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SWOG CANCER RESEARCH NETWORK

S1714, A PROSPECTIVE OBSERVATIONAL COHORT STUDY TO DEVELOP A PREDICTIVE MODEL OF TAXANE-INDUCED PERIPHERAL NEUROPATHY IN CANCER PATIENTS

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by SWOG with the participation of the network of NCTN organizations: Alliance for Clinical Trials in Oncology; ECOG-ACRIN Medical Group; and NRG.

NCT# 03939481

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PROTOCOL CONTACT INFORMATION

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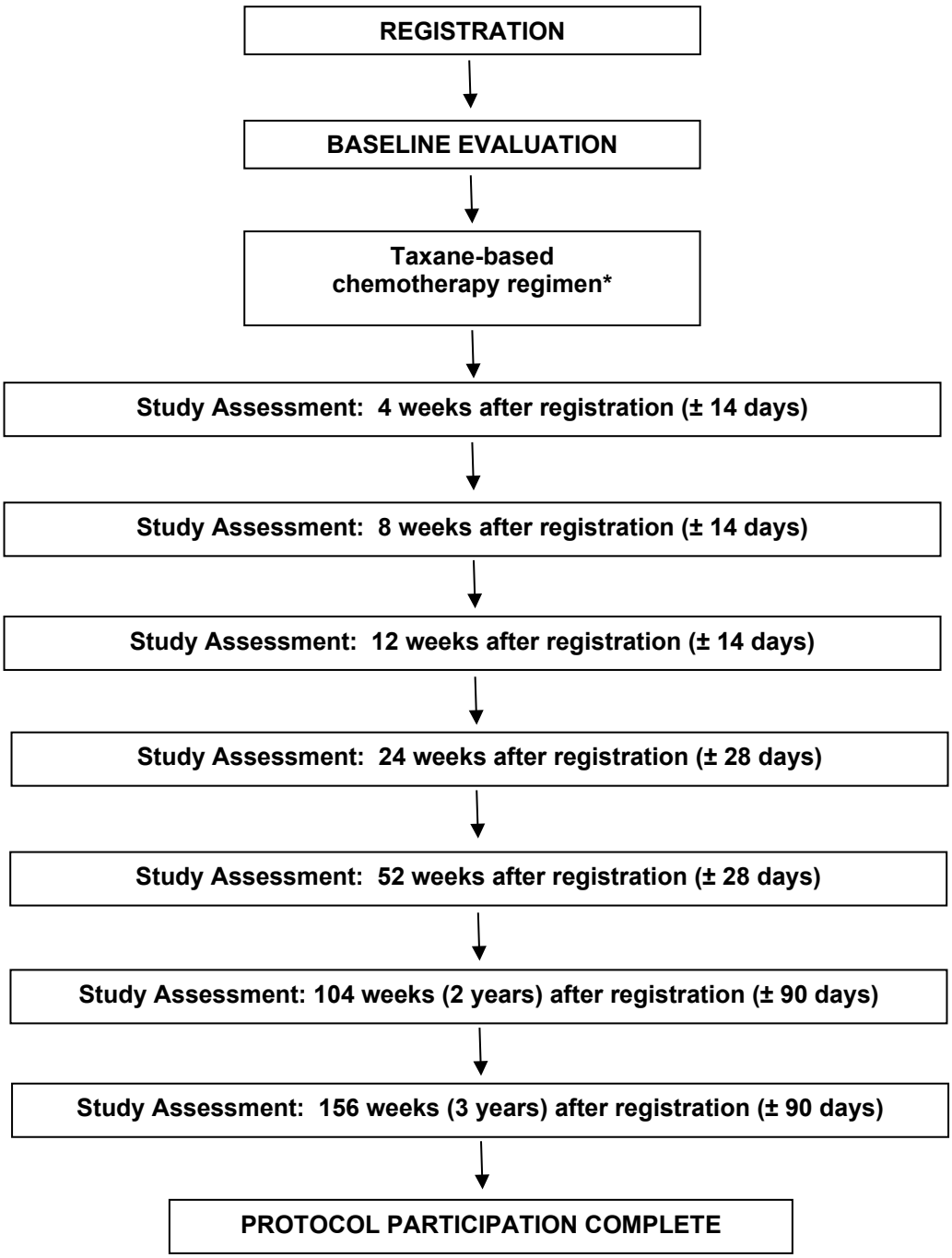
Study Assessment-Related questions:	Email: S1714@swog.org
Protocol Specific Training: • NeuroPen • 128 Hertz Tuning Fork • Timed Get Up and Go	Email: S1714@swog.org • Section 7.6 • Section 7.7 • Section 7.8 https://www.swog.org/required-s1714-training
Patient Advocate	Amy R. Geschwender, PhD ageschwender@gmail.com
Specimen Tracking System (STS) Amendments, Errors, Connectivity Issues and Technical issues with the SWOG CRA Workbench:	technicalquestion@crab.org
Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM)	To review CTEP-IAM account (new requests, reset passwords): https://ctepcore.nci.nih.gov/iam/index.jsp
Access to iMedidata Rave or Delegation of Task Log (DTL)	See Protocol Section 14 or contact CTSU Help Desk: Phone: 1-888-823-5923 or Email: ctsucontact@westat.com
Questions related to: Oncology Patient Enrollment Network (OPEN)	See Protocol Section 13.3 or contact CTSU Help Desk: Phone: 1-888-823-5923 or Email: ctsucontact@westat.com
Patient Transfers:	patienttransfer@crab.org

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at https://www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN 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 by phone or email: 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions. Other Tools and Reports: Institutions participating through the CTSU continue to have access to other tools and reports available on the SWOG CRA Workbench via the SWOG website (www.swog.org).
The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). 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 Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website.		
For patient eligibility or data submission questions contact the SWOG Statistics and Data Management Center (SDMC) in Seattle, Washington by phone or email: 206/652-2267 cancercontrolquestion@crab.org **For study assessment-related questions** contact the Study Chairs by e-mail at S1714@swog.org.		
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 Website is located at https://www.ctsu.org.		

SCHEMA



* Can be administered with a non-neurotoxic chemotherapy, such as cyclophosphamide, and/or biologic agents, such as trastuzumab, and/or carboplatin.

1.0 OBJECTIVES

1.1 Primary Objective

a. To develop and validate a clinical risk prediction model using clinical factors for the development of peripheral neuropathy in patients receiving taxane-based chemotherapy regimens.

1.2 Secondary Objectives

a. To examine patient-reported outcomes (PROs) and objective measures of chemotherapy induced peripheral neuropathy (CIPN) to better define the phenotype of peripheral neuropathy in this patient population.

b. To assess the incidence of CIPN within one year in this patient population.

c. To identify predictors of treatment dose reductions, delays, and discontinuations associated with CIPN symptoms in this patient population.

1.3 Other Objectives

a. To collect serum and plasma samples for future testing for biomarker and mechanistic studies of CIPN.

1.4 Imaging Objectives

To estimate SMA-based taxane infusion rates for 1-hour paclitaxel (Pac1h) and docetaxel (Doc1h) to prevent supratherapeutic Cmax and reduce TIPN risk in female patients with breast cancer.

2.0 BACKGROUND

2.1 Chemotherapy-Induced Peripheral Neuropathy (CIPN)

Chemotherapy-induced peripheral neuropathy (CIPN) is a common adverse effect of many anti-cancer drugs, including platinum analogs, antitubulins such as taxanes and vinca alkaloids, and bortezomib. It can present as sensory symptoms in the hands and/or feet, typically in a “stocking-glove” pattern manifested as pain, numbness, or tingling, or as motor symptoms, manifested as weakness or cranial nerve deficits, or as autonomic neuropathy. In a meta-analysis of 31 CIPN studies involving 4179 patients, the aggregate prevalence of CIPN was 48%; however, the methods used to assess for the presence of CIPN varied widely among the studies included. *(1)* Within the first month of finishing chemotherapy, the prevalence of CIPN was 68.1%. After 6 or more months of completing chemotherapy, the prevalence of CIPN decreased to 30.0%. *(2)* In SWOG **S0715**, a randomized, double-blind, multi-center trial comparing acetyl-L-carnitine versus placebo for prevention of CIPN in women with stage I-III breast cancer undergoing taxane-based chemotherapy, symptoms of neuropathy were persistent 2 years following treatment. *(3)* The course of CIPN can be unpredictable. Although some symptoms may improve with time, other symptoms may persist or worsen as a result of permanent nerve damage. The incidence of CIPN varies not only with the chemotherapeutic agent used but also the dose or frequency with which an agent is given, and the cumulative dose received (Table 2.1). *(4,5)*

Studies of CIPN have been limited by the absence of a clearly defined phenotype for CIPN. There are several methods available to assess CIPN; however, there is no consensus on the best method to evaluate CIPN. Postma *et al.* developed a CIPN subscale as part of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life

Questionnaire 30 (QLQ-30), called the QLQ-CIPN-20 module. *(6)* The instrument contains 20 questions evaluating sensory, motor, and autonomic symptoms and has been validated as an assessment tool for CIPN. *(7)* There are several therapeutic and observational trials that have used the CIPN-20 as the primary outcome. *(8,9,10,11)* The challenge is how to incorporate CIPN measures into clinical practice and standardize this approach across multiple centers.

A further challenge in managing and preventing CIPN is that the exact pathophysiology is not well understood and is likely multifactorial with both genetic and non-genetic risk factors. *(12)* Additionally, the pathophysiology appears to vary depending upon the chemotherapeutic agent. The hypothesized mechanisms of taxane-induced peripheral neuropathy include the disruption of the axonal microtubule structure and a deficit in axonal energy supply through the toxic effect of chemotherapy on mitochondria in primary afferent neurons. *(13,14)* Platinum agents are thought to cause CIPN by exerting damage in the dorsal root ganglion through neuronal apoptosis, either by DNA crosslinking or oxidative stress, and mitochondrial dysfunction. *(15,16)*

Table 2.1. Incidence of CIPN based on chemotherapeutic agent

Chemotherapy regimen	**Disease**	**Incidence of CIPN**		
		Motor neuropathy (all grades)	Sensory neuropathy (all grades)	Grade 3-4 sensory neuropathy
Docetaxel and Carboplatin *(17,18,19)*	Ovarian/Fallopian tube/ Peritoneal cancer tube, breast, and lung cancer	5- 9%	45-46%	1-2%
FOLFOX *(20,21,22)*	Colorectal cancer	-	59-92%	7-12%
Bortezomib *(23,24)*	Multiple myeloma	6%	44%	13%
Paclitaxel *(25,26)*	Breast cancer	9-17%	33-45%	12-24%

2.2 Drug Pharmacokinetics and CIPN

The association of drug pharmacokinetics with the development of CIPN has also been studied. In a study of patients with advanced cancer receiving weekly paclitaxel (N=24), having exposure to a concentration of total paclitaxel above 0.05 mcmol/L ($T_{c>0.05}$) for greater than or equal to 10.6 hours was the most important pharmacokinetic factor influencing the development of CIPN. *(27)* In this study, 12-14 serum samples were obtained from each patient during and until 48 hours after the end of paclitaxel administration. Confirmation that paclitaxel exposure, not dose, is the critical determinant of paclitaxel-induced peripheral neuropathy (PIPN) was provided by a prospective, randomized, phase III trial of 3-weekly paclitaxel (200 mg/m2)/carboplatin in lung cancer patients. Patients who received individualized dosing to maintain a therapeutic paclitaxel exposure target had significantly lower PIPN occurrence (38% vs. 23%, $p<0.001$) than patients receiving standard maximum tolerated dosing, with similar efficacy. *(28)* Preliminary data from an observational clinical study by one of the Co-Is (NCT02338115, PI: Daniel Hertz) further supports the importance of paclitaxel exposure in determining neuropathy. The observational clinical trial enrolled 60 women with early stage breast cancer scheduled to receive weekly paclitaxel (80 mg/m2 x 12 cycles) who had no existing neuropathy, family history of hereditary neuropathy, or prior neurotoxic chemotherapy treatment. *(29,30)* Paclitaxel concentration (exposure) was measured in plasma collected just prior to the end of the first infusion and 16-24 hours later via liquid chromatography-

mass spectroscopy. The end of infusion sample provides an estimate of the maximum concentration (C_{max}), and the 16–24-hour sample was used to estimate the patient's time above threshold ($T_{c>0.05}$) using a previously published population-pharmacokinetic model. *(31)* PIPN data were collected at baseline (prior to paclitaxel) and weekly throughout treatment using the sensory subscale of the CIPN-20. *(32,33)* The change in the sensory subscale from baseline was calculated for each patient at each weekly cycle to estimate neuropathy progression. All patients with neuropathy and exposure data were included in a logistic regression model to predict treatment-limiting neuropathy (*i.e.* paclitaxel dose decrease, delay, or discontinuation). Each exposure parameter significantly contributed to this prediction model; a one standard deviation increase in C_{max} (664.8 ng/mL) and $T_{c>0.05}$ (2.7 hours) were associated with 174% (OR=2.74, 95% CI: 1.45-5.20, p=0.0020) and 76% (OR =1.76, 95% CI: 1.45-2.14, p=0.0294) higher risk of treatment-limiting PIPN, confirming the contribution of exposure to neuropathy development.

2.3 CIPN Risk Factors

Several studies have attempted to identify risk factors for the development of CIPN, which also vary with chemotherapeutic agent. Some of the clinical factors implicated in the development of CIPN include increasing age, *(34)* baseline neuropathy, *(35,36)* presence of diabetes, *(37,38)* smoking history, *(39)* and decreased creatinine clearance. *(40)* One study found that the presence of autoimmune disease reduced the risk of CIPN development. *(41)* Additionally, there is interest in pharmacogenomics and identifying genes that may play a role in the development of CIPN. Although numerous genes have been investigated (Table 2.2), there have been no conclusive findings. *(42)* The lack of a well-defined phenotype of CIPN has limited the identification of CIPN risk factors and genetic predictors. Despite investigations leading to hypotheses of several mechanisms of CIPN, none of these have resulted in clinically relevant therapeutic interventions. Given the many variables that seem to affect the development of CIPN, particularly the differences among each neurotoxic chemotherapeutic agent, it is likely that CIPN cannot be defined as a single entity.

Table 2.2. Putative genetic predictors of CIPN

Chemotherapy agent	Predictive genes
Oxaliplatin	*CCNH(43), ABCG2(44), TAC1(45), FOXC1(46) GMDS(47), ITGA1(48), PELO(49), ACYP2(50), TSPYL6(51), DLEU7(52)*
Bortezomib	*RDM1(53), CASP9(54), ALOX12(55), LSM1(56), CTLA4(57), PSMB1(58)*[1]
Taxane	*FDG4(59), EPHA5(60), FZD3(61), ABCB1(62), TUBB2A(63), FANCD2(64), CYP2C8*3(65), EPHA4(66)*

2.4 CIPN Clinical Implications

One of the clinical implications of CIPN is that the symptoms can lead to treatment dose reduction or discontinuation, which may ultimately affect overall survival. *(67)* In addition, for cancer survivors, CIPN symptoms can significantly impact quality of life and functional status. *(68,69)* The primary objective of this study is to develop a risk prediction model for CIPN due to taxanes that can be utilized in the clinic. By focusing on identifying the predictors of peripheral neuropathy caused by a single class of chemotherapy agents, the investigators will be able to develop a clinically meaningful prediction model. Although it is

anticipated that age, pre-existing neuropathy, and paclitaxel exposure will be strong predictors of taxane induced peripheral neuropathy, our goal is to examine a broad range of factors from an agnostic perspective, with no a priori design specification favoring any particular factor. In addition, this study will aim to characterize the clinical phenotype of CIPN due to taxanes and describe the trajectory of CIPN. This will be accomplished by collecting patient reported outcome measures and objective measures of CIPN over the course of 12 months. Through this prospective cohort study, the investigators will build an associated repository of biospecimens that can be used for future biomarker and mechanistic studies. It is anticipated that over the course of the study, new proteomic, metabolomic, or genomic biomarkers will be identified. The biospecimen repository developed from this study will allow us to investigate such biomarkers and potentially incorporate these new findings into our risk prediction model in the future.

Taxanes are commonly used in the treatment of cancer and given the clinical implications of this frequently occurring adverse effect, it is important to understand the risk factors for development of CIPN and its clinical course. This study will also include a broader population of patients than is generally enrolled in clinical trials, including patients with co-morbidities such as diabetes and pre-existing peripheral neuropathy. By better characterizing CIPN due to taxanes, the investigators may be able to select cancer treatment regimens more appropriately for patients at higher risk of CIPN. Furthermore, these data would inform future clinical trial designs for therapeutic trials and symptom research intended to prevent or relieve CIPN.

2.5 Inclusion of Women and Minorities and Planned Enrollment Report

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	2	0	1	0	3
Asian	40	6	3	0	49
Native Hawaiian or Other Pacific Islander	8	2	0	0	10
Black or African American	68	10	5	0	83
White	692	105	51	3	851
More Than One Race	2	0	0	0	2
Total	812	123	60	3	998

INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	27	4	31
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	0	0	0	0
White	0	0	245	36	281
More Than One Race	0	0	0	0	0
Total	0	0	272	40	312

3.0 DRUG INFORMATION

Drug information is not applicable to this protocol.

4.0 STAGING CRITERIA

This protocol will use the American Joint Committee on Cancer (AJCC) 8th Edition. *(70)* See Appendix 18.2 for complete definitions and staging.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the SWOG Statistics and Data Management Center at 206/652-2267 or cancercontrolquestion@crab.org prior to registration. NCI policy does not allow for waiver of or deviation within any eligibility criterion (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm).

In calculating days of tests and measurements, the day of registration is Day 0. Therefore, if the day of registration is on a Monday, the Monday 4 weeks later would be considered Day 28.

5.1 Disease Related Criteria

a. Patients must have Stage I, II, or III primary non-small cell lung, primary breast, or primary ovarian/fallopian tube/ peritoneal cancer based on clinical or pathologic evaluation. Patients with Stage IV disease are not eligible.

5.2 Prior/Concurrent Therapy Criteria

a. Patients must be planning to start treatment with a taxane-based chemotherapy as part of one of the study-approved taxane regimens (docetaxel chemotherapy

regimens for treatment of breast or ovarian/fallopian tube/ peritoneal cancer, or paclitaxel chemotherapy regimens for treatment of breast, non-small cell lung, or ovarian/fallopian tube/ peritoneal cancer) within 14 days after registration. (Note that carboplatin is allowed only as described in Appendix 18.1. However, any of the regimens in Appendix 18.1 may be combined with a non-neurotoxic chemotherapy, such as cyclophosphamide, and/or a biologic agent, such as trastuzumab. **Permitted biologic agents include, but are not limited to, pembrolizumab, bevacizumab, trastuzumab, and/or pertuzumab.** Nab-paclitaxel may **not** be substituted for paclitaxel for purposes of this study.) See Appendix 18.1 for the study-approved docetaxel and paclitaxel-based regimens.

b. Patients who will receive treatment in the setting of any other clinical trial are eligible as long as it is one of the study-approved regimens listed in Appendix 18.1. Patients may receive additional treatments (i.e., experimental therapy, immunotherapy, biologics, etc.) as part of another clinical trial in addition to any regimen approved in this study.

c. Patients must not have received a taxane (paclitaxel, docetaxel, or protein-bound paclitaxel), platinum (cisplatin, carboplatin, or oxaliplatin), vinca alkaloid (vinblastine, vincristine, or vinorelbine), or bortezomib-based chemotherapy regimen prior to registration. (Note that while patients must not have received carboplatin in the past, patients may receive a carboplatin-containing regimen after registration as part of the docetaxel or paclitaxel regimen.)

5.3 Clinical/Laboratory Criteria

a. Patients must be ≥ 18 years of age.

b. Patients must be able to complete Patient-Reported Outcome (PRO) instruments in English or Spanish. Patients must:
   1) agree to complete PROs at all scheduled assessments; and
   2) complete the baseline PRO forms **prior to registration** as outlined in Section 7.5.

c. Patients with pre-existing neuropathy are eligible, including those with diabetes and neurological conditions such as multiple sclerosis or Parkinson's disease.

5.4 Specimen Submission Criteria

a. Patients must agree to submit required specimens for defined translational medicine as outlined in Section 15.1.

b. Patients must be offered the opportunity to submit additional optional specimens for future, unspecified translational medicine and banking. With patient's consent, specimens must be submitted as outlined in Section 15.1.

5.5 Regulatory Criteria

a. Patients ***must*** be informed of the investigational nature of this study and must sign and give informed consent in accordance with institutional and federal guidelines.

b. As a part of the OPEN registration process (see Section 13.3 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

6.0 STRATIFICATION FACTORS

Patients will be classified by primary cancer (lung vs breast vs ovarian/fallopian tube/ peritoneal) and planned taxane (paclitaxel vs docetaxel) in order to ensure a representative balance of registrations by cancer and treatment type. When 250 lung cancer patients have been accrued, the lung cancer category will be closed to further accrual.

7.0 STUDY ASSESSMENTS

See Section 14.0 for forms submission requirements.

