further details are given in the Supplementary Materials (available online).

Statistical Analysis

The trial tested two primary hypotheses separately: 1) the proportion of patients achieving pCR is higher in responders than in nonresponders; 2) the proportion of patients achieving pCR is different in the two treatment arms. With 336 patients (including 5% dropouts), the trial was powered to detect a difference of 17% in pCR ($\alpha = 0.01$, $\beta = 0.2$, one-sided) between responders and nonresponders, as well as a 15% difference with carboplatinum vs gemcitabine ($\alpha = 0.04$, $\beta < 0.2$, two-sided), assuming 60% responders and 25% pCR overall. The primary end points were tested (*P* values by the Fisher exact test) in an intention-to-treat collective of all patients randomly assigned to study treatment and with surgery or histological confirmation for pCR. We report 95% confidence intervals (CI) of pCR differences $d_{XY} = P_X - P_Y$ (Newcombe-Wilson) (for details, see the Supplementary Materials, available online).

Results

Patient Population

Between May 2013 and January 2015, 385 patients were screened at 48 sites in Germany and 336 (A/B: 182/154) were randomly assigned to the treatment arms (Figure 1); baseline characteristics (Table 1) were well balanced. The median age was 50 years (range = 26–75 years); at baseline (A vs B), 62.6% and 62.9% had cT2–4c tumors; 26.2% were clinically node positive. Of 207 patients with sentinel node biopsy prior to chemotherapy (A/B: 110/97), 39 had at least one positive lymph node (A: 19, B: 20);

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Table 1. Patient characteristics

Characteristic	Total (n = 336) No. (%)	Arm A: nab-paclitaxel/ gemcitabine (n = 182) No. (%)	Arm B: nab-paclitaxel/carboplatin (n = 154) No. (%)
Age, y			
<40	59 (17.6)	26 (14.3)	33 (21.4)
40–<50	94 (28.0)	59 (32.4)	35 (22.7)
50–<60	90 (26.8)	50 (27.5)	40 (26.0)
≥60	92 (27.4)	47 (25.8)	45 (29.3)
Missing	1 (0.3)	0 (0.0)	1 (0.6)
Menopausal status			
Postmenopausal	157 (46.7)	81 (44.5)	76 (49.4)
Premenopausal	163 (48.5)	89 (48.9)	74 (48.1)
Unknown/unclear	16 (4.8)	12 (6.6)	4 (2.6)
Clinical tumor stage			
1	125 (37.2)	68 (37.4)	57 (37.0)
2	188 (56.0)	102 (56.0)	86 (55.8)
3	18 (5.4)	10 (5.5)	8 (5.2)
4	5 (1.5)	2 (1.1)	3 (1.9)
Histological type			
Missing	4 (1.2)	2 (1.1)	2 (1.3)
No special type, ductal	304 (90.5)	164 (90.1)	140 (90.9)
Invasive lobular	7 (2.1)	2 (1.1)	5 (3.2)
Medullary	9 (2.7)	6 (3.3)	3 (1.9)
Other	12 (3.6)	8 (4.3)	4 (2.6)
Clinical nodal status			
0	248 (73.8)	135 (74.2)	113 (73.4)
1	77 (22.9)	42 (23.1)	35 (22.7)
2–3	11 (3.3)	5 (2.7)	6 (3.9)
Sentinel node biopsy, axilla surgery performed prior to chemotherapy	207 (61.6)	110 (60.4)	97 (63.0)
Pathological nodal status, prior to chemotherapy			
0	168 (50.0)	91 (50)	77 (50.6)
1	33 (9.8)	18 (9.9)	15 (9.7)
1mi	4 (1.2)	1 (0.5)	3 (1.9)
2	2 (0.6)	0 (0.0)	2 (1.3)
Nodal surgery after therapy*	144 (42.9)	80 (44)	64 (41.6)
0	91 (27.1)	49 (26.9)	42 (27.3)
1	37 (11.0)	20 (11.0)	17 (11.0)
2	11 (3.3)	7 (3.8)	4 (2.6)
3	5 (1.5)	4 (2.2)	1 (0.6)
Tumor grade, central lab†			
Missing	2 (0.6)	0 (0.0)	2 (1.3)
2	22 (6.5)	10 (5.5)	12 (7.8)
3	312 (92.9)	172 (94.5)	140 (90.9)
Ki67, centrally measured			
Median (range)‡	75.0 (10–100)	75.0 (15–100)	70.0 (10–95)
Missing	12	6	6

*In 23 patients, axillary intervention was performed before and after treatment.
†74% were G3 by local pathology
‡50% by local measurement.

