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Lumpectomy plus tamoxifen with or without irradiation in women age 70 or older with early breast cancer: Long-term follow-up of CALGB 9343

Hughes, et al

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CANCER AND LEUKEMIA GROUP B
PROTOCOL CALGB 9343
(ECOG C9343, RTOG 97-02)

EVALUATION OF LUMPECTOMY, TAMOXIFEN, AND IRRADIATION OF THE BREAST COMPARED WITH LUMPECTOMY PLUS TAMOXIFEN IN WOMEN 70 YEARS OF AGE OR OLDER WHO HAVE CARCINOMA OF THE BREAST THAT IS LESS THAN OR EQUAL TO 2 CM AND CLINICALLY NEGATIVE AXILLARY NODES: A PHASE III STUDY

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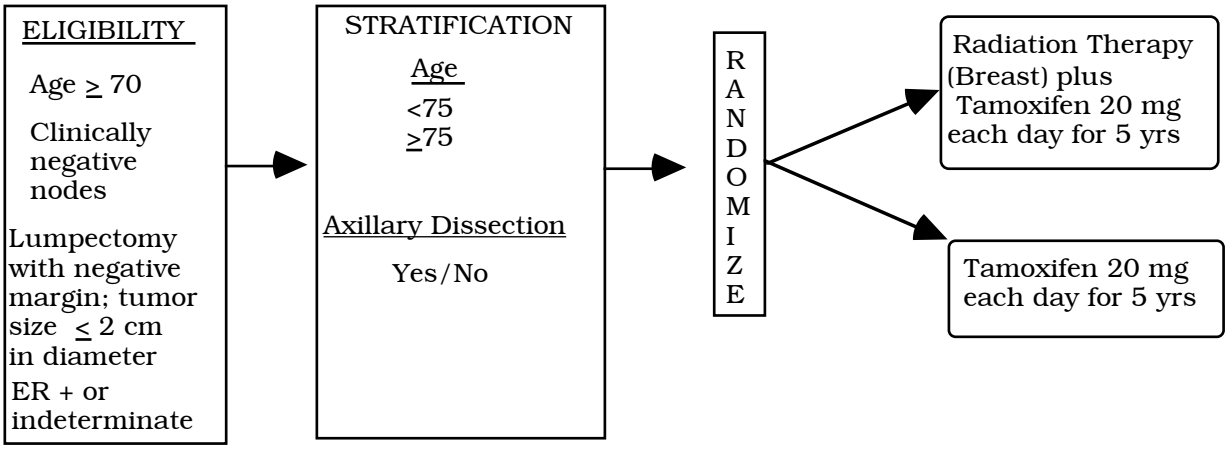
EVALUATION OF LUMPECTOMY, TAMOXIFEN, AND IRRADIATION OF THE BREAST COMPARED WITH LUMPECTOMY PLUS TAMOXIFEN IN WOMEN 70 YEARS OF AGE OR OLDER WHO HAVE CARCINOMA OF THE BREAST THAT IS LESS THAN OR EQUAL TO 2 CM AND CLINICALLY NEGATIVE AXILLARY NODES

SCHEMA



RT: Breast tangent: Weeks 1-5 1.8 Gy/day, 5 days/week
Boost: Week 6-6.5 2.0 Gy/day, 7 days total

Toxicities: Elevated blood calcium levels, fluid retention, hot flashes, nausea or vomiting, vaginal bleeding or discharge, rash, carcinoma of the uterus, thrombosis/embolism, eye problems. Less frequent side effects associated with tamoxifen use include loss of appetite, distaste for food, vaginal itching, leg cramps, dizziness, light-headedness, headache, mental depression, confusion, fatigue, and possible fetal abnormalities. Carcinoma of the liver may also occur.

Randomization: **CALGB**: Main institutions call the CALGB Data Management Center (919) 286-4704, Monday through Friday 9:00 am- 5:00 pm Eastern Time with the information contained in section 5.0.

ECOG institutions telephone the Randomization Desk at the ECOG Coordinating Center, (617) 632-2022, Monday -Friday, 9:00 AM to 4:30 PM ET (see Section 5.1).

RTOG Registration: RTOG institutions will register a patient by faxing the completed current version of the eligibility checklist to RTOG Headquarters (215-928-0153). This material must be transmitted between the hours of 8:30 AM and 4:00 PM Eastern Time, Monday through Friday. All items must be completed. RTOG Headquarters will call the RTOG institution after obtaining the group ID numbers and treatment assignment from CALGB.

Off-Study: Patients will be followed until either distant metastases or mastectomy of the ipsilateral breast subsequent to initial lumpectomy, whichever comes first. In the event of distant metastasis first, patients will be followed for second primary and death. In the event of ipsilateral mastectomy first, patients will be followed for second primary and death.

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1.0 INTRODUCTION

Longer average life expectancy[1] and a rising incidence of carcinoma of the breast[2,3] have combined to produce a steady increase in the absolute number of elderly women presenting with carcinoma of the breast. At the same time, an increasing knowledge of the biology of carcinoma of the breast has made available many different strategies for treating this disease (tamoxifen and lumpectomy, for example). The paucity of clinical trials in which women over 70 years of age were involved has forced us to extrapolate the results of trials involving younger women to determine the best treatment for elderly women. Inherent biases relative to life expectancy and comorbid diseases have led researchers to recommend an entire spectrum of treatments, ranging from tamoxifen alone without removal of the tumor (because elderly women are often too frail to withstand operation)[4,5] to modified radical mastectomy for all patients (because elderly women do not need preservation of the breast or are unable to commute to a radiation therapy facility.)[6,7]

Radiation therapy is a standard component of breast conserving therapy and enhances local control. The assumption that in every circumstance, eliminating radiation treatments yields unacceptable rates of local recurrence has not been directly tested. Despite the lack of precise descriptions of low risk subsets, recently published articles have recommended partial mastectomy without breast irradiation.[8,9,10,11] Randomized studies are needed to better define exactly who these low risk women are before untested therapies come into routine use.

Radiation Does Not Change Survival

The following table shows the currently available prospective data:

Author	n	Follow-up	RT	No RT
Fisher[12]	930	10 Years	71%	65%
Liljegren[13]	381	5 Years	91%	87.1%
Veronesi[14]	567	4 Years	No Difference	
Clark[15]	837	3 Years	91.1 - 96.0%	90.5 - 96%

Ipsilateral Breast Tumor Recurrence Decreases with Age

The findings of the Milan Trial III[14] include the observation that ipsilateral breast tumor recurrence (IBTR) decreases with age. Patients less than 45 years of age had a rate of IBTR of 17.5%. The group with patients between the ages of 46 to 55 years had a rate of IBTR of 8.7%, and the group with patients greater than 55 years of age had a rate of IBTR of 3.8%[5]. The overall trend of decreasing rates of recurrence with increasing age is suggestive that older patients may be at less risk for recurrence than younger patients.

Comorbid conditions and a relatively decreased life expectancy shorten the period in which an elderly patient is at risk of experiencing a recurrence.[16,17] Frequently, geriatric patients have serious comorbid conditions that diminish life expectancy to a greater degree than does the diagnosis of carcinoma of the breast. For example, a 70-year-old patient with carcinoma of the breast has an 8% risk of dying of carcinoma of the breast and a 13% risk of dying of comorbid disease within 5 years. In contrast, an 85-year-old women has a 12% risk of dying of

carcinoma of the breast and a 49% risk of dying of other causes.[18] This relationship deserves consideration when recommending both primary and adjuvant treatment.

Tamoxifen Decreases the Rate of Ipsilateral Breast Tumor Recurrence

Adjuvant tamoxifen therapy diminishes the rate of IBTR. Patients who receive tamoxifen have nearly half the risk of experiencing IBTR compared with patients who receive a placebo.[19,20]

Local Recurrence Does Not Preclude Breast Preservation

Preservation of the breast often remains a viable option even after local recurrence. A higher rate of IBTR in the non-irradiated group does not necessarily exclude preservation of the breast. Preservation of the breast after recurrence of tumor has been assessed in three randomized trials. Liljegren et al[13] found that 11 of 37 patients (30%) who developed local recurrences could be treated with repeat lumpectomy followed by radiation therapy. Clark et al[15] and Veronesi et al[14] demonstrated that the breast could be preserved in many women who experienced local recurrences. These studies indicate that for many women, the goal of preservation of the breast is not necessarily compromised by the omission of initial adjuvant radiation therapy.

The large variation in therapy and the lack of prospective data make it imperative to study an organized approach to treatment in a prospective manner.

In collating the available data, certain suppositions can be drawn regarding the care of the elderly woman with carcinoma of the breast. The treatment of the elderly woman with carcinoma of the breast can be thought of in terms of three objectives:

1) prevention of local recurrence of carcinoma in the breast or chest wall

2) prevention of recurrence in regional lymph nodes, and

3) prevention of distant recurrence.

NSABP Protocol B-06[8,9] suggests that local recurrence of carcinoma, when analyzed at 8 years, can be prevented by mastectomy (8% rate of recurrence in the chest wall) or lumpectomy plus irradiation of the breast (11% rate of recurrence in the breast or scar). Lumpectomy without radiation therapy will prevent recurrence of carcinoma in the breast in 60% of patients (40% rate of recurrence in the breast). There is no difference in overall survival.

NSABP Protocol B-04[10] suggests that axillary recurrence can be prevented in the clinically node-negative patient by axillary dissection or irradiation to the axilla, whereas observation alone results in a 20% rate of axillary recurrence. Survival is the same whether or not the axilla is treated. Therefore, the role of axillary dissection is limited to staging for prognosis to aid in the choice of adjuvant therapy and prevention of local recurrence.

