Efficacy of Weekly Carboplatin and Paclitaxel with Trastuzumab and Pertuzumab (wPCbTP) and Switching to an Anthracycline-based Regimen (AC) in Non-responding Patients as Neoadjuvant Therapy in Clinical Stage I-III HER2-positive Breast Cancer: BrUOG BR-308

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I. Introduction

Administration of neoadjuvant chemotherapy and HER2-targeted therapy results in high clinical and pathologic response rates in patients with stage II-III HER2-positive breast cancer, and achievement of a pathologic complete response (pCR), usually defined as the absence of residual invasive disease in the breast and axillary nodes (ypT0/is N0), in these patients is associated with excellent long-term outcomes (1,2). However, the optimal chemotherapy regimen, in terms of efficacy and toxicity, is not clear. In the adjuvant setting, patients exposed to both an anthracycline and trastuzumab have significantly higher rates of cardiac toxicity and leukemogenesis than patients treated with a non-anthracycline-containing regimen and trastuzumab (such as docetaxel, carboplatin and trastuzumab, TCH), while long-term breast cancer-free outcomes are not significantly different (3). In the neoadjuvant setting, the addition of pertuzumab to the combination of chemotherapy and trastuzumab appears to substantially increase the percentage of patients who achieve a pCR, though the impact of this enhanced locoregional response on long-term outcomes is not yet known (4,5). On the randomized phase II TRYPHAENA neoadjuvant trial, patients who received a non-anthracycline-containing regimen consisting of TCH plus pertuzumab (TCHP) administered every 3 weeks for 6 cycles had a pCR rate of 64% compared to 55% for patients who received sequential therapy with an anthracycline-based regimen, with or without concurrent trastuzumab and pertuzumab, followed by docetaxel with trastuzumab and pertuzumab (FEC+/-HP→THP) (5). While these results support the efficacy of the non-anthracycline-containing TCHP regimen, they do not rule out the existence of a subset of HER2-positive patients who would benefit from treatment with an anthracycline. TCH is associated with such severe and prolonged neutropenia that many patients require the administration of a myeloid growth factor such as pegfilgrastim to reduce the risk of infections, and the addition of pertuzumab to this regimen increases the risk of severe and occasionally life-threatening toxicities, especially neutropenia and diarrhea (5). In HER2+ metastatic breast cancer, the combination of weekly paclitaxel with trastuzumab and pertuzumab has similar antitumor efficacy as docetaxel with trastuzumab and pertuzumab and a much more favorable toxicity profile (6). In the neoadjuvant setting, administration of the combination of weekly paclitaxel and carboplatin with trastuzumab has been shown to induce a high pCR rate (7-9). This pilot study is designed to test the addition of pertuzumab to this well-tolerated combination in patients with stage I (clinical T=2.0 cm)-III HER2-positive breast cancer, and to assess whether patients with a suboptimal response to 12 weeks of the weekly paclitaxel and carboplatin with trastuzumab and pertuzumab (wPCbTP) regimen benefit from switching to an anthracycline-based regimen, specifically doxorubicin and cyclophosphamide (AC).

II. Objectives

A. Primary

1. Measure the percent of patients who achieve a pCR (ypT0/isN0) in the following populations:

a. The overall study population

b. Patients with an optimal clinical response (≥50% reduction in the sum of their breast tumor's two-dimensional measurements) to wPCbTP at 12 weeks

i. who complete 18 weeks of the wPCbTP regimen

ii. who complete less than 18 weeks of the wPCbTP regimen but do not receive any additional chemotherapy

iii. who switch to AC in the neoadjuvant setting for any reason

c. Patients with a suboptimal clinical response (<50% reduction in the sum of their breast tumor's two-dimensional measurements) to wPCbTP at 12 weeks

i. who switch to AC in the neoadjuvant setting

ii. who complete 18 weeks of the wPCbTP regimen (did not switch despite the suboptimal response at 12 weeks)

iii. who complete less than 18 weeks of the wPCbTP regimen but did not receive any additional chemotherapy

2. Measure the percent of patients who achieve pCR or RCB I in the same patient populations

3. Measure the percentage of patients with optimal and suboptimal response to wPCbTP at 12 weeks

4. Measure the percentage of patients who develop major toxicities (defined below) during their neoadjuvant therapy (wPCbTP or AC)

a. Neutropenia (grade$\geq$2)

b. Febrile neutropenia (grade 3-4)

c. Thrombocytopenia (grade $\geq$2)

d. Anemia (grade $\geq$2)

e. Diarrhea (any grade, grade $\geq$3)

f. Neuropathy (any grade, grade 2, grade $\geq$3)

g. Vomiting (any grade, grade $\geq$3)

h. Other grade $\geq$3 toxicities

5. Measure delivery of treatment with the wPCbTP regimen over 12 weeks and (where appropriate) 18 weeks

a. Frequency of and reasons for treatment delays and dose modifications

B. Secondary objectives

1. Measure the percentage of patients who were clinically node-positive at study entry who become pathologically node-negative at surgery

2. Measure the impact of neoadjuvant therapy on surgical options

a. The percentage of patients who were not candidates for breast-conserving surgery (BCS) at baseline who become candidates for BCS after treatment (whether or not the patient opts for BCS or mastectomy)

b. The percentage of patients who would have required a full axillary lymph node dissection (ALND) at study entry who become candidates for sentinel node sampling (SLN) after treatment

c. Assess the impact of splitting the loading dose of pertuzumab between weeks 1 and 2 of cycle 1 and the percentage of these patients in whom the week 2 dose is held for early onset diarrhea versus administering the standard loading dose (840 mg) on week 1 on the incidence and severity of diarrhea and other toxicities experienced during cycles 1 and 2 of wPCbTP.

III. Protocol synopsis

A. Prior to enrollment on study, patients will have had diagnostic biopsies of their breast cancer and, when indicated, sampling (FNA or needle biopsy) of a suspicious ipsilateral axillary node, ultrasound and/or MRI of the breast for tumor measurement, baseline blood tests, including a pregnancy test when appropriate, cardiac evaluation (echocardiogram or MUGA scan), and staging studies to rule out overt metastatic disease (strongly recommended for stage III or if clinical suspicion).

B. Once the patient agrees to participate in the study, her treating doctors will record their assessment as to whether, prior to treatment, the patient would have required a mastectomy, and if so why, or if the patient would have been a candidate for BCS, and whether the patient would require an ALND or would be a candidate for SLN sampling.