7.1 Pre-Treatment Laboratory Assessment

Patients must have creatinine clearance or serum creatinine (for calculation of creatinine clearance) collected either:

1) within 30 days prior to registration, OR
2) after registration but prior to beginning their taxane-based chemotherapy regimen.

$$\text{Estimated creatinine clearance} = \frac{(140 - \text{age}) \times \text{wt (kg)} \times 0.85 \text{ (if female)}}{72 \times \text{creatinine (mg/dl)}}$$

7.2 Medical History

Active medical problems, past medical history, smoking history, and concomitant medications will be documented at baseline for this study and reported on the appropriate baseline form. Oncologic history, including primary tumor size and grade, lymph node status, stage, hormone receptor status (for breast cancer), Her2/neu status (for breast cancer), and treatment history (including prior regimens) will be collected. Data will also be collected on other comorbidities, including but not limited to diabetes, thyroid disease, vitamin B12 deficiency, vitamin D deficiency, autoimmune disease, and neurological conditions, as well as Zubrod performance status and history of falls. Data regarding the causes of pre-existing neuropathy will also be collected. A comprehensive list of neuropathies is included in Appendix 18.6.

7.3 Chemotherapy Treatment Schedule

This protocol will not dictate which treatment is given or any dose reductions, dose delays, or discontinuation of therapy; however, a list of protocol-specified allowable treatment regimens at the time of patient registration per eligibility requirements in Section 5.0 is in Appendix 18.1. Radiation may be administered concurrently with chemotherapy and will be documented and reported. Document and report chemotherapy drugs, doses, and schedules. Any chemotherapy dose reductions, delays, or discontinuations will be determined by the treating physician and will also be documented and reported. A treatment will be considered dose reduced if the dose administered is ≥ 20% less than the standard taxane dose listed for the regimen in Appendix 18.1. A treatment will be considered delayed if the dose is administered ≥ 7 days later than the standard taxane interval for the regimen in Appendix 18.1. A treatment discontinuation is defined as stopping the taxane-based chemotherapy prior to the standard number of doses listed for the regimen in Appendix 18.1. The reason for change in treatment will also be noted (i.e., CIPN symptoms, neutropenia, patient preference, progression of disease, etc.). Assessment of treatment schedule will occur at baseline prior to chemotherapy, then at 4 weeks, 8 weeks, and 12 weeks (± 14 days), at 24 weeks, 52 weeks, (± 28 days), and 104 weeks (2 years), and 156 weeks (3 years) (± 90 days) after registration as outlined in Section 9.0. Efforts should be made to perform the 4-week, 8-week, and 12-week assessments on a day of taxane treatment that falls within the study window period and prior to taxane administration.

If additional adjuvant therapies are administered following the completion of the taxane-based regimen, this will be documented and reported in the follow up treatment forms. Adjuvant therapies may include, but are not limited to, chemotherapy (*i.e.* capecitabine), biologic therapy (*i.e.* trastuzumab), immunotherapy (*i.e.* pembrolizumab), or targeted therapy *(i.e.* PARP inhibitor). This protocol will not dictate which treatment is given or any dose reductions, dose delays, or discontinuation of therapy.

7.4 Active Topical Agents/Medications/Supplements/Interventions

Sites will collect information regarding the patient's use of all topical agents, medications, vitamins and multivitamins, supplements, or acupuncture and will document and report the information via the **S1714** Supplements, Topical Agents, and Other Treatments Form. The use of cooling gloves or socks (or other means of cooling hands and feet) and compression gloves or socks as a means of CIPN prevention will also be collected. If any of the above are used specifically for CIPN symptoms, this will also be reported. Assessment will occur at baseline prior to chemotherapy, then at 4 weeks, 8 weeks, and 12 weeks (± 14 days), and at 24 weeks and 52 weeks (± 28 days) after registration as outlined in Section 9.0. Efforts should be made to perform the 4-week, 8-week, and 12-week assessments on a day of taxane treatment that falls within the study window period and prior to taxane administration.

7.5 Patient and Physician-Reported Outcomes

Patients are to complete the instruments in English or Spanish and physicians will complete questionnaires at baseline prior to registration and chemotherapy and as outlined in Section 9.0, throughout the patient's participation in the study. The instruments that will be used and assessments to be performed are:

- European Organization for Research and Treatment of Cancer (EORTC) QLQ-CIPN20 (CIPN-20)
- Patient-Reported Outcomes Measurement Information System 29 (PROMIS-29)
- Godin-Shephard Leisure-Time Physical Activity Questionnaire (GSLTPAQ)
- Patient Reported Symptom (and Side Effect) Burden
- Visual Analog Toxicity Score
- PRO-CTCAE
- NCI-CTCAE
- FACT-GOG-NTX-4

Complete details regarding each instrument, the associated grading scales and time points for administration are in Appendix 18.5.

NOTE: Patients should continue to complete questionnaires at study time points even if patient discontinues taxane-based chemotherapy, disease progression or relapse prior to 52 weeks after registration per Section 7.10 and 7.12.

NOTE: For all patient reported outcome questionnaire timepoints, participating sites may follow-up with patients via telemedicine (phone or virtual visit) to conduct the questionnaires and patient follow-up provided that the Responsible Investigator determines that the phone/virtual visit is adequate to achieve the central purpose of the visit and assure the safety of the patient. Patient must be provided with a copy of the questionnaire via mail or email.

7.6 Neuropen (provided to each participating site)

Sites must have a Neuropen prior to the first patient registration. Neuropen ordering instructions are in Section 7.6a. Additionally, at least one clinician (physician, nurse practitioner, registered nurse, licensed practical nurse, or physician assistant) at each site must be certified to use the Neuropen (see Section 7.6b for details on obtaining certification) prior to first patient registration. Neuropen assessments must be performed by a certified clinician. Local site authority logs should be updated to include this task. Note: CRA may not conduct the testing.

a. Neuropen Ordering

Sites may order Neuropen at the time that IRB approval has been submitted to the CTSU Regulatory Office (see Section 13.2b). Requests should be submitted via e-mail to S1714@swog.org. The subject of the e-mail should be "**S1714** Neuropen Order." (Note that this order may be combined with the 128 Hertz tuning fork order (see Section 7.7) by specifying "**S1714** Neuropen and Tuning Fork Order.") The e-mail must include the following information:

- site name
- site NCI code
- mailing address to which the Neuropen should be shipped
- contact information (phone number and e-mail address) for a staff contact at the site in the event there are questions about the order
- verification that the site's IRB approval has been submitted to Regulatory Office
- name of the clinician(s) who will complete the Neuropen training and certification

NOTE: Only 150 tools are available (first come, first serve basis) for this study. A notification will be circulated to sites via the SWOG and CTSU mailout once this number has been met.

b. General Neuropen Information

The Neuropen has a 10-g monofilament on one end and Neurotip on the other end. Instructions on how to replace the monofilament and Neurotip are in the user manual. The Neuropen may be reused and is not patient-specific.

- The monofilament should be replaced after 100 uses. A single use is defined as a single 10-point examination on the dominant foot of a subject.
- The Neurotip should be replaced with each 10-point examination on the dominant foot of a subject.

Neuropathy evaluation is to be performed by a clinician certified to perform the testing. A clinician can be certified to perform Neuropen testing by completing the steps below.

First, the clinician must review the user manual and instructional video for the Neuropen, which are available on the protocol abstract pages of the SWOG website (www.swog.org) and the CTSU website (www.ctsu.org). Note that the user manual outlines the basic instructions for use of the Neuropen, but more detailed, study-specific instructions are included in Sections 7.6c and 7.6d below. For purposes of this study, sites should use the more detailed instructions outlined below. Once the clinician has reviewed the instructions below, the instructional video, and user manual, the clinician must complete a training verification available

on the protocol abstract page of the SWOG website (www.swog.org) and the verification must be submitted via CTSU (see Section 13.2b.3).

Second, the clinician must be observed demonstrating proficiency in using the Neuropen. This can be done in one of 2 ways: 1) in-person observation at a bi-annual SWOG meeting, or 2) observation via video-conference. One of the Study Chairs or the Clinical Nurse Coordinator will be responsible for assessing the proficiency demonstration. Observation via video-conference may be arranged by e-mailing S1714@swog.org. Once the clinician has been observed performing Neuropen testing, he/she will obtain a certificate of training via email from the SWOG Operations Office which must be submitted via CTSU Regulatory Portal (see Section 13.2b.3).

All clinicians who will perform Neuropen assessments must submit certification of training. Any questions regarding the use of the Neuropen can be directed to the Clinical Nurse Coordinator for the study.

Assessments will occur at baseline prior to start of taxane treatment, then at 4 weeks, 8 weeks, and 12 weeks (± 14 days), and at 24 weeks and 52 weeks (± 28 days) as outlined in Section 9.0. Efforts should be made to perform the 4-week, 8-week, and 12-week assessments on a day of taxane-based treatment that falls within the study window period and prior to taxane administration. Results of this assessment will be submitted via the **S1714** Neuropathy Assessment Form. The Neuropen assessment will take approximately 5-10 minutes to complete.

c. Instructions for Assessing Touch and Pressure Perception

Touch and Pressure Perception: Touch and pressure sensation is assessed using the 10-g monofilament in the Neuropen on the subject's dominant foot. The dominant foot can be identified by asking the subject with which foot they would kick a ball. The clinician will follow the subsequent steps using the subject's dominant foot:

1. Ask the subject to remove sock and/or shoe on the dominant foot and lay flat or sit up on an examination table.
2. Fully extend the monofilament by sliding the button to the end of the device until a click is heard.
3. Wipe the end of the monofilament with an alcohol wipe or antiseptic solution.
4. The 10 sites in the below figure (Figure 7.1) are to be tested at random on the dominant foot. Press the monofilament at a 90-degree angle to the skin surface and increase the pressure until it bows. **The subject should not be able to see which site is being tested.**
5. Hold in position for 1-2 seconds.
6. For each of the 10 sites tested, ask the subject if he/she can detect pressure applied from monofilament and name the location of sensation. Subjects may use the unmarked picture of the feet (similar to Figure 7.1) which is included in Appendix 18.7 to point to the location of sensation if they are unable to adequately name the location. Record subject response for each site tested. The sensation must be detected in the accurate location to be marked as correct.

d. Instructions for Assessing Protective Pain and Sharpness Sensation

Protective Pain and Sharpness Sensation: This is a calibrated and sterile pain/sharpness test on the subject's dominant foot. The spring mechanism is calibrated to exert a force of 40 grams to help identify subjects with a loss of pain sensation. The dominant foot can be identified by asking the subject with which foot they would kick a ball. The clinician will follow the subsequent steps using the subject's dominant foot:

1. Ask the subject to remove sock and/or shoe on the dominant foot and lay flat or sit up on an examination table.
2. Take an unused Neurotip and hold by the cap. Do not use if Neurotip cap has previously been removed.
3. Press Neurotip firmly down into the Neurotip carrier of the Neuropen as far as it will go and clicks into position. The Neurotip is correctly positioned when only one chevron can be seen on the Neurotip.
4. To expose the sterile semi-sharp tip, place thumb gently over the Neurotip pressure gauge and remove Neurotip cap by twisting and pulling outwards.
5. The 10 sites in the below figure (Figure 7.1) are to be tested at random. Press the Neurotip against the skin surface at a 90-degree angle. **The subject should not be able to see which site is being tested**.
6. Hold in position for 1-2 seconds before removing, taking care to depress within the 40-gram marked white area.
7. For each of the sites tested, ask the subject if they detect a sharp sensation and name the location of sharp sensation. Subjects may use the unmarked picture of the feet (similar to Figure 7.1) which is included in Appendix 18.7 to point to the location of sensation if they are unable to adequately name the location. Record subject response for each site tested. The sensation must be detected in the accurate location to be marked as correct.
8. Remove and discard the used Neurotip in an appropriate sharps container after completing the 10 site examinations.

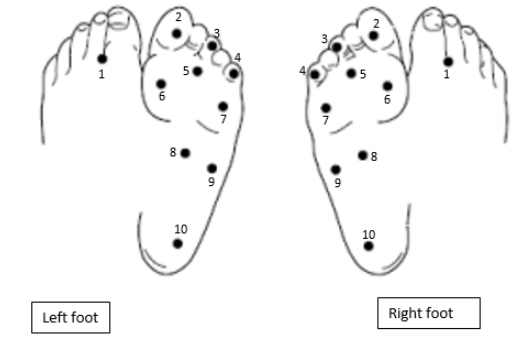


Figure 7.1 Sites on the feet to be evaluated with Neuropen monofilament and Neurotip

7.7 128 Hertz Tuning Fork *(71, 72)* (provided to each participating site)

Sites must have a 128 Hertz tuning fork prior to the first patient registration.

128 Hertz Tuning Form ordering instructions are in Section 7.7a. Additionally, at least one clinician (physician, nurse practitioner, registered nurse, licensed practical nurse, or physician assistant) at each site must be certified to use the tuning fork (see Section 7.7b for details on obtaining certification) prior to first patient registration. 128 Hertz tuning fork assessments must be performed by a certified clinician. Local site authority logs should be updated to include this task. Note: CRA may not conduct the testing.

a. 128 Hertz Tuning Fork Ordering

Sites may order the 128 Hertz tuning fork at the time that IRB approval has been submitted to the CTSU Regulatory Office (see Section 13.2b). Orders should be submitted via email to S1714@swog.org. The subject of the e-mail should state "**S1714** Tuning Fork Order." (Note that this order may be combined with the Neuropen order (see Section 7.6) by specifying "**S1714** Neuropen and Tuning Fork Order.") The e-mail must include the following information:

- site name
- site NCI code
- mailing address to which the 128 Hz tuning fork should be shipped
- contact information (phone number and e-mail address) for a staff contact at the site in the event there are questions about the order
- verification that the site's IRB approval has been submitted to the CTSU Regulatory Office
- name of the clinician(s) who will complete the tuning fork training and certification

NOTE: Only 150 tools are available (first come, first serve basis) for this study. A notification will be circulated to sites via the SWOG and CTSU mailout once this number has been met.

b. 128 Hertz Tuning Fork Information

Neuropathy evaluation is to be performed by a clinician certified to perform the testing. A clinician can be certified to perform 128 Hz tuning fork testing by completing the following steps below.

First, the clinician must review the detailed instructions on how to perform the testing included below and the instructional video for the 128 Hz tuning fork, which is available on the protocol abstract page of the SWOG website (www.swog.org) and the CTSU website (www.ctsu.org). Once the clinician has reviewed the instructions below and the instructional video, the clinician must complete a training verification available on the protocol abstract page of the SWOG website (www.swog.org) and the verification must be submitted via CTSU (see Section 13.2b.3).

Second, the clinician must be observed demonstrating proficiency in using the 128 Hz tuning fork. This can be done in one of 2 ways: 1) in-person observation at a bi-annual SWOG meeting, or 2) observation via video-conference. One of the study chairs or the clinical nurse coordinator will be responsible for assessing the proficiency demonstration. Observation via video-conference may be arranged by e-mailing S1714@swog.org. Once the clinician has been observed performing 128 Hz tuning fork testing, he/she will obtain a certificate of training via email from the SWOG Operations Office which must be submitted via CTSU Regulatory Portal (see Section 13.2b.3).

All clinicians who will perform 128 Hz tuning fork assessments must submit certification of training. Any questions regarding the use of the 128 Hz tuning fork can be directed to the Clinical Nurse Coordinator for the study.

The 128 Hz tuning fork will be used to assess vibration sensation in the dominant upper extremity and dominant lower extremity. Results of this assessment will be submitted via the **S1714** Neuropathy Assessment Form. Assessment will occur at

baseline prior to start of chemotherapy, then at 4 weeks, 8 weeks, and 12 weeks (± 14 days), and at 24 weeks and 52 weeks (± 28 days) as outlined in Section 9.0. Efforts should be made to perform the 4-week, 8-week, and 12-week assessments on a day of taxane-treatment that falls within the study window period and prior to taxane administration. The 128 Hertz tuning fork assessment will take about 5 minutes to complete.

c. Instructions for Dominant Lower Extremity Vibration Sensation Testing

1. The tuning fork should be firmly tapped on the palm of the hand of the clinician to initiate vibration.

2. The vibrating tuning fork is first placed on the interphalangeal joint of the great toe of the dominant foot (Figure 7.2 [2a] below). The dominant foot can be identified by asking the subject with which foot they would kick a ball. A timer is started once the vibrating tuning fork is placed on the interphalangeal joint of the great toe of the dominant foot.

3. The patient is instructed to report when vibration is no longer detected. The time at which the vibration is no longer detected should be noted.

4. If the patient feels the vibration for 15 seconds or longer, this is defined as normal and should be recorded as such. If vibration sensation is normal at the great toe, additional assessments of the lower extremity are not needed.

5. If vibration sensation in the great toe of the dominant foot is less than 15 seconds, this is defined as absent or decreased vibration sensation and should be recorded as such. If vibration sensation is absent or decreased in the interphalangeal joint of the great toe of the dominant foot, the clinician then conducts the testing at all additional sites listed below on the dominant side. For each site tested, the tuning fork should be firmly tapped on the palm of the hand of the clinician to initiate vibration and the vibrating tuning fork is placed on the site. Once the vibrating tuning fork is placed on the testing site, a timer is started to measure the time at which the vibration is no longer detected. This time should be noted for each site.

    a. The middorsal foot (Figure 7.2 [2b]): If the patient feels the vibration for 15 seconds or longer, this is defined as normal. If the patient feels the vibration less than 15 seconds, this is defined as absent or decreased vibration sensation.

    b. The medial malleolus (ankle) (Figure 7.2 [2c]): If the patient feels the vibration for 15 seconds or longer, this is defined as normal. If the patient feels the vibration less than 15 seconds, this is defined as abnormal.

    c. The midfibular region of the dominant lower extremity (Figure 7.2 [2d]): If the patient feels the vibration for 15 seconds or longer, this is defined as normal. If the patient feels the vibration less than 15 seconds, this is defined as absent or decreased vibration sensation.

    d. The patellar region of the dominant lower extremity (Figure 7.2 [2e]): If the patient feels the vibration for 10 seconds or longer, this is defined as normal. If the patient feels the vibration less than 10 seconds, this is defined as absent or decreased vibration sensation.

Figure 7.2: Sites of lower extremity vibration sensation testing *(73)*

Note: The tuning fork is firmly tapped on the palm and then placed on the interphalangeal joint of the great toe (2a). If vibration sensation is diminished or absent in the great toe, testing should be performed at the middorsal foot (2b) and the medial malleolus (2c), followed by the midfibular (2d) and patellar (2e) regions.

d. Dominant upper extremity vibration sensation testing

1. The clinician will conduct the testing at all three sites below on the dominant upper extremity. The dominant upper extremity can be identified by asking the subject with which hand they write.

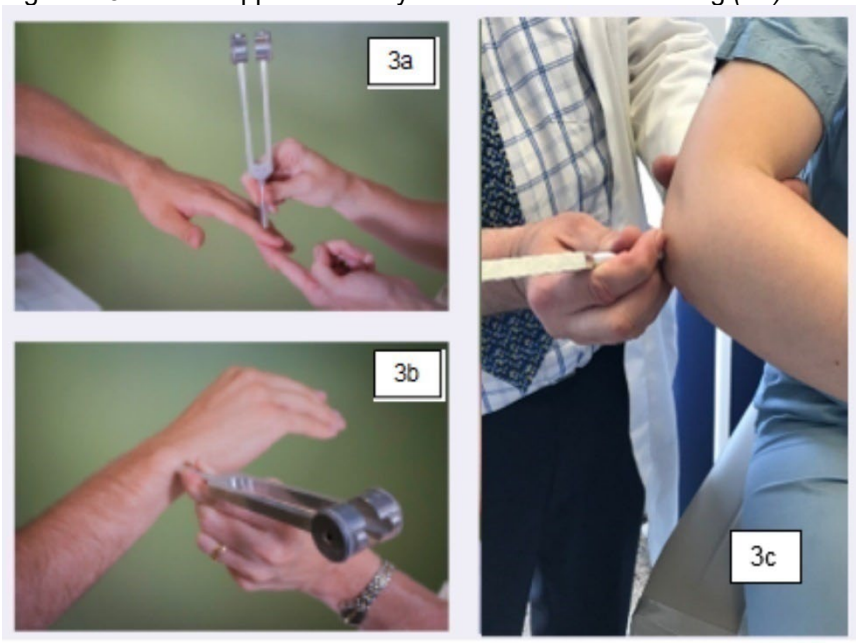
2. For each site tested, the tuning fork should be firmly tapped on the palm of the hand of the clinician to initiate vibration and the vibrating tuning fork is placed on the site. Once the vibrating tuning fork is placed on the testing site, a timer is started to measure the time at which the vibration is no longer detected. This time should be noted for each site. The three sites to be tested on the dominant upper extremity vibrating tuning fork are:

   a. The distal interphalangeal joint of the index finger (Figure 7.3 [3a]): If the patient feels the vibration for 25 seconds or longer, this is defined as normal. If the patient feels the vibration less than 25 seconds, this is defined as absent or decreased vibration sensation. Regardless of sensation at site (a), all three upper extremity sites will be tested.

b. The ulnar styloid (wrist) (Figure 7.3 [3b]): If the patient feels the vibration for 15 seconds or longer, this is defined as normal. If the patient feels the vibration less than 15 seconds, this is defined as absent or decreased vibration sensation.

c. The lateral epicondyle (elbow) (Figure 7.3 [3c]): If the patient feels the vibration for 15 seconds or longer, this is defined as normal. If the patient feels the vibration less than 15 seconds, this is defined as absent or decreased vibration sensation.

