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Phase I Dose Escalation Study of Topical Bexarotene in Women at High Risk for Breast Cancer

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Abstract

Agents that can reduce the incidence of hormone receptor negative breast cancer are currently lacking. Rexinoids such as bexarotene significantly reduced mammary tumor development in preclinical mouse models. Oral bexarotene in BRCA mutation carriers significantly decreased cyclin D1 in breast cells suggesting biological activity on breast tissue. This study evaluated topical bexarotene 1% gel applied to one unaffected breast in women at high risk for breast cancer for 4 weeks to assess safety and toxicity. Secondary objectives included assessment of bexarotene

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concentrations in the plasma and breast tissue. In the dose escalation phase, women were assigned to one of three different dose levels: 10mg (1ml) every other day, 10mg (1ml) daily, 20mg (2ml) daily. Dose limiting toxicity (DLT) was defined as a grade 2 skin adverse event for at least 6 days or any grade 3 or 4 adverse event related to study drug. A total of 14 women were enrolled with 10 participants at the every other day dose level and 4 participants at daily dosing. Two skin DLTs were experienced at daily dosing and therefore further enrollment was discontinued per protocol. An additional 10 participants were enrolled at the maximum tolerated dose as part of the dose expansion phase. These individuals tolerated the treatment with minimal adverse events. Maculopapular rash at the treatment site was the most common adverse event related to study drug and resolved within a few days of discontinuation. Bexarotene was detectable in breast tissue at the 10mg daily every other day dose.

Keywords

rexinoid; breast cancer; prevention; bexarotene

Introduction

Breast cancer is the most common malignancy among women in the US, and prevention of this disease is therefore a major public health concern. Preventive therapy with anti-estrogens, including tamoxifen, raloxifene, and exemestane, has been shown to reduce the incidence of hormone receptor (HR)-positive breast cancer. However, agents that can reduce the incidence of hormone receptor negative breast cancer are currently lacking.

Rexinoids such as bexarotene are vitamin A analogues that have been shown to be involved in cell differentiation, growth, and apoptosis (1). In preclinical mouse models that develop ER-negative breast cancers, bexarotene showed a significant reduction in mammary tumor development(2–4). In p53-null mice, bexarotene was given at 10mg/kg and 100mg/kg by gastric gavage and a 75% reduction in mammary tumor development was found in virgin mice at the higher dose level (4). Similar to humans, (MMTV)-ErbB2 mice undergo a multistage process of mammary tumorigenesis that progresses from normal mammary tissue to hyperplasia, mammary intraepithelial neoplasia (MIN) and finally invasive cancer. Li and colleagues gave bexarotene at 100mg/kg by oral gavage for 2 to 4 months in MMTV-erbB2 transgenic mice starting at three months of age(3). They found that bexarotene prevented the development of premalignant mammary lesions such as hyperplasia and MIN that is similar to human ductal carcinoma in situ (3).These findings highlight that the cancer preventive effect of bexarotene is mainly from inhibition of cell proliferation. Bexarotene has also shown prevention of mammary tumor development in ER+ NMU induced rat mammary tumor models(5). Animals treated with bexarotene had a 90% reduction in tumor burden(5).

Oral bexarotene was initially clinically evaluated in phase 2 and 3 clinical trials for refractory or persistent early stage cutaneous T-cell lymphoma (CTCL). Responses of greater than 50% improvement in skin lesions were noted in 54% of patients receiving bexarotene at 300mg/m^2 and 67% of patients at doses greater than 300mg/m^2. Seventy-three percent of patients that crossed over from a lower dose to higher doses responded to the

increased dose. Hypertriglyceridemia, hyperlipidemia, headache, and hypothyroidism were noted in a significant number of patients and were reversible with discontinuation of drug. Since increased toxicity was noted at dose level greater than 300mg/m^2, the recommended dose is 300mg/m^2 in patients with refractory CTCL(6).

Bexarotene has been developed as a gel and evaluated in clinical trials in patients with early stage CTCL. Based on the positive results of these studies, topical bexarotene is currently an FDA approved drug for the treatment of CTCL. In phase I and II trials conducted by Breneman and colleagues, topical bexarotene was applied to the skin lesions directly at different concentration levels of 0.1%, 0.5%, and 1% bexarotene gel. Patients started at the lowest concentration and applied the gel to affected skin lesions daily, and titrated to twice daily dosing after 2 weeks if they were tolerating the medication. As patients were able to tolerate gel application, bexarotene concentration was increased to 0.5% and then 1% and applying gel up to 4 times daily as tolerated. Most patients were able to tolerate 1% gel at twice daily dosing. The total dosage each patient received depended on the size and the number of lesions. Bexarotene gel was well tolerated and the most frequent adverse events in 67 patients were rash (73%), pruritus (33%), and pain (24%) with most being mild to moderate in severity. Systemic concentrations of bexarotene were extremely low and systemic side effects noted with oral bexarotene such as hyperlipidemia, hypothyroidism, and hypertriglyceridemia were not detected when medication was applied topically(7). Bexarotene 1% gel was also evaluated in a Phase I/II trial for alopecia areata and was applied to half of participants' scalp to assess response. Out of 42 patients, 31 (73%) experienced some dermal irritation with only 4 patients experiencing grade 3 dermal irritation(8). The most common adverse event noted was mild erythema in the area of treatment and it resolved with discontinuation of the drug(8).

