

**PFIZER INC.**

These results are supplied for informational purposes only.  
Prescribing decisions should be made based on the approved package insert.  
For publications based on this study, see associated bibliography.

**PROPRIETARY DRUG NAME/INN: Ellence<sup>®</sup> / epirubicin**

**THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:** See UPSI.

**PROTOCOL NO.:** Protocol 378-ONC-0030-184

**PROTOCOL TITLE:** Phase III, Randomized Study of Epirubicin/Cyclophosphamide Followed by Taxane (Sequential Chemotherapy) versus Epirubicin/Taxane (Concurrent Chemotherapy) as Adjuvant Treatment for Operable, Node-Positive Breast Cancer

**Study Center(s):** 53 centers in the United States

**Study Initiation and Completion Dates:** 21 November 2000 to 08 March 2006

**Phase of Development:** Phase 3

**Study Objectives:**

*Primary objective:* To evaluate whether concurrent epirubicin and taxane (ET) improves disease-free survival (DFS) at three years compared with the sequential administration of epirubicin and cyclophosphamide (EC) followed by a taxane (EC→T).

*Secondary objectives:* (1) To compare overall survival (OS) between the two treatment arms at three years, and (2) to assess safety in both treatment arms at three years.

**METHODS**

**Study Design:**

**Study Design:** This was a randomized, open-label, multi-center, two-arm trial designed to compare DFS of ET therapy with EC→T therapy in female subjects as adjuvant therapy for operable, node-positive breast cancer. At the time of enrollment of his/her first subject, each physician was to have selected the taxane (paclitaxel or docetaxel) to be used in all subjects enrolled by that physician.

Subjects were assigned to one of the following treatment arms: Arm A, EC therapy for four cycles followed by taxane therapy for four cycles (a total of eight cycles); or Arm B, ET therapy for eight cycles. Subjects were stratified according to nodal status (one to three, four to ten, more than ten positive nodes, or positive sentinel node [if the number of positive

axillary nodes was unknown]), menopausal status as estimated by age (<50, ≥ 50 years), estrogen receptor (ER) and/or progesterone receptor (PgR) status (positive or other), and human epidermal growth factor receptor-2 (Her2) status (overexpression or other). Subjects were to receive eight 21-day cycles of chemotherapy (study medication was administered on Day 1 of each cycle). At the conclusion of chemotherapy (Day 21 of Cycle 8), subjects with ER- or PgR-positive tumors were to initiate tamoxifen or equivalent hormonal therapy (ie, aromatase inhibitors in post-menopausal women) and continue this therapy for five years, as per physician discretion. After the last cycle (Day 21 of Cycle 8), regional radiotherapy was to be administered as medically indicated. Subjects scheduled to receive radiotherapy and/or tamoxifen (or equivalent hormonal therapy) were to start the treatments within five weeks after the completion of chemotherapy. The total follow-up for the study was five years.

In light of the known cardiotoxicity of anthracycline compounds, monitoring of cardiac function using left ventricular ejection fraction (LVEF) was to be evaluated after four cycles of EC and prior to beginning taxane treatment for subjects randomized to the EC→T treatment arm, and at the end of treatment in all subjects in both treatment arms.

Pre-treatment evaluations were performed not more than 14 days prior to first treatment on study. On-study treatment evaluations were performed during each cycle (Days 1, 8 and 14) and at the end of chemotherapy (Day 21 of Cycle 8). Off-study treatment (follow-up) evaluations were performed every three months for the first year (Year 1) following treatment (starting the day after Day 21 of Cycle 8) and every six months for the next two years (Years 2 and 3) until disease recurrence. Subjects were then to be followed up every six months for a further two years (Years 4 and 5) for drug-related serious adverse events (SAEs), disease status and survival.

#### **Number of Patients (planned and analyzed):**

**Planned:** 600 subjects (300 subjects in each treatment arm)<sup>a</sup>

**Analyzed:** 603 subjects (305 subjects in Arm A [EC→T], of whom 84 subjects received paclitaxel and 221 subjects received docetaxel; 298 in Arm B [ET], of whom 67 received paclitaxel and 231 subjects received docetaxel)

**Diagnosis and Main Criteria for Inclusion:** Female non-pregnant subjects using adequate contraception were eligible if they were at least 18 years of age and had histologically confirmed adenocarcinoma of the breast (T<sub>1-3</sub>, N<sub>1</sub>, M<sub>0</sub>), in accordance with the American Joint Committee on Cancer Cancer Staging Manual (5th edition), that had been completely excised (total mastectomy or breast conserving surgery). In addition, eligible subjects were to: be considered suitable for adjuvant, anthracycline-containing chemotherapy; have had positive lymph node(s), as determined by positive hematoxylin and eosin staining of either axillary-node dissection or sentinel-node finding; have an Eastern Cooperative Oncology Group (ECOG) performance score (PS) of 0 or 1; be no more than 12 weeks from mastectomy (or 12 weeks from axillary dissection if the most extensive breast surgery was a breast-sparing procedure); have adequate hematologic status (absolute neutrophil count

---

<sup>a</sup> Sample size estimation required 300 subjects per arm. The primary analysis was to be performed after 90 events had occurred in both treatment arms overall.

[ANC]  $\geq$  1500/ $\mu$ L and platelet count  $\geq$  100,000/ $\mu$ L); have adequate hepatic function (total bilirubin  $\leq$  1.5 mg/dL, aspartate aminotransferase  $\leq$  2 times the institutions' upper limit of normal); and were to have a LVEF (by multi-gated radionuclide angiography scan or by echocardiography; same method was to have been used consistently throughout the whole study) above institutional lower limit of normal. Subjects could have received hormonal therapy for the purpose of chemoprevention but must have been willing to discontinue such treatment prior to enrollment and while participating in the study. Subjects were not to have received any prior chemotherapy, immunotherapy or radiotherapy for breast cancer. Subjects must also have been willing to discontinue hormonal therapy, eg, birth control pills, ovarian hormonal replacement therapy, etc, prior to enrollment.