Figure 7.3 Sites of upper extremity vibration sensation testing *(74)*



Note: The tuning fork is firmly tapped on the palm and then placed at the distal interphalangeal joint of the index finger (3a), the ulnar styloid (3b), and the lateral epicondyle (3c).

7.8 Timed Get Up and Go *(75)*

The 'Timed Get Up and Go' test is a simple, quick, and widely used clinical performance-based measure of lower extremity function, mobility, and fall risk. Subjects are asked to stand up from a standard chair (seat height between 44 and 47 cm), walk a distance of 3 meters (marked on the floor) at a comfortable pace, turn, walk back and sit down. Subjects are permitted to use routine walking aids and are instructed not to use their arms to stand up. No physical assistance is given. The time to complete the task is measured with a stopwatch to the tenth of a second. Timing commences on the command 'go' and stops when the subject's back is positioned against the back of the chair after sitting down. Shorter times indicate better performance. Patients who are wheelchair-bound will not be required to complete this assessment. Training on this test is available online (https://www.youtube.com/watch?v=grrYoBucNPE) and any questions can be directed to the Clinical Nurse Coordinator of the study. Once the CRA has viewed the online training video, the CRA must also complete a training verification available on the protocol abstract page of the SWOG website (www.swog.org) and the verification must be submitted via CTSU (see Section 13.2b.3). All CRAs who will be performing this assessment must submit verification of training. The training certificate may be obtained from the **S1714** protocol abstract page on the SWOG website. Click "Required **S1714** Training," complete the required information certifying that you have successfully completed the training and click "Submit." The website will generate a confirmation. At the end of the confirmation

page, click “Print Confirmation.” The printed confirmation serves as the certificate of completion which must be submitted via CTSU Regulatory Portal (see Section 13.2b.3).

Results of this assessment will be reported on the **S1714** Neuropathy Assessment form. Assessments will occur at baseline, 24 weeks, and 52 weeks as outlined in Section 9.0. The Timed Get Up and Go assessment will take about 5-10 minutes to complete.

At the time of Timed Get Up and Go assessments at 24 weeks and 52 weeks, a history of falls within the past 6 months will also be collected on the **S1714** Neuropathy Assessment Form.

7.9 Research Biospecimens

Study assessments will include mandatory specimen submission of translational research biospecimens and optional specimen submission for banking for future research as outlined in Section 15.1.

7.10 Criteria for Removal from Protocol Participation

a. Patient completes 156 weeks (3 years) of protocol participation.*

b. Patient does not receive at least one cycle of taxane-containing chemotherapy within 30 days after registration.

c. Patient receives another chemotherapy regimen and does not receive at least one cycle of one of the study-approved taxane regimens included in Appendix 18.1.

d. The patient may withdraw from the study at any time for any reason. (Research staff should only submit the **S1714** Off Protocol Notice if the patient refuses both direct and indirect follow-up (e.g., follow-up for vital status via medical records or contact with the patient’s physician) on the study. If the patient allows for indirect follow-up or is refusing to complete any further patient forms but will allow the site to follow them indirectly, do not submit the **S1714** Off Protocol Notice and continue to submit the site-completed forms (**S1714** Treatment Form or **S1714** Off Treatment Follow-up Form, as appropriate, and **S1714** Solicited Neuropathy Events Form at the time points required as outlined in Section 14.4c.

e. Patient has disease progression or relapse after the 52-week assessment. A patient’s disease progression or relapse prior to 52-week assessment does not necessitate removal from protocol participation.

f. Patient death

* NOTE: A patient’s completion or discontinuation of taxane-based chemotherapy does not necessitate removal from protocol participation, if prior to completion of 156 weeks (3 years) of protocol participation. Patients should continue to have their protocol-scheduled assessments and submit their protocol-scheduled Patient Reported Outcomes (see Section 7.5) until one of the outlined criteria for removal listed in Section 7.10 has been met.

7.11 Discontinuation of Protocol Participation

All reasons for discontinuation of protocol participation as defined in Section 7.10, including patient death, must be documented in the **S1714** Off Protocol Notice and submitted per Section 14.4d.

7.12 Follow-Up Period

No further follow-up will be required once the patient completes 156 weeks (3 years) of protocol participation, or if the patient meets one of the criteria for removal from protocol participation outlined in Section 7.10 prior to completion of 156 weeks (3 years) of participation and the **S1714** Off Protocol Notice is submitted.

NOTE: Sites must continue to follow all patients per study requirements even if the patient completed or discontinued taxane-based chemotherapy prior to completion of 156 weeks (3 years) of protocol participation (see Section 7.10a). Patients should continue to have their protocol-scheduled assessments until one of the outlined criteria for removal listed in Section 7.10 has been met.

7.13 COVID-19 Guidance

Patient-Reported Outcome Questionnaires via Telemedicine (Phone or Virtual Visit).

Follow-up Visits via Telemedicine (Phone or Virtual Visit):

- Follow-up visits at timepoints indicated in Section 9.0, may be conducted via telemedicine (Phone or Virtual Visit) to provide continuity of care and patient follow-up provided that the Responsible Investigator determines that the phone/virtual visit is adequate to achieve the central purpose of the visit and assure the safety of the patient.
- Study visits may also be delayed or missed if in the judgment of the Responsible Investigator the benefit of delay/omission of a visit outweighs the risks of exposure of the patient to the virus by coming in for an in-person visit and an alternative method (phone or virtual visit) is not possible.
- The above alterations would need to be thoroughly documented in the medical record by the Responsible Investigator with the reason for the deviation and brief justification for why the deviation was considered to be minor (e.g., routine follow-up on patient no longer on active therapy).

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

Toxicity monitoring and dose modifications are not relevant to this study, (but will be collected per Section 7.3) and occurrence of neuropathy-related events will be collected using CTCAE v. 5.0.

9.0 STUDY CALENDAR

REQUIRED	Registration	1st Taxane Cycle [C]	WK 4 [A]	WK 8 [A]	WK 12 [A]	WK 24 [A]	WK 52 [A]	WK 104[A]	WK 156 [A]
TESTS/ASSESSMENTS									
History	X								
Chemotherapy Treatment Schedule	X		X	X	X	X	X	X	X
Active Topical Agents, Medications, Supplements, and Interventions	X		X	X	X	X	X		
Visual Analog Toxicity Score [G]	X		X	X	X	X	X		
NCI-CTCAE [H]	X		X	X	X	X	X	X	X
Serum Creatinine or Creatinine Clearance [E]	X								
History of Falls Assessment	X					X	X		
SENSORY TESTS									
Neuropen (Monofilament and Neurotip) [F]	X		X	X	X	X	X		
128 Hertz Tuning Fork [F]	X		X	X	X	X	X		
FUNCTIONAL TEST									
Timed Get Up and Go	X					X	X		
PATIENT REPORTED OUTCOMES (PROs) [G,H]									
CIPN-20	X		X	X	X	X	X	X	X
PROMIS-29	X		X	X	X	X	X		
Symptom (and Side Effect) Burden Score	X		X	X	X	X	X		
Godin-Shephard Leisure-Time Physical Activity Questionnaire (GSLTPAQ)	X		X	X	X	X	X		
PRO-CTCAE	X		X	X	X	X	X	X	X
FACT-GOG-NTX-4	X				X	X	X	X	X
SPECIMEN SUBMISSION									
Blood (Lavender Top EDTA – Whole Blood for DNA) [D]	X								
Blood (Lavender Top EDTA– Plasma for Taxane Maximum Concentration [C_{max}]) [D]		X [C]							
Blood (Red Top no additive – Serum for Proteomics) [B]	X	X [C]	X	X	X	X	X		
Blood (Green Top sodium heparin – Plasma for Metabolomics) [B]	X	X [C]	X	X	X	X	X		

Click here for footnotes.

NOTE: the study calendar is a good tool for a general snapshot of study requirements but does not replace details provided in the relevant sections of the protocol. Use the study calendar in conjunction with the detailed procedures and information in the protocol but not as the sole or primary source for managing this trial.

NOTE: Forms are found on the protocol abstract page on the SWOG website (www.swog.org) and on the CTSU website (www.ctsu.org). Forms submission guidelines are found in Section 14.0.

NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in https://www.swog.org/protocol-workbench.

Footnotes for Calendar 9.1

A Study assessments, sensory tests, functional test, PROs, physician assessments, and specimen submissions should be attempted to be obtained on the same day as a taxane-based chemotherapy treatment that falls within ± 14 days of Weeks 4, 8, and 12, within ± 28 days of Weeks 24 and 52, and within ± 90 days 104 (2 years) and 156 (3 years) and prior to taxane administration.
B Optional research biospecimen: The optional research biospecimens should be attempted to be obtained during a clinical blood drawn that occurs within the allowed visit window for each timepoint. See Section 15.1.
C Draw specimen during the last 10 minutes of infusion of the cycle of taxane-based chemotherapy (see Section 15.1c.2). NOTE: Blood (Lavender Top EDTA– Plasma for Taxane Maximum Concentration [C_{max}]) can be collected in the last 10 minutes of any cycle if it is missed with the first cycle.
D The lavender top for DNA and lavender top for C_{max} submissions are mandatory (see Section 15.0).
E To be collected either 1) within 30 days prior to registration, OR 2) after registration but prior to start of taxane-based chemotherapy per Section 7.1.
F Sensory tests may only be performed by the site's certified clinician(s). Refer to Sections 7.6b and 7.7b for instructions on obtaining certification
G See Section 7.5.
H See Appendix 18.5.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 Primary Endpoint

Development of peripheral neuropathy: an absolute increase of ≥ 8 points over the baseline CIPN-20 sensory neuropathy subscale score (Appendix 18.4; scale 0-100) before or at 24-week assessment (occurring during the 24 weeks +/- 28 days window).

The primary endpoint will be collected before or at the 24-week assessment as the taxane-based chemotherapy regimens in this study are expected to be completed within 8 to 18 weeks. Thus, it is anticipated that those participants who are going to develop clinically significant CIPN would develop symptoms while receiving treatment. The presence of CIPN will be captured at 104 and 156 weeks (3 years) to evaluate the duration of neuropathy which is anticipated to wane after treatment discontinuation.

Multiple studies in the literature indicate that patients with CIPN experience approximately a 7 to 10-point increase in the CIPN-20 sensory neuropathy subscale score. For instance, Smith *et al.* showed that those not receiving neurotoxic therapy had a CIPN-20 sensory subscale score of around 10, whereas those who did had a score of around 20, *(76)* while Floortje Mols *et al.* showed an increase from 8 to 15. *(77)* Finally, Cavaletti *et al.* reinforce the idea that a mean score of about 20 on the 0-100 sensory subscale is reasonable for those with CIPN. *(78)* Thus, a reasonable indication of a meaningful increase in the CIPN-20 would be an absolute increase of ≥ 8 points. Based on these considerations, patients having an absolute increase of ≥ 8 points over the baseline sensory neuropathy subscale score (scale 0-100) at the 4, 8, 12, or 24-week assessment will be defined as having experienced CIPN for the purposes of this study. The 24-week assessment cannot be measured later than 28 weeks (24 weeks +/- 28 day window)

10.2 Secondary Endpoints

Patients experiencing a treatment change attributed to CIPN symptoms will be considered to have reached the corresponding secondary endpoint.

Dose reductions, delays, and discontinuations of treatment (prior to completing the original treatment plan) will be collected during follow-up visits. Definitions of these treatment changes can be found in Section 7.3. Study sites will be asked to classify the reasons for these changes (i.e., CIPN symptoms, neutropenia, patient preference, progression of disease).

Other patient and physician reported outcomes including the Patient-Reported Outcomes Measurement Information System 29 (PROMIS-29; Section 18.5b), the Godin-Shephard Leisure-Time Physical Activity Questionnaire (GSLTPAQ; Section 18.5c), Visual Analog Toxicity Score and Symptom Burden Score (Section 18.5d), PRO-CTCAE items for severity of numbness and tingling and interference caused by numbness and tingling (Section 18.5e), and the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grading Scale (Section 18.5f).

10.3 Performance Status

Patients will be graded according to the Zubrod performance status scale.

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

11.0 STATISTICAL CONSIDERATIONS

11.1 CIPN Predictors and Risk Factors

Previous studies have described a variety of clinical, biologic, and treatment-related factors implicated in the development of CIPN. In this study, clinical and treatment-related factors potentially predictive of CIPN will be investigated in order to identify the strongest predictors. The primary objective is to develop and validate a clinical risk prediction model for CIPN. This model will enable rapid identification of patient risk of developing CIPN for individuals treated with taxane-based therapy using common factors obtained during clinical exams, aiding in timely care decision-making. The clinical factors (including treatment factors) to be considered in the risk prediction model are shown in Table 11.1.

Table 11.1. Clinical factors to be incorporated in the risk prediction model

Clinical factor	Scale
Demographics	Age in years (continuous) Sex: Male/Female (dichotomous) Race: White/Black/Asian/Other (categorical) Ethnicity: Hispanic/Non-Hispanic (categorical)
Baseline co-morbid conditions	Diabetes: yes/no (dichotomous) Thyroid disease: yes/no (dichotomous) Vitamin B12 deficiency*: yes/no (dichotomous) Autoimmune disease: yes/no (dichotomous) Vitamin D deficiency ***: yes/no (dichotomous) Neurological condition: yes/no (dichotomous) Pre-existing neuropathy as evaluated by baseline CIPN20 sensory subscale score (continuous) Creatinine clearance < 30 mL/min: yes/no (dichotomous) Zubrod performance status: 0-4 (categorical)
Falls history	History of falls** within past 6 months: yes/no (dichotomous), assessed at baseline
Smoking history	Never smoker/Former smoker/Active smoker (categorical) Number of pack years (continuous)
Oncologic history	Malignancy: Breast/Lung/Ovary/Fallopian tube/ peritoneal (categorical) Prognostic stage at diagnosis: I/II/III (categorical)
Treatment factors	Taxane: paclitaxel/docetaxel (dichotomous) Planned Frequency: weekly/biweekly/triweekly (categorical) Planned taxane dosing: full dose/reduced dose (dichotomous) Planned use of platinum agent: yes/no (dichotomous); if yes: full dose/reduced dose (dichotomous) Concurrent radiation: yes/no

* Defined as requiring B12 repletion (patient reported)

** Defined as unintentionally coming to rest on the ground or at some other lower level, not as a result of a major intrinsic event (*e.g.*, stroke or syncope) or an overwhelming hazard. The patient will be asked if he/she has had been any falls in the past 6 months

*** Defined as requiring vitamin D supplements ≥ 50,000 IU per week (patient-reported).

A two-step approach will be used. In Step 1, factors that are independently predictive of CIPN will be identified, from which a candidate model will be built. In Step 2, the investigators will undertake independent validation of the model. Each step will be considered a separate experiment and independently powered. Multiplicity will be handled by the validation set. As secondary analysis, the investigators will consider the joint distribution of the different endpoints to adjust the alpha.

11.2 Sample Size and Analysis Plan

Assuming 5% ineligibility rate, the sample size will be N = 1,310 to accrue 1,245 eligible patients. The goal is to establish accurate prediction of CIPN among important and commonly used taxane treatments. The goal is to enroll at least 500 docetaxel and paclitaxel patients to each group; based on a feasibility/enrollment assessment conducted in April, 2021, this goal is expected to be met with the total sample size. This design will ensure a large enough population of docetaxel and paclitaxel users to model CIPN in those groups. Further, the investigators plan to cap accrual of lung cancer patients at 250 to ensure variability in dose and frequency among paclitaxel users. Accrual of 35-50 patients per month is estimated for a total accrual time of 35 months. Data from 60% of eligible patients, or n=745 (stratified by primary cancer type and taxane regimen) will be randomly used to develop the model in Step 1. Potential risk factors (Table 11.1) using the prospectively

collected baseline data will be evaluated in univariate fashion, and rank ordered according to their chi-square statistic under logistic regression. As an illustration of power to identify a statistically significant univariate predictor of CIPN with 600 patients and using 2-sided alpha=.05 tests under a two-arm binomial design (without continuity correction), there will be sufficient power (>=85%) to identify an absolute 10% difference in CIPN rates between equal numbers of low and high-risk patients for each factor, for CIPN rates up to 30% (i.e., 25% vs. 35% if the overall CIPN rate is 30%). (Low risk patients are defined as those having a risk score below the median [based on individual values on the predictors chosen in the model]; high risk patients are defined as those having a risk score above the median.)

Best subset selection will be used to identify a best k-variable model from among the factors most predictive of CIPN in univariate examinations. *(79)* Model building will be based on logistic regression to simplify identification and interpretation of adverse risk within each individual factor. The goal is to minimize the predictive error (*i.e.,* logistic model deviance) across a range of k-variable models. K-fold cross validation of the entire model building approach, including the identification of univariate predictors for inclusion in best-subset selection analysis, will be used to limit overfitting and provide insight into how the model will generalize in Step 2. *(80)* This will allow identification of optimal models when choosing between models with different numbers of factors, for instance a 4-variable vs. 5-variable model, as well as for choosing between models which are not nested. Once a best model is identified, a risk model will be built, by summing the number of adverse risk factors from among the k-variables in the best model to create a score, split at the median to identify high vs. low risk patients. The use of K-fold cross validation of the model building process also enables evaluation of different modeling techniques to assess sensitivity to the chosen analytic approach, for instance Lasso. *(81)*

Before a risk-prediction model can be used in clinical practice it is essential to validate it in an independent study. Risk models that have not been validated but implemented into clinical care can lead to potential harm if the model is over- or under-predicting risk. Thus, in Step 2 the investigators would test the k-variable risk model identified in Step 1. The risk model from Step 1 will be tested in the remaining 500 patients. This sample size is sufficient to identify an absolute difference of 12% in CIPN rates for high vs. low risk patients for CIPN rates up to 30%, with > 90% power using a one-sided binomial test with alpha=.05.

If a difference of this magnitude is not achieved in the validation step, this will indicate that this experiment failed to differentiate risk under the protocol design, and will suggest the difficulty of predicting CIPN based on clinical factors alone. In this scenario, future analyses using biological factors to characterize CIPN risk will gain added importance.

To avoid dropping variables or samples in risk modeling, in which all variables are considered simultaneously, each variable needs to be available for all samples and in all studies. Although completeness of data submission is encouraged by prospective data collection, in combination with SWOG SDMC's data Expectation system and the Rave Data Quality Portal (DQP) both of which identify data delinquencies, even small numbers of missing can lead to sizable loss of data when multiple variables are modeled together. Therefore, missing data will be imputed in Step 2. Resampling will be used to acknowledge the sampling error on the test sample, and cross validation will be used in the model building process to select model complexity.

The investigators will examine whether the clinical risk model can predict the other outcomes collected in the study (Table 11.2), to assess whether the experience of CIPN reflects a more comprehensive patient symptom experience that includes both subjective measures of outcome – based on PRO data – and objective measures of neuropathy symptoms. To accomplish this, we will consider the derived clinical risk model as the main independent variable in a multivariable regression model that also incorporates the baseline score for the respective outcome as a covariate. Linear (Timed Get Up and Go and PROMIS 29 and its subscales) and logistic (diminished touch and pressure sensation

according to the Neuropen, GSLTPAQ, and PRO-CTCAE [moderate or worse, yes vs. no]) regressions will be used as appropriate to assess whether the model predicts outcomes at individual timepoints *(i.e.* 4 weeks, 8 weeks, etc.). We will also conduct linear mixed models with continuous and binary outcomes, as appropriate, to examine trajectories of outcomes over time, with patient as the random effect. Vibration sensibility according to the tuning fork will be examined both as a continuous variable and as a binary categorical variable based on an optimal splitpoint to maximize power (*i.e.* splitpoint closest to the median) using observed distributions.

The correlation between the secondary outcome measures and neuropathy as measured by the CIPN20 will also be described to aid in the interpretation of the neuropathy phenotype. This analysis will allow better characterization and definition of the taxane-induced peripheral neuropathy phenotype.

Table 11.2. Outcome measures

Outcome	**Scale**	**Follow-Up Assessment Times (in weeks)**
Neuropen	Diminished touch and pressure sensation (yes/no) Diminished pain and sharpness sensation (yes/no)	4, 8, 12, 24, 52
128 Hertz tuning fork	Vibration sensibility (categorical, 0-4)	4, 8, 12, 24, 52
Timed Get Up and Go	Continuous scale (seconds)	24, 52
PROMIS-29	Physical function (continuous, 4-20) Anxiety (continuous, 4-20) Depression (continuous, 4-20) Fatigue (continuous, 4-20) Sleep disturbance (continuous, 4-20) Ability to participate in social roles and activities (continuous, 4-20) Pain interference (continuous, 4-20) Pain intensity (continuous, 0-10)	4, 8, 12, 24, 52
GSLTPAQ	Active (yes/no)	4, 8, 12, 24, 52
PRO-CTCAE	Numbness and tingling, severity (none, mild, moderate, severe, very severe) Numbness and tingling, interference (not at all, a little bit, somewhat, quite a bit, very much) General pain, frequency (never, rarely, occasionally, frequently, almost constantly) General pain, severity (none, mild, moderate, severe, very severe) General pain, interference (not at all, a little bit, somewhat, quite a bit, very much)	4, 8, 12, 24, 52, 104, 156
FACT-GOG-NTX-4	Neurotoxicity (continuous, 0-16)	12, 24, 52, 104,156

* All measures are collected at baseline.