Based on the preclinical findings in ER-negative mouse models, oral bexarotene at 200mg/m^2 has been evaluated in women at high risk for breast cancer based on their genetic risk. Bexarotene was found to reduce cyclin D1 RNA expression in breast cells from postmenopausal women(9). A non-significant reduction in Ki-67 expression was also seen in these post-menopausal women. Significant systemic side effects such as hypertriglyceridemia, hypercholesterolemia, and hypothyroidism were also found and were reversible after discontinuation of the drug(9). These results demonstrated that bexarotene has a biological effect on breast cells in women at high risk of breast cancer.

Broad uptake among appropriate populations has been low for other cancer prevention medications such as tamoxifen and raloxifene due to the systemic side effects of menopausal symptoms and blood clots. Topical agents applied directly to the breast could positively affect the breast tissue without leading to systemic side effects. Mauvais-Jarvis and colleagues evaluated trans-4-hydroxytamoxifen (4-OHT), an active metabolite of tamoxifen, by topical administration to the breast(10). They evaluated 4-OHT absorption through the skin and its metabolism by applying 80 muCi, [^{3}H]-4-OHTto the breast in patients with invasive breast cancer whom subsequently underwent mastectomy for their tumor. 4-OHT was detected in the cytosol as well as in the nuclear extract as early as 24 hours of application and decreased in concentration over time at 7 days after application. Topical

application of 4-OHT to the breast revealed delayed appearance of radioactivity in plasma and urine after administration in comparison to administration on the abdomen (10).

Rouanet *et al.* evaluated topical 4-OHT in a pre-surgical trial of 55 postmenopausal women with invasive ER positive breast cancer. Patients applied 4-OHT for 2 to 3 weeks at various dose levels compared to another group receiving oral tamoxifen at 20mg/day. Tissue proliferation, as measured by Ki-67 levels between baseline and after treatment, decreased in all groups(11). Lee and colleagues evaluated topical 4-OHT in women with DCIS for 6 to 10 weeks prior to surgery(12). Women were randomized to either 4-OHT (4mg/day) or oral tamoxifen (20mg/day) and assessed change in Ki-67 in their DCIS lesions. Tissue concentration of drug was similar between 4-OHT and oral tamoxifen whereas systemic concentrations of 4-OHT were lower than oral tamoxifen. Changes in proliferation were also similar across both arms. No serious adverse events were noted with topical 4-OHT gel in this study. These studies highlight the efficacy of using topical agents on the breast without significant toxicitiesy

We hypothesized that topical bexarotene can be applied to the breasts as a prevention agent with penetration to the breast tissue without having the high systemic drug levels and toxicity seen with oral bexarotene. Data from previous prevention studies with topical tamoxifen support the concept of topical agents penetrating the breast tissue and exhibiting biological activity in the tissue(10–13). Preclinical models have clearly shown the effect of bexarotene in reducing the incidence of estrogen receptor-negative and estrogen receptor positive breast cancer(2–5). Based on this data, we conducted a phase I study with an expansion phase to evaluate topical 1% bexarotene gel in women at elevated risk for developing breast cancer.

Methods

Patient Population:

Women 18 years old or older that were at elevated risk for breast cancer, defined as a history of breast cancer and at least 5 years from diagnosis, precancerous high risk breast lesion such as lobular carcinoma in situ or atypical hyperplasia, BRCA1/2 mutation carrier, or a breast cancer risk assessment >1.7% in 5 years or a lifetime risk >20% assessed by Gail or Tyrer-Cuzick models were eligible for the study. Risk factors for development of either ER+ or ER- breast cancer were included for eligibility criteria as the main mechanism of action for bexarotene is inhibition of cell proliferation and both subtypes of breast cancer could be affected. Women must have had adequate accessible breast tissue that consisted of one breast unaffected by invasive cancer and not radiated. History of benign core biopsy in the unaffected breast was permitted. Benign breast imaging within 6 months of study drug initiation was required. Participants were not to have used anti-estrogen therapy or any other investigational treatment for breast cancer prevention or therapy within six months of study enrollment. Participants were required to have normal organ function, ECOG performance status of ≤1. Women of reproductive potential must have had a negative pregnancy test at baseline and be willing use a reliable contraceptive method 1 month prior to study entry, through the duration of study, and at least 1 month after discontinuation of study drug. Women had to discontinue any retinoids or retinol containing agents at least 1 month prior

to study entry and not have any prior history of allergies to retinoids or bexarotene. Eligible participants completed and signed an informed consent and the study was approved by the NCI Central Institutional Review Board, which follows US Common Rule.