**Study Treatment:** Subjects were assigned to one of the following treatment arms for eight 21-day cycles:

- **Arm A:** Epirubicin intravenously (IV) at a dose of 90 mg/m<sup>2</sup> over a period of 3 to 20 minutes on Day 1 of Cycles 1 to 4.  
Cyclophosphamide IV at a dose of 600 mg/m<sup>2</sup> on Day 1 of Cycles 1 to 4.  
Paclitaxel IV at a dose of 175 mg/m<sup>2</sup> or docetaxel IV at a dose of 75 mg/m<sup>2</sup> on Day 1 of Cycles 5 to 8.
- **Arm B:** Epirubicin IV at a dose of 75 mg/m<sup>2</sup> over a period of 3 to 20 minutes on Day 1 of Cycles 1 to 8.  
Paclitaxel IV at a dose of 175 mg/m<sup>2</sup> or docetaxel IV at a dose of 75 mg/m<sup>2</sup> on Day 1 of Cycles 1 to 8.

The doses of chemotherapy were based on body surface area. Dose escalations were not permitted in either study arm.

Prior to taxane treatment, subjects were to be pre-medicated according to the Prescriber Information for Taxol™ (paclitaxel) or Taxotere™ (docetaxel) to prevent hypersensitivity reactions and fluid retention, with the exception that ranitidine was to be used rather than cimetidine, due to known pharmacokinetic interactions of cimetidine with epirubicin. Study treatments were provided from commercially available stock.

### **Efficacy Evaluations:**

Subjects on both treatment arms were followed at specified intervals and evaluated for evidence of disease recurrence. If there was any suspicion of disease recurrence based on the required evaluations, further tests were to be performed as medically indicated, including X-rays, computerized tomography (CT) scans, magnetic resonance imaging (MRI) bone scans, etc. At the time of each re-evaluation, subjects were classified in the following manner:

- No evidence of disease.
- Breast cancer recurrence.
  - Local/regional breast cancer recurrence was defined as the development of tumor (except lobular carcinoma in situ [LCIS]) in the ipsilateral breast (after

lumpectomy); in the soft tissue/chest wall and/or skin of the ipsilateral chest wall; or in the ipsilateral internal mammary, supraclavicular, infraclavicular, or axillary nodes or soft tissue of ipsilateral axilla. Suspected tumor recurrence in the ipsilateral breast, chest wall structures, supraclavicular, or lower (level I ± II) axillary nodal areas were confirmed by biopsy or cytology. Histologic or cytologic confirmation of tumor was recommended for internal mammary or infraclavicular/high axillary nodal recurrence.

- A distant recurrence was defined as development of tumor in areas other than the local/regional area that was documented by a positive cytology aspirate, biopsy, or imaging studies.
- New primary.
  - A new primary was defined as the development of contralateral breast cancer or a second cancer, other than squamous or basal cell carcinoma of the skin, carcinoma in situ of the cervix, or LCIS of the breast that was histologically confirmed.

*Primary efficacy endpoint:* Disease-free survival (DFS) time was defined as the time from the first dose of study medication to the earliest recorded documentation of recurrent disease, new primary, or death in the absence of previous documentation of disease recurrence. In the absence of confirmation of recurrent disease, new primary, or death, DFS time was censored at the last date of follow-up at which time a subject was known to be alive and to have had no recurrence.

*Secondary efficacy endpoint:* Overall survival (OS) time was defined as the time from the first dose of study medication to date of death. In the absence of confirmation of death, OS time was censored at the last date of follow-up at which time a subject was known to be alive.

**Safety Evaluations:** Safety evaluations included adverse events (AEs); serious AEs (SAEs); hematologic and blood chemistry toxicities with CTC grades; LVEF and electrocardiogram (ECG); discontinuation of treatment early and reasons for discontinuation; and ECOG PS (assessed on Day 1 of each cycle). Investigators were to evaluate the severity of adverse events in accordance with the National Cancer Institute Common Toxicity Criteria (NCI CTC) (Version 2.0).

**Statistical Methods:** The modified intent-to-treat (mITT) population was defined as all subjects who received at least one dose of study medication, with study medication assignment designated according to initial randomization, regardless of whether subjects received a different medication from that to which they were randomized. The as-treated (AT) population was defined as all subjects who received at least one dose of study medication, with treatment assignments designated according to actual study medication received. Analysis by taxane therapy was also performed on both the mITT and AT populations.

*Efficacy:* The primary analysis on DFS was performed on the mITT subjects. The secondary efficacy analyses were performed on the mITT and the AT populations. The difference in

Kaplan-Meier survival curves for both efficacy endpoints was assessed using the log-rank test; the hazard ratio (HR) and 95% confidence interval (CI) for the HR were computed, based on Cox proportional hazards models with treatment as the only covariate.

Cox regression models were also used to explore the influence of stratification and prognostic factors on both DFS and OS. Both the ‘as randomized’ and ‘corrected’ nodal status values were used in the analyses. The ‘as randomized’ nodal status was defined as the nodal status as per stratification at the time of randomization. ‘Corrected’ nodal status was defined as the nodal status recorded on the baseline case report form. Treatment-by-stratification variable interactions were included in the Cox regression models. All covariates based on the stratification variables were included in the models. Hazard ratios and 95% CIs for the HRs were computed. Efficacy analyses were performed on both the mITT and AT populations.

All statistical tests of significance were performed as two-sided test at the alpha = 5% level of significance. No adjustments were made for multiple comparisons.

