New Presurgery Treatment Combination More Effective for Women With Triple-negative Breast Cancer

SAN ANTONIO — Adding the chemotherapy drug carboplatin and/or the antibody therapy bevacizumab to standard presurgery chemotherapy increased the number of women with triple-negative breast cancer who had no residual cancer detected at surgery, according to results of a randomized, phase II clinical trial presented here at the 2013 San Antonio Breast Cancer Symposium, held Dec. 10–14.

An increasing number of patients with triple-negative breast cancer are receiving chemotherapy before surgery, a treatment approach called neoadjuvant chemotherapy. In about one-third of these patients, no identifiable cancer cells are found in breast tissue and lymph nodes removed at surgery performed after the neoadjuvant chemotherapy. These patients are said to have had a pathologic complete response and have a much lower risk of cancer recurrence compared with patients whose cancers do not respond this well to the neoadjuvant chemotherapy.

“Our study was designed to find out if adding either carboplatin or bevacizumab to standard preoperative chemotherapy would increase the percentage of patients in whom cancer is eliminated before surgery,” said William M. Sikov, M.D., F.A.C.P., associate professor of medicine at the Warren Alpert Medical School of Brown University in Providence, R.I. “We are excited to report that adding either therapy significantly increased the percentage of patients in whom cancer was eliminated from the breast, and that adding both was even more effective.

“While our results show increases in pathologic complete response rates with both carboplatin and bevacizumab, we do not yet know how large an impact, if any, these differences will have on cancer recurrences or deaths. Although the study is not large enough to detect significant differences in these endpoints, we plan to follow patients for 10 years after their surgery to see if patient outcomes suggest long-term benefits from the investigational treatments.”

Sikov and colleagues treated 443 patients with operable, stage 2 or 3 triple-negative breast cancer in the randomized, phase II clinical trial. The study was conducted by the Cancer and Leukemia Group B, which is now part of the Alliance for Clinical Trials in Oncology, and is called CALGB/Alliance 40603. Patients were randomly assigned to standard neoadjuvant
chemotherapy, standard neoadjuvant chemotherapy plus carboplatin, standard neoadjuvant chemotherapy plus bevacizumab, or standard neoadjuvant chemotherapy plus carboplatin and bevacizumab. Surgery was performed from four to eight weeks after the completion of neoadjuvant treatment.

The researchers found that among the 108 patients who were randomly assigned to standard neoadjuvant chemotherapy alone, at surgery, cancer had been eliminated from the breast in 42 percent of these patients and from both the breast and lymph nodes in 39 percent. These proportions increased to 50 percent and 43 percent, respectively, for the 110 patients who were randomly assigned to standard neoadjuvant chemotherapy plus bevacizumab; 53 percent and 49 percent, respectively, for the 113 patients who were randomly assigned to standard neoadjuvant chemotherapy plus carboplatin; and 67 percent and 60 percent, respectively, for the 112 patients who were randomly assigned to standard neoadjuvant chemotherapy plus carboplatin and bevacizumab.

The increases in the pathologic complete response rates in the breast and in the breast and lymph nodes observed among patients randomly assigned to standard neoadjuvant chemotherapy plus carboplatin were statistically significant. Among patients randomly assigned to standard neoadjuvant chemotherapy plus bevacizumab, only the increase in the pathologic complete response rate in the breast met the study’s criteria for significance.

“Patients who were treated with carboplatin had more problems with low blood counts and were more likely to miss doses of chemotherapy or to have their chemotherapy treatments delayed or the doses of the chemotherapy drugs reduced compared with patients who did not receive carboplatin,” said Sikov. “In addition, about 10 percent of patients who were treated with bevacizumab developed high blood pressure and more of these patients had problems with blood clots, bleeding, and infections.”

This study was funded by the National Institutes of Health, Genentech, and the Breast Cancer Research Foundation. Sikov declares no conflicts of interest.

