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Neoadjuvant bevacizumab and anthracycline–taxane-based chemotherapy in 678 triple-negative primary breast cancers; results from the geparquinto study (GBG 44)†

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Background: We evaluated the pathological complete response (pCR) rate after neoadjuvant epirubicin, (E) cyclophosphamide (C) and docetaxel containing chemotherapy with and without the addition of bevacizumab in patients with triple-negative breast cancer (TNBC).

Patients and methods: Patients with untreated cT1c-4d TNBC represented a stratified subset of the 1948 participants of the HER2-negative part of the GeparQuinto trial. Patients were randomized to receive four cycles EC (90/600 mg/m^2; q3w) followed by four cycles docetaxel (100 mg/m^2; q3w) each with or without bevacizumab (15 mg/kg; q3w) added to chemotherapy.

Results: TNBC patients were randomized to chemotherapy without ($n = 340$) or with bevacizumab ($n = 323$). pCR (ypT0 ypN0, primary end point) rates were 27.9% without and 39.3% with bevacizumab ($P = 0.003$). According to other pCR definitions, the addition of bevacizumab increased the pCR rate from 30.9% to 41.8% (ypT0 ypN0/+; $P = 0.004$), 36.2% to 46.4% (ypT0/is ypN0/+; $P = 0.009$) and 32.9% to 43.3% (ypT0/is ypN0; $P = 0.007$). Bevacizumab treatment [OR 1.73, 95% confidence interval (CI) 1.23–2.42; $P = 0.002$], lower tumor stage (OR 2.38, 95% CI 1.24–4.54; $P = 0.009$) and grade 3 tumors (OR 1.68, 95% CI 1.14–2.48; $P = 0.009$) were confirmed as independent predictors of higher pCR in multivariate logistic regression analysis.

Conclusions: The addition of bevacizumab to chemotherapy in TNBC significantly increases pCR rates.

Key words: triple-negative breast cancer, bevacizumab, neoadjuvant chemotherapy, pathological response rate

introduction

Patients with triple-negative breast cancer (TNBC) are at highest risk of relapse and death among all breast cancer subtypes [1]. At present, anthracycline–taxane-based chemotherapy represents the standard of care for TNBC patients, as no specific treatments are available for this heterogeneous disease. TNBC is highly proliferative, with an enhanced angiogenesis, high intratumoral vascular endothelial growth factor (VEGF) levels and activation of genes involved in angiogenesis [2–5]. Therefore, anti-angiogenic drugs may be particularly effective. Bevacizumab, a monoclonal antibody directed against the VEGF-A ligand, has shown clinical efficacy in patients with metastatic TNBC [6, 7].

In the GeparQuinto study, we have shown that addition of bevacizumab to neoadjuvant chemotherapy significantly