Study Design:

Women at high risk for breast cancer were recruited for the trial at the Cancer Prevention Center at MD Anderson Cancer Center from June 2018 until November 2021 and received treatment with bexarotene 1% gel to one unaffected breast for a duration of 4 weeks (Figure 1A). Participants received a phone call to assess for toxicity at Day 8 and presented for an in-person study visit at Day 15 and Day 28 (End of treatment). Participants enrolled in the dose escalation phase could have an optional breast biopsy at the end of treatment to assess for bexarotene concentration in the tissue. Participants in the dose expansion phase were required to have end of treatment biopsies. Primary endpoints were to assess safety and toxicity of gel application to the one unaffected breast. Adverse events were assessed using NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) criteria. Based on previous topical bexarotene studies, adverse events were likely to be expected in the application site area and thus CTCAE v4.0 criteria assessing skin toxicity were modified (Table 1). Secondary endpoints included assessment of bexarotene concentrations in the plasma and breast tissue as well as changes in safety biomarkers including lipid profile, thyroid function, and calcium.

Bexarotene gel was provided by Bausch Health and repackaged by the NCI DCP Repository in dose metered pumps to allow for correct dose dispensing for application. Canisters were metered to dispense 1mL per actuation and thus contain 1g of bexarotene gel per actuation. One gram of bexarotene gel contained 10mg of active bexarotene. Each gel canister contained approximately 30 reliable doses. All participants were given CeraVe moisturizing lotion which they could be applied to the breast at least 4 hours after drug application to keep the skin moisturized. They were advised to keep the application area dry and covered as well as to avoid sun exposure to the area.

Dose Escalation Phase:

Women were initially recruited to the dose escalation phase and enrolled into one of three dose cohorts: 10mg (1ml of gel) every other day, 10mg (1ml of gel) daily, 20mg (2mls of gel) daily. The first three participants were assigned to the lowest dose level of 10 mg every other day. New cohorts of 3–4 participants were enrolled after toxicity had been evaluated for all current participants for 4 weeks (Figure 1B). Dose Limiting Toxicity (DLT) was defined as a grade 2 skin adverse event that persisted for at least 6 days or any grade 3 or greater adverse event related to the study drug. In addition, a grade 2 skin adverse event that recurred and persisted for at least 3 days was considered a DLT. The Maximum Tolerated Dose (MTD) was defined as the highest dose level with at most 2 participants with DLT out of 10 participants treated.

Participants were instructed to apply the gel to the upper outer and upper inner quadrants of one breast to minimize skin to skin contact. Since the lower quadrants of the breast have an increased chance to retain moisture and have direct contact with skin from the chest wall,

gel was not permitted for application in these areas due to greater chance for adverse skin reactions. Participants applied the gel every other day for one week and then increased the dose to daily for 3 weeks if they were assigned to the daily dosing arm. If participants were assigned to every other day dosing, they continued with this dosing schedule for the entire 4 weeks. Participants that were assigned to 20 mg (2ml) daily were intended to first start with application of 10mg (1ml) to the breast every other day for 1 week, then increase to 10mg (1ml) daily for 1 week, and then increase to 20mg (2ml) daily for the remaining 2 weeks as long as it is tolerated. Compliance was defined as applying at least 75% of the bexarotene gel doses.

Dose Expansion Phase:

An additional 10 participants were enrolled in the dose expansion phase once it was established that the 10mg (1ml gel) every other day dosing was the MTD (Figure 1C). Participants in the dose expansion phase were all enrolled at the every other day dose level for 4 weeks and were required to have a breast biopsy at the end of treatment. Toxicity and monitoring for DLTs continued with all participants. Participants underwent the same schedule of events as the dose escalation phase participants.

Breast Core Biopsy and Tissue Processing:

Six women in the dose escalation phase and nine women in the dose expansion phase completed end of study ultrasound guided core breast biopsies. Four tissue cores were obtained from each participant. Two cores were flash frozen for drug concentration analysis. One core was formalin fixed and paraffin-embedded for histological evaluation to rule out malignancy and stored for future use. One additional core was stored in RNA later and placed in −80°C freezer for future exploratory gene expression analysis.

Bexarotene Tissue and Plasma Analysis:

Bexarotene drug level was determined using LC-MS/MS (Triple Quad™ 5500; SCIEX, Framingham, MA). A 100 μL aliquot of plasma sample was spiked with 0.5 ng of bexarotene-d_4 (internal standard) in methanol, mixed with 300 μL of water and extracted with 1000 μL of methyl tert-butyl ether (MTBE). The MTBE layer was decanted, dried under a nitrogen flow and reconstituted with 300 μL of 30% acetonitrile (ACN) in water before instrumental analysis. Mammary gland tissue specimens were homogenized in saline using steel balls in a 1600 MiniG® homogenizer (SPEX SamplePrep, Metuchen, NJ) and processed as above. Samples were stored frozen (−70°C) before analysis.

