ECOG-ACRIN cancer research group
Reshaping the future of patient care

EAZ171

Prospective validation trial of taxane therapy (docetaxel or weekly paclitaxel) and risk of chemotherapy-induced peripheral neuropathy in African American women

STUDY CHAIR:	Bryan P. Schneider, MD
STUDY STATISTICIAN:	Fengmin Zhao, PhD
STUDY CO-CHAIR:	Joseph Sparano, MD
QUALITY OF LIFE CO-CHAIR:	Sofia F. Garcia, PhD
TRANSLATIONAL SCIENCE CO-CHAIR:	Fei Shen, MD
COMMUNITY CO-CHAIR:	Shamsuddin Virani, MD
CANCER CONTROL AND SURVIVORSHIP COMMITTEE CHAIR:	Lynne Wagner, PhD
HEALTH EQUITY COMMITTEE CO-CHAIRS:	Edith Mitchell, MD Melissa Simon, MD
BREAST CANCER COMMITTEE CHAIR:	Antonio Wolff, MD

Version Date: February 26, 2021

STUDY PARTICIPANTS	***ACTIVATION DATE***
ALLIANCE / Alliance for Clinical Trials in Oncology	June 27, 2019
NRG / NRG Oncology	Addendum #1
SWOG / SWOG	Addendum #2

Agents	**IND#**	**NSC#**	**Supply**
Docetaxel	IND Exempt Study	NSC 628503	Commercially Available
Paclitaxel		NSC 673089	Commercially Available

Table of Contents

STUDY CHAIR

Bryan P. Schneider, MD,
Indiana University,
535 Barnhill Dr. RT 473
Indianapolis, IN 46202,
Phone: 317-948-3855
Fax: 371-948-3646
bpschnei@iu.edu

STUDY CHAIR LIAISON (SCL)-
RECRUITMENT & STUDY KITS/LABS

Casey Bales,
Indiana University,
535 Barnhill Dr. RT 473
Indianapolis, IN 46202,
Phone: 317-274-2840
Fax: 371-948-3646
calallen@iupui.edu

STUDY CHAIR LIAISON (SCL) -
NURSING

Jessica Sollars, RN
Indiana University,
535 Barnhill Dr. RT 473
Indianapolis, IN 46202,
Phone: 317-278-5117
Fax: 317-948-6796
jlsherma@iupui.edu

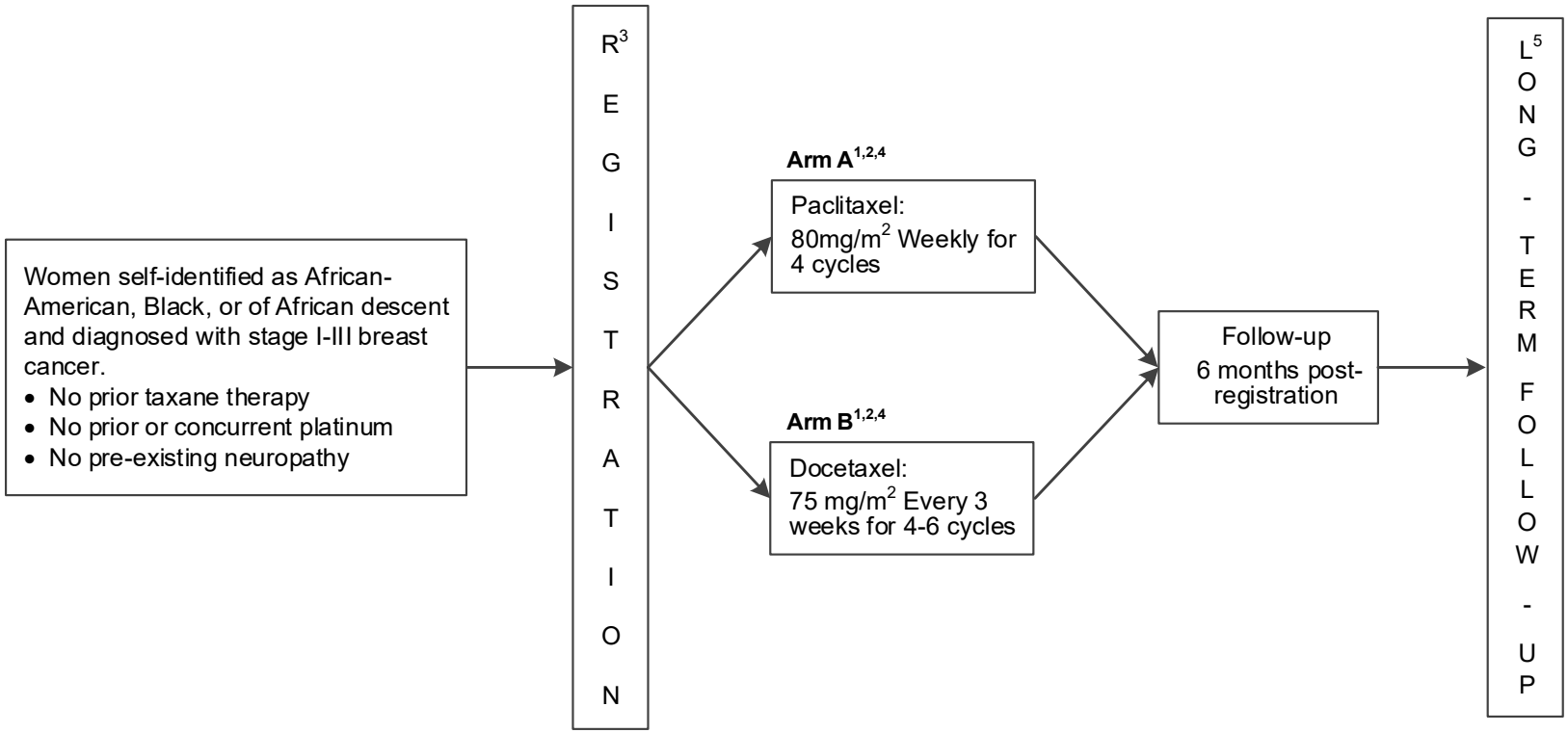
CANCER TRIALS SUPPORT UNIT (CTSU) CONTACT INFORMATION

Rev. Add2

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation can be submitted to the CTSU via the Regulatory Submission Portal. (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done through Medidata Rave. Please see the data submission section of the protocol for further instructions. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For clinical questions (i.e., patient eligibility or treatment-related) Contact the Study PI of the Coordinating Group.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org		

Rev Add1
Rev Add2

Schema



Accrual = 240

1 cycle = 21 days

1. Peripheral blood samples are to be collected and submitted following registration, prior to treatment for the mandatory protocol-defined laboratory research studies.
2. PROs are to be administered per Section 5.6. PROs for administration are: Functional Assessment of Cancer Therapy Gynecological Oncology Group Neurotoxicity (FACT/GOG-NTX) PROMIS Physical Function v2.0 Short Form 10a, Comprehensive Score for Financial Toxicity (COST-FACIT), five items from the Alliance Patient Questionnaire for Clinical Trials In Oncology, PRO CTCAE items, and CIPN20 sensory neuropathy subscale.
3. Treatment arm will be determined at the discretion of the treating investigator.
4. Concurrent therapy is to be administered per Sections 5.1 and 5.4.
5. Every 3 months if patient is < 2 years from their date of registration, every 6 months if patient is 2-5 years from their date of registration. Patients will be followed for 5 years from their date of registration.

1. Introduction

1.1 Rationale for Proposed Study

We have compiled compelling evidence in a retrospective fashion to suggest that African American patients have substantially higher risk of experiencing taxane-induced peripheral neuropathy (TIPN) than Caucasian patients when treated with adjuvant weekly paclitaxel, a commonly employed regimen in the curative setting for breast cancer.[1,2] Further, we have demonstrated that this toxicity leads to more dose reductions and is associated with higher breast cancer recurrence rates in African Americans compared with Caucasians. On the other hand, we have also shown that weekly paclitaxel is associated with significantly reduced rates of breast cancer recurrence and improved survival compared with other taxane regimens, including docetaxel given every 3 weeks, in triple negative breast cancer (TNBC),[3] a particularly aggressive and potentially lethal breast cancer subtype which is more common in African-American women.[4] However, compared to Caucasian patients, African American patients had a lower rate of TIPN from every three-week docetaxel treatment.[3,5,6] We have also demonstrated the ability to use germline variability to better predict the likelihood of taxane-associated neuropathy in African American patients, including variants that are associated with higher risk (SBF2) or those that are protective (FCAMR).[1,7] We now set out to evaluate the following in African American patients with breast cancer: (1). Prospectively validate the association of germline variants with TIPN from commonly used taxane regimens, including weekly paclitaxel (80 mg/m2 weekly × 12 doses) and every 3-week docetaxel (75 mg/m^2 every 3 weeks × 4 doses) (2). Demonstrate that every three-week docetaxel causes fewer dose reductions due to TIPN than weekly paclitaxel (3).Use both physician reported (CTCAE) and patient reported outcomes (PRO) to assess and compare both acute neuropathy (CTCAE grade 2 or higher occurring during taxane therapy) leading to taxane dose reductions and delayed onset (occurring for the first time or recurring after resolution or improvement > 6 months based on CTCAE criteria) between weekly paclitaxel and three week docetaxel. The objective of this study is to prospectively validate the association of germline variants that we have previously identified that are either associated with increased risk (SBF2) or protective (FCAMR) against TIPN, with the ultimate goal of identifying the preferred taxane based on both potential for efficacy and toxicity to be used in the curative setting for African Americans with breast cancer.

Compared to Caucasians, African Americans have a higher risk of being diagnosed with advanced stage of breast cancer[8] and higher breast cancer mortality rate.[9,10] African Americans had a 42% higher breast cancer death rate in the period of 2008-2012.[11] The reason for this imbalance is multifactorial and includes higher stage, higher grade, more triple negative breast cancer (TNBC), and poorer responsiveness to chemotherapy.[12,13] These imbalances in outcome have previously been attributed to both socioeconomic factors and a different underlying biology of the tumor.[10,14,15] ***Recently, we have demonstrated that another significant contributor is the increased need for dose reductions of weekly paclitaxel in the curative setting for African Americans due to significantly higher rates of TIPN.[2]*** While the taxanes are considered a crucial component to improve the cure rate in both the adjuvant and neoadjuvant settings, peripheral neuropathy is one of the major adverse effects from taxanes, which can be dose-limiting, painful, impact quality of life, and is sometimes

irreversible. The American Society of Clinical Oncology deemed TIPN to be one of the three most important survivorship issues impacting cancer patients,[16] thus this toxicity appears to preferentially impact the quality of life of African Americans and results in a less cumulative dose of an important drug resulting in inferior care.

TIPN is common for all patients but its frequency and severity are impacted by the type and schedule of the taxane. Weekly paclitaxel for 12 weeks has become a commonly employed regimen in the curative setting based on the outcomes of E1199.[3] E1199 compared every three-week paclitaxel with weekly paclitaxel, or every three-week docetaxel, or weekly docetaxel. Weekly paclitaxel was the most efficacious type and dose of taxane along with every three-week docetaxel in the overall population, whereas weekly paclitaxel was associated with significantly improved disease free survival (hazard ratio [HR]=0.69, p=0.001) and overall survival (HR=0.69, p=0.019) in women with triple negative breast cancer (TNBC).[6] Weekly paclitaxel had more grade 2-4 and grade 3-4 TIPN than every three-week docetaxel but otherwise was associated with much less overall acute hematologic and non-hematologic toxicity; thus due to its general tolerability profile has been largely considered the favored regimen. There are two major flaws with the generalizability of this conclusion. First, it assumes that the likelihood of toxicities is uniform across populations. Second, it assumes that differential likelihoods of toxicities do not impact efficacy in specific subgroups.

We evaluated the rates of TIPN in two consecutive trials coordinated by ECOG-ACRIN, including the E1199 trial that compared 4 different taxane regimens (every 3 week paclitaxel 175 mg/m^2 × 4, weekly paclitaxel 80 mg/m^2 ×12, every 3 week docetaxel 100 mg/m^2 × 4, and weekly docetaxel 35 mg/m^2 × 12), and the E5103 trial which employed weekly paclitaxel (80 mg/m^2 × 12 weeks) in all patients; in both trials, the taxane therapy was given sequentially after doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 3 weeks (in E1199 or E5103) or every 2 weeks (in E5103). At least 8% of patients in both trials were of self- reported African American race. The rates of TIPN are summarized in Table 1, with a focus on the weekly paclitaxel and every 3-week docetaxel arms that were the most efficacious.

While African American patients are markedly under-represented within clinical trials,[17] retrospective subgroup analyses from E1199 demonstrated that self-described African American patients had fewer dose reductions than self-described Caucasian patients in the every-three week docetaxel arm,[5] the only arm in E1199 for which this was true. Additional evidence that weekly paclitaxel has serious limitations specific to African American patients came from another adjuvant phase III trial, E5103.[18] In E5103 all patients received a standard backbone of weekly paclitaxel with a randomization to bevacizumab or placebo. E5103 was a perfect testing ground for these questions as it had a markedly greater number of African Americans compared with some of the contemporary adjuvant breast cancer trials and collected germline genetic information.[1] In this trial we demonstrated that African American patients had markedly more grade 2-4 (HR=2.1, p = 5.6 x 10^{-16}) and grade 3-4 TIPN (HR=2.6, p = 1.1 x 10^{-11}) compared with other races (Figure 1).[1]

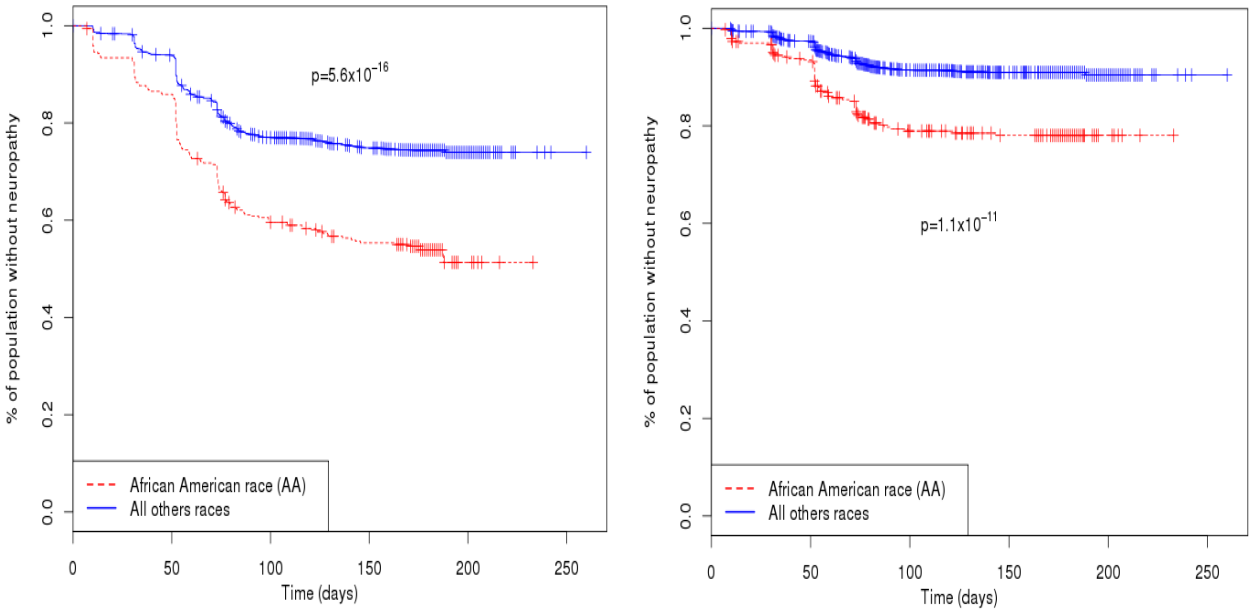


Figure 1. ***Comparison of Grade 2-4 (left) and Grade 3-4 (right) TIPN by genetically determined race in E5103. The frequency of Grade 2-4 TIPN in the genotyped cohort was 39.4% for those of AA vs. 22.9% for all other races combined ($p = 5.6 \times 10^{-16}$). The frequency of G3-4 TIPN in the genotyped cohort was 21.5% for those of AA vs. 8.7% for all other races combined ($p = 1.1 \times 10^{-11}$).***

Table 1. Frequency of TIPN in E1199 and E5103

Dataset	Treatment	TIPN Grade	EA* (%)	AA**(%)
E1199	Every 3 week Docetaxel	Grade 2-4	17.8	13.2
		Grade 3-4	5.2	4.4
E1199	Weekly paclitaxel	Grade 2-4	22.4	27.7
		Grade 3-4	7.3	10.9
E5103 (Genotyped cohort)	Weekly paclitaxel	Grade 2-4	22.9	39.4
		Grade 3-4	8.7	21.5

*Caucasian or patients of European ancestry

**African American or patients of African ancestry

We subsequently assessed the intersection of genetic ancestry on both efficacy and toxicity in E5103 using ancestry informative markers. Much of the prior work has been based on self-reported race, which has limitations. Race, when assessed in this fashion, is typically based on skin color and often neglects the genetic ancestry and studies suggest there is substantial admixture and misclassification of race in the United States when based on self-reported skin color.[19,20] Thus our findings using genetic ancestry represented the true impact of genetic/biological differences at its most accurate level. We compared toxicity and efficacy outcomes in E5103 from 386 patients of African ancestry and 2473 patients of European ancestry (Figure 2).[2]

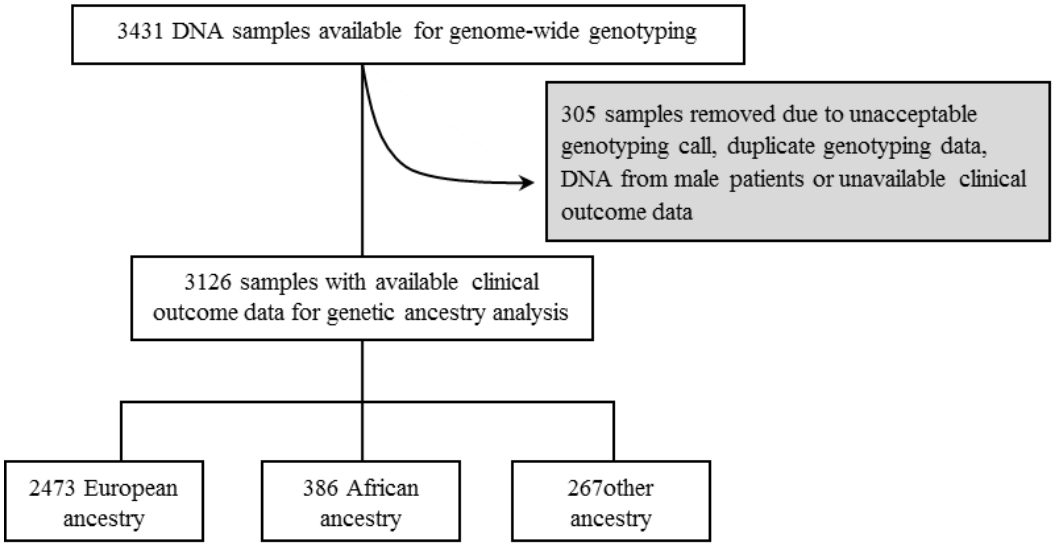


Figure 2. ***CONSORT for E5103***

We demonstrated that patients of African ancestry had markedly inferior disease free survival (the primary endpoint of E5103) (p=0.02) compared with other races (Figure 3).[2] As expected, because African Americans had more TIPN, they had significantly more dose reductions for the paclitaxel portion of the therapy ($p=6.6 \times 10^{-6}$). Most importantly, however, the dose reductions in paclitaxel for African Americans had a significant negative impact on DFS (p=0.03); whereas in European Americans, dose reductions did not impact outcome (p=0.35) (Figure 4). This was a function of severity of dose reductions and less total cumulative dosage.[2]