C. The patient will then initiate neoadjuvant therapy with paclitaxel 80 mg/m^2 (or nab-paclitaxel 80-100 mg/m^2) and carboplatin AUC 2 administered weekly with no planned treatment breaks (3 weeks = 1 cycle). Trastuzumab can be administered either every 3 weeks (8 mg/kg cycle 1 then 6 mg/kg cycles 2-4) or weekly (4 mg/kg week 1 then 2 mg/kg weeks 2-12). Pertuzumab will be administered every 3 weeks, with either a loading dose (840 mg) week 1 of cycle 1, or two doses (420 mg each) weeks 1 and 2 of cycle 1, with the week 2 dose held if the patient is already experiencing grade $\geq$1 diarrhea to see if this modified dosing schedule reduces the frequency and severity of toxicities, especially diarrhea, during the first 3-6 weeks of treatment. The choice of dosing schedule for pertuzumab is left to the discretion of the treating oncologist.

D. While dose modifications will be left to the discretion of the treating oncologist, our recommendation is that chemotherapy be delayed or modified only for moderately severe neutropenia (<800/mm^3) or thrombocytopenia (<50,000/mm^3) or persistent grade $\geq$2 non-hematologic toxicities (neuropathy, diarrhea, etc.) on the day of treatment, or for a serious or life-threatening toxicity, such as an episode of febrile neutropenia or a bleed requiring an urgent platelet transfusion, during the previous cycle. If chemotherapy is delayed, the HER2-targeted therapies should continue.

E. Patients should be assessed clinically every q3 weeks and as indicated for any significant new symptoms or findings; patients with disease progression on the wPCbTP regimen should be switched to doxorubicin and cyclophosphamide (AC) every 2 or 3 weeks for 4 cycles followed by surgery, taken immediately to surgery or removed from the study (in which case they will be considered a non-pCR).

F. At the end of 4 cycles of wPCbTP, patients will undergo repeat breast US or MRI to assess their response to treatment. Patients with $\geq$50% reduction in the sum of the 2 greatest dimensions of their breast tumor (or axillary node, if the breast tumor is occult) will be labelled optimal responders and should continue the wPCbTP regimen for another 2 cycles. Patients with <50% reduction in the sum of the 2 greatest dimensions of their breast tumor will be considered suboptimal responders and should be switched to AC for 4 cycles. While this is the recommended treatment plan based on response to the first 4 cycles of wPCbTP, each patient's treatment is left to the discretion of the treating oncologist based on response evaluation and toxicity concerns.

G. In patients switched to AC, a repeat cardiac evaluation to rule out a significant fall in

their LVEF prior to starting that treatment is recommended. Patients who receive AC every 2 weeks (dose-dense AC) should receive growth factor support, either pegfilgrastim or filgrastim.

H. If there is uncertainty regarding a patient's response to treatment after 4 cycles of wPCbTP based on imaging studies, a repeat tumor biopsy can be performed; a complete or near-complete pathologic response in this biopsy sample would justify continuing wPCbTP as opposed to switching to AC.

I. After the completion of neoadjuvant therapy, the patient's eligibility for breast conserving surgery vs. mastectomy and ALND vs. SLN sampling will be reassessed, and the surgical plan recorded.

J. After surgery, the patient's actual surgical management will be recorded. Her pathologic response to treatment will be scored by the institutional pathologist according to TN staging and RCB criteria (if residual invasive disease is present).

K. Post-op, patients may receive additional chemotherapy, endocrine therapy (if ER or PR positive) and radiation treatments at physician discretion, as well as completing a year of trastuzumab. Adjuvant pertuzumab may be added if the results of the APHINITY trial demonstrate a benefit to this treatment. Post-op treatments and any residual or delayed toxicities attributed to the patient's neoadjuvant therapy will be collected at a follow-up visit approximately 3 months after surgery. Sexually active premenopausal patients will be advised to continue contraception for at least 2 months after completion of protocol chemotherapy (longer if they receive post-op chemotherapy).

L. Patients will be asked to give permission to collect residual tumor tissue from their diagnostic biopsies, any other biopsies that were performed (such as after week 12) and their surgical specimens (if present) to be used for future correlative studies.

M. Our assumption is that pCR (ypT0/isN0) will be achieved in at least 70% of patients with wPCbTP +/- AC and this response assessment/switching strategy.

IV. Inclusion and Exclusion Criteria

A. Inclusion Criteria

1 Histologically confirmed adenocarcinoma of the breast, with sufficient tissue available from needle or incisional biopsy (excisional biopsy not permitted) for ER, PR and HER2 testing. The diagnostic biopsy pathology report, including hormone receptor and HER2 analysis, will be submitted to BrUOG.
2. Resectable - clinical stage I (only with T=2.0 cm), IIA-IIIA – T2 N0-T3N0 or T1-3 N1-N2a - or unresectable – clinical stage IIIB-C - T4 or N2b-3 - disease. No evidence of M1 disease. Pretreatment clinical stage will be recorded by the treating physician.
3. Breast tumor measuring at least 1 cm in greatest dimension by ultrasound or MRI; patients without measurable disease in the breast (TX) by imaging studies are eligible if they have measurable disease (a node measuring at least 1 cm along its short axis, and histologically confirmed to contain metastatic disease) in the

axilla. The report from the imaging study to be used for the baseline tumor measurements will be submitted to BrUOG.
4. HER2+, defined by either IHC 3+ or amplification of the HER2 gene by FISH analysis (ratio ≥2.0 or >6 HER2 targets per cell; patients with equivocal HER2 testing, 2+ by IHC with a FISH ratio of <2.0 and 4-6 HER2 signals per nucleus, are not eligible).
5. Patients with multiple foci of invasive cancer in the same breast are eligible if any single lesion meets the above size criteria and all sampled lesions > 1 cm in maximum dimension are histologically similar and HER2+. Patients are also eligible if there is a focus of HER2- invasive cancer that is ≤1 cm in maximum dimension in a different quadrant of the breast from the HER2+ cancer, such that its presence will not interfere with clinical or pathologic assessment of response of the HER2+ cancer; whether radiographically detected lesions adjacent to but separate from the target lesion - 'satellite' lesions - are sampled for histologic evaluation and marker analysis is left to the discretion of the treating physicians. The presence of DCIS or LCIS in either breast will not render a patient ineligible. Patients with a small focus of invasive cancer detected in the contralateral breast (clinical T1a/bN0) are eligible, whether the contralateral tumor is HER2+ or HER2-, while patients with a more advanced invasive cancer in the contralateral breast are not eligible; in patients with a small focus of invasive cancer in the contralateral breast or a small focus of HER2- cancer in the same breast only the histologic response in the HER2+ target lesion will be considered in determining the patient's pathologic response.
6 It is recommended that patients have a pretreatment echocardiogram or MUGA scan with an LVEF above the institutional lower limit of normal. If performed, site should submit confirmation that results were above institutional lower limit.
7. Female, age ≥18, Zubrod PS 0-1.
8. It is recommended that patients have adequate bone marrow, renal and hepatic function. Examples of this include: ANC ≥ 1000/ul, platelet count ≥100,000/ul, HGB≥ 9.0 g/dl, serum creatinine ≤1.5 mg/dl or measured creatinine clearance of >30 ml/min and AST ≤5 x ULN. Site must submit confirmation from treating physician that patient's labs were deemed adequate, but is not required to submit results as values are only recommended.
9. Signed informed consent. Per GCP guidelines, if patient signs consent more than 30 days prior to starting treatment patient is to be re-consented. The signed consent will be sent to BrUOG.