Chromatographic separation was achieved with a Gemini NX-C18 3μ column, 50×2 mm (Phenomenex, Torrance, CA). The mobile phase was A: 0.05% ammonium hydroxide in water and B: 0.05% ammonium hydroxide in acetonitrile. After injection, initial conditions with A at 65% were held for 0.3 min, decreased to 20% in 2 min and held for 1 min before returning to initial conditions for 2 min of re-equilibration time. The flow rate was 0.3 ml/min at 40 °C. Retention times for bexarotene and bexarotene-d_4 was 1.2 min. Total run time was 5 min. A turbo ion spray interface was used operating in negative mode. Acquisition was performed in multiple reaction monitoring mode (MRM) using m/z

347.3 → 303.3 and 351.2 → 507.2 at low resolution for bexarotene and bexarotene-d_4, respectively.

Statistical Analysis:

Measurements were summarized using descriptive statistics, including the mean, standard deviation, median, range, frequencies and percentages for study characteristics at baseline and at each subsequent follow-up time point for variables measured longitudinally. The Wilcoxon rank-sum test was used to assess differences of continuous variables between participant characteristics of interest. Categorical variables were measured using the chi-square test or Fisher's exact test, if more appropriate. In order to explore the changes over time, biomarkers levels in serum were plotted as functions of time (baseline, Day 15, and Day 28). Linear models were fitted to the biomarker data to explore general trends over time for all participants by dose level. Finally, descriptive methods were used to describe bexarotene concentrations in the breast tissue at 28 days.

Data Availability:

Summary data generated in this study are available within the article and its supplementary data files. Primary data will be available through the CDAS website (https://cdas.cancer.gov/learn/eppt/browse/).

Results

Study Participants:

A total of 41 women consented to the study; 24 were assigned to a dose level in either the dose escalation or dose expansion phase (Figure 2). The main reasons for ineligibility were abnormalities in baseline labs such as elevated cholesterol, triglycerides, and elevated liver function enzymes. Ten women were enrolled at dose level 1 and no DLTs were noted with every other day dosing. Therefore, enrollment continued to dose level 2, 10mg daily dosing, and 4 participants were enrolled at this dose. Two participants experienced DLTs and thus no further participants were enrolled at this dose level per protocol stopping rules. No participants were enrolled at dose level 3 (20 mg daily). MTD was determined to be the every other day dosing regimen and, therefore, the dose expansion phase enrolled an additional 10 women at this dose level. All women were compliant with study gel application.

Women enrolled in the study were from 43–70 years old and most of participants were postmenopausal in all cohorts (Table 2). The majority of participants were Caucasian, and 4 participants were African American.

Adverse Events:

The most common adverse events noted were skin toxicity to the application site such as rash and pruritis. Six participants in the dose escalation phase reported grade 2 adverse events and all were related to rashes or pruritus (Table 3). No grade 3 or 4 adverse events were reported (Supplemental Table 1).

DLTs were reported in 2 participants - maculopapular rash consisting of >25% of the application site area with other associated symptoms such as pruritis and/or burning at application site (Figure 3). Both participants were instructed to hold their study gel and did not have enough subsequent improvement in their symptoms to restart gel application. These were considered DLT because they were Grade 2 AE that persisted for 6 days (Table 3). Thus, the daily dosing level was discontinued.

Secondary Biomarkers

Oral bexarotene has been shown to affect serum levels of calcium, thyroid markers, and triglycerides. These levels were monitored in all participants at baseline, Day 15 and end of study visit. No significant changes were seen in any of these markers from baseline levels except in one patient in the expansion phase. The participant tolerated study gel, but triglycerides increased to a Grade 2 AE at the Day 15 visit. She was instructed to hold study gel, repeat levels at end of study returned to baseline. The patient denied any changes to diet and elevation in triglycerides was felt to be possibly related to the study drug.

Bexarotene Concentrations in Plasma and Breast Tissue:

Plasma concentrations of bexarotene were evaluated in all participants at baseline and at the end of study. Breast tissue concentrations were available only in those women who underwent breast biopsies. Bexarotene was undetectable in all baseline specimens of all participants.

In the dose escalation phase, no drug was detectable in the plasma at dose level 1 or dose level 2 .However, bexarotene was detectable in the breast tissue at dose level 1 (from 9.30ng/g to 21.4ng/g) and at dose level 2 (13.2ng/g) (Table 4). Quantification of bexarotene concentration in these tissue specimens was affected by the amount of tissue available for analysis for each individual. Although 4 cores of breast tissue were obtained at each biopsy, sizes of the cores were variable. In the dose escalation phase, 5 participants in dose 1 level and 1 participant in dose 2 level had tissue specimens for analysis and all except one had some detection of bexarotene drug in the tissue. One specimen had low detection and was also under the limit of quantification (Table 4).

In the dose expansion phase of the study, two participants had detectable bexarotene levels in the plasma at the end of treatment, but the drug concentration was below the limit of quantitation. Thus, no quantifiable bexarotene was detected in the plasma specimens. In the dose expansion phase, breast tissue samples were available for nine participants. Three participants with detectable levels, drug concentrations that ranged from 3.3ng/g to 169ng/g (Table 4). Four of the nine women that underwent breast biopsy had undetectable drug levels in the breast tissue while the remaining 2 women had drug levels under the limit of quantitation. (Table 4).