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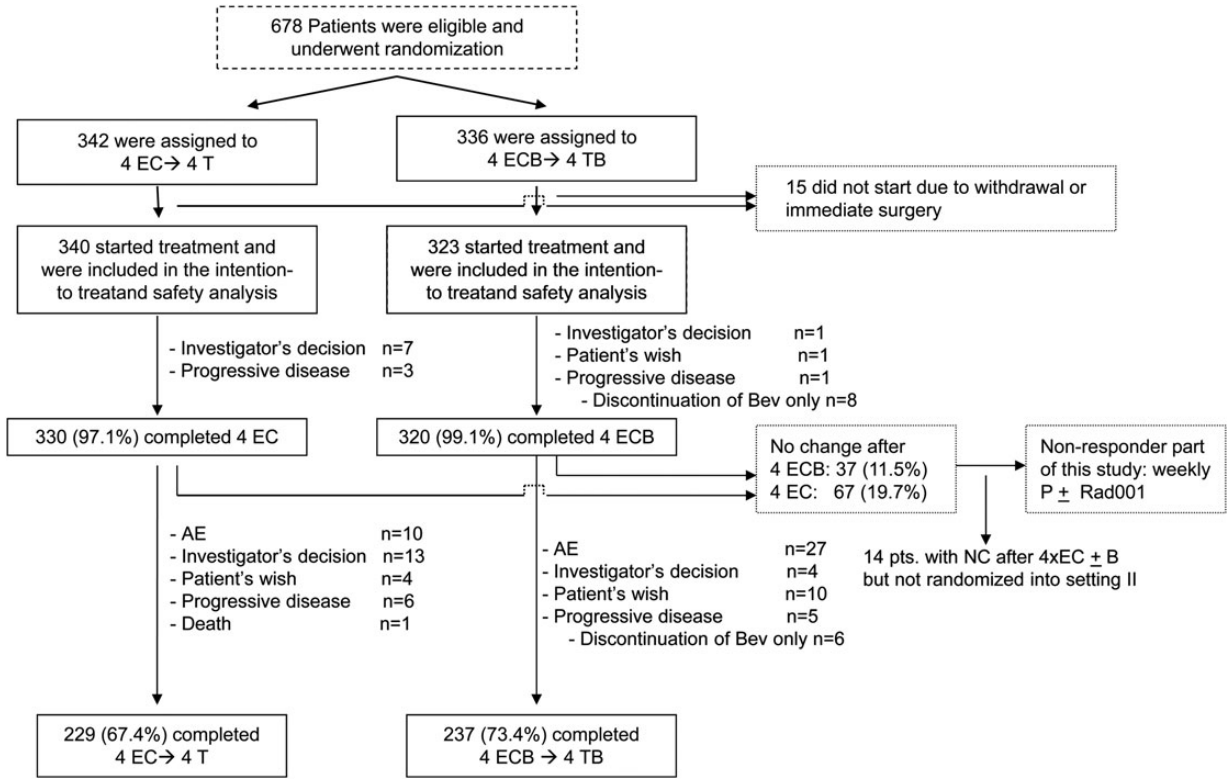

Figure 1. Consort statement.

Table 1. Baseline characteristics of all TNBC patients who started therapy

Parameter	Statistic	EC-D ($N = 340$) *n* (%)	ECB-DB ($N = 323$) *n* (%)	Overall, *n* (%)	*P*-value
Age (years)	Mean	48	48	48	0.936
	Min, max	28, 75	21, 75	21, 75	
Tumor size (mm) by palpation	Mean	41.4	41.6	41.5	0.577
	Min, max	10.0, 70.0	10.0, 190.0	10.0, 190.0	
Tumor size (mm) by sonography	Mean	31.3	31.2	31.3	0.865
	Min, max	9.0, 167.0	11.0, 100.0	9.0, 167.0	
cT	cT1-2	286 (84.4)	271 (84.2)	557 (84.3)	0.720
	cT3-4a-c	26 (7.7)	21 (6.5)	47 (7.1)	
	cT4d	27 (8.0)	30 (9.3)	57 (8.6)	
	Missing	1	1	2	
cN	Negative	140 (42.8)	132 (42.0)	272 (42.4)	0.873
	Positive	187 (57.2)	182 (58.0)	369 (57.6)	
	Missing	13	9	22	
Grading	G1	3 (0.9)	4 (1.2)	7 (1.1)	0.851
	G2	91 (27.0)	91 (28.2)	182 (27.6)	
	G3	243 (72.1)	228 (70.6)	471 (71.4)	
	Missing	3	0	3	
Histological tumor type	Ductal	291 (85.8)	282 (87.6)	573 (86.7)	0.629
	Lobular	10 (2.9)	6 (1.9)	16 (2.4)	
	Other	38 (11.2)	34 (10.6)	72 (10.9)	
	Missing	1	1	2	
ER/PgR	Strictly negative[a]	305 (89.7)	293 (90.7)	598 (90.2)	0.696

[a]ER/PgR = 0%.

increased the pCR rate in HER2-negative early-stage breast cancer [8]. The most notable and pronounced pCR rate was seen in the TNBC subgroup. Moreover, TNBC is the subtype with the greatest difference in disease-free and overall survival in patients with and without pCR after neoadjuvant chemotherapy [9–11].