B. Exclusion criteria
1. Prior chemotherapy or radiation therapy for this cancer; hormonal therapies, including LHRH analogs, contraceptives, and antitumor endocrine therapies, are permitted prior to and during protocol therapy at the discretion of the treating physician.
2. Patients with congestive heart failure, unstable angina pectoris, uncontrolled clinically significant arrhythmia or grade II or greater peripheral vascular disease are not eligible. Patients with BP >180 (systolic) or >100 (diastolic) are excluded; patients with BP 160-180/90-100 are eligible with assurance from the treating

physician that this is being addressed and that the physician is comfortable initiating study treatment despite the elevated value(s),
3. Patients with myocardial infarction, stroke or arterial thrombotic event within the past 12 months are not eligible.
4. Pregnant women are not eligible. Lactating women are eligible only if they are not breast-feeding. All patients of reproductive potential should have a negative pregnancy test at baseline and be advised to use an effective barrier method of contraception as per institutional standard of care. Sites will be asked to confirm the patient's menopausal status at study entry and that premenopausal women had a negative pregnancy test performed within 7 days of starting treatment, but will not be required to submit test results.
5. Active (defined as symptomatic, currently requiring treatment or likely to require treatment within the 6 months following study enrollment, or likely to affect the efficacy or tolerability of the study treatment) non-breast malignancy.
6. Baseline grade $\geq$2 peripheral neuropathy

V. Treatment plan

A. Neoadjuvant therapy

1. wPCbTP

Paclitaxel 80 mg/m^2 IV or nab-paclitaxel (Abraxane) 80-100 mg/m^2 IV weekly x 12 (18 if indicated)
Carboplatin AUC 2 IV (for calculation of dose, GFR capped at 125 ml/min) weekly x 12 (18 if indicated)
Trastuzumab IV 8 mg/kg day 1 cycle 1 then 6 mg/kg day 1 cycles 2-4 (weeks 4, 7, and 10) and cycles 5-6 (weeks 13 and 16) if indicated **or** 4 mg/kg week 1 then 2 mg/kg weeks 2-12 and weeks 13-18 if indicated
Pertuzumab IV 840 mg cycle 1 then 420 mg cycles 2-4 (weeks 4, 7, and 10) and cycles 5-6 (weeks 13 and 16) if indicated **or** 420 mg weeks 1 and 2 then 420 mg cycles 2-4 (weeks 4, 7, and 10) and cycles 5-6 (weeks 13 and 16) if indicated. Patients whose treating physician selects the 420 mg cycle 1 weeks 1 and 2 dosing schedule for pertuzumab must be assessed prior to administration of the week 2 dose; this dose will be omitted for grade $\geq$1 diarrhea.

2. AC

Dose-dense AC: Doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 IV day 1 every 2 weeks x 4 cycles with pegfilgrastim 6 mg SC day 2 or Neulasta on-body injector OBI applied day 1 for injection on day 2 or filgrastim 5 mcg/kg (typically rounded to 300 mcg or 480 mcg) SC daily starting day 2-3 and continued for a minimum of 7 days until recovery of ANC from nadir

Standard AC: Doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 IV day 1 r every 3 weeks x 4 cycles (administration of pegfilgrastim or filgrastim at the discretion of the treating oncologist)

B. Adjuvant therapy
   1. Additional chemotherapy at the discretion of the treating oncologist
   2. It is recommended that patients resume trastuzumab 6 mg/kg IV every 3 weeks x 11 cycles (if received 6 cycles of wPCbTP preop) or 13 cycles (if received 4 cycles of wPCbTP preop) after surgery or completion of any adjuvant chemotherapy. Pertuzumab 420 mg IV every 3 weeks x 11-13 cycles can be added if indicated based on results of the APHINITY trial, when available.
   3. Adjuvant endocrine therapy (in ER+/HER2+ patients) and radiation per treating physicians

VI. Suggested dose modifications for chemotherapy

While decisions regarding treatment delays or modifications will be left to the treating oncologist, and their occurrence and rationale collected, the following are guidelines and not requirements:

A. Hematologic toxicities:
   1. Neutropenia – OK to proceed with paclitaxel/nab-paclitaxel and carboplatin with ANC $\geq$800. If treatment is held for neutropenia this should be a treatment delay; skipping doses should be avoided. If treatment is held 2 consecutive weeks for neutropenia, when treatment is resumed the dose of paclitaxel/nab-paclitaxel should be reduced by 25% to paclitaxel 60 mg/m^2 or nab-paclitaxel 60-75 mg/m^2. Filgrastim 5 mcg/kg SC daily x 3-5 days per week (between days 2 and 6) may be added to try to avoid further dose modification. If neutropenia requiring a second hold of 2 consecutive weeks recurs at the lower dose, when treatment is resumed the treating oncologist has the option of reducing the paclitaxel/nab-paclitaxel dose by another 25% and the carboplatin dose by 25% or adding filgrastim (if not added previously) 5 mcg/kg SC daily x 3-5 days per week (between days 2 and 6) to try to avoid further reduction of the chemotherapy doses.
   2. Febrile neutropenia – Should reduce paclitaxel/nab-paclitaxel by 25%. Filgrastim 5 mcg/kg SC daily x 3-5 days per week (between days 2 and 6) may be added to try to avoid further episodes or dose modification.
   3. Thrombocytopenia – OK to proceed with paclitaxel/nab-paclitaxel and carboplatin with platelet count $\geq$50,000. If treatment is held for thrombocytopenia even once, when treatment is resumed the dose of carboplatin should be reduced by 25% (to AUC 1.5). If treatment has to be held for thrombocytopenia on AUC 1.5, should reduce carboplatin to AUC 1.0. If treatment has to be held for thrombocytopenia on AUC 1.0, should discontinue carboplatin.
   4. Anemia – No recommended dose modifications. Transfuse as indicated.