50% of patients were histologically confirmed node-negative prior to chemotherapy.

Treatment Efficacy

Five patients violating inclusion criteria did not begin therapy; three withdrew consent and were excluded from further analysis; 324 (97.9%) underwent surgery or a second biopsy for histological confirmation of residual disease. Addition of carboplatin resulted in higher pCR (ypT0/is ypN0) than addition of gemcitabine (45.9%, 95% CI = 0.38 to 0.54, vs 28.7%, 95% CI = 0.22 to 0.36; 95% CI(d_{BA}) = 6.2% to 27.9%, $P = .002$; odds ratio [OR] = 2.11, 95% to CI = 1.34 to 3.36); 12 pCR labels were missing (3.6%) (Figure 2). Rates of ypT0/ypN0 also favored the carboplatinum-containing arm (45.2%, 95% CI = 0.37 to 0.54 (B), vs 25.8% (A), 95% CI = 0.20 to 0.33; 95% CI(d_{BA}) = 8.4% to 29.8%, $P < .001$).

Excluding patients with pN+ after axillary surgery performed prior to therapy from the analysis resulted in pCR of

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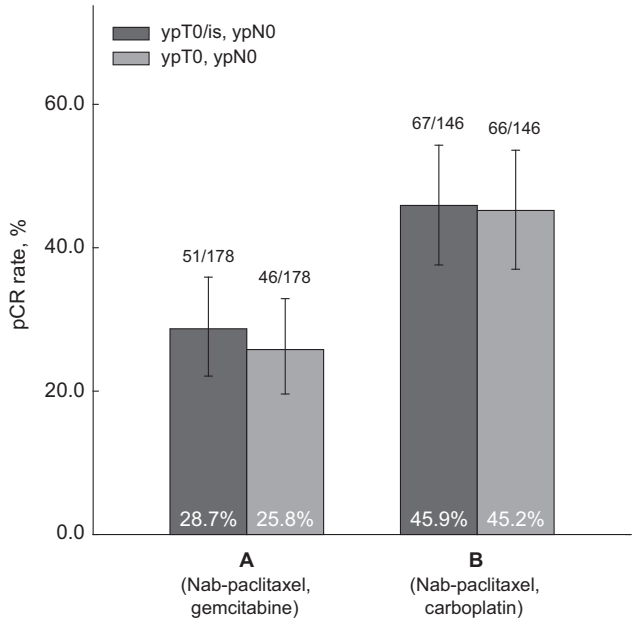

Figure 2. Pathological complete response (pCR; ypT0/is, ypN0) and total pCR (ypT0/ypN0) by treatment arms. Error bars represent 95% confidence intervals. Arm A (nab-paclitaxel/gemcitabine) included 178 patients, and arm B (nab-paclitaxel/carboplatinum) included 146 patients. pCR = pathological complete response.

48.0% vs 30.0% in favor of nab-paclitaxel/carboplatinum (P = .002; data not shown). In a subgroup defined by cT2–4 or cN+ tumors, pCR rates were 41.8% (B) and 25.5% (A; P = .02), respectively.

Three hundred nine patients underwent surgery after 12 weeks of therapy; in 15 patients, NACT was continued after histological confirmation of residual disease or progression (with subsequent pCR in four patients). Omission of postoperative chemotherapy was documented in 70 patients with pCR (59.3%).

In logistic regression, baseline Ki-67 had a strong prognostic impact on pCR in all patients (OR = 2.99, 95% CI = 1.65 to 5.40, P < .001) but was not predictive (ie, had no therapy interaction; data not shown). Figure 3 suggests that the benefit of carboplatinum (vs gemcitabine) for pCR may be more pronounced in the premenopausal subgroup (P < .001); nonetheless, menopausal status did not have statistically significant prognostic or predictive impact on pCR by interaction analysis. Not surprisingly, lower clinical tumor stage had favorable prognostic impact on pCR (OR = 0.48, 95% CI = 0.30 to 0.77, P = .002), but had no predictive interaction with therapy. There is no statistically significant interaction between the responder status and pCR.