Currently, tamoxifen is indicated in adjuvant treatment of the postmenopausal, estrogen receptor (ER) positive patient whether her condition is node positive (Consensus Conference 1986)[11,12,13] or node negative.[12,13,14]Additionally, the recent meta-analysis suggests that tamoxifen is useful even in the ER negative patient.[12,13]

NSABP Protocol B-14 compared the use of tamoxifen to placebo in node-negative, estrogen-receptor positive women with invasive breast cancer. The results initially published in 1989 indicated a significant prolongation of disease-free survival in favor of the group receiving tamoxifen treatment, along with a concomitant improvement in overall survival in favor of tamoxifen as well. A secondary goal of B-14 was to compare the effectiveness of five years of tamoxifen treatment to ten years of tamoxifen treatment. Results from this re-randomized component of the trial indicate that there is no additional advantage derived from extending the administration of tamoxifen to ten years. As a result of this finding, the Data Monitoring

Committee for the NSABP treatment trials has recommended that the B-14 trial be stopped and patients unblinded. Similarly, tamoxifen will be stopped in all NSABP treatment trials at five years. Since treatment with tamoxifen for five years has been found to be as least as effective as long term therapy, we believe this to be the optimal dose regimen for meeting the objectives of this study.

We can predict, therefore, that in the elderly patient, lumpectomy plus breast radiation and adjuvant treatment with tamoxifen should be comparable to a modified radical mastectomy plus adjuvant treatment with tamoxifen.

The question is then raised as to whether irradiation is necessary for all patients in this population. Several facts suggest that it may not always be necessary.

1) In B-04 and in B-06, radiation therapy prevented locoregional recurrence but did not change the rate of survival.

2) The $\geq$75 year-old patient with localized carcinoma of the breast has an actual 5-year rate of survival of 47.7%, despite a relative rate of survival of 74.4%.[15] This means that many of these patients die from competing causes and are at risk of locoregional recurrence for a shorter time.

3) Tamoxifen has a role in decreasing locoregional recurrence (as suggested by Castiglione et al[16]).

Therefore, the combination of decreased time at risk plus decreased recurrence because of adjuvant treatment with tamoxifen may minimize the benefits of radiation therapy.

The advantage of avoiding a modified radical mastectomy or an axillary dissection is that lumpectomy can be accomplished under local anesthesia with or without sedation, whereas a modified radical mastectomy or an axillary dissection necessitates general anesthesia. Morbidity resulting from pre-existing illness can be minimized by the avoidance of general anesthesia or prolonged hospitalization.

The advantage of avoiding radiation therapy is that radiation therapy in the elderly patient has social and economic costs. For the elderly patient, daily trips to the radiation oncology center are often time consuming and difficult. In addition, radiation therapy costs $5,000 or more. Unwillingness to undergo radiation treatment may influence the patient to opt for mastectomy when it is not necessarily the treatment of choice.

2.0 OBJECTIVES

To determine the net value of radiation therapy in patients 70 years or older who have carcinoma of the breast that is $\leq$2 cm and who are without palpable axillary nodes, all of whom receive tamoxifen. This study has four principal objectives:

2.1 To assess whether radiation therapy decreases the rate of locoregional recurrence when added to tamoxifen.

2.2 To assess whether radiation therapy decreases the incidence of eventual mastectomy.

2.3 To estimate overall survival, disease-free survival, and breast cancer-specific mortality for patients in the two treatment groups.

2.4 To assess morbidity on each treatment arm.

3.0 STATISTICAL CONSIDERATIONS

3.1 End Points: The following are the major end points of the study, where time intervals will be measured from study entry.

Time until locoregional recurrence: an event is a local or regional recurrence. Locoregional recurrence will include any recurrence in the supraclavicular, infraclavicular and/or ipsilateral axillary nodes, any ipsilateral breast recurrence and any recurrence in the soft tissues of the ipsilateral chest wall (an area bounded by the midline of the sternum, extending superiorly to the clavicle, posteriorly along the lateral edge to the latissimus dorsi, and interiorly to the costal margin). In addition, soft tissue recurrences within this zone but extending into the bony chest wall or across the midline can also be considered as locoregional recurrence. Death, distant metastasis, carcinoma in the opposite breast, and other carcinomas *are not* events.

Time to subsequent mastectomy: an event is a mastectomy of the ipsilateral breast. Death, local or distant metastasis, carcinoma in the opposite breast, and other carcinomas *are not* events.

Breast cancer-specific survival: An event will be death from breast cancer. Deaths from causes other than metastatic breast cancer *are not* events.

Survival time: an event is death from any cause.

Time to distant metastasis: an event is the appearance of distant metastasis.

The following are **secondary end points**:

Cosmetic result: Assessed by both patient and physician at baseline, 4 months, 1 year and 2 years after study entry.

Excellent: little difference, perceptible only with difficulty.

Good: Differences easily observed, but a very acceptable result.

Fair: Obvious differences from an unaffected breast.

Poor: Major differences from an unaffected breast.

Morbidity: Includes breast pain, breast edema, chest wall and shoulder pain, shoulder/arm stiffness, skin color changes, fibrosis or retraction and swelling of extremities. These will be assessed by both patient and physician at baseline, 4 months, 1 year and 2 years after study entry. The scale for breast pain, chest wall and shoulder pain, breast edema, arm/shoulder stiffness, skin color changes and fibrosis or retraction is:

1 = None (sides are the same)

2 = Minimal (affected side is slightly worse than unaffected side)

3 = Moderate (affected side is considerably worse than unaffected side)

4 = Severe (affected side is much worse than unaffected side)

Also, record any other morbidity using this scale.

Arm edema: The treating physician will assess the timing of swelling (1 - Never; 2 - Seldom; 3 - Often; 4 - Always). Circumferential measures of both arms at ulnar styloid, olecranon and 35 cm proximal to the ulnar styloid will be recorded. (21)

3.2 Costs of medical care per year

Whereas almost all patients will be covered by Medicare insurance, it may be possible to obtain health care expenses through the Health Care Finance Administration (HCFA).

3.3 Sample size

There is a substantial uncertainty in accrual rate for this study. The main source of uncertainty is the attitude of clinicians concerning the treatment of elderly patients. Because patients with axillary dissection can be included in the study, we anticipate accrual of about 12 patients per month. Over a 38-month period, we expect to accrue about 572 patients.

Accrual to the study may stop sooner than the currently planned end of the study. In particular, it will stop if the actual accrual rate is lower than required to achieve useful results by study's end. Also, if the actual accrual rate is greater than expected, the duration of the study may be less than that currently planned.

3.4 Expert Panel

• As part of this study and concurrent with patient accrual to the study, we will convene an Expert Panel. The purpose is to assess panel members' opinions and reactions to various aspects of the study. It may also be used in publications and other reports at the conclusion of the study. The panel will not have access to interim data from the study.

Panel members' views concerning various end points will be elicited by the study statistician. The panel will consist of individuals who are not directly associated with the study. The panel will have at least 10 members: 2 medical oncologists, 2 surgeons, 2 radiation oncologists, 2 psychotherapists, and 2 oncology nurses. The study statistician will not be a member of the panel but will lead the assessment process.

We will assess the panel members' opinions concerning the use of tamoxifen with radiation therapy and without radiation therapy in this population, as follows:

• Value to the patient of various levels of effectiveness for each of the end points described in Section 3.1. For example, we will assess the panel members' opinions concerning the importance to the patient of decreasing the rate of locoregional recurrence by various amounts.

The panel will also be asked to assess the impact of morbidity on the quality of life. This will be done by addressing the possible answers to the questions asked on the patient and physician "evaluation of treatment results" forms. Patients who experience pain, swelling, or stiffness have a lower quality of life. The quality level of each condition will be assessed by the panel on a scale from 0 to 100. Maximum quality of life is 100 per cent. This will enable assigning a quality score to each patient between follow-up visits and will, in turn, enable calculating average quality-adjusted life years by therapeutic group.

3.5 Power Calculations

If patients who have lumpectomy alone can expect 40% breast recurrence and 20% axillary recurrence, and if half of the axillary recurrence occurred concurrently with breast recurrence, then we could expect a 50% locoregional recurrence in this group. Due to competing mortality of 20-25%, only about 40% would recur before death. Assuming tamoxifen can halve locoregional recurrence in the elderly, we could expect about 20% to 25% locoregional recurrence. (At 3 years, we could expect a decrease to 15-18%).

With radiation therapy plus tamoxifen, expecting some overlap in benefit, locoregional recurrence might be half, or about 9%.

While this is a large expected benefit from radiation therapy in terms of locoregional recurrence, the benefit in terms of eventual mastectomy, survival and breast cancer-specific mortality is expected to be small. Therefore, the value of radiation therapy overall may not be significant.

Power calculations are based on time to locoregional recurrence. Accrual is expected to be 12 patients per month, in part because of the inclusion of patients with axillary dissection. Approximately 20% of these patients will be lost to follow-up, death, or experience distant relapse. The 3-year breast/axilla recurrence rate without irradiation is expected to be 16%, and with irradiation is expected to be 9%. Assume a (one-sided) significance level of 5% and four years of follow-up after accrual ends. To achieve 90% power for detecting a decrease in 3-year recurrence rate from 16% to 9% (which represents a 46% decrease in hazard rate assuming exponential time to recurrence) requires accruing 572 patients (458 not lost to follow-up or competing risks) over a period of 38 months.

3.6 Data Analysis

Time to locoregional recurrence will be compared for the two treatment groups using Kaplan-Meier survival curves and a proportional hazards model. Covariates considered in this model will be patient's age and axillary dissection status. Censoring variables include death, other cancers, and lost to follow-up.

Time to mastectomy will be compared for the two treatment groups using Kaplan-Meier survival curves and a proportional hazards model. Covariates considered in this model will be patient's age and axillary dissection status. Censoring variables include death, distant metastasis, other cancers and lost to follow-up.

Survival time will be compared for the two treatment groups using Kaplan-Meier curves and a proportional hazards model, with covariates as indicated above.

Breast cancer specific survival time will be compared for the two treatment groups using Kaplan-Meier curves and a proportional hazards model, with covariates as indicated above.

Relapse-free survival time will be compared for the two treatment groups using Kaplan-Meier curves and a proportional hazards model, with covariates as indicated above. Death is a censoring variable.

Short- and Long-term morbidity: The two treatment arms will be compared as regards range of motion of the shoulder, swelling of the arm, breast pain, chest wall pain, and cosmetic result for each assessment at baseline, 6 months, 1 year, 2 years and 4 years using a quantitative scale. The treatment groups will be compared using a t-test on the basis of this scale.

Total medical costs: If possible, the distribution of these costs will be compared for the two treatment groups. They will also be related with the benefits of the treatment strategies as described previously.