B. Non-hematologic toxicities
   1. Neuropathy – Should reduce paclitaxel/nab-paclitaxel by 25% for grade 2 peripheral neuropathy. Should hold treatment for grade 3 neuropathy, resume with 25% reduction of paclitaxel/nab-paclitaxel when improves to grade $\leq$ 2. If does not improve to grade $\leq$2 within 3 weeks, or if progresses from grade 2 to

grade 3 despite the 25% reduction in dose of paclitaxel/nab-paclitaxel, should discontinue wPCbTP regimen and either switch to AC, take to surgery or remove from study.

2. Diarrhea – A) Patients receiving pertuzumab 420 mg cycle 1 weeks 1 and 2 must be assessed for diarrhea prior to administration of the week 2 dose, and the dose omitted for grade ≥1 diarrhea. B) At all other times during study treatment, all treatment (including trastuzumab and pertuzumab) should be held for grade ≥ 2 when due to resume treatment. If treatment is held for >2 weeks for grade 2 diarrhea or patient develops grade 3 diarrhea, when treatment resumes should temporarily discontinue pertuzumab; resumption of pertuzumab following improvement in or control of diarrhea on medication is at the discretion of the treating oncologist. If grade ≥2 diarrhea recurs despite discontinuation of pertuzumab and administration of antidiarrheal medications, discontinue the wPCbTP regimen and either switch to AC, take to surgery or remove from study.
3. Vomiting – Should hold treatment for grade ≥2 vomiting on day of treatment. Intensify antiemetic regimen as indicated for post-chemotherapy nausea or vomiting that resolves by next scheduled treatment.
4. Allergic reactions –
    a. Paclitaxel - Patients who experience a significant (grade ≥2) hypersensitivity reaction to paclitaxel may, at the discretion of the treating oncologist, be re-challenged with additional premedications and/or changes in the rate of administration of the drug or switched to nab-paclitaxel.
    b. Carboplatin – Patients who experience a significant (grade≥2) hypersensitivity reaction to carboplatin may, at the discretion of the treating oncologist, be re-challenged with additional premedications and/or changes in the rate of administration of the drug or undergo desensitization with the goal of continuing this part of their treatment, or treatment with carboplatin may be permanently discontinued. If this occurs prior to the week 12 reassessment, the patient should continue on treatment with paclitaxel/nab-paclitaxel, trastuzumab and pertuzumab (wPTP) until week 12. It is left to the discretion of the treating oncologist as to whether this would influence his/her decision to continue wPTP or switch to AC at any time after week 12.
5. Other grade ≥2 toxicities. Physician discretion as to whether toxicity warrants treatment delay, dose modification or discontinuation of wPCbTP regimen.

C. If paclitaxel/nab-paclitaxel and carboplatin chemotherapy is delayed due to hematologic or non-hematologic toxicity, the patient should continue trastuzumab (every 3 weeks or weekly) and pertuzumab (every 3 weeks).

D. Dose modifications during AC are left to the discretion of the treating oncologist.

E. Adverse event reporting -See Appendix I

VII. Required data

To reduce the burden of data collection, and because treatment modifications are primarily left up to the treating investigator, lab results will not be collected. Submission of data sheets collecting pertinent data is required at the following time points:

A. On-study data sheet: Baseline tumor stage, measurements (US or MRI), histologic confirmation of malignancy with ER, PR and HER2 status (pathology report), clinical/histologic status of ipsilateral axilla PS, pretreatment assessment of operability (mastectomy vs. lumpectomy, ALND vs.SLN only). On study information required for BrUOG review before registration.
B. s/p 2 cycles wPCbTP: Treatment and toxicity data
C. s/p 4 cycles wPCbTP: Treatment and toxicity data, results of reassessment (US or MRI), treatment plan going forward
D. Pre-op (s/p 6 cycles of wPCbTP or 4 cycles of AC): Treatment and toxicity data, pre-op assessment of operability (including US or MRI, if done)
E. Post-op: Surgical outcomes, pathology results, RCB number and class if not pCR
F. 3 months post-op: Post-op treatment received and planned, delayed or persistent toxicities

VIII. Pathologic analysis

A. Definition of pCR: A patient will be considered to have achieved a pCR if there is no residual invasive cancer in the submitted breast tissue (the presence of DCIS or microinvasion (T1mic) will not disqualify a patient from being defined a pCR) or in any sampled axillary nodes (the presence of isolated tumor cells – N0i+ - will not disqualify a patient from being defined a pCR).
B. Residual Cancer Burden: In patients who do not meet the definition of pCR, the pathologist will be asked to quantify the residual cancer burden (RCB), as defined by Symmans et al. The RCB value can be calculated using an online calculator that can be accessed at the site below, and the necessary data to calculate the value is listed below:

http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3

(1) Primary Tumor Bed

Primary Tumor Bed Area: _____ (mm) X _____ (mm)

Overall Cancer Cellularity (as percentage of area): _____ (%)

Percentage of Cancer That Is *in situ* Disease: _____ (%)

(2) Lymph Nodes

Number of Positive Lymph Nodes: _____

Diameter of Largest Metastasis: _____ (mm)

IX. Recording Surgical options: Surgical data will not be collected on patients who come off study prior to the week 12 assessment, but response and surgical data (including pathology report results) will be collected on all patients who come off study any time after the 12 week assessment.

A. Eligibility for BCS: At baseline and again after completion of neoadjuvant therapy, the patient's physicians (ideally her surgeon) will be asked to assess whether she is a candidate for BCS – whether or not the patient is interested in BCS – and, if not, why (tumor size or location, multicentric invasive disease, DCIS or other imaging or histologic findings elsewhere in the breast, poor candidate for radiation, etc.) This will be recorded on the pre- and post-treatment surgical assessment form.
B. Axillary management: At baseline and again after completion of neoadjuvant therapy, the patient's physicians (again, ideally her surgeon) will be asked to assess the clinical status of her axilla and whether she requires an ALND or, if clinically N0, is a candidate for SLN sampling only. This is also recorded on the surgical assessment form.
C. At the patient post-op visit, the surgery performed (breast and axilla) should be recorded, and whether this was different from her pre-op surgical plan and if so why.

X. Pharmaceutical information – See Appendix II

XI. Record Retention

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

The Brown University Oncology Research Group, as coordinator of this study, is responsible for ensuring proper conduct of the study with regard to protocol adherence and the validity of the data recorded on the case report forms. The Principal Investigators (William Sikov, M.D. and Mary Lopresti, D.O.) and Brown University Oncology Research Group Director of Operations (Kayla Rosati) will monitor this study. The case report forms will be monitored against the submitted documents for accuracy, completeness, adherence to the protocol and regulatory compliance.