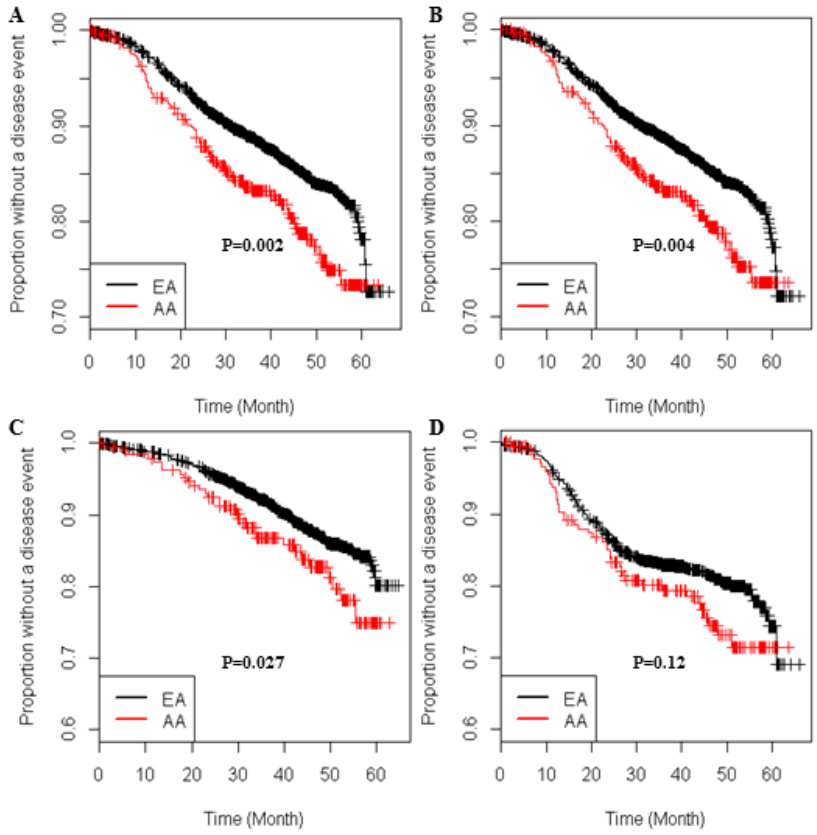


Figure 3. ***Disease Free Survival (DFS) for African ancestry (AA) compared with European ancestry (EA) for all patients (A), DFS for all self-reported patients (B), DFS for genetic ancestry with estrogen receptor or progesterone receptor positive disease (C), and for genetic ancestry with triple negative breast cancer (D).***

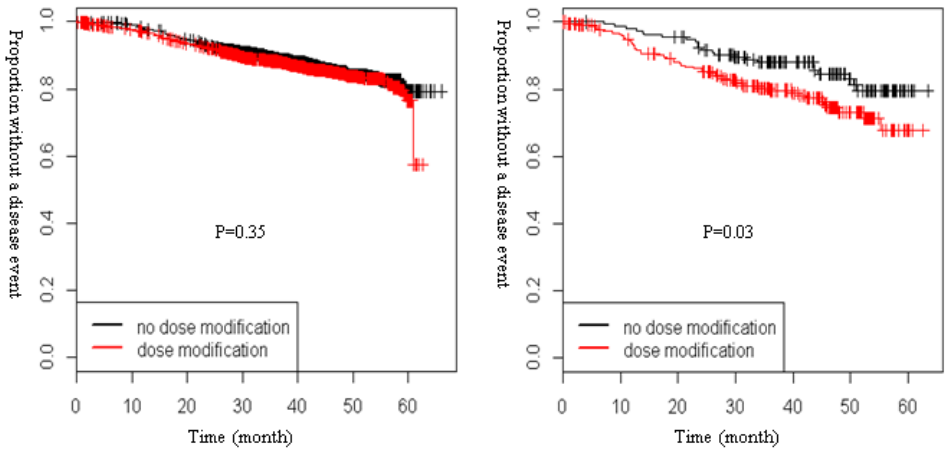


Figure 4. ***Disease free survival for European ancestry (left) and African ancestry (right) patients who experienced any dose reduction or early cessation of paclitaxel compared with those who did not have a dose reduction or early cessation.***

The planned pragmatic trial outlined in this proposal will now allow for the unique opportunity to uncover the preferred taxane in the curative setting (weekly

paclitaxel vs. every-three week docetaxel) for an enriched population of African Americans. Our powerful preliminary data allow us to consider clinically significant TIPN as a surrogate for inferior outcome in African American patients. ***Further, the focus on TIPN affords the unique opportunity to both improve the quality of life and curability within a relatively small number of patients in a short period of time.*** When considering both resources and impact, this pragmatic trial design has the potential to move the needle substantially and efficiently.

While African Americans as a group are markedly more likely to experience TIPN, there is clearly still heterogeneity from patient to patient. The ability to further predict the likelihood of this toxicity at the individual patient level would only further refine the ability to make the best therapeutic decision for each and every patient. Several prior studies, largely composed of Caucasian patients, have shown that germline genetic variability might impact likelihood of TIPN.[1,2,7,21,22] Our group recently identified both common and rare germline variants that predicted differential likelihood of TIPN in African Americans in E5103.[1,7] Through a genome wide association study in E5103, we identified a variant in FCAMR that was strongly associated with a decreased likelihood of TIPN (Figure 5).[1] We further evaluated the impact of an imbalance in deleterious rare variants across the exome using whole exome sequencing.[7] In this scan, we found a significant increase in the risk of TIPN for those who carried deleterious mutations in SBF2. When inheriting two mutations in SBF2, patients are destined to have the most common form of hereditary neuropathy, Charcot-Marie Tooth.[23] When carrying one mutation, it appears African American patients are set up for a marked increase risk of TIPN (Figure 6).[7]

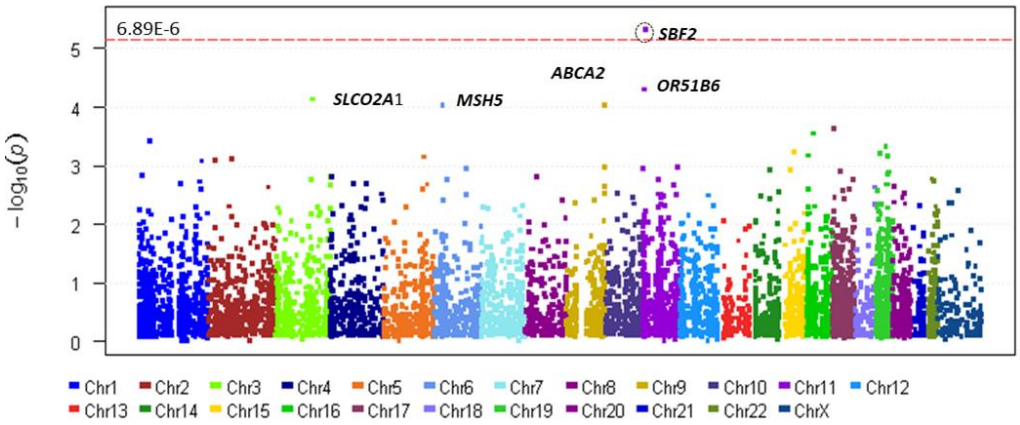


Figure 5. ***Manhattan plot for Grade 2-4 TIPN from patients with African ancestry in E5103. The x-axis indicates the chromosomal position of each SNP analyzed; Y-axis denotes magnitude of the evidence for association, shown as –log10(p-value).***

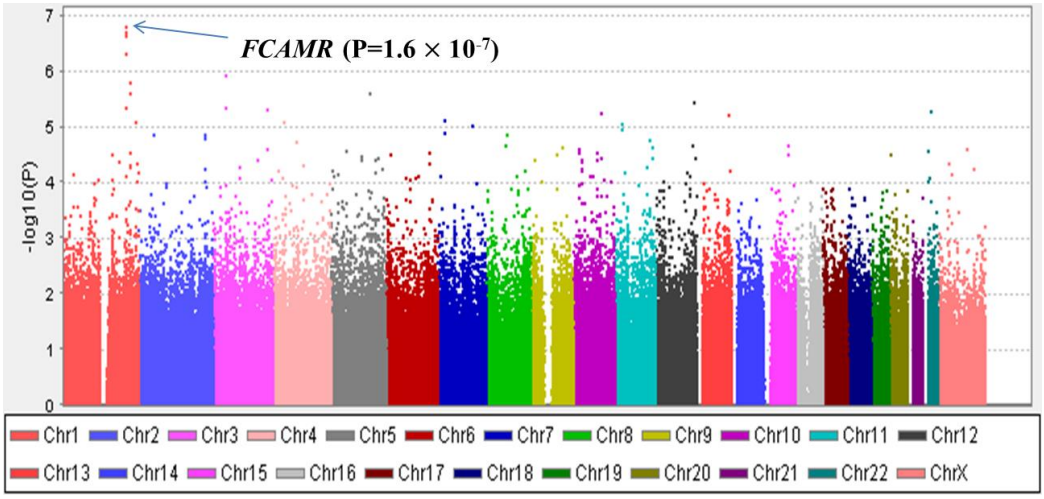


Figure 6. ***Manhattan plot for Grade 2-4 TIPN from African ancestry in E5103. The x-axis indicates the chromosomal position of each gene analyzed; Y-axis denotes magnitude of the evidence for association, shown as –log10(p-value); Each dot represents an evaluable gene. The dashed line indicates the exome-wide significance threshold.***

Thus, by further uncovering the power of genomic variation, we can predict a range of grade TIPN in African ancestry from 7%-65% (Figure 7).[1,7] Further, our group has previously shown that the impact of these markers are deemed relevant from a patient's vantage and these markers could even impact the type of therapy they would choose in the curative setting (Figure 8).[24] To optimally validate these germline predictive markers in a prospective trial, we will plan to categorize patients as: "high risk" or "low risk" (Table 2). The trial will be powered to confirm that "high risk" patients who receive weekly paclitaxel are more likely to experience clinically significant (Grade 2+) TIPN compared with "low risk" patients.

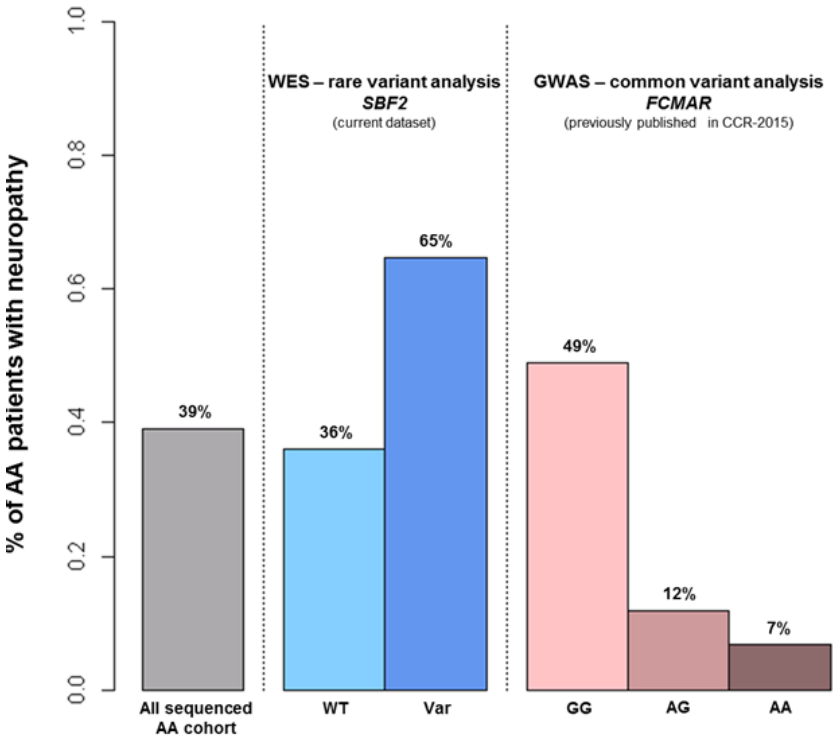


Figure 7. ***Frequency of TIPN Grade 2-4 in African ancestry broken down by those with and without a mutated SBF2 gene (rare variant) and those who carry one or two variant alleles (rs1856746) in FCAMR (common variant). Each bar represents the estimated frequency of TIPN based on the relative likelihood of an event. The gray bar represents the frequency of TIPN in the entire E5103 sequenced African ancestry cohort. The blue bars represent an estimated frequency as determined by the odds ratio for an unmutated SBF2 versus carriage of any deleterious mutation. The pink bars represent the GG, GA, AA genotypes of rs1856746 in FCMAR, respectively. The percentage value above each bar represents the estimated likelihood of a patient with that variant or genotype experiencing TIPN. The percentage value on the x-axis represents the fraction of the African ancestry with that specific genotype. WT= wild type gene with no deleterious mutations. Var = variant gene that carries at least one of the 5 deleterious mutations.***

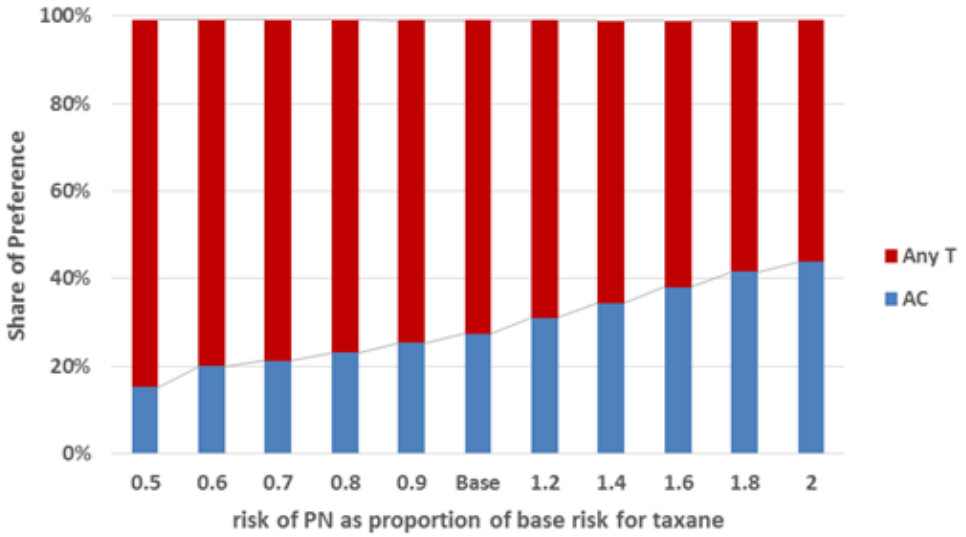


Figure 8. Patient preference share for any taxane containing regimen (T) versus a non-taxane regimen (AC) as the likelihood of TIPN changes.

Table 2. Genotypes and expected frequencies for high and low risk TIPN genotypes

Clinical Category	Genotypes	Expected % of trial population	Expected % of Grade 2+ TIPN
High risk TIPN	*FCAMR* GG or*SBF2* mutated	76%	37%
Low risk TIPN	*FCAMR* AA or GA AND *SBF2* wild-type	24%	10%

The assessment of germline predictive markers for TIPN in this planned pragmatic trial design will allow for a ***unique opportunity to validate a clinically significant and impactful biomarker in the prospective setting and for an enriched population of African Americans. This level of evidence will be unprecedented in depth and scope and adds additional utility to the impact of the planned trial.*** In addition to the validation of our markers using the conventional reporting methodology (CTCAE), we will also assess the reproducibility using PROs as an alternative phenotype. Recent data have suggested superior sensitivity with PROs when compared to physician reported TIPN[25-28] and thus we hypothesize this may further improve the strength of the genotype-phenotype relationship.

Finally, while this protocol boldly sets out to delineate the preferred adjuvant taxane use in the African American population and to prospectively validate well-curated biomarkers, mechanistic insights and additional biomarker enrichment (using whole genome sequencing) can also be gained through this pragmatic trial design. Although intensively studied, the mechanism of TIPN has not been entirely elucidated.[29] Unraveling the mechanism will serve as the most definitive way to identify drug targets that might lead to therapeutics designed to treat or

altogether prevent TIPN. This, in turn, has the potential to improve quality of life, drug adherence, and improve therapeutic index of drugs intended to improve cancer-specific survival. While assessment of the peripheral nerve in taxane-treated patients before and after exposure would represent a gold-standard approach for mechanistic studies, peripheral nerve biopsies in patients can cause severe and irreversible pain and are typically not considered acceptable. Recently developed induced pluripotent stem cell (iPSC) technology has established a new human platform for the study of TIPN.[30] iPSC allows for the generation of cells derived from the patient's blood, which retain the genetic diversity and landscape of the donor and have morphologically assessable changes in the face of neurotoxins that mimic clinical onset of TIPN.[31,32] This proposal allows for an unprecedented opportunity to directly compare the fidelity and sensitivity of onset of clinically relevant TIPN with ex vivo morphological taxane induced neurite damage from the same patient in the context of a clinical trial; EAZ171. In addition, this ex vivo model will allow for comprehensive multi-omic evaluation (transcriptomic and epigenomic changes) of pre- and post-treatment sensory neurons (iPSC-iSNs) while retaining the patient's germline genomic identity.

1.2 Significance of the Study

The overall goal for this study is to reduce the increased risk of chemotherapy induced toxicity for African American patients with breast cancer.

Despite our compelling retrospective data from unplanned subgroups, we recognize that a phase III clinical trial with a primary endpoint of efficacy outcome confined to African American patients would require a substantial number of patients, many years to complete, and unlikely to happen. Thus, this non-randomized, pragmatic trial design will uniquely allow for rapid enrollment and provide the essential prospective data to optimize the preferred use of taxane in the curative setting for African American patients with breast cancer. This pragmatic clinical trial will simultaneously address the impact of taxanes on the quality of life and curability while prospectively building a testing infrastructure to validate previously discovered germline predictive biomarkers for neuropathy and creating a discovery platform using cutting edge technology.

1.3 Advantages of this Trial Design

1.3.1 ***Prospective validation of germline predictors of peripheral neuropathy:*** This pragmatic clinical trial is the perfect setting to further validate our germline markers for neuropathy. The evaluation is non-obtrusive; including only a single venipuncture. This will allow direct validation of the markers for the paclitaxel arm. It will also allow for an assessment of another taxane, docetaxel, determining whether the markers are specific to paclitaxel or more likely to be generalizable to the entire class of taxanes. It will also provide an opportunity to see if improving the phenotype [patient reported outcomes (PROs) as opposed to physician reported outcomes] might further strengthen the associations. In addition, the implementation of whole genome sequencing will allow for further broad discovery with no additional invasive interventions.

1.3.2 ***Enrichment of African American patients:*** Clinical trials across the United States have been plagued by a lack of accrual for African

Americans. Thus, much of the generalized conclusions about best treatment options have been made from the risk/benefit ratio observed in patients of European descent. We recognize there are inherent imbalances in outcomes, toxicity, and biology and thus these conclusions may be false for specific populations. Further, much of the data regarding disparate outcomes is derived from retrospective, unplanned subgroup analyses. This trial will prospectively enroll and follow African American patients to determine accurate risk and benefits.

For this study, we will rely on self-reporting of race as an eligibility criteria, which is a reasonable surrogate for genetic ancestry.[2]In addition, the primary analysis will be performed using genetic assessment of ancestry to further validate links between African ancestry and neuropathy outcomes. We recognize that self-identified race and ethnicity is a complex and evolving field[33] and we have adjusted our sample size for the trial to allow for adequate power for the expected differences. Our goal is to determine genetic links between ancestry and neuropathy to improve standard of care for African American women.

1.3.3 ***Non-randomized trial design:*** This approach will allow for a direct comparison of dose reductions due to TIPN for every three-week docetaxel vs. weekly paclitaxel using homogenous phenotype definitions. The assigned, non-randomized approach will allow for treatment to be delivered in a fashion that is commonly used in clinical practice based on disease setting. Because the primary endpoint will be centered on toxicity and dose reductions, stratification for important disease co-variables can be obviated, which will further facilitate rapid enrollment. The design and value of having both arms, however, allows for a prospective comparator using identical criteria for toxicity and normalizing the conclusions.

1.3.4 ***Use of clinician reported outcomes AND patient reported outcomes:*** The use of the Common Toxicity Criteria for Adverse Events (CTCAE) to be reported by the physician will allow for a prospective assessment that can be compared directly to historical clinical trials. Thus, marked differences here might be attributed to different patient populations or temporal trends in reporting. The patient reported outcomes (PROs) can provide a more sensitive and superior methodology for reporting. The PROs will likely provide the most accurate assessment of the impact on quality of life. Comparisons between the methodologies, however, will also allow for a direct comparison of the utility of the toxicity marker as a predictor of dose reduction and appropriately infer its intersection with efficacy.

1.3.5 ***Assessment of global gene expression (transcriptome) in sensory neurons derived from iPSC of patients:*** The evaluation of global gene expression in patient iPSC derived neurons may identify the molecular function and biological process-related genes associated with TIPN. This, in turn, will help to understand the underlying mechanisms of TIPN and allow for the development of targeted therapies to prevent and treat TIPN.

1.4 Patient Reported Outcomes

Patient-reported outcomes (PROs) capture unique data on treatment toxicities and disease symptoms in ways that complement clinician-rated toxicities. It is important to understand from the patient perspective how the different taxane therapies may impact health-related quality of life (HRQoL) and influence treatment decision making (e.g., discontinuation in the case of severe symptoms). Research has indicated that there can be substantial discrepancy in severity grading among clinicians as well as underestimation of symptom severity by clinicians (compared to patient report).[34] Collecting PROs to document treatment toxicities from the patient's perspective will also provide invaluable data to inform patient-centered education regarding the risks and benefits of taxane therapies.[26]

In addition to using physician reports of adverse events (CTCAE), we will assess concurrent patient reported neuropathy with items from the National Cancer Institute's (NCI's) Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). The PRO-CTCAE data collected will be used to provide descriptive and parallel information about using this measurement system to gather information directly from patients about the symptomatic adverse effects of their treatment. This trial offers the opportunity to validate PRO-CTCAE items to measure two neuropathic symptoms: numbness / tingling and pain. If well-validated, in the future, those items could provide information to intervene earlier to manage symptoms that may interfere with treatment adherence.