Post hoc exploratory subgroup analyses of DFS and OS were performed to compare treatment effects in subsets of the mITT population. DFS and OS were compared (1) between paclitaxel and docetaxel, within each treatment arm (EC→T and ET), and (2) between treatment arms (EC→T versus ET) among subjects treated with docetaxel and among subjects treated with paclitaxel.

*Safety:* Analyses were conducted on the AT population. For all safety parameters, data were analyzed and presented using descriptive statistics. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 8.1); the number and percentage of subjects with TEAEs were tabulated by preferred term and system organ class (SOC). TEAEs were summarized by maximum severity, worst CTC grade, and reported relationship to study medication. All SAEs were reportable from the time the subject provided informed consent (ie, prior to undergoing any study-related procedure and receiving investigational product) until 30 days after the last administration of investigational product.

LVEF evaluations were performed after four cycles of EC treatment in the EC→T arm. LVEF evaluations were also performed at the end of treatment (ie, 8 cycles) for all subjects in both treatment arms. Subjects with a post-study LVEF value by multi-gated radionuclide angiography (MUGA) scan or echocardiogram that was <45% or had an absolute decrease >15% from baseline had to have a post-study follow-up LVEF evaluation repeated around three months after the post-treatment LVEF evaluation. If the LVEF value at the post-study follow-up evaluation had not recovered either to or above 45% or the institutional lower limit of normal (whichever was higher), additional LVEF evaluations were recommended in six-month intervals. The LVEF findings were summarized by treatment group and by taxane treatment.

The shift from baseline to end of treatment in ECOG PS and the shift from baseline to post-treatment follow-up in ECG status were both summarized by treatment group and by taxane regimen.

## RESULTS

**Subject Disposition and Demography:** Table S1 below presents subject disposition and subjects analyzed.

**Table S1. Subject Disposition and Subjects Analyzed**

Number of Subjects	EC→T (Sequential chemotherapy)	ET (Concurrent chemotherapy)
Planned	300	300
Assigned to Treatment	309	308
Treated (Paclitaxel:Docetaxel)	305 (84:221)	298 (67:231)
Completed	266	255
Discontinued from treatment	39	43
Disease recurrence	2	3
New primary	0	0
Treatment delays >3 weeks due to toxicities	1	1
Adverse events or toxicities	22	17
Intercurrent non-cancer related illness	1	0
Protocol violation	4	1
Investigator decision (other than progressive disease)	1	10
Subject's withdrawal of consent	8	5
Death	0	3
Other	0	3
Analyzed for Efficacy	305	298
Analyzed for Safety <sup>a</sup>	304	299
Adverse events	304	299
Laboratory data	304	298

<sup>a</sup> One subject randomized to sequential chemotherapy actually received concurrent chemotherapy.

C: Cyclophosphamide; E: Epirubicin; T: Taxane.

The median follow-up time for both treatment arms was approximately 31 months. The percentage of subjects completing 3 years of follow-up was 32.5% for the ET treatment arm and 29.8% for the EC→T treatment arm.

Demography and baseline ECOG performance status are summarized in Table S2, below.

**Table S2. Demography and Baseline ECOG Performance Status - Modified Intent-to-Treat Population**

	EC→T (Sequential Chemotherapy) (N=305)	ET (Concurrent Chemotherapy) (N=298)
<b>Race, n (%)</b>		
White	211 (69.2)	210 (70.5)
Black	62 (20.3)	64 (21.5)
Asian or Pacific Islander	6 (2.0)	5 (1.7)
Hispanic	24 (7.9)	19 (6.4)
Other	2 (0.7)	0
<b>Gender, n (%)</b>		
Female	305 (100.0)	298 (100.0)
<b>Age (years)</b>		
Mean (SE)	52.4 (0.6)	52.3 (0.6)
Median (Min, Max)	53.0 (29.0, 79.0)	52.0 (30.0, 81.0)
<b>ECOG PS, n (%)</b>		
0	261 (85.6)	265 (88.9)
1	44 (14.4)	33 (11.1)

C: Cyclophosphamide; E: Epirubicin; ECOG PS: Eastern Cooperative Oncology Group Performance Status; SE: Standard error; T: Taxane.

**Efficacy Results:**

*Primary Efficacy Results.* There was no significant difference in disease-free survival (DFS) between the two treatment arms (ET versus EC→T) in the mITT population (HR=0.983; 95% CI=[0.68, 1.42]; p=0.9295) (Table S3).

**Table S3. Comparisons of Disease-Free Survival Time - Modified Intent-to-Treat Population**

Treatment	N	Subjects with events <sup>a</sup>		Subjects censored <sup>b</sup>		Disease-Free Survival Time (Months) <sup>c</sup>		Hazard Ratio (95% CI) <sup>d</sup>	p-value <sup>e</sup>
		n	(%)	n	(%)	Median <sup>f</sup>	Min, Max		
EC→T (Sequential)	305	57	(18.7)	248	(81.3)	NC	0.69, 59.56+		
ET (Concurrent)	298	56	(18.8)	242	(81.2)	NC	0.03, 59.96+	0.983 (0.68, 1.42)	0.9295

<sup>a</sup> Recurrent disease, new primary or death in the absence of previous documentation of disease recurrence.

<sup>b</sup> Number of subjects with no event.

<sup>c</sup> In the absence of confirmation of event, censored to the last date of follow-up.

<sup>d</sup> Hazard ratio (ET/EC→T) and 95% CI from the Cox Proportional Hazards Model with treatment as the covariate.

<sup>e</sup> Log-rank test for comparing Kaplan-Meier survival curves.

<sup>f</sup> Kaplan-Meier method was used to estimate the median disease-free survival time and the corresponding 95% CI.