All records and documents pertaining to the conduct of this study and the distribution of drug, including CRFs, consents forms, laboratory test results and medication inventory records, must be retained by the Principal Investigator for 2 years after the investigation is discontinued, study is published and once BrUOG confirms records can be destroyed or moved.

XII. Data Safety and Monitoring Board

All trials initiated by the Brown University Oncology Research Group (BrUOG) are subject to oversight by the Data Safety Monitoring Board (DSMB). This board meets two times per year with any additional meetings scheduled when needed. The responsibilities are as follows:

- Familiarize themselves with the research protocol (s)
- The DSMB reviews trial performance information such as accrual information.
- Review interim analyses of outcome data and cumulative toxicity data summaries to determine whether the trial should continue as originally designed, should be changed, or should be terminated based on these data.
- The DSMB also determines whether and to whom outcome results should be released prior to the reporting of study results.
- All adverse events are reviewed by the committee, with assurances that these have been in fact sent for review to all pertinent IRBs.
- Review of reports of related studies to determine whether the monitored study needs to be changed or terminated.
- Review major proposed modifications to the study prior to their implementation (e.g., termination, dropping an arm based on toxicity results or other reported trial outcomes, increasing target sample size).
- Following each DSMB meeting, provide the study leadership with written information concerning findings for the trial as a whole related to cumulative toxicities observed and any relevant recommendations related to continuing, changing, or terminating the trial.

The study leadership will provide information on cumulative toxicities and relevant recommendations to the local principal investigators to be shared with their IRB's.

XIII. Statistical design

The study will continue until at least 30 evaluable patients are enrolled and treated. The pCR and pCR + RCB I rates for the overall study population and the subpopulations listed in Section II. A. 1-2 will be calculated with 95% confidence intervals. If we achieve an overall pCR rate of 70% in 30 patients, the 95% confidence interval for the pCR rate (50-85%) will essentially exclude an actual pCR with these regimens and this 'switching' strategy of less than 50%, with an alpha 0.07 and power of 77%, according to both the Fleming design and exact binomial tests.

XIV. References

1. Cortazar P, Zhang L, Untch M, et al. Pathologic complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014; 384(9938): 164-172.
2. Broglio KR, Quintana M, Foster M, et al. Association of pathologic complete response to neoadjuvant therapy in HER2-positive breast cancer with long-term outcomes: a meta-analysis. JAMA Oncol 2016 Feb 25; EPub Ahead of Print.
3. Slamon DJ, Eiermann W, Robert NJ, et al. Ten-year follow-up of BCIRG-006 comparing doxorubicin plus cyclophosphamide followed by docetaxel (AC→T) with doxorubicin plus cyclophosphamide followed by docetaxel and trastuzumab (AC→TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2+ early breast cancer. 38th Annual San Antonio Breast Cancer Symposium, San Antonio, Texas, December 8-12, 2015, Abstract S5-04.

4. Gianni L, Pienkowski T, Im Y, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol 2012; 13 (1): 25-32.
5. Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Ann Oncol 2013; 24: 2278–2284.
6. Dang C, Iyengar M, Datko F, et al. Phase II Study of paclitaxel given once per week along with trastuzumab and pertuzumab in patients with human epidermal growth factor receptor 2–positive metastatic breast cancer. J Clin Oncol 2015; 33(5), 442-447.
7. Sikov WM, Dizon DS, Strenger R, et al. Frequent pathologic complete responses in aggressive stages II to III breast cancers with every-4-week carboplatin and weekly paclitaxel with or without trastuzumab: a Brown University Oncology Group Study. J Clin Oncol 2009; 27:4693-4699.
8. Sinclair NF, Sakr BJ, Abu-Khalaf MM, et al. Multicenter phase II trial of neoadjuvant carboplatin, weekly nab-paclitaxel, and trastuzumab in stage II-III HER2+ breast cancer: A BrUOG study. J Clin Oncol 2013; 31 (suppl; abstr 619)
9. Yu KD, Liu GY, Chen CM, et al. Weekly paclitaxel/carboplatin/trastuzumab therapy improves pathologic complete remission in aggressive HER2-positive breast cancers, especially in luminal-B subtype, compared with a once-every-3-weeks schedule. Oncologist 2013; 18(5):511-7.

Appendix I: Adverse Event Reporting

The only Adverse events that will be captured by participating sites during this clinical trial will be the pre-determined hematological and non-hematological toxicities noted in section II. A. 4, which are:

a. Neutropenia (grade≥2)
b. Febrile neutropenia (grade 3-4)
c. Thrombocytopenia (grade ≥2)
d. Anemia (grade ≥2)
e. Diarrhea (any grade, grade ≥3)
f. Neuropathy (any grade, grade 2, grade ≥3)
g. Vomiting (any grade, grade ≥3)
h. Other grade ≥3 toxicities

No other adverse events are required to be documented, captured, or reported to BrUOG and therefore, BrUOG will not be reporting on any adverse events other than the pre-determined toxicities noted above. All adverse events and special reporting situations, related or unrelated, will be reported from the time a signed and dated ICF is obtained until 3 months post-operative, or until the subject withdraws consent from study participation (declines participation) or at the time patient becomes a screen failure, whichever occurs first. If a patient comes off study early, prior to completion of all treatment, the SAE review period will be 30 days from the last treatment.

Regarding SAEs: All SAEs, whether related or unrelated, will be reported from the time a signed and dated ICF is obtained until 3 months post-operative, or until the subject withdraws consent from study participation (declines participation) or at the time patient becomes a screen failure, whichever occurs first. If a patient comes off study early, prior to completion of all treatment, the SAE review period will be 30 days from the last treatment.

This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication).

This study will utilize the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for grading all adverse events. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use treatment regimen whether or not considered related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of drug.

During clinical trials, adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more adverse events.)

Adverse events (AEs) will be recorded in the case report form for the duration of the trial, regardless of whether or not the event(s) are considered related to trial medication. All AEs considered related to trial medication will be followed until resolution even if this occurs post-trial.

Definitions

An adverse event is any new, undesirable medical experience or change of an existing condition that occurs during or after treatment, whether or not considered product-related.

Serious adverse event (SAE)

An adverse event occurring at any dose that results in any of the following outcomes (CFR 312.32):

- death
- is life-threatening
- inpatient hospitalization or prolongation of existing hospitalization excluding those for study drug administration, transfusion support, disease staging/re-staging procedures, concomitant radiotherapy, thoracentesis / paracentesis, or placement of an indwelling catheter, unless associated with other serious events.
- persistent or significant disability or incapacity,
- congenital anomaly / birth defect.