Discussion

This study evaluated topical 1% bexarotene gel for safety and toxicity in this phase 1 trial of women at elevated risk for breast cancer. The study evaluated the effects of gel application to one unaffected breast at various dose levels over a four-week period. Overall, patients

were compliant on study and the most common adverse events noted were rash and pruritis at the application site. These findings are consistent with adverse events noted in previous bexarotene studies in alopecia areata and CTCL. Similarly, bexarotene was not detected in the plasma of participants at the end of treatment and significant adverse events in thyroid function or hyperlipidemia were not observed. Thus, topical Bexarotene was generally well tolerated; however, the skin rash may limit acceptability of this treatment.

Bexarotene was detected in the breast tissue of some participants, but concentration levels varied amongst samples. Multiple factors need to be taken into consideration regarding these findings. First, the composition of breast tissue can contain varying amounts of fibroglandular tissue and adipose tissue. The composition of the tissue can affect drug distribution(13). Tissue specimens were obtained by core biopsy and therefore it is a limited sampling of the entire area where study drug was applied. The core biopsy was consistently completed in the upper outer quadrant in all participants, but it does not take into account if the drug was absorbed and distributed to other areas of the breast and if the amounts varied across the breast. RXR receptors are found in the skin and contribute to the toxicities observed. Skin toxicity may limit the amount of gel applied and prevent achieving the necessary concentration in the breast tissue for activity. This is a limitation and future studies will need to address how bexarotene or other rexinoids are absorbed and distributed throughout the breast tissue.

The number of gel applications may have had some effect on whether or not drug was detected in the tissue. Of note, all participants except one who had detectable levels of bexarotene on biopsy had applied gel to the breast on the morning of the biopsy. The 3 participants with trace levels of drug detected, last applied the gel 1–2 days prior to the breast biopsy. Similar to our findings, studies evaluating transdermal application of 4-OHT noted that concentration of the drug was detectable 12–24 hours after 1 dose(10). Further studies are needed to evaluate retention of study drug and biological activity in the breast tissue.

Although the participants on the study were compliant with gel application, skin adverse events can limit the use of this gel and topical interventions will need to take this into account. In this study, areas of skin damage from sun exposure were more likely to negatively react to study gel in comparison to the actual breast skin which did not show signs of sun damage. Areas of increased moisture were more likely to develop a rash and thus rash was generally seen close to the axilla and near the sternum of the application site area. Although limited to a sample size of four, African American individuals on study did not report any skin AEs and need to be further evaluated to learn if increased melanin had a protective effect.

Other rexinoids such as 9cUAB30 have been evaluated for its chemoprevention activity in animal models and phase 1 studies. 9cUAB30 has been shown to prevent ER+ and ER- breast cancers in mouse models(14–16). In a phase 1, placebo controlled, double blinded dose escalation study, 9cUAB30 was well tolerated with no dose limiting toxicities with dosing up to 160mg daily(17). No significant changes in hyperlipidemia or triglycerides were noted with the oral medication(17). Based on the favorable safety profile, 9cUAB30

may be a preferred rexinoid and is currently being evaluated for breast cancer prevention in an early phase presurgical trial (NCT02876640).

This study identified the maximally tolerated dose of 1% topical bexarotene to be 10mg/per one unaffected breast, every other day. It also showed that topical 1% bexarotene gel can be applied to the breast and penetrate into the breast tissue, and is generally well tolerated, but dose limiting skin pruritis and rash may reduce compliance in healthy women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Prevention Relevance:

Bexarotene is a rexinoid that has been shown to prevent mammary tumors in mouse models but oral dosing has toxicities. This phase 1 study evaluates topical bexarotene, as a potential chemoprevention agent, for safety and toxicity in high risk women for breast cancer.