The GeparQuinto trial was designed to compare the pCR rates in patients with HER2-negative primary breast cancer. A secondary objective was to analyze the effect of bevacizumab in the predefined and stratified subgroup of TNBC patients.

patients and methods

objectives

The primary objective of this study was to compare the pCR rates (no invasive and no noninvasive residuals in breast and lymph nodes; ypT0 ypN0) after neoadjuvant chemotherapy ± bevacizumab among predefined patients with TNBC. Secondary end point was pCR according to different definitions, i.e. ypT0/Tis ypN0; ypT0/Tis ypN0/+; and ypT0 ypN0/+ (no invasive and no *in situ* residuals in breast, irrespective of nodal status after therapy) [12–14]. Further secondary end points were the evaluation of response rates of breast tumors and axillary nodes assessed by clinical examination and imaging (breast ultrasound, mammography or magnetic resonance imaging) after therapy and before surgery, the rate of breast conservation and compliance.

patients

Women with previously untreated, unilateral or bilateral, primary invasive breast carcinoma were enrolled in the GeparQuinto study after written informed consent [8]. Breast cancer diagnosis had to be confirmed histologically by a core biopsy. TNBC was defined as no HER2 overexpression (Dako-HercepTest: score 0 or 1+, in score 2 no gene amplification by *in situ* hybridization) and hormone receptor (HR) expression (estrogen and progesterone receptor <10%) by immunohistochemistry as assessed by the local pathology. Tumors without any HR expression (estrogen and progesterone receptor 0%) were defined as strictly triple-negative. Inclusion and exclusion criteria have been reported recently [8].

treatment

All patients received epirubicin (E, 90 mg/m^2) plus cyclophosphamide (C, 600 mg/m^2), both administered on day 1, every 3 weeks for four cycles, followed by four cycles of docetaxel (D, 100 mg/m^2) on day 1, every 3 weeks. Patients were randomly assigned to receive either eight cycles of bevacizumab (B, 15 mg/kg body weight) intravenously every 3 weeks starting on day 1 of the first EC cycle (ECB-DB) or no additional treatment (EC-D).

Patients showing neither clinical nor sonographical response (<50% tumor size reduction) after four cycles of EC ± B were classified as nonresponders and were analyzed as having no pCR. These patients were taken off the initial treatment plan and were randomized within nonresponder arm (Setting II) to weekly paclitaxel ± the mTOR inhibitor RAD001 (everolimus, 10 mg/day orally) [15].

Table 2. Efficacy of treatment according to histological, surgical and clinical outcome

Parameter	Category	EC-D ($N = 340$) *n* (%)	ECB-DB ($N = 323$) *n* (%)	Overall, *n* (%)	*P*-value
pCR breast and nodes (primary end point), RG5, ypT0ypN0					
All patients included	No	245 (72.1)	196 (60.7)	441 (66.5)	0.003
	Yes	95 (27.9)	127 (39.3)	222 (33.5)	
	95% CI	(23.2%, 33.0%)	(34.0%, 44.9%)		
All included patients, including pCR achieved in setting II	No	242 (71.2)	191 (59.1)	433 (65.3)	0.001
	Yes	98 (28.8)	132 (40.9)	230 (34.7)	
	95% CI	(24.1%, 34.0%)	(35.5%, 46.4%)		
Strictly negative patients	No	217 (71.1)	176 (60.1)	393 (65.7)	0.006
	Yes	88 (28.9)	117 (39.9)	205 (34.3)	
	95% CI	(23.8%, 34.3%)	(34.3%, 45.8%)		
pCR breast, RG5+4, ypT0 ypN0/+	No	235 (69.1)	188 (58.2)	423 (63.8)	0.004
	Yes	105 (30.9)	135 (41.8)	240 (36.2)	
	95% CI	(26.0%, 36.1%)	(36.4%, 47.4%)		
pCR invasive, RG5+4+3, ypT0/is ypN0/+	No	217 (63.8)	173 (53.6)	390 (58.8)	0.009
	Yes	123 (36.2)	150 (46.4)	273 (41.2)	
	95% CI	(31.1%, 41.5%)	(40.9%, 52.0%)		
pCR invasive breast and nodes, RG5+3, ypT0/is ypN0	No	228 (67.1)	183 (56.7)	411 (62.0)	0.007
	Yes	112 (32.9)	140 (43.3)	252 (38.0)	
	95% CI	(28.0%, 38.2%)	(37.9%, 48.9%)		
Clinical response after EC ± B	CR	29 (8.5)	39 (12.2)	68 (10.3)	
	PR	230 (67.6)	233 (73.0)	463 (70.3)	
	ORes (CR+PR)	259 (76.2)	272 (85.3)	531 (80.6)	0.004
	95% CI for ORes	(71.3%, 80.6%)	(80.9%, 89.0%)		
	Missing	0	4	4	
Clinical response at surgery	CR	94 (27.6)	102 (31.8)	196 (29.7)	
	PR	180 (52.9)	178 (55.5)	358 (54.2)	
	ORes (CR+PR)	274 (80.6)	280 (87.2)	554 (83.8)	0.026
	95% CI for ORes	(76.0%, 84.7%)	(83.1%, 90.7%)		
	Missing	0	2	2	
Breast-conserving surgery	No	79 (25.1)	85 (28.1)	164 (26.6)	0.441
	Yes	236 (74.9)	217 (71.9)	453 (73.4)	
	Missing	25	21	46	
	95% CI	(69.8%, 79.6%)	(66.4%, 76.9%)		