3.7 Data Monitoring Committee

A monitoring committee will be established to monitor the progress of this trial in accordance with the standard procedures of the CALGB. In addition to the analysis at four years after accrual ends (See Section 3.6), there will be interim analyses at two, four and six years after the study opens. These will be kept confidential and reported to the Data Monitoring Committee. P values and confidence intervals will use O'Brien-Fleming adjustments (22) with Lan-DeMets spending function (23) based on these four analysis points.

3.8 Race as a Prognostic Factor:

A recent review of the medical literature provided abundant evidence for differences in the stage of breast cancer between black and white women at time of first medical consultation (1), but only a minor difference in the interval between symptom recognition and medical consultation. Controlling for socioeconomic status in cancer patients reduces or eliminates differences in survival that might otherwise be attributed to race (2,3,4). Patients of low socioeconomic status are more likely to present with more advanced disease, and are likely to receive care of lower quality (5). The underrepresentation of minority or socially disadvantaged women in clinical trials is also documented in the experience of the CALGB and other cooperative groups.

We have also searched for reports of race/ethnic differences in treatment outcome, rather than stage of disease of patients included in treatment trials. Here, there is a paucity of information. Le Marchand (6) describes the survival advantage of Japanese breast cancer patients compared to white breast cancer patients, and raises the issue of the impact of lower body weight and fat intake in the Japanese women as a possible contributing factor. Inter-country comparisons especially when based upon selected hospital series used for portions of this analysis are hazardous, however. Evidence is offered in this article that Japanese women treated by mastectomy in Japan fare better than white women treated with surgery in New York.

Perhaps the most informative treatment of the issue of race as a prognostic factor would be our own analysis of a recently completed CALGB study, 8541. This recent analysis looked at race as a prognostic factor in a protocol which tested three dose of CAF in 1550 women with positive axillary nodes. There were a totals of 1325 white (84%), 185 (12%) black, 15(1%) Hispanic, 11 (1%) Oriental, & 34 (2%) Other & unknown. There was similar representation of each group in the three treatment arms.

We examined race as it univariately relates to overall survival and disease-free survival (DFS). Note that this is a univariate analysis, that is, an assessment of race alone as related to clinical outcome. In the subsequent multivariate analyses we adjust for other variables of prognostic importance. In this analysis black patients are 1.35 times more likely to fail (with respect to survival) than non-black patients (P=0.04). The 95% confidence interval about this risk ratio is from 1.01 to 1.80. While none of these results is of strong statistical significance, there is a consistent trend that race is related to clinical outcome, with black and Hispanic patients having the disadvantage. These results, however, do not adjust for any other demographic or clinicopathologic variables.

Multivariate Analysis: The data were then analyzed to give the multivariate relationship between several clinical variables with survival and Disease Free Survival (DFS). The variables significantly associated with survival and DFS were: CAF dose, number of positive lymph nodes, size of primary tumor, ER and/or PR status of primary tumor and patient age at study entry. After accounting for these variables, no other variables added significant predictive value for survival or DFS. In addition, there were no significant interactions between either dose and other independent variables or between pairs of independent variables. The addition of race does not improve the predictive ability of clinical prognosis. That is, after accounting for dose, number of positive nodes, tumor size, receptor status and age, race is no longer of prognostic importance for clinical outcome. In fact, the inclusion of race hardly changes the risk ratios. In addition, there is no differential effect of CAF dose for black patients. The 3-year Kaplan-Meier survival probability is .89, .82 and .85 for low-, standard- and high-dose arms, respectively. The 3-year disease-free probability is .61, .69 and .69 for low-, standard-, and high-dose arms, respectively.

A correlation of race with other clinical variables was then made. Race was moderately associated with tumor size, receptor status, type of surgery, pretreatment weight and pretreatment body surface area (BSA). The tables below show that black women were more likely than non-black women to: have larger tumors, have tumors with negative receptor status, and have undergone mastectomy rather than breast sparing surgery. Black women also tended to weigh more and have larger BSAs prior to treatment than non-black patients. Clearly, larger tumor size and negative receptor status are related to poorer prognosis.

Race by Tumor Size

	Tumor Size		
Race	≤2 cm	> 2 cm	Total
Other	503	858	1361
	37%	63%	
Black	50	130	180
	28%	72%	
Total	553	988	1541

N Missing = 9
Chi-Square (1 df) = 5.823, P=0.02

Race by Receptor Status

	Receptor Status		
Race	ER/ PR-	ER/ PR+	Total
Other	350	1000	1350
	26%	74%	
Black	60	119	179
	34%	66%	
Total	410	1119	1529

N Missing = 21
Chi-Square (1 df) = 4.644, P=0.03

Race by Type of Surgery

	Surgery		
Race	Lumpectomy	Mastectomy	Total
Other	222	1147	1369
	16%	84%	
Black	18	163	181
	10%	90%	
Total	240	1310	1550

Chi-Square (1 df) = 4.805, P=0.03

Race by Pretreatment Weight

	Race	
	Black	Other
Pretreatment weight (kg)		
Median	76	67
Range	43-140	42-159

N Missing = 2
Kruskal-Wallis Chi-Square (1 df)=52.293, P=<0.01

When used multivariately, the Cox proportional hazards model controls for the effect of other variables included in the model. Thus, although tumor size and receptor status correlate with race, when these variables are controlled for in the above multivariate Cox model, race is no longer of prognostic importance. That is, tumor size and receptor status are more important than race.

Summary: Black patients tend to present with more advanced disease (larger tumors) and worse clinicopathologic features (receptor negative tumors) compared to non-black patients. It follows that more black patients therefore underwent mastectomy than lumpectomy.

These patients presented with more advanced disease. This may result from later detection of disease. Possible reasons for this delay include the decreased availability of diagnostic procedures due to socioeconomic causes, or lack of willingness to participate in such medical options. Another possibility is that increased body weight may make clinical detection more difficult. These hypotheses, however, are beyond the scope of this study. At any rate, after considering the standard clinical variables of CAF dose, extent of nodal involvement, tumor size, receptor status and age, race is no longer prognostically important. Nor do race and dose interact.

3.9 An analysis of toxicities and outcome in ethnic minorities will be carried out on those minority patients entered into this study, similar to the analysis of patients entered into CALGB 8541 reported above. In addition, comparisons will be made across ethnic groups, and also in comparison with historical data from CALGB 7581, 8082 and 8541. However, because of the small sample sizes, these analyses will have very little statistical power.

4.0 ELIGIBILITY CRITERIA

4.1 Eligibility

- Patients must be women and 70 years of age or older.

- The size of the tumor must be determined to be ≤2 cm by clinical, mammographic, or pathologic criteria.

- Patients must be physically able to undergo radiation therapy (See Exclusion Criteria).

- Patients on estrogen replacement therapy may be admitted to the study immediately after discontinuation of estrogen replacement.

- Patients must have histologically documented invasive adenocarcinoma of the breast.

  - The primary tumor must be mobile and not fixed to the chest wall.

  - Patients must have ***clinically negative axillary and supraclavicular lymph nodes.***

  - Patients with abnormal results on liver function tests must undergo ultrasound scan, CT scan, or MRI of the liver to exclude metastatic disease.

- Estrogen receptor level must be considered positive or unable to be determined (indeterminate). An estrogen receptor positive level will be defined as ≥10 fmol/mg cytosol protein, or by ≥10% of cells staining positive by immunohistochemistry.

- Eligible patients must undergo breast-sparing operation (partial mastectomy/lumpectomy) (See Section 7.1). Excisional biopsy, including the entire palpable mass or mammographic abnormality with a small rim of normal breast tissue is considered a lumpectomy.

- Patients who have excisional biopsy or lumpectomy and who show pathologic margins involved with tumor are still eligible for randomization after re-excisions of the operative site until margins free of tumor are obtained.

- The interval between definitive operation and randomization cannot exceed 12 weeks. The date of definitive operation is the date of either excisional biopsy with negative pathologic margins or lumpectomy with negative pathologic margins.

- The general health of the patient should be such that the physician believes the protocol to be both feasible and appropriate.

- Patients will not be excluded from the study if they have begun tamoxifen treatment following surgery. The start date should be documented on the flow sheet.

*Abnormal laboratory values are **not** contraindications to this protocol.*

4.2 Exclusion Criteria

- Estrogen receptor levels considered negative are excluded. An estrogen receptor negative level will be defined as < 10 fmol/mg cytosol protein, or by less than 10% of cells staining positive by immunohistochemistry.

- The patient who is unable to lie on her back or raise her arm superior to her head sufficiently to undergo radiation therapy is excluded.

- Patients undergoing simple mastectomy, modified radical mastectomy, or radical mastectomy are excluded.

- Patients who have undergone previous radiation therapy to the ipsilateral breast, chest wall, or axilla are excluded.

- Pre-therapy studies must reveal no evidence of metastatic disease.

- Tumors must not exhibit skin ulceration, peau d'orange, or inflammatory changes. *Local microscopic dermal or dermal lymphatic involvement is allowed.*

- No previous or concurrent malignant disease is allowed, except inactive nonmelanoma skin cancer, in-situ carcinoma of the cervix, or other cancer if the patient has been disease-free for $\geq$5 years. (Patients with contralateral breast cancer who have been disease-free for $\geq$5 years are eligible).

- Although axillary dissection is not encouraged, it will not exclude a patient from eligibility for this protocol. It will be used as a stratification factor when the patient is randomized. If an axillary dissection has been done, the nodes may be pathologically negative or positive, *if they were clinically negative pre-operatively.*

4.3 Informed Consent: The patient must aware of the neoplastic nature of her disease and must willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. **(Human protection committee approval of this protocol and a consent form is required.)**

4.4 Patient Background Information Form: The patient will be asked to complete a Patient Background Information Form (C-187). The form must be returned with a signed Informed Consent, even if the patient declines to complete the form

5.0 REGISTRATION/RANDOMIZATION, STRATIFICATION, DATA SUBMISSION, AND MODALITY REVIEW

5.1 Randomization will be accepted through the Main Institution only. Confirm eligibility criteria (Sec. 4.0). Call the CALGB Registrar (919-286-4704, Monday-Friday, 9am-5pm Eastern Time) with the following information:

Your name
Study #
Institution #
Treating physician
Patient's social security #
Patient's name, I.D.#
Signed informed consent (date)
Race, sex, date of birth of patient
Zip code of residence of patient
Method of payment
Diagnosis, date of diagnosis
Eligibility criteria met (Sec. 4.0) (yes, no)
List previous CALGB protocols

Date of most recent Institutional Review
Board approval (<1 year)

The Main Member Institution will receive a Confirmation of Randomization. Please check for errors. Submit corrections in writing to CALGB Data Management Center, First Union Plaza, Suite 340, 2200 West Main Street, Durham, NC 27705.