Rev Add2

This study will also assess a secondary phenotype of neurotoxicity using the FACT/GOG- NTX, which is a well-validated measure for evaluating HRQoL (via the FACT-G portion) and neurotoxicity (via the neurotoxicity subscale) in patients receiving taxanes.[36,72] The FACT/GOG-NTX is an easy-to-interpret PRO measure for comparing the neurotoxicity and HRQoL between the two groups in this study. Specifically, we will compare the change in the FACT/GOG-NTX scores between low- and high-risk genotype groups of the paclitaxel arm, and between the paclitaxel arm and the docetaxel arm. In order to harmonize data

Rev Add1

collection with a concurrent SWOG trial developing a predictive model of taxane-induced peripheral neuropathy, we are adding an additional measures assessing neuropathy. The European Organization for Research and Treatment of Cancer (EORTC) chemotherapy-induced peripheral neuropathy (CIPN-20)70 includes a 9-item sensory neuropathy subscale, which has been validated and extensively

Rev Add1

used in prior clinical trials evaluating interventions for treatment of chemotherapy induced peripheral neuropathy.[71]

Further, given that neuropathy can significantly impact physical function, [40,41] we will also compare participant scores on the PROMIS Physical Function v.2 Short Form 10a between the two treatment arms. Additionally, we are interested in examining the financial toxicity experienced by participants in the two treatment arms as reported on the Comprehensive Score for Financial Toxicity (COST-FACIT). Lastly, in addition to race/ethnicity (discussed earlier), other demographic characteristics are important determinants of cancer-related outcomes. Research has demonstrated that residents of poorer US counties tend to have higher death rates from cancer compared to those in more affluent counties.[42] Across numerous studies, along with race/ethnicity, poverty is associated with poorer survival and worse cancer-related outcomes.[42,8,43] Along those lines, we will assess various sociodemographic variables (zip code, marital

status, education, income and insurance status) in order to better examine the role these well-known social determinants of health may play on participant outcomes (treatment discontinuations, toxicities and HRQoL).

2. Objectives

2.1 Primary Objectives

2.1.1 Prospectively validate a prior germline predictor of paclitaxel-induced peripheral neuropathy (TIPN) using the CTCAE. Specifically, this study will demonstrate that patients with a high-risk TIPN genotype have significantly more Grade 2-4 TIPN than patients with a low risk genotype.

2.2 Secondary Objectives

Rev Add2

2.2.1 Validate a prior germline predictor of TIPN using the FACT/GOG-NTX neurotoxicity subscale in Arm A.

2.2.2 Compare grade 2-4 TIPN based on CTCAE between weekly paclitaxel (Arm A) vs. every three-week docetaxel (Arm B).

2.2.3 Prospectively confirm dose reductions due to TIPN are lower for every three-week docetaxel compared with weekly paclitaxel in a prospective cohort of patients of African ancestry.

2.2.4 Prospectively confirm dose reductions due to any cause are lower for every three-week docetaxel compared with weekly paclitaxel in a prospective cohort of patients of African ancestry.

2.2.5 Assess the ability of the high-risk genotype to predict TIPN risk for docetaxel.

2.3 Correlative Study Objectives

2.3.1 Identify novel markers of TIPN and elucidate the mechanism.

2.3.2 Whole genome sequencing of germline blood to evaluate for additional predictors of TIPN.

2.3.3 Create iPSC derived neurons from patient samples.

2.3.3.1 Evaluate whether clinical findings can be mimicked in vitro.

2.3.3.2 Evaluate gene expression (RNA seq) and the epigenome at baseline versus after exposure in those prone to TIPN versus those not.

2.3.4 Create a biorepository of patient derived samples for future translational research.

2.4 Patient Reported Outcome Objectives

2.4.1 Compare Grade 2-4 TIPN (moderate to life threatening) based on PRO-CTCAE items between weekly paclitaxel (Arm A) vs. every three-week docetaxel (Arm B).

Rev Add2

2.4.2 Prospectively compare FACT/GOG-NTX HRQOL scores (from the FACT-G portion and PROMIS Physical Function v.2 SF 10a, scores between every three-week docetaxel and weekly paclitaxel and between high risk and low risk genotypes (Arm A) in a cohort of African ancestry.

Rev Add1

2.4.3 Compare CIPN-20 sensory neuropathy score between weekly paclitaxel (Arm A) vs. every three-week docetaxel (Arm B).

Rev Add2

2.4.4 Compare the impact on financial toxicity (COST-FACIT scores) for every three-week docetaxel compared with weekly paclitaxel.

2.4.5 Examine associations between social determinants of health (zip code, marital status, education, income & insurance status) and dose reductions and treatment discontinuation.

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: CTEP Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 3 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 3 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.ExecOfficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

3.1 Eligibility Criteria

_____ 3.1.1 Patients must be women with a known stage I-III invasive breast cancer diagnosis.

_____ 3.1.2 Patients must be age ≥ 18 years.

_____ 3.1.3 Patients must be capable and willing to provide informed consent.

_____ 3.1.4 Patients must have plans to receive either neoadjuvant or adjuvant:

_____ 3.1.4.1 Every 3-week docetaxel x 4-6 cycles

OR

_____ 3.1.4.2 Weekly paclitaxel x 4 cycles

NOTE: Recommended therapies for various therapy regimens are outlined in Section 5.1 based on ER/PR/HER2 and nodal status. Where there are options, the treating physician will choose a regimen best fitted for that patient. If the physician does not feel any of the regimens are the best fit for the patient, the patient should not be enrolled. Physicians will also document why a regimen was felt to be inappropriate when an option. Patients who have already started the anthracycline portion of their therapy are eligible assuming

Rev Add1

they have not yet begun the taxane portion and assuming they will be receiving one of the regimens deemed appropriate for her disease setting as outlined in Section 5.1.

_____ 3.1.5 Patients must self-identify their race as black, African American, or of African descent. Patients may be of any ethnicity.

_____ 3.1.6 Patients must not have received prior taxane or prior/concurrent platinum therapy.

_____ 3.1.7 Patients must not have received neoadjuvant anti-HER2 therapy.

_____ 3.1.8 Patients with a history of other cancers are eligible if they have not received prior taxane or platinum or vinca alkaloid therapy.

_____ 3.1.9 Patients must not have pre-existing peripheral neuropathy.

Rev Add2 _____ 3.1.10 Patient must have an ECOG Performance status 0-1.

_____ 3.1.11 Patients must not have a total bilirubin > ULN or AST and/or ALT above 1.5 times the ULN concomitant with alkaline phosphatase above 2.5 times the ULN. These labs must be obtained within 3 weeks prior to registration.

Total bilirubin:_____ ULN:_____

AST:_____ALT:_____ ULN:_____

Alkaline phsosphatase:_____ULN:_____

_____ 3.1.12 Patients must not be pregnant or lactating.

Rev Add2 All patients of childbearing potential must have a blood test or urine study within 2 weeks prior to registration to rule out pregnancy.

A patient of childbearing potential is anyone, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy, or 3) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Rev Add2 Patient of child-bearing potential? _____ (Yes or No)

Date of blood test or urine study: _____

_____ 3.1.13 Patients of childbearing potential must be strongly advised to use an accepted and effective method of contraception or to abstain from sexual intercourse for the duration of their participation in the study.

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

Rev Add2

4. Registration Procedures

CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr).

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., Roster Update Management System (RUMS), OPEN, Rave,);
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✔	✔			
Financial Disclosure Form	✔	✔	✔		
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔		
GCP training	✔	✔	✔		
Agent Shipment Form (if applicable)	✔				
CV (optional)	✔	✔	✔		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

Rev Add2

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment must be rostered at the enrolling site with a participating organization (i.e.,

Alliance). Additional information can be found on the CTEP website at <https://ctep.cancer.gov/investigatorResources/default.htm>.

For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov

CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

Rev Add2

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval (applies to US and Canadian sites only) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and

Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

Downloading Site Registration Documents:

Rev Add2

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To

participate, the institution and its associated investigators and staff must be associated with the LPO or a PO on the protocol.

- Log on to the CTSU members' website https://www.ctsu.org using your CTEP-IAM username and password
- Click on the Protocols in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the ECOG-ACRIN link to expand, then select trial protocol EAZ171
- Click on Documents, select the Site Registration, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CSTU website.

Rev Add2

To access the Regulatory Submission Portal log on to the CSTU members' website → Regulatory → Regulatory Submission

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Required Protocol Specific Regulatory Documents

1. Copy of IRB Informed Consent Document.

   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

2. A. CTSU IRB Certification Form.
   Or
   B. Signed HHS OMB No. 0990-0263 (replaces Form 310).
   Or
   C. IRB Approval Letter

   NOTE: The above submissions must include the following details:
   - Indicate all sites approved for the protocol under an assurance number.
   - OHRP assurance number of reviewing IRB
   - Full protocol title and number
   - Version Date
   - Type of review (full board vs. expedited)
   - Date of review.
   - Signature of IRB official

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory at the top of the screen;
- Click on the Site Registration;
- Enter your 5-character CTEP Institution Code and click on Go

Rev Add2 **NOTE:** The status shown only reflects institutional compliance with site registration requirements as outlined above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Patient Enrollment

Patients must not have started taxane (paclitaxel or docetaxel) treatment prior to registration.

Rev Add1 **Treatment should start within fifteen working days after registration. This requirement can be fulfilled by starting the anthracycline portion of therapy when appropriate.**

Rev Add2 The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

Rev Add2 Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

NOTE: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.1 Registration Information

4.1.1 Protocol Number

4.1.2 Investigator Identification

- Institution and affiliate name
- Investigator's name

4.1.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID and/or Social Security number
- Patient demographics
  - Gender
  - Birth date (mm/yyyy)
  - Race
  - Ethnicity
  - Nine-digit ZIP code
  - Method of payment
  - Country of residence

4.2 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.

4.3 Classification Factors

Treatment arm per discretion of the treating investigator:

- Arm A: Paclitaxel 80 mg/m^2 every 7 days for 4 cycles

Rev Add1

- Arm B: Docetaxel 75 mg/m^2 every 3 weeks for 4-6 cycles

4.4 Additional Requirements

4.4.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

4.4.2 Peripheral blood specimens must be submitted for defined laboratory research studies as outlined in Section 10.

4.4.3 Plasma specimens are to be submitted for future undefined laboratory research studies per patient consent as outlined in Section 10.

Rev Add2

4.4.4 Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. To access Rave via iMedidata:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account; and

Rev Add1

- Assigned one of the following Rave roles on the relevant Lead Protocol Organization (LPO) or Participating Organization roster at the enrolling site: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.
- To hold Rave CRA or Rave CRA (Lab Admin) role, site staff must hold a minimum of an AP registration type;
- To hold Rave Investigator role, the individual must be registered as an NPIVR or IVR; and
- To hold Rave Read Only role, site staff must hold an Associates (A) registration type.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the

Rev Add2

iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the Rave EDC link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will display under the study name.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

Rev Add2

4.4.5 The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

NOTE: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

4.5 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted through Medidata Rave according to the schedule in the EAZ171 Forms Completion Guidelines. PRO completion and specimen submissions are not required.

5. Treatment Plan

5.1 Administration Schedule

NOTE: Recommended therapies for various therapy regimens are outlined below based on ER/PR/HER2 and nodal status. Where there are options, the treating physician will choose a regimen best fitted for that patient. If the physician does not feel any of the regimens are the best fit for the patient, the patient should not be enrolled. Physicians will also document why a regimen was felt to be inappropriate when an option.

5.1.1 Treatment Arm A

Paclitaxel 80 mg/m^2 every 7 days (weekly) for 4 cycles (1 cycle = 21 days).

- **ER+/HER2-/ LN+ (anthracycline appropriate)** = AC→weekly paclitaxel x 4 cycles (or refer to Section 5.1.2 for docetaxel treatment regimen options)
- **TNBC regardless of LN status (anthracycline appropriate)** = AC→weekly paclitaxel x 4 cycles (or refer to Section 5.1.2 for docetaxel treatment regimen options)
- **HER2+, <3cm, LN-** =weekly paclitaxel x 4 cycles + trastuzumab
- **HER2+ (anthracycline preferred)** = AC→weekly paclitaxel x 4 cycles + trastuzumab +/- pertuzumab (or refer to Section 5.1.2 for docetaxel treatment regimen option)

**anthracycline inappropriate: to be determined by treating physician based on: 1. risk of tumor recurrence, 2. co-morbidities or medical factors, 3. both, or, 4. other. The decision to use or not use an anthracycline will be in accordance with that physician's standard practice and with proper discussion with the patient. Physicians will document the reason why the individual patient is anthracycline inappropriate. If response 4 (i.e. other) is chosen, the specific reason needs to be stated.*

NOTE: Trastuzumab and pertuzumab are to be administered in the **adjuvant setting** per institution routine care per the treating physician's discretion.

5.1.2 Treatment Arm B

Docetaxel 75 mg/m^2 every 3 weeks (1 cycle = 21 days).

- **ER+/HER2-/ LN-** = docetaxel/cyclophosphamide x 4-6 cycles
- **ER+/HER2-/ LN+ (anthracycline inappropriate*)** = docetaxel/cyclophosphamide x 4-6 cycles
- **ER+/HER2-/ LN+ (anthracycline appropriate)** = AC→every 3 week docetaxel x 4 cycles -OR- docetaxel/doxorubicin/cyclophosphamide (TAC) every 3 weeks x 6 cycles (or refer to Section 5.1.1 for paclitaxel treatment regimen option)

- **TNBC regardless of LN status (anthracycline appropriate)** = AC→every 3 week docetaxel x 4 cycles -OR- docetaxel/doxorubicin/cyclophosphamide (TAC) every 3 weeks x 6 cycles (or refer to Section 5.1.1 for paclitaxel treatment regimen option)
- **TNBC regardless of LN status (anthracycline inappropriate*)** = docetaxel/cyclophosphamide x 4-6 cycles
- **HER2+ (anthracycline preferred)** = AC→every 3 week docetaxel x 4 cycles + trastuzumab +/- pertuzumab (or refer to Section 5.1.1 for paclitaxel treatment regimen option)

**anthracycline inappropriate: to be determined by treating physician based on: 1. risk of tumor recurrence, 2. co-morbidities or medical factors, 3. both, or, 4. other. The decision to use or not use an anthracycline will be in accordance with that physician's standard practice and with proper discussion with the patient. Physicians will document the reason why the individual patient is anthracycline inappropriate. If response 4 (i.e. other) is chosen, the specific reason needs to be stated.*

NOTE: Cyclophosphamide is to be administered per institution routine care per the treating physician's discretion.

NOTE: Trastuzumab and pertuzumab are to be administered in the **adjuvant setting** per institution routine care per the treating physician's discretion.

5.2 Adverse Event Reporting Requirements

All toxicity grades described in this protocol and all reportable adverse events on this protocol will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Adverse events will only be reported during the taxane portion of therapy. Since the anthracyclines portion of therapy will be used in the context of standard of care and are not the interest of this study, events will not be collected unless the taxane is being used concurrently with the anthracycline.

Rev Add1

All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

Clinician graded CTCAE is the AE (adverse event) safety standard. PRO-CTCAE items are to complement CTCAE reporting. Patients will respond to PRO-CTCAE items but no protocol directed action will be taken. PRO-CTCAE is not intended for expedited reporting, real time review or safety reporting.

5.2.1 Purpose

Adverse event (AE) data collection and reporting, which are a required part of every clinical trial, are done so investigators and regulatory agencies can detect and analyze adverse events and risk situations to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

5.2.2 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of an agent in humans, whether or not considered agent related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is *clearly NOT related* to treatment.
Unlikely	The AE is *doubtfully related* to treatment.
Possible	The AE *may be related* to treatment.
Probable	The AE is *likely related* to treatment.
Definite	The AE is *clearly related* to treatment.

- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.
- **Expectedness:** Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes, when either the type of event or the severity of the event is NOT listed in the protocol or drug package insert.
- **Hospitalization (or prolongation of hospitalization):** For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.
- **Life Threatening Adverse Event:** Any AE that places the subject at immediate risk of death from the AE as it occurred.

5.2.3 Mechanism for Adverse Event Reporting

Routine reporting: Adverse events are reported in a routine manner at scheduled times during a trial using the Medidata Rave clinical data management system. Please refer to Section 4 of the protocol for more information on how to access the Medidata Rave system and the EAZ171 forms packet for instructions on where and when adverse events are to be reported routinely.

Symptomatic Adverse Events reported by patients through PRO-CTCAE are not safety reporting and may be presented with other routine AE data.

Expedited reporting: In addition to routine reporting, certain adverse events must be reported in an expedited manner for timelier monitoring of patient safety and care. The remainder of this section provides information and instructions regarding expedited adverse event reporting.

5.2.4 Expedited Adverse Event Reporting Procedure

Adverse events requiring expedited reporting will use CTEP's Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov.

For this study, a CTEP-AERS report must be submitted electronically via the CTEP-AERS Web-based application located at http://ctep.cancer.gov, so that ECOG-ACRIN and all appropriate regulatory agencies will be notified of the event in an expeditious manner.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (857-504-2900)
- the FDA (1-800-FDA-1088)

An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Supporting and follow up data: Any supporting or follow up documentation must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the FDA (800-332-0178) in the same timeframe.

CTEP Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

5.2.5 Determination of Reporting Requirements

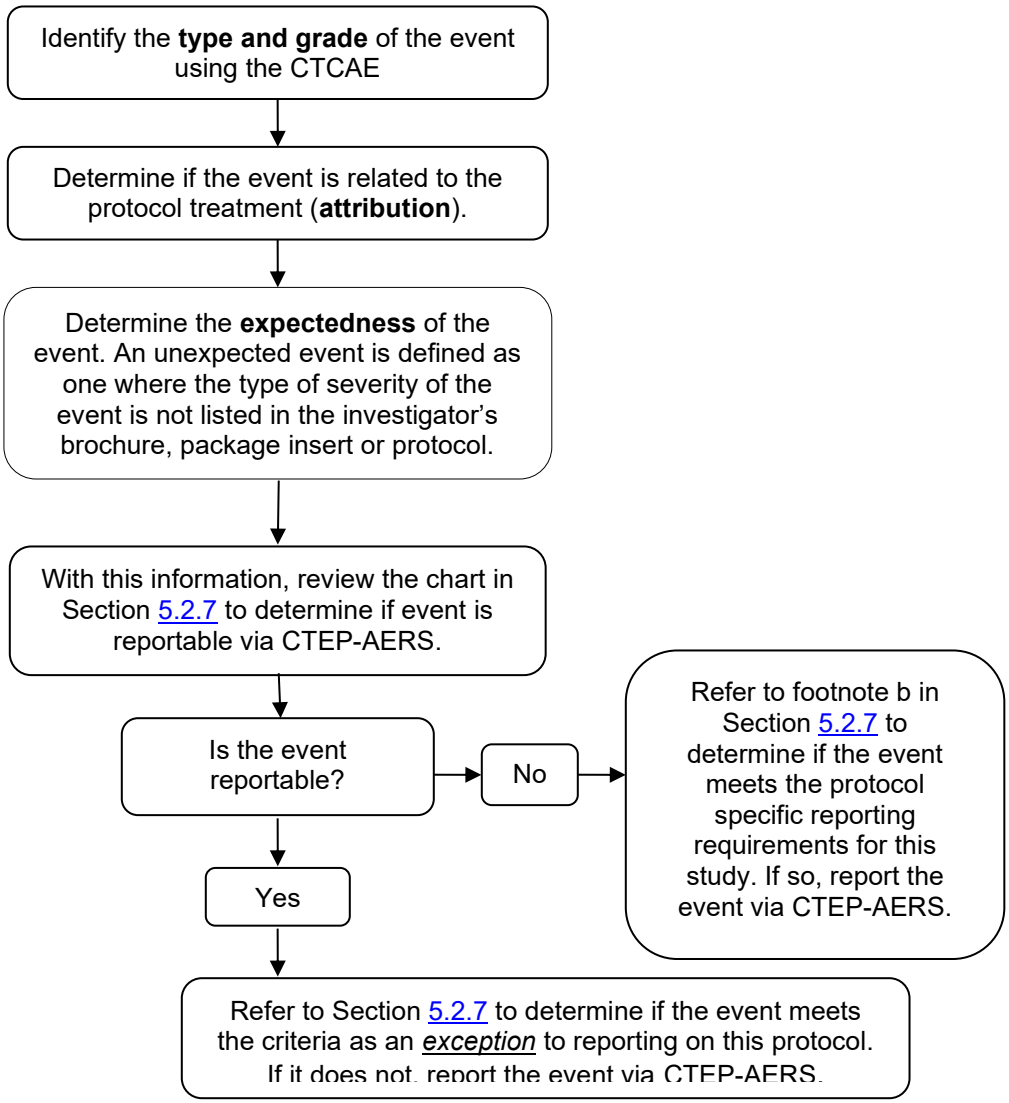
Many factors determine the reporting requirements of each individual protocol, and which events are reportable in an expeditious manner, including:

- the phase (0, 1, 2, or 3) of the trial
- whether the patient has received an investigational or commercial agent or both
- the seriousness of the event
- the Common Terminology Criteria for Adverse Events (CTCAE) grade
- whether or not hospitalization or prolongation of hospitalization was associated with the event
- when the adverse event occurred (within 30 days of the last administration of certain agent vs. ≥ 30 days after the last administration of certain agent)
- the relationship to the study treatment (attribution)
- the expectedness of the adverse event

Using these factors, the instructions and tables in the following sections have been customized for protocol EAZ171 and outline the

specific expedited adverse event reporting requirements for study EAZ171.