+ Maximum time was censored.

C: Cyclophosphamide; CI: Confidence interval; E: Epirubicin; NC: Not calculable; T: Taxane.

Results of the Cox regression model analysis, to explore the influence of stratification and prognostic factors on DFS using initial (as randomized) nodal status, showed that the only

significant factors influencing DFS were nodal status (4 to 10 positive nodes versus ‘other’) and ER and/or PgR status. Similar results were seen for ‘corrected’ nodal status (ie, nodal status as recorded on the baseline CRF) (Table S4).

**Table S4. Cox Model on Disease-Free Survival Time - Modified Intent-to-Treat Population**

Variable	Hazard Ratio	95% Confidence Interval	p-value
<b>As Randomized Nodal Status</b>			
Treatment (ET versus EC→T)	1.014	0.70, 1.47	0.9419
ECOG PS (1 versus 0)	1.179	0.71, 1.96	0.5243
Body Mass Index	0.993	0.96, 1.02	0.6649
Menopausal status (< 50 years versus ≥50 years)	0.959	0.65, 1.41	0.8313
Nodal Status (4-10 versus other) <sup>a</sup>	1.881	1.27, 2.78	<b>0.0016</b>
Nodal Status (>10 versus other) <sup>a</sup>	1.522	0.69, 3.38	0.3013
ER and/or PgR status (positive versus other)	0.409	0.28, 0.60	<b>&lt;0.0001</b>
Her2 status (overexpression versus other) <sup>b</sup>	1.360	0.87, 2.12	0.1740
<b>Corrected Nodal Status</b>			
Treatment (ET versus EC→T)	1.014	0.70, 1.47	0.9424
ECOG Performance Score (1 versus 0)	1.179	0.71, 1.96	0.5244
Body Mass Index	0.993	0.96, 1.02	0.6647
Menopausal status (< 50 years versus ≥50 years)	0.963	0.66, 1.41	0.8449
Nodal Status (4-10 versus other) <sup>a</sup>	1.850	1.25, 2.74	<b>0.0021</b>
Nodal Status (>10 versus other) <sup>a</sup>	1.406	0.63, 3.12	0.4019
ER and/or PgR status (positive versus other)	0.409	0.28, 0.60	<b>&lt;0.0001</b>
Her2 status (overexpression versus other) <sup>b</sup>	1.370	0.88, 2.13	0.1637

<sup>a</sup> Nodal status categories: “4-10 positive nodes,” “>10 positive nodes,” or “other.” (The “other” category includes subjects with “1-3 positive nodes” or, if the number of positive nodes was unknown, “positive sentinel node”).

<sup>b</sup> Overexpression [3+ score on HercepTest or positive fluorescence in situ hybridization (FISH) test] or other [<3+ score on HercepTest or negative FISH test or not available].

C: Cyclophosphamide; CI: Confidence interval; E: Epirubicin; ECOG: Eastern Cooperative Oncology Group; ER: Estrogen receptor; Her2: Human epidermal growth factor receptor-2; PgR: Progesterone receptor; PS: Performance status; T: Taxane.

*Secondary Efficacy Results.* There was no significant difference in overall survival (OS) between the treatment arms (ET versus EC→T) in the mITT population (HR=0.788; 95% CI=[0.49, 1.27]; p=0.3294) (Table S5).

**Table S5. Comparisons of Overall Survival Time - Modified Intent-to-Treat Population**

Treatment	N	Subjects who died		Subjects censored <sup>a</sup>		Survival Time (Months) <sup>b</sup>		Hazard Ratio (95% CI) <sup>c</sup>	p-value <sup>d</sup>
		n	(%)	n	(%)	Median <sup>e</sup>	Min, Max		
EC→T (Sequential)	305	38	(12.5)	267	(87.5)	NC	0.69, 59.56+		
ET (Concurrent)	298	30	(10.1)	268	(89.9)	NC	0.33, 59.96+	0.788 (0.49, 1.27)	0.3294

<sup>a</sup> Number of subjects still alive at the time of the analysis.

<sup>b</sup> In the absence of confirmation of death, censored to the last date of follow-up.

<sup>c</sup> Hazard ratio (ET/EC→T) and 95% CI from the Cox Proportional Hazards Model with treatment as covariate.

<sup>d</sup> Log-rank test for comparing Kaplan-Meier survival curves.

<sup>e</sup> Kaplan-Meier method was used to estimate the median disease-free survival time and the corresponding 95% CI.

+ Maximum time was censored.

C: Cyclophosphamide; CI: Confidence interval; E: Epirubicin; NC: Not calculable; T: Taxane.

Results of Cox regression model analysis, to explore the influence of stratification and prognostic factors on OS using initial (as randomized) nodal status, showed that the only significant factors influencing OS were nodal status (4 to 10 positive nodes versus ‘other’) and ER and/or PgR status. Similar results were seen for ‘corrected’ nodal status (Table S6).