The investigators will further examine whether the clinical risk model predict treatment dose reductions, delays, discontinuations, and treatment changes associated with CIPN symptoms.

The incidence of CIPN within one year as measured by the CIPN-20 will be assessed in all 1245 eligible enrolled patients. Using a test of proportions without continuity correction, a sample size of 1245 will allow us to estimate the confidence interval to within ± 3.1%, or in proportion to the assumed incidence, to within ± 6.2% (based on the upper bound of 95% confidence interval – the "relative accuracy"), if the incidence of CIPN is 50% and the dropout rate at year 1 is 20%. The relative accuracy will improve with higher incidence, as shown in Table 11.3 below. These estimates are conservative as they are based on the assumption of no information from the 20% of patients estimated to drop out. The cumulative incidence of CIPN at 1, 2, and 3 years will also be estimated to account for censoring and the competing risk of death. Conservative estimates of the confidence interval (as calculated from the exact binomial in patients with complete follow-up) are shown in Table 11.3 for different rates of assumed incidence of CIPN.

Table 11.3. Table of relative accuracy

Assumed incidence	95% confidence interval about p	Relative accuracy [(95% CI upper bound – p)/p]
20%	17.6%-22.6%	13.0%
30%	27.2%-32.9%	9.7%
40%	37.0%-43.1%	7.7%
50%	46.9%-53.1%	6.2%

To examine the applicability of the derived clinical risk prediction model in important patient groups, rather than build separate models for each meaningful marginal subset, our plan is to build the model using the entire data set. The investigators will then examine the extent to which the model meaningfully predicts development of CIPN within subgroups to see if the risk prediction model will hold. Important potential subsets of patients are defined by pre-existing CIPN (yes vs. no), age (< 65 vs. ≥ 65), sex, race (black vs. other), and treatment groups (i.e., paclitaxel versus docetaxel). For each factor, the investigators will examine whether the relationship between the clinical risk model and CIPN20 differs by levels of the factor (*i.e.*, blacks vs. non-blacks) using interaction tests. The absence of any interactions will suggest no statistical evidence that the clinical risk model performance differed substantially based on these factors. If a statistically significant interaction is evident ($p < 0.05$), examinations separately within subgroups will be conducted to enable interpretation of the observed differences by subgroup.

11.3 Data and Safety Monitoring Committee

There is no formal data and safety monitoring committee for this study. Monitoring of study conduct and accrual for feasibility will be performed routinely by the Study Chair, Study Statistician, and the Disease Committee Chair. Accrual reports will be generated monthly.

12.0 DISCIPLINE REVIEW

There is no discipline review for this study.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patients must be registered no more than 14 calendar days prior to planned start of treatment with a taxane-containing regimen.

13.2 Investigator/Site Registration

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet to CTEP.

a. CTEP Registration Procedures

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain Cancer Therapy Evaluation Program (CTEP) credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes four person registration types that are applicable to this study.

- Investigator (IVR) — MD, DO, or international equivalent;
- Non Physician Investigator (NPIVR) — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- Associate Plus (AP) — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials.

RCR requires the following registration documents:

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

IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites in RCR to allow the following:

- Addition to a site roster;
- Selection as the treating, credit, or consenting person in OPEN;
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting or treating investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Refer to the NCI RCR page on the CTEP website for additional information. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

b. CTSU Registration Procedures

Permission to view and download this protocol and its supporting documents is restricted and is based on the person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the Cancer Trials Support Unit (CTSU) members' website.

This study is supported by the NCI CTSU.

1. **IRB Approval:**

As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (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. 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 through the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context 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 email (CTSURegPref@ctsu.coccg.org) or by 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 for

the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Have an active CTEP status;
- Have an active status at the site(s) on the IRB/REB approval (applies to US and Canadian sites only) on at least one participating organization's roster;
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

2. **Additional Requirements**

Additional site 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);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all protocol-specific requirements (PSRs).

3. **Downloading Site Registration Documents:**

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 to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website (https://www.ctsu.org);
- Click on *Protocols* in the upper left of the screen
    - Enter the protocol number in the search field at the top of the protocol tree; or
    - Click on the By Lead Organization folder to expand, then select **SWOG**, and protocol number **S1714**.
- Click on *Documents*, *Protocol Related Documents*, and use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4. **Requirements for S1714 Site Registration:**

- CTSU Transmittal Sheet (optional)
- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/ Declaration of Exemption Form, or combination is accepted)

Sites must complete the following Protocol Specific Requirements (PSRs) prior to patient registration and submit the certificates and verifications to

CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

- Certificate that at least one clinician at the site has completed the Neuropen training outlined in Section 7.6.
- Certificate that at least one clinician at the site has completed the 128 Hertz tuning fork training outlined in Section 7.7.
- Verification that at least one CRA at the site has completed the 'Timed Get Up and Go' training outlined in Section 7.8

In addition, sites must also have ordered and received both the Neuropen and 128 Hertz tuning fork prior to consenting a patient to the study.

5. **Submitting Regulatory Documents:**

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the *Regulatory* section and select *Regulatory Submission*.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support.

6. **Checking Your Site's Registration Status:**

Site registration status may be verified on the CTSU members' website.

-
- Click on Regulatory at the top of your screen;
- Click on Site Registration; and
- Enter the sites 5-character CTEP Institution Code and click on Go:
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. 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.

13.3 OPEN Registration Requirements

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 LPOs' registration/randomization systems or the 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:

- ;
- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the Institutional Review Board (IRB) number used on the site's IRB approval on their Form Food and Drug Administration (FDA) 1572 in the Registration and Credential Repository (RCR). If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

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

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may 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 in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

13.4 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and the CTSU website (www.ctsu.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see below for details.

14.3 Data Submission / Data Reporting Procedures

a. Medidata Rave is the 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.

Requirements to access Rave via IMedidata:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;

  and

- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only or Rave SLA role must have at a minimum an Associate (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. No action will be required; each study invitation will be automatically accepted and study access in Rave will be automatically granted. Site staff 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 eLearning link in the Tasks pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the Studies pane located in the center of the iMedidata screen; 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 replace the eLearning link under the study name.

Action will be required by site staff (to activate their account) who have not previously activated their iMedidata/Rave account at the time of initial site

registration approval for the study in the Regulatory application. Account activation instructions are located on the CTSU website in the Data Management section under the Data Management Help Topics > Rave Resources > Medidata Account Activation and Study Invitation (to activate your iMedidata account). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management Rave Resources section or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

b. Data Quality Portal

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, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status, and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms..

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available in the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

To learn more about DQP use and access, click on the Help Topics button displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

14.4 Data Submission Overview and Timepoints

a. WITHIN 15 DAYS OF REGISTRATION:

Collect baseline specimens as outlined in Section 15.0.

Submit the following:

S1714 Onstudy Form

S1714 Baseline Tumor Description (Breast, Lung, or Ovarian/Fallopian/Peritoneal tube, as applicable)

S1714 Supplements, Topical Agents, and Other Treatments

S1714 Baseline Physician CTCAE Assessment

S1714 Neuropathy Assessment

S1714 Cover Sheet for Patient-Completed Questionnaires

S1714 EORTC QLQ-CIPN20

S1714 Patient-Reported Outcomes Measurement Information System 29 (PROMIS-29)

S1714 Baseline Patient Reported Symptom Burden

S1714 Godin-Shephard Leisure-Time Physical Activity Questionnaire

S1714 PRO-CTCAE

S1714 FACT-GOG-NTX-4

Upload source documentation in Rave necessary to support diagnosis of primary Breast, Lung, or Ovarian/Fallopian tube/ Peritoneal cancer and establish stage (I, II, or III) (e.g., pathology report, radiology reports), if available.

b. DURING THE LAST 10 MINUTES OF THE FIRST TAXANE INFUSION:

Collect specimens as outlined in Section 15.0.

c. WITHIN 15 DAYS OF ASSESSMENTS AT 4 WEEKS (± 14 DAYS), 8 WEEKS (± 14 DAYS), 12 WEEKS (± 14 DAYS), 24 WEEKS (± 28 DAYS) AND 52 WEEKS (± 28 DAYS):

NOTE: Assessments should be scheduled so that patient-completed forms can be completed on the same day (and prior to) taxane-containing chemotherapy treatment (if applicable).

Collect follow-up specimens as outlined in Section 15.0.

Submit the following:

S1714 Treatment Form (if patient's taxane treatment was not previously indicated complete).

S1714 Off Treatment Follow-up Form (if patient's taxane treatment was previously indicated complete).

S1714 Supplements, Topical Agents, and Other Treatments

S1714 Solicited Neuropathy Events Form

S1714 Follow-Up Physician Assessment

S1714 Neuropathy Assessment

S1714 Cover Sheet for Patient-Completed Forms

S1714 EORTC QLQ-CIPN20

S1714 Patient-Reported Outcomes Measurement Information System 29 (PROMIS-29)

S1714 Follow-up Patient Reported Symptom and Side Effect Burden Questionnaire

S1714 Godin-Shephard Leisure-Time Physical Activity Questionnaire (GSLTPAQ)

S1714 PRO-CTCAE

S1714 FACT-GOG-NTX-4 (12, 24, and 52 weeks only)

d. WITHIN 15 DAYS OF ASSESSMENTS AT 104 WEEKS (2 YEARS, ± 90 DAYS), AND 156 WEEKS (3 YEARS, ± 90 DAYS) :

S1714 Solicited Neuropathy Event

S1714 EORTC QLQ-CIPN20

S1714 PRO-CTCAE

S1714 FACT-GOG-NTX-4

S1714 Off Treatment Follow-up Form (if patient's taxane treatment was previously indicated complete).

e. WITHIN 15 DAYS AFTER DISCONTINUATION OF PROTOCOL PARTICIPATION:

Submit the following:

S1714 Off Protocol Notice

f. WITHIN 30 DAYS OF KNOWLEDGE OF DEATH:

Submit the Notice of Death and **S1714** Off Protocol Notice documenting death information.

15.0 SPECIAL INSTRUCTIONS

M = Mandatory; Opt = Optional

Specimen	Baseline	End of 1st Taxane Cycle	Wk 4	Wk 8	Wk 12	Wk 24	Wk 52
Blood (**Lavender Top EDTA** – Whole Blood for DNA) *	**M**		N/A	N/A	N/A	N/A	N/A
Blood (**Lavender Top** EDTA– Plasma for Taxane Maximum Concentration [C_{max}]) *		**M**	N/A	N/A	N/A	N/A	N/A
Blood (**Red Top** no additive – Serum for Proteomics)	Opt	Opt	Opt	Opt	Opt	Opt	Opt
Blood (**Green Top** sodium heparin – Plasma for Metabolomics)	Opt	Opt	Opt	Opt	Opt	Opt	Opt

***International site please follow EDTA blood processing instruction in Section 15.1h.**

15.1 Translational Medicine (REQUIRED) and Banking (OPTIONAL FOR PATIENT)

Specimens for translational medicine and banking (submitted to the SWOG Biospecimen Bank – Solid Tissue, Myeloma and Lymphoma Division, Lab #201).

a. Collection instructions are outlined in Section 15.1c and submission instructions are outlined in Section 15.1e.

b. With patient's consent, specimens must be collected at the time points listed below. It is recommended that the optional banking specimens be collected at the time of a clinical blood draw in order to minimize blood draws in the subject.

1. Baseline (within 14 days after registration), prior to taxane treatment

2. First Taxane Cycle During Last 10 minutes of infusion

3. Follow Up (Prior to infusion or pre-medication at 4 Weeks (± 14 days), 8 Weeks (± 14 days), 12 Weeks (± 14 days), 24 Weeks (± 28 days), and 52 Weeks (± 28 days) after beginning taxane-based chemotherapy.)

c. Specimen Collection and Processing Instructions

Note that specimen processing outlined below is to be performed at the site prior to storage and shipping.

1. Baseline:

Tubes for Collection

Three (3) 10-mL tubes of whole blood will be collected:

- **Collect 10 mL of whole blood into a 10-mL lavender top EDTA tube* (MANDATORY)**
- Collect 10 mL of whole blood into a 10-mL green top sodium heparin tube (preferably BD catalog # 367874)* (OPTIONAL)
- Collect 10 mL of whole blood into a 10-mL red top no-additive tube (preferably BD catalog # 367820)* (OPTIONAL)

* If 10 mL tubes are not available, two 5 mL tubes may be used.

Site Sample Handling Instructions for the LAVENDER TOP Tube (for Collecting DNA):

2. Immediately following collection, invert blood in lavender tube by hand 10 times to ensure the blood and EDTA are thoroughly mixed.

I. Do not process – send to the SWOG Biospecimen Bank at ambient temperature.

Site Sample Processing for RED TOP Tube for Serum (for Serum Proteomics):

II. Following blood collection, the red top tube should be left upright and undisturbed at room temperature for at least 30 minutes but no more than 2 hours to allow a clot to form.

III. Place a conical vial (or two 2-mL microcentrifuge tubes) in an ice-water bath to pre-chill (for step 5).

IV. After clot formation, centrifuge the red top tube at 1,300 x g for 10 minutes (at 4°C if a refrigerated centrifuge is available) separate serum from the blood cells.

V. Immediately after centrifugation, place the red top tube in an ice-water bath.

VI. Using a pipette, transfer serum into the pre-chilled, labeled conical vial (or microcentrifuge tubes). Avoid disturbing the red blood cell layer.

VII. From these samples, generate a total of six (6) 600 mcL (0.6 mL) serum aliquots into 2-mL, pre-labeled, screw-top cryovials. Discard any remaining plasma and blood cells.

VIII. Store specimens in a -80°C freezer until shipment to the SWOG Bank. If a -80°C freezer is not available, then specimens may be stored in a -20°C freezer before shipment.

IX. If samples are stored at > -70°C until shipment, make a note of the actual storage temperature and duration of storage in the instructions field when the specimen is logged into the SWOG Specimen Tracking System.

Site Sample Processing for the GREEN TOP Tube for Plasma (for Plasma Metabolomics):

I. Immediately after collection, invert the green top tube by hand 10 times to ensure the blood and sodium heparin are thoroughly mixed, and then immediately place in an ice-water bath. Place a conical vial (or two 2-mL microcentrifuge tubes) in the ice-water bath to pre-chill (for step 4).

II. Centrifuge the green top tube at 1,300 x g for 10 minutes at 4°C to separate plasma from red and white blood cells.

III. Immediately after centrifugation, return the green top tube to the ice-water bath.

IV. Using a pipette, transfer the plasma into the pre-chilled, labeled conical vial (or microcentrifuge tubes).

V. From these samples, generate a total of six (6) 600 mcL (0.6 mL) plasma aliquots into 2-mL, pre-labeled, screw-

top cryovials. Discard any remaining plasma and blood cells.

VI. Store specimens upright in a -80°C freezer until shipment to the SWOG Bank. If a -80°C freezer is not available, then specimens may be stored in a -20°C freezer before shipment.

VII. If samples are stored at > -70°C until shipment, make a note of the actual storage temperature and duration of storage in the instructions field when the specimen is logged into the SWOG Specimen Tracking System.

3. First Cycle of Taxane-Based Chemotherapy

Three (3) 10-mL tubes of whole blood will be collected before the taxane infusion ends, *but no more than 10 minutes prior to the end of infusion*. Sample must be collected by venipuncture or through a peripheral IV line to avoid contamination by the infusing drug. **DO NOT collect the blood sample from the infusion IV port or peripheral IV port used to administer the taxane chemotherapy. The site of collection must not be near the site of concurrent taxane administration and the supplies used to collect the sample must not have previously been or currently be administering the taxane. Any of these will lead to sample contamination and incorrectly elevated measurements.**

The sample should be collected from the arm contralateral to the infusion, if possible. If a contralateral arm collection is not possible (*i.e.* due to axillary lymph node dissection), then the sample may be collected on the ipsilateral arm distal to the site of infusion. If the sample is collected from an IV saline lock using a syringe, then draw a waste before collecting the sample to avoid risk of the sample being diluted with saline.

The end of infusion plasma sample provides an estimate of the maximum concentration (C_{max}). This sample must be collected before infusion ends, but no more than 10 minutes prior to the end of infusion. **NOTE: The plasma for Taxane Maximum Concentration [C_{max}]) can be collected in the last 10 minutes of any cycle if it is missed with the first cycle.**

Please note that the start time of infusion, stop time of infusion, and the time of the specimen collection must be entered into the Specimen Tracking System.

Tubes for Collection

- **Collect 10 mL of whole blood into a lavender top EDTA tube* (MANDATORY)**
- Collect 10 mL of whole blood into a green top sodium heparin tube (preferably BD catalog # 367874) (OPTIONAL)
- Collect 10 mL of whole blood into a red top no-additive tube (preferably BD catalog # 367820) (OPTIONAL)

* If 10 mL tubes are not available, two 5 mL tubes may be used.

Site Sample Processing for the LAVENDER TOP Tube for Plasma (for Plasma Cmax):

I. Immediately after collection, invert the lavender tube by hand 10 times to ensure the blood and EDTA are thoroughly mixed and immediately placed on ice.
II. Process the sample within 30 minutes of collection. Maintain the sample on ice until processing.
Note: For sites that must transport samples prior to processing, processing can occur up to 2 hours from time of collection as long as the samples remain on ice until that time.
III. Centrifuge the lavender top tube at 1,300 x g for 10 minutes (at 4°C if a refrigerated centrifuge is available) to separate plasma from red and white blood cells.
IV. Using a pipette, transfer the entire volume of plasma (top layer) into a labeled conical vial (or 2-mL microcentrifuge tubes).
V. From this sample, generate at least two (2) 1-mL plasma aliquots in 2-mL, pre-labeled cryovials.
VI. Place the remaining plasma (up to 2 mL) in a third pre-labeled cryovial. Discard remaining blood cells.
VII. Store specimens in a -80°C freezer until shipment to the SWOG Bank. If a -80°C freezer is not available, then specimens may be stored in a -20°C freezer before shipment.
VIII. If samples are stored at > -70°C until shipment, make a note of the actual storage temperature and duration of storage in the instructions field when the specimen is logged into the SWOG Specimen Tracking System.

Sample processing for the RED TOP and GREEN TOP tubes for serum proteomics and plasma metabolomics:

Process the red top tube for serum (serum proteomics) and green top tube for plasma (plasma metabolomics) as described above in Sections 15.1c.1c and 15.1c.1d, respectively.

4. Follow Up

For the follow up blood collections (4 Weeks [± 14 days], 8 Weeks [± 14 days], 12 Weeks [± 14 days], 24 Weeks [± 28 days], and 52 Weeks [± 28 days] after beginning taxane-based chemotherapy), two (2) 10-mL tubes of whole blood will be collected prior to infusion and administration of pre-medications.

Tubes for Collection

- Collect 10 mL of whole blood into a green top sodium heparin tube(s) (preferably BD catalog #367874) (OPTIONAL)
- Collect 10 mL of whole blood into a red top no-additive tube(s) (preferably BD catalog # 67820)* (OPTIONAL)

* If 10 mL tubes are not available, two 5 mL tubes may be used.

Site Sample Processing for the RED TOP and GREEN TOP Tubes for Serum Proteomics and Plasma Metabolomics:

- Process the red top tube for serum (serum proteomics) and process the green top tube for plasma (plasma metabolomics) as described above in Sections 15.1c.1c and 15.1c.1d, respectively.

d. Specimen Kits

Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

e. Specimen Labeling Instructions

Specimens must be labeled with the following:
- SWOG patient number
- Patient initials (L, FM)
- Date of specimen collection (month/day/year)
- Specimen type (ex: whole blood, serum, plasma, etc.)

f. Specimen Submission Instructions

Frozen serum and plasma specimens should be stored in a -70 to -80°C freezer after processing and prior to packaging/shipping. Specimens should be shipped completely covered in dry ice to ensure that they remain frozen during shipment.

For specimens stored at -70 to -80°C: Specimens may be batched and shipped at least quarterly, or after specimens from 5 patients are ready to be shipped, whichever is sooner.

For specimens stored at -20°C to -70°C: Specimens may not be batched; they should be shipped following collection and processing. Refer to the SWOG Specimen Submission webpage for shipping instructions. Note: The site must make a note of the actual storage temperature and duration of storage in the instructions field when the specimen is logged into the SWOG Specimen Tracking System.

For specimens to be shipped at ambient temperature: Refer to the SWOG Specimen Submission webpage for shipping instructions for ambient whole blood specimens.

All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. Complete specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (https://www.swog.org/member-resources/biospecimen-resources/solid-tissue-specimen-submission). If collection/submission instructions differ from those in the protocol, the protocol instructions should be followed; otherwise, the website instructions should be followed.

g. Genetic Data Sharing Plan

The investigators will share anonymized, large-scale germ-line data in accordance with NIH Genomic Data Sharing (GDS) policy. The Data Sharing Policy requires controlled access to the genomic data based on the informed consent document. Access to de-identified, individual-level participant data will be controlled, unless participants explicitly consent to allow unrestricted access to and use of their data for any purpose.

h. International Specimen Processing Instructions

LAVENDER TOP EDTA Tube:

Note that specimen processing of blood plasma is outline below and done at site prior to storage.