Treatment Compliance and Toxicity

Eighty-six point eight percent and 90.9% completed treatment per protocol in the two trial arms, respectively. The most frequent reasons for early treatment discontinuation in arm A were toxicity (5.5%) and progression. Dose reduction of one or both drugs was required in 20.6% of patients in arm A vs 11.9% in arm B (P = .04; data not shown).

No treatment-related deaths occurred. Serious adverse events (SAEs) occurred more frequently in arm A (31, 17.2%) than in arm B (16, 10.6%; P = .11); 20 treatment-related SAEs occurred in arm A (11.1%) vs eight (5.3%) in arm B (P = .07; data not shown).

Incidence rates of neutropenia and of elevated liver enzymes (any grade) were higher in arm A (Table 2). Grade 3–4 toxicities were infrequent: 1% peripheral neuropathy (PNP) and 10% to 12% neutropenia in both trial arms. A trend to lower incidence of grade 3–4 infections (7.2% vs 2.6%, P = .07) and two vs one cases of febrile neutropenia favored the nab-pac/carbo arm. Only elevated ALAT (grade 3–4) was statistically significantly more frequent in the nab-pac/gem arm (11.7% vs 3.3%, P = .01).

Impact of Early Response

A coprimary objective of the WSG-ADAPT TN trial was to compare therapy efficacy in early responders vs nonresponders (38). Among 324 patients with evaluable pCR status, 144 (44.4%) were early responders (78 by low cellularity and 66 by KI-67 decrease), 118 were nonresponders (36.4%), and 62 (19.1%) were unclassifiable due to missing second biopsy; the respective pCR rates were 44.4%, 19.5%, and 50.0% (P < .001 for early responders vs nonresponders) (Figure 4). Responders had 25.0% (98% CI = 11.5% to 36.9%) higher pCR than nonresponders (P = .01). Both early responders and nonresponders (Figure 4) had similarly improved pCR with carboplatinum (Arm B). In responders (36.1% vs 52.8%), the 95% confidence interval for the 16.7% difference was –0.5% to 32.6%; in nonresponders (13.5% vs 29.5%), the 95% confidence interval for the 16.0% difference was –0.1% to 33.2% (both exploratory).

Discussion

In the prospective, randomized, phase II, ADAPT TN trial, addition of carboplatin to a 12-week, taxane-based, anthracycline-free regimen resulted in remarkably high pCR (45.9%) and was superior to addition of gemcitabine (28.7%). Our results are also in line with most other studies supporting a statistically significant benefit on pCR from addition of carboplatinum to standard chemotherapy. First, the phase III CALGB 40603 trial reported a pCR increase from 39% to 49% by adding carboplatinum AUC6 q3w to weekly paclitaxel, followed by dose-dense Adriamycin/Cyclophosphamide (AC) (indeed, 60% with additional bevacizumab) (5). However, increased efficacy of adding carboplatinum came at the cost of increased toxicity. Discontinuation rates were 40% with paclitaxel/carboplatinum vs 16% in the control arm.

The phase II GeparSixto trial also showed superior pCR for carboplatinum addition (AUC 2 or 1.5 weekly) to 18 weeks of the experimental chemotherapy backbone regimen (liposomal anthracycline [Myocet], bevacizumab, and weekly paclitaxel) in TNBC (n = 315, 43% vs 53%). This pCR increase was seen despite early therapy discontinuation rates of 36% vs 49% due to adverse events (SAE incidence 39% vs 44%) (32). Only one trial—in patients with "basal-like" tumors—failed to show positive impact on pCR by adding carboplatinum to docetaxel after 4xEC (33).

However, our results have recently been confirmed by data from the TnAcity trial among metastatic firstline TNBC patients, showing higher efficacy of nab-paclitaxel/carboplatinum vs nab-paclitaxel/gemcitabine or gemcitabine/carboplatinum. Remarkably, no toxicity difference was observed in this trial between carboplatinum vs gemcitabine-containing therapies, possibly due to a longer treatment duration in association with carboplatinum (39).

