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To interview William Sikov, contact Julia Gunther at julia.gunther@aacr.org or 267-250-5441. For a photo of Sikov, click here.

Pathologic Complete Response to Presurgery Chemotherapy Improves Survival For Patients With Triple-negative Breast Cancer

SAN ANTONIO — Patients with stage 2 or stage 3 triple-negative breast cancer (TNBC) who had a pathologic complete response (pCR) after presurgery chemotherapy had increased event-free and overall survival compared with those who had more than minimal residual invasive disease at surgery following presurgery chemotherapy, according to results from the randomized phase II CALGB/Alliance 40603 clinical trial presented at the 2015 San Antonio Breast Cancer Symposium, held Dec. 8–12.

Many patients with TNBC, especially those with breast tumors larger than 2 cm or evidence that the cancer has spread to lymph nodes in the axilla (underarm), receive chemotherapy before surgery, a treatment approach called neoadjuvant chemotherapy. Previously published results from the CALGB/Alliance 40603 clinical trial showed that adding carboplatin or bevacizumab to standard neoadjuvant chemotherapy increased the number of patients with stage 2 or stage 3 TNBC who had a pCR, meaning that they had no residual invasive cancer detectable in breast tissue and lymph nodes removed during surgery, explained William Sikov, MD, associate director of clinical research in the Program in Women's Oncology at Women and Infants Hospital of Rhode Island, and associate professor of medicine and obstetrics and gynecology at the Warren Alpert Medical School of Brown University in Providence, Rhode Island.

"Our new data show that patients on any arm of this study who had a pCR had far superior outcomes compared with those who did not have a pCR," said Sikov. "After three years of follow-up, only 9 percent of patients who had a pCR had developed a distant recurrence and only 6 percent had died, compared to 27 percent and 25 percent, respectively, of patients who did not have a pCR.

"While this is important, our study was not sufficiently large to have the statistical power to determine whether adding carboplatin or bevacizumab to standard neoadjuvant chemotherapy improved event-free and overall survival," continued Sikov. "On the basis of these results, at the

present time, neither carboplatin nor bevacizumab should be considered part of the standard neoadjuvant chemotherapy regimen for stage 2 or 3 TNBC."

The CALGB/Alliance 40603 clinical trial enrolled 443 patients with operable stage 2 or 3 TNBC. 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.

Sikov and colleagues found that, at three years after starting the study treatment, patients who had no residual invasive cancer detected in either breast tissue or lymph nodes had a 70 percent reduced risk of disease recurrence and an 80 percent reduced risk of death compared with those who did not have a pCR in both the breast and lymph nodes. Including in the analysis both patients with minimal residual invasive disease in either the breast or lymph nodes, as defined by the Residual Cancer Burden method, and those who achieved a pCR in both the breast and lymph nodes, did not significantly alter outcomes: Risk of disease recurrence was reduced by 71 percent and risk of death was reduced by 79 percent.

No significant differences in event-free and overall survival were observed when the researchers evaluated whether adding carboplatin or bevacizumab to standard neoadjuvant chemotherapy affected these outcomes.

"In regards to the question as to whether there is a benefit to adding either carboplatin or bevacizumab to standard chemotherapy for stage 2 or 3 TNBC, it is important to highlight that this is not a negative study," said Sikov. "Rather, it is underpowered, meaning that it was not designed to be large enough to prove or disprove a benefit for either agent. Our results need to be considered alongside data from prior and ongoing studies with these agents in TNBC. Going forward, the question is whether we want to commit the additional patients and resources necessary to answer this question or instead focus our research efforts in TNBC on other opportunities to improve outcomes."

This study was supported by the National Cancer Institute's Cancer Therapy Evaluation Program, Genentech, and the Breast Cancer Research Foundation. Sikov declares no conflicts of interest.

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The mission of the 2015 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.

Abstract: S2-05

Title: Event-free and overall survival following neoadjuvant weekly paclitaxel and dose-dense AC +/- carboplatin and/or bevacizumab in triple-negative breast cancer: Outcomes from CALGB 40603 (Alliance)

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Background: CALGB (Alliance) 40603 measured the effects of adding carboplatin (Cb) and/or bevacizumab (Bev) to standard neoadjuvant chemotherapy (weekly paclitaxel x 12 then doxorubicin/cyclophosphamide every 2 weeks x 4) on pathologic complete response (pCR) rates in stage II-III triple-negative breast cancer (TNBC). As previously reported (Sikov et al, JCO 2015), pCR breast (ypT0/is) and pCR breast/axilla (pCR Br/Ax) (ypT0/isN0) rates increased from 46% to 60% and 41% to 54%, respectively, with Cb and from 48% to 59% and 44% to 52%, respectively, with Bev. Secondary endpoints included event-free survival (EFS) and overall survival (OS).

Methods: EFS is measured from study entry to ipsilateral invasive breast or locoregional recurrence, distant recurrence or death from any cause and OS from study entry to death from any cause in all patients (pts) who started study treatment. Pts without an event were censored as of their last clinical assessment. Hazard ratios (HR) were calculated for pts who achieved pCR vs. not and for pts assigned to receive drug (Cb or Bev) vs. not. All p-values are 2-sided.

Results: 443 pts started study treatment. Median follow-up was 39 months (range 28-66). 110 EFS events and 77 deaths have been reported. At 3 yrs, overall EFS was 74.1% and OS 83.2%. Pts who achieved pCR breast had 3-yr EFS of 84.8% vs. 61.8% for those who did not. Table 1 shows the association between pCR and pCR or minimal residual invasive disease (Residual Cancer Burden Class I (RCB I), Symmans et al, JCO 2007) and outcomes; p-values for all comparisons <0.0001:

Table 1

	pCR Breast	pCR Br/Ax	pCR Br/Ax or RCB I
Yes/No N (%)	231 (52%)/212 (48%)	207 (47%)/236 (53%)	266 (60%)/177 (40%)
EFS-HR	0.33 (0.22-0.50)	0.30 (0.19-0.46)	0.29 (0.20-0.43)
OS-HR	0.28 (0.17-0.46)	0.20 (0.11-0.36)	0.21 (0.13-0.34)

Pts assigned to Cb vs. not had 3-yr EFS 76.5% vs. 71.6% and OS 81.9% vs. 84.6%. Pts assigned to Bev vs. not had 3-yr EFS 75.5% vs. 72.9% and OS 85.5% vs. 80.9%. Table 2 shows HRs by assigned treatment:

Table 2

	Cb	Bev
N (Yes/No)	225/218	222/221
EFS - HR	0.84 (0.58-1.22) p=0.36	0.80 (0.55-1.17) p=0.25
OS - HR	1.15 (0.74-1.79) p=0.53	0.76 (0.49-1.19) p=0.23

Conclusions: Pts with TNBC who achieved pCR with study treatment had significantly better EFS and OS than pts who did not, consistent with findings from a published meta-analysis (Cortazar et al, Lancet 2014); the addition of RCB I did not weaken this association. Our study was not powered to assess the impact of Cb or Bev on these endpoints. While our findings are consistent with predictions from the meta-analysis as to the impact of raising the pCR rate on EFS (Berry-Hudis, JAMA Oncology 2015), the wide confidence intervals illustrate the challenge of conclusively demonstrating a correlation between pCR increment and EFS benefit, especially as the control pCR rate rises. While the addition of Bev has failed to improve long-term outcomes in TNBC in large randomized adjuvant trials, our results support ongoing and planned neoadjuvant and adjuvant studies designed to further assess the value of Cb-containing regimens in stage II-III TNBC.

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