

Breast cancer

ROLE OF BEVACIZUMAB IN NEOADJUVANT, ADJUVANT BREAST CANCER THERAPY

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TRIAL SUMMARY: Addition of bevacizumab to neoadjuvant chemotherapy improves pCR and cCR

Bear HD, Tang G, Rastogi P, Geyer CE. The effect on pCR of bevacizumab and/or antimetabolites added to standard neoadjuvant chemotherapy: NSABP protocol B-40. ASCO 2011. *J Clin Oncol* 2011;29 (suppl): Abstract LBA1005.

The study objectives were to determine if adding capecitabine (X) or gemcitabine (G) to docetaxel (T) would increase breast pathologic complete response (pCR) rates in operable, HER2– breast cancer and if adding bevacizumab (B) to T-based regimens would increase pCR rates. Patients received one of 3 T-based regimens +/- B 15 mg/kg every 3 weeks x 4: T 100 mg/m² on day 1; T 75 mg/m² on day 1 and X 825 mg/m² twice daily on days 1–14; T 75 mg/m² on day 1 and G 1000 mg/m² on days 1 and 8. Patients then received preoperative doxorubicin and cyclophosphamide (AC) x 4, +/- B for the initial 2 cycles of AC. Patients randomized to B resumed B for 10 postoperative doses. The

primary endpoint was pCR in the breast. The groups were balanced, with 47% clinically N+, 56% poorly differentiated and 59% hormone receptor-positive (HR+). Assessments for pCR were available from 1180 of 1206 randomized patients: 29.7% and 32% for TX and TG vs 32.7% for T. Neither TX nor TG increased clinical complete response rate (cCR) rates relative to T (58.3% and 60.4% vs 61.5%). Toxicity increased with TX and TG. Addition of B increased pCR (28.4 vs 34.5%; p=0.027) and cCR (55.8 vs 64.3%; p=0.007) rates. The effect of B was predominantly in the HR+ subset (15.2 vs 23.3%; p=0.008), with minimal effect in the hormone receptor-negative (HR–) subset (47.3% vs 51.3%; p=0.44). Higher Grades 2/3/4 toxicities with B were hypertension (1%/<1%/0% vs 13%/9%/<1%), hand-foot syndrome (11%/7%/0% vs 15%/11%/0%) and mucositis (10%/3%/0% vs 20%/5%/0%). The addition of B to neoadjuvant chemotherapy improved pCR and cCR rates, but the addition of X or G to T did not improve outcomes.

TRIAL SUMMARY: Neoadjuvant bevacizumab in TNBC

Gerber B, Eidmann H, Rezaei MA. Neoadjuvant bevacizumab and anthracycline–taxane-based chemotherapy in 686 triple-negative primary breast cancers: Secondary endpoint analysis of the GeparQuinto study (GBG 44). ASCO 2011. *J Clin Oncol* 2011;29(suppl):Abstract 1006.

The secondary aim of the GeparQuinto study was to determine pCR rates in patients with triple-negative primary breast cancer (TNBC). Unselected patients with untreated TNBC (ER and PR <10% and HER2 immunohistochemistry [IHC] score 0/1 or fluorescence in situ hybridization [FISH] negative; detected locally) were included in GeparQuinto if they had T1c–T4d tumours and showed no increased cardiac or bleeding risks. Patients were randomized to 4 cycles epirubicin and cyclophosphamide (EC; 90/600 mg/m²) every 3 weeks followed by 4 cycles T (100 mg/m²) +/- B 15 mg/kg every 3 weeks added to chemotherapy (CT) cycles. Patients were a stratified subset of the 1948 participants of the HER2– part of GeparQuinto. In total, 684 patients with

TNBC were randomized to EC-T (n=345) and EC-T + B (n=339). Median tumour size was 35/35 (–B/+B) mm (clinically) and 28.5/28 mm (sonographically); 15.7%/16.0% had T3 to T4a–d, 1.2%/1.5% bilateral, 13.3%/12.7% multifocal and 5.8%/6.5% multicentric disease; 97.1%/97.9% had nonlobular, 71.6%/69.6% Grade 3, 57.2%/58.0% N+ disease; 32.9% 28.7% discontinued treatment, 20.7%/12.3% due to no response after 4 x EC. An additional 4.7% of patients continued CT but stopped B. The pCR rate (histopathologic [yp] T0N0; primary endpoint) was 27.8%/36.4% (p=0.021). The rate of patients with ypT0N0 was 36.5%/44.6% (p=0.04) and ypT0N0 was 32.7%/40.1% (p=0.059). If pCRs in nonresponding patients were included, ypT0N0 rates rose to 28.7%/38.2%; ypT0N0 rates to 33.9%/41.9%. If only patients with ER=0%, PR=0% were considered, ypT0N0 was 32.3%/40.1%. B treatment (p=0.013), age (p=0.021), CT (p=0.042) and grade (p=0.004) were independent predictors for pCR in multivariate logistic regression analysis. Breast conservation was achieved in 75.2%/71.5% (p=0.39). Long-term followup is awaited.

TRIAL SUMMARY: Bevacizumab + second-line CT in TNBC

Brufsky A, Valero V, Tiangco B. Impact of bevacizumab (B) on efficacy of second-line chemotherapy (CT) for triple-negative breast cancer (TNBC): Analysis of RIBBON-2. ASCO 2011. *J Clin Oncol* 2011;29(suppl): Abstract 1010.