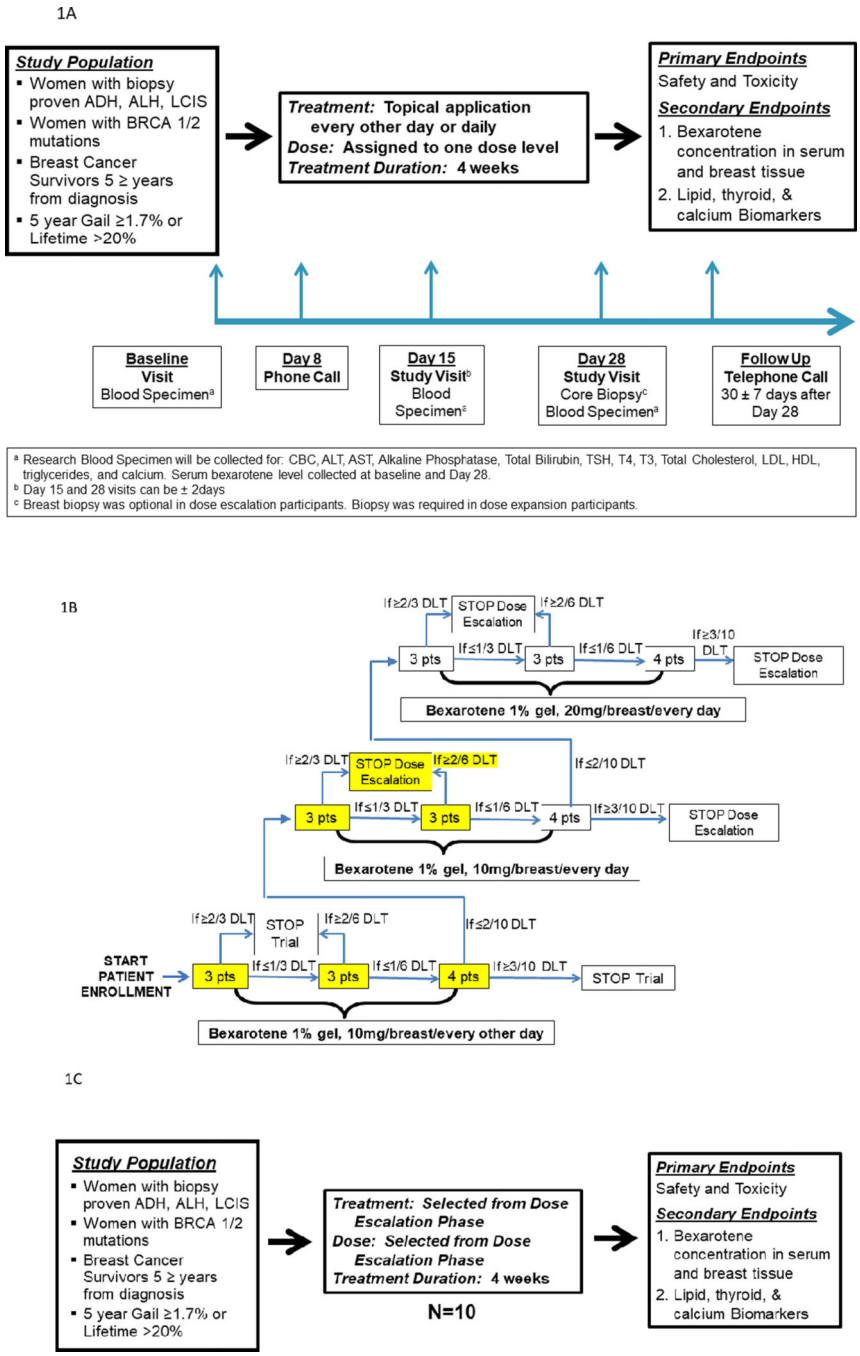

Figure 1. A. Clinical Trial Schema.

Women with elevated risk for breast cancer received study gel at one of the designated dose levels and completed the visits as outlined over a 4 week period and including an optional biopsy. **(B) Dose Escalation Schema.** The algorithm outlines the process of enrolling 3–4 participants at one time and assessing for dose limiting toxicities (DLT) before proceeding with the next cohort. Participants started at the lowest dose level of 10mg every other day. If there was <2 DLTs, enrollment in the second dose level of 10mg daily occurred. The dose escalation phase was terminated at the cohort highlighted in yellow. **(C) Dose Expansion**

Schema. An additional 10 participants were enrolled to the dose expansion phase after 10mg every other day dosing was determined to be the maximum tolerated dose. Participants applied study gel for 4 weeks and completed an end of treatment breast biopsy.