Please do NOT use LAVENDER TOP EDTA tubes that have a separation gel. The laboratory is unable to extract remaining cells from these tubes. The specimens should be collected in plastic EDTA tubes.

1. Centrifuge the lavender top tube(s) at 1,200 x g for 10 minutes at room temperature.

   Distinct layers should be present after centrifugation.
   - The plasma layer will be clear and yellowish and comprise the top layer.
   - A thin, white, and cloudy buffy coat layer will be visible just below the plasma layer.
   - The bottom layer will be red and contain other cell types and debris.

2. Using a pipette, remove only the plasma (top layer) place into a labeled 15-mL conical tube. (Avoid pulling up the buffy coat layer by leaving about 0.25-0.5 mL of plasma in the collection tube.)
3. From this sample, generate at least two (2) 1 mL plasma aliquots in 2-mL, pre-labeled cryovials.
4. After the plasma has been drawn off the specimen, use a sterile transfer pipette to gently mix the buffy coat layer and red blood cells together. Ensure the mixture is homogenous before freezing. The remnant blood can be frozen in the EDTA collection tube.
5. Store both specimens in at -70 to -80C freezer until shipment to the SWOG Bank. If a -80°C freezer is not available, then specimens may be stored in a -20°C freezer before shipment.
6. If samples are stored at > -70°C until shipment, make a note of the actual storage temperature and duration of storage in the instructions field when the specimen is logged into the SWOG Specimen Tracking System.

15.2 Imaging Ancillary Study (***OPTIONAL FOR PARTICIPANT / REQUIRED IF PARTICIPANT CONSENTS***)

The study team has developed an ancillary study aimed at identifying ways to prevent or reduce peripheral neuropathy from taxane treatment. As part of this study, the team is requesting access to imaging that has already been collected as part of standard of care. No additional or new scans will be required from patients.

a. Digital Clinical CT Scan of the chest, abdomen, or thorax must be submitted to IROC Ohio for review at the following timepoint:
   - Baseline: performed within 6 months prior or 1 month after **S1714** registration

   If a patient consents, sites must submit the images to the Imaging and Radiation Oncology Core (IROC) at Ohio via TRIAD Imaging Submission within 30 days.

b. TRIAD Digital Image Submission

   Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

   TRIAD Access Requirements:

   - Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
   - Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR). Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR; and
   - TRIAD Site User role on an NCTN, ETCTN, or other relevant roster.

   TRIAD Access Requirements:

   - Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
   - Registration type of: Associate (A), Associate Plus (AP), Non-Investigational New Drug (IND)/Non-Treatment (NINT), Non-Physician Investigator (NPIVR), or Investigator (IVR). Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR; and
   - TRIAD Site User role on an NCTN, ETCTN, or other relevant roster.

   All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

   TRIAD Installation:

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/.

This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

Adverse Experiences

There is no SAE Reporting for this study.

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18.0 APPENDIX

18.1 Protocol - Specified Chemotherapy Regimens for Breast, Lung, and Ovarian/Fallopian tube/Peritoneal Cancer

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18.1 Protocol-Specified Chemotherapy Regimens for Breast, Lung, and Ovarian/Fallopian tube Cancer

Breast cancer		
Regimen	**Standard Taxane Dose**	**Frequency**
*P x 4	Paclitaxel 175 mg/m2	Every 2 weeks for 4 cycles
*P x 12 +/- Carboplatin (AUC 2 for weekly or AUC 5-6 for every 3 weeks)	Paclitaxel 80 mg/m2	Every week for 12 weeks (1 week = 1 cycle)
TC x 4 or TC x 6	Docetaxel 75 mg/m2	Every 3 weeks for 4 or 6 cycles
TAC x 6	Docetaxel 75 mg/m2	Every 3 weeks for 6 cycles
*T x 4	Docetaxel 100 mg/m2	Every 3 weeks for 4 cycles
T/Carboplatin (AUC 6)	Docetaxel 75 mg/m2	Every 3 weeks for 6 cycles
Lung cancer		
Regimen	**Standard Taxane Dose**	**Frequency**
Carboplatin (AUC 6) + P x 4	Paclitaxel 200 mg/m2	Every 3 weeks for 4 cycles
Ovarian/Fallopian tube/ Peritoneal cancer		
Regimen	**Standard Taxane Dose**	**Frequency**
Carboplatin (AUC 5-6) + P x 6	Paclitaxel 175 mg/m2	Every 3 weeks for 6 cycles
Carboplatin (AUC 5-6) + ddP x 6	Paclitaxel 80 mg/m2	Carboplatin every 3 weeks and paclitaxel weekly for 18 weeks
Carboplatin (AUC 2) + P x 18	Paclitaxel 60 mg/m2	Weekly for 18 weeks
Carboplatin (AUC 5-6) + T x 6	Docetaxel 60-75 mg/m2	Every 3 weeks for 6 cycles
Abbreviations: dd, dose-dense; A, doxorubicin; C, cyclophosphamide; P, paclitaxel; T, docetaxel Biologic agents, including but not limited to trastuzumab and/or pertuzumab, may be added to any of the regimens. * Can be preceded or followed by AC.		

See Section 5.2 for additional information regarding allowable prior/concurrent therapy.

18.2 Staging Criteria: Definitions and Staging

a. Breast Definitions *(1)*

1. Definitions

Primary Tumor (T)

T0 No evidence of primary tumor

Tis (DCIS)* Ductal carcinoma *in situ*

* Note: Lobular carcinoma *in situ* (LCIS) is a benign entity and is removed from TNM staging in the AJCC Cancer Staging Manual, 8th Edition.

Tis (Paget) Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma *in situ* (DCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted.

T1 Tumor ≤ 20 mm in greatest dimension

T1mi Tumor ≤ 1 mm in greatest dimension

T1a Tumor > 1 mm but ≤ 5 mm in greatest dimension (round any measurement > 1.0–1.9 mm to 2 mm)

T1b Tumor > 5 mm but ≤ 10 mm in greatest dimension

T1c Tumor > 10 mm but ≤ 20 mm in greatest dimension

T2 Tumor > 20 mm but ≤ 50 mm in greatest dimension

T3 Tumor > 50 mm in greatest dimension

T4 Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or macroscopic nodules); invasion of the dermis alone does not qualify as T4

T4a Extension to the chest wall; invasion or adherence to pectoralis muscle in the absence of invasion of chest wall structures does not qualify as T4

T4b Ulceration and/or ipsilateral macroscopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criteria for inflammatory carcinoma

T4c Both T4a and T4b are present

T4d Inflammatory carcinoma (see "Rules for Classification")

T Suffix (m) Select if synchronous primary tumors are found in a single organ

2. Regional Lymph Node (N)

cNX* Regional lymph nodes cannot be assessed (e.g., previously removed)

cN0 No regional lymph node metastases (by imagining or clinical examination)

cN1 Metastases to movable ipsilateral Level I, II axillary lymph node(s)

cN1mi** Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm

cN2 Metastases in ipsilateral Level I, II axillary lymph nodes that are clinically fixed or matted; *or* in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases

cN2a Metastases in ipsilateral Level I, II axillary lymph nodes fixed to one another (matted) or to other structures

cN2b Metastases only in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases

cN3 Metastases in ipsilateral infraclavicular (Level III axillary) lymph node(s) with or without Level I, II axillary lymph node involvement; *or* in ipsilateral internal mammary lymph node(s) with Level I, II axillary lymph node metastases; *or* metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement

cN3a Metastases in ipsilateral infraclavicular lymph node(s)

cN3b Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)

cN3c Metastases in ipsilateral supraclavicular lymph node(s)

Note: (sn) and (f) suffixes should be added to the N category to denote confirmation of metastasis by sentinel node biopsy or fine needle aspiration/core needle biopsy, respectively.

* The cNX category is used sparingly in cases where regional lymph nodes have previously been surgically removed or where there is no documentation of physical examination of the axilla.

** cN1mi is rarely used but may be appropriate in cases where sentinel node biopsy is performed before tumor resection, most likely to occur in cases treated with neoadjuvant therapy

N Suffix (sn) Select if regional lymph node metastasis identified by SLN biopsy only

N Suffix (f) Select if regional lymph node metastasis identified by FNA or core needle biopsy only

3. Distant Metastasis (M)

The terms pM0 and MX are NOT valid categories in the TNM system.

Assignment of the M category for clinical classification may be cM0, cM1, or pM1. Any of the M categories (cM0, cM1, or pM1) may be used with pathological stage grouping.

cM0 No clinical or radiographic evidence of distant metastases*

cM0(i+) No clinical or radiographic evidence of distant metastases in the presence of tumor cells or deposits no larger than 0.2 mm detected microscopically or by molecular techniques in circulating blood, bone marrow, or other nonregional nodal tissue in a patient without symptoms or signs of metastases.

cM1 Distant metastases detected by clinical and radiographic means

pM1 Any histologically proven metastases in distant organs; or if non-regional nodes, metastases greater than 0.2 mm

* Note that imaging studies are not required to assign the cM0 category.

4. Histologic Grade (G)

Invasive Carcinoma

GX Grade cannot be assessed

G1 Low combined histologic grade (favorable), SBR score of 3-5 points

G2 Intermediate combined histologic grade (moderately favorable); SBR score 6-7 points

G3 High combined histologic grade (unfavorable); SBR score of 8-9 points

Carcinoma *in situ*

GX Grade cannot be assessed

G1 Low nuclear grade

G2 Intermediate nuclear grade

G3 High nuclear grade

5. HER2 Status

Positive

Negative

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
T1* N0 M0 T0 N1mi M0 T1* N1mi M0	G1	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
	G2	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
	G3	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB
				Negative	IB
T0 N1** M0 T1* N1** M0 T2 N0 M0	G1	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
	G2	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
	G3	Positive	Positive	Positive	IB
				Negative	IIA

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
T2 N1*** M0 T3 N0 M0	G1	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
	G2	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIIB
	G3	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IIB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB
T0 N2 M0 T1* N2 M0 T2 N2 M0 T3 N1*** M0 T3 N2 M0	G1	Positive	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB
	G2	Positive	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB
	G3	Positive	Positive	Positive	IIB
				Negative	IIIA
			Negative	Positive	IIIA

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
				Negative	IIIA
		Negative	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC
T4 N0 M0 T4 N1*** M0 T4 N2 M0 Any T N3 M0	G1	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC
	G2	Positive	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC
	G3	Positive	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB
				Negative	IIIC
			Negative	Positive	IIIC
				Negative	IIIC

*T1 includes T1mi
**N1 does not include N1mi. T1 N1mi M0 cancers are included for prognostic staging with T1 N0 M0 cancers of the same prognostic factor status.
***N1 includes n1mi. T2, T3, and T4 cancers are included for prognostic staging with T2 N1, T3 N1, and T4 N1, respectively.

Notes:

1. Because N1mi categorization requires evaluation of the entire node, and cannot be assigned on the basis of an FNA or core biopsy, N1mi can only be used with Clinical Prognostic Staging when clinical staging is based on a resected lymph node in the absence of resection of the primary cancer, such as the situation where sentinel node biopsy is performed prior to receipt of neoadjuvant chemotherapy or endocrine therapy.
2. For cases where HER2 is determined to be “equivocal” by ISH (FISH or CISH) testing under the 2013 ASCO/CAP HER2 testing guidelines, the HER2 “negative” category should be used for staging in the Clinical Prognostic Stage Group table.
3. The prognostic value of these Prognostic Stage Group is based on populations of persons with breast cancer that have been offered and

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
mostly treated with appropriate endocrine and/or systemic chemotherapy (including anti-HER2 therapy).					

Equivocal (use negative category for prognostic stage group assignment)

6. ER Status

   Positive

   Negative

7. PR Status

   Positive

   Negative

8. Oncotype Dx® Recurrence Score

   Less than 11

   11 or greater

   Not performed

   Not available

9. Clinical Prognostic Stage

10. Pathological Prognostic Stage

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
T1* N0 M0 T0 N1mi M0 T1* N1mi M0	G1	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
	G2	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
	G3	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
T0 N1** M0 T1* N1** M0 T2 N0 M0	G1	Positive	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB
				Negative	IIA
		Negative	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB
				Negative	IIA
	G2	Positive	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB
				Negative	IIA
		Negative	Positive	Positive	IA
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
	G3	Positive	Positive	Positive	IA
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IB
				Negative	IIA

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
			Negative	Positive	IIA
				Negative	IIA
T2 N1*** M0 T3 N0 M0	G1	Positive	Positive	Positive	IA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
	G2	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
	G3	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIIA
T0 N2 M0 T1* N2 M0 T2 N2 M0 T3 N1*** M0 T3 N2 M0	G1	Positive	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
	G2	Positive	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB
	G3	Positive	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIB
				Negative	IIIA
			Negative	Positive	IIIA

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
				Negative	IIIC
T4 N0 M0 T4 N1*** M0 T4 N2 M0 Any T N3 M0	G1	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
	G2	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC
	G3	Positive	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB
				Negative	IIIC
			Negative	Positive	IIIC
				Negative	IIIC

*T1 includes T1mi
**N1 does not include N1mi. T1 N1mi M0 cancers are included for prognostic staging with T1 N0 M0 cancers of the same prognostic factor status.
***N1 includes n1mi. T2, T3, and T4 cancers are included for prognostic staging with T2 N1, T3 N1, and T4 N1, respectively.

Notes:

1. For cases where HER2 is determined to be “equivocal” by ISH (FISH or CISH) testing under the 2013 ASCO/CAP HER2 testing guidelines, the HER2 “negative” category should be used for staging in the Pathological Prognostic Stage Group table.
2. The prognostic value of these Prognostic Stage Group is based on populations of persons with breast cancer that have been offered and mostly treated with appropriate endocrine and/or systemic chemotherapy (including anti-HER2 therapy).

b. Non-Small Cell Lung *(2)*

1. Definitions

Primary Tumor (T)

T1 Tumor ≤ 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more

proximal than the lobar bronchus (for example, not in the main bronchus)*

T1mi Minimally invasive adenocarcinoma: adenocarcinoma (≤ 3 cm in greatest dimension) with a predominantly lepidic pattern and ≤ 5 mm invasion in greatest dimension

T1a Tumor ≤ 1 cm in greatest dimension. A superficial, spreading tumor of any size whose invasive component is limited to the bronchial wall and may extend proximal to the main bronchus also is classified as T1a, but these tumors are uncommon.

T1b Tumor > 1 cm but ≤ 2 cm in greatest dimension

T1c Tumor > 2 cm but ≤ 3 cm in greatest dimension

T2 Tumor > 3 cm ≤ 5 cm or having any of the following features
- involves main bronchus regardless of distance to the carina, but without involvement of the carina
- invades visceral pleura (PL1 or PL2)
- associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung

T2a Tumor > 3 cm but ≤ 4 cm in greatest dimension

T2b Tumor > 4 cm but ≤ 5 cm in greatest dimension

T3 Tumor > 5 cm but ≤ 7 cm in greatest dimension or directly invading any of the following:
- parietal pleural (PL3)
- chest wall (including superior sulcus tumors)
- phrenic nerve
- parietal pericardium
- separate tumor nodule(s) in the same lobe as the primary

T4 Tumor > 7 cm or tumor of any size invading one or more of the following:
- diaphragm
- mediastinum
- heart
- great vessels
- trachea
- recurrent laryngeal nerve
- esophagus
- vertebral body
- carina
- separate tumor nodule(s) in a different ipsilateral lobe

T Suffix (m) Select if synchronous primary tumors are found in a single organ

2. Regional Lymph Node (N)

N0 No regional lymph node metastasis

N1 Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension

N2 Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)

N3 Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

N Suffix (sn) Select if regional lymph node metastasis identified by SLN biopsy only

N suffix (f) Select if regional lymph node metastasis identified by FNA or core needle biopsy only

3. Distant Metastasis (M)

M0 No distant metastasis

cM1 Distant metastasis

cM1a Separate tumor nodule(s) in a contralateral lobe, tumor with pleural or pericardial nodules or malignant pleural or pericardial effusion. Most pleural (pericardial) effusions with lung cancer are a result of the tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and not an exudate. If these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.

cM1b Single extrathoracic metastasis in a single organ (including involvement of a single nonregional node)

cM2c Multiple extrathoracic metastases in a single organ or in multiple organs

pM1 Distant metastasis, microscopically confirmed

pM1a Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodules or malignant pleural or pericardial effusion, microscopically confirmed. Most pleural (pericardial) effusions with lung cancer are a result of the tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is non-bloody and not an exudate. If these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.

pM1b Single extrathoracic metastasis in a single organ (including involvement of a single nonregional node), microscopically confirmed

pM1c Multiple extrathoracic metastases in a single organ or in multiple organs, microscopically confirmed

* The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.

** Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as M0.

4. Prognostic Stage Groups

When T is…	And N is…	And M is…	Then the stage group is…
T1mi	N0	M0	IA1
T1a	N0	M0	IA1
T1a	N1	M0	IIB
T1a	N2	M0	IIIA
T1a	N3	M0	IIIB
T1b	N0	M0	IA2
T1b	N1	M0	IIB
T1b	N2	M0	IIIA
T1b	N3	M0	IIIB
T1c	N0	M0	IA3
T1c	N1	M0	IIB
T1c	N2	M0	IIIA
T1c	N3	M0	IIIB
T2a	N0	M0	IB
T2a	N1	M0	IIB
T2a	N2	M0	IIIA
T2a	N3	M0	IIIB
T2b	N0	M0	IIA
T2b	N1	M0	IIB
T2b	N2	M0	IIIA
T2b	N3	M0	IIIB
T3	N0	M0	IIB
T3	N1	M0	IIIA
T3	N2	M0	IIIB
T3	N3	M0	IIIC
T4	N0	M0	IIIA
T4	N1	M0	IIIA
T4	N2	M0	IIIB
T4	N3	M0	IIIC

c. Ovarian/Fallopian tube/ Peritoneal *(3)*

1. Definitions

Primary Tumor (T) and FIGO Stages in ()

T1(I) Tumor limited to ovaries (one or both) or fallopian tube(s)

T1a(IA) Tumor limited to one ovary (capsule intact) or fallopian tube, no tumor on ovarian or fallopian tube surface; no malignant cells in ascites or peritoneal washings

T1b(IB) Tumor limited to one or both ovaries (capsules intact) or fallopian tubes; no tumor on ovarian or fallopian tube surface, no malignant cells in ascites or peritoneal washings

T1c(IC) Tumor limited to one or both ovaries or fallopian tubes with any of following:

T1c1(IC1) Surgical spill

T1c2(IC2) Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface

T1c3(IC3) Malignant cells in ascites or peritoneal washings

T2(II) Tumor involves one or both ovaries or fallopian tubes with pelvic extension below pelvic brim or primary peritoneal cancer

T2a(IIA) Extension and/or implants on uterus and/or fallopian tube(s) and/or ovaries

T2b(IIB) Extension to and/or implants on other pelvic tissue

T3(III) Tumor involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with microscopically confirmed peritoneal metastasis outside the pelvis and/or metastasis to the retroperitoneal (pelvic and/or para-aortic) lymph nodes

T3a(IIIA2) Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes

T3b(IIIB) Macroscopic peritoneal metastasis beyond pelvis 2 cm or less in greatest dimension with or without metastasis to the retroperitoneal lymph nodes

T3c(IIIC) Macroscopic peritoneal metastasis beyond pelvis more than 2 cm in greatest dimension with or without metastasis to the retroperitoneal lymph

nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ)

T Suffix (m) Select if synchronous primary tumors are found in single organ

2. Regional Lymph Node (N) and FIGO Stage in ()

N0 Regional lymph nodes cannot be assessed

N0(i+) Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm

N1(IIIA1) Positive retroperitoneal lymph nodes only (histologically confirmed)

N1a(IIIA1i) Metastasis up to and including 10 mm in greatest dimension

N1b(IIIA1ii) Metastasis more than 10 mm in greatest dimension

N Suffix (sn) Select if regional lymph node metastasis identified by SLN biopsy only

N Suffix (f) Select if regional lymph node metastasis identified by FNA or core needle biopsy only

M1(IV) Distant metastasis excluding peritoneal metastases

M1a(IVA) Pleural effusion with positive cytology

M1b(IVB) Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph node s outside the abdominal cavity)

3. Distant Metastasis (M) and FIGO Stage in ()

M0 No distant metastasis

cM1 (IV) Distant metastasis, including pleural effusion with positive cytology; liver or splenic parenchymal metastasis; metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity); and transmural involvement of intestine

cM1a (IVA) Pleural effusion with positive cytology

cM1b (IVB) Liver or splenic parenchymal metastasis; metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity); and transmural involvement of intestine

pM1 (IV) Distant metastasis, including pleural effusion with positive cytology; liver or splenic parenchymal metastasis; metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity); and transmural involvement of intestine, microscopically confirmed

pM1a (IVA) Pleural effusion with positive cytology, microscopically confirmed

pM1b (IVB) Liver or splenic parenchymal metastasis; metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity); and transmural involvement of intestine, microscopically confirmed

4. Prognostic Stage Groups

When T is…	And N is…	And M is…	Then the stage group is…
T1	N0	M0	I
T1a	N0	M0	IA
T1b	N0	M0	IB
T1c	N0	M0	IC
T2	N0	M0	II
T2a	N0	M0	IIA
T2b	N0	M0	IIB
T1/T2	N1	M0	IIIA1
T3a	NX, N0, N1	M0	IIIA2
T3b	NX, N0, N1	M0	IIIB
T3c	NX, N0, N1	M0	IIIC

Appendix 18.2 References

1 AJCC 8 Breast

2 AJCC 8 Lung

3 AJCC 8 Ovarian/Fallopian tube/Peritoneal

18.3 Instructions for the SWOG Biospecimen Bank

Frozen Serum and Plasma Aliquots
The SWOG Biospecimen Bank will receive frozen vial of serum and plasma (from sodium heparin) at seven time points, and plasma (from EDTA) at one time point. Upon receipt, serum and plasma vials will be accessioned, barcoded, and banked in a -80°C freezer until distribution for testing and/or future studies.