5.2.6 Steps to determine if an event is to be reported in an expedited manner



5.2.7 Expedited Reporting Requirements for protocol EAZ171

Commercial Agents: Paclitaxel and Docetaxel

Expedited reporting requirements for adverse events experienced by patients on arm(s) with commercial agents only

Attribution	Grade 4		Grade 5[a]		ECOG-ACRIN and Protocol-Specific Requirements
	Unexpected	Expected	Unexpected	Expected	See footnote (b) for special requirements.
Unrelated or Unlikely			7 calendar days	7 calendar days	
Possible, Probable, Definite	7 calendar days		7 calendar days	7 calendar days	

7 Calendar Days: Indicates a full CTEP-AERS report is to be submitted within 7 calendar days of learning of the event.

a A death occurring while on study or within 30 days of the last dose of treatment requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

NOTE: A death due to progressive disease should be reported as a Grade 5 "*Disease progression*" under the System Organ Class (SOC) "*General disorder and administration site conditions*". Evidence that the death was a manifestation of underlying disease (e.g. radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

NOTE: Any death that occurs > 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the treatment must be reported within 7 calendar days of learning of the event.

b Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited reporting for this trial:

Serious Events: Any event following treatment that results in *persistent or significant disabilities/incapacities, congenital anomalies, or birth defects* must be reported via CTEP-AERS within 7 calendar days of learning of the event. For instructions on how to specifically report these events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

5.2.8 Other recipients of adverse event reports and supplemental data

Adverse events determined to be reportable via CTEP-AERS must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.2.9 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN using Medidata Rave

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**

1. Complete a Second Primary Form in Medidata Rave within 14 days.
2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.

- **A <u>secondary malignancy</u> is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**

1. Complete a Second Primary Form in Medidata Rave within 14 days.

Rev Add2

2. Report the diagnosis on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave

   Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy

   NOTE: When reporting attribution on the AE Form, assess the relationship between the secondary malignancy and the current protocol treatment ONLY (and NOT relationship to any anti-cancer treatment received either before or after protocol treatment).

3. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov

   Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy

4. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
5. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: The ECOG-ACRIN Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the ECOG-ACRIN Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should

be submitted via CTEP-AERS or by the ECOG-ACRIN Second Primary Form.

5.3 Dose Modifications

PRO-CTCAE data should not be used for determining dose delays, dose modifications, or any other protocol directed action.

5.3.1 Paclitaxel Dose Modifications: AC dose modification or delay will not impact paclitaxel therapy.

NOTE: Day 1 of paclitaxel may be delayed. However, held doses on Day 8 (week 2) and Day 15 (week 3) are considered missed doses and will not be made up.

NOTE: If paclitaxel is not administered for > 3 weeks due to toxicity, stop paclitaxel.

Event	**Paclitaxel Dose Modification**
Neutrophil Count Decrease/Neutropenia	
Grade 0-2 ≥ 1000/mm^3	No change
≥ Grade 3 < 1000/mm^3	Hold until ANC ≥1000, resume based on timing of recovery: ≤ 1 week – no change >1 but ≤ 3 weeks - reduce dose 20% for subsequent cycles > 3 weeks – stop paclitaxel.
Febrile Neutropenia	
≥ Grade 3 ANC < 1000/mm^3 with a single temperature of > 38.3° C or a sustained temperature of ≥38° C for more than one hour	Interrupt until resolved (ANC ≥1000/mm^3, fever ≤ 38.3° C), resume according to number of episodes: 1st = no change 2nd = 20% dose reduction 3rd = stop paclitaxel.

Event	Paclitaxel Dose Modification
Platelet Count Decrease/Thrombocytopenia	
≥ 100,000/mm^3	No change
Grade 1 < LLN - 75,000/mm^3	Hold until ≥ 100,000, resume based on timing of recovery: If ≤ 1 week – no change. If >1 but ≤ 3 weeks - reduce dose 20% for subsequent cycles. If > 3 weeks delay is required, stop paclitaxel.
Grade 2 < 75,000	Hold until ≥ 100,000, Resume with 20% dose reduction for subsequent cycles. If > 3 weeks delay is required, stop paclitaxel.
Anemia	
All grades	No change.
Hepatobiliary Disorders	
Grade 0 or 1	No change
≥ Grade 2	Interrupt until ≤ Grade 1, then resume previous dose. If > 3 weeks delay is required, stop paclitaxel.
Nausea or Vomiting	
Grade 0 – 2	No change
≥ Grade 3	Hold until resolved to ≤ Grade 1, reduce dose 20% in subsequent cycles.
Mucositis (any)	
Grade 0 – 2	No change
≥ Grade 3	Hold until resolved to ≤ Grade 1, reduce dose 20% in subsequent cycles.
Nervous system-Neurotoxicity	
Grade 0 - 1	No change
Grade 2	If Grade 2 toxicity has resolved to ≤ Grade 1 on the day of treatment, proceed with treatment at the previous dose. If Grade 2 toxicity is present on the day of treatment, reduce dose 20% for all subsequent cycles.
Grade 3	Hold until resolved to ≤ Grade 1, reduce dose 20% in all subsequent cycles. If > 3 weeks delay is required, stop paclitaxel.
Grade 4	Discontinue paclitaxel.

Event	Paclitaxel Dose Modification
Hypersensitivity or Anaphylaxis	
Mild Symptoms: mild flushing, rash, pruritis	No treatment needed. Supervise at bedside and complete paclitaxel infusion.
Moderate Symptoms: moderate flushing, rash, mild dyspnea, chest discomfort	Stop paclitaxel. Administer diphenhydramine 25 mg and dexamethasone 10 mg IV. After recovery, resume infusion at half the previous rate for 15 minutes. If no further symptoms occur, complete the infusion at the full dose rate. If symptoms recur, stop paclitaxel.
Severe Symptoms: hypotension requiring pressors, angioedema, respiratory distress requiring bronchodilators	Stop paclitaxel. Administer diphenhydramine 25 mg and dexamethasone 10 mg IV. Add epinephrine or bronchodilators as needed. Do not restart paclitaxel.
Life threatening symptoms: Anaphylaxis, urgent intervention indicated	Stop Paclitaxel. Do not restart. NO FURTHER STUDY THERAPY
Other clinically significant toxicity excluding fatigue, alopecia and white blood cell decrease/leukopenia	
Grade 0 or 1	No change
Grade 2	Hold until resolved to ≤ Grade 1, resume at previous dose. Increase supportive care measures if possible.
≥ Grade 3	Hold until resolved to ≤ Grade 1, resume with 20% dose reduction for subsequent cycles. If Grade 3 or greater toxicity recurs, stop paclitaxel.

5.3.2 **Docetaxel Dose Modifications**: No more than two dose modifications should be allowed for any patient. If a patient requires a third reduction of docetaxel, they will be followed every 12 weeks and treated at their physician's discretion.

NOTE: Dose adjustments are to be made according to the system showing the greatest degree of toxicity.

NOTE: Dose adjustments for toxicity should be made according to the guidelines that follow. If a dose is reduced due to toxicity the dose will not be re-escalated back to starting level. Treatment may be delayed no more than three weeks to allow recovery from toxicity.

Dose Level	Docetaxel (mg/m^2)
Level 0	75 mg/m^2
Level 1	65 mg/m^2
Level 2	55 mg/m^2

Event	Docetaxel Dose Modification
Platelet Count Decrease/Thrombocytopenia	
≥ 100,000/mm^3	No change
Grade 1 < LLN - 75,000/mm^3	Hold until ≥ 100,000, resume based on timing of recovery: If ≤ 1 week – no change. If >1 but ≤ 3 weeks - reduce dose by one dose level for subsequent cycles. If > 3 weeks delay is required, stop docetaxel.
≥ Grade 2 < 75,000/mm^3	Hold until ≥ 100,000, Resume with one dose level reduction for subsequent cycles. If > 3 weeks delay is required, stop docetaxel.
White Blood Cell Decrease/Leukopenia	
Grade 0 or 1	No change
Grade 2	Hold until resolved to ≤ Grade 1, resume at previous dose. Increase supportive care measures if possible.
≥ Grade 3	Hold until resolved to ≤ Grade 1, resume dose by one dose level reduction for subsequent cycles. If Grade 3 or greater toxicity recurs, stop docetaxel.
Febrile Neutropenia	
≥ Grade 3 ANC < 1000/mm^3 with a single temperature of >38.3^o C or a sustained temperature of ≥38^o C for more than one hour	Interrupt until resolved (ANC $\geq$1000mm^3, fever $\leq$ 38.3^o C), resume according to number of episodes: 1st = no change 2nd = dose reduction by one dose level 3rd = stop docetaxel.
Hepatic Dysfunction (Blood Bilirubin or Alanine aminotransferase increase)	
Grade 0 or 1	Treat without delay but reduce docetaxel dose by one dose level. If Grade 1 bilirubin, docetaxel should be held until resolved to Grade 0.
≥ Grade 2	Interrupt until ≤ Grade 1, then resume reduced docetaxel dose by one dose level. If > 3 weeks delay is required, stop docetaxel.
Diarrhea*	
Grade 0 or 1	No change
≥ Grade 2	Treat prophylactically in subsequent cycles with loperamide or diphenoxylate. If patient experiences $\geq$ grade 2 despite prophylaxis, docetaxel should be dose reduced by one dose level. If diarrhea continues despite prophylaxis AND dose reduction, stop docetaxel.
*If patients experience > grade 2 diarrhea and concurrent grade 3 or 4 neutropenia, hold Docetaxel until ANC ≥ 1000/mm3 and diarrhea ≤ grade 2.	

Event	Docetaxel Dose Modification
Peripheral (Motor or Sensory) Neuropathy	
Grade 0-1	No change
≥ Grade 2	Hold until resolved to ≤ Grade 1, reduce dose by one dose level in subsequent cycles. If > 3 weeks delay is required, stop docetaxel.
Mucositis (any)	
Grade 0 - 2	No change
≥ Grade 3	Hold until resolved to ≤ Grade 1, reduce dose by one dose level in subsequent cycles.
Hypersensitivity or Anaphylaxis	
Mild symptoms: mild flushing, rash, pruritis	• Consider decreasing the rate of infusion until recovery from symptoms, stay at bedside or monitor patient • Then, complete docetaxel infusion at initial planned rate.
Moderate symptoms: moderate flushing, rash, mild dyspnea, chest discomfort	• Stop docetaxel. • Administer diphenhydramine 50 mg and dexamethasone 10 mg IV. • After recovery, resume infusion at half the previous rate for 15 minutes. If no further symptoms occur, complete the infusion at the full dose rate. • Depending on the intensity of the reaction observed, additional oral or IV premedication with an antihistamine should be given for the **next cycle** of treatment, and the rate of infusion should be decreased initially ante increased back to initial planned rate.
Severe symptoms: hypotension requiring pressors, angioedema, respiratory distress requiring bronchodilators	• Stop docetaxel. • Administer diphenhydramine 50 mg and dexamethasone 10 mg IV. Add epinephrine or bronchodilators as needed. • Do not restart.
Life threatening symptoms: Anaphylaxis, urgent intervention indicated	Stop Docetaxel. Do not restart. NO FURTHER STUDY THERAPY

5.4 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study. Hematologic growth factors are not required but may be used in accordance with the ASCO guidelines.

5.5 Patient-Reported Outcomes (PRO) Administration

A detailed description of the PRO measures to be administered has been included in Section 6.

Rev Add1

5.5.1 PRO Instruments to be administered

1. Functional Assessment of Cancer Therapy Gynecological Oncology Group Neurotoxicity (FACT/GOG-NTX)
2. PROMIS Physical Function v2.0 Short Form 10a
3. EORTC QLQ-CIPN 20 Sensory Neuropathy subscale
4. Comprehensive Score for Financial Toxicity – Functional Assessment of Chronic Illness Therapy (COST-FACIT)

Rev Add2

5. Five social determinants of health items from the Alliance Patient Questionnaire for Clinical Trials In Oncology
6. PRO-CTCAE items to be administered: # 39 & 48 - Numbness and Tingling a-b and General Pain a-c.

Rev Add1

5.6 PRO Assessment Schedule

The FACT-G portion (HRQoL) portion of the FACT/GOG-NTX and the PROMIS Physical Function Short Form 10a will be used to assess patient-reported HRQoL and physical function using the following schedule:

1. Baseline (Prior to first taxane treatment: must be within 14 days prior to or on the day of taxane therapy but prior to delivery of treatment)
2. Day 1 Cycle 3.
3. At end of protocol treatment, including treatment discontinuation for any reason (i.e. toxicity, progression, completion of protocol therapy)
4. Follow-up at 6 months, 1, 2 and 3 years after initiation of taxane treatment

Rev Add2

The FACT/GOG-NTX 11-item neurotoxicity scale, CIPN-20 9-item sensory neuropathy subscale and PRO-CTCAE items assessing neuropathy (#39a-b) and general pain (#48a-c) will be administered using the following schedule to be consistent with the Symptom/Toxicity Assessments:

1. Baseline (Prior to first taxane treatment: must be within 14 days prior to or on the day of taxane therapy but prior to delivery of treatment)
2. Day one of every cycle except cycle 1 (baseline evaluation will take the place of cycle 1), following the same schedule as trial symptom/toxicity assessments
3. At end of protocol treatment, including treatment discontinuation for any reason (i.e. toxicity, progression, completion of protocol therapy)
4. Follow-up at 6 months, 1, 2 and 3 years after initiation of taxane treatment

NOTE: The PRO-CTCAE items should be completed each time a Symptom/Toxicity Assessments is completed.

Rev Add2

The COST-FACIT to assess financial toxicity will be administered using the following schedule:

1. Baseline (Prior to first taxane treatment: must be within 14 days prior to or on the day of taxane therapy but prior to delivery of treatment)
2. At end of protocol treatment, including treatment discontinuation for any reason (i.e. toxicity, progression, completion of protocol therapy)
3. At 6 months after initiation of taxane treatment

The Alliance Patient Questionnaire for Clinical Trials In Oncology (items from education, marital status, health insurance status income) and current zip code to capture important social determinants of health. These variables will be assessed at the following time points:

Rev Add1

1. Baseline (Prior to first taxane treatment: must be within 14 days prior to or on the day of taxane therapy but prior to delivery of treatment)
2. At end of protocol treatment, including treatment discontinuation for any reason (i.e. toxicity, progression, completion of protocol therapy)

Rev Add1

The total length of PRO assessment is dependent on the assessment time point. One of the lengthiest assessments will occur at Baseline (PRO-CTCAE items, FACT/GOG-NTX, PROMIS Physical Function Short Form 10a, CIPN-20 sensory neuropathy items, COST-FACIT, & social determinants of health items) is 78 multiple-choice items. The anticipated time to complete all items is approximately 16 minutes (roughly, an average of five items completed per minute). We have scheduled PRO assessments with standard clinic office visits to minimize participant and site burden, thus minimizing the risk of missing PRO data.

PRO assessments at treatment discontinuation and follow-up time points post-treatment discontinuation for all participants, regardless of the reason for treatment discontinuation (toxicity, progression), will provide valuable information on HRQoL and symptom burden. Patient HRQoL can appear to improve overall as the trial progresses due to participant selection bias.[44] Participants with poorer performance status, more aggressive disease, and greater treatment toxicities come off treatment earlier. To obtain more unbiased assessment of HRQoL and treatment toxicities, PRO assessments at the end of treatment and follow-up for all participants is needed. Otherwise, PRO assessments only capture data on participants who remain on treatment and are likely to be healthier, therefore, presenting a biased source of data that will likely indicate that HRQoL improves over time.

5.7 PRO Instructions

All PRO questionnaires will be administered as a paper survey at the time points listed above. Ideally, participants will complete questionnaires at the time of scheduled study visits. If the PRO assessments are not administered in clinic, the study questionnaires will be mailed to participants who will be asked to complete questionnaires and return by mail to clinic. After 7 days, clinic or research staff may contact participants by telephone and ask participants to complete the questionnaire on paper and then read their answers over the telephone to the staff person. This procedure will minimize mode effect, whereby participants report less symptoms burden during phone or in-person interviews than with

written surveys. This approach will approximate the completion of PROs in clinic as closely as possible. This will also compensate for potential responder bias, wherein healthier patients are more likely to return to clinic and thus, to complete the post-treatment surveys.

The patient should be instructed to respond to the questionnaires in terms of her experience during the timeframe specified on each questionnaire. The patient should be asked to read the instructions at the beginning of each questionnaire and complete all the items. It is permissible to assist the patient with the completion of the questionnaires as long as the staff person does not influence the patient's responses.

Rev Add2

PRO-CTCAE items assessing numbness/tingling (#39a-b) and general pain (#48a-c) will be administered on paper along with other study PRO measures following procedures for PRO administration as described above. PRO-CTCAE items will be administered prior to clinic visits, or prior to participant's discussion of disease status and treatment side effects with health-care professionals. This is modeled after NCI PRO-CTCAE study procedures employed in other clinical trial validation studies. Clinicians will be instructed to complete clinician-rated treatment toxicities (CTCAE) prior to reviewing PRO-CTCAE ratings. This will minimize the extent to which PRO-CTCAE responses introduce a bias to clinician CTCAE ratings. PRO-CTCAE are currently undergoing validation and exploratory in nature. Therefore, at this point, PRO-CTCAE item responses should not be used to inform clinician CTCAE ratings. Clinicians will be instructed to review PRO-CTCAE items after clinician toxicity ratings have been completed in order to identify any patient-reported symptoms and toxicities that warrant clinical attention.

The questionnaires should be reviewed by the protocol nurse or research coordinator as soon as the patient completes them to ensure all items were marked appropriately. If more than one answer was marked, the patient should be asked to choose the answer which best reflects how she is feeling. If a question was not answered, the patient should be asked if she would like to answer it. The patient should always have the option to refuse. If the patient refuses, it should be indicated on the questionnaire that she declined to answer the item. If the patient cannot complete a questionnaire, or if the patient refuses to complete the questionnaire, the reason should be noted according to the instructions in the EAZ171 Forms Completion Guidelines.

Rev Add1

Given the geographic locations of recruitment sites concurrent with a sample of Black / African-American women, we do not anticipate a significant number of Spanish-speaking participants. However, we are committed to making study recruitment as inclusive as possible. Therefore, in accordance with the NCORP Part 3 Guidelines, we will make all PRO measures with validated Spanish-language versions available to any eligible Spanish-language patients interested in participating.

5.8 Duration of Therapy

Patients will receive protocol therapy unless:

- Completion of protocol therapy
- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be

discontinued. In this event, submit forms according to the instructions in the EAZ171 Forms Packet.

- Patient has relapse of disease.
- Patient withdraws consent.
- Patient experiences unacceptable toxicity.
- Non-protocol therapies are administered.

5.9 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for recurrence and second primary cancer, even if non-protocol anti-cancer therapy is initiated, and for survival for 5 years from the date of registration. All patients must also be followed through completion of all protocol therapy.

6. Measurement of Effect

NOTE: The primary endpoint of the trial is grade 2-4 TIPN based on CTCAE, and a secondary phenotype of neurotoxicity will be assessed using patient reported outcome via FACT/GOG-NTX questionnaire. This study also will evaluate several other PRO endpoints. Although there is no efficacy endpoint in the study, it is standard for ECOG-ACRIN to collect disease recurrence and survival information on treatment and long-term follow-up forms.

Rev Add2

Rev Add1

6.1 Grade 2-4 neuropathy

Grade 2-4 TIPN is the primary endpoint of the study, and will be assessed by treating physician using the CTCAE. While on taxane treatment, AE assessment will be administered on the first day of each cycle (1 cycle=21 days on both arms) and at the end of treatment to collect any occurrence of neuropathy during treatment. After treatment completion, AE assessment will be administered at 6 months, 1, 2, and 3 years after initiation of taxane treatment to collect any long-term TIPN. For the primary endpoint, the observation period will be from initiation of taxane treatment until 1 year after that (i.e. total period of 1 year including taxane treatment time). Patients will be coded as having the event as long as grade 2-4 neuropathy based on the CTCAE occurred at any time during the observation period. Patients without neuropathy or with maximum of grade 1 neuropathy during the whole observation period (including patients without grade 2-4 TIPN during the whole year and patients without grade 2-4 TIPN before loss to follow up within 1 year) will be coded as having no event. Of note, only neuropathy with a treatment relationship code of 3-5 (possibly, probably, definitely) will be considered as taxane-induced neuropathy, and neuropathy with a treatment relationship code of 1-2 (unrelated or unlikely) will not be considered in the study design.

Rev Add1

6.2 PRO-based neuropathy

Rev Add2

The PRO-based neurotoxicity will be assessed using the 11-item neurotoxicity subscale of the FACT/GOG-NTX. Each item is scored from 0–4, and the neurotoxicity total score is the sum of the scores for the 11 items, and ranges from 0 to 44[26,36,38]. Lower values of the FACT/GOG-NTX neurotoxicity total score indicate higher neurotoxicity.