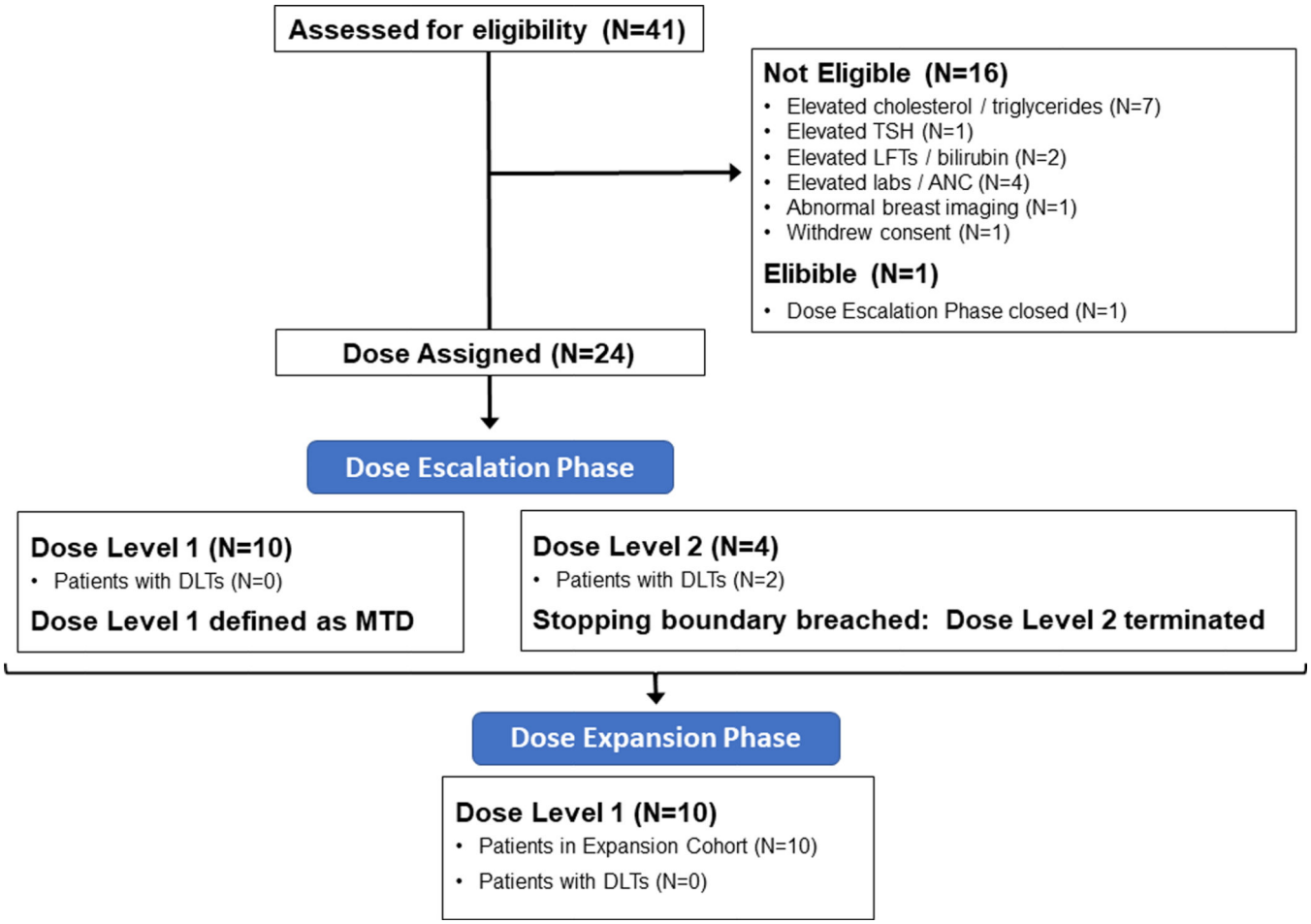

Figure 2. Consort Diagram.

Forty-one women were assessed for the study and 24 participants were assigned to either dose level 1 or dose level 2. Dose limiting toxicities were noted in dose level 2 and thus, the dose expansion phase was completed at dose level 1.

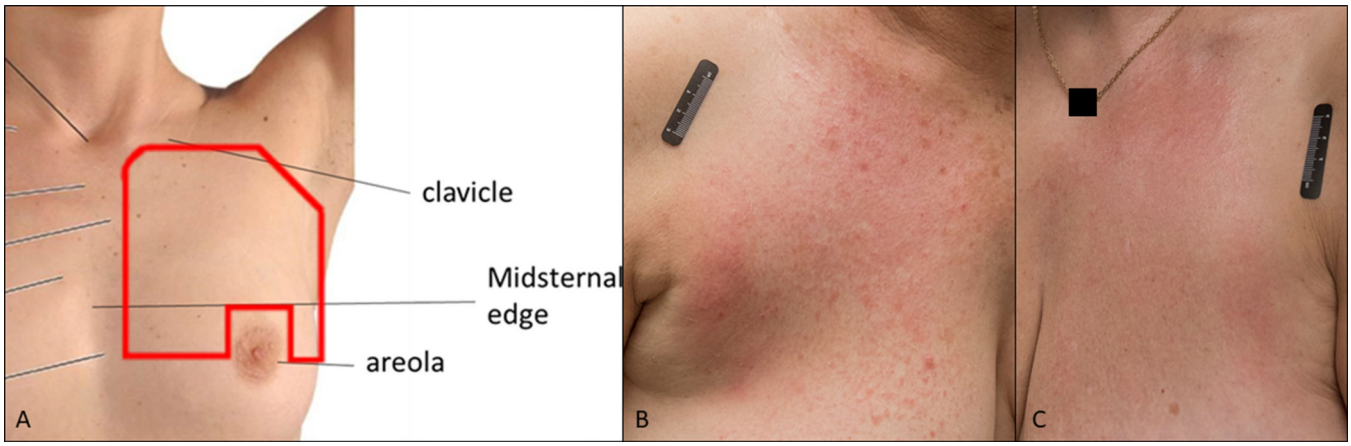

Figure 3. Gel Application Area and Dose Limiting Toxicities (DLT).

(A) Guide on where to apply study gel given to all participants. **(B)** DLT #1 with maculopapular rash >25% of application site area and associated pruritus. **(C)** DLT#2 with maculopapular rash >25% of application site area that went to below the clavicle.