**Table S6. Cox Model on Overall Survival Time - Modified Intent-to-Treat Population**

Variable	Hazard Ratio	95% Confidence Interval	p-value
<b>As Randomized Nodal Status</b>			
Treatment (ET versus EC→T)	0.811	0.50, 1.31	0.3934
ECOG PS (1 versus 0)	1.023	0.52, 2.01	0.9473
Body Mass Index	1.009	0.97, 1.05	0.6224
Menopausal status (< 50 years versus ≥ 50 years)	1.108	0.68, 1.82	0.6840
Nodal Status (4-10 versus other) <sup>a</sup>	2.043	1.23, 3.40	<b>0.0059</b>
Nodal Status (>10 versus other) <sup>a</sup>	2.358	0.98, 5.69	0.0564
ER and/or PgR status (positive versus other)	0.276	0.17, 0.45	<b>&lt;0.0001</b>
Her2 status (overexpression versus other) <sup>b</sup>	0.991	0.54, 1.81	0.9778
<b>Corrected Nodal Status</b>			
Treatment (ET versus EC→T)	0.810	0.50, 1.31	0.3905
ECOG Performance Score (1 versus 0)	1.020	0.52, 2.00	0.9539
Body Mass Index	1.009	0.97, 1.05	0.6231
Menopausal status (< 50 years versus ≥ 50 years)	1.112	0.68, 1.82	0.6752
Nodal Status (4-10 versus other) <sup>a</sup>	2.017	1.21, 3.36	<b>0.0069</b>
Nodal Status (>10 versus other) <sup>a</sup>	2.220	0.92, 5.36	0.0764
ER and/or PgR status (positive versus other)	0.275	0.17, 0.45	<b>&lt;0.0001</b>
Her2 status (overexpression versus other) <sup>b</sup>	0.998	0.55, 1.82	0.9959

<sup>a</sup> Nodal status categories: “4-10 positive nodes,” “>10 positive nodes,” or “other.” (The “other” category includes subjects with “1-3 positive nodes” or, if the number of positive nodes was unknown, “positive sentinel node”).

<sup>b</sup> Overexpression [3+ score on HercepTest or positive fluorescence in situ hybridization (FISH) test] or other [ $<3+$  score on HercepTest or negative FISH test or not available].

C: Cyclophosphamide; CI: Confidence interval; E: Epirubicin; ECOG: Eastern Cooperative Oncology Group; ER: Estrogen receptor; Her2: Human epidermal growth factor receptor-2; PgR: Progesterone receptor; PS: Performance status; T: Taxane.

Similar results for DFS and OS were seen in the AT population.

*Post Hoc Exploratory Efficacy Analysis Results.* Post-hoc exploratory analyses did not show a significant difference in DFS between subjects receiving paclitaxel versus those receiving docetaxel in either the EC→T arm (HR=0.641; 95% CI=[0.33, 1.24]; p=0.1850) or the ET arm (HR=1.150; 95% CI=[0.64, 2.08]; p= 0.6432). In addition, there was no significant difference in DFS between the EC→T arm versus the ET arm among subjects treated with paclitaxel (HR=0.649; 95% CI=[0.30, 1.41]; p=0.2769) or among subjects treated with docetaxel (HR=1.177; 95% CI=[0.77, 1.79]; p=0.4470).

Similarly, no significant difference in OS was seen between subjects receiving paclitaxel versus those receiving docetaxel in either the EC→T arm (HR=0.408; 95% CI=[0.16, 1.05]; p=0.0618) or the ET arm (HR=1.152; 95% CI=[0.51, 2.59]; p= 0.7331), or between the ET→C arm versus the ET arm among subjects treated with paclitaxel (HR=0.539; 95% CI=[0.18, 1.65]; p=0.2794) or among those treated with docetaxel (HR=1.568; 95% CI=[0.91, 2.69]; p=0.1020).

**Safety Results:** An overview of TEAEs is presented in Table S7, below.

**Table S7. Overview of Treatment-Emergent Adverse Events – As-Treated Population**

	EC→T (Sequential chemotherapy) (N=304) n (%)	ET (Concurrent chemotherapy) (N=299) n (%)
Subjects with at least one TEAE	304 (100.0)	298 (99.7)
Subjects with at least one treatment related TEAE	300 (98.7)	294 (98.3)
Subjects with at least one serious TEAE	38 (12.5)	71 (23.7)
Subjects discontinued due to an TEAE	21 (6.9)	21 (7.0)
Subjects who died	38 (12.5)	30 (10.0)

TEAE: treatment-emergent adverse event

The most frequently reported CTC Grade 3 and 4 TEAEs in each treatment arm were those commonly associated with chemotherapy (febrile neutropenia, alopecia, fatigue, nausea and vomiting). A greater percentage of subjects in the ET arm experienced febrile neutropenia than in the EC→T arm (15.1% and 5.9%, respectively) whereas the incidence of vomiting was slightly greater in the EC→T arm compared with the ET arm (7.2% and 3.0%, respectively). Generally, within each treatment arm, the incidence of TEAEs was similar, irrespective of the taxane administered. The largest differences in the incidence of TEAEs between the different taxane therapies were the incidence of alopecia in the EC→T arm (8.5% in subjects who received docetaxel compared with 0% in subjects who received paclitaxel), and in the ET arm, the incidences of febrile neutropenia (18.2% and 4.4%, respectively) and alopecia (6.9% and 1.5%, respectively).

All-causality CTC Grade 3 and 4 TEAEs that occurred in at least 2% of subjects in either treatment arm (ET or ET→C) are summarized overall and by taxane therapy in Table S8, below.

**Table S8. Treatment-Emergent All-Causality CTC Grade 3 and 4 Adverse Events Occurring in ≥2% of Total Number of Subjects in Either Treatment Arm – As-Treated Population**