Whole Blood
The SWOG Biospecimen Bank will receive ambient whole blood at one time point. Upon receipt, whole blood in EDTA will be accessioned and barcoded. Blood will be processed for plasma and then DNA will be extracted and stored in a -80°C freezer for future studies (including for DNA for pharmacogenetic analyses).

Distribution of Specimens from SWOG Biospecimen Bank

Assay	Specimen Type	Collection Tube	Timepoint	Amount	Lab	Shipping
Kinetics	Plasma	EDTA	w/in 10 min prior to end of 1st infusion	1 x 0.6ml	UM Pharmacokinetics Core	Room 3400 of Building 520, North Campus Research Complex (1600 Huron Parkway, Ann Arbor, MI 48109)
Genetics	DNA	EDTA	Baseline	250 uL at 20 ng/uL (5 ug total DNA)	UM Advanced Genomics	UM Advanced Genomics Core, NCRC Building 14, Room 122, University of Michigan, 2800 Plymouth Rd, Ann Arbor, MI 48109-2800
Vitamin D	Plasma	NaHep	Baseline	1 x 0.6ml	Heartland Assays	Iowa State University Research Park, 2711 S. Loop Dr., Ste 4400, Ames, IA 50010
Amino Acids	Plasma	NaHep	Baseline	1 x 0.6ml	Metabolon, Inc	617 Davis Dr. Suite 100 Morrisville, NC 27560
Lipidomics	Plasma	NaHep	Baseline	1 x 0.6ml	Metabolon, Inc	617 Davis Dr. Suite 100 Morrisville, NC 27560
Proteomics	Serum	Red Top	Baseline	2 x 0.6ml	University of Michigan	College of Pharmacy, Room 4065, 428 Church Street, Ann Arbor, MI 48104,

18.4 CTCAE Version 5.0 Nervous System Disorders Category *(1)*

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Abducens nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Accessory nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Acoustic nerve disorder NOS	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Akathisia	Mild restlessness or increased motor activity	Moderate restlessness or increased motor activity; limiting instrumental ADL	Severe restlessness or increased motor activity; limiting self care ADL	-	-
Amnesia	Mild; transient memory loss	Moderate; short term memory loss; limiting instrumental ADL	Severe; long term memory loss; limiting self care ADL	-	-
Anosmia	Present	-	-	-	-
Aphonia	-	-	Voicelessness; unable to speak	-	-
Arachnoiditis	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Ataxia	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; mechanical assistance indicated	-	-
Brachial plexopathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Central nervous system necrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; corticosteroids indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Cerebrospinal fluid leakage	Post-craniotomy: asymptomatic; Post-lumbar puncture: transient headache; postural care indicated	Post-craniotomy: moderate symptoms; medical intervention indicated; Post-lumbar puncture: persistent moderate symptoms; blood patch indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	-	-
Concentration impairment	Mild inattention or decreased level of concentration	Moderate impairment in attention or decreased level of concentration; limiting instrumental ADL	Severe impairment in attention or decreased level of concentration; limiting self care ADL	-	-
Depressed level of consciousness	Decreased level of alertness	Sedation; slow response to stimuli; limiting instrumental ADL	Difficult to arouse	Life-threatening consequences; coma; urgent intervention indicated	Death
Dizziness	Mild unsteadiness or sensation of movement	Moderate unsteadiness or sensation of movement; limiting instrumental ADL	Severe unsteadiness or sensation of movement; limiting self care ADL	-	-
Dysarthria	Mild slurred speech	Moderate impairment of articulation or slurred speech	Severe impairment of articulation or slurred speech	-	-
Dysesthesia	Mild sensory alteration	Moderate sensory alteration; limiting instrumental ADL	Severe sensory alteration; limiting self care ADL	-	-

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Dysgeusia	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	-	-	-
Dysphasia	Awareness of receptive or expressive characteristics; not impairing ability to communicate	Moderate receptive or expressive characteristics; impairing ability to communicate spontaneously	Severe receptive or expressive characteristics; impairing ability to read, write or communicate intelligibly	-	-
Edema cerebral	-	-	New onset; worsening from baseline	Life-threatening consequences; urgent intervention indicated	Death
Encephalopathy	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Extrapyramidal disorder	Mild involuntary movements	Moderate involuntary movements; limiting instrumental ADL	Severe involuntary movements or torticollis; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Facial muscle weakness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Facial nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Glossopharyngeal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Guillain-Barre syndrome	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated; intubation	Death
Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hydrocephalus	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; intervention not indicated	Severe symptoms or neurological deficit; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Hypersomnia	Mild increased need for sleep	Moderate increased need for sleep	Severe increased need for sleep	-	-
Hypoglossal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Intracranial hemorrhage	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Ischemia cerebrovascular	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	-	-	-
Lethargy	Mild symptoms; reduced alertness and awareness	Moderate symptoms; limiting instrumental ADL	-	-	-
Leukoencephalopathy	Asymptomatic; small focal T2/FLAIR hyperintensities; involving periventricular white matter or <1/3 of susceptible areas of cerebrum +/- mild increase in subarachnoid space (SAS) and/or mild ventriculomegaly	Moderate symptoms; focal T2/FLAIR hyperintensities, involving periventricular white matter extending into centrum semiovale or involving 1/3 to 2/3 of susceptible areas of cerebrum +/- moderate increase in SAS and/or moderate ventriculomegaly	Severe symptoms; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving 2/3 or more of susceptible areas of cerebrum +/- moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Life-threatening consequences; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving most of susceptible areas of cerebrum +/- moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Death

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Memory impairment	Mild memory impairment	Moderate memory impairment; limiting instrumental ADL	Severe memory impairment; limiting self care ADL	-	-
Meningismus	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Movements involuntary	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Muscle weakness left-sided	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL	-	-
Muscle weakness right-sided	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL	-	-
Myasthenia gravis	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Nervous system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Neuralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Nystagmus	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Oculomotor nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Olfactory nerve disorder	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Paresthesia	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Peripheral motor neuropathy	Asymptomatic; clinical or diagnostic observations only	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Peripheral sensory neuropathy	Asymptomatic	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	-
Phantom pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Presyncope	-	Present (e.g., near fainting)	-	-	-
Pyramidal tract syndrome	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Radiculitis	Mild symptoms	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Recurrent laryngeal nerve palsy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	Severe symptoms; medical intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening consequences; urgent intervention indicated	Death
Reversible posterior leukoencephalopathy syndrome	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization	Life-threatening consequences	Death
Seizure	Brief partial seizure and no loss of consciousness	Brief generalized seizure	New onset seizures (partial or generalized); multiple seizures despite medical intervention	Life-threatening consequences; prolonged repetitive seizures	Death
Somnolence	Mild but more than usual drowsiness or sleepiness	Moderate sedation; limiting instrumental ADL	Obtundation or stupor	Life-threatening consequences; urgent intervention indicated	Death

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Spasticity	Mild or slight increase in muscle tone	Moderate increase in muscle tone and increase in resistance through range of motion	Severe increase in muscle tone and increase in resistance through range of motion	Life-threatening consequences; unable to move active or passive range of motion	Death
Spinal cord compression	-	-	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Stroke	Incidental radiographic findings only	Mild to moderate neurologic deficit; limiting instrumental ADL	Severe neurologic deficit; limiting self care ADL; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Syncope	-	-	Fainting; orthostatic collapse	-	-
Tendon reflex decreased	Ankle reflex reduced	Ankle reflex absent; other reflexes reduced	Absence of all reflexes	-	-
Transient ischemic attacks	Mild neurologic deficit with or without imaging confirmation	Moderate neurologic deficit with or without imaging confirmation	-	-	-
Tremor	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Trigeminal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Trochlear nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Vagus nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Vasovagal reaction	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death

Appendix 18.4 References

1 https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50

18.5 Patient and Physician-Reported Outcomes Instruments

a. European Organization for Research and Treatment of Cancer (EORTC) QLQ-CIPN20 (CIPN-20) *(1)*

The **S1714** EORTC QLQ-CIPN20 is a 20-item questionnaire that evaluates CIPN using 3 subscales that assess sensory (9 items), motor (8 items), and autonomic (3 items) symptoms and functioning with each item measured on a 1-4 scale (1, not at all; 4, very much). The sensory subscale raw scores range from 1 to 36. The 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. This questionnaire has been extensively used in prior clinical trials evaluating interventions for treatment of CIPN. The questionnaire is available in English and Spanish. Assessment will occur at baseline prior to registration and beginning chemotherapy, 4 weeks, 8 weeks, and 12 weeks (± 14 days), at 24 weeks, 52 weeks (± 28 days), and at 104 weeks (2 years) and 156 weeks (3 years) (± 90 days) as outlined in Section 9.0. Efforts should be made to perform the 4-week, 8-week, and 12-week assessments on a day of taxane-treatment that falls within the study window period and prior to taxane administration. The questionnaire takes approximately 2-5 minutes to complete.

b. Patient-Reported Outcomes Measurement Information System 29 (PROMIS-29) *(2)*

The **S1714** Patient-Reported Outcomes Measurement Information System 29 (PROMIS-29) is a well validated assessment tool that offers both qualitative and quantitative measures of health-related quality of life. The PROMIS-29 includes 29 questions evaluating areas of physical function, anxiety, depression, fatigue, sleep, social functioning, and pain interference. The PROMIS-29 assesses severity levels of symptoms and their effect on the patient's functioning. The questionnaire is available in English and Spanish. Patients will complete the questionnaire at baseline prior to registration and beginning chemotherapy, then 4 weeks, 8 weeks, and 12 weeks (± 14 days), and at 24 weeks and 52 weeks (± 28 days) as outlined in Section 9.0. Efforts should be made to perform the 4-week, 8-week, and 12-week assessments on a day of taxane-based treatment that falls within the study window period and prior to taxane administration. The questionnaire takes approximately 6-14 minutes to complete.

c. Godin-Shephard Leisure-Time Physical Activity Questionnaire (GSLTPAQ) *(3,4)*

The **S1714** Godin-Shephard Leisure-Time Physical Activity Questionnaire is a brief 4 item self-administered questionnaire of usual leisure-time exercise habits over a typical 7-day period. The Leisure Score Index (LSI) is calculated based on the first 3 questions. The LSI scores can be used to classify respondents into active (LSI $\geq$ 24) and insufficiently active (LSI $\leq$ 23) categories. The questionnaire is available in English and Spanish. *(5)* Patients will complete the questionnaire at baseline prior to registration and beginning chemotherapy, then 4 weeks, 8 weeks, and 12 weeks (± 14 days), and at 24 weeks and 52 weeks (± 28 days) as outlined in Section 9.0. Efforts should be made to perform the 4-week, 8-week, and 12-week assessments on a day of taxane-treatment that falls within the study window period and prior to taxane administration. The questionnaire takes less than 5 minutes to complete and has been used in several cancer survivor studies as a measure of physical activity.

d. Visual Analog Toxicity Score and Patient Reported Symptom (and Side Effect) Burden Score

For the physician, the Visual Analog Toxicity Score is a single question asking the physician to rate how the physician feels the patient's disease and treatment affects their daily life on a scale from 0 (no symptoms and no effect on life) to 10 (severe effects of treatment and patient would rather be dead). At baseline, the instrument is incorporated into the **S1714** Onstudy Form; at follow-up, the instrument appears on the **S1714** Follow-Up Physician Assessment Form.

For the patient, the Symptom Burden Score at baseline contains one question to assess how cancer symptoms affect the patient's life (scale 0 [no burden at all] to 10 [a great burden]); this is submitted on the **S1714** Baseline Patient Reported Symptom Burden Questionnaire. At follow-up, the Symptom Burden Score contains five questions: 1) to assess burden of side effects of cancer treatment on life (scale 0 [no burden at all] to 10 [a great burden]), 2) to assess severity of side effects from cancer treatment (scale 0 [no side effects]) to 10 [side effects extremely severe and unbearable]), 3) to assess tolerability of side effects for set time periods (yes/no), 4) to assess level at which treatment would be considered intolerable (scale 0 [side effects not severe at all] to 10 [side effects extremely severe and unbearable]), and 5) to assess the burden of cancer symptoms and treatment symptoms (scale 0 [no burden at all] to 10 [a great burden]). Responses to this questionnaire will be submitted via the **S1714** Follow-up Patient Reported Symptom and Side Effect Burden Questionnaire. Baseline and Follow-up patient questionnaires are available in English and Spanish.

The patient and physician will complete the baseline questionnaire prior to registration and prior to the start of chemotherapy, then patient and physician will complete the follow-up questionnaires on the same day as taxane-based chemotherapy at 4 weeks, 8 weeks, and 12 weeks (± 14 days), and at 24 weeks and 52 weeks (± 28 days) as outlined in Section 9.0. Efforts should be made to perform the 4-week, 8-week, and 12-week assessments on a day of taxane-based treatment that falls within the study window period and prior to taxane administration. The questionnaire takes less than 2-3 minutes for the patient to complete and 1-2 minutes for the physician to complete.

e. Patient-Reported Outcomes version of the Common Terminology criteria for Adverse Events (PRO-CTCAE) *(6)*

The US National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology criteria for Adverse Events (PRO-CTCAE [CTCAE Version 5.0]) assesses 78 adverse events by self-report with 124 items. Each item uses a plain language term for the adverse event, the attribute of interest, and the standard recall period of "the past 7 days". The tool has been validated in a large, heterogeneous US sample of patients. The following five items will be assessed: 1) severity of numbness & tingling, 2) interference caused by numbness & tingling, 3) frequency of general pain, 4) severity of general pain, and 5) interference of general pain. The questionnaire is available in English and Spanish. Responses to this questionnaire will be submitted via the **S1714** PRO-CTCAE Form. Patients will complete the questionnaire at baseline prior to registration and beginning chemotherapy, then on the same day as taxane-containing chemotherapy at 4 weeks, 8 weeks, and 12 weeks (± 14 days), at 24 weeks and 52 weeks (± 28 days), and at 104 weeks (2 years) and 156 weeks (3 years) (± 90 days) as outlined in Section 9.0. Efforts should be made to perform the 4-week, 8-week, and 12-week assessments on a day of taxane-treatment that falls within the study window period and prior to taxane administration. The questionnaire takes approximately 3-5 minutes to complete.

f. National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grading Scale *(7)*

The NCI-CTCAE is a subjective method to evaluate CIPN performed by a healthcare professional. The treating physician will grade the subject's dysesthesia, paresthesia, neuralgia, peripheral sensory neuropathy, and peripheral motor neuropathy on a scale of 0 to 5 depending on the severity. The advantage of the NCI-CTCAE is that the assessment is quick and easy for providers to perform, *(8)* but it is limited by the subjectivity of interpretation, lack of detail about location, type, and severity of impairment, narrow scoring range, and lack of direct patient involvement in rating/reporting. *(9)* The investigators will be able to compare patient reported neuropathy measures (CIPN-20, PROMIS-29 pain scale, PRO-CTCAE [CTCAE Version 5.0]) to the physician assessed grading. CTCAE data will be collected at baseline and reported on the **S1714** Baseline Physician CTCAE Assessment Form, and then collected and reported on the **S1714** Solicited Neuropathy Events Form on the same day as taxane-containing chemotherapy at 4 weeks, 8 weeks, and 12 weeks (± 14 days), at 24 weeks and 52 weeks (± 28 days), and at 104 weeks (2 years) and 156 weeks (3 years) (± 90 days) as outlined in Section 9.0. Efforts should be made to perform the 4-week, 8-week, and 12-week assessments on a day of taxane-treatment that falls within the study window period and prior to taxane administration. A table of the nervous system disorders category of the CTCAE is included in Section 18.4

g. Functional Assessment of Cancer Therapy/ Gynecologic Oncology Group Neurotoxicity (FACT/GOG-NTX-4)

The FACT/GOG-NTX-4 is a patient reported outcome measure to evaluate neurotoxicity symptoms. This questionnaire includes the first 4 items from the (10) 11-item FACT/GOG-NTX and assesses numbness or tingling and discomfort in the hands and feet over the recall period of the "past 7 days". Each item is scored from 0-4 (corresponding to "Not at all" to "Very much"). The total score is the sum of the scores for the 4 items multiplied by 4 and divided by the number of items answered (range, 0-16). The questionnaire is available in English and Spanish. Responses to this questionnaire will be submitted via the **S1714** FACT-GOG-NTX-4 Form. Patients will complete the questionnaire at baseline and beginning chemotherapy, then on the same day as taxane-containing chemotherapy at 12 weeks (± 14 days), at 24 weeks and 52 weeks (± 28 days), and at104 weeks (2 years) and 156 weeks (3 years) (± 90 days) as outlined in Section 9.0. Efforts should be made to perform the 12-week assessments on a day of taxane-treatment that falls within the study window period and prior to taxane administration. The questionnaire takes approximately 2-3 minutes to complete.

Appendix 18.5 References

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18.6 Causes of Neuropathy *(1, 2)*

a. Diabetic neuropathy

b. Idiopathic neuropathy (also called cryptogenic neuropathy)

c. Chronic inflammatory demyelinating polyradiculoneuropathy

d. Neuropathy associated with B12 deficiency

e. Neuropathy associated with other vitamin or mineral deficiency (*i.e.* Niacin deficiency (pellagra), B1 deficiency, B6 deficiency, Vitamin D deficiency, Copper deficiency, Vitamin E deficiency, *etc*)

f. Neuropathy associated with alcohol abuse

g. Charcot Marie Tooth

h. Hereditary neuropathy (sensory and autonomic neuropathy, motor neuropathy, or with tendency to pressure palsy)

i. Neuropathy associated with a genetic disorder (Adrenomyeloneuropathy, MNGIE [mitochondrial neuropathy, with gastrointestinal symptoms and encephalopathy], NARP [neuropathy ataxia retinal pigmentosa], CANOMAD [chronic ataxic neuropathy, with ophthalmoplegia, monoclonal protein, cold agglutins and disialosyl antibodies], *etc*)

j. Amyloid associated neuropathy (Transthyretin familial amyloid polyneuropathy, AL amyloidosis, POEMS (polyneuropathy, organomegaly, endocrinopathy, m protein, skin changes)

k. Neuropathy associated with other autoimmune disorder (*i.e.* Anti myelin associated glycoprotein (MAG) neuropathy, Anti-sulfatide antibody neuropathy, Multifocal motor neuropathy, Guillain barre syndrome, Celiac disease, *etc*)

l. Neuropathy associated with rheumatologic autoimmune disease (*i.e.* Systemic lupus erythematosus, Vasculitis, Sjogren's disease, Wegener's granulomatosus, Churg-Straus, cryoglobulinemia, Sarcoidosis, Rheumatoid arthritis, *etc*)

m. Toxic neuropathy (*i.e.* Pyridoxine (B6) toxicity, Amiodarone, Colchicine, Isoniazid, Dapsone, Phenytoin, disulfiram, Dideoxynucletides, Metronidazole, Nitrofurantoin, Arsenic, Lead, Mercury, Thallium, Acrylamide, N-hexane, *etc*)

n. Neuropathy associated with infectious etiology (*i.e.* HIV, Leprosy, Lyme disease, Hepatitis C, Diphtheria, *etc*)

o. Paraneoplastic neuropathy (*i.e.* associated with Anti-hu antibodies or Anti-CV2 (crmp5) antibodies, *etc*)

p. Critical illness neuropathy

q. Uremic Neuropathy

r. Neuropathy associated with thyroid disease (Hyperthyroidism or Hypothyroidism)

s. Other cause of neuropathy

t. Unknown cause of neuropathy

Appendix 18.6 References

1 Peter J Dyck, PK Thomas, eds. Peripheral Neuropathy. Philadelphia: WB Saunders, 2005.

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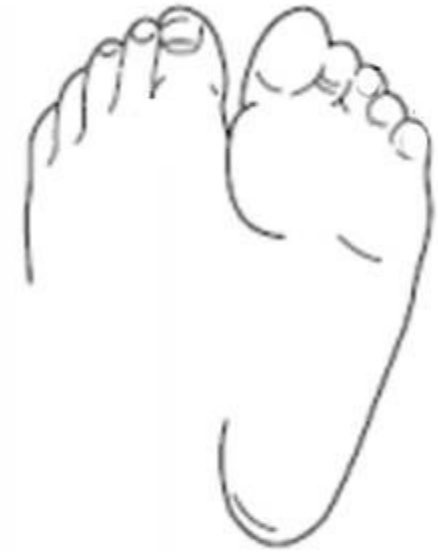
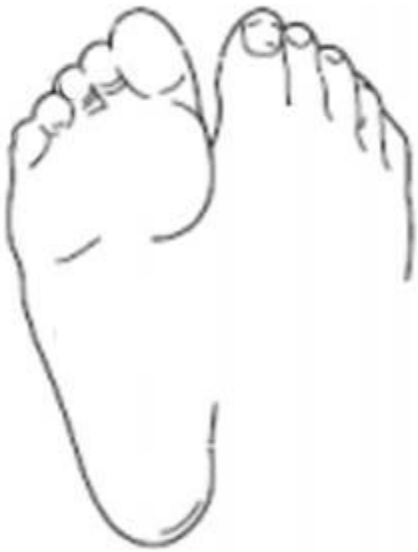
18.7 Foot Diagram



Left foot



Right foot

18.8 Translational Medicine - Pharmacokinetic Prediction of Taxane-Induced Peripheral Neuropathy

a. Primary Objectives

1. The primary pharmacokinetic (PK) objective is to confirm the association between paclitaxel maximum concentration (Cmax) at the end of first infusion and the occurrence of peripheral neuropathy (PN) in patients receiving weekly 1-hour paclitaxel infusions of 80 mg/m2.

b. Secondary Objectives

1. Investigate the association between paclitaxel Cmax at the end of first infusion and the occurrence of PN in patients receiving other paclitaxel regimens.