Follow-up data of the first two trials suggest that improved pCR with addition of carboplatinum may translate into improved survival: three-year DFS was statistically significantly

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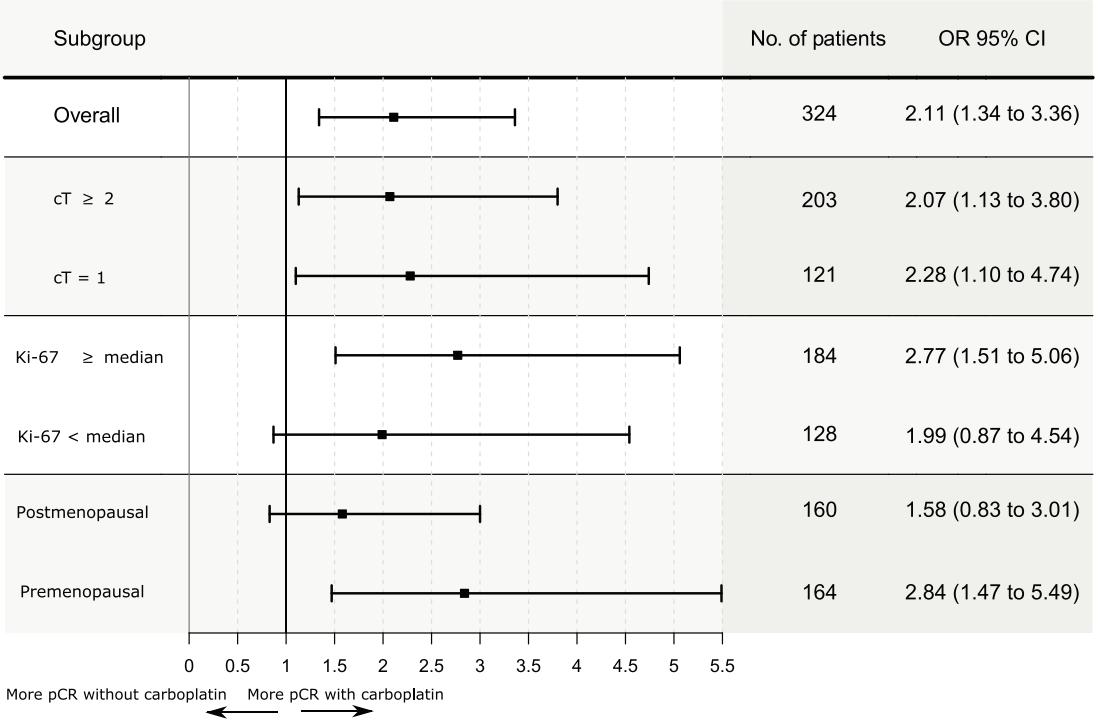

Figure 3. Pathological complete response (pCR) subgroup analyses (forest plot). Overall odds ratio (arm B [nab-paclitaxel/carboplatinum] vs arm A [nab-paclitaxel/gemcitabine]) is calculated by univariate logistic regression. All odds ratios are given with 95% confidence intervals calculated by profile-likelihood (for overall odds ratio) or Wald confidence interval (for subgroups). Odds ratios are given for arm B vs arm A by cT2 (clinical tumor stage 2–4c vs cT1, <2 cm), by greater than or equal to the median Ki-67 (75%) vs less than the median, by premenopausal vs postmenopausal status, and by early responder vs early nonresponder status. CI = confidence interval; OR = odds ratio; pCR = pathological complete response.