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The mission of the 2013 San Antonio Breast Cancer Symposium is to produce a unique and comprehensive scientific meeting that encompasses the full spectrum of breast cancer research, facilitating the rapid translation of new knowledge into better care for patients with breast cancer. The Cancer Therapy & Research Center (CTRC) at The University of Texas Health Science Center at San Antonio, the American Association for Cancer Research (AACR), and Baylor College of Medicine are joint sponsors of the San Antonio Breast Cancer Symposium. This collaboration utilizes the clinical strengths of the CTRC and Baylor and the AACR’s scientific prestige in basic, translational, and clinical cancer research to expedite the delivery of the latest scientific advances to the clinic. For more information about the symposium, please visit www.sabcs.org.

**Publication Number:** S5-01
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Title: Impact of the addition of carboplatin (Cb) and/or bevacizumab (B) to neoadjuvant weekly paclitaxel (P) followed by dose-dense AC on pathologic complete response (pCR) rates in triple-negative breast cancer (TNBC): CALGB 40603 (Alliance)

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Background: Anthracycline- and taxane-based neoadjuvant chemotherapy (NAC) results in a pCR in 30-35% of TNBC patients (pts), which is associated with improved recurrence-free and overall survival (RFS/OS). Thus, pCR rates may be useful in evaluating novel regimens in TNBC. In advanced TNBC, platinum analogues like Cb are active and addition of B to chemotherapy increases response rates and time to progression. CALGB 40603 is a 2x2 randomized phase II study designed to determine if the addition of either Cb or B to standard NAC significantly increases pCR rates in TNBC.

Methods: Pts had operable clinical stage II-III TNBC, defined as hormone receptors <10% and HER2 IHC 0-1+ or FISH <2.0 in IHC 2+. Pretreatment biopsies for correlative studies were required. Using a factorial design, pts received P 80 mg/m2 weekly x 12 followed by doxorubicin 60 mg/m2 and cyclophosphamide 600 mg/m2 q2wks x 4 (ddAC) with or without Cb AUC 6 q3wks x 4 during P and with or without B 10 mg/kg q2wks x 9. Surgery was performed 4-8 wks later. Post-op therapy was not specified. The primary endpoint is pCR (breast), defined as the absence of residual invasive disease (ypT0/is). Secondary endpoints include pCR (breast/axilla) (ypT0/isN0), toxicities, adverse events (AEs), RFS and OS. The primary analysis is factorial for main effects of Cb and B and their interaction; statistical power assumed no interaction. Analysis is by intent-to-treat; pts not taken to surgery are considered non-pCRs.

Results: 454 pts enrolled, median age 48, stage II 68%/stage III 32%. Of 354 pts with treatment data, 59 did not complete NAC, 30 withdrew due to AEs, more often with B vs. not (11.5% vs. 3.5%). B was discontinued in 23% of assigned pts vs. 6-13% for other agents. Grade 3-4 neutropenia (56% vs. 20%) and thrombocytopenia (22% vs. 4%) were more common with Cb vs. not, while grade 3 hypertension was more common with B vs. not (11% vs. <1%). Febrile neutropenia, usually during ddAC, was more common in pts who received both Cb and B (19% vs. others 7%). Unaudited pCR results for the first 369 pts, with effects reported as increments in
pCR (95% CI), assuming no interaction, are as follows: pCR (breast) pCR (breast/axilla) No Cb Cb B effect No Cb Cb B effect No B 30/89 33.7% 44/94 47.8% 14.9% (4.8-25.0%) 25/89 28.2% 39/92 42.4% 10.5% (0.5-20.5%) B 48/94 51.1% 57/94 60.6% p=0.004 40/94 42.6% 47/94 50.0% p=0.031 Cb effect 11.7% (1.6-21.8%) p=0.022 10.3% (0.3-20.3%) p=0.034 There is no evidence of an interaction between the effects of Cb and B (p=0.64 and 0.44, for breast and breast/axilla, respectively).

Conclusions: Preliminary results suggest that adding Cb or B to standard NAC significantly increases pCR rates in stage II-III TNBC. These increases are additive, with pCR (breast) in 60.6% and pCR (breast/axilla) in 50% of pts who received both. Complete and confirmed results will be reported, including pCR rates for basal-like tumors vs. not. Pts will be followed for RFS/OS to assess the impact of pCR on these endpoints. Conduct of the trial was supported by grants from the NIH (ACTNOW and CA31946/CA33601), Genentech and the BCRF. Clinical trial information: NCT00861705.