**BACKGROUND**

This study tested the effectiveness of 4 cycles of cyclosphosphamide and doxorubicin (CA) against 4 cycles of paclitaxel as adjuvant therapy for breast cancer in women with 0-3 positive axillary lymph nodes.

1. **OBJECTIVES**

**Primary**

1. To determine the equivalence of paclitaxel given every two weeks with CA given every two weeks as adjuvant therapy for women with 0-3 positive axillary lymph nodes, for disease-free survival.

**Secondary**

1. To determine the equivalence of paclitaxel given every two weeks with CA given every two weeks, and the potential superiority of longer vs. shorter therapy, in relation to overall survival, local control (regardless of metastatic status) and time to distant metastases (regardless of local recurrence status).
2. To compare toxicities of short and long course CA and paclitaxel as adjuvant therapy for women with 0-3 positive axillary lymph node breast cancer.
3. To determine the effect of long and short course CA and paclitaxel on the induction of menopause for pre-menopausal patients.
4. **STUDY DESIGN**

**Design**

The design is a 2x2 factorial. The factors are chemotherapy agent and treatment length. Cyclophosphamide plus doxorubicin (CA) is the standard agent; the experimental agent is paclitaxel (T). The standard length is shorter (4 cycles) treatment duration; the experimental length is longer (6 cycles) duration. The trial is designed to show: (1) equivalence of the experimental agent T with the standard agent combination CA; and (2) superiority of longer versus shorter treatment duration. Patients will be randomized with equal probability to one of the four possible treatment arms. Prior to randomization, patients will be stratified by menopausal status (pre vs. post), ER/PgR status (either positive or unknown vs both negative) and HER-2 status (positive, negative or unknown).

**End Points**

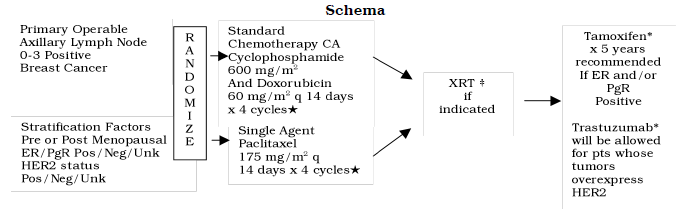
The primary end point is duration of disease-free survival (DFS), which will be measured from study entry until first relapse, either local or distant, or death due to any cause, whichever occurs first. Surviving patients who are disease-free will be censored at the date last known to be free from disease. Secondary end points are overall survival (OS), local control, time to distant metastases and toxicity. OS will be measured from study entry until death due to any cause. Survivors will be censored at the date of last follow-up. Local control and distant metastasis will be calculated as the cumulative incidence of first local relapse and first distant metastasis, respectively.

**Power Considerations**

The primary study end point upon which power is based is DFS. Power calculations were designed to detect effects in the marginal distributions of the two study factors, agent and length, and assume no interaction between the two factors. Calculations also assume exponential DFS and a total of 4556 treated patients accrued over 29 months and followed for four years after accrual termination for a total study time of 6.4 years.

Regarding the first factor, chemotherapeutic agent, we assume that the 5-year DFS of CA therapy is 88%. Regarding the other factor, length, we assume a 5-year DFS of 84.7% for the shorter duration. These assumptions are based upon results of SWOG 8897, in which an 18-week CA regiment was used to treat a similar but not identical patient population.

1. **TREATMENT SCHEMA**



★ Administration of filgrastim, sargramostim or pegfilgrastim is recommended.

\* Aromatase inhibitors may be substituted for tamoxifen in postmenopausal women. The use of tamoxifen or an aromatase inhibitor should be documented on the CALGB 40101 Follow-Up Form C-929. Trastuzumab will be allowed for patients whose tumors overexpress HER2 based on IHC 3+ staining, or FISH amplification receive trastuzumab.

‡ Patients who have undergone lumpectomy must receive XRT according to local institutional standards. Patients who have undergone mastectomy may receive chest wall and nodal XRT.

Patients should be followed for the occurrence of both first local and distant disease progression. After the occurrence of local progression, follow the patient for distant progression, secondary malignancy and survival with appropriate documentation. In the event of distant progression first, continue to follow the patient for local recurrence, secondary malignancy and survival. After both local and distant progression, follow the patient for secondary malignancy and survival. Follow all patients registered to this study, including those who do not receive any protocol treatment, for first local and first distant progression and survival for 15 years from study entry or until death, whichever occurs first.

1. **STUDY HISTORY**

* 5/15/02: Protocol Activation
* 7/15/10: Study closure due to slow accrual

1. **ACCRUAL**

|  |  |
| --- | --- |
| Date of first accrual | June 27, 2002 |
| Final Accrual | 3871 |
| Closed | July 30, 2010 |
| Patients included in manuscript | 3871 |
|  |  |

1. **REFERENCES**

Shulman LN, Berry DA, Cirrincione CT, Becker HP, Perez EA, O'Regan R, Martino

S, Shapiro CL, Schneider CJ, Kimmick G, Burstein HJ, Norton L, Muss H, Hudis CA,

Winer EP. Comparison of doxorubicin and cyclophosphamide versus single-agent

paclitaxel as adjuvant therapy for breast cancer in women with 0 to 3 positive

axillary nodes: CALGB 40101 (Alliance). J Clin Oncol. 2014 Aug 1;32(22):2311-7.