This trial presents a prespecified analysis of subgroup data in patients with TNBC from RIBBON-2 (Regimens in Bevacizumab for Breast Oncology), which enrolled patients with metastatic breast cancer (MBC) who had progressed on first-line non-B-containing CT. After CT was selected (taxane, gemcitabine, capecitabine or vinorelbine), patients were randomized 2:1 to receive CT + B (10 mg/kg every

2 weeks or 15 mg/kg every 3 weeks) or placebo. The primary endpoint was PFS. Of 684 patients treated in RIBBON-2, 159 (23%) had TNBC. Patients with TNBC derive significant relative risk (RR) and PFS benefit from the com-

ination of B with second-line CT. Despite the small sample size, there was a trend (hazard ratio [HR] 0.624; $p=0.0534$) toward OS benefit (Table 2).

COMMENTARY: As the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-40 trial shows, more is not necessarily better. The antimetabolite CT agents gemcitabine and capecitabine added to docetaxel (Taxotere) resulted in toxicity without improving outcome. All patients in this trial were HER2- and received 4 cycles of preoperative AC. The addition of B did improve the outcome, showing a 6% and 9% increase in pCR and cCR, respectively. Interestingly, the 9% advantage was in the 59% HR+ subgroup and not in the HR- group. As expected, the addition of B caused hypertension, hand-foot syndrome and mucositis. Study participants were operable patients (i.e. smaller tumours more amenable to treatment) and not the locally advanced patients usually treated in neoadjuvant trials. This choice of patients was presumably made to improve the chance of success.

The GeparQuinto study has some flaws in that it included HR <10%, which is not a standard definition of HR-status.

Trialists also employed local analysis of HER2 status using 0/1 as negative, or negative FISH. This was a subpopulation of the main study and included 684 individuals. Unlike in the NSABP B-40 study, the trial population had locally advanced disease: 70% Grade 3, 58% node-positive, median ultrasound size 2.8 cm and clinically 3.5 cm with 16% stage T3 to T4a-d, and 9% with inflammatory breast cancers. In the analysis of true HR- patients there was an almost 9% advantage for B in addition to CT for pCR, defined as no invasive cells in either the primary site or in the nodes, a more stringent definition than in most studies. At present, there is no standard definition of pCR, which makes cross-study comparison very hazardous.

In the RIBBON-2 trial, the study population received second-line CT (unlike operable women included in NSABP B-40 trial and locally advanced patients in the GeparQuinto study). The prespecified subgroup analysis of TNBC patients in the RIBBON-2 trial showed that by adding B to CT, the RR doubled from 18% to 40%, with just over a 3-month improvement in PFS and a 5-month OS survival advantage, just under statistical significance

TABLE 2. CT + B vs CT + placebo: baseline characteristics and efficacy results

Characteristics	B + CT (n=112)	Placebo + CT (n=47)
Median age, years (range)	55 (28–86)	49 (33–79)
Metastatic sites, %		
≥3	48	32
Visceral (%)	74	62
CT partner (%)		
Taxane	42	43
Gemcitabine	23	28
Capecitabine	16	21
Vinorelbine	19	9
PFS		
Events, n (%)	94 (84)	42 (89)
Median, months	6.0	2.7
HR* (95% CI)	0.494 (0.33–0.74)	
P value (log-rank)	$p=0.0006$	
OS		
Events, n (%)	52 (46)	29 (62)
Median, months	17.9	12.6
HR* (95% CI)	0.624 (0.39–1.007)	
P value (log-rank)	$p=0.0534$	
1-year OS, % (95% CI)	63 (52–72)	50 (34–64)
Difference in rates, % (95% CI)	13 (–6 to 31)	
	$p=0.1758$	
Objective RR, % (95% CI)*	41 (31–51)	18 (8–34)
Difference, % (95% CI)	23 (7–39)	
P value*	$p=0.0078$	

* Stratified analysis (CT regimen and disease-free interval)
 CT=chemotherapy; B=bevacizumab; HR=hazard ratio; CI=confidence interval;
 PFS=progression-free survival; OS=overall survival; RR=relative risk

IN BRIEF

Already known

- The role of bevacizumab remains unclear in the neoadjuvant and adjuvant settings. In metastatic breast cancer, it provides some modest improvement in outcome, but FDA approval may still be withdrawn for this indication.

What these studies showed

- In the neoadjuvant setting for hormone receptor-positive (HR+) patients, bevacizumab improved pathologic complete response (pCR). In triple-negative breast cancer (TNBC) patients in the GeparQuinto study, bevacizumab a 9% advantage for pCR. In the RIBBON-2 trial of second-line chemotherapy with bevacizumab, there was a significant progression-free survival benefit and a trend for overall survival benefit for the TNBC patients.

Next steps

- Adjuvant trials are ongoing, including BETH, which is studying the effects of bevacizumab plus chemotherapy plus trastuzumab in human epidermal growth factor receptor 2-positive (HER2+) patients, and BEATRICE, which is evaluating the addition of bevacizumab to standard chemotherapy in patients with TNBC.

($p=0.0534$). Since this was only 159 (23%) of the total of 684 patients, the results are limited by the small sample size. However, unlike NSABP B-40, this study suggests benefit for B in HR- and not HR+ patients.

The role of B in metastatic, adjuvant and neoadjuvant breast cancer patients remains uncertain, the key issue being that we have not yet identified the group of patients most likely to benefit from antiangiogenesis therapy.

The US Food and Drug Administration (FDA) Oncologic Drugs Advisory Committee (ODAC) panel has recently voted again to remove B as an approved drug for MBC. This

is likely to result in FDA agreement, which in turn will lead insurance companies to remove B from their list of reimbursed treatments. Meanwhile, we await the results of adjuvant trials, such as BETH (BEvacizumab and Trastuzumab Adjuvant Therapy in HER2-positive Breast Cancer), in which B is added to CT and trastuzumab in human epidermal growth factor receptor 2-positive (HER2+) patients, and BEATRICE, in which B is added to standard CT in TNBC patients.

Disclosure:

The author reports no conflicts of interest relevant to this article.