Registration, ECOG Investigators:

A signed HHS 310 Form, a copy of the institution's IRB-approved informed consent document, and written justification for any changes made to the informed consent for this protocol must be on file at the ECOG Coordinating Center before an ECOG institution may enter patients. These will be submitted to: ECOG Coordinating Center, Frontier Science, Attn: IRB, 303 Boylston Street, Brookline, MA, 02146-7648. Patients must not start protocol treatment prior to registration.

To register eligible patients on study, the investigator will telephone the Randomization Desk at the ECOG Coordinating Center at (617) 632-2022, Monday-Friday, between the hours of 9 am and 4:30 pm ET to allow time to call CALGB that same day. ECOG members should not call CALGB directly. The following information will be requested: Protocol Number, Investigator Identification (including institution and/or affiliate name and investigator's name); Patient Identification (including patient's name or initials, chart number, social security number and demographics [sex, birth date, race, nine-digit zip code and method of payment]); Signed informed consent (date), diagnosis, date of diagnosis, previous CALGB protocols; Eligibility Verification. Patients must meet all of the eligibility requirements listed in Section 4.0. The randomization specialist will verify eligibility by asking questions from the checklist, and will also verify IRB approval. The ECOG Randomization Desk will then contact the CALGB Registrar (919-286-4704) to enter the patient, after which the ECOG Office will contact the institution to relay the treatment assignment for that patient. The CALGB Data Management Center will forward a confirmation of treatment assignment to the ECOG Coordinating Center for routing to the ECOG participating institution.

RTOG Registration:

RTOG institutions will register a patient by faxing the completed current version of the eligibility checklist to RTOG Headquarters (215-928-0153). This material must be transmitted between the hours of 8:30 AM and 4:00 PM Eastern Time, Monday through Friday. All items must be completed. RTOG will call the RTOG institution after obtaining the group ID numbers and treatment assignment from CALGB.

5.2 Stratification: Patients will be stratified according to age (<75/$\geq$75), and axillary dissection (yes/no).

5.3 Treatment Assignment: Patients will be randomized to receive radiation therapy to only the breast or no further local treatment.

All eligible patients will receive treatment with tamoxifen.

5.4 Data Submission

Submit forms to the CALGB Data Management at the following intervals (schedule follows):

ECOG Institutions: The original data forms as listed in this section should be submitted at the required intervals to the ECOG Coordinating Center. Include the CALGB and ECOG study number and patient number. The ECOG Coordinating Center will forward the forms to the CALGB Data Management Office.

RTOG institutions will submit data forms to RTOG Headquarters, 1101 Market Street, Philadephia, PA, 19107. Both CALGB and RTOG study and case numbers must be included.

Data Submission Schedule:

FORM		SUBMISSION SCHEDULE
C-187	CALGB Patient Background and Information Form*	At registration
C-294	CALGB Adjuvant Breast Cancer: On-Study Form	Within 1 week of registration
ST-3	CALGB Solid Tumor Initial Flow Sheet	Within 1 week of registration
	Path and Operative Reports	Within 1 week of registration
C-286	CALGB (Physician) Evaluation of Treatment Results	Within 4 wks of randomization, 4 mo, 1 yr and 2 and 4 yrs
C-287	CALGB Patient Evaluation of Treatment Results	Within 4 wks of randomization, 4 mo, 1 yr and 2 and 4 yrs
RT-1	Dosimetry Summary Form	Submitted to QARC within 3 days of RT start, copy to CALGB DMC
RT-2	RT Total Dose Form	Submitted to QARC within 2 week of completion of RT. Copy to CALGB DMC
C-341 ST-4	CALGB 9343 Follow-up Form Solid Tumor Flow Sheet***	q 4 months for 5 yrs; annually thereafter; at any local recurrence; at first distant metastases; at mastectomy; at death
C-215	CALGB Notification of Second Malignancy	At diagnosis of 2nd malignancy
C-113	CALGB Notification of Death Form	At patient death

* Each patient will be asked to complete a Patient Background Information Form (C-187). Even if the patient declines, the form should be submitted with the completed Prestudy Form.

***Submit ST-4 with C-341 only for significant clinical events: recurrence, re-lumpectomy, mastectomy, significant non-protocol medication, significant treatment-related toxicity, distant metastasis, and death.

Off-Study: Patients will go off-study at either distant metastasis or mastectomy of the ipsilateral breast subsequent to initial lumpectomy, whichever occurs first. Continue to follow these patients for second malignancy and death.

5.5 Histologic Studies

Histology: *Required:* Within six months of registration, submit a parrafin block with representative tumor, in a proper container (to avoid breakage), labeled with patient's name, CALGB patient number, institution, date, CALGB study number, and tissue source. A copy of the responsible pathologist's surgical pathology report from the TREATING insitutution, and if applicable, from the REFERRING institution, and a completed **original** CALGB Form C-490 should be sent to Dr. Maurice Barcos at the address below. If the block cannot be obtained, (e.g., insufficient amounts of tumor tissue, or similar reason), this requirement may be waived upon notification of the study chair, and written documentation of the reason.

These tissue blocks will be stored at 4° C and sectioned by the CALGB Pathology Reference Laboratory according to companion protocol guidelines.

CALGB and RTOG institutions should send materials directly to:
CALGB Pathology Coordinating Office
The Ohio State University
B054 Graves Hall
333 West 10th Avenue
Columbus, OH 43210-1239
Ph: 614-688-3495; Fax: 614-292-5618

ECOG institutions: All ECOG institutions will send the parrafin block with representative tumor and corresponding pathology reports to the ECOG Pathology Coordinating Office. These blocks will be sent to the ECOG Central Histology lab in Albany, NY, where the appropriate slides will be prepared. The slides will be forwarded to the CALGB Pathology Coordinating Office and the block will be returned to ECOG for banking.

6.0 REQUIRED DATA

Unless exceptions are made in the following table, pre-therapy tests must be completed as follows:

Guidelines For Pre-Study Testing:

NOTE: Required laboratory tests must be obtained within 3 MONTHS of registration. Chest x-ray and mammography must be completed within 6 MONTHS of registration.

*Patient must have had a lumpectomy within **12** weeks of randomization.*

	Before Study	Follow-up During TAM*	Follow-up After TAM**
Tests and Observations			
Signed Consent Form	X		
History and progress notes	X	X	X
Physical examination (including pelvic exam with cytology†•)	X	X	X
Pulse, blood pressure	X		
Performance Status	X	X	
Drug Toxicity		X	
Cosmetic result/morbidity assessment	X	E	
Laboratory			
CBC, platelet count	X	B	
Creatinine, BUN	X	B	
Ca^{++}	X	B	
SGOT/alk. phos./bili	X	PRN	
Glucose	X	PRN	
Staging			
Mammography	X	D	X
Chest x-ray	X	B	
Other			
Bone Scan	F	PRN	
Ultrasound, CT, or MRI of the liver	C	PRN	

* At least every 4 months for 5 years

**Annually

† Pelvic examination with cytology must have been performed within 12 months prior to randomization and repeated annually. •Pelvic exam not required of women s/p hysterectomy

B = Once each year

PRN = When clinically appropriate

C = If liver function elevated; w/in 3 months of registration

D = Every 6 months for 1 year

E = At 4 months, 1 year, and 2 years

F = Recommended but not required

7.0 TREATMENT PLAN

The operation that will be acceptable for this protocol will be lumpectomy with or without axillary dissection. Eligible patients will include those with primary tumors that are freely mobile and that clinically do not involve the skin.

7.1 Surgical Guidelines

Lumpectomy will be considered to have been performed when the entire palpable tumor has been excised with a rim of pathologically negative tissue. This can either be accomplished (1) at the initial excisional biopsy for a palpable mass or a mammographic abnormality, (2) at the time of formal lumpectomy following fine needle or core needle biopsy for diagnosis, or (3) for definitive resection following biopsy showing margins pathologically or grossly involved with tumor.

For optimum cosmetic results, the incision should be made directly over the mass or overlying the mammographic abnormality using transverse or curvilear incisions in the upper breast and radial incisions in the lower breast. Excision of an ellipse of skin overlying the tumor or following the biopsy scar may be performed but is not required. If axillary dissection is planned, this should be done through a separate transverse incision following the axillary skin lines between the pectoralis major muscle and the latissimus dorsi muscle.

The abnormality should be as completely excised as possible in a circumscribed fashion, with a complete rim or grossly normal-appearing breast tissue. After achieving appropriate hemostasis, subcutaneous fat and skin should be approximated. No attempt should be made to close the dead space and drains should not be used. Rather, the wound should be allowed to heal by formation of a seroma to achieve the natural contour and texture of the breast. Placement of metal clips in the tumor bed is strongly encouraged to aid in planning the tangential and boost ports, but is not required.

The surgeon should orient the lumpectomy specimen for the pathologist who must then ink the specimen to examine the margins histologically and then reserve representative portions of the tissue for hormone receptors. If tumors are too small to obtain fresh tissue for hormone receptors, this may be done on paraffin sections. Excision of the nipple/areolar complex will be permitted for central lesions at the discretion of the individual surgeon and the radiation oncologist. To be eligible for protocol, lumpectomy margins must be histologically free of tumor.