2. Investigate the association between docetaxel Cmax at the end of first infusion and the occurrence of PN in patients receiving any docetaxel regimen.

c. Other Objectives

1. Investigate the association between paclitaxel or docetaxel Cmax at the end of first infusion with a secondary phenotype of the cumulative dose at occurrence of treatment-limiting PN (dose delay, decrease, or discontinuation.

d. Background

Paclitaxel pharmacokinetics, or exposure, has been associated with peripheral neuropathy (PN) in retrospective analyses of multiple patient cohorts receiving mixed paclitaxel regimens. (*1*) In a randomized clinical trial of lung cancer patients receiving 3-hour paclitaxel infusions in combination with a platinum agent every 2 weeks, patients randomized to PK-guided paclitaxel had significantly decreased PN incidence (grade ≥2 (38% vs. 23%, $P < 0.001$) and grade ≥3 (9% vs. 2%, $P < 0.001$)), with no corresponding decrease in treatment efficacy. (*2*,*3*) This confirms the importance of exposure from 3-hour paclitaxel infusions in PN occurrence. The paclitaxel exposure parameter used within this study was the “Time Above Threshold,” which is the number of hours that the patient’s systemic concentration remains above a concentration threshold of 0.05 uM (Tc>0.05). This parameter requires collection of a sample 16-26 hours after paclitaxel infusion, limiting its clinical use. Cmax can be collected at the end of infusion, providing a much more clinically feasible biomarker for personalizing taxane treatment.

e. Rationale and Hypothesis

Our preliminary data, prospectively collected within an observational clinical trial of 60 patients with breast cancer receiving weekly 1-hour infusions of 80 mg/m2 paclitaxel, confirmed an increased incidence of treatment-limiting PN in patients with higher paclitaxel Tc>0.05 (odds ratio (OR)=1.79, 95% confidence interval (CI): 1.06-3.01, p=0.029) or maximum concentration (Cmax) (OR=2.74, 95% CI: 1.45-5.20, p=0.002) after the first dose. (*4*) Importantly, Cmax, conveniently collected at the end of infusion, was a stronger predictor of PN than Tc>0.05. The primary objective of this analysis is to confirm that paclitaxel Cmax at the end of standard 1-hour infusion is associated with risk of PN.

There is limited evidence about the relationship between paclitaxel Cmax and PN for other commonly used regimens and there is a paucity of data regarding the relationship between docetaxel exposure and PN, likely because PN is not typically the dose-limiting toxicity of docetaxel. This study provides a unique opportunity to investigate the relationships between paclitaxel and docetaxel Cmax in the first cycle and the eventual onset of PN, in order to identify evidence-based exposure targets for prospective clinical trials of exposure-guided treatment.

f. Eligibility

All patients enrolled on S1714 with a plasma specimen collected at the end of infusion (PK) will be eligible for analysis.

g. Experimental Approach and Assays

1. Specimen Collection and Timepoints

Sites have collected and processed 10 mL of whole blood for PK as outlined in Section 15.0. Samples were collected before infusion ends, but no more than 10 minutes prior to the end of infusion.

2. Laboratory Plan

University of Michigan Pharmacokinetics Core
Amit Pai, PharmD, Deputy Director:
Room 3400, Building 520
North Campus Research Complex
1600 Huron Parkway, Ann Arbor, MI 48109
Phone: 734-615-3470
Email: amitpai@med.umich.edu

3. Description of Assay or Platform

Similar to the previous work of Dr. Hertz (*5*), plasma samples will be analyzed at the UM PK Core (Directors Duxin Sun, PhD, and Amit Pai, PharmD) to measure Cmax via a validated liquid chromatography/mass spectroscopy assay described below.

4. Methods

Measurement of plasma paclitaxel concentration for all samples in a single batch was conducted by the University of Michigan College of Pharmacy Pharmacokinetics Core using a liquid chromatography/mass spectroscopy assay. Briefly, a Shimadzu HPLC system, and chromatographic separation of tested compound was achieved using a Waters XBridge-C18 column (5 cm × 2.1 mm, 3.5 µm). An AB Sciex QTrap 5500 mass spectrometer equipped with an electrospray ionization source (Applied Biosystems, Toronto, Canada) in the positive-ion multiple reaction monitoring (MRM) mode was used for detection. This assay is highly sensitive (lower limit of quantification=5 ng/mL), with a dynamic range of 5-5000 ng/mL and has inter-batch coefficient of variation <15%. Briefly, proteins were removed from plasma samples by precipitation with Acetonitrile and centrifugation for 10 minutes at 14,000 rpm. Supernatants were collected and further separated using liquid chromatography with gradient elution containing mobile phases of water and acetonitrile ACN with 1% formic acid. Paclitaxel and internal standard docetaxel were detected using multiple reaction monitoring transitions from 854.5 to 286.1 m/z and 808.6 to 226.0 m/z, respectively. Mass spectrometry parameter r optimization was performed using an automated quantitative method provided by the manufacturer. The highest signal intensities were obtained using a declustering potential of 27.80 V, entrance potential of 9.00 V, collision energy of 22.00 V, and collision cell exit potential of 2.5 V. Optimized parameters enable quantitation of paclitaxel concentrations over the linear range of 5 – 5000 ng/ml.

h. Statistical Design and Underlying Assumptions

1. Variable definitions:

Primary endpoint (dependent variable): Development of peripheral neuropathy (PN)
The primary endpoint in this study is development of peripheral neuropathy, as defined in Section 10.1. We will code patients in binary categories; specifically, patients will be coded as a 1 if they have experienced an increase of ≥8 points and 0 if they have not. A continuous score will also be analyzed, and additional cut points will also be explored.

Secondary endpoints (dependent variable): Treatment limiting PN and Cumulative dose at occurrence of treatment-limiting PN
Dose delay, decrease, or discontinuation is collected on the treatment form as a delay, change or discontinuation of the regimen due to symptoms of peripheral neuropathy (and not other reasons). We will examine the occurrence of treatment-limiting PN as 0 (no) and 1 (yes).

For patients who report one of these outcomes, we will use the total reported dose in mg/m2 at the time of the event.

2. Main independent variables:

- Cmax (maximum concentration) at the end of the first infusion.
  - As a continuous measure
  - Classified as above/below a cutoff (if a cutoff of interest can be identified)

i. Data Analysis

1. Analysis population

We expect 60% of eligible patients to enroll to the paclitaxel cohort and 40% to the docetaxel cohort. All patients are required to have a PK sample collected at the end of the first infusion.

2. Analytic Plan

a. Primary/integrated pharmacokinetic (PK) objective

We will explore the relationship of Cmax with occurrence of PN as follows:

- Logistic regression, with PN as the endpoint and Cmax as a continuous measure (transformations will be explored if Cmax is poorly distributed)
- Linear regression, with the CIPN-20 sensory subscale as the endpoint and Cmax as a continuous measure (transformations will be explored if the sensory subscale and/or Cmax are poorly distributed)
- If possible, using a classification tree to define a cutoff beyond which Cmax is associated with occurrence of PN, then using this cutoff in a logistic regression model to describe the applicable increase in risk.

b. Secondary/integrated PK objectives

Similar analyses will be performed within the other Paclitaxel regimens. Within the docetaxel regimens, all regimens will be examined individually with linear regression, logistic regression and a classification tree followed by logistic regression. All Paclitaxel regimens and all Docetaxel regimens will be combined into single Paclitaxel/Docetaxel analyses to look for a regimen-independent cutoff for Cmax.

Appendix 18.8 References

1 Hertz DL. Exploring pharmacogenetics of paclitaxel- and docetaxel-induced peripheral neuropathy by evaluating the direct pharmacogenetic-pharmacokinetic and pharmacokinetic-neuropathy relationships. Expert Opin Drug Metab Toxicol. 2021 Feb;17(2):227-239. doi: 10.1080/17425255.2021.1856367. Epub 2021 Jan 6. PMID: 33401943; PMCID: PMC7864890.

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3 Hertz DL, Kidwell KM, Vangipuram K, Li F, Pai MP, Burness M, Griggs JJ, Schott AF, Van Poznak C, Hayes DF, Lavoie Smith EM, Henry NL. Paclitaxel Plasma Concentration after the First Infusion Predicts Treatment-Limiting Peripheral Neuropathy. Clin Cancer Res. 2018 Aug 1;24(15):3602-3610. doi: 10.1158/1078-0432.CCR-18-0656. Epub 2018 Apr 27. PMID: 29703818; PMCID: PMC6386454.

4 Hertz DL, Kidwell KM, Vangipuram K, Li F, Pai MP, Burness M, Griggs JJ, Schott AF, Van Poznak C, Hayes DF, Lavoie Smith EM, Henry NL. Paclitaxel Plasma Concentration after the First Infusion Predicts Treatment-Limiting Peripheral Neuropathy. Clin Cancer Res. 2018 Aug 1;24(15):3602-3610. doi: 10.1158/1078-0432.CCR-18-0656. Epub 2018 Apr 27. PMID: 29703818; PMCID: PMC6386454.

5 Hertz DL, Kidwell KM, Vangipuram K, Li F, Pai MP, Burness M, Griggs JJ, Schott AF, Van Poznak C, Hayes DF, Lavoie Smith EM, Henry NL. Paclitaxel Plasma Concentration after the First Infusion Predicts Treatment-Limiting Peripheral Neuropathy. Clin Cancer Res. 2018 Aug 1;24(15):3602-3610. doi: 10.1158/1078-0432.CCR-18-0656. Epub 2018 Apr 27. PMID: 29703818; PMCID: PMC6386454.

18.9 Translational Medicine – Genome-wide Pharmacogenetic Prediction of Taxane-Induced Peripheral Neuropathy (TIPN) (Funded R01)

a. Objectives

1. Primary

The primary pharmacogenetic (PGx) objective is to examine the association of EPHA5 (rs7349683) with sensitivity to TIPN after adjusting for systemic exposure and other clinical TIPN predictors.

2. Secondary

The secondary PGx objective is to conduct genome-wide association of all genotypes and imputed genetic variants with sensitivity to TIPN after adjusting for systemic exposure and other clinical TIPN predictors.

3. Exploratory

Another objective is to explore whether SNP associations identified in primary and secondary objectives are taxane-specific or shared between the two drugs.

Additionally, exploratory analyses will determine whether SNP associations with TIPN sensitivity are also associated with other TIPN endpoints (e.g., CTCAE, quality of life, objective measures) and the clinically relevant endpoint of taxane treatment alteration due to TIPN.

Finally, exploratory analyses will determine whether gene-based analyses identify genes or genetically-defined pathways that are associated with TIPN sensitivity or other TIPN-related endpoints.

b. Background

Many candidate single nucleotide polymorphisms (SNPs) have been reported as predictors of taxane-induced PN, however, most of these studies were conducted in small, heterogeneous patient cohorts and used liberal statistical cutoffs. The strongest candidate SNPs have derived from unbiased genome-wide association studies (GWAS) conducted within large, prospective clinical trial cohorts. There have been several GWAS of taxane-induced PN, some of which have yielded candidate SNPs that have been challenging to replicate. (*1*, *2*) Of these candidates, the EPHA genes have been replicated most consistently (*3*, *4*, *5*) strongly suggesting that the EPHA gene family, which are known to be critical to nervous system development and nerve injury repair, is involved in determining genetic predisposition to paclitaxel-induced neuropathy.

Paclitaxel systemic concentration is a validated biomarker of TIPN *(6)*. Paclitaxel dose reduction to achieve target systemic concentrations decreases TIPN, but ~10% of patients still experience TIPN *(7)*. These patients have an inherent sensitivity to TIPN, likely due to some genetic predisposition. Previous studies have been unable to validate genetic TIPN predictors due to their *inability to adjust for systemic taxane concentrations.*

c. Rationale and Hypothesis

This large cohort of paclitaxel and docetaxel treated patients (n=1,321) with systematically collected, patient-reported PN data provides a unique opportunity to validate previously reported candidate SNPs and determine whether validated associations are shared between the taxanes or are taxane-specific. This is critical for clinical translation, as taxane-specific markers would provide an evidence-based reason to select one taxane or the other.

Dr. Hertz previously conducted a proof-of-principle analysis in his cohort of paclitaxel treated patients with patient-reported TIPN data (UMCC2014.002, n=60). *(8)* First, a Clinical TIPN Prediction Model including patient (age, baseline neuropathy), treatment (cumulative paclitaxel dosing), and systemic paclitaxel exposure was generated. *(9)* Then, genetic variants in hereditary neuropathy-linked genes previously associated with TIPN risk, including *EPHA4/5/6*, *ARGHEF10*, and *FZD3,* were sequenced and tested for association with TIPN by incorporating them into the Clinical TIPN Prediction Model that adjusted for measured systemic paclitaxel concentrations. These studies demonstrated that *EPHA5* rs7349683, which had been reported to increase TIPN in several studies, increases TIPN and *this association was only detectable when controlling for other TIPN risk factors including systemic exposure. (10)* Our hypothesis is that genetic variants associated with TIPN sensitivity can be validated (*EPHA5* rs7349683) and discovered (genome-wide association) in S1714 by following this model of integrating PGx into a clinical TIPN Risk Prediction Model.

d. Experimental Approach and Assays

1. Sample Collection and Timepoints

Sites have processed 10 mL of whole blood for PGx into lavender top EDTA tubes as outlined in Section 15.0. PGx samples were collected at baseline (within 14 days after registration to S1714 and prior to first taxane administration).

2. Laboratory Plan

University of Michigan Advanced Genomics Core
C560 MSRB II, 1150 W. Medical Center Dr.
Ph. 734-647-4776
Fax. 734-936-2622
Email: okoues@med.umich.edu
Personnel: Olivia Koues, PhD, Director of UM Advanced Genomics Core

3. Description of Assay or Platform

Genome-wide genotyping panel.

4. Methods

Germline DNA will be genotyped on the Infinium Global Diversity Array with Enhanced PGx-8 v1.0 in the University of Michigan Advanced Genomics Core. This array contains more than 1.9M variants, including a robust genome-wide backbone and comprehensive coverage of functionally consequential variants in relevant pharmacogenes based on data from CPIC, PharmGKB, and other curated sites. The PI has previously conducted GWAS in collaboration with the UM Advanced Genomics Core using this same GWAS array. *(11,12)*

e. Statistical Design and Underlying Assumptions

1. Variable definitions:

Primary endpoint (dependent variable): Development of peripheral neuropathy (PN)

The primary endpoint in this study is the development of peripheral neuropathy, as defined in Section 10.1. We will code patients in binary categories; specifically, patients will be coded as a 1 if they have experienced an increase of ≥8 points and 0 if they have not. A continuous score will also be analyzed, and additional cut points will also be explored.

Secondary endpoints (dependent variable): Treatment limiting PN and Cumulative dose at occurrence of treatment-limiting PN

Dose delay, decrease, or discontinuation is collected on the treatment form as a delay, change or discontinuation of the regimen due to symptoms of peripheral neuropathy (and not other reasons). We will examine the occurrence of treatment-limiting PN as 0 (no) and 1 (yes).

For patients who report one of these outcomes, we will use the total reported dose in mg/m2 at the time of the event.

2. Main independent variables:

- Variant genotype (genotyped or imputed) at each genetic position.
  - Assuming a dominant genetic effect
  - Assuming an additive genetic effect)

f. Data Analysis

The primary analysis will test the association of each variant with our PN endpoint after adjustment for measured systemic taxane concentration and other clinical variables associated with PN from the primary analysis of S1714 using a trend test assuming an additive genetic effect. Each genotyped or imputed variant that passes quality control will be tested for an association using a standard genome-wide significance threshold ($\alpha=5x10^{-8}$) in PLINK 2.0. The primary analysis will attempt to validate that patients who carry candidate variants in *EPHA5* rs7349683 have increased TIPN risk after accounting for systemic taxane exposure and other clinical variables. Prior to analysis, we will review all TIPN pharmacogenetics literature to generate a list of candidate variants, particularly those listed previously in genes related to hereditary neuropathy, to test in pre-specified, Bonferroni-corrected confirmatory secondary analyses.

Variants associated with TIPN, and those in linkage disequilibrium, will be investigated in secondary analyses to identify functionally consequential causal variants using various *in silico* tools commonly used in GWAS. (*13*, *14*, *15*, *16*)

Gene-based approaches will also be explored to identify genes or networks that are enriched in our most strongly associated variants including gene set enrichment analysis (GSEA) methodology. (*17*)

Since sample collection of whole blood was mandatory, we have already banked samples from over 1100 eligible patients (with more being submitted by SWOG sites). Assuming 30% of patients have PN, then for our primary analysis of *EPHA5* rs7349683, we anticipate 80% power to detect a true genetic OR of 1.30 based on the known minor allele frequency (MAF) ~35%. For the remaining SNPs, at the genome wide significance level ($5x10^{-8}$), we anticipate 80% power to detect a true genetic OR of 1.90, 1.81, and 1.78 for a SNP with MAF of 25%, 35%, or 45%. Accordingly, we anticipate sufficient power for our primary analyses and modest power for the secondary agnostic screen, while noting that TIPN is an unusual phenotype as it has not been subjected to the same degree of evolutionary pressures as more typical complex traits such that we can anticipate larger effect sizes.

Appendix 18.9 References

1 Hertz DL, Owzar K, Lessans S et al. Pharmacogenetic Discovery in CALGB (Alliance) 90401 and Mechanistic Validation of a VAC14 Polymorphism that Increases Risk of Docetaxel-Induced Neuropathy. Clin Cancer Res 2016; 22 (19): 4890-4900.

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5 Abraham JE, Guo Q, Dorling L et al. Replication of Genetic Polymorphisms Reported to be Associated with Taxane-Related Sensory Neuropathy in Early Breast Cancer Patients treated with Paclitaxel. 2014.

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7 Joerger M, von Pawel J, Kraff S, Fischer JR, Eberhardt W, Gauler TC, Mueller L, Reinmuth N, Reck M, Kimmich M, Mayer F, Kopp HG, Behringer DM, Ko YD, Hilger RA, Roessler M, Kloft C, Henrich A, Moritz B, Miller MC, Salamone SJ, Jaehde U. Open-label, randomized study of individualized, pharmacokinetically (PK)-guided dosing of paclitaxel combined with carboplatin or cisplatin in patients with advanced non-small-cell lung cancer (NSCLC). Ann Oncol. 2016 Oct;27(10):1895-902. doi: 10.1093/annonc/mdw290. Epub 2016 Aug 8. PMID: 27502710.

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18.10 Translational Medicine – Nutrient Prediction of Taxane-Induced Peripheral Neuropathy (TIPN) (Funded R01)

a. Objectives

1. Primary

Evaluate the hypothesis that pre-treatment vitamin D insufficiency is associated with the risk of taxane-induced peripheral neuropathy.

2. Secondary

a. Evaluate the hypothesis that pre-treatment histidine level is associated with the risk of taxane-induced peripheral neuropathy.

b. Evaluate the hypothesis that pre-treatment sphingomyelin 42:6;O2 level is inversely associated with the risk of taxane-induced peripheral neuropathy.

c. To explore pre-treatment metabolomic signatures that predict taxane-induced peripheral neuropathy

b. Background

A pre-specified objective of S1714 was to collect samples in anticipation of future assessment of biomarkers including kinetics, genetics, and metabolomics. In prior work conducted in a cohort of 60 paclitaxel treated patients, Dr. Hertz demonstrated that patients who have vitamin D insufficiency (<20 ng/mL, n=15) have greater increase in patient-reported neuropathy during paclitaxel treatment (36.39 vs. 16.29, p=0.035) (*1*), which he then confirmed in a retrospective analysis of the prospective SWOG S0221 cohort. (*2*)

Dr. Hertz then conducted NMR metabolomics analysis of pre-treatment blood samples, which identified three amino acids that were inversely associated with patient-reported neuropathy severity, of which the strongest association was for histidine (r=-0.38, p=0.008). (*3*) He is currently analyzing these amino acids in S0221 using ACS funding.