Table 2. Frequency of patients with particular adverse events, based on the safety population

	Arm A* (n = 180)No. (%)		Arm B* (n = 151)No. (%)			
Toxicity	All grades	Grade 3–4	All grades	Grade 3–4	P† (all grades)‡	P† (grade 3–4)‡
Alanine aminotransferase increased	56 (31.3)	21 (11.7)	19 (12.6)	5 (3.3)	<.001	.01
Anemia/decreased hemoglobin	31 (17.3)	0	29 (19.2)	0	.67	NA
Arthralgia	19 (10.6)	1 (0.6)	25 (16.6)	2 (1.3)	.14	.59
Aspartate aminotransferase increased	36 (21.1)	2 (1.1)	14 (9.3)	3 (2.0)	.01	.66
Bone pain	21 (11.7)	1 (0.6)	17 (11.3)	2 (1.3)	1.00	.59
Constipation	50 (27.9)	1 (0.6)	40 (26.5)	0	.80	1.00
Diarrhea	30 (16.7)	4 (2.2)	21 (13.9)	1 (0.7)	.38	.38
Fatigue	3 (1.7)	0	2 (1.3)	0	1.00	NA
Febrile neutropenia	2 (1.1)		1 (0.7)		NA	1.00
Gamma-glutamyltransferase increased	13 (7.3)	2 (1.1)	7 (4.6)	3 (2.0)	.36	1.00
Headache	26 (14.5)	0	21 (13.9)	0	1.00	NA
Hypertension	3 (1.7)	1 (0.6)	5 (3.3)	1 (0.6)	.48	1.00
Leukopenia	23 (12.8)	3 (2.0)	27 (17.9)	3 (2.0)	.22	1.00
Liver function test increased	6 (3.4)	5 (2.8)	0 (0.0)	0	.03	.07
Mucosal inflammation	24 (13.4)	1 (0.6)	10 (6.6)	0	.05	1.00
Nausea	49 (27.4)	1 (0.6)	50 (33.1)	2 (1.3)	.28	.59
Neutropenia/decreased neutrophils or granulocytes	71 (39.4)	29 (16.1)	38 (25.2)	24 (15.8)	.007	.6
Peripheral sensory neuropathy/polyneuropathy	38 (21.1)	1 (0.6)	34 (22.5)	2 (1.3)	.79	.59
Pneumonia	2 (1.1)	2 (1.1)	2 (1.3)	2 (1.1)	1.00	.50
Subclavian vein thrombosis	3 (1.7)	3 (2.0)	2 (1.3)	0	1.00	.50
Thrombocytopenia/decreased platelet count	12 (6.7)	2 (1.3)	10 (6.6)	0	1.00	.50

*Number of patients with at least one adverse event occurrence. NA = not applicable.
†Arm A vs arm B; flagging device only (no correction for multiple comparison).
‡Two-sided Fisher exact test.

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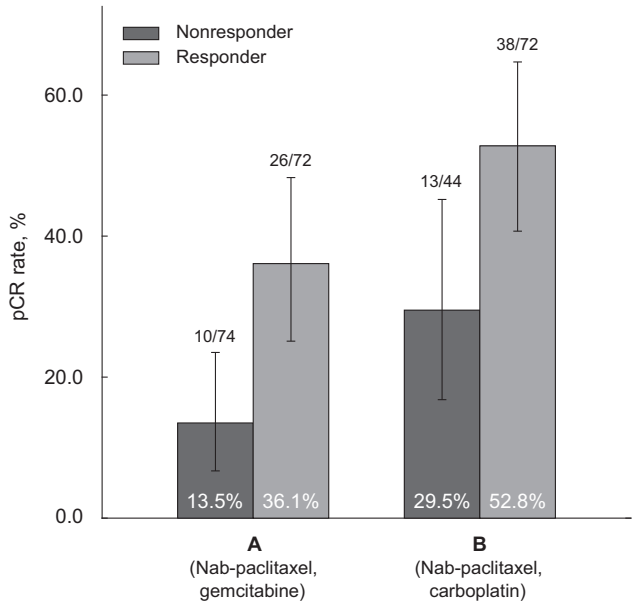

Figure 4. Exploratory pathological complete response (ypT0/is/ypN0) analysis by early response and treatment arms. Arm A included 146 patients, and Arm B included 116 patients. All results are given with 95% confidence intervals, represented by the error bars. pCR = pathological complete response.

improved in GeparSixto, while only a statistically nonsignificant trend occurred in the CALGB 40603 trial (34,40). Due to the higher toxicity profile and the unclear survival impact, the use of carboplatinum in treatment of early TNBC remains a matter of debate.