Should the patient be referred having had total excision of the primary carcinoma of the breast without a proven tumor-free margin, a “re-excision lumpectomy” may be performed by the surgeon. This procedure should mimic a primary lumpectomy in that the site of the biopsy or initial lumpectomy should be completely excised. As with initial lumpectomy, the re-excision specimen must be oriented for the pathologist who should then ink the specimen. Permanent sections must be taken for the histologic evaluation of margins and to assess any signs of residual disease. Patients who undergo re-excision lumpectomy and who have invasive tumor at the margin of the second lumpectomy may still be eligible for this protocol provided that repeated excisions of involved areas are carried out and ultimately result in a negative margin. This may be done at multiple procedures.

7.2 Tamoxifen

Administration schedule is 20 mg as a single dose each day for five years. If necessary, tamoxifen can be given in two divided doses of 10 mg b.i.d.

- Begin administration of tamoxifen within 8 weeks of randomization; it may be concurrent with radiation therapy.

7.3 Radiation Therapy: General Guidelines

Criteria for receiving radiation therapy: Patients who are randomized to the group receiving radiation therapy plus tamoxifen shall receive breast irradiation.

Relation to other modalities: Radiation should begin as close to between 3 and 6 weeks after lumpectomy as possible, or between 0-4 weeks after randomization. Tamoxifen, which is to be initiated within 8 weeks, may be given concurrently.

Goals of radiation therapy: To achieve local control with good cosmesis. In particular, to compare rate and timing of local recurrence, rate of breast conservation, survival, and quality of life with and without irradiation in an elderly population ($\geq$70 years old) given tamoxifen.

Equipment

Modality: External photon beams shall be used for treatment of the entire breast. Electrons shall be used for the boost to the primary site.

Energy: Co-60 minimum, and 6 MV-maximum for photon tangents. 6 MeV to 20 MeV for electron boost, depending on depth needed to encompass the primary site.

Dose Rate: 0.5-3 Gy/min at 100 cm SAD and 10 cm depth, for photons; 1-3 Gy/min at 100 cm SSD to the d_{max} for electrons.

Calibration and beam data verification: The calibration of each machine used for this protocol shall be verified by the Radiological Physics Center (RPC).

Target Volumes

Anatomic Description

Clinical Target volume: Tumor bed plus entire ipsilateral breast.

Planning Target volume: Entire ipsilateral breast with margin for motion *including areas of lower axillary lymph nodes.*.

Treated volume: Ipsilateral breast in tangent fields with a minimum of 1 cm margin around the breast as visualized on simulation films with a wire outlining the circumference of the breast. Corner blocks may be used only at the inferior deep border (Appendix A) to protect normal tissues. The intent is to include levels I and II axillary nodes in the angled tangent fields. The widest portion of lung visualized on the simulation films should not exceed 3 cm.

Volume modifications: Boost clinical target volume: Tumor bed with potential microscopic extension of disease. Boost planning target volume: surgical scar plus area of tumor bed beyond scar if it is known that surgeon did not place scar directly over the tumor with a 2-cm margin in all directions; at the ends of the scar, 1-cm margin is permissible (Appendix B). Depth may be determined by small clips placed at the time of lumpectomy or by treating at a depth determined by the distance from the skin surface at the middle of the scar to the outer border of the rib cage if depth is not otherwise ascertainable. A simulation film orthogonal to the beam angle for the boost may be used with magnification correction to aid in determining this depth.

Treatment Dose

Prescription point (breast): Dose shall be prescribed to the midseparation along the posterior border, in the transverse plane containing the isocenter, at the level of the interface of inner chest wall and the lung $\pm$ 1 cm.

Dose definition

- Absorbed dose shall be described in Gy to water.
- Tissue heterogeneity corrections are not to be done.
- Total treatment dose (breast): 45 Gy
- Dose modification: Boost to volume shall receive 14 Gy, to begin immediately after completion of the breast tangents. *Prescription point boost* defined at the isodose level that completely encompasses excision site with margin. Use clips pre-excision, mammography, etc. to define excision site.
- Other dose modifications
- No other dose modifications are permitted.

Time-Dose Considerations

- Dose:

  Breast: 1.8 Gy/day (45 Gy total)

  Boost: 2 Gy/day (14 Gy total)

- Number of fractions per day: One (1).
- Number of treatment days per week: Five (5).
- Total treatment time

Breast: 5 weeks (25 fractions)

Boost: 1 1/2 weeks (7 fractions)

- Time interval between breast tangents and boost: None (Boost shall be begun the day after the last breast fraction).

Rests

Treatment may be interrupted for no longer than 1 week for confluent moist desquamative skin reactions.

Dose Uniformity and Reference Points:

- Uniformity requirement (Central transverse plane): The dose variation in the target volume shall be within +7 and -5% of the dose to the prescription point within breast parenchyma, i.e., from >3 mm below the skin surface.
- Methods of dose compensation:

  Wedge compensators should be used to achieve dose uniformity. Bolus shall not be used.

Treatment Technique

- Acceptable treatment techniques: Any breast tangent and electron boost techniques that meet described protocol criteria are acceptable.
- Treatment SSD limits: Minimum SSD allowed is 70 cm for SAD = 80 cm or 85 cm for SAD = 100 cm.

- Patient treatment position: Supine with ipsilateral arm raised above head as close to the coronal plane as comfortably possible with patient reproducibly positioned, preferably by a mold.

- Field shaping: *Breast:* Inferior corner blocks may be used (Appendix) to spare normal tissue. *Boost:* Shaped to encompass target volume with margin, as previously described (see Appendix B).

Normal Tissue Sparing

- Techniques to limit critical organ dose: Minimizing lung volume and heart volumes (for left breast tumors) is achieved by careful simulation with a wire around the breast and by keeping the maximum width of lung in the tangent fields to 3 cm and blocking heart as much as possible by appropriate collimator angles and use of an inferior corner block (Appendix A).

- Calculations and Treatment Planning

Required dose calculations:

Prescription point: isodose curves from tangent fields in central transverse plane with inner chest wall indicated, so that 100% is given to the prescription point.

Quality Assurance Documentation

On Treatment Review

Within 3 days of the onset of radiation therapy, forward the following data to:

Arvin S. Glicksman, M.D.
Director
Quality Assurance Review Center
Roger Williams Medical Center
825 Chalkstone Ave
Providence, RI 02908
Tel: 401-456-6500
FAX: 401-456-6550

1) Copies of simulation films

2) Copies of verification films
Picture of the patient in the treatment position with the fields appropriately indicated.

3) RT-1 Dosimetry Summary form

4) Copies of isodose plan and dose calculations.

Within one week of completion of radiation therapy, the following should be submitted to Dr. Glicksman for post-treatment review:

1) Photograph of patient with boost field clearly marked.

2) Copies of localization and verification films for the boost volume and films of any field modifications made subsequent to initial "on treatment" submission. Simulation film(s) with wire indicating the boost field.

3) Copies of all off-axis dose calculations and isodose maps showing tumor, lung and spinal cord volumes.

4) Copies of original dose calculations, and additional dose calculations or isodose curves performed subsequent to the submission of the initial data.

5) A copy of the patient's treatment record (show daily doses and all dose calculations).

6) RT Total Dose Form (RT-2)

ECOG and RTOG institutions should submit radiation therapy materials directly to Dr. Glicksman as noted above.

Any questions regarding the dose calculations or documentation should be directed to:

Bengt Bjarngard, Ph.D., Chief Physicist or
Anita Corrao, Senior Dosimetrist
Quality Assurance Review Center
Roger Williams Medical Center
825 Chalkstone Ave
Providence, RI 02908
Tel: 401-456-6500
FAX: 401-456-6550

Any questions regarding the radiation therapy section of this protocol should be directed to:

Brenda Shank, M.D., Ph.D.
Radiation Oncology Department, Box 1236
Mount Sinai Medical Center
One Gustave L. Levy Place
New York, NY 10029-6574
Tel: 212-241-7500
FAX: 212-410-7194
or
Keith DeWyngaert, Ph.D.
Tel: 212-241-9335
FAX: 212-410-7194

Definitions of Deviations in Protocol Performance

Dose

Minor Deviation: >5% or <5% at the prescription point.

Major Deviation: >10% or <10% at the prescription point.

Volume Considerations

Minor Deviation: >3 cm but ≤4 cm maximum width of lung in tangent fields.

Major Deviation: >4 cm maximum width of lung in tangent fields.

Minor Deviation: Margin around breast or tumor bed less than specified.

Major Deviation: Transecting breast tissue.

Excessive Interruptions

Minor Deviation: Interruption of radiation treatment for > 1 week but ≤2 weeks.

Major Deviation: Interruption of radiation treatment for >2 weeks.

8.0 POTENTIAL TOXICITY, DOSE MODIFICATIONS, AND MANAGEMENT

Tamoxifen (Nolvadex) (NSC-180973):

Animal Studies

In the rat, mouse, beagle dog, and rhesus monkey, maximal blood levels of tamoxifen are seen 1- 6 hours and 24-44 hours after an oral dose. The drug is hydroxylated in the liver to a number of different compounds and excreted in the bile. After a conjugation, an extensive enterohepatic circulation exists, and the conjugated metabolites are hydrolyzed to the unconjugated metabolite, reabsorbed, and reconjugated. Eventually, the drug is excreted in the feces in the metabolized form. Very little drug is excreted in the urine. Biophasic half-lives of 5-12 hours and 62-170 hours were seen in the animal experiments. The antiestrogenic properties of the metabolite are unknown; however, the monohydroxyl metabolite is thought to have activity. Tamoxifen has been shown to cause liver tumors in rats, when they receive doses 20-100 times the human dose.

Human Studies

Using a method incorporating ion pair extraction, photochemical activation, and chromatographic analysis, maximal blood levels of tamoxifen and metabolite are found to occur within 3-12 hours after a single dose of tamoxifen of 10 mg. Preliminary data indicate a half-life after a single dose in excess of 24 hours. Metabolism in humans is similar to animals with extensive enterohepatic circulation. Half-life after prolonged 10 mg BID dosage is variable but appears to be between 4 and 14 days.

Human Toxicity (Please also refer to Model Consent Form)

Toxicity attributable to tamoxifen is minimal and consists mainly of hot flashes (20%), transient nausea (10%), and vaginal discharge (9%). Vaginal bleeding, skin rash, and edema occur rarely (3%). A mild leukopenia or thrombocytopenia will develop in up to 20% of the patients, usually during the second week of therapy, which resolves spontaneously within a week and does not require discontinuation of the drug. Hypercalcemia developed in approximately 1% of patients.