The definition of serious adverse event (experience) also includes *important medical event*. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. A new diagnosis of cancer during the course of treatment should be considered an important medical event.

The definition of "related" being that there is a reasonable possibility that the drug caused the adverse experience**.**

Unexpected adverse event

An adverse event that is not mentioned in the package insert or informed consent or the specificity or severity of which is not consistent with the investigator's brochure or package insert.

Life-threatening

Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death.

BRUOG ADVERSE EVENT REPORTING REQUIREMENTS

Investigators are required by Federal Regulation to report adverse drug reactions. Questions regarding drugs as used in this study should be directed to the Brown University Oncology Research Group (BrUOG) Central Office, Phone: (401) 863-3000 Fax (401) 863-3820, which will in turn notify the Principal Investigator.

Intensity for each adverse event will be scored using CTCAE Version 4.0. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov). All appropriate treatment areas have access to a copy of the CTCAE Version 4.0. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

Pregnancies

Pregnancies occurring while the subject is on study drug or within 4 weeks after the subject's last treatment are considered expedited reportable events. If the subject is receiving treatment, the drugs are to be discontinued immediately. The pregnancy must be reported by the Brown University Oncology Research Group within 24 hours and BrUOG will in turn report to FDA within 24 hours of the Investigator's knowledge of the pregnancy by phone and/or facsimile using the 3500A MedWatch form. Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on treatment (drug), or within 4 weeks (30 days) of the subject's last treatment, are considered immediately reportable events. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to BrUOG via the Medwatch3500A form.

The Investigator will follow the subject until completion of the pregnancy, and must notify BrUOG of the outcome as specified below. The Investigator will provide this information as a follow-up to the initial report. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting SAEs (i.e., report the event to BrUOG who will then report to the FDA).

Any suspected fetal exposure must be reported to BrUOG within 24 hours who will then report to the FDA within 1 working day of being made aware of the event. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects to be related to the in utero exposure to the study drug should also be reported.

Types of Report: For sites:

Telephone report: For SAE's contact BrUOG Central Office (401) 863-3000 (or via email), immediately upon learning of the event (within 24 hours).

Written report: Send the copy of the MedWatch 3500A form within 5 business days of the event (24 hours if pregnancy or related death) to the BrUOG Central Office by email, scan or Fax:

Brown University Oncology Research Group

Phone: (401) 863-3000, Fax: (401) 863-3820

Emails: Kayla_rosati@brown.edu and Kristen_Mitchell@brown.edu

All SAEs and deaths during treatment or within 3 months post-operative must be reported within 5 business days or as soon as the investigator is made aware of the event. If the death is thought to be related to the study drug, deaths must be reported within 24 hours of the investigator being made aware of the event. If a patient comes off study early, prior to completion of all treatment, the SAE review period will be 30 days from the last treatment.

MedWatch 3500A Reporting Guidelines:

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- **Description of event, severity, treatment, and outcome, if known**
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each product and suspect medication
- SAE must be typed
- ****It is required that you put the following numbers on the MedWatch form for tracking:**
    - **BrUOG 308**

A final report to document resolution of the SAE (such as discharge from hospital) is required.

Follow-up information:

Additional Info may be added to a previously submitted report by any of the following methods.

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form

Summarize new information and fax it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted. (The subject identifiers are important so that the new information is added to the correct initial report).

The principal Investigator is required to notify his/her Institutional Review Board (IRB) of a serious adverse event according to institutional policy.

BrUOG Responsibility Regarding Reporting:

The BrUOG Central Office will notify by phone and/or fax all drug reaction reports to the FDA, the Principal Investigator, and the participating sites (who will in turn notify their local IRBs) as soon as possible but no later than 7 calendar days after initial receipt of the information. SAEs will be reported as an amendment to the IND (if applicable) within 15 days of sponsor notification. They will all receive a simultaneous copy via facsimile or email of all adverse events filed with the FDA (which will be sent to the MedWatch fax line for IND exemption or to the division fax if there is an IND). A copy of the form will be kept by the BrUOG Central Office.

Fax: 1-800-FDA-0178 (1-800-332-0178) For IND exempt study or for IND study the SAE will be sent to Center Drug Evaluation Division fax line that has responsibility for review of IND)

Mail: For IND studies BrUOG will send the SAE as an amendment to the IND as well

Appendix II: Pharmaceutical information

Qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling and safe disposal of chemotherapeutic agents in a self-contained, protective environment. *For full instructions and guidelines, please always refer to the package inserts for the drugs being used in this trial, below is just a summary of basic information for each drug.*

1. Paclitaxel (Taxol)

Formulation: Commercially available for injection 6 mg/mL (5 mL, 16.7 mL, 25 mL, and 50 mL) (contains alcohol and purified Cremophor EL {polyoxyethylated castor oil}).

Preparation, Storage and Stability:

Unopened vials of TAXOL (paclitaxel) Injection are stable until the date indicated on the package when stored between 20°–25° C (68°–77° F), in the original package. Neither freezing nor refrigeration adversely affects the stability of the product. Upon refrigeration, components in the TAXOL vial may precipitate, but will redissolve upon reaching room temperature with little or no agitation. There is no impact on product quality under these circumstances. If the solution remains cloudy or if an insoluble precipitate is noted, the vial should be discarded. Solutions for infusion prepared as recommended are stable at ambient temperature (approximately 25° C) and lighting conditions for up to 27 hours.

Procedures for proper handling and disposal of anticancer drugs should be considered.

TAXOL (paclitaxel) Injection must be diluted prior to infusion. TAXOL should be diluted in 0.9% Sodium Chloride Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP; or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2 mg/mL. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25° C) and room lighting conditions. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle. No significant losses in potency have been noted following simulated delivery of the solution through IV tubing containing an in-line (0.22 micron) filter.

Administration: Administer under the supervision of a health care provider experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

TAXOL should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns.

Administer dose per the protocol.

Drug Interactions:

The metabolism of TAXOL is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when TAXOL is concomitantly administered with known substrates (eg, midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (eg, atazanavir, clarithromycin, indinavir,

itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (eg, rifampin and carbamazepine) of CYP3A4.

Caution should also be exercised when TAXOL is concomitantly administered with known substrates (eg, repaglinide and rosiglitazone), inhibitors (eg, gemfibrozil), and inducers (eg, rifampin) of CYP2C8.

Adverse Events Consult the package insert for the most current and complete information. Percentages reported with single-agent therapy.