1. **DATA FILES**

**All\_finalb**

| **Variable description** | **Variable name** | **Codes** | **Notes** |
| --- | --- | --- | --- |
| Identifier | Mask\_id |  | CALGB patient ID |
| Status ID | Sstat | 7=Alive  8=Dead  9=Lost  65=Withdrawn Consent to follow for survival |  |
| Ethnicity | Ethnic\_ID | 1= Hispanic or Latino  2=Non-Hispanic  9=Unknown |  |
| Status ID | scase | 10=On Study  11=Off Study  13=Lost  66=Withdrawn consent to follow for clinical status |  |
| Group | GROUP\_ID | 1=Alliance for Clinical Trials in Oncology  37=Cancer Trials Support Unit |  |
| Race | RACE\_ID | 1=White  3=Black or African American  4=Asian  5= Native Hawaiian or Pacific Islander or American Indian or Alaska Native  99=Unknown |  |
| Survival status | Survstat | 0=Alive  1=Dead |  |
| Eligibility | elig | 1=ineligible  2=eligible  -1=pending |  |
| Menopause status | Stra1 | 1=pre-menopause  2=post-menopause |  |
| Receptor status | Stra2 | 1=recep+,unk  2=recep- |  |
| Her2-neu status | Stra3 | 1=positive  2=negative  3=unknown |  |
| Treatment assigned | indrx | 1=CA-4  2=CA-6  3=T-4  4=T-6 |  |
| Tumor laterality | OH002 | 1=left  2=right  3=bilateral |  |
| Receptor Status ER | OH003 | 1=Negative  2=Positive |  |
| Receptor Status PgR | OH004 | 1=Negative  2=Positive |  |
| Histologic grade | OH005 | 1=Low  2=Intermediate  3=High |  |
| Prior hormonal therapy | OH011 | 1=no  2=yes |  |
| HT Tamoxifen | OH012 | 1=no  2=yes | HT = prior hormonal therapy |
| HT Raloxifen | OH013 | 1=no  2=yes | HT = prior hormonal therapy |
| HT Other | OH014 | 1=no  2=yes | HT = prior hormonal therapy |
| Prior adjuvant chemo | OH016 | 1=no  2=yes |  |
| Type biopsy | OH027 | 1=Core needle  2=Incisional  3=Excisional |  |
| Most extensive primary surgery | OH028 | 1=Partial mastectomy/lumpectomy/  2=Mastectomy, NOS |  |
| Sentinel node biopsy | OH032 | 1=no  2=yes |  |
| Sentinel node biopsy results | OH036 | 1=negative  2=positive |  |
| Axillary dissection performed | OH037 | 1=no  2=yes |  |
| Number of positive axillary nodes | Num\_pos\_nodes |  |  |
| Tumor Size | tsize | 1=less than 2cm  2=between 2 and 5cm  3=greater than 5cm | Maximum diameter of the invasive component; if multiple lesions, use longest lesion. Measured in cm |
| Survival Months | survmos |  |  |
| Disease Free Survival Months | dfsmos |  |  |
| Cause of death | cod | 0=Alive  1=Due to protocol treatment/Other Cause/Unknown  2=Due to this disease |  |
| Age category | agecat | 1=20<=ageatent<30  2=30<=ageatent<40  3=40<=ageatent<50  4=50<=ageatent<60  5=60<=ageatent<70  6=70<=ageatent | Ageatent=age at end of active treatment |
| Amendment | Preamend | 1=”preamend”  0=”postamend” | Referring to amendment where 6 cycle arms were closed. |
| Event | event | 1=local only  2=dist only  3=loc+dist conc  4=dth, wo rel |  |
| Disease Free Survival Stat | Dfsstat | 0=no event  1=event |  |
| Agent | Agent | 0=CA  1=T |  |
| Length of treatment | Length | 0=4 cycles  1=6 cycles |  |

**Aeclean\_finalb**

| **Variable description** | **Variable name** | **Codes** | **Notes** |
| --- | --- | --- | --- |
| Identifier | Mask\_id |  | CALGB patient ID |
| Adeers report submitted | AER\_SUBMITTED | 1=No  2=Yes |  |
| Meddra code | MEDDRA\_CODE |  |  |
| Meddra dictionary version | MEDDRA\_VERSION |  |  |
| AE grade | GRADE\_ID |  | Grades 3 or 4 adverse events included |
| Event category | Eventcat |  |  |
| Event description | eventname |  |  |
| AE related | Relation\_id | 1=Unrelated  2=Unlikely  3=Possible  4=Probable  5=Definitely |  |