Analysis of data from NSABP protocol P-1E, an ancillary study to NSABP B-14 designed to evaluate ocular toxicity in women taking tamoxifen, and the Breast Cancer Prevention Trial suggests that women taking tamoxifen may be at a slightly increased risk for developing cataracts. In addition, women who have a cataract prior to beginning to take tamoxifen may be more likely to have cataract surgery. Other eye problems, such as corneal scarring or retinal changes, have been reported in a few patients.

An association between tamoxifen therapy and thromboembolic events has been supported by case reports, and the findings of decreased antithrombin levels inpatients receiving tamoxifen in some, but not all studies. Data from a large prospective placebo controlled adjuvant tamoxifen trial shows that the incidence of thromboembolic events was 0.9% in tamoxifen-treated patients versus 0.2% in patients receiving placebo [19].

In placebo controlled adjuvant tamoxifen trials, no hepatocellular tumors have been observed in over 3000 tamoxifen-treated patients and over 3000 patients who received placebo [20]. In a Swedish adjuvant trial in which patients received 40 mg/day of tamoxifen, 2/931 (0.2%) cases of liver cancer were observed in contrast to 0/915 cases in patients treated with placebo.

Tamoxifen has an estrogenic effect on the endometrium, and cases of endometrial cancer in women on tamoxifen have been reported. Some of these resulted in death. The incidence of endometrial cancer is 0.3% (9/3097) in patients receiving 20 mg/day of adjuvant tamoxifen, in contrast to 0.1% (4/3091) in patients treated with placebo. The incidence of endometrial cancer was higher (1.4% versus 0.2%) in a Swedish adjuvant study which treated patients with 40 mg/day of tamoxifen.

Other adverse reactions reported infrequently include distaste for food, depression, dizziness, and light-headedness. Unpublished data suggest a possible increase in second cancers of the gastrointestinal tract among women receiving tamoxifen, and there have been a few reports of liver cancer that have occurred in women taking tamoxifen.

9.0 ANCILLARY THERAPY

9.1 Patients should receive **full supportive care,** including transfusions of blood and blood products, antibiotics, and antiemetics, when appropriate. The reason(s) for treatment, dosage, and the dates of treatment should be recorded on the flow sheets.

9.2 Treatment with other **hormones or analogues or chemotherapeutic agents** may not be administered except for steroids given for adrenal failure or hormones administered for nondisease-related conditions (e.g., insulin for diabetes).

10.0 CRITERIA FOR RELAPSE

Objective Relapse: The appearance of new areas of malignant disease. Biopsy of area of recurrence for histologic documentation and for ER status is encouraged.

11.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

11.1 Extraordinary Medical Circumstances

If at any time the constraints of this protocol are detrimental to the patient's health or the patient no longer wishes to continue protocol therapy or both, the patient shall be withdrawn from this study. In this event:

- Notify the Study Chair.
- Document the reason(s) for withdrawal on flow sheets.
- Follow the patient for all endpoints, i.e., local and distant progression, subsequent mastectomy, survival, second malignancy and death, with flowsheets and appropriate follow-up forms.

11.2 Duration of Treatment - Tamoxifen

Patients will be treated with tamoxifen for five years, cessation of tamoxifen therapy will be at the discretion of the treating physician.

11.3 Recurrence of Carcinoma in the Breast may be treated at the discretion of the treating physician.

Patients in the radiation therapy group may be treated by re-excision or by mastectomy with or without axillary dissection at the discretion of the treating physician.

Patients who have not received radiation therapy may be treated by re-excision with or without radiation therapy or by mastectomy with or without axillary dissection at the discretion of the treating physician.

12.0 DRUG FORMULATION, AVAILABILITY, AND PREPARATION

12.1 Pharmaceutical Data

Formulation: Tamoxifen is supplied in tablets containing the equivalent 10 mg of tamoxifen ICI 46,474 base.

12.2 Storage and Stability

The drug substance is stable for at least 5 years under normal storage conditions and should be protected from light and moisture. Minimal shelf-life appears to be 2 years.

12.3 Administration: Oral.

12.4 Supplier: The drug is commercially available for purchase. *This drug will not be supplied by the NCI.* Tamoxifen is available as 10 mg tablets from Zeneca Wilmington, Delaware, under the trade name Nolvadex.

13.0 REPORTING OF ADVERSE EVENTS

Investigators are required by federal regulation to report possible adverse events. CALGB investigators are required to notify the IRB, the CALGB Central Office, and the Study Chair. As a tracking mechanism, **CALGB requires investigators to route toxicity reports through the Central Office** (see below). All investigators are required to report secondary malignancies that occur during or after treatment on NCI-sponsored protocols using commercial drugs. Reporting of cases of secondary AML/MDS is to be performed using the NCI/CTEP Secondary AML/MDS Report Form. This form is to be used in place of the form FDA #3500 (MedWatch) or the DCT Adverse Event Form for reporting this type of second malignancy. All other secondary malignancies should be reported using the form FDA 3500 (MedWatch). CALGB Form C-215, CALGB Notice of Second Malignancy, must also be completed for all cases of secondary malignancy.

Direct all questions regarding drug therapy to the Study Chair.

- **All deaths** during treatment or within 30 days following completion of active protocol treatment must be reported on FDA Form 3500 within 5 working days.

ADVERSE EVENT REPORTING CHART FOR TAMOXIFEN

PHASE II or III	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Commercial••					
Expected	Flow Sheets	Flow Sheets	Flow Sheets	Ref. to Study	Ref. to Study
Unexpected	Flow Sheets	Flow Sheets	Flow Sheets	Phone/ Written#	Phone/ Written#

••The FDA form 3500 is used for reporting commercial drug toxicities.

***** Grade 4 hematosuppression does not have to be reported for agents known and expected to cause hematosuppression at the dose used.

Phone information **ONLY** to the Study Chair and to the CALGB Central Office within 24 hours. The Central Office is not required to telephone NCI. The notification of the Study Chair and to the Central Office will allow suspension/modification of the study, if the toxicity is greater than anticipated before a large number of patients are put at risk.

"Refer to Study": If the toxicity is well-described in the toxicity section of the protocol and may be anticipated in some patients, phone and written responses to Central Office are not required unless specified in the Adverse Event section of the protocol. For instance, diarrhea requiring hospitalization (Grade 4 GI toxicity) on a 5 FU/leucovorin protocol, may not require reporting unless it is mandated by instructions in the protocol.

The reporting of adverse events described in the table above is in addition to and does not supplant the reporting of toxicities as part of the report of the results of the clinical trial, e.g., study summary forms, cooperative group data reporting or Clinical Trials Monitoring Service case report forms. **All adverse events should also be reported to your local Institutional Review Board.**

All reactions in a "reportable" category must be reported unless it is documented on flow sheets or follow-up forms or both that the treatment is definitely not responsible for the toxicity.

ECOG Institutions:

ADR reporting should be based on the CALGB Common Toxicity Criteria (Appendix 1).

ECOG suggests Adverse Drug Reaction reports be submitted on the Adverse Reaction (ADR) Form for Investigational Drugs (Form 391RF), and the form must be signed by the treating investigator. However, the MedWatch (FDA Form #3500) is also acceptable for reporting ADRs on commercial arms. All ADR reports sent to ECOG are to be accompanied by copies of all available and updated study data (on-study forms, flow sheets, follow-up forms, etc.), as well as evidence of notification to the institutional IRB.

The protocol does not contain IND agents; toxicities occurring on treatment arms are to be considered commercial.

Guidelines for reporting of toxicities occurring with commercially available agents:

- Any ADR which is BOTH serious (Grade 4) or life-threatening (Grade 5) AND unexpected.
- Any Grade 5 event while on treatment if CLEARLY related to the commercial agents(s).
- Any increased incidence of a known ADR

Submit original written ADR form to the IDB and a copy to the ECOG Coordinating Center within 5 working days of the event.

The ECOG Coordinating Center will call the CALGB Operations Office to report the telephone ADR calls. The ADR forms will be forwarded to the CALGB Operations Office by the ECOG Coordinating Center.

NCI Telephone Number: (301) 230-2330
NCI Mailing Address:
Investigational Drug Branch
P. O. Box 30112
Bethesda, MD 20824

ECOG Telephone Number: (617) 632-3610
ECOG Address:
ECOG Coordinating Center
Frontier Science
ATTN: ADR
303 Boylston Street
Brookline, MA 02146-7648

Reporting of All Second Primary Cancers

	NCI/CTEP Secondary AML/MDS Report Form[1]	ECOG Second Primary Form[2] (Form # 630)
AML/MDS	**X**	
All other secondary cancers		**X**

[1] To be completed within 30 days of diagnosis of AML/MDS that has occurred during or after protocol treatment. A copy is to be sent to ECOG and to the NCI, accompanied by copies of the pathology report and when available, a copy of the cytogenetic report.

[2] To be submitted to ECOG within 30 days of diagnosis of a new primary cancer during or after protocol treatment, regardless of relationship to protocol treatment. Not for use for reporting recurrence or metastatic disease. A copy of pathology report should be sent, if available.

Non-Treatment Related Toxicities: If a toxicity is felt to be outside the definitions listed above and unrelated to the protocol treatment, this must be clearly documented on the flow sheets which are submitted to the ECOG Coordinating Center according to the Data Submission Schedule. This does not in any way obviate the need for reporting the toxicities described above.

RTOG Institutions:

Any fatal (grade 5) or life threatening (grade 4) adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman by telephone within 24 hours of discovery. Known grade 4 hematologic toxicities need not be reported by telephone. Unknown adverse reactions ($\geq$ 2) resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters' Data Management Staff, to the Study Chairman and to the IDB within 10 working days of discovery. FDA Form 3500 is to be used in reporting details. All relevant data forms must accompany the RTOG copy of Form 3500. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting. A special written report may be required. Reactions definitely thought not to be treatment related should not be reported; however, a report should be made if there is a reasonable suspicion that the effect is due to protocol treatment.