TAXOL is contraindicated in patients who have a history of hypersensitivity reactions to TAXOL or other drugs formulated in Cremophor® EL (polyoxyethylated castor oil).

Toxicities

U.S. Boxed Warning: Bone marrow suppression is the dose-limiting toxicity; do not administer if baseline absolute neutrophil count (ANC) is <1500 cells/mm3 (1000 cells/mm3 for patients with AIDS-related KS); reduce future doses by 20% for severe neutropenia. U.S. Boxed Warning: Severe hypersensitivity reactions have been reported.

Common known potential toxicities, > 10%:

Cardiovascular: Flushing, ECG abnormal, edema, hypotension. Dermatologic: Alopecia, rash. Gastrointestinal: Nausea/vomiting, diarrhea, mucositis, stomatitis, abdominal pain (with intraperitoneal paclitaxel) Hematologic: Neutropenia, leukopenia, anemia, thrombocytopenia, bleeding. Hepatic: Alkaline phosphatase increased, AST increased. Local: Injection site reaction (Erythema, tenderness, skin discoloration, swelling). Neuromuscular & skeletal: Peripheral neuropathy, arthralgia, myalgia, weakness. Renal: Creatinine increased. Miscellaneous: Hypersensitivity reaction, infection

Less common known potential toxicities, 1% - 10%: Cardiovascular: Bradycardia,

tachycardia, hypertension, rhythm abnormalities, syncope, venous thrombosis. Dermatologic: Nail changes. Hematologic: Febrile neutropenia. Hepatic: Bilirubin increased. Respiratory: Dyspnea

Rare known potential toxicities, <1% (limited to important or life-threatening):

Anaphylaxis, ataxia, atrial fibrillation, AV block, back pain, cardiac conduction abnormalities, cellulitis, CHF, chills, conjunctivitis, dehydration, enterocolitis, extravasation recall, hepatic encephalopathy, hepatic necrosis, induration, intestinal obstruction, intestinal perforation, interstitial pneumonia, ischemic colitis, lacrimation increased, maculopapular rash, malaise, MI, necrotic changes and ulceration following extravasation, leukoencephalopathy, neutropenic enterocolitis, ototoxicity, pancreatitis, paralytic ileus, phlebitis, pruritus, pulmonary embolism, pulmonary fibrosis, radiation recall, radiation pneumonitis, pruritus, renal insufficiency, seizure, skin exfoliation, skin fibrosis, skin necrosis, Stevens-Johnson syndrome, supraventricular tachycardia, toxic epidermal necrolysis, ventricular tachycardia (asymptomatic), visual disturbances.

Nursing Guidelines:

Premedicate with steroids, antihistamines, and H2 blockers as per institutional guidelines. Mix the infusion bag well. Thorough admixture of this drug often prevents a hypersensitivity reaction.

Assess the patient frequently for the first 30 minutes. Taxol® hypersensitivity reactions, which may include chest pain, back pain, flushing, diaphoresis, dyspnea, pruritus, hypotension, hypertension, bronchospasm and/or urticaria, usually occur early in the infusion. Have the anaphylaxis tray available. If a reaction occurs, stop the infusion immediately. Epinephrine, IV fluids, diphenhydramine, and methylprednisolone may be used as per physician's order.

Approximately 60% of patients experience peripheral sensory neuropathy (numbness, tingling, burning pain, fine motor skills impairment, paresthesias, distal sensory loss). Nonsteroidal anti-inflammatory agents and opiates have not been effective in treating neuropathic pain.

Monitor CBC closely. Neutropenia is most severe in patients who have had previous chemotherapy. Instruct patient to report signs or symptoms of infection, unusual bruising or bleeding to the health care team.

Monitor IV site closely and establish patency before administration. Paclitaxel is an irritant, however rarely rash, radiation recall, and ulceration have occurred with infiltration of drug.

Monitor liver function tests

Inform patient about total alopecia.

If given on the same day as a platinum agent, paclitaxel should be administered first to limit myelosuppression and enhance efficacy of agent.

Availability: Commercial product will be utilized.

2. Nab-Paclitaxel

Packaging, Labeling, and Storage

Each single-use 50 ml vial will contain paclitaxel (100 mg) and approximately 900 mg human albumin (HA) as a stabilizer. Unreconstituted Abraxane should be stored at controlled room temperature (20° to 25°C or 68° to 77°F) in its carton. Reconstituted Abraxane should be used immediately. If not used immediately, the vial of reconstituted Abraxane must be placed in its carton and be placed in a refrigerator at 2° to 8°C (36° to 46°F) for a maximum of 8 hours. Both forms should be stored in an area free of environmental extremes and must be accessible only to study personnel.

Administration

NOTE: It is not a requirement to use filter needles in the preparation of, or in-line filters during the administration of Abraxane. In any event, filters of pore-size less than 15 micrometers must not be used.

Abraxane will be reconstituted by appropriate study personnel and administered to the patient in the study site. The investigator will calculate the body surface area (BSA) of the patient in order to determine the total amount of paclitaxel to be administered.

Administer dose per the protocol.

Reconstitution and use of Abraxane:

- Calculate the patient's body surface area at the beginning of the study and if the weight changes by > 10% by using the formula provided in the study manual.
- Calculate the total dose (in mg) to be administered = BSA x 100 mg/m^2 (unless dose is modified by criteria listed above).
- Calculate the total number of vials required by:

  Total Number of Vials = $\frac{\text{Total Dose (mg)}}{\text{100 (mg/vial)}}$

  Round up the number of vials to be reconstituted to the next higher whole number when a fractional number of vials is obtained by the above formula (e.g., if the total number of vials = 4.05 or 4.5, then 5 vials would be reconstituted).

  Using sterile technique, prepare the vials for reconstitution.

  Swab the rubber stoppers with alcohol.

  Reconstitute each Abraxane vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP or equivalent into each vial over a period of not less than 1 minute.

- **Slowly** inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of **1 minute**, using the sterile syringe directing the solution flow onto the **inside wall** of the vial.

DO NOT INJECT the 0.9% Sodium Chloride Injection, USP solution directly onto the lyophilized cake as this will result in foaming.

- Once the injection is complete, allow the vial to sit for a **minimum of 5 (five) minutes** to ensure proper wetting of the lyophilized cake/powder.
- **Gently** swirl and/or invert the vial **slowly** for at least **2 minutes** until complete dissolution of any cake/powder occurs. Rapid agitation or shaking will result in foaming.
- If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.
- Each ml of reconstituted product will contain 5 mg of paclitaxel.
- Calculate the exact total dosing volume of 5 mg/ml suspension required for the patient:

  Dosing volume (ml) = Total dose (mg) / 5 (mg/ml)

- The reconstituted sample should be milky and homogeneous without visible particulates. If unsuspended powder is visible, the vial should be **gently** inverted again to ensure complete resuspension, prior to use.