Lipidomics is a subtype of metabolomics that focuses on circulating lipid levels. Our lipidomics analysis quantified 821 lipids, of which 18 were associated with TIPN severity (false discovery rate (FDR)<0.05), including a shorter-chain sphingomyelin SM 42:6;O2 (β=3.5, 95% CI: 1.8, 5.1, p<0.001, FDR=0.04, unpublished data). Other investigators have reported that baseline and on-treatment concentrations of shorter-chain sphingomyelin (34:1;O2) and 1-deoxysphinganine were associated with vincristine- and paclitaxel-induced neuropathy. (*4*, *5*)

We will attempt to validate these prior findings and conduct further neuropathy biomarker discovery using this large cohort with uniquely detailed neuropathy phenotype data and banked biosamples.

c. Rationale and Hypothesis

This large cohort of paclitaxel and docetaxel treated patients (n=1,321) with systematically collected, patient-reported PN data provides a unique opportunity to validate previously reported candidate nutrient and metabolomic biomarkers. We will attempt to validate our previously identified biomarker candidates and conduct additional biomarker discovery using this large cohort of patients with comprehensive TIPN data.

d. Experimental Approach and Assays

1. Sample Collection and Timepoints

Sites have processed 6 aliquots each of baseline serum and plasma. The requested samples for this analysis include 1 aliquot (0.6 mL) of plasma for vitamin D and metabolomics.

2. Laboratory Plan

Vitamin D Analysis
Heartland Assays
Iowa State University Research Park, 2711 S. Loop Dr.,
Ste 4400, Ames, IA 50010
Ph.515-296-0909, Fax.515-296-0908
Email: John.Rathmacher@heartlandassays.com
Personnel: Andrew J Makowski, Analytical Chemist

Amino Acid Metabolomics and Lipidomics Analyses
Metabolon, Inc
617 Davis Dr Suite 100, Morrisville, NC 27560
Scott Evans (regional Metabolon representative)
Ph. 734-972-2195
Email: sevans@metabolon.com
Personnel: per Metabolon

3. Description of Assay or Platform and Methods

Measurement of Serum Vitamin D
25-hydroxyvitamin D will be measured via HPLC/MS/MS by Heartland Assays (*6*), who are certified through the CDC's Vitamin D Standardization-Certification Program and the DEQAS proficiency program.

Measurement of Serum Amino Acids and Lipids
Amino acid metabolomics and plasma lipidomics will be measured simultaneously by Metabolon (Durham, NC). We will use Metabolon's Global Discovery Panel, which identifies >5,000 metabolites including >450 metabolites (i.e., amino acids, cofactors, nutrients) and >1,000 lipids (i.e., phospholipids, sphingolipids). Metabolon is the industry leader in metabolomics analysis, with >3,500 publications using their metabolomics panels. Dr. Kathleen Stringer (Co-I of the S1714 R37) is a metabolomics expert who has recent experience analyzing Metabolon data.

e. Statistical Design and Underlying Assumptions

1. Variable definitions:

Primary endpoint (dependent variable): Development of peripheral neuropathy (PN)
The primary endpoint in this study is development of peripheral neuropathy (PN), as defined in Section 10.1. We will code patients in binary categories; specifically, patients will be coded as a 1 if they have experienced an increase of ≥8 points and 0 if they have not. A continuous score will also be analyzed, and additional cutpoints will also be explored.

Secondary endpoints (dependent variable): Treatment limiting PN and Cumulative dose at occurrence of treatment-limiting PN
Dose delay, decrease, or discontinuation is collected on the treatment form as a delay, change or discontinuation of the regimen due to symptoms of peripheral neuropathy (and not other reasons). We will examine the occurrence of treatment-limiting PN as 0 (no) and 1 (yes).

For patients who report one of these outcomes, we will use the total reported dose in mg/m2 at the time of the event.

2. Main independent variables:

- Vitamin D
  - Deficiency defined by <20 ng/mL
  - Measured concentration on a continuous scale
- Histidine
  - Measured concentration on a continuous scale
- Sphingomyelin 42:6;O2
  - Measured concentration on a continuous scale

f. Data Analysis

Primary Objective 1: To assess whether pre-treatment VitD insufficiency (<20 ng/mL) is associated with PN, we will use logistic regression to regress PN status on dichotomous VitD insufficiency. Significance will be called at the 2-sided α=0.05 level using a 1-df test. Assuming that the rate of PN is approximately 30% in patients without VitD insufficiency and that 35% (350) patients are VitD insufficient prior to treatment, then we anticipate 80% power to detect a relative risk of 1.29.

Secondary Objective 1: To assess whether pre-treatment histidine levels are inversely associated with PN, we will use logistic regression to regress PN status on quantitative histidine levels, again using a 1-df test at the 2-sided α=0.05 level. Then assuming population risk of PN of 30%, we anticipate 80% power to detect relative risks of 1.21, 1.22, and 1.23 per standard deviation increase in histidine levels if the observed proportion of patients with PN is 35%, 30% and 25%, respectively.

Secondary Objective 2: To assess whether pre-treatment sphingomyelin 42:6;O2 levels are associated with PN, we will use logistic regression to regress PN status on quantitative sphingomyelin 42:6;O2 levels, again using a 1-df test at the 2-sided

α=0.05 level. Then assuming population risk of PN of 30%, we anticipate 80% power to detect relative risks of 1.21, 1.22, and 1.23 per standard deviation decrease in sphingomyelin 42:6;O2 levels if the observed proportion of patients with PN is 35%, 30% and 25%, respectively.

Secondary Objective 3: To further discover potential pre-treatment metabolomic, lipidomic, and proteomic signatures that predict PN, we will apply sure-independence screening(61) to reduce the number of potential metabolites, lipids and proteins. Then we will use sparse penalized regression to regress PN status on the remaining metabolites and proteins, using cross-validation to select the regularization parameters. The regression coefficients will be used as weights to construct the final signature. The in-sample prediction error and the (doubly) cross-validated prediction error will serve as theoretical upper and lower-bounds on the true prediction error. As secondary analysis, we will consider the use of alternative tree-based, margin-based, and boosting classifiers. Separate analyses will be conducted focused on targeted and named proteins.

For all analyses, we will carefully consider adjustment for covariates, including age, diabetes, taxane regimen, and relative dose intensity, and potential technical confounders (e.g. batch variables). Continuous variables will be carefully transformed to encourage normality. Alternative, including robust and rank based, approaches will be considered in the situation in which regression models are unstable or when distributional assumptions are violated. Possible nonlinearity and interactive effects will be considered.

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18.11 Imaging Study – Personalized Taxane Infusion Rate Recommendations to Reduce Neuropathy Risk in Patients with Low Skeletal Muscle Area

a. Objectives

1. Primary:

   Estimate SMA-based taxane infusion rates for 1-hour paclitaxel (Pac1h) and docetaxel (Doc1h) to prevent supratherapeutic Cmax and reduce TIPN risk in female patients with breast cancer.

2. Secondary

   a. Estimate SMA-based taxane infusion rates for other regimens (i.e., 3-hour paclitaxel), tumor types (i.e., lung, ovarian), and sexes (males) to prevent supratherapeutic Cmax and reduce TIPN risk.

   b. Generate a longitudinal TIPN prediction model to simulate the potential TIPN reduction from SMA-based personalized taxane infusion rate dosing.

b. Background

Approximately 70% of patients who receive taxanes (e.g., paclitaxel, docetaxel) are affected by taxane-induced peripheral neuropathy (TIPN), which diminishes long-term functional ability and quality of life. Since there are no effective TIPN treatments, ~25% of patients require treatment alterations (e.g., delay, decrease, discontinue dosing) that compromise efficacy. Taxanes are dosed by body surface area and typically infused over one hour: paclitaxel 80 mg/m^2 (Pac1h), docetaxel 75 mg/m^2 (Doc1h). Patients with higher systemic paclitaxel concentrations at the end of infusion (C_{max}) experience greater TIPN *(1)*. Reducing paclitaxel doses in patients with supratherapeutic concentrations (i.e., therapeutic drug monitoring) reduces TIPN *(2)*, but measuring concentrations is clinically impractical and reducing doses could reduce efficacy. There is a need to develop clinically practical personalized dosing strategies that reduce TIPN while preserving full taxane dosing and efficacy.

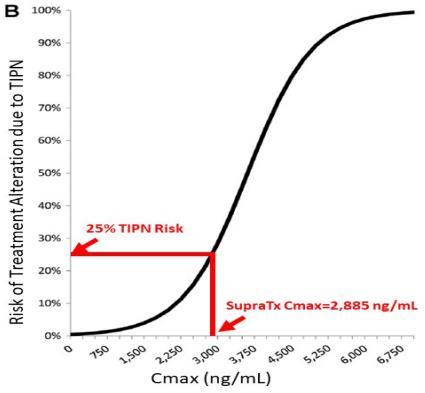

Figure 1: Supratherapeutic C_{max}=2,885 ng/mL for Pac1h, above which risk of TIPN is >25%. Adapted from Ref 1.

Patients with the same BSA can have different body composition, including differences in skeletal muscle area (SMA) that can be estimated from clinical computed tomography (CT) scans. Our UM Rogel Pilot (UMCC 2015.02, NCT02338115, PI: DL Hertz) enrolled 59 patients with breast cancer receiving adjuvant weekly 80 mg/m^2 Pac1h. Higher C_{max} was associated with greater TIPN-induced treatment alteration (n=19, 32%, OR = 2.74, p = 0.002) *(1)*. Our modeling estimated the supratherapeutic C_{max}, above which the risk of TIPN-induced treatment alteration was unacceptable (>25%), is 2,885 ng/mL **(Figure 1**) *(1)*.

Patients with lower skeletal muscle area (SMA), also referred to as “sarcopenia,” have higher rates of chemotherapy toxicity, including taxanes *(3)*. 39 (66%) participants in our Pilot had a clinical CT scan to estimate >200 body composition measures using an automated image analysis process developed by the UM Morphomics Analysis Group. The optimal Pac1h pharmacokinetic model included SMA at the Thoracic 11 (T11) vertebra as a covariate on volume of distribution, which determines C_{max}; patients with lower SMA have higher paclitaxel C_{max}, likely explaining their higher risk of toxicity.

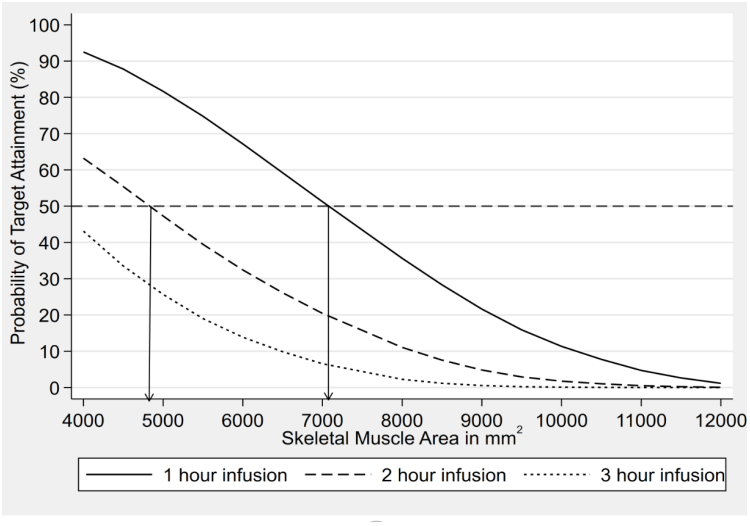

Figure 2: Model simulations were conducted to estimate SMA-based infusion rate recommendations for paclitaxel 80 mg/m^2. The threshold for supratherapeutic C_{max} was set at 50% (horizontal hatched line). Patients with SMA>7,080 mm^2 should receive a standard 80 mg/m^2 1-hour infusion. Extended 2-hour and 3-hour infusions of 80 mg/m^2 are recommended for patients with Low-SMA (4,907-7,080 mm^2) and sarcopenic SMA (<4,907 mm^2), respectively.

The SMA-C_{max} model was used to estimate the likelihood of exceeding supratherapeutic C_{max} (i.e., 2,885 ng/mL) for a patient with any physiological SMA receiving the standard Pac1h 80 mg/m^2 infusion. Using an acceptability threshold of <50% risk of exceeding supratherapeutic C_{max} (**Figure 2**, horizontal hatched line), patients with SMA<7080 mm^2 have unacceptable risk (Solid curved Line). We then simulated the risk of supratherapeutic C_{max} in patients with any physiological SMA who received the standard 80 mg/m^2 dose over a slower 2-hour (Dashed Line) or 3-hour (Dotted Line) infusion. Based on these simulations, patients with SMA 4907-7080 mm^2 (~23% of age-adjusted females) should receive a 2-hour infusion and patients with sarcopenic SMA (SMA<4907 mm^2, ~2%) should receive a 3-hour infusion of paclitaxel 80 mg/m^2 to avoid supratherapeutic C_{max} and unacceptable TIPN risk. *(4)*

Slowing taxane infusion rates in patients with low SMA, based on existing CT scans, is a clinically practical personalized dosing strategy that could reduce TIPN while preserving full dosing (i.e., 80 mg/m^2). An ongoing Interventional Pharmacokinetics study is investigating whether slowing taxane infusion rates in

patients with low SMA receiving Pac1h normalizes their taxane C_{max} (UMCC 2021.109, PI: DL Hertz). This SWOG proposal will allow us to validate our SMA-based Pac1h dosing recommendations in patients with breast cancer and extend this approach to Doc1h and Pac3h, and other tumor types, using SWOG S1714 data. This preliminary data is critical to design a prospective SWOG trial to investigate whether SMA-based taxane infusion rate dosing reduces TIPN and treatment alterations, thus preserving treatment efficacy. This would justify using this strategy as standard of care to reduce TIPN and improve treatment outcomes in patients with cancer.

c. Rationale

Existing clinical CT scans will obtained for S1714 participants and analyzed by the UM Morphomics Analysis Group to estimate SMA and other body composition metrics *(4)* to be used in modeling similar to that performed in our Rogel Pilot. All other data are already available within the S1714 clinical trial including taxane Cmax and TIPN.

d. Eligibility

All S1714 participants (n=1,353) who have a clinical CT scan available at their enrolling institution will be eligible, though the primary analysis will be conducted in female patients with breast cancer who received Pac1h (n=562) or Doc1h (n=489). Clinical CT scans of the chest, abdomen, or thorax within 6 months prior or 1 month after S1714 enrollment will be collected for S1714 participants following the process used by Co-I Dr. Richard Dunne to obtain CT scans from participants on the URCC13059 NCORP trial. One of the highest accruing S1714 sites randomly selected n=20 S1714 participants and found 6 (30%) had an evaluable CT scan, yielding an estimated n≈400 S1714 participants with evaluable CT scans.

e. Clinical Data

The primary endpoint for our modeling is the taxane C_{max}, which we have already measured for S1714 participants in the UM Pharmacokinetics Core. In order for our group to conduct all of the modeling we propose, we will need the S1714 primary endpoint data, specifically the sensory subscale of the CIPN20 (CIPN8) from baseline to 24-weeks. *(5)* Additionally, we will need patient (height, weight and calculated BSA) and taxane treatment (infusion start and stop time and taxane doses administered, pharmacokinetic sample collection time) data for our modeling.

f. Experimental Approach:

The experimental approach follows the approach we used in our Rogel Pilot (Described in Brief Justification) to model the SMA-C_{max} and C_{max}-TIPN relationships, and use simulations to determine the SMA thresholds below which

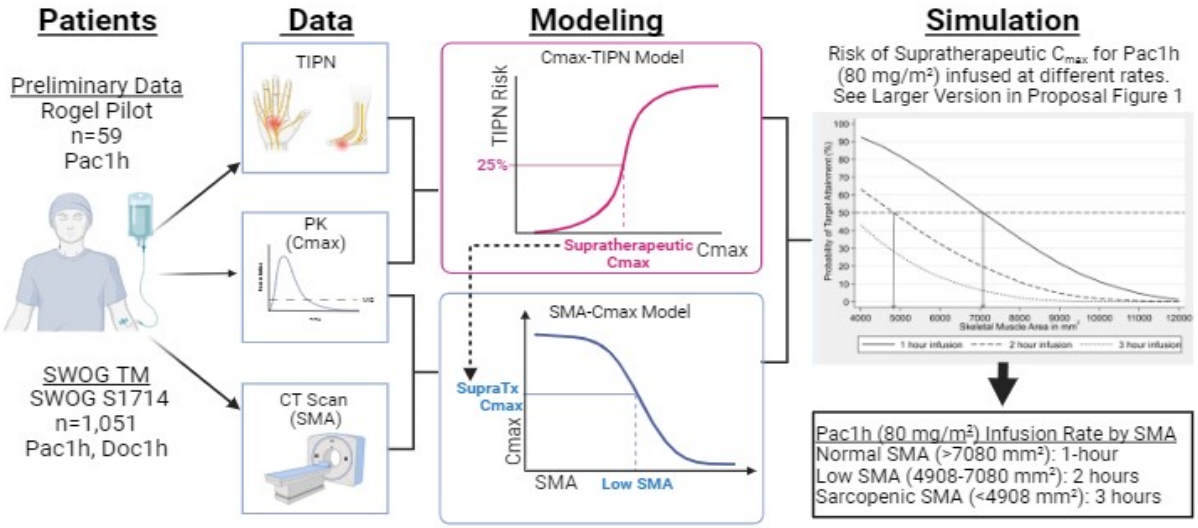

Figure 3: Workflow for Preliminary Data (Pac1h) and this SWOG TM Proposal (Pac 1h, Doc1h) to estimate SMA-based infusion rates to prevent supratherapeutic C_{max} and reduce TIPN risk.

patients require an extended infusion to prevent supratherapeutic C_{max} and unacceptable TIPN risk (**Figure 3)**.

The PI, Daniel Hertz, PharmD, PhD, is a clinical pharmacologist with expertise in TIPN biomarker analysis and taxane clinical pharmacology. He is the translational medicine chair of S1714 and the submitting MPI of a funded R37 (1R37CA277043) to conduct TIPN biomarker analyses in S1714. This proposal describes an analysis workflow that is nearly identical to that which he already completed in the Rogel Pilot for Pac1h *(4)*. He is collaborating with a team of Co-I who have already used this process to: collect existing clinical CT scans for an NCORP study (Dr. Richard Dunne), analyze CT scans to estimate SMA (Dr. Sven Holcombe), PK modeling and simulation to estimate SMA-based infusion rate recommendations (Dr. Amit Pai), and the clinical PI of S1714 (Dr. Meghna Trivedi) and co-chair of the SWOG Symptom Control and Quality of Life committee (Dr. Lynn Henry).

g. Statistical Plan:

Our primary analysis will use PK modeling to generate SMA-based infusion rate recommendations for Pac1h (n=562) and Doc1h (n=489) in females with breast cancer with existing clinical CT scans.

S1714 also enrolled n=52 participants who received paclitaxel 175 mg/m^2 infused over 3-hours, n=123 participants with ovarian or lung cancer, and n=8 males. We will use the C_{max} data from these participants and attempt to extrapolate from the Pac1h SMA-C_{max} and C_{max}-TIPN models to generate SMA-based taxane infusion rate recommendations for Pac3h, and patients with other tumor types and male patients in secondary analyses.

The other secondary analysis will use the C_{max}-TIPN model to simulate the longitudinal effect of SMA-based taxane infusion rate dosing throughout treatment on the predicted incidence of TIPN. We anticipate the simulations will support our

hypothesis that SMA-based infusion rate dosing will limit the risk of TIPN to <25% in all patients.

h. Data analysis performed by:

Image analysis will be performed by Co-I Sven Holcombe and the University of Michigan Morphomics Analysis Group within the Department of Surgery: https://www.med.umich.edu/surgery/morphomics/, 1150 W. Medical Center Drive, 3328 Med Sci 1-SPC 5677, Ann Arbor, Michigan 48109, 734.764.7841, morphomics@umich.edu

Modeling and simulation will be performed by Yuchen Sun, a PhD candidate being advised by Co-Is Drs. Hertz, Pai, and Henry. Dr. Pai conducted the modeling and simulation for the Rogel Pilot study described in the preliminary data[6] *(4)*. Dr. Henry is a co-author on this prior work and co-Chair of the SWOG Symptom Management and Survivorship Committee that ran **S1714**.

Data to be correlated with images:

C_{max}: Measured in plasma samples collected at the end of first infusion in **S1714** (data already exist)
TIPN: Sensory CIPN8 subscale from CIPN20 collected during SWOG **S1714** (data already exist)

i. Image Requirements and Timepoints:

Patients are being asked to provide clinical CT scans that were performed as part of standard of care. No new scans will be performed. The clinical CT scans of the chest, abdomen, or thorax performed within 6 months prior or 1 month after **S1714** registration will be submitted via TRIAD. See Section 15.2 for submission details.

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