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15.0 MODEL CONSENT FORM: EVALUATION OF LUMPECTOMY, TAMOXIFEN, AND IRRADIATION OF THE BREAST COMPARED WITH LUMPECTOMY PLUS TAMOXIFEN IN WOMEN 70 YEARS OF AGE OR OLDER WHO HAVE CARCINOMA OF THE BREAST THAT IS LESS THAN OR EQUAL TO 2 CM AND CLINICALLY NEGATIVE AXILLARY NODES: A PHASE III STUDY

We invite you to take part in a research study for women 70 years old or older who have breast cancer. It is important that you read and understand several general principles that apply to all who take part in our studies: (a) taking part in the study is entirely voluntary; (b) personal benefit may not result from taking part in the study, but knowledge may be gained that will benefit others; (c) any significant new findings that relate to your treatment will be discussed with you; (d) you may withdraw from the study at any time without penalty or loss of any benefits to which you are otherwise entitled. The nature of the study, the benefits, the risks, inconveniences, discomforts, and other pertinent information about the study are discussed below. You are urged to discuss any questions you have about this study with the staff members who explain it to you.

Study Description

Approximately 572 patients will participate in this study. We are trying to determine how effective radiation therapy after lumpectomy, with or without removal of lymph glands from your armpit, is for older women. All patients will receive tamoxifen which is taken by mouth each day for five years, unless your physician tells you to discontinue it. During treatment, various blood tests and x-rays will be used to monitor your disease.

Procedure for Randomization

It is not clear at the present time which of the treatments in this program would be better for you. For this reason, the plan offered to you will be picked by a method called randomization. Randomization means that your physician will call a statistical office, which will assign one of the therapies to you. The chances of your receiving either of the treatments are approximately equal. After the randomization, you would receive one of the following treatment programs:

1) Radiation therapy plus Tamoxifen

2) Tamoxifen

If one treatment is found to be less effective than the other, you will be informed and further treatment will be discussed.

Risks

Adverse reactions to tamoxifen are infrequent and seldom severe enough to require discontinuing treatment. The following information discusses the side effects that have been observed.

A. Secondary Cancer

1. Endometrial cancer - Tamoxifen may cause changes in the lining of the uterus (endometrium). An early sign of these changes may be abnormal vaginal bleeding or pelvic pain. Patients should report such symptoms to their physician immediately and seek evaluation in a timely fashion. The level of increased risk of uterine cancer associated with tamoxifen is still uncertain. After an average of 8 years of follow-up, the annual (per year) risk observed in a large-scale trial (NSABP B-14) of breast cancer patients taking 20 mg of tamoxifen daily is about 2 per 1,000 women. This means that on the average 2 cases of endometrial cancer were diagnosed among every 1000 women receiving tamoxifen during each year of study participation and follow-up. This level of risk is approximately 3 times greater than that of a similar group of women in the general population. Uterine cancer is a potentially life-threatening illness. Some breast cancer patients who develop uterine cancer while taking tamoxifen in the above studies have subsequently died from uterine cancer. However, most of

the uterine cancers that have occurred have been diagnosed at an early stage when treatment is highly effective. The treatment for early-stage uterine cancer usually involves a hysterectomy (surgical removal of the uterus) as well as removal of the fallopian tubes and ovaries, and may include radiation therapy. In view of this risk, it is currently recommended that all patients receiving tamoxifen have a gynecologic exam before starting treatment and at least yearly thereafter. Of course, if you have had a total hysterectomy, there is no risk of getting uterine cancer.

2. Other cancers - Data from one large U.S. study have not shown an increase in other (non-uterine) cancers in women taking tamoxifen. However, other unpublished data suggest a possible increase in second cancers of the gastrointestinal tract among women receiving the drug. There have been a few reports of liver cancer that have occurred in women taking tamoxifen. Although tamoxifen can cause liver cancer in rats, it is not known to be a cause of liver cancer in humans. Whether an increased risk for other (non-uterine) cancers is associated with tamoxifen is still uncertain and continues to be evaluated.

B. Side-Effects

Frequent

1. Hot flashes

2. Nausea and/or vomiting

3. Menstrual irregularities including vaginal bleeding and vaginal discharge and dryness.

Infrequent

4. Thrombotic Events (abnormal occurrence of blood clots) - Some studies, but not all, have shown that tamoxifen causes an approximate 1% increase in the incidence of thrombotic events. These included superficial phlebitis, deep vein thrombosis, and pulmonary embolism. Rarely, death has occurred from such events. Patients with a pre-existing history of such problems should discuss the indication for tamoxifen treatment carefully with their physician.

5. Liver toxicity - Abnormal liver function tests including rare cases of more severe liver abnormalities such as fatty liver, cholestasis (back-up of bile), hepatitis, and hepatic necrosis (destruction of liver cells). A few of these serious cases resulted in death but whether tamoxifen was the cause of these problems still remains uncertain.

6. Eye changes - Women taking tamoxifen may be at a slightly increased risk for developing cataracts (a clouding of the lens inside the eye). As women age, they are more likely to develop cataracts whether or not they take tamoxifen. Cataracts may lead to a decrease in vision. Eye surgery may be required to remove the cataract and improve vision. Women who have a cataract before beginning to take tamoxifen may be more likely to have cataract surgery. Other eye problems, such as corneal scarring or retinal changes, have been reported in a few patients. You should report any changes in your vision, or other eye problems, to your study physician.

7. Skin rash

8. Peripheral edema (swelling)

9. Pruritus vulvae (genital itching)

10. Depression

11. Dizziness and light-headedness

12. Headache

13. Hair thinning and/or partial hair loss

14. Ovarian cysts have been noted in premenopausal women.

15. Endometrial (uterine lining) changes including polyps, hyperplasia, and endometriosis (endometrial cells outside the uterus).

16. Thrombocytopenia (decrease in platelet count)

17. Tumor flare manifested by bone and tumor pain and sometimes hypercalcemia in those patients treated for metastatic disease. Patients with increased pain may require additional analgesics. Often such symptoms signal a good response to treatment and these symptoms usually subside rapidly.

C. Benefits

Tamoxifen has been shown to decrease the risk of breast cancer recurrence after appropriate surgery. For this reason, it was approved by the Food and Drug administration for treatment of postmenopausal women with axillary node-positive disease and for women with axillary node-negative breast cancer. It is also approved for treatment of metastatic breast cancer in women and men. Studies have also shown that tamoxifen can reduce the occurrence of secondary breast cancers in women who are taking the drug to prevent recurrence of their original tumor. In addition, it has been shown to lower the level of cholesterol and other fats in the blood, and this may reduce the risk of heart disease. Loss of bone minerals is also slowed by tamoxifen which may result in less bone fractures as women age.

The **side effects of radiation therapy** include: redness and irritation of the skin with peeling and increased pigmentation of the skin that may be persistent. There may be some increased fullness of the breast for a period of time. Very rarely a transient dry cough with or without fever may develop a month or two after irradiation is completed. Also, extremely rarely, a rib may develop a small fracture in the area of the chest that was treated, and a sharp pain may suddenly develop. This is highly unusual with modern radiation therapy techniques, and if it should occur, heals on its own in a month or two without any local treatment required. Even more rarely, a second cancer may develop in the tissues exposed to irradiation.

Unanticipated side effects may occur that have not been reported. If you have any unusual symptoms, report them immediately to your physicians.

In an attempt to avoid side effects, your physician will examine you and obtain laboratory tests (blood tests, chest x-rays, and scans) to determine the effects of your treatment.

Alternatives

Most patients with breast cancer have the lymph nodes under their arms removed. This surgical procedure is not being recommended in this study as we feel its risks may outweigh its benefits. There are 2 benefits to removing the lymph nodes: (1) it may prevent cancer recurrence under the arm in 5-15 patients out of 100, and (2) looking at the lymph nodes under the microscope often helps to make the decision about whether further non-surgical treatment is needed. In this study, all participants will receive further treatment with the drug tamoxifen (Nolvadex®), so we do not need to look at the lymph nodes in order to make this decision. Additionally, tamoxifen may prevent cancer recurrence under the arm in those patients in which it might recur. The risk of removing the lymph nodes is a 1-2 hour operation under general anesthesia with possible injury to nerves and blood vessels in the area, resulting in some persisting pain, numbness, limitation of motion and swelling of the arm. If you have already had an axillary dissection and your surgeon thinks that you would benefit from participating, you are still eligible for enrollment in this protocol.

Other treatments for your disease include modified radical or simple mastectomy.

No clear evidence exists that other treatments are significantly more effective than those used in this study.

Costs

Any procedure related solely to research which would not otherwise be necessary will be explained. Some of these procedures may result in added costs, and some of these costs may not be covered by insurance. Your doctor will discuss these with you.

Circumstances Under Which Your Participation May Be Terminated Without Your Consent

If health conditions occur that would make your participation possibly dangerous or if other conditions occur that would make participation detrimental to you or your health, your doctor may discontinue this treatment.

Patient Protection

If at any point during the duration of this treatment you feel that you have been:

1) inadequately informed of the risks, benefits, or alternative treatments, or

2) encouraged to continue in this study beyond your wish to do so,

you may contact either the investigator in charge or a member of the human protection committee of _____Hospital; names and phone numbers are listed at the end of this form.

In the event that complications occur as a result of this treatment, you will be provided with the necessary care. However, you will not automatically be reimbursed for medical care or receive other compensation as a result of any complications.

Participation is voluntary. If you choose not to participate or wish to withdraw your consent to participate in this treatment at any time, it will in no way affect your regular treatments or medical care.

You should understand that research studies of patients may be conducted on other aspects of health care, which may include topics such as the cost and convenience of treatment, and other issues directly affecting patient care. Your signature below indicates your permission to be included in such group studies. You should also understand that cancer patients and their family members are sometimes asked to complete voluntary questionnaires to assess their quality of life. Your signature indicates that you would consider participating in additional, related surveys, if they are carried out.

You will be asked to complete a Background Information Form; the information you supply on this form helps us to define groups of patients being treated so that we may better understand the relationship between these groups and results of their treatment. Completion of the form is voluntary, and your cooperation is appreciated.

The results of this study may be published, but individual patients will not be identified in these publications.

A record of your progress will be kept in a confidential manner at _____

Hospital and also in a computer file at the statistical headquarters of the Cancer and Leukemia Group B (CALGB) and the Eastern Cooperative Oncology Group (ECOG).