To harmonize with the SWOG1714 trial, we will also be assessing patient-reported neuropathy with the CIPN20 9-item sensory neuropathy subscale. Each item is measured on a 1-4 scale (1, not at all; 4, very much). The sensory subscale raw scores range from 1 to 36. CIPN-20 subscale raw scores are linearly converted to a 0-100 scale such that a high score corresponds to a worse condition or more symptoms.

Assessment of PRO-based neurotoxicity will take place at the same schedule as CTCAE (i.e., baseline or day 1 of cycle 1, at first day of each following cycle, at treatment completion, and at 6 months, 1, 2, and 3 years post initiation of taxane treatment). The FACT/GOG-NTX neurotoxicity total score and CIPN-20 sensory neuropathy subscale score will be analyzed as continuous variables.

6.3 PROMIS Physical Function v2 Short Form 10

The PROMIS Physical Function v2 Short Form 10a measures self-reported capability rather than actual performance of physical activities. This includes the functioning of one's upper and lower extremities (dexterity), lower extremities (walking or mobility), and central regions (neck, back), as well as instrumental activities of daily living. Starting with the PROMIS pool of universal physical function items, members of the PROMIS-Cancer team and multidisciplinary panels of clinical experts working in oncology selected the items for this short form based on information from cancer-specific focus groups, expert reviewers and large-scale field-testing. Item selection emphasized, clinical relevance, content coverage and ability to identify cases in need of intervention[64]. As for all PROMIS measures, summary scores are calculated as a T-score (with 50 = mean & 10 = SD of the reference population) and higher scores reflecting more of the concept being measured (physical function). There are multiple options for calculating PROMIS T-scores. If an electronic data collection platform cannot be used, as in this study, the free web-based HealthMeasures Scoring Service is preferred because it provides accuracy.[66] Users download an Excel template from the site, add the raw responses from a PROMIS measure, and then upload the file and receive by email a spreadsheet with calculated T-scores and standard errors. The HealthMeasures Scoring Service can handle missing data and multiple timepoints. No participant protected health information is requested or used by the service. If it is not possible to utilize response pattern scoring, PROMIS Scoring Manuals include tables for transforming the sum of all raw responses to a T-score. We will compare PROMIS Physical Function v.2 SF 10a scores for the two treatment arms (A&B) and for the high risk vs. low risk genotypes (in arm A).

Rev Add1

6.4 Health-related quality of life

The FACT/GOG-NTX questionnaire referenced above also contains 27 core items (the FACT-G) that cover four areas of HRQoL: physical, social, emotional, and functional well-being. HRQoL will be measured by the summed total score of the 27 core items, which will range from 0 to 108. The FACT-G total score will be analyzed as a continuous variable. The primary comparison will be change in HRQoL total score between registration and treatment completion between two groups.

6.5 Comprehensive Score for Financial Toxicity – Functional Assessment of Chronic Illness Therapy (COST-FACIT)

The Comprehensive Score for Financial Toxicity (COST-FACIT) is an 11-item patient-reported measure of financial toxicity that uses a 7-day time window and a 5-point Likert response scale ranging from 0 ("not at all") to 5 ("a lot"). Higher COST-FACIT scores (range: 0-44) represent better financial well-being.[67] We will compare the total COST-FACIT scores for the two treatment arms (A and B).

Rev Add2

6.6 Alliance Patient Questionnaire Items on Social Determinants of Health

To further examine social determinants of health that may be related to participants' treatment and HRQoL, we will ask participants to complete items from the Alliance Patient Questionnaire for Clinical Trials In Oncology (education, marital status, health insurance status income) and current zip code to capture important social determinants of health. We will examine associations between

those social determinants of health and participant's dose reductions or treatment discontinuation, reported toxicities and HRQoL.

6.7 PRO-CTCAE

We will compare scores on the two patient-reported neuropathic-related adverse events, as assessed by the two PRO-CTCAE items between the two taxane regimens (arm A vs. arm B). PRO-CTCAE responses are scored from 0 to 4, and there are as yet no standardized scoring rules for how to combine attributes into a single score or how best to analyze PRO-CTCAE data longitudinally. PRO-CTCAE scores for each attribute (frequency, severity and/or interference) should be presented descriptively. PRO-CTCAE scores should be presented in conjunction with CTCAE grades for the corresponding time periods. The items we have selected (#39a-b – numbness & tingling and #48a-c – general pain) include ratings of severity and interference with usual activities; the pain item also includes a frequency rating.

Rev Add2

6.8 Disease recurrence

Recurrence should be diagnosed by radiological examination and/or histopathological confirmation when the lesion is easily accessible for biopsy. Abnormal blood studies alone (e.g., elevated transaminases or alkaline phosphatase) are not sufficient evidence of relapse. Disease recurrence or new cancers should be reported on the clinical database as soon as possible after they are discovered. This includes events diagnosed during study visits but also any event diagnosed during non-study visits.

6.9 Survival

Date of registration to date of death from any cause.

7. Study Parameters

7.1 Therapeutic Parameters for Arms A and B

1. All required baseline assessments must be done ≤ 3 weeks prior to registration, with the exception of pregnancy tests for patients of childbearing potential.

Rev Add2

Rev Add1

Assessment	Time-points						
	Baseline/ Registration	Cycle1[1,3]	Cycles 2,4,6[1,3]	Cycles3,5[1,3]	End of treatment[7]	6 months post initiation of taxane	Long-term follow-up[8]
	- 21 days	± 7 days	± 7 days		± 7 days	± 14 days	± 30 days
Informed Consent	X						
History and physical (must include height, weight, and ECOG performance status)	X	X	X	X		X	X
Laboratory Assessments[2]	X	X	X	X	X	X	
Pregnancy Test[2]	X						
Symptom/Toxicity Assessment	X	X	X	X	X	X	X[11]
Survival and relapse		X	X	X		X	X
PRO Instrument Administration[4]							
PRO-CTCAE Items[10]	X[12]		X	X	X	X	X[11]
FACT/GOG-NTX 11 neurotoxicity items	X[12]		X	X	X	X	X[11]
CIPN-20 9-item sensory neuropathy subscale	X[12]		X	X	X	X	X[11]
PROMIS Physical Function v2 Short Form 10a	X[12]			X	X	X	X[11]
FACT-G	X[12]			X	X	X	X[11]
COST-FACIT	X[12]				X	X	

Assessment	Time-points						
Rev Add2 Alliance Patient Questionnaire for Clinical Trials In Oncology (social determinants of health items)	X[12]				X		
Biological Sample Submissions[5,9]							
MANDATORY: Peripheral Blood, one (1) 6mL EDTA Purple Top Tube[13]		X[12]					
MANDATORY: Peripheral Blood, one (1) 10mL Sodium Heparin Green Top Tube[13]		X[12]					
OPTIONAL: Plasma and residual cells from one (1) 10mL EDTA Purple Top Tube[6]		X[12]				X	

Rev Add2 1. Cycles are 21 days long. Data will be collected on the 1st day of each treatment cycle. +/- 7 day window for cycles 1-6.

Rev Add2 2. **Baseline:** History & Physical, CBC, ANC, CMP, and Hemoglobin A1C. Assessments are to be drawn and results obtained ≤ 3 weeks prior to registration. Patients of childbearing potential must have a negative serum or urine pregnancy test ≤ 2 weeks prior to registration.

   Treatment cycles: CBC and CMP.

   End of treatment: CBC and CMP

   6 months post initiation of taxane treatment: Hemoglobin A1C

3. Investigators must specify why they did not choose to use an anthracycline in those scenarios where it is considered an option.

Rev Add2 4. PROs for administration are: Functional Assessment of Cancer Therapy Gynecological Oncology Group Neurotoxicity (FACT/GOG-NTX), PROMIS Physical Function Short Form 10a, Functional Assessment of Cancer Therapy – General (FACT-G), CIPN-20 9-item sensory neuropathy subscale, Comprehensive Score for Financial Toxicity (COST-FACIT), five social determinants of health items from the Alliance Patient Questionnaire for Clinical Trials In Oncology, and PRO CTCAE items. Please refer to Section 5.6 for complete information regarding instruments to be administered and the instrument administration schedule. For the baseline assessments, these

Rev Add1 must occur within 14 days of the beginning of the taxane portion of therapy. This baseline assessment will take the place of the assessment for C1.

5. All specimens submitted must be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS).
6. Submit from patients who answer “Yes” to “I agree to provide additional samples for research.”
7. 30 days post treatment.

Rev Add2 8. After patient has completed treatment, every 3 months if patient is < 2 years from their date of initiation of taxane treatment, every 6 months if patient is 2-5 years from their date of initiation of taxane treatment. Patients will be followed for 5 years from their initiation of taxane.

9. Kits are being provided for the collection and shipment of the blood specimens. Allow up to two (2) weeks for kit delivery. See Section 10 for instructions.
10. The PRO-CTCAE items should be completed each time a Symptom/Toxicity Assessment is completed.
11. Long-term follow-up at 1, 2, and 3 years from initiation of treatment.
12. Baseline specimen collection and PROs are to be done after registration, but prior to taxane treatment on C1D1.
13. Draw Monday – Thursday only.

8. Drug Formulation and Procurement

All agents in this protocol are commercially available; drug will be obtained from institutional pharmacy supply.

8.1 Paclitaxel

NOTE: Please refer to the commercial package insert for more information.

8.1.1 Other Names

Taxol, NSC 673089.

8.1.2 Classification

Anti-microtubule agent.

8.1.3 Mode of Action

Promotes microtubule assembly and stabilizes tubulin polymers by preventing their depolarization, resulting in the formation of extremely stable and nonfunctional microtubules, and consequently inhibition of many cell functions.

8.1.4 Storage and Stability

The intact vials are stored under refrigeration. Freezing does not adversely affect the product. Solutions diluted to a concentration of 0.3 to 1.2 mg/mL in normal saline, 5% dextrose, 5% dextrose and normal saline, or 5% dextrose in Ringer's solution are stable for up to 27 hours when stored at room temperature and normal room light.

8.1.5 Dose Specifics

80 mg/m^2

8.1.6 Preparation

The concentrated solution must be diluted prior to use in normal saline, 5% dextrose, 5% dextrose and normal saline, or 5% dextrose in Ringer's solution to a concentration of 0.3 -1.2 mg/mL. Solutions exhibit a slight haze, common to all products containing non-ionic surfactants. Glass, polypropylene, or polyolefin containers and non-PVC-containing (nitroglycerin) infusion sets should be used. A small number of fibers (within acceptable limits established by the USP) have been observed after dilution. Therefore, a hydrophilic 0.22 micron in-line filter should be used. Analyses of solutions filtered through IVEX-2 and IVEX-HP (Abbott) 0.2 micron filters showed no appreciable loss of potency.

Solutions exhibiting excessive particulate formation should not be used.

8.1.7 Route of Administration

Paclitaxel will be administered to patients as an IV infusion over approximately three hours, or per institutional standards for care.

8.1.8 Incompatibilities

Avoid the use of PVC bags and infusion sets due to leaching of DEHP (plasticizer). Ketoconazole may inhibit paclitaxel metabolism, based on *in vitro* data.

8.1.9 Availability

Paclitaxel is commercially available, and is to be obtained from institutional pharmacy supply.

8.1.10 Side Effects

Please refer to the package insert.

8.1.11 Nursing/Patient Implications

1. Monitor CBC and platelet count prior to drug administration.
2. Symptom management of expected nausea, vomiting, and stomatitis.
3. Monitor for and evaluate abdominal pain occurring after paclitaxel administration (especially in severely neutropenic patients and in those receiving G-CSF) due to the risk of ischemic and neutropenic enterocolitis.
4. Advise patients of possible hair loss.
5. Cardiac monitoring for assessment of arrhythmias in patients with serious conduction abnormalities.
6. Monitor liver function tests.
7. Advise patient of possible arthralgias and myalgias which may occur several days after treatment. Monitor for symptoms of peripheral neuropathy.
8. Monitor for signs and symptoms of hypersensitivity reactions. Insure that the recommended premedications have been given. Premedications (diphenhydramine, steroids, and H2 blocker) appear to reduce the incidence and severity of hypersensitivity reactions but do not provide complete protection. Emergency agents (diphenhydramine and epinephrine) should be available.
9. Evaluate IV site regularly for signs of infiltration. It is not known if paclitaxel is a vesicant; however, the CremophorEL vehicle for this drug can cause tissue damage.
10. In-line filtration with a 0.22 micron filter should be used.

8.1.12 References

Rowinsky EK, Casenave LA, Donehower RC. Taxol: A novel investigational microtubule agent. J Natl Cancer Inst 1990; 82:1247-1259.

Gregory RE, DeLisa AF. Paclitaxel: A new antineoplastic agent for refractory ovarian cancer. Clin Pharm 1993; 12: 401-415.

Rowinsky EK, Eisenhauer EA, Chaudry V, et al. Clinical toxicities encountered with paclitaxel. Semin Oncology 1993; 20:1-15.

Walker FE. Paclitaxel: Side effects and patient education issues. Semin Oncology Nurs 1993; 9(suppl 2):6-10.

8.2 Docetaxel

NOTE: Please refer to the commercial package insert for more information.

8.2.1 Other Names

Taxotere, RP 56976, NSC #628503.

8.2.2 Classification

Antimicrotubule agent.

8.2.3 Mode of Action

Docetaxel, a semisynthetic analog of taxol, promotes the assembly of tubulin and inhibits microtubule depolymerization. Bundles of microtubules accumulate and interfere with cell division.

8.2.4 Storage and Stability

Store intact vials between 2° and 25°C (36° and 77°F). Retain in the original package to protect from bright light. The final dilution (in either 0.9% sodium chloride or 5% Dextrose solution) is stable for 4 hours if stored between 2° and 25°C (36° and 77°F).

8.2.5 Dose Specifics

75 mg/m^2

8.2.6 Preparation

Just prior to use, allow the docetaxel vial to reach room temperature for 5 minutes. Add the entire contents of the ethanol diluent vial and mix by gently rotating the vial for 45 seconds. Allow to stand for 5 minutes at room temperature, and check that the solution is homogeneous and clear (persistent foam is normal). The resulting solution contains 10 mg/mL of docetaxel. Please note that the solution contains 15% overfill. Dosing amounts should be based in the concentration per extractable volume, not the total volume of the vial. The desired dose is diluted in D5W or NS. The volume of the infusion should be adjusted in order to have a final docetaxel concentration of between 0.3 mg/mL and 0.74 mg/mL. Non-PVC-containing intravenous infusion bags and administration sets should be used to avoid patient exposure to the plasticizer DEHP.

8.2.7 Administration

Docetaxel will be administered to patients as an IV infusion over approximately one hour, or per institutional standards for care.

8.2.8 Incompatibilities

Intravenous bags and administration sets containing DEHP (di-[2-ethylexyl] phthalate). No further information available.

8.2.9 Availability

Docetaxel is commercially available, and is to be obtained from institutional pharmacy supply.

8.2.10 Side Effects

Please refer to the package insert.

8.2.11 Nursing Implications

1. Monitor CBC and platelet count prior to drug administration.
2. Symptom management of expected nausea, vomiting, and mucositis.
3. Advise patients of possible hair loss.
4. Monitor for signs and symptoms of hypersensitivity reactions. Insure that recommended pre-medications are given.
5. Monitor liver function tests.
6. Evaluate site regularly for signs of infiltration.
7. Monitor for symptoms of peripheral neuropathy.
8. Monitor for signs of fluid retention and cutaneous reactions.

8.2.12 References

Investigator's Brochure: Docetaxel. Rhone-Poulenc Rorer, June 14, 1995.

Pazdur R, *et al.* Phase I trial of Taxotere; Five-day schedule. J Natl Cancer Inst 84:1781-8, 1992.

Pazdur R, *et al.* Phase I trial of Taxotere (RP56976). Proc Am Soc Clin Oncol 11:111, 1992.

Burris H, *et al.* A phase I clinical trial of Taxotere as a 6-hour infusion repeated every 21 days in patients with refractory solid tumors. Proc Am Soc Clin Oncol 11:137, 1992.

Bissett D, *et al.* Phase I study of Taxotere (RP56976) given as a 24-hour infusion. Proc Am Assoc Cancer Res 33:526, 1992.

Bruno R, *et al.* Clinical pharmacology of Taxotere (RP56976) given as a 1-2 hour infusion every 2-3 weeks. Proc Am Assoc Cancer Res 33:261, 1992.

DeValeriola D, *et al.* Phase I pharmacokinetic study of Taxotere (RP56976) administered as a weekly infusion. Proc Am Assoc Cancer Res 33:1563, 1992.

9. Statistical Considerations

The study is designed primarily to validate a previously identified germline predictor (homozygous wild-type allele in FCAMR and/or mutations in SBF2) for paclitaxel-induced peripheral neuropathy (TIPN) in African American women diagnosed with early stage breast cancer. The over-arching goal of this study, however, is to change the standard of care for patients of African descent. This requires both confirmation of the higher risk of neuropathy with weekly paclitaxel AND a lower risk of neuropathy with docetaxel in the study patients. Thus the study includes two treatment arms based on taxane type: weekly paclitaxel and every 3 weeks docetaxel. Self-identified African American or black women with histologically confirmed early stage invasive adenocarcinoma of the breast will be registered to the trial and assigned to one of two neoadjuvant or adjuvant taxane regimens based on their disease characteristics (receptor status determined by local site, lymph node, tumor size, and anthracycline appropriate or not). Specifically,

Paclitaxel 80 mg/m^2 - weekly for 4 cycles (1 cycle = 21 days);

- **ER+/HER2-/ LN+ (anthracycline appropriate) =** AC→weekly paclitaxel x 4 cycles
- Rev Add2 **TNBC regardless of LN status (anthracycline appropriate) =** AC→weekly paclitaxel x 4 cycles
- **HER2+, <3cm, LN- =** weekly paclitaxel x 4 cycles + trastuzumab
- **HER2+ (anthracycline preferred) =** AC→weekly paclitaxel x 4 cycles + Trastuzumab +/- Pertuzumab

-OR-

Docetaxel 75 mg/m^2 - every 3 weeks x 4 cycles (1 cycle = 21 days)

- **ER +/HER2 -/ LN- =** docetaxel/cyclophosphamide x 4 cycles
- **ER+/HER2-/ LN+ (anthracycline inappropriate*) =** docetaxel/cyclophosphamide x 4-6 cycles
- Rev Add2 **ER+/HER2-/ LN+ (anthracycline appropriate)** = AC→every 3 week docetaxel x 4 cycles -OR- docetaxel/doxorubicin/cyclophosphamide (TAC) every 3 weeks x 6 cycles
- **TNBC regardless of LN status (anthracycline inappropriate*) =** docetaxel/cyclophosphamide x 4-6 cycles OR
- **TNBC regardless of LN status (anthracycline inappropriate*) =** docetaxel/cyclophosphamide x 4-6 cycles
- **HER2+ (anthracycline preferred) =** AC→every 3 week docetaxel x 4 cycles + trastuzumab +/- pertuzumab

***anthracycline inappropriate:** to be determined by treating physician based on risk of tumor recurrence and co-morbidities or medical factors in accordance with that physician's standard practice

For the evaluation of the germline predictor for TIPN, the two arms will be assessed separately. Section 9.1 provides the details for sample size consideration (n=120) for the paclitaxel arm (primary endpoint). The same number of patients will be enrolled to the docetaxel arm as well to explore whether the germline predictor can predict TIPN in patients receiving docetaxel as well, and to compare the two arms regarding the incidence of grade 2-4 TIPN (the top secondary endpoint, see Section 9.2.1), dose reduction due to TIPN, dose reduction due to any cause, and health-related quality of life

(QOL). Since patients will be assigned to treatment arm based on their disease characteristics (receptor status, lymph node, tumor size, and anthracycline appropriate or not), the treatment arm that meets the accrual goal first will be closed while accrual is continuing for the other arm.

The two taxane regimens are both standard of care, and there is no efficacy endpoint, no interim analysis is planned for the study. Final analysis will take place at about 1.5 years after the enrollment of the last patient (1 year of follow up + 6 months of data cleaning), i.e., about 2.5 years after study activation assuming accrual will be completed within 12 months (see Section 9.1).

Rev Add1

9.1 Primary Objective

The primary objective of this validation study is to determine whether homozygous wild-type allele in FCAMR and/or mutations in SBF2 (high risk genotype) can predict taxane-induced peripheral neuropathy (TIPN) in self-identified African American or black women diagnosed with early stage breast cancer and receiving neoadjuvant or adjuvant weekly paclitaxel treatment (arm A).