In cases of tumor progression, the study treatment was discontinued and further local or systemic treatment was permitted at the investigator's discretion. Patients could undergo surgery at least 28 days after the last chemotherapy ± bevacizumab.

assessment of end points

The breast tumor and regional lymph nodes were examined by palpation at every cycle and by sonographic examination after every second cycle; breast ultrasound, clinical examination and mammography were carried out before breast surgery. Clinical complete response was defined according to WHO criteria [16]. Pathological response in the breast and of axillary lymph nodes was assessed by the local pathologist according to modified Sinn criteria [17]. Pathological reports were reviewed centrally by a breast oncologist and a pathologist who were blinded to treatment assignments, and response was staged according to the tumor–node–metastasis system [18]. Patients were considered to have breast-conserving surgery (BCS) if the final surgical procedure was tumorectomy, segmentectomy or quadrantectomy.

statistical analysis

Statistical details of the GeparQuinto study have been published recently [8]. All patients who received at least one cycle of chemotherapy ± bevacizumab were included in the efficacy and safety analyses (Figure 1). Missing data on response were counted as no response. Multivariate logistic regression analysis was used to adjust for baseline factors. Univariate logistic regression was carried out in subgroups; a Breslow–Day test was used for testing the homogeneity of odds ratios (OR) across subgroups. All statistical analyses were carried out using SAS software, version 9.2.

results

patients

From November 2007 to June 2010, a subgroup of 678 patients with TNBC was randomized, 663 of whom started treatments (intent-to-treat population). The baseline characteristics of the patients were balanced between both arms (Table 1).

