

ECOG/S0221 – Phase III Trial of Continuous Schedule AC + G vs. Q 2 week Schedule AC, Followed by Paclitaxel Given Earlier Every 2 weeks or weekly for 12 weeks as Post-Operative Adjuvant Therapy in Node-Positive or High-Risk Node Negative Breast Cancer.

Primary Objective: To compare the disease-free survival with node-positive or high-risk node-negative breast cancer treated with the combination of Doxorubicin and cyclophosphamide given every 2 weeks with pegfilgrastim support with that of patients treated with weekly Doxorubicin and daily oral cyclophosphamide with filgrastim support, with both treatments to be followed by paclitaxel given according to one of two schedules.

Eligibility Criteria:

- Pts. must be women or men with a histologically confirmed diagnosis of operable Stage I, II or III invasive breast carcinoma with known estrogen and progesterone receptor status.
- Pts. with bilateral synchronous breast cancer diagnosed within 1 moth of each other are eligible if the higher TNM stage primary tumor meets the eligibility criteria for this trial.
- Pts. must be high risk by meeting at least one of the following criteria:
 - a.) Tumor ≥ 2 cm in greatest diameter. Size must be determined by pathology specimen. Size is equal to the maximum diameter of entire lesion, including both invasive and Intraductal components. In the case of multi-focal tumors, the largest lesion with an invasive component must be used to determine size. If the tumor is resected in pieces, the pathologist must re-orient the tumor fragments to determine maximum size. Pts. whose only evidence of nodal involvement is on the basis of immunohistologic staining (i.e., nodal involvements is not obvious on routine exam with H and E staining) will be considered to be node-negative, and must have primary tumors ≥ 2 cm in size. *High risk node negative patients must have primary tumors ≥ 2 cm.* Pts. registered to NCI-funded national sentinel node studies (ACOSOG Z0010, Z0011, and NSABP B-32) are eligible. Pts. who hare node negative on the basis of a sentinel node procedure may be entered even if fewer than 6 axillary nodes were removed; otherwise, at least 6 axillary or intramammary nodes must be negative for a patient to be considered node negative.
 - b.) One or more axillary or intramammary nodes are involved by metastatic breast cancer. If one or more nodes is involved, a minimum of 6 axillary or intramammary nodes must have been examined histologically. In order to be considered “node positive”, malignant involvement must be detectable using routine pathologic examination with Hematoxylin and eosin staining.
- *Pts. with HER-2 positive tumors (3+ by immunohistochemical staining or amplified by fluorescence in-situ hybridization) are eligible. Such pts. must be treated in compliance with Section 7.7. The use of Trastuzumab should be documented in the treatment forms.*
- Pts. must have had either a modified radical mastectomy or local excision of all tumors plus an axillary lymph node dissection or sentinel node resection prior to registration. Final resection margins for the primary tumor must be histologically negative for invasive cancer and ductal carcinoma in situ. Pts. with resection margins positive for lobular carcinoma in-situ will be eligible.
- Pts. must be registered within 84 days from the final surgical procedure required to adequately treat the primary tumor and/or axilla.
- Pts. must ***not*** have received prior cytotoxic chemotherapy for this breast cancer. Pts. must ***not*** have had prior chemotherapy with an anthracycline, anthracenedione, or a Taxane for any condition.
- Pts. must ***not*** have received prior radiation therapy for the current malignancy. Pts. who have received prior radiation therapy for ductal carcinoma in –situ are eligible provided that radiation therapy was completed at least 2 weeks prior to registration.
- Pts. with the clinical diagnosis of congestive heart failure or angina pectoris are **NOT** eligible. Pts. with a history of hypertension or age ≥ 60 years must have a MUGA or echocardiogram scan

performed within 42 days prior to registration and LVEF% must be greater than the institutional lower limit of normal.

- Pts. must have normal lab values.
- Sexually active pre-menopausal female pts. must have a negative pregnancy test determined within 28 days of study entry due to the possibility of fetal harm or of harm to nursing infants from this treatment regimen. All pts. of reproductive potential must agree to use an effective contraceptive method during the entire period of drug treatment.
- No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, *any* in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease-free for 5 years.
- Pts. must be of age 18 or greater. Performance status 0 – 2 by Zubrod criteria. Pts. known to be HIV positive are not eligible due to the fact that the compromised immune system of these patients and the possibility of early death may compromise study objectives.

TREATMENT SCHEMA:

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Arm 1	Adriamycin IV bolus on Day 1 Cyclophosphamide rapid IV Day 1 Pegfilgrastim SubQ on Day 2 AC & Peg given every 14 days x 6	14 days following last cycle of AC, start: Paclitaxel IV on Day 1 q 2 weeks x 6 & Pegfilgrastim on day q 2 q wks x 6	For ER+ or PR+ Pre-menopausal women received tamoxifen or ovarian ablation. Post-menopausal women can receive tamoxifen or aromatase inhibitor.
Arm 2	Adriamycin IV bolus weekly x 15 Cyclophosphamide PO daily x 15 wks Filgrastim SubQ Days 2-7 weekly x 15 wks Bactrim DS PO Days 4 & 5 wk x 15 wks	14 days following last cycle of AC, start: Paclitaxel IV on Day 1 q 2 weeks x 6 and Pegfilgrastim on Day 2 q 2 wks x 6	
Arm 3	Adriamycin IV bolus on Day 1 Cyclophosphamide rapid IV Day 1 Pegfilgrastim SubQ on Day 2 AC & Peg given every 14 days x 6	14 days following last cycle of AC, start: Paclitaxel IV on Day 1 q 2	
Arm 4	Adriamycin IV bolus weekly x 15 Cyclophosphamide PO daily x 15 weeks Filgrastim SubQ Days 2-7 weekly x 15 wks Bactrim DS PO Days 4 & 5 wk x 15 wks	14 days following last dose of oral cyclophosphamide, start: Paclitaxel IV q week x 12	