- Once the exact volume of reconstituted Abraxane has been withdrawn from the vials, discard any excess solution left over in accordance with standard operating procedures.
- Further dilution is not necessary. Inject the calculated dosing volume of reconstituted Abraxane suspension into an empty sterile, standard PVC IV bag using an injection port. Inject perpendicularly into the center of the injection port to avoid dislodging plastic material into the IV bag.
- Administer the calculated dosing volume of reconstituted Abraxane suspension by IV infusion over 30 minutes. The use of in-line filters is not necessary. If used, in-line filters with pore sizes of < 15μ should not be used.
- Use within 8 hours of reconstitution. If not used immediately, store reconstituted Abraxane in a refrigerator for no longer than 8 hours.

***Availability*:** Commercial supply will be utilized.

3. Carboplatin

Availability

Carboplatin Injection is supplied as a sterile, aqueous solution available in 50 mg/5 mL, 150 mg/15 mL, 450 mg/45 mL or 600 mg/60 mL multi-dose vials containing 10 mg/mL of carboplatin for administration by intravenous infusion. Each mL contains 10 mg carboplatin and Water for Injection, USP. Refer to the package insert for further information.

Commercial supply will be utilized.

Preparation

Carboplatin Injection is a premixed aqueous solution of 10mg/mL carboplatin.

Carboplatin Injection can be further diluted to concentrations as low as 0.5mg/mL with 5% Dextrose in Water or 0.9% sodium chloride injection, USP. When prepared as directed carboplatin solutions are stable for eight hours at room temperature. Since no antibacterial preservative is contained in the formulation it is recommended that carboplatin solutions be discarded eight hours after dilution.

Carboplatin Injection is supplied as follows:

Vial Strength	Diluent Volume
50 mg	5 ml
150 mg	15 ml
450 mg	45 ml
600 mg	60 ml

These dilutions all produce a carboplatin concentration of 10 mg/ml.

***Note*:** Aluminum reacts with carboplatin causing precipitate formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin.

Storage and Stability
Unopened vials of carboplatin are stable for the life indicated on the package. Store unopened vials of Carboplatin Injection at 30º to 25ºC (68º to 77ºF); excursions permitted between 15º and 30ºC (59º to 86ºF). Protect from light.

Administration
Infuse over at least 15 minutes; usually infused over 15 to 60 minutes.

Hazardous agent; use appropriate precautions for handling and disposal.

Administer dose per the protocol.

Toxicities
Bone marrow suppression: Bone marrow suppression is dose related and may be severe, resulting in infection or bleeding. Anemia may be cumulative and may require transfusion support.
Vomiting: Vomiting is a frequent drug-related side effect.
Hypersensitivity reactions: Anaphylactic-like reactions to carboplatin have been reported and may occur within minutes of carboplatin administration. Epinephrine, corticosteroids, and antihistamines have been employed to alleviate symptoms.

4. Trastuzumab

Availability and Supply
Trastuzumab (Herceptin™) will be obtained from commercial sources for this study.

Supply
Herceptin is supplied in a multi-use vial containing 440 mg trastuzumab as a lyophilized sterile powder, under vacuum. Each carton contains one vial Herceptin and one vial (20 mL) of Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative.

Preparation and Administration:
Reconstitution
Reconstitute each 440 mg vial of Herceptin with 20 mL of Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative to yield a multi-dose solution containing 21 mg/mL trastuzumab. In patients with known hypersensitivity to benzyl alcohol, reconstitute with 20 mL of Sterile Water for Injection (SWFI) without preservative to yield a single use solution.
Use appropriate aseptic technique when performing the following reconstitution steps:

- Using a sterile syringe, slowly inject the 20 mL of diluent into the vial containing the lyophilized cake of Herceptin. The stream of diluent should be directed into the lyophilized cake.
- Swirl the vial gently to aid reconstitution. **DO NOT SHAKE**.
- Slight foaming of the product may be present upon reconstitution. Allow the vial to stand undisturbed for approximately 5 minutes.

• Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Inspect visually for particulates and discoloration. The solution should be free of visible particulates, clear to slightly opalescent and colorless to pale yellow.
• Store reconstituted Herceptin at 2-8○C; discard unused Herceptin after 28 days. If Herceptin is reconstituted with SWFI without preservative, use immediately and discard any unused portion.

Dilution

• Determine the dose (mg) of Herceptin. Calculate the volume of the 21 mg/mL reconstituted Herceptin solution needed, withdraw this amount from the vial and add it to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection, USP. **DO NOT USE DEXTROSE (5%) SOLUTION.**
• Gently invert the bag to mix the solution.

Administer per the protocol.

Storage and Stability

Vials of Herceptin are stable at 2-8°C (36-46°F) prior to reconstitution. Do not use beyond the expiration date stamped on the vial. A vial of Herceptin reconstituted with BWFI, as supplied, is stable for 28 days after reconstitution when stored refrigerated at 2-8°C (36-46°F). Discard any remaining multi-dose reconstituted solution after 28 days. A vial of Herceptin reconstituted with unpreserved SWFI (not supplied) should be used immediately and any unused portion discarded.
Do not freeze Herceptin following reconstitution or dilution.
The solution of Herceptin for infusion diluted in polyvinylchloride or polyethylene bags containing 0.9% Sodium Chloride Injection, USP, should be stored at 2-8°C (36-46°F) for no more than 24 hours prior to use.

Administration

Administer dose per the protocol. For intravenous (IV) infusion only. Do not administer as an IV push or Bolus.

Toxicities

The following adverse reactions are discussed in greater detail in other sections of the label:
• Cardiomyopathy *[see package insert for details]*. **US Boxed Warning:** Trastuzumab is associated with symptomatic and asymptomatic reductions in left ventricular ejection fraction (LVEF) and heart failure (HF); the incidence is highest in patients receiving trastuzumab with an anthracycline-containing chemotherapy regimen. Evaluate LVEF in all patients prior to and during treatment; discontinue for cardiomyopathy. Extreme caution should be used in patients with pre-existing cardiac disease or dysfunction.
• Infusion Reactions *[see package insert for details]* **US Boxed Warning:** Infusion reactions (including fatalities) have been associated with use; discontinue for anaphylaxis or angioedema. Most reactions occur during or within 24 hours of the first infusion; interrupt infusion for dyspnea or significant hypotension; monitor until symptoms

resolve. Infusion reactions may consist of fever and chills, and may