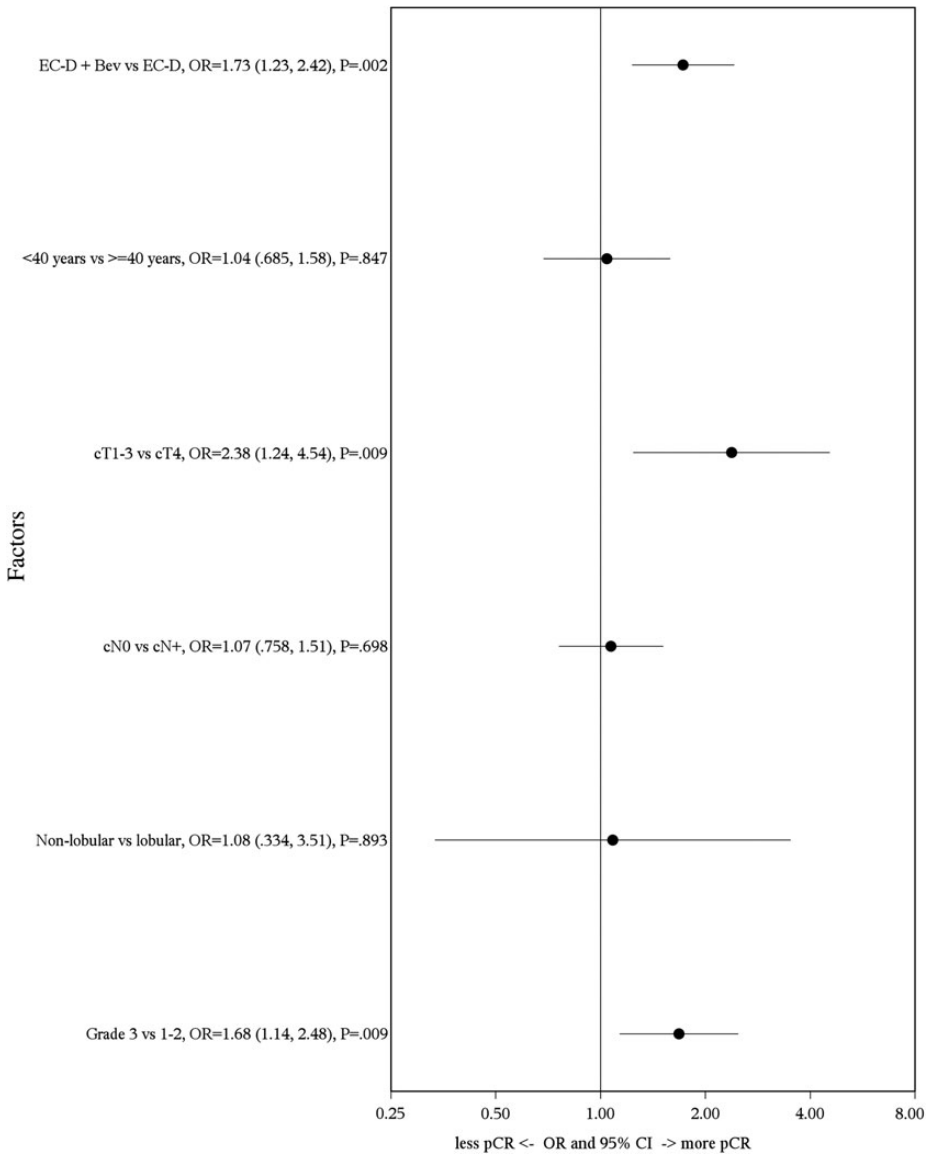

Figure 2. Forrest plot multivariate analysis for pCR in the TNBC cohort.

efficacy

A total of 95 (27.9%; 95% confidence interval [CI] 23.2–33.0) patients who received EC-D and 127 (39.3%; 95% CI 34.0–44.9) treated with ECB-DB had a pCR (ypT0 ypN0; $P = 0.003$; Table 2). The pathological response rates according to other definitions are shown in Table 2.

The overall clinical response rate (complete and partial response), determined by palpation and imaging, was significantly higher in the bevacizumab group after four cycles of EC (76.2% versus 85.3%; $P = 0.004$) and before surgery (80.6% versus 87.2%; $P = 0.026$) compared with no bevacizumab.

The rate of BCS was identical between patients treated without or with bevacizumab: (EC-D: 74.9% and ECB-DB: 71.9%; $P = 0.441$). In patients with strictly negative tumors, this rate was 74.3% (EC-D) and 72.2% (ECB-DB; $P = 0.636$).

An analysis adjusted by age, tumor and nodal stage, histological type and grade revealed an increase in pCR rate for the addition of bevacizumab to EC-D (OR 1.73, 95% CI 1.23–2.52; $P = 0.002$). Additionally, lower tumor stage (OR 2.38, 95% CI 1.24–4.54; $P = 0.009$) and grade 3 tumors (OR 1.68, 95% CI 1.14–2.48; $P = 0.009$) were confirmed as independent predictors of higher pCR rates (Figure 2). The increase in pCR rate with the addition of bevacizumab was consistent across subgroups (Figure 3), except for cT4 tumors. Breslow–Day test for interaction was not significant for all subgroup parameters, including clinical tumor stage ($P = 0.081$).

