## CALGB-40603:

# Randomized Phase II 2 x 2 Factorial Trial of the Addition of Carboplatin +/- Bevacizumab to Neoadjuvant Weekly Paclitaxel Followed by Dose-Dense AC in Hormone Receptor-Poor/HER2-Negative Resectable Breast Cancer

**ClinicalTrials.gov Identifier**: NCT00861705

## Study Background

**Trial Design:** This was a Phase II trial that used a randomized 2x2 factorial design. Protocol treatment included paclitaxel +/- carboplatin followed by dose dense AC +/- bevacizumab. Factor A was the addition or not of carboplatin to paclitaxel; the experimental regimen included carboplatin. Factor B was the addition or not of bevacizumab to paclitaxel (+/- carboplatin) followed by dose dense AC; the experimental regimen included bevacizumab (see schema below).
Patients were randomized with equal probability to one of the four possible treatment combinations:

- Arm 1 = Paclitaxel → ddAC
- Arm 2 = Paclitaxel + bevacizumab → ddAC + bevacizumab
- Arm 3 = Paclitaxel + carboplatin → ddAC
- Arm 4 = Paclitaxel + carboplatin + bevacizumab → ddAC + bevacizumab

Randomization was stratified by pretreatment clinical stage (II vs. III).

**Objectives:** Primary

- To determine whether adding bevacizumab to neoadjuvant weekly paclitaxel (+/- carboplatin) and subsequent dose-dense doxorubicin and cyclophosphamide (ddAC) significantly increases the rate of pathologic complete response (pCR) in the breast in patients with HR-poor/HER2 (-), resectable breast cancer.
- To determine whether adding carboplatin every 3 weeks to neoadjuvant weekly paclitaxel followed by ddAC (+/- bevacizumab) significantly raises the rate of pCR in the breast in patients with HR-poor/HER2(-), resectable breast cancer.
- To determine whether adding bevacizumab every 2 weeks to neoadjuvant weekly paclitaxel (+/- carboplatin) and subsequent ddAC significantly raises the rate of pCR in the breast in patients with basal-like breast cancers, as defined by gene expression array.
- To determine whether adding carboplatin every 3 weeks to neoadjuvant weekly paclitaxel followed by ddAC (+/- bevacizumab) significantly raises the rate of pCR in the breast in patients with basal-like breast cancers, as defined by gene expression array.

Secondary

- To determine the pCR rates in the breast and axilla, using AJCC TNM criteria (Version 6), to neoadjuvant weekly paclitaxel, with or without carboplatin, followed by ddAC, with or without bevacizumab, given concurrently with the weekly paclitaxel and ddAC, in (a) patients with HR-poor/HER2(-), resectable breast cancer and (b) the subset of patients with basal-like breast cancers, as defined by gene expression array.
- To assess whether there is an interaction between the addition of carboplatin and bevacizumab to neoadjuvant chemotherapy (NAC) with weekly paclitaxel followed by ddAC as regards the path pCR rates in (a) patients with HR-poor/HER2(-), resectable breast cancer and (b) the subset of patients with basal-like breast cancers, as defined by gene expression array.
- To assess the toxicity of the control regimen (weekly paclitaxel followed by ddAC) and any incremental toxicities associated with the addition of carboplatin and/or bevacizumab in this patient population, including the incidence of febrile neutropenia, grade > 3 thrombocytopenia, grade > 2 neurotoxicity, grade > 3 hypertension, and clinically significant bleeding or thrombotic (including cardiovascular and cerebrovascular) events.
- To determine the recurrence-free survival (RFS) measured from definitive surgery to first event, and time to first failure (TFF) measured from study entry to first event (see Section 16.2).
- To determine overall survival (OS), defined as time from registration to death from any cause.
- To assess the impact of NAC with weekly paclitaxel followed by ddAC, with or without carboplatin and/or bevacizumab, on axillary lymph node involvement at surgery, particularly in patients with clinically or histologically positive axillary lymph nodes prior to initiation of NAC.
- To assess the impact of the addition of bevacizumab to NAC on the incidence and severity of post-op complications, especially excessive bleeding, delayed wound healing, and thrombotic complications.
- To evaluate residual cancer burden (RCB) as a predictor of RFS, TFF and OS.
- To determine the correlation between clinical, radiographic, and pathologic response.
- Given the prevalence of the triple-negative phenotype in young African-American women, the study team, the CALGB Committee on Advocacy, Research Communications and Ethics (CARE) and the CARE Disparities Subcommittee will collaborate to develop a plan intended to enhance accrual of this patient subgroup.

**Stratification Factors:**

- Pretreatment clinical stage:
  1) stage II
  2) stage III

**Study History:**

5/15/2009 Activation with planned N=362.

11/15/11 Accrual suspended. This study was powered to address the correlative questions regarding basal-like tumors. Because the incidence of tumors with poor quality was higher than anticipated, an amendment was prepared to increase target accrual.

02/15/12 Accrual reactivated. The revised target of total patients was increased from 362 to 445.

08/31/12: Trial permanently closed to accrual having reached its target.

# Publication Information

**Analysis Type:** Primary Endpoint Analysis

**PubMed ID:** 25092775

**Citation:** Sikov WM, Berry DA, Perou CM, Singh B, Cirrincione CT, Tolaney SM, Kuzma CS, Pluard TJ, Somlo G, Port ER, Golshan M, Bellon JR, Collyar D, Hahn OM, Carey LA, Hudis CA, Winer EP. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). J Clin Oncol. 2015 Jan 1;33(1):13-21. doi: 10.1200/JCO.2014.57.0572. Epub 2014 Aug 4.

**Associated Datasets:** NCT00861705-D1-Dataset.csv (aeclean)
NCT00861705-D2-Dataset.csv (treated2)

## Dataset Information

**Dataset Name:** NCT00861705-D1-Dataset.csv (aeclean)

**Description:** The NCT00861705-D1-Dataset.csv (aeclean) dataset is one of 2 datasets associated with PubMed ID 25092775. This dataset contains adverse event data for each treated patient (N=443).

Data can be used to approximate published study findings, but exact reproduction of previous manuscripts may not be possible in some cases (e.g., when data must be modified for de-identification purposes or have undergone further data cleaning).

## NCT00861705-D1 (aeclean) Data Dictionary

| Variable Description | Variable Name | Code | Notes |
|---|---|---|---|
| Was AER submitted? | aer_submitted | 1 = Yes<br>2 = No<br>99 = Missing | |
| Version of CTC used | ctc_version | 2,<br>3,<br>99 = missing | |
| AE category | eventcat | | |
| AE name | eventname | | |
| Grade of AE reported | grade_id | -1 = Unknown event<br>0 = None<br>1 = Mild<br>2 = Moderate<br>3 = Severe<br>4 = Life-threatening<br>5 = Fatal<br>99 = Not Evaluated | |
| AE MEDDRA code | meddra_code | 99 = Missing | |
| Version of MEDDRA used | meddra_version | 5,<br>6,<br>99 = Missing | |
| Treatment attribution | relation_id | -1 = Not Applicable<br>0 = Unknown<br>1 = Unrelated<br>2 = Unlikely<br>3 = Possible<br>4 = Probable<br>5 = Definite | |

| | | | |
|---|---|---|---|
| Option selected | select_ae | 99 = Missing | |
| Study number | study | 40603 | |
| De-identified patient identifier | mask_id | | De-identified patient identifier |
| Number of days from registration to end of AE period | aeend | 9999=Missing | |
| Number of days from registration to start of AE period | aestart | 9999=Missing | |