Results of your tests, including blood samples and pathology slides, and confidential information contained in your medical record may not be furnished to anyone unaffiliated with Hospital or CALGB without your written consent, except as required by federal regulation. There is a possibility that your medical record, including identifying information, may be inspected or photocopied or both by the National Cancer Institute, the sponsor of this study, the Food and Drug Administration, or other federal or state government agencies in the ordinary course of carrying out their governmental functions. If your record is used or disseminated for government purposes, it will be done under conditions that will protect your

privacy to the fullest extent possible consistent with laws relating to public disclosure of information and the law-enforcement responsibilities of the agency.

This research project and its treatment procedures have been fully explained to you. All experimental procedures have been identified and no guarantee has been given about possible results. You have had the opportunity to ask questions concerning any and all aspects of the project and any procedures involved.

By signing below, you grant permission for the use of your bodily fluids, substances and tissues, which may be obtained during testing, operative procedures or other standard medical practices to which you have or will give your consent during the course of your treatment, for use in scientific research, teaching purposes or development of new tests or products. Your signature indicates that you have read this form, have received acceptable answers to any questions, and willingly consent to participate. You will receive a copy of this form.

(THE FOLLOWING SECTIONS ARE FOR CALGB INSTITUTIONS ONLY; PATIENT AND WITNESS SHOULD INITIAL AND DATE EACH PAGE)

Other research being done in connection with this project: The United States Army Medical Research and Material Command is supporting CALGB research concerning the causes of breast cancer and its response to various treatments. The following part of this consent form has been approved by the U.S. Army and contains certain statements required in consents for research conducted with support from the Department of Defense.

Collection of tissue, blood and urine: This protocol provides for the collection and use in research of portions of tissue obtained at the time of your surgery for breast cancer. With your permission, blood and urine will also be collected and stored for future research conducted by investigators working with CALGB. The tissue, blood and urine samples collected will form a "registry" of material to be used for breast cancer research. Urine and blood samples will be obtained during routine urine and blood tests performed for your care, including before your treatment begins, after your treatment is completed, and at other times during your treatment and follow-up care. About one-half cup of urine and one extra tube of blood, about 1-1/2 tablespoons, will be sent to a central laboratory where it will be stored and used for breast cancer research. There will be no additional cost to you as a result of obtaining the tissue, blood, and urine samples used in this study.

Benefits: You are not expected to benefit personally from participation in these studies involving tissue, blood, and urine samples. Your participation may help investigators to better understand breast cancer and lead to improved treatment for future breast cancer patients.

Confidentiality: Information about your participation and test results will be stored only at the CALGB Statistical Office at Duke University. This information will not be put in your medical records and will not be available to you, your doctors, or to individual researchers in CALGB. All information is stored under conditions to protect the privacy of study participants. In our analyses, you will never be listed by name. The results of these studies may be published, but individual patients will not be identified. Representatives of the U.S. Army Medical Research and Material Command, the sponsor of this study, may review research records as a part of their responsibility to protect human subjects in research.

I give permission for my tissue_____ blood_____ and urine_____ to be collected for research purposes (please initial each item for which you grant permission. If you do not give permission for any of these specimens, leave blank.)

Retention of rights: You are permitted to retain rights to any commercial application that may arise because of the use of your specimens in this project. Retention of these rights, however, increases the cost and paperwork for the CALGB and for the granting agencies supporting this research. Because of this you may wish to sign the statement below:

I voluntarily and freely donate any and all blood, urine and tissue samples to the U.S. Government and hereby relinquish all right, title, and interest to said items:
_____Yes ____No Initial_____

Questionnaire: If you consent, you may be asked to participate in studies that attempt to assess the quality of life during and after treatment. We request that you take a few minutes to complete a questionnaire providing information about cancer in your family. On the basis of this questionnaire, a trained interviewer from CALGB may call you and ask you if you are willing to answer additional questions.

I agree to complete the questionnaire and give permission to be contacted by phone, if chosen for an interview: If yes, initial here:_____

Use of these specimens: Because it is impossible for you, your doctors, or CALGB to know what laboratory tests may be discovered in the future, you have given your permission for such studies to be performed without restrictions except as noted in this consent form, and do not wish to be contacted for permission to conduct each specific test. Investigators wishing to perform research using samples collected in this study must first receive approval from the CALGB Steering Committee for this project, and agree in writing that the samples will be used only as agreed upon by the CALGB. The registry will be used only for studies on or related to breast cancer. Neither you nor your doctors will receive the results of these research tests.

Statements required by the granting agency: The United States Army Medical Research and Materiel Command which supports the registry functions described above, not your treatment, requires the statements that follow in this section. These statements pertain only to the registry function described above, not your treatment for breast cancer on the clinical trial that you are entering.

"You are authorized all necessary medical care for injury or illness which is the proximate result of your participation in this research. Contractors must provide such medical care when conducting research on private citizens. Other than medical care that may be provided there is no compensation available for your participation in this research study; however, you understand this is not a waiver or release of your legal rights."

By signing below, you indicate that you have read this form, received acceptable answers to any questions, and willingly consent to participate. You will receive a copy of this form.

_____ _____
(Patient's Signature) (Date) (Name of Responsible Investigator (Phone #)

_____ _____
(Physician's Signature) (Date) (Name of IRB Representative) (Phone #)

_____
(Witness's Signature) (Date)

CONSENT FOR STUDIES OF HERITABLE (FAMILIAL) CANCER GENES (CALGB INSTITUTIONS ONLY)

In addition to the studies above, the registry will be used for studies of cancer genes that can be inherited. A number of factors contribute to the risk of developing breast cancer. Some of these are cancer susceptibility genes that are carried from one generation to the next in certain families. These appear to cause a small fraction of all breast cancer cases. We ask that you agree to participate in our studies of genes that may be involved in the evolution of breast cancer. It is not likely that information generated from our studies will be of benefit to you

individually. However, your participation in this study may help us to better understand breast cancer and lead to a benefit for future patients.

Risks, Safeguards, and Reduction of Risk:

There are no absolute legal protections against discrimination on the basis of genetic information. For this reason, CALGB will treat all studies using these specimens as **research only, and will not furnish results of the analyses to anyone, including you or your physician.** Instances are known in which a patient has been required to furnish genetic information as a precondition for application for health insurance and/or a job. Participation in this study **does not** mean that you have had genetic testing. Genetic testing means having a test performed and the results provided to you and your physician. If you are interested in having genetic testing performed, you should consult your physician, as commercial tests are available. Your physician can provide you with the necessary information to determine if such a test would be appropriate for you.

Research laboratories that test your blood will not be given any information about you. Information about your participation and about the results of these tests will be stored only at the CALGB Statistical Office at Duke University. This information will not be made available to your doctors or to individual researchers in CALGB. This information will not be put in your medical records. All information in the CALGB computer is stored under conditions which limit access in order to protect the privacy of study participants. Information on the presence or absence of familial cancer genes will be stored in separate files with the highest level of security and linked with the rest of your data only for the performance of statistical analyses that are carried out under the direction of CALGB statisticians. As indicated above, these analyses will not list you by name.

If you decide not to allow your specimens to be used for studies of cancer genes that can be inherited, you should **not** sign this section of the consent form. However, you may still agree to donate tissue, blood and urine for studies of traits that cannot be passed from one generation to another, and to complete the questionnaire.

Method: As part of providing your care and adjusting your treatment your doctor will be drawing routine blood tests on a regular basis. With your approval, three extra tubes of blood will be drawn (about 5 tablespoons) once during routine blood tests performed before you begin your treatment. You should experience no extra discomfort or side effects. Your blood specimen or non-cancerous cells that were removed at surgery will be the source of DNA that will be used for research studies, including studies of genes that are passed from generation to generation. Your DNA will become the property of the CALGB specialized registry and may be shared with investigators from a number of qualified academic institutions that are studying the genetic causes of cancer. Specimens shared with these investigators will not by identified by patient name.

I hereby give my permission for a blood sample to be obtained that will allow for the study of my genes, including possible family cancer genes. I understand that results of the research studies will not be made available to me or my physician.

_____		_____	
(Patient's Signature)	(Date)	(Name of Responsible Investigator)	(Phone #)
_____		_____	
(Physician's Signature)	(Date)	(Name of IRB Representative)	(Phone #)
_____			
(Witness's Signature)	(Date)		

CALGB EXPANDED COMMON TOXICITY CRITERIA

CALGB EXPANDED COMMON TOXICITY CRITERIA

1. Toxicity grade should reflect the most severe degree or most abnormal lab value occurring during the evaluated period.

2. Toxicity grade = 5 if that toxicity caused or contributed to the death of the patient.

3. Do not code if the symptoms are certainly or most likely due to disease or other non-treatment cause.

4. If patient at baseline has grade 1 or greater, do not code unless patient worsens due to toxicity. If there is worsening, code the level the patient increases to - DO NOT adjust for baseline.

5. Note that for some Toxicity certain grades are not defined and may not be coded, e.g. no grade 3 or 4 Alopecia.

6. Granulocytes (mature cells) refers to segmented neutrophils (Segs, Polys, PMN, Polymorphonuclear leukocytes) plus bands (Staff cells, Stabs). To calculate granulocyte count multiply the white count by the % bands + % segmented neutrophils.

7. All coded toxicities must be documented and described on accompanying flowsheets.

September 11, 1989

APPENDIX II
(Including Appendices A and B)

Appendix A	Radiation Therapy diagram
Appendix B	Radiation Therapy diagram
C-187	CALGB Patient Background and Information Form
C-294	CALGB Adjuvant Breast Cancer: On-Study Form
ST-3	CALGB Solid Tumor Initial Flow Sheet
C-490	CALGB Tracking Form (Tissue Blocks)
C-286	CALGB Physician Evaluation of Treatment Results
C-287	CALGB Patient Evaluation of Treatment Results
RT-1	Dosimetry Summary Form
RT-2	RT Total Dose Form
C-341	CALGB 9343 Follow-up Form
ST-4	Solid Tumor Flow Sheet
C-215	CALGB Notification of Second Malignancy
C-113	CALGB Notification of Death Form