MedDRA Preferred Term	EC→T (Sequential Chemotherapy)			ET (Concurrent Chemotherapy)		
	Paclitaxel (N=77) n (%)	Docetaxel (N=211) n (%)	Total (N=304) <sup>a</sup> n (%)	Paclitaxel (N=68) n (%)	Docetaxel (N=231) n (%)	Total (N=299) n (%)
Febrile neutropenia	6 (7.8)	12 (5.7)	18 (5.9)	3 (4.4)	42 (18.2)	45 (15.1)
Alopecia	0	18 (8.5)	19 (6.3)	1 (1.5)	16 (6.9)	17 (5.7)
Fatigue	3 (3.9)	13 (6.2)	17 (5.6)	4 (5.9)	14 (6.1)	18 (6.0)
Nausea	5 (6.5)	11 (5.2)	16 (5.3)	3 (4.4)	14 (6.1)	17 (5.7)
Vomiting	5 (6.5)	17 (8.1)	22 (7.2)	2 (2.9)	7 (3.0)	9 (3.0)
Constipation	1 (1.3)	5 (2.4)	6 (2.0)	2 (2.9)	7 (3.0)	9 (3.0)
Diarrhea	1 (1.3)	7 (3.3)	8 (2.6)	0	7 (3.0)	7 (2.3)
Bone pain	3 (3.9)	6 (2.8)	9 (3.0)	0	3 (1.3)	3 (1.0)
Deep vein thrombosis	2 (2.6)	5 (2.4)	7 (2.3)	1 (1.5)	4 (1.7)	5 (1.7)
Arthralgia	3 (3.9)	6 (2.8)	9 (3.0)	2 (2.9)	0	2 (0.7)
Myalgia	1 (1.3)	7 (3.3)	8 (2.6)	0	3 (1.3)	3 (1.0)
Syncope	1 (1.3)	4 (1.9)	5 (1.6)	2 (2.9)	4 (1.7)	6 (2.0)
Abdominal pain	2 (2.6)	2 (0.9)	4 (1.3)	2 (2.9)	4 (1.7)	6 (2.0)
Amenorrhoea	2 (2.6)	5 (2.4)	7 (2.3)	0	3 (1.3)	3 (1.0)
Catheter-related infection	0	1 (0.5)	1 (0.3)	0	6 (2.6)	6 (2.0)
Neutropenia	0	0	0	0	7 (3.0)	7 (2.3)

<sup>a</sup> Sixteen subjects did not receive taxane therapy.

C: Cyclophosphamide; E: Epirubicin; MedDRA: Medical Dictionary for Regulatory Activities; T: Taxane.

The incidence of treatment-related CTC Grade 3 and 4 TEAEs followed similar patterns to the all-causality TEAEs. Treatment-related CTC Grade 3 and 4 TEAEs that occurred in at least 2% of subjects in either treatment arm (ET or ET→C) are summarized overall and by taxane therapy in Table S9, below.

**Table S9. Treatment-Emergent Treatment-Related CTC Grade 3 and 4 Adverse Events Occurring in ≥2% of Total Number of Subjects in Either Treatment Arm – As-Treated Population**

MedDRA Preferred Term	EC→T (Sequential Chemotherapy)			ET (Concurrent Chemotherapy)		
	Paclitaxel (N=77) n (%)	Docetaxel (N=211) n (%)	Total (N=304) <sup>a</sup> n (%)	Paclitaxel (N=68) n (%)	Docetaxel (N=231) n (%)	Total (N=299) n (%)
Febrile neutropenia	4 (5.2)	12 (5.7)	16 (5.3)	3 (4.4)	41 (17.7)	44 (14.7)
Alopecia	0	18 (8.5)	19 (6.3)	1 (1.5)	16 (6.9)	17 (5.7)
Fatigue	3 (3.9)	13 (6.2)	17 (5.6)	4 (5.9)	14 (6.1)	18 (6.0)
Nausea	5 (6.5)	9 (4.3)	14 (4.6)	2 (2.9)	14 (6.1)	16 (5.4)
Vomiting	5 (6.5)	14 (6.6)	19 (6.3)	2 (2.9)	7 (3.0)	9 (3.0)
Amenorrhoea	2 (2.6)	5 (2.4)	7 (2.3)	0	3 (1.3)	3 (1.0)
Diarrhea	0	6 (2.8)	6 (2.0)	0	3 (1.3)	3 (1.0)
Myalgia	1 (1.3)	6 (2.8)	7 (2.3)	0	1 (0.4)	1 (0.3)
Neutropenia	0	0	0	0	7 (3.0)	7 (2.3)

<sup>a</sup> Sixteen subjects did not receive taxane therapy.

C: Cyclophosphamide; E: Epirubicin; MedDRA: Medical Dictionary for Regulatory Activities; T: Taxane.

There were a total of 68 deaths reported in this study, 38 (12.5%) in the EC→T arm and 30 (10.0%) in the ET arm. Of these deaths, 14 (seven in each treatment arm) were not due to cancer progression. Two of the non-cancer deaths (heart failure and septic shock) were considered related to treatment (both events reported in the ET arm). A summary of the 14 non-cancer progression deaths (seven in each treatment arm) is presented in Table S10, below.

**Table S10. Summary of Deaths Other than Cancer Progression**

Taxane received	Age / Race	Probable cause of death	Treatment duration (days)	Number of cycles	Days from first dose to death	Days from last dose to death
<b>EC→T</b>						
Paclitaxel	51 / White	Post-operative complication	177	8	454	299
Docetaxel	55 / Asian <sup>a</sup>	Unknown	168	8	1600	1454
Docetaxel	69 / Hispanic	Unknown	197	8	486	311
Docetaxel	53 / White	Subacute liver failure	169	8	507	360
Docetaxel	60 / White	Amyotrophic lateral sclerosis <sup>b</sup>	175	8	831	678
None	72 / White	Congestive heart failure	85	4	105	42
Docetaxel	57 / White	Bowel perforation / Sepsis	168	8	576	430
<b>ET</b>						
Paclitaxel	65 / Black	Cardiomyopathy	170	8	492	344
Paclitaxel	67 / White	Pneumonia and Cardiomyopathy	169	8	1178	1031
Docetaxel	69 / White	Myocardial infarction	169	8	932	785
Docetaxel	70 / White	Acute respiratory distress syndrome; Pneumonia	65	3	80	37
Docetaxel	46 / Black	Heart failure <sup>c</sup>	189	8	801	634
Docetaxel	62 / White	Septicemia, candidemia immunosuppression <sup>d</sup>	43	2	68	47
Docetaxel	63 / White	Septic shock <sup>c</sup>	22	1	10	10

<sup>a</sup> Or Pacific Islander.