From a clinical perspective, the key finding of the WSG-ADAPT TN trial is the substantial pCR rate of 45.9% (locally assessed) in the nab-paclitaxel-carboplatinum arm after only 12 weeks of therapy, together with a very favorable safety profile. This result seems to be comparable to efficacy observed with longer and more toxic anthracycline-taxane+/-carboplatinum-based combinations, as well as more toxic taxane-carboplatinum-based combinations given for 18 to 24 weeks (3–5,8,22,23,32). Recent reports support the validity of locally determined pCR, showing a high level of "local" pCR confirmation by central pathological review: greater than 99% of locally pCR-positive cases had a "central" residual cancer burden score of 0–1; these scores are associated with similarly favorable prognosis in TNBC (41,42), in contrast to previous studies (43).

There are some further important limitations and issues in our study. First, we have used nab-paclitaxel instead of solvent-based paclitaxel, which has shown promising NACT efficacy, particularly in TNBC. In the recent GeparSepto trial, neoadjuvant weekly 12xnab-paclitaxel (150 mg/m^2, later 125 mg/m^2) was superior to solvent-based paclitaxel weekly (80 mg/m^2) followed by 4xEC in TNBC regarding pCR (48.9% vs 29.2%) (4,44), but it had higher toxicity (PNP of 8%, dose reduction in about 30% of patients) (45). Results of GeparSepto are only partly supported by the recently presented ETNA trial, using 12xnab-paclitaxel (125 mg/m^2, d1,8,15 q28d) vs paclitaxel 90 mg/m^2 followed by 4xEC/FEC: nab-paclitaxel showed only a weak (statistically nonsignificant) trend (41.3% vs 37.3%) to higher pCR in TNBC. These findings may be attributable to differences in nab-paclitaxel scheduling (d1,8,15 q4w), lower relative dose intensity per week in the 28-day ETNA trial regimen, or restriction to higher-risk patients (only T2–4d tumors) compared with GeparSepto. However, a more favorable toxicity profile compared with the GeparSepto schedule (eg, PNP of 4.5%) was observed (8). The positive impact of this intermittent concept is also supported by the WSG-ADAPT TN trial, which has shown a favorable toxicity profile with nab-paclitaxel (125 mg/m^2, d1,8 q21d): a substantially lower PNP rate of only 1%, and a dose reduction rate of 11.9% in the nab-paclitaxel/carboplatinum arm. Together with results from the metastatic setting, these results imply higher efficacy of nab-paclitaxel compared with other taxanes if administered as monotherapy without bevacizumab at a dose of 100 to 125 mg/m^2 (7,46).

Another limitation is that a somewhat unusual taxane-gemcitabine combination was used within the study for the comparison arm. Although recent adjuvant data incorporating gemcitabine as a fourth agent in the polychemotherapy setting do not support use of gemcitabine-containing regimens in EBC (24), given the positive results for two-agent gemcitabine-containing combinations in the metastatic setting (16,18,20), the pCR difference cannot solely be explained by a weakness of the gemcitabine-containing arm: a pCR rate of 28.7% exceeds that previously obtained for 12 weeks of paclitaxel alone (47).

Also, the baseline characteristics of the WSG-ADAPT TN patients were somewhat more favorable than in other trials (fewer clinically node-positive tumors, no inflammatory BC). However, even restricting to patients with high clinical tumor burden (cT2–4 or cN+ tumors), pCR (particularly in the nab-paclitaxel/carboplatinum arm) was still clinically very meaningful, exceeding 40%. The remarkably high percentage of high-grade and high-Ki-67 tumors is largely attributable to central pathological assessment. About one-third of central G3 tumors were not G3 by local assessment.

Here we have used a relatively short, 12-week taxane-based anthracycline-free backbone in both study arms. At first glance, standard anthracycline-containing chemotherapy given after pCR assessment (and strongly recommended only in patients without pCR) seems to be a weakness of the study, following publication of early results of the ABC trial confirming positive impact of standard A/T-containing vs A-free chemotherapy after a median follow-up of 3.3 years, particularly in TNBC patients (12). However, Danish trials and the PlanB randomized trial do not show statistically significant benefit of anthracyclines even in TNBC patients after a five-year follow-up (14,48); moreover, none of these trials had a control arm with carboplatinum-containing chemotherapy.