Incidence of grade 2-4 TIPN is the primary endpoint of the study, and will be assessed by treating physician using CTCAE. While on taxane treatment, AE assessment will be administered on the first day of each cycle (1 cycle=3 weeks on both arms) and at the end of taxane treatment to collect any occurrence of neuropathy during treatment. After treatment completion, AE assessment will be administered at 6 months after initiation of taxane treatment, and then every 3 months within 2 years of initiation of taxane treatment and every 6 months in year 3-post initiation of taxane treatment to collect any long-term TIPN. For the primary endpoint, the observation period will be from initiation of taxane treatment until 1 year after that (i.e. total period of 1 year including treatment time). Patients will be coded as having the event as long as grade 2-4 neuropathy based on CTCAE occurred at any time during the observation period. Patients without neuropathy or with maximum of grade 1 neuropathy during the whole observation period (including patients without grade 2-4 TIPN during the whole year and patients without grade 2-4 TIPN before loss to follow up within 1 year) will be coded as having no event. Sensitivity analysis will be conducted by excluding patients without any grade 2-4 TIPN before loss to follow up within 1 year from the denominator. Of note, only neuropathy with a treatment relationship code of 3-5 (possibly, probably, definitely) will be considered as taxane-induced neuropathy, and neuropathy with a treatment relationship code of 1-2 (unrelated or unlikely) will not be considered in the study design.

The germline predictor of interest in the study is homozygous wild-type allele in *FCAMR* and/or mutations in *SBF2*. Previously, we identified a common variant in *FCAMR* (*rs1856746*) that predicted a decreased risk for TIPN[1] and rare variants in *SBF2* associated with an increased risk of TIPN.[7] Overall, 76% of patients of African descent in E5103 carried homozygous wild-type allele in *FCAMR* and/or mutations in *SBF2* (high risk genotypes), which predicted a 37% likelihood of TIPN. Conversely, 24% of patients of African descent carried the *FCAMR* variant and had no *SBF2* mutations (low risk genotypes), which predicted a 10% likelihood of TIPN. We assume the same distribution of the germline predictor in the current study (ie, 76% with high risk genotype and 24% with low risk genotype in the study patients).

With an accrual of 102 analyzable patients of African descent in the paclitaxel arm (arm A), there is 81% power to detect a 27% difference (37% vs.10%) in risk of TIPN between the previously determined high and low risk genotypes (76% vs. 24%) using Fisher exact test with one-side alpha of 0.05. Assuming 10% of misclassification of race via patient's self-report and 5% assay failure rate for testing the germline predictor, a total of 120 African American or black patients based on self-report will be enrolled to the paclitaxel arm.

This study is open to patients who self-identify as black, African American, and/or of African descent. Approximately 15-16 African American patients were enrolled per month in E5103 and TAILORx. Given the simplistic design, minimal exclusion criteria, and focused attention to accrual specific to African Americans, it is expected to complete the accrual of 240 patients (120 patients in each arm) in approximately 12 months (average accrual rate of 20 patients per month).

9.2 Secondary Objectives

9.2.1 Grade 2-4 TIPN based on CTCAE between Arm A vs. Arm B.

Our top secondary objective is to compare the incidence of grade 2-4 TIPN based on CTCAE between the two taxane regimens (arm A vs. arm B). Incidence of grade 2-4 TIPN is defined the same as that used for the primary objective. With an accrual of the same number (n=120) of patients and the same misclassification rate (10%) in arm B (docetaxel arm) as that in arm A, there is 81% power to detect a lower incidence of grade 2-4 TIPN in arm B (13.2%) compared to arm A (27.7%) using Fisher exact test with one-side alpha of 0.05.The expected incidence of grade 2-4 TIPN (13.2% and 27.7%) was based on the estimated TIPN rates caused by every 3-week docetaxel and weekly paclitaxel in the E1199 trial (*Table 1*). As exploratory analysis, we will also perform subset analyses to estimate the frequency of TIPN across the various docetaxel-containing regimens (i.e. 4 vs. 6 cycles) if there are 20 or more patients in a subset (95% confidence interval for frequency of TIPN will be no wider than 0.46 with 20 patients), and to estimate frequency of TIPN at the end of each cycle in the docetaxel arm.

Rev Add1

9.2.2 PRO-based neurotoxicity

The preliminary data for this study was based on physician reported neuropathy via CTCAE. Recent data have supported improved accuracy and sensitivity for use of patient reported outcomes (PROs).[25,26,28] Thus, in this trial we will simultaneously assess neuropathy, using PRO as a secondary phenotype of the primary endpoint. The PRO-based neurotoxicity will be assessed using the 11

Rev Add2

items about neurotoxicity in the FACT/GOG-NTX questionnaire and the CIPN-20 9-item sensory neuropathy subscale.

For the FACT/GOG-NTX, each item is scored from 0–4, and the neurotoxicity total score is the sum of the scores for the 11 items, and ranges from 0 to 44[26,36,38]. Lower values of the FACT/GOG-NTX neurotoxicity total score indicate higher neurotoxicity. Assessment of PRO-based neurotoxicity will take place at the same schedule as CTCAE (i.e., at first day of each cycle, at end of treatment, and at 6 months, 1, 2, and 3 years post initiation of taxane therapy). The

FACT/GOG-NTX reference time frame is the past 7 days, but we don't expect the total neurotoxicity score has significant change from week to week.

Rev Add2

The FACT/GOG-NTX neurotoxicity total score will be analyzed as a continuous variable. The sample size/power calculation for repeated measures usually requires some assumptions about the study design. Based on Hershman,et al trial[68], we assume the variance of the FACT/GOG-NTX neurotoxicity total score is 114.5 (i.e., standard deviation of 10.7). The following power calculation provides some idea about the effect size that the available sample size can detect under certain assumption about the correlation between repeated PRO measures. Assuming the correlation between repeated PRO measures is 0.7, there will be about 80% power to detect the group effect of the magnitude of 0.3 (i.e., variance explained by the between-subjects effect is 6.7) based on F test for between subjects using two-way repeated measure ANOVA analysis at two-sided significance level of 0.05, with 77 patients in high risk genotype group and 24 patients in low risk genotype group (accrual of 120 patients and estimated 10% misclassification rate and 5% missing PRO data). A lower correlation between repeated measures and a smaller variance for the FACT/GOG-NTX neurotoxicity total score will result in a higher power.

Linear mixed effect models with random intercept (repeated measures within single patients with unstructured covariance matrices) will be fit to estimate the average difference in FACT/GOG-NTX neurotoxicity total score between high vs. low risk genotype groups in the paclitaxel arm. Time and patient and disease characteristics will be included as covariates in the linear mixed effect model. Likelihood ratio test will be used to determine whether time will be coded as a continuous variable or dummy variables in the model. Genotype group-by-time interaction will be tested to see whether the difference between the two genotype groups depends on time.

For comparison between arm A and arm B, the FACT/GOG-NTX neurotoxicity total score change between the baseline and at end of treatment will be compared using two sample t test. With 102 evaluable patients in each arm (accrual of 120 patients and estimated 10% misclassification rate and 5% missing PRO data), we will have 80% power to detect an effect size of 0.4 in change of FACT/GOG-NTX neurotoxicity total score between the two treatment arms at two-sided significance level of 0.05 using a two-sample t test. In addition, multivariable linear mixed effect model will be used to estimate the time trend and treatment group difference after adjusting for other covariates.

The CIPN-20 9 item sensory neuropathy subscale is added to the trial to harmonize with the SWOG1714 trial, and the subscale score will be analyzed in a similar way as the FACT/GOG-NTX score as supportive analysis.

9.3 PRO Objectives

9.3.1 HRQoL

Rev Add1

Rev Add2

The FACT/GOG-NTX questionnaire referenced above also contains 27 core items (the FAT-G) that cover four areas of HRQoL: physical, social, emotional, and functional well-being. QOL will be measured by the summed total score of the 27 items, which will range from 0 to 108. The HRQoL total score will be analyzed as a continuous variable and compared between low and high-risk genotypes groups of the paclitaxel arm, and between the paclitaxel arm and the docetaxel arm groups, using two-sample t tests. The primary comparison will be change in HRQoL total score between registration and treatment completion between two groups. With 77 patients (76%) in the high risk group and 24 patients (24%) in the low risk group in the paclitaxel arm (a total accrual of 120 patients in the paclitaxel arm and an assumed 10% misclassification rate and 5% missing data), we will have 80% power to detect an effect size of 0.67 in HRQoL score change between the high and low risk genotype groups at two-sided 0.05 significance level using a two-sample t test.

For comparison between the two treatment arms, with 102 evaluable patients in each arm (accrual of 120 with an assumption of 10% misclassification in race and 5% missing data), we will have 80% power to detect an effect size of 0.4 in HRQoL score change at two-sided 0.05 significance level using a two-sample t test. In addition, multivariable linear mixed effect models will also be fit to evaluate the time trend of HRQoL and to estimate the average group difference in HRQoL after adjusting for other covariates. Group-by-time interaction will be tested to see whether the difference in HRQoL between groups depends on time.

9.3.2 Physical Function

Physical function will be assessed using PROMIS Physical Function v2.0 Short Form 10a. Summary scores are calculated as a T-score (with 50 = mean & 10 = SD of the reference population) and higher scores reflecting better physical function. The PROMIS Physical Function T score will be analyzed as a continuous variable, and it will be compared between the two treatment arms (A&B) and for the high risk vs. low risk genotypes (in arm A) using two-sample t tests. The primary comparison will be change in Physical Function T-scores between registration and treatment completion between two groups. The power calculation and analysis plan will be similar with that for the above HRQoL endpoint measured via FACT/GOG-NTX questionnaire.

Rev Add2

9.3.3 Financial Toxicity

Financial toxicity will be assessed via the 11-item Comprehensive Score for Financial Toxicity (COST-FACIT) questionnaire. The level of financial toxicity will be measured by the total score (range: 0-44), which will be analyzed as a continuous variable. Higher COST scores represent better financial well-being.[66] The COST-FACIT total score will be compared across the two treatment arms (A and B) using two-

Rev Add2

sample t tests. The primary comparison will be change in COST-FACIT scores between registration and treatment completion between the two groups. The power calculation and analysis plan will be similar with that for the above HRQoL endpoint measured via FACT/GOG-NTX questionnaire.

9.3.4 PRO-CTCAE Items

Rev Add2

The PRO-CTCAE items we have selected (#39a-b – numbness & tingling and #48a-c – general pain) include ratings of severity (none-very severe) and interference with usual activities (not at all- very much)); the pain item also includes a frequency rating (never- almost constantly). We will present PRO-CTCAE scores for each attribute (frequency, severity and/or interference) separately and compare PRO-CTCAE severity (coded 0-4) with CTCAE grades for the corresponding time periods. In addition, the two patient-reported neuropathic-related PRO-CTCAE items will be compared between the two taxane regimens (Arm A vs. Arm B) and the two genotype risk groups in arm A. The association between PRO-CTCAE neurotoxicity and dose reduction and early treatment discontinuation will also be explored (Of note, the analyses will be exploratory in nature and the purpose of the analysis is hypothesis generating).

9.3.5 Social Economic Determinants

Rev Add2

The five social determinants of health items from the Alliance Patient Questionnaire for Clinical Trials in Oncology (education, marital status, health insurance status income, and current zip code), will be collected at baseline. We will explore the association between these factors with treatment completion per protocol, dose reduction, toxicities (PRO-CTCAE, FACT/GOG-NTX neurotoxicity & CIPN sensory neuropathy scores) and HRQoL (Physical Function & FACT-G scores). Of note, all these analyses will be exploratory in nature, and the purpose of the analysis is hypothesis generating.

9.4 Safety Monitoring

Adverse events and study progress are monitored twice yearly for all ECOG-ACRIN studies. Reports of these analyses are sent to the ECOG-ACRIN Principal Investigator or Senior Investigator at the participating institutions. Expedited reporting of certain adverse events is required, as described in Section 5.2.

9.5 Gender and Ethnicity

This study will be open only to self-identified African American women. Men are not eligible for the study. Women with race other than African American are not eligible for the study. The anticipated accrual in subgroups defined by gender and race is:

Ethnic Category	**Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	10	0	10
Not Hispanic or Latino	230	0	230

Ethnic Category: Total of all subjects	**240**	**0**	**240**

Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	0	0	0
Black or African American	240	0	240
Native Hawaiian or other Pacific Islander	0	0	0
White	0	0	0
Racial Category: Total of all subjects	**240**	**0**	**240**

The accrual targets in individual cells are not large enough for definitive subgroup analyses. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

Study Monitoring

This study will be monitored by the ECOG-ACRIN Data and Safety Monitoring Committee (DSMC). The DSMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DSMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DSMC meetings are included in the study reports prepared for the ECOG-ACRIN group meeting (except that for double blind studies, the DSMC may review unblinded toxicity data, while only pooled or blinded data will be made public). These group meeting reports are made available to the local investigators, who may provide them to their IRBs. Only the study statistician and the DSMC members will have access to interim analyses of outcome data. Prior to completion of this study, any use of outcome data will require approval of the DSMC. Any DSMC recommendations for changes to this study will be circulated to the local investigators in the form of addenda to this protocol document. A complete copy of the ECOG-ACRIN DSMC Policy can be obtained from the ECOG-ACRIN Operations Office – Boston.

Rev Add1

10. Specimen Submissions

Peripheral blood must be submitted for defined laboratory research studies. These studies are defined in Section 11.

Plasma and the residual cells are to be submitted for future undefined laboratory research studies per patient consent.

Detailed instructions to obtain study kits, as well as specimen collection, processing, and shipping guidelines can be found in the EAZ171 Biospecimen Manual of Procedures which can be found on the CTSU website under 'Education and Promotion' tab and will also be included with the kits.

Kits are available to order and will include materials necessary for the preparation and shipment of the specimens. Please allow two weeks for delivery. Kits can be ordered using Indiana University's online kit module for institutions that have the protocol open for patient enrollment: http://kits.iu.edu/EAZ171

All specimens must be logged and tracked via the ECOG-ACRIN Sample Tracking System (Section 10.3). An STS shipping manifest form and IU Sample Record form (http://j.mp/2XBbnEo) must be included with every submission.

All specimens must be labeled clearly with the ECOG-ACRIN protocol number (EAZ171), ECOG-ACRIN patient sequence number, patient initials, date and time of collection, time point, and specimen type.

10.1 Submissions to Indiana University

Rev Add1

10.1.1 Collection and Submission Schedule

Peripheral blood for the mandatory laboratory research studies must be collected at baseline (after registration, prior to start of taxane treatment) and submitted day of collection.

Plasma for the optional future undefined research studies is to be collected at baseline (after registration, prior to start of taxane treatment and six (6) months post treatment per patient consent.

If you have any questions concerning specimen collection and shipment please contact Indiana University (IU) at (317)274-2840.

Rev Add1

10.1.2 Preparation Guidelines

Rev Add2

Blood draw order is sodium heparin (10mL green top), EDTA for plasma (10mL purple top) and then EDTA for whole blood (6mL purple top). Peripheral blood samples are to be shipped Monday through Thursday only. Please note full list of holidays and closures in in the Biospecimen Manual.

10.1.2.1 Peripheral Blood – Green Top (MANDATORY)

- Draw 10mL of peripheral blood into one (1) green top sodium heparin tube
- Immediately after blood draw, invert tube 8-10 times
- Package and ship day of collection at ambient temperature during the cool season and on cool packs during the hot season

Rev Add2

- Do not collect on Fridays, Weekends, or days before a holiday.

10.1.2.2 Peripheral Blood – Purple Top (MANDATORY)

- Draw 6mL of peripheral blood into one (1) 6mL purple top EDTA tube
- Immediately after blood draw, invert tube 8-10 times
- Store tube upright at -80ºC until batch shipment overnight on dry ice. If specimens cannot be stored at –80ºC, store at –20ºC and ship on dry ice within one (1) week of collection.

10.1.2.3 Plasma – EDTA Purple Top (Submit from patients who answer "Yes" to "I agree to provide additional samples for research")

- Draw 10mL of peripheral blood into one (1) 10mL purple top EDTA tube
- Immediately after blood draw, invert tube 8-10 times
- Centrifuge within 30 minutes of draw at room temperature at 1500g for 15 minutes

Rev Add1

- Aliquot plasma into four (4) cryovials

Cryovial Cap Color	Specimen Type
Purple	Plasma, 1.5mL
Blue	Plasma, residual

- Replace the cap on the purple top tube
- Freeze cryovials and residual cells at –80ºC until shipment. Batch ship overnight on dry ice. If specimens cannot be stored at –80ºC, store at –20ºC and ship on dry ice within one (1) week of collection.

Rev Add1
Rev Add2

10.1.3 Shipping Procedures

Peripheral blood specimens are to be shipped PRIORITY overnight the day of collection at ambient temperature.

Ship ambient specimens Monday – Thursday only, do not ship on Fridays, weekends or day before a holiday.

Frozen specimens are to be batch shipped overnight on dry ice.

Ship frozen specimens Monday, Tuesday, and Wednesday only. Do not ship the day before the weekend or holiday.

Notify Indiana University of all incoming shipments prior to shipping the specimens by emailing wbobb@iu.edu the copy of the completed Shipping Manifest Form.

Rev Add1

Ship to:

EAZ171 Study

IU Genetics Biobank
351 W. 10th Street, TK342
Indianapolis, IN 46202-4118

An STS shipping manifest form and IU Sample Record form (http://j.mp/2XBbnEo) must be generated and shipped with all specimen submissions.

10.2 Use of Specimens in Research

See Section 11 for the description of the laboratory research studies to be performed at Indiana University.

Specimens from patients who consented to allow their specimens to be used for future undefined ECOG-ACRIN approved research studies, including the residuals and derivatives of the specimens used for the EAZ171 protocol-defined laboratory research studies, will be routed to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF) at MD Anderson and stored for future use.

Specimens submitted will be processed for the purposes of the defined research studies and, if possible, to maximize their utility for current and future research projects and may include, but not limited to, extraction of plasma, serum, DNA and RNA.

If future use is denied or withdrawn by the patient, the specimens will be removed from consideration for use in any future research study.

10.3 ECOG-ACRIN Sample Tracking System

It is **required** that all specimens submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). The software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the specimens required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst

Important: Please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html

Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated shipping manifest form should be shipped with all specimen submissions.

Please direct your questions or comments pertaining to the STS to ecog.tst@jimmy.harvard.edu

Study Specific Notes

Generic Specimen Submission Form (#2981v3) will be required only if STS is unavailable at time of specimen submission. Notify the laboratory of the shipment by faxing a copy of the completed form to the laboratory.

Retroactively enter all specimen collection and shipping information when STS is available.

10.4 Sample Inventory Submission Guidelines

Inventories of all specimens submitted will be tracked via the ECOG-ACRIN STS and receipt and usability verified by the receiving laboratory. Inventories of specimens forwarded and utilized for the approved laboratory research studies will be submitted by the investigating laboratories to the ECOG-ACRIN Operations Office - Boston on a monthly basis in an electronic format defined by the ECOG-ACRIN Operations Office - Boston.

11. Laboratory Research Studies

Results of these studies are for the purposes of the trial only and will not be returned to the institution or reported to the patient.

11.1 To prospectively validate & discover additional germline predictive biomarkers for paclitaxel-induced peripheral neuropathy in EAZ171.

11.1.1 Rationale & strategy

There are no prospectively validated and clinically implemented predictive biomarkers for TIPN. Our previously discovered, genetically categorized high- and low-risk populations have the strongest level of evidence to date for prediction of TIPN in patients of African descent. These genetic predictors will be prospectively validated or refuted in the prospective clinical trial, EAZ171. EAZ171 also provides the perfect opportunity to further assess the impact of genetic variation on risk; specifically, the role of non-coding variants throughout the genome.

11.1.2 Experimental design

We will prospectively test for associations between genotypes and phenotypes as outlined below. The primary objective will be to validate the genetically determined high/low-risk category for TIPN. This will assume that those who had TIPN in EAZ171 will have the high-risk genotype and those who did not have TIPN will have the low-risk genotype. A secondary objective will be to evaluate for associations between non-coding variants throughout the genome with TIPN. For the secondary objective, we will evaluate for an association with genotypes using a case/control analysis plan. For analyses, we will first call all variants but subsequently use bioinformatic algorithms to prioritize functional variants to minimize multiple testings and to improve statistical power. Finally, the top non-coding variant candidates will be subsequently validated or refuted in patients of African descent patients from E5103 (n=386) using TaqMan genotyping.

11.1.2.1 Phenotypes

Phenotypes will be formally assessed and reported in prospective fashion using two definitions. The primary definition will be physician-reported CTCAE grade 2-4 TIPN. The secondary definition will be patient-reported TIPN, which is considered more sensitive, using the validated FACT/GOG-NTX & CIPN 20 sensory neuropathy subscale.[26,28] Controls (for the secondary objectives) will include patients who did not experience Grade 2+ TIPN and received the fully intended dose of paclitaxel.

Rev Add2
Rev Add1

11.1.2.2 Whole Genome Sequencing (WGS)

Genotyping will be completed through WGS as outlined below using germline DNA derived from 120 patients in EAZ171. The primary genotype for evaluation will be the

composite high- and low-risk categories (Table 1). This categorical classification will include the combination of protective, common variants in FCAMR and permissive, rare variants in SBF2. The secondary analyses will include non-coding variants across the genome. The genetic variants in the promoter regions are all known to have biological significance, including the enhancer regions; 3'-untranslated regions (UTR) that are enriched in microRNA targeting sites; and intronic regions that have an impact on splicing regulation. To date, no data have previously been reported in this arena.