<sup>b</sup> Complications associated with Lou Gehrig's disease.

<sup>c</sup> Treatment-related.

<sup>d</sup> Secondary to rheumatoid arthritis and perforated sigmoid diverticulitis.

C: Cyclophosphamide; E: Epirubicin; T: Taxane.

TEAEs leading to discontinuation of more than one subject were peripheral sensory neuropathy, adverse drug reaction, fatigue and hypersensitivity in the EC→T arm and ejection fraction decreased, fatigue, hypersensitivity and neuropathy in the ET arm. The majority of these events occurred in subjects who received docetaxel. This reflects the greater number of subjects treated with docetaxel versus paclitaxel (452 versus 151 subjects, respectively). A summary of the TEAEs leading to permanent discontinuation in two or more subjects in either treatment (ET or ET→C) is presented in Table S11, below.

**Table S11. Discontinuations Due To Treatment-Emergent Adverse Events in ≥2 Subjects in Either Treatment Arm – As-Treated Population**

MedDRA Preferred Term	EC→T (Sequential Chemotherapy)			ET (Concurrent Chemotherapy)		
	Paclitaxel (N=77) n (%)	Docetaxel (N=211) n (%)	Total (N=304) <sup>a</sup> n (%)	Paclitaxel (N=68) n (%)	Docetaxel (N=231) n (%)	Total (N=299) n (%)
Ejection fraction decreased	0	0	0	0	4 (1.7)	4 (1.3)
Fatigue	0	1 (0.5)	2 (0.7)	0	2 (0.9)	2 (0.7)
Hypersensitivity	0	2 (0.9) <sup>b</sup>	2 (0.7) <sup>b</sup>	1 (1.5)	1 (0.4) <sup>b,c</sup>	2 (0.7) <sup>b,c</sup>
Adverse drug reaction	0	1 (0.5)	2 (0.7)	0	1 (0.4)	1 (0.3)
Neuropathy	0	1 (0.5)	1 (0.3)	0	2 (0.9)	2 (0.7)
Peripheral sensory neuropathy	0	3 (1.4) <sup>c</sup>	3 (1.0)	0	0	0

Note: Subjects may have experienced more than one adverse event leading to discontinuation. Data presented in this table are based on data reported on the Adverse Event CRF.

<sup>a</sup> Sixteen subjects did not receive taxane therapy.

<sup>b</sup> Serious adverse event (in both treatment arms only one subject had hypersensitivity considered to be serious).

<sup>c</sup> Adverse events NOT considered to be related to study treatment.

C: Cyclophosphamide; E: Epirubicin; MedDRA: Medical Dictionary for Regulatory Activities; T: Taxane.

The most frequently reported SAEs were those commonly associated with chemotherapy (febrile neutropenia, vomiting, nausea and neutropenia). In the ET arm, compared with the EC→T arm, there were more SAEs of febrile neutropenia (10.7% and 3.3%, respectively) and neutropenia (2.3% and 0%, respectively). In the ET arm, a greater percentage of subjects with serious events of febrile neutropenia or neutropenia had received treatment with docetaxel than with paclitaxel, whereas in the EC→T arm, there was a similar percentage of subjects with serious febrile neutropenia in both paclitaxel-treated subjects and docetaxel-treated subjects; there were no SAEs of neutropenia reported in the EC→T arm. Treatment-emergent SAE events that occurred in at least 1% of subjects in either treatment arm (ET or ET→C) are summarized in Table S12, below.

**Table S12. All Serious Treatment-Emergent Adverse Events Occurring in ≥1% of Total Number of Subjects in Either Treatment Arm – As-Treated Population**

MedDRA Preferred Term	EC→T (Sequential Chemotherapy) <sup>a</sup>			ET (Concurrent Chemotherapy) <sup>a</sup>		
	Paclitaxel (N=77)	Docetaxel (N=211)	Total (N=304) <sup>b</sup>	Paclitaxel (N=68)	Docetaxel (N=231)	Total (N=299)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Febrile neutropenia <sup>c</sup>	3 (3.9)	7 (3.3)	10 (3.3)	2 (2.9)	30 (13.0)	32 (10.7)
Nausea	1 (1.3)	2 (0.9)	3 (1.0)	2 (2.9)	3 (1.3)	5 (1.7)
Vomiting	1 (1.3)	3 (1.4)	4 (1.3)	2 (2.9)	2 (0.9)	4 (1.3)
Neutropenia	0	0	0	0	7 (3.0)	7 (2.3)
Dehydration <sup>c</sup>	0	1 (0.5)	1 (0.3)	1 (1.5)	5 (2.2)	6 (2.0)
Cellulitis <sup>c</sup>	0	0	0	1 (1.5)	4 (1.7)	5 (1.7)
Deep vein thrombosis	0	1 (0.5)	1 (0.3)	0	3 (1.3)	3 (1.0)
Abdominal pain	0	0	0	1 (1.5)	3 (1.3)	4 (1.3)
Infection	1 (1.3)	0	1 (0.3)	0	3 (1.3)	3 (1.0)
Syncope	0	0	0	0	3 (1.3)	3 (1.0)

<sup>a</sup> Serious adverse events including those that occurred from baseline to within 30 days of the last dose of study medication.

<sup>b</sup> Sixteen subjects did not receive taxane therapy.

<sup>c</sup> Includes events of CTC grade 2, 3 and 4.

C: Cyclophosphamide; E: Epirubicin; T: Taxane.