The very high efficacy of taxane-carboplatinum-based anthracycline-free combinations in ADAPT TN and several further trials (showing pCR up to 55%) (49,50) raises an issue: given the controversial discussion concerning carboplatinum as an addition to the standard anthracycline-taxane combinations and the substantial efficacy of anthracycline-free platinum combinations seen in our trial, one might also speculate whether it would be best to begin with such an anthracycline-free combination and add anthracycline only if no pCR can be achieved (15); based on the prognostic impact of pCR on survival in TNBC (1,2), a substantial proportion of TNBC patients responding very early to NACT (eg, already after 12 weeks) are potentially being overtreated by further (longer or non-cross-resistant) therapy. Moreover, lengthening therapy duration (eg, from 12 to 18 weeks) seems to be less important for increasing pCR in Hormone recpetor status (HR)-negative than in HR-positive disease (51); hence, longer duration of the same treatment seems unlikely to increase pCR.

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Another limitation of our study is that analysis of BRCA1 status, which is extensively under discussion as a predictive marker for platinum efficacy (28), as well as BRCA-ness status and PAM-50-based subtyping, is still ongoing and will be reported later. Unfortunately, there are no established predictive factors allowing patient selection for carboplatinum: tumor-infiltrating lymphocytes, family history, somatic and/or germline BRCA1 mutation, and/or homologous recombination deficiency (HRD) score are under investigation but seem to indicate increased general chemo-sensitivity, rather than particular carboplatinum benefit (52,53). Premenopausal status (associated with a higher percentage of BRCA1 mutations in TNBC) (26) seems to be associated with efficacy, particularly in the nab-pac/carbo arm in our study, but this trend could be partly attributable to higher baseline Ki-67 (which is associated with younger age).

However, GeparSixto (40), as well as recently published results for 6xdocetaxel+carboplatinum, does not support BRCA1 status and/or HRD score as unique predictors of carboplatin efficacy in a polychemotherapy setting (15), in contrast to studies that evaluated less efficacious combinations (28,54). Together with results from other trials implicating BRCA1 mutation status as a strong predictor for efficacy of taxane-anthracycline-based combinations (31,55), our findings imply its nonselective role for chemotherapy sensitivity regarding most drugs used in BC treatment. The substantial benefit from the carboplatinum- vs gemcitabine-containing combination regarding pCR, particularly in young patients, cannot be explained solely by a higher-than-expected incidence of BRCA1 mutation in this group, but rather by high proliferation characteristics.

In summary, the results of the WSG-ADAPT-TN trial support a personalized postneoadjuvant treatment strategy in patients with TNBC based on pCR after 12 weeks and/or early response biomarkers. They imply a substantial association between morphological changes in the tumor (revealed after one cycle of therapy) and subsequent pCR—regardless of treatment (though a refined definition of "early response" in TNBC might have had an impact on the relatively high pCR rate in nonresponders of the nab-paclitaxel/carboplatinum arm). Although GEPAR-Trio data did not support a switch of chemotherapy in case of clinical nonresponse, our results indicate that patients with TNBC could benefit from a response-guided treatment approach. Similarly promising results toward optimal assessment of early treatment efficacy (prediction of pCR and/or survival) have been reported in association with early imaging changes in positron emission tomography and computed tomography in TNBC (56); potential for improved classification of early response by imaging (eg, ultrasound and/or magnetic resonance imaging) is currently under investigation.

In view of the high efficacy with our well-tolerated, anthracycline-free (though nonstandard) nab-paclitaxel-carboplatinum regimen, the criterion of pCR after 12 weeks of anthracycline-free neoadjuvant chemotherapy could be used for treatment de-escalation decisions in TNBC patients. In the WSG-ADAPT-TN trial, only those patients failing to achieve pCR following anthracycline-free neoadjuvant chemotherapy received mandatory anthracycline-containing adjuvant chemotherapy; however, to conclusively address the question of optimal treatment in TNBC—which WSG-ADAPT-TN was not designed to answer—large adjuvant trials are needed. Moreover, optimization of our neoadjuvant regimen, for example, by addition of immunotherapy, could also be addressed by further prospective trials, particularly in patients without early pCR.

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