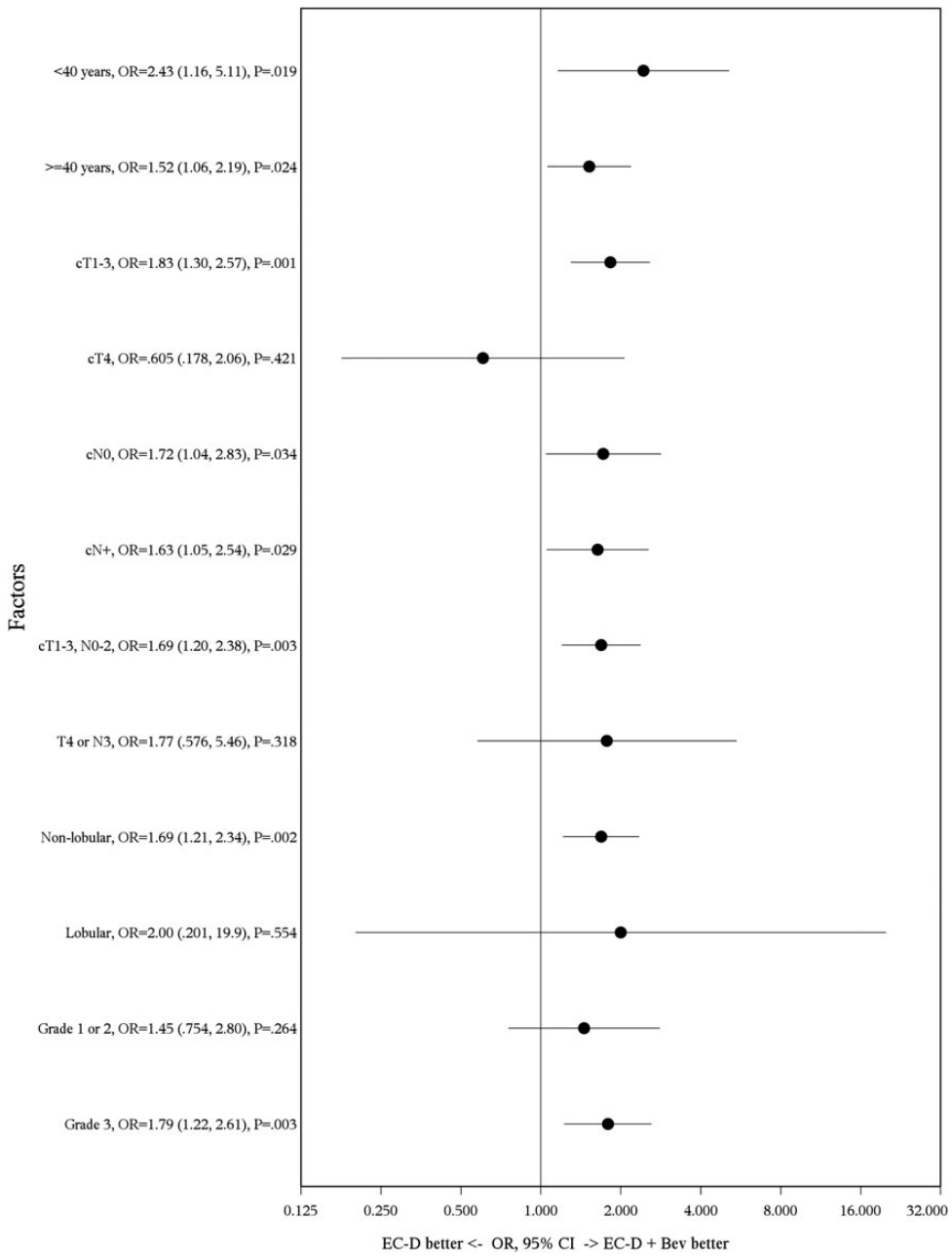

Figure 3. Forrest plot on pCR rates (ypT0 ypN0) after chemotherapy without or with bevacizumab in various subgroups of patients with TNBC.

compliance and safety profile

Of the 663 patients who started treatment, 330 (97.1%) finished four cycles EC and 320 (99.1%) four cycles ECB. No change in tumor size was seen in 20.1% ($n = 71$; EC) and in 14.1% ($n = 45$; ECB) of patients. All these patients, except 12 (EC: $n = 4$; ECB: $n = 8$), were randomized into setting II. Treatment with four cycles of docetaxel in the remaining responders was finished by 229 (67.4%; EC-D) and 237 (73.4%; ECB-DB) patients. Fourteen patients discontinued bevacizumab therapy alone due to adverse events, patient's wish or investigator`s advice (Figure 1).