In both treatment arms, there was a greater incidence of dose reductions due to TEAEs for subjects treated with docetaxel than for subjects treated with paclitaxel; this may reflect the greater number of subjects treated with docetaxel versus paclitaxel (Table S13).

**Table S13. Dose Reductions Due To Treatment-Emergent Adverse Events Occurring in >2% of Subjects for Any Treatment – As-Treated Population**

MedDRA Preferred Term	EC→T (Sequential Chemotherapy)			ET (Concurrent Chemotherapy)		
	Paclitaxel (N=77)	Docetaxel (N=211)	Total (N=304) <sup>a</sup>	Paclitaxel (N=68)	Docetaxel (N=231)	Total (N=299)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Febrile neutropenia	2 (2.6)	9 (4.3)	11 (3.6)	2 (2.9)	31 (13.4)	33 (11.0)
Vomiting	1 (1.3)	6 (2.8)	7 (2.3)	1 (1.5)	0	1 (0.3)
Fatigue	0	1 (0.5)	1 (0.3)	0	5 (2.2)	5 (1.7)
Diarrhea	0	5 (2.4)	5 (1.6)	0	0	0
Neuropathy	2 (2.6)	0	2 (0.7)	1 (1.5)	1 (0.4)	2 (0.7)

Note: Subjects may have experienced more than one adverse event leading to dose reductions.

<sup>a</sup> Sixteen subjects did not receive taxane therapy.

C: Cyclophosphamide; E: Epirubicin; MedDRA: Medical Dictionary for Regulatory Activities; T: Taxane.

*Other Safety Results.* A larger percentage of subjects had ECG evaluations that shifted from abnormal at pre-treatment to normal at the end of treatment (34.6% in the EC→T arm and 44.4% in the ET arm) than shifted from normal to abnormal (23.9% and 17.6% in the EC→T and ET arms, respectively). Similar findings were observed for the shift in ECG evaluations when assessed by taxane treatment. For the assessment of LVEF in subjects in the EC→T arm following four cycles of EC, one subject had an LVEF value of <45% after 4 cycles of treatment, and one subject had an absolute decrease in LVEF from baseline of >15%. In

addition, for the majority of all subjects in both arms, the fall in LVEF post-treatment (ie, after 8 cycles) was <10%, irrespective of chemotherapy arm or type of taxane treatment received. A small number of subjects (13 [4.3%] in the EC→T arm and 21 [7.0%] in the ET arm) fulfilled the criteria requiring them to undergo a further post-study follow-up evaluation three months after the end of the study.

Overall, there were very few Grade 3 and/or 4 hemoglobin or platelet count toxicities in either arm. Approximately 65% of subjects in each treatment arm experienced a Grade 3 or 4 WBC toxicity. In the EC→T arm, these toxicities were reported in a greater percentage of subjects who received paclitaxel (72.7%) compared with docetaxel (64.5%), whereas for subjects receiving concurrent therapy (ET), a higher percentage of Grade 3 and 4 WBC toxicities were seen in subjects who received docetaxel (68.4%) versus those who received paclitaxel (53.7%). Approximately 88% of subjects in each arm experienced a Grade 3 or 4 absolute neutrophil counts (ANC) toxicity; in each treatment arm, over 90% of subjects who received paclitaxel experienced these toxicities. No subjects in either treatment arm had bilirubin toxicities of Grade 3 or 4.

The majority of subjects had the same ECOG PS at the end of treatment as at baseline. Approximately 34% of subjects in the EC→T arm and 27% of subjects in the ET arm had a change in ECOG PS from 1 to 0 over the course of the study. Overall, 23% of subjects in the EC→T arm experienced a deterioration in performance score (from 0 to 1 or 2, or from 1 to 2), compared with 22% of subjects in the ET arm (Table S14).

**Table S14. Eastern Cooperative Oncology Group Performance Status - Shift from Baseline – As-Treated Population by Chemotherapy Arm**

	EC→T (Sequential Chemotherapy) (N=304)		ET (Concurrent Chemotherapy) (N=299)	
	ECOG at Baseline		ECOG at Baseline	
	0 (N=260) n (%)	1 (N=44) n (%)	0 (N=266) n (%)	1 (N=33) n (%)
<b>ECOG at End of Treatment</b>				
0	190 (73.1)	15 (34.1)	192 (72.2)	9 (27.3)
1	67 (25.8)	28 (63.6)	63 (23.7)	23 (69.7)
2	2 (0.8)	1 (2.3)	2 (0.8)	0
Not done	1 (0.4)	0	9 (3.4)	1 (3.0)

ECOG: Eastern Cooperative Oncology Group.

The ECOG PS results by taxane treatment were consistent with those seen for each overall chemotherapy treatment arm. There were no apparent differences between the taxane groups.

**CONCLUSIONS:**

In this Phase 3 study of adjuvant therapy in patients with operable, node-positive breast cancer, concurrent epirubicin and taxane (ET) therapy and sequential epirubicin and cyclophosphamide therapy followed by a taxane (EC→T) had similar 3-year disease-free

survival (DFS) and overall survival (OS) times. The median follow-up time for both treatment arms was approximately 31 months; the percentage of subjects completing three years of follow-up was 32.5% for the ET treatment arm and 29.8% for the EC→T treatment arm. The only significant factors influencing DFS and OS were nodal status (4 to 10 versus other) and ER and/or PgR status.

The incidence and type of AEs reported was consistent with the nature of the study treatment and the disease under study. Serious AEs were reported more frequently in the ET than EC→T treatment arm, but the incidence of AEs leading to discontinuation was similar between arms. In addition, analysis of the safety results by taxane demonstrated docetaxel was more frequently associated with AEs and resulting dose modifications, but paclitaxel was more frequently associated with hematological and chemistry related toxicities.