Table 1. *Likelihood and frequency of TIPN by risk group*

Clinical Category	Genotypes	Expected % in trial population	Expected % of Grade 2+ TIPN
High Risk TIPN	FCAMR GG or SBF2 mutated	76%	37%
Low Risk TIPN	FCAMR AA or GA AND SBF2 wild-type	24%	10%

11.1.3 Methodology

11.1.3.1 Whole genome sequencing (WGS) in EAZ171

WGS will be performed in the IUSM Center for Medical Genomics (CMG) laboratory, directed by Dr. Yunlong Liu (co-PI). We have established standard operating procedures and by following industry standards, we will ensure 30X average depth for over 90% of the human genome from the blood. The sequencing data will be analyzed following standard pipelines including quality control (QC), sequence alignment (including refined alignment), variant calling, and variant annotation. A key component analysis will be conducted using Sentieon DNA-seq pipeline, which uses identical algorithms as Broad Institute's BWA-GATK Best Practice Workflow, but is over 10X faster for generating variant call format (VCF) file from FASTQ sequencing data. We will further conduct vigorous QC to ensure the integrity of the data. Major metrics include the transition-transversion ratios and the percentage of variants that are documented in the latest dbSNP release. Findings on significant genomic loci will be examined visually using the Integrative Genomic Viewer (IGV) software.

11.1.3.2 Validation of high/low-risk genotypes

EAZ171 is designed to serve as an independent cohort to replicate the previous GWAS/WES findings[1,7]and is powered to validate a difference in risk of TIPN between our "high-risk" and "low-risk" categories based on FCAMR and SBF2 mutation status (Table 1). We will extract the genotyping data for the candidate common variants in

FCAMR and the deleterious variants in SBF2 based on our previous GWAS and WES data, respectively.

11.1.3.3 Prioritization of non-coding variants

The secondary objectives are to identify non-coding variants that are associated with TIPN. In order to reduce the total number of hypotheses to be tested, we will first use a broad array of bioinformatics tools to prioritize the candidate variants, based on their genomic loci and the predicted impact on gene regulation, such as detlaSVM, CADD, and deepSeq. We will further conduct burden test focusing on the variants that are predicted to be functionally important. This strategy will effectively reduce the non-functional variants before conducting statistical analysis, and therefore increase statistical power.

We will use our own computational algorithms[45,46] in predicting functions of various genetic variants, including promoter variants, micro-INDELs, and intronic variants. Top functionally associated variants in the gene promoter and enhancer regions of the genes within expression quantitative trait loci (eQTL) regions will be further analyzed for their roles in transcriptional regulation using data generated in the ENCODE and Epigenomic Roadmap consortia as outlined below.

Cis-regulatory element: We will focus our analysis on the variants identified in gene promoter and enhancer regions of the genes within expression quantitative trait loci (eQTL) regions. In recent years, many studies reported that genetic variants in the key regulatory regions are causal variants for complex disease. For instance, a recent study reports that a Parkinson-associated risk variant in distal enhancer of α–synuclein affects disease phenotype through modulating target gene expression.[47] The candidate promoter and enhancer regions will be derived from the data generated in the ENCODE and Epigenomic Roadmap consortia. In addition, we will also include the regions identified from ATAC-seq data that is proposed in Aim 3 (Section 11.3). The eQTL regions will be derived from the data generated in the GTEx consortium, which provided a comprehensive transcriptome profile on 17 tissues of neuronal origin in dozens to hundreds of individuals. These data will offer comprehensive measurements on the expression levels of the transcription factors and variant target genes in tissues relevant to neuropathy. We will also extend our prior data on regSNPs (which prioritizes the functional impact of promoter SNPs) to neuropathy, using variants in open chromatin regions that are enriched with regulatory regions. We expect to find functional variants that will alter the likelihood of TIPN by affecting transcription factor binding in promoter and enhancer regions. These variant effects will be validated

using the RNA-seq data available in the public domain (e.g., GTEx; https://www.gtexportal.org/).

11.1.3.4 Association analysis of non-coding variants

The top variants from prioritization will be further evaluated for their association with TIPN in EAZ171. Variants located in a gene promoter or 3'-UTR region, or predicted to disrupt or create a transcription factor-binding motif that cis-regulate that gene, will be aggregated to a variant set, and the gene based on Sequence Kernel Association Test (SKAT)[48] will be applied to the variant sets in the association with TIPN. Similarly, variants predicted to alter the splicing outcome in the intron or exon region of a gene will be aggregated to a variant set. The tests will be adjusted for clinical covariates including age, body surface area or principal components (from WGS data) that are significantly associated with TIPN in a multi-variate logistic regression model at α=0.05 significance level. The Bonferroni correction for multiple comparisons will be applied to the gene-based multi-variant tests.

11.1.3.5 Validation of top candidate non-coding genetic variants in E5103

The top candidate genes with non-coding variants identified from EAZ171 will be validated/refuted in the African American patients (n=386) from E5103.[18] 151 out of 386 African Americans in E5103 experienced grade 2-4 TIPN, and DNA is available for genotyping.[7] TaqMan assays will be used for validation of non-coding variants. The number of candidates will be based on statistical power after effect size is established in EAZ171 (See below).

11.1.3.6 Sample Size and Power Calculations

Primary objective: Based on our prior published data (Table 1),[1,7] 76% of patients of African descent in EAZ171 will be expected to be in the high-risk category and 24% in the low-risk category. For the proposed validation study with 120 patients, our power calculation demonstrates that there is at least 80% power to validate that the high-risk group will be more likely to have TIPN than those in the low-risk group using a one-sided t-test at α=0.05 significance level.

Secondary objective and validation: The top 5 genes from the SKAT analysis will be validated in E5103 (151 cases and 235 controls). If we assume the average length of the transcriptional regulation region will be 5,000 base pairs, and 30% of the variants will be causal variants with an odds ratio of 4.5, there will be 80% power to validate an association at the statistical significance level of α=0.01 with Bonferroni correction. Similarly, if we assume the

average length of splicing regulation region will be 10,000 base pairs, there will be 82% power to validate an association between gene splicing mutations and TIPN at the significance level of α=0.01.

11.2 To determine the impact of germline variability on paclitaxel-induced phenotypic changes in patient derived iPSC-iSNs and compare and contrast the accuracy and sensitivity of these changes with clinical outcomes in EAZ171.

11.2.1 Rationale & strategy

The ability to evaluate for phenotypical changes in iPSC-iSNs from patients treated in EAZ171 will provide a real-world test of this ex vivo tool and increase our understanding of the biology of TIPN. [29,49,50] While the assessment of peripheral nerves from patients before and after treatment would be ideal for mechanistic studies, these types of invasive biopsies are not possible. Data have suggested the fidelity of gene expression between the primary neuron dorsal root ganglion and the iPSC-iSNs generated by the method proposed below.[32] Thus, the iPSC-iSNs proposed in the current study are the most relevant, genetically representative, human model available for studying TIPN. The patient-derived iPSC-iSNs have advantages over other animal models or lymphoblastoid cells models: 1). they will be directly derived from patients with matching clinical outcomes; 2). they will be differentiated in a way to mimic sensory-specific neurons; 3). they will allow for accurate integration of the complex role of genetic variation on TIPN in each individual patient. Importantly, these proposed studies might ultimately demonstrate that iPSC-iSNs can serve as an exemplary model for other types of therapy-induced neuropathies in cancer and other disease states.

11.2.2 Experimental design

iPSC-iSNs will be derived from all patients in the paclitaxel arm of EAZ171. Baseline peripheral blood cells will be reprogrammed to human induced pluripotent cells (iPSCs), and iPSCs will subsequently be differentiated to form sensory neurons (iPSC-iSNs). The cultured iPSCs-iSNs will be treated ex vivo with paclitaxel at 50nM for 48 hours. Morphological changes in the iPSCs will be measured and compared with and without exposure to paclitaxel using the five most established neurite outgrowth phenotypes[51] (serving as ex vivo surrogates for neuronal damage) including: 1. mean process length, 2. median process length, 3. maximum process length, 4. total outgrowth, and 5. mean outgrowth intensity. A decrease in mean process length will serve as the primary phenotypic endpoint as it has been the most sensitive across the five phenotypes.[51] In addition, we will develop a “composite score” which will comprehensively consider all five phenotypes simultaneously. Our primary objective for this aim will be to compare the development of conventional physician reported CTCAE grade 2+ TIPN in EAZ171 with ex vivo neuronal damage (from each patient’s own iPSC-iSNs). A secondary analysis will compare patient-reported TIPN [25,27]using the FACT/GOG-NTX[26,28] with ex vivo neuronal damage. The patient-reported outcomes are considered more sensitive and thus this analysis will determine the

sensitivity of the ex vivo model in addition to its clinical validity. Another secondary analysis will compare evidence of ex vivo neuronal damage (using both individual and composite neurite outgrowth phenotypes) with high/low-risk genotypes.

11.2.3 Methodology

11.2.3.1 Generation of patient derived iPSC-iSNs

Baseline peripheral blood cells of individual patients from EAZ171 will be reprogrammed to human iPSCs following the protocol of StemCell Technologies. Erythroid progenitor cells will be isolated and expanded from peripheral blood for 7 days and subsequently reprogrammed into iPSCs with Epi5TM episomal vector through a transfection process. iPSC colonies will be obtained in 18-25 days and the pluripotent nature (trilineage differentiation) of the iPSC line will be confirmed using immunofluorescence markers. iPSCs will subsequently be differentiated to sensory neurons (iPSC-iSNs) using the method as described by Cai et al.[52] Briefly, iPSCs will be maintained in mTeSR™1 medium (StemCell Technologies) on Corning Matrigel®-coated dishes until reaching 80% confluency and then induced for iSN differentiation. On day 5, the cells will be passaged and seeded into Matrigel®-coated chamber slides at a density of 1 x 10 cells/well[21] in neural induction media until day 8. The differentiation to sensory neurons will be confirmed by immunofluorescence staining. Patient derived iPSC-iSNs will then be maintained in neural maintenance media until exposed to paclitaxel.

11.2.3.2 Exposure of iPSC-iSNs to paclitaxel

The iPSC-iSNs will be treated with paclitaxel at 50nM for 48 hours. The duration and dose (50nM) of paclitaxel have been selected based on literature[51,53,54] and our own preliminary data. The morphology will be assessed immediately before and after the 48-hour exposure to paclitaxel. Prior to the post-paclitaxel morphological analyses, we will assess for cell viability using CellTiter-Glo assay to re-confirm that the concentration of paclitaxel at 50nM was not excessively high (< 80% viable) for that patient, to preclude proper morphological assessment. Our preliminary data indicated that iPSC-iSNs treated with 50nM paclitaxel for 48 hours uniformly had > 90% viability compared to the untreated iPSC-iSNs. Fifty iPSC-iSNs from each patient will be used to collect data for each of the five neurite outgrowth phenotypes. If there are insufficient cells (n < 50) due to unexpected cell death for a given patient, we will repeat generation of iPSC-iSNs from that same patient. If the sum of the first and second set of viable iPSC-iSNs is not > 50, that patient's sample will not be included in the planned analyses as apoptosis is not an

established parameter for assessing ex vivo neuropathy. Although we expect few to no cases of insufficient viable cells, we will perform an exploratory and descriptive assessment of cells with exceptional apoptosis/cell death to see if these correspond to patients with clinical evidence of exceptionally severe TIPN.

11.2.3.3 Quantification of morphological changes

Five iPSC-iSN neurite outgrowth phenotypes and a composite score will be assessed and compared from baseline to post-paclitaxel treatment to determine ex vivo neuronal damage. The iPSC-iSNs will be stained with Hoechst 33342 (Life Technologies, Carlsbad, CA) and labeled with an immunofluorescent marker against peripherin (Abcam, San Francisco, CA) and imaged using EVOS FI Cell Imaging System (Thermo Fisher Scientific) for measuring neurite outgrowth. At least nine fields will be imaged and neurite outgrowth phenotypes will be assessed using the Simple Neurite Tracer of the Image J (https://imagej.nih.gov/ij/). The changes of neurite outgrowth will be analyzed using individual cell data. Fifty cells will be quantified to obtain the five outgrowth phenotypes as follows 1). mean process length (primary phenotype)-the mean process length from each cell averaged over 50 cells; 2). median process length- the median process length from each cell averaged over 50 cells; 3). maximum process length- the maximum process length from each averaged over 50 cells, 4). total outgrowth- the sum of the length of all processes from each cell averaged over 50 cells, and 5). mean outgrowth intensity- the mean thickness/diameter of all outgrowths from each cell averaged over 50 cells.

11.2.3.4 Neurite outgrowth composite score

To develop a single ex vivo phenotype of neuronal damage that integrates all of the established five phenotypes, we will develop a “composite score” using a logistic regression model. Assuming the prevalence of TIPN in patients of African descent to be 39% based on the clinical data from E5103, we expect 47 patients will experience TIPN among the 120 patients enrolled in EAZ171. Depending on the number of variables selected, which could be from 5 (five individual phenotypes) to 2 (neurite length and thickness) the resulting events per variable (EPV) will range from 9 to 24, respectively. At this level of EPV, we can expect stable estimates and thus decrease the chance of overfitting.[55] The data will be split into 70% for training and 30% for testing, and the model will be evaluated using a stratified 10-fold cross-validation. The overall performance and discriminatory power of the model will be accessed using metrics such as the Brier score and receiver operating characteristic (ROC). The

results will be compared with the clinical measures of TIPN from the donor patients. This process will also provide insights on the preferential influence of paclitaxel on each of the five phenotypes. Changes in neurite outgrowth composite score before and after treatment will ultimately be compared with mean process length (primary ex vivo phenotype) in an exploratory fashion to determine whether this score outperforms the primary ex vivo phenotype.

11.2.3.5 Data analysis and statistics

Power analysis for the number of cells required to detect morphological changes: Based on our preliminary data, the average length of neurite processes is 250μm with a standard deviation of 159μm in the control cells, and an average length of 123μm with a standard deviation of 58μm after the treatment with 50nM paclitaxel for 48 hours. 50 cells in each group will be measured in order to have at least 95% power to detect the decrease in paclitaxel-induced neurite process length, using a t-test at a significance level of $\alpha=0.05$.

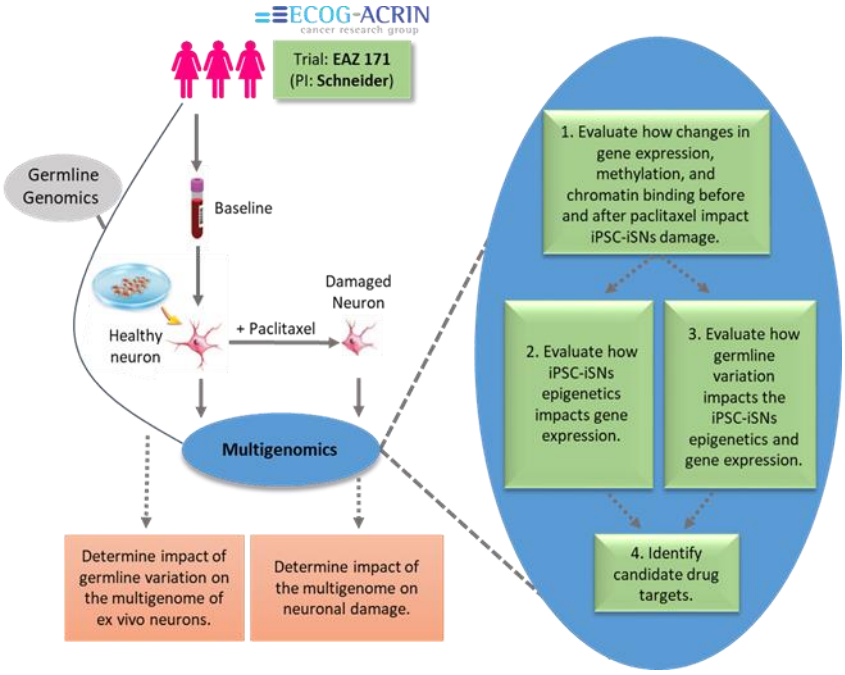
Primary and secondary analyses: For the primary analysis, we will compare grade 2+ TIPN with a change in mean process length using a one-sided t-test. Based on the clinical data from E5103, there will be 47 patients (39%) who develop TIPN and 73 patients (61%) who won't. Assuming the standard deviance in neurite length is 58 μm based on our preliminary data, there will be at least 80% power to test for a > 28μm decrease (an effect size of 0.48) in the paclitaxel-induced neurite process length between those with grade 2+ TIPN and the control group at the $\alpha=0.05$ significance level. Similarly, we will use a t-test for our secondary analyses, including: patient-reported TIPN vs. change in mean neurite length; high/low-risk genotype group vs. change in mean neurite length; grade ≥ 2 TIPN vs. composite score; high/low-risk genotype group vs. composite score; and patient-reported TIPN vs. composite score.

11.3 <u>To assess the impact of paclitaxel on gene expression, DNA methylation, and chromatin accessibility in patient-derived iPSC-iSNs</u>

11.3.1 Rationale & strategy

Despite substantial prior work, the molecular mechanism for TIPN has not been completely elucidated. A deeper understanding of the mechanism has the potential to uncover therapeutic targets to prevent and treat this toxicity; which in turn can improve the therapeutic index of the paclitaxel and quality of life for patients. We will use cutting-edge high-throughput technologies to measure paclitaxel-induced changes in gene expression, DNA methylation, and chromatin accessibility. Using a systems biology approach, these experiments will allow for the unprecedented profiling of a broad array of molecular

characterizations in a well-controlled patient-derived system as shown below:



11.3.2 Experimental design

We will perform ATAC-seq, MethylCap-Seq, and RNA-seq experiments in patient derived (from EAZ171) iPSC-iSNs, before and after paclitaxel exposure to assess the chromatin accessibility, DNA methylation in promoter/enhancer/CpG island regions, and gene expression. The iPSC-iSNs will be derived from each of 120 patients recruited in EAZ171.

11.3.3 Methodology

11.3.3.1 Molecular characterization of patient-derived iPSC-iSNs

Gene expression: We will use RNA-seq technology to measure the global gene expression levels in patient-derived iPSC-iSNs, with or without 50nM paclitaxel exposure. The library will be constructed from total RNA isolated from the cells using the Illumina “TruSeq Stranded mRNA Library Prep Kit” and followed by sequencing (HiSeq 4000). To capture the gene expression differences with or without drug exposure, sequencing will be conducted using 75 base pair (bp) paired-end configuration with more than 30 million clusters (read pairs) per sample. This coverage will reliably measure the variability in gene expression, and capture splicing variants at the transcriptome level. This will allow investigation of other possible molecular mechanisms that could impact the response of neuronal cells to paclitaxel exposure.

DNA Methylation: As one of the most stable epigenetic signals, DNA methylation plays key roles in modulating the

activity of DNA elements and typically acts to repress gene transcription through inactivating promoters and enhancers. Analysis of DNA methylation will be achieved using MethylCap-seq, a robust procedure for genome-wide profiling that readily allows detection of DNA methylation in known and novel regions as previously described by our group.[56-58] Enrichment of methylated DNA will be performed using the Methylminer kit (Invitrogen). Libraries will be generated using the Illumina TruSeq protocol, and further sequenced using the 75bp paired-end protocol.

Chromatin accessibility: ATAC-seq will be used to examine the chromatin accessibility at gene promoters and enhancers in iPSC-iSNs. It will also help us to define neuronal-specific enhancer regions that will be used Section 11.1. This approach will allow for the assessment of key regulatory regions (promoters and enhancers) that may be altered by paclitaxel exposure. The sequencing will be done on HiSeq 4000 with 50 million 75bp paired-end reads per sample, which will be adequate for identifying open chromatin regions.

11.3.3.2 Bioinformatic processing and statistical analyses

RNA-seq: The overarching informatics approach for RNA-seq is composed of multiple key components including read QC and pre-processing (TrimGalore), sequence alignment (STAR[59]), post-alignment QC (NGSUtils[60]), and gene expression quantification (NGSUtils[60]). The derived RNA-seq counts in each gene will be normalized to the total number of sequencing reads falling into all the annotated gene regions in each sample, and will be further scaled based on a trimmed mean of log transformed counts per million (CPM) value.[61] The scaled CPM or CPM_RNA will then be used as a gene level quantification in each sample and will be the base for the further association analyses on paclitaxel induced neuronal damage. Taxane-induced changes in gene expression levels will be identified using edgeR,[62] based on a generalized linear model assuming negative binomial distribution. In this model, sample identity will be treated as a random variable, which effectively increases the statistical power by pairing the measurements of pre- and post-taxane treatment. Effects of multiple comparisons will be corrected using Benjamini and Hochberg's (BH) method.

MethylCap-seq: MethylCap-seq data will be processed as previously described.[56-58] Briefly, after QC and pre-processing with TrimGalore, sequencing reads will be mapped to human reference genome hg38 using Burrows-Wheeler Aligner (BWA). Genome-wide methylation will be identified using MACS2[63,64] and methylation-enriched regions will be derived from the union of all the regions

identified across all samples. The derived MethylCap-seq counts in each region will then be normalized to the total number of sequencing reads falling into all the identified methylation enriched regions, and further scaled based on a trimmed mean of log transformed counts per million (CPM) value. The scaled CPM or CPM_methyl, will be used as a region-specific quantification of methylation in each sample. Taxane-induced methylation changes will be calculated using edgeR,[61] followed by correction for multiple comparisons using BH method.