Chemotherapy was delayed in 35.7% (EC-D) and 45.6% (ECB-DB) of patients; the dose was reduced in 12.4% and 19.7% of patients, respectively.

As expected, the safety profile of bevacizumab in TNBC patients was similar to that in the overall population treated in GeparQuinto (data not shown) [8].

discussion

Our study shows that the addition of bevacizumab to neoadjuvant anthracycline–taxane-containing chemotherapy significantly increased the pCR rate (ypT0 ypN0) from 27.9% to 39.3% in patients with operable or locally advanced TNBC independent of different pCR definitions. The magnitude of the differences in pCR rates were the same when alternative TNBC definitions were considered. In TNBC, the pCR rate is an important surrogate marker concerning prognosis [9–11].

When this randomized trial started in 2007, patients with <10% of tumor cells stained positive for HRs were classified as HR-negative [19]. The new classification, considering tumors with ≤1% positively stained tumor cells, was recommended after the end of the GeparQuinto recruitment [20,21].

In contrast to our results, the NSABP B-40 study did not show a benefit in the TNBC subgroup of 490 patients by adding bevacizumab to anthracycline–taxane-based neoadjuvant chemotherapy [12]. The reasons for these divergent results have been discussed in detail previously [8]. To summarize, these results might be attributed to the smaller sample size of TNBC in the NSABP B-40 compared with our study, the exclusion of patients with T4a-d carcinomas in NSABP B-40, which corresponded to 12% of our TNBC cohort; the inclusion of patients with HR-positive, HER2-negative and node-negative tumors in NSABP B-40, who were excluded in GeparQuinto. Patients with lack of response after four EC ± B were considered nonresponders and excluded from the following taxane-based therapy; however, only 18 of these nonresponders had a pCR and did not relevantly change the pCR rate in the total population. Also, the sequence anthracycline-containing regimen followed by docetaxel in our study was reversed in the NSABP study. Moreover, the NSABP B-40 study tested the additive effect of two antimetabolites using a 2-by-3 factorial design and therefore applied a decreased dose of docetaxel (75 mg/m^2) in the experimental arms. Bevacizumab was administered during the first six chemotherapy cycles only.

By adjusting the analysis for subgroups, the addition of bevacizumab, lower tumor stage and grade 3 were confirmed as predictors of a higher pCR rate in TNBC. There are several strengths and limitations of our study. The multicenter GeparQuinto trial prospectively stratified for the TNBC and represents the largest TNBC cohort with neoadjuvant chemotherapy and bevacizumab. The results were consistent even when using other pCR definitions, and when the nonresponding patients after four EC+B were included. The definition of TNBC (<10% versus <1% ER-positivity) did not influence the results. The results from further confirmatory study in TNBC like GeparSixto (NCT00567554; recruitment finished) or CALGB 40603 (NCT00861705, recruitment finished) trials should be awaited. The recently presented phase III BEATRICE study (NCT00528567) could not find a benefit for 3-year-invasive disease-free survival for adjuvant treatment with bevacizumab in resected TNBC [22].

In vitro and *in vivo* data, suggesting that cessation of bevacizumab will stimulate tumor growth, have yet to be confirmed in metastatic breast cancer [23]. Based on preclinical models, the concern is that anti-angiogenic agents might stimulate cancer stem cells by generating intratumoral hypoxia, and might increase invasive and metastatic properties of breast cancer cells, impairing patient outcome [24]. A proposed phase III trial to test the suitability of VEGF-A as a biomarker for effectiveness of bevacizumab in breast cancer seems to be a step in the right direction [25].

In conclusion, the addition of bevacizumab to anthracycline–taxane-based chemotherapy in TNBC increased the pCR rate significantly. It has to be awaited if the observed increase in pCR rate is large enough to translate into a survival benefit [26], especially in the light of the negative results of the BEATRICE study.

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disclosure

No conflicts of interest: GB; EH; RM; TH; EH; SI; KK; HC; KR; SC; JC; KG; BJU; HM; NV; UM; Honoraria: LS (Roche); FPA (Novartis); HJ (Roche, Sanofi-Aventis); MG (Roche).

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