Table 1.

Modified CTCAE v4.0 criteria for assessing skin toxicity of bexarotene gel applied to the breast skin (application site).

	Grade 1	Grade 2	Grade 3	Grade 4
Dry Skin	No erythema or pruritus	With erythema or pruritus	With erythema and pruritus	-
Pain of Skin	Mild pain	Moderate Pain	Severe Pain	-
Photosensitivity	Painless erythema	Mild to Moderate Pain with erythema	Erythema with blistering or skin breakdown	Erythema with ulceration
Pruritus	Mild, requiring topical intervention	Intense, with changes from scratching, oral intervention needed	Intense, constant, limiting ADL or sleep, oral steroids needed	-
Rash, maculopapular	Macules or papules <25% of treated area, with or without symptoms (pruritus, burning, tightness)	Macules or papules >25% of treated area, with or without symptoms (pruritus, burning, tightness), limiting instrumental ADL	Macules or papules >25% of the treated area, with or without symptoms (pruritus, burning, tightness), limiting self care ADL	-
Urticaria	Asymptomatic or mild symptoms, not requiring therapy	Moderate, limited local therapy needed, limiting instrumental ADL	Urticarial lesions covering >30% of application site; oral or IV intervention indicated	-

Table 2.

Patient Characteristics.

Characteristic	Dose Level 1 10mg every other day		Dose Level 2 10mg every day		Expansion Cohort 10mg every other day	
	N	%	N	%	N	%
Total Assigned	10	(100%)	4	(100%)	10	(100%)
Age, years						
40 to 49	2	(20%)	0	(0%)	1	(10%)
50 to 59	3	(30%)	0	(0%)	6	(60%)
60 to 69	5	(50%)	3	(75%)	2	(20%)
70 and over	0	(0%)	1	(25%)	1	(10%)
Menopause						
Pre-Menopausal	2	(20.0%)	0	(0.0%)	3	(30%)
Post-Menopausal	8	(80.0%)	4	(100.0%)	7	(70%)
Race						
Black	2	(20.0%)	1	(25.0%)	1	(10.0%)
White	8	(80.0%)	3	(75.0%)	8	(80.0%)
Unknown	0	(0.0%)	0	(0.0%)	1	(10.0%)
Ethnicity						
Not Hispanic/Latino	10	(100%)	4	(100%)	9	(90.0%)
Not Reported	0	(0.0%)	0	(0.0%)	1	(10.0%)

Table 3.

Grade 2 Skin adverse events related to bexarotene 1% gel (10mg/ml).(DLT = Dose Limiting Toxicity)

Dose Level	Adverse Event	Grade	Attribution	Onset Day	End Day	Drug Hold	Restarted if Held	DLT	Outcome
Dose Escalation Phase									
1	Itching of upper outer quadrant of left breast, not at application site	2	Possible	Day 28	Day 29	No	NA	No	Resolved
1	Itching (application area of upper breast)	2	Probable	Day 24	Day 27	No[1]	NA	No	Resolved
1	Fine maculopapular rash at application site	2	Possible	Day 13	Day 15	Yes	Yes	No	Resolved
2	Maculopapular rash with intermittent pruritus at application site	2	Probable	Day 26	Day 28	No	NA	No	Resolved
2	Maculopapular rash with pruritus at application site	2	Definite	Day 13	Day 19	Yes	No	Yes	Resolved
2	Redness with some mild intermittent rash over approximately 60% of left chest including superior aspect of left breast to below left clavicle (at entire application site)	2	Definite	Day 17	Day 25	Yes	No	Yes	Resolved
Dose Expansion Phase									
1	Rash (painless erythema) over 50–75 % of application area	2	Probable	16	17	No	NA	No	Resolved
1	Pruritis of upper portion of right breast at application site (<25% area)	2	Probable	27	31	No	NA	No	Resolved

[1]No drug hold as it was the end of study treatment.

Table 4.

Plasma and Tissue Concentrations of Bexarotene 1% gel.

Plasma Concentration (ng/ml)	**Dose Escalation Phase**														**Dose Expansion Phase**									
Dose Level	1	1	1	1	1	1	1	1	1	1	2	2	2	2	1	1	1	1	1	1	1	1	1	1
Participant Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Baseline Visit	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
End of Treatment Visit	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	TLD	ND	ND	ND	ND	ND	ND	ND	TLD
ND = Not detected (below the quantitation limit of 0.5 ng/mL)																								
Tissue Concentration (ng/g)																								
Dose Level	1	1	1	1	1	2									1	1	1	1	1	1	1	1	1	1
Participant Number	1	2	3	6	9	12									15	16	17	18	19	20	21	22	23	24
Tissue Concentration	9.3	16.9	TLD	ND	21.4	13.2									ND	13.8	ND	ND	3.3	†	ND	TLD	TLD	169

ND = Not detected (below the quantitation limit of 2.5 ng/g for a 10mg sample)

TLD = Trace levels detected (below the quantification limit of 2.5ng/g; estimated value)

† = Not analyzed