ATAC-seq: Chromatin accessibility will be quantified with the ATAC-seq data using a similar analysis plan to the MethylCap-seq (above). We will also use the combination of BWA (sequence alignment), MACS2 (region identification), and edgeR (differential chromatin changes) algorithms. In our preliminary data from ~50,000 cells, we identified 25,525 open chromatin regions overlapping with promoter regions of 16,368 genes (within 3000-bp upstream of transcriptional start site). Chromatin accessibility will be quantified by counting reads falling into identified regions, following proper normalization and scaling procedures, as described above. Similar to RNA-seq and MethylCap-seq, the scaled counts per million CPM, or CPM_ATAC, will be used as a region-specific quantification of chromatin accessibility in each sample. The paclitaxel-induced changes in chromatin accessibility will be calculated using edgeR, followed by correction for multiple comparisons using BH method.

Statistical power: If we assume 10,000 genes that passed QC will be tested for an association between paclitaxel induced changes of the transcriptome or epigenome and paclitaxel induced ex vivo neuronal damage, there will be > 80% power to detect this association at the significance level of 5×10-6. This also assumes that > 21% of ex vivo neuronal damage variance will be explained by changes in the transcriptome or epigenome.

Impact of the baseline epigenome on TIPN: We will evaluate whether the molecular signals, including gene expression, DNA methylation patterns and/or chromatin accessibility of key genes, at the baseline level (pre-Taxane treatment) can predict TIPN. This analysis goes beyond traditional association studies that merely examine the genetic markers that are associated with a phenotype, and will shed insight on the role of epigenetic markers on TIPN. Specifically, we will calculate the basal level differences of gene expression and epigenetic factors on the iPSC-iSNs between patients with TIPN and those without, through the quantification of gene expression (CPM_RNA), chromatin accessibility (CPM_ATAC) and DNA methylation levels (CPM_methylation). A standard

differential analysis will be calculated using edgeR. Finally, correction for multiple comparisons will be made using the BH method. If an excessive number of candidate genes are identified, we will conduct pathway analyses (as outlined above) to maintain adequate power.

Statistical power: Based on the preliminary data and power calculations for EAZ171, there will be 47 patients with TIPN and 73 without TIPN. We will assume that we can reliably detect the expression of 10,000 genes from the iPSC-SNs, and 5% of these genes will be differentially expressed. Thus with 120 samples (47 cases and 73 controls), there will be >90% power to identify genes differentially expressed with >1.25 fold-change at the significance level of 5% false-discovery rate (FDR). Similar levels of statistical power will be applicable to the Methylcap-seq and ATAC-seq data.

Impact of germline genetic variants on paclitaxel-induced epigenetic and gene expression alterations: Taxane-induced epigenetic and gene expression changes serve as an important molecular endophenotype that can be used for stratifying TIPN. We will examine whether DNA variants identified in Section 11.1 are associated with these changes. For each patient, edgeR-reported log fold changes of CPM_RNA, CPM_ATAC, and CPM_methyl will be used for the analysis. Due to the limited sample size, we will focus our analysis on genes significantly associated with neuronal damage, and on variants with cis-acting effects, in which only variants in the putative regulatory regions (promoters, enhancers, and 3'-UTR regions) will be evaluated. These regions will be derived from the existing gene annotations, as well as the union of the enriched regions identified using the ATAC-seq and methylCap-seq assays above. Variants will be clustered to gene sets as discussed above. Additional follow-up studies will be warranted for validation of these specific findings.

Statistical power: Assuming the log fold change in either gene expression or epigenetic data follows a standard normal distribution, 20% of the variances can be explained by germline genetic variants. If we assume the possibility that an extraordinarily high number of genes (maximum=1000) impact ex vivo neuronal damage, we will still maintain > 80% power to detect an association with a message or epigenetic changes after paclitaxel exposure with 120 patients using a 2-sided test.

11.4 Lab Data Transfer Guidelines

The data collected on the above mentioned laboratory research studies will be submitted electronically using a secured data transfer to the ECOG-ACRIN Operations Office - Boston by the investigating laboratories on a quarterly basis or per joint agreement between ECOG-ACRIN and the Investigator.

12. Electronic Data Capture

Please refer to the EAZ171 Forms Completion Guidelines for the forms submission schedule. Data collection will be performed exclusively in Medidata Rave.

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office – Boston to CTEP by electronic means.

13. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

14. References

1. Schneider BP, Li L, Radovich M, et al. Genome-Wide Association Studies for Taxane-Induced Peripheral Neuropathy in ECOG-5103 and ECOG-1199. Clinical cancer research : an official journal of the American Association for Cancer Research 2015;21:5082-91.
2. Schneider BP, Shen F, Jiang G, et al. Impact of genetic ancestry on outcomes in ECOG-ACRIN-E5103. J Clin Oncol PO 2017 (Accepted).
3. Sparano JA, Wang M, Martino S, et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. The New England journal of medicine 2008;358:1663-71.
4. Dietze EC, Sistrunk C, Miranda-Carboni G, O'Regan R, Seewaldt VL. Triple-negative breast cancer in African-American women: disparities versus biology. Nat Rev Cancer 2015;15:248-54.
5. Sparano JA, Wang M, Zhao F, et al. Race and hormone receptor-positive breast cancer outcomes in a randomized chemotherapy trial. Journal of the National Cancer Institute 2012;104:406-14.
6. Sparano JA, Zhao F, Martino S, et al. Long-Term Follow-Up of the E1199 Phase III Trial Evaluating the Role of Taxane and Schedule in Operable Breast Cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2015;33:2353-60.
7. Schneider BP, Lai D, Shen F, et al. Charcot-Marie-Tooth gene, SBF2, associated with taxane-induced peripheral neuropathy in African Americans. Oncotarget 2016;7:82244-53.
8. Bach PB, Schrag D, Brawley OW, Galaznik A, Yakren S, Begg CB. Survival of blacks and whites after a cancer diagnosis. Jama 2002;287:2106-13.
9. Albain KS, Unger JM, Crowley JJ, Coltman CA, Jr., Hershman DL. Racial disparities in cancer survival among randomized clinical trials patients of the Southwest Oncology Group. Journal of the National Cancer Institute 2009;101:984-92.
10. Keenan T, Moy B, Mroz EA, et al. Comparison of the Genomic Landscape Between Primary Breast Cancer in African American Versus White Women and the Association of Racial Differences With Tumor Recurrence. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2015;33:3621-7.

11. DeSantis CE, Siegel RL, Sauer AG, et al. Cancer statistics for African Americans, 2016: Progress and opportunities in reducing racial disparities. CA: a cancer journal for clinicians 2016;66:290-308.
12. Carey LA, Perou CM, Livasy CA, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. Jama 2006;295:2492-502.
13. Silber JH, Rosenbaum PR, Clark AS, et al. Characteristics associated with differences in survival among black and white women with breast cancer. Jama 2013;310:389-97.
14. DeSantis C, Jemal A, Ward E. Disparities in breast cancer prognostic factors by race, insurance status, and education. Cancer causes & control : CCC 2010;21:1445-50.
15. Tichy JR, Deal AM, Anders CK, Reeder-Hayes K, Carey LA. Race, response to chemotherapy, and outcome within clinical breast cancer subtypes. Breast cancer research and treatment 2015;150:667-74.
16. Hershman DL, Lacchetti C, Dworkin RH, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2014;32:1941-67.
17. Vicini F, Nancarrow-Tull J, Shah C, et al. Increasing accrual in cancer clinical trials with a focus on minority enrollment: The William Beaumont Hospital Community Clinical Oncology Program Experience. Cancer 2011;117:4764-71.
18. Miller K, O'Neill AM, Dang CT, et al. Bevacizumab (Bv) in the adjuvant treatment of HER2-negative breast cancer: Final results from Eastern Cooperative Oncology Group E5103. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2014;32:Abstr 500.
19. Bryc K, Durand EY, Macpherson JM, Reich D, Mountain JL. The genetic ancestry of African Americans, Latinos, and European Americans across the United States. American journal of human genetics 2015;96:37-53.
20. Cobb RJ, Thomas CS, Laster Pirtle WN, Darity Jr WA. Self-identified race, socially assigned skin tone, and adult physiological dysregulation: Assessing multiple dimensions of “race” in health disparities research. SSM - Population Health 2016;2:595-602.
21. Rivera E, Cianfrocca M. Overview of neuropathy associated with taxanes for the treatment of metastatic breast cancer. Cancer Chemother Pharmacol 2015;75:659-70.
22. Sucheston-Campbell LE, Clay-Gilmour AI, Barlow WE, et al. Genome-wide meta-analyses identifies novel taxane-induced peripheral neuropathy-associated loci. Pharmacogenet Genomics 2018;28:49-55.
23. Mathis S, Goizet C, Tazir M, et al. Charcot–Marie–Tooth diseases: an update and some new proposals for the classification. Journal of Medical Genetics 2015;52:681-90.
24. Ballinger TJ, Kassem N, Shen F, et al. Discerning the Clinical Relevance of Biomarkers in Early Stage Breast Cancer. Breast cancer research and treatment 2017 (accepted).

25. (U.S. Department of Health and Human Services FaDA. http://wwwfdagov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282pdf 2009.
26. Hershman DL, Weimer LH, Wang A, et al. Association between patient reported outcomes and quantitative sensory tests for measuring long-term neurotoxicity in breast cancer survivors treated with adjuvant paclitaxel chemotherapy. Breast cancer research and treatment 2011;125:767-74.
27. Kluetz PG, Papadopoulos EJ, Johnson LL, et al. Focusing on Core Patient-Reported Outcomes in Cancer Clinical Trials-Response. Clinical cancer research : an official journal of the American Association for Cancer Research 2016;22:5618.
28. Kushner DM, Connor JP, Sanchez F, et al. Weekly docetaxel and carboplatin for recurrent ovarian and peritoneal cancer: a phase II trial. Gynecol Oncol 2007;105:358-64.
29. Cavaletti G, Marmiroli P. Chemotherapy-induced peripheral neurotoxicity. Nature reviews Neurology 2010;6:657-66.
30. Sterneckert JL, Reinhardt P, Scholer HR. Investigating human disease using stem cell models. Nature reviews Genetics 2014;15:625-39.
31. Wing C, Komatsu M, Delaney SM, Krause M, Wheeler HE, Dolan ME. Application of stem cell derived neuronal cells to evaluate neurotoxic chemotherapy. Stem cell research 2017;22:79-88.
32. Young GT, Gutteridge A, Fox HD, et al. Characterizing human stem cell-derived sensory neurons at the single-cell level reveals their ion channel expression and utility in pain research. Molecular therapy : the journal of the American Society of Gene Therapy 2014;22:1530-43.
33. Newman LA, Kaljee LM. Health Disparities and Triple-Negative Breast Cancer in African American Women: A Review. JAMA Surg 2017;152:485-93.
34. Postma TJ, Heimans JJ, Muller MJ, Ossenkoppele GJ, Vermorken JB, Aaronson NK. Pitfalls in grading severity of chemotherapy-induced peripheral neuropathy. Ann Oncol 1998;9:739-44.
35. Hay JL, Atkinson TM, Reeve BB, et al. Cognitive interviewing of the US National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Qual Life Res 2014;23:257-69.

Rev Add2

36. Calhoun EA, Welshman EE, Chang CH, et al. Psychometric evaluation of the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-NTX) questionnaire for patients receiving systemic chemotherapy. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society 2003;13:741-8.
37. Basch E, Pugh SL, Dueck AC, et al. Feasibility of Patient Reporting of Symptomatic Adverse Events via the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) in a Chemoradiotherapy Cooperative Group Multicenter Clinical Trial. International journal of radiation oncology, biology, physics 2017;98:409-18.
38. Hile E, Levangie P, Ryans K, Gilchrist L. Oncology Section Task Force on Breast Cancer Outcomes: Clinical Measures of Chemotherapy-induced Peripheral Neuropathy—A Systematic Review. Rehabilitation Oncology 2015;33:32-41.

39. Cella D, Peterman A, Hudgens S, Webster K, Socinski MA. Measuring the side effects of taxane therapy in oncology: the functional assesment of cancer therapy-taxane (FACT-taxane). Cancer 2003;98:822-31.
40. Monfort SM, Pan XJ, Patrick R, et al. Longitudinal changes in patient-reported symptoms and physical function during taxane-based chemotherapy in breast cancer patients. Journal of Clinical Oncology 2016;34.
41. Sasane M, Tencer T, French A, Maro T, Beusterien KM. Patient-Reported Outcomes in Chemotherapy-Induced Peripheral Neuropathy: A Review. The Journal of Supportive Oncology 2010;8:e15-e21.
42. Ward E, Jemal A, Cokkinides V, et al. Cancer disparities by race/ethnicity and socioeconomic status. CA: a cancer journal for clinicians 2004;54:78-93.
43. Pollitt RA, Swetter SM, Johnson TM, Patil P, Geller AC. Examining the pathways linking lower socioeconomic status and advanced melanoma. Cancer 2012;118:4004-13.
44. Rini BI, Powles T. Biology and treatment of advanced renal cell carcinoma: a global perspective. Semin Oncol 2013;40:419-20.
45. Teng M, Ichikawa S, Padgett LR, et al. regSNPs: a strategy for prioritizing regulatory single nucleotide substitutions. Bioinformatics 2012;28:1879-86.
46. Zhang X, Li M, Lin H, et al. regSNPs-splicing: a tool for prioritizing synonymous single-nucleotide substitution. Hum Genet 2017;136:1279-89.
47. Soldner F, Stelzer Y, Shivalila CS, et al. Parkinson-associated risk variant in distal enhancer of alpha-synuclein modulates target gene expression. Nature 2016;533:95-9.
48. Wu MC, Lee S, Cai T, Li Y, Boehnke M, Lin X. Rare-variant association testing for sequencing data with the sequence kernel association test. American journal of human genetics 2011;89:82-93.
49. Hu BY, Weick JP, Yu J, et al. Neural differentiation of human induced pluripotent stem cells follows developmental principles but with variable potency. Proc Natl Acad Sci U S A 2010;107:4335-40.
50. Xie Y, Schutte RJ, Ng NN, Ess KC, Schwartz PH, O'Dowd DK. Reproducible and efficient generation of functionally active neurons from human hiPSCs for preclinical disease modeling. Stem cell research 2017;26:84-94.
51. Wheeler HE, Wing C, Delaney SM, Komatsu M, Dolan ME. Modeling chemotherapeutic neurotoxicity with human induced pluripotent stem cell-derived neuronal cells. PLoS One 2015;10:e0118020.
52. Cai S, Han L, Ao Q, Chan YS, Shum DK. Human Induced Pluripotent Cell-Derived Sensory Neurons for Fate Commitment of Bone Marrow-Derived Schwann Cells: Implications for Remyelination Therapy. Stem Cells Transl Med 2017;6:369-81.
53. Nokihara H, Yamamoto N, Ohe Y, Hiraoka M, Tamura T. Pharmacokinetics of Weekly Paclitaxel and Feasibility of Dexamethasone Taper in Japanese Patients with Advanced Non-small Cell Lung Cancer. Clin Ther 2016;38:338-47.
54. Zasadil LM, Andersen KA, Yeum D, et al. Cytotoxicity of paclitaxel in breast cancer is due to chromosome missegregation on multipolar spindles. Sci Transl Med 2014;6:229ra43.

55. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 1996;49:1373-9.

56. Huang RL, Gu F, Kirma NB, et al. Comprehensive methylome analysis of ovarian tumors reveals hedgehog signaling pathway regulators as prognostic DNA methylation biomarkers. Epigenetics 2013;8:624-34.

57. Rao X, Evans J, Chae H, et al. CpG island shore methylation regulates caveolin-1 expression in breast cancer. Oncogene 2013;32:4519-28.

58. Tang J, Fang F, Miller DF, et al. Global DNA methylation profiling technologies and the ovarian cancer methylome. Methods Mol Biol 2015;1238:653-75.

59. Dobin A, Davis CA, Schlesinger F, et al. STAR: ultrafast universal RNA-seq aligner. Bioinformatics 2013;29:15-21.

60. Breese MR, Liu Y. NGSUtils: a software suite for analyzing and manipulating next-generation sequencing datasets. Bioinformatics 2013;29:494-6.

61. Robinson MD, McCarthy DJ, Smyth GK. edgeR: a Bioconductor package for differential expression analysis of digital gene expression data. Bioinformatics 2010;26:139-40.

62. Robinson MD, Oshlack A. A scaling normalization method for differential expression analysis of RNA-seq data. Genome biology 2010;11:R25.

63. Feng J, Liu T, Qin B, Zhang Y, Liu XS. Identifying ChIP-seq enrichment using MACS. Nature Protocols 2012;7:1728-40.

64. Zhang Y, Liu T, Meyer CA, et al. Model-based analysis of ChIP-Seq (MACS). Genome biology 2008;9:1-9.

65. Garcia, S. F., Cella, D., Clauser, S. B., Flynn, K. E., Ladd, T., Lai, J-S, Reeve, B., Smith, A. W., Stone, A. A., & Weinfurt, K. (2007). Standardizing patient-reported outcomes assessment in cancer clinical trials: A PROMIS initiative. Journal of Clinical Oncology, 25, 5106-5112.

66. https://www.assessmentcenter.net/ac_scoringservice

67. de Souza JA, Yap BJ, Wroblewski K, et al: Measuring financial toxicity as a clinically relevant patient-reported outcome: The validation of the COmprehensive Score for financial Toxicity (COST). Cancer 123:476-484, 2017

68. Hershman DL, Weimer LH, Wang A, Kranwinkel G, Brafman L, Fuentes D, Awad D, Crew KD. Association between patient reported outcomes and quantitative sensory tests for measuring long-term neurotoxicity in breast cancer survivors treated with adjuvant paclitaxel chemotherapy. Breast Cancer Research and Treatment 2011;125(3):767-74

Rev Add1

69. Jensen RE, Potosky AL, Reeve BB, et al. Validation of the PROMIS physical function measures in a diverse US population-based cohort of cancer patients. Quality of life research: an international journal of quality of life aspects of treatment, care and rehabilitation. 2015;24(10):2333-2344

70. Postma TJ, Aaronson NK, Heimans JJ, et al. The development of an EORTC quality of life questionnaire to assess chemotherapy-induced peripheral neuropathy: the QLQ-CIPN20. European journal of cancer. 41(8):1135-1139, 2005

71. Lavoie Smith EM, Barton DL, Qin R, Steen PD, Aaronson NK, Loprinzi CL. Assessing patientreported peripheral neuropathy: the reliability and validity of the European Organization for Research and Treatment of Cancer QLQ-CIPN20

Questionnaire. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 22(10):27872799, 2013

72. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy Scale: development and validation of the general measure. J Clin Oncol 1993; 11:570-79.

Prospective validation trial of taxane therapy (docetaxel or weekly paclitaxel) and risk of chemotherapy-induced peripheral neuropathy in African American women

Appendix I

Rev Add1

ECOG-ACRIN Generic Specimen Submission Form (#2981v3)

ECOG-ACRIN Generic Specimen Submission Form

Form No. 2981v3

Institution Instructions: This form is to be completed and submitted with **all specimens** ONLY if the Sample Tracking System (STS) is not available. **Use one form per patient, per time- point.** All specimens shipped to the laboratory must be listed on this form. Enter all dates as MM/DD/YY. Keep a copy for your files. Retroactively log all specimens into STS once the system is available. **Contact the receiving lab to inform them of shipments that will be sent with this form.**

Protocol Number _____ **Patient ID** _____ **Patient Initials** Last _____ First _____

Date Shipped _____ **Courier** _____ **Courier Tracking Number** _____

Shipped To (Laboratory Name) _____ **Date CRA will log into STS** _____

FORMS AND REPORTS: Include all forms and reports as directed per protocol, e.g., pathology, cytogenetics, flow cytometry, patient consult, etc.

Required fields for all samples				**Additional fields for tissue submissions**				**Completed by Receiving Lab**
Protocol Specified Timepoint:								
Sample Type (fluid or fresh tissue, include collection tube type)	**Quantity**	**Collection Date and Time 24 HR**		**Surgical or Sample ID**	**Anatomic Site**	**Disease Status** (e.g., primary, mets, normal)	**Stain or Fixative**	**Lab ID**

CRA Name _____ **CRA Phone** _____ **CRA Email** _____

Comments

9/12/14

Prospective validation trial of taxane therapy (docetaxel or weekly paclitaxel) and risk of chemotherapy-induced peripheral neuropathy in African American women

Appendix II

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we hope to improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and ECOG-ACRIN, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

Prospective validation trial of taxane therapy (docetaxel or weekly paclitaxel) and risk of chemotherapy-induced peripheral neuropathy in African American women

Appendix III

ECOG Performance Status

PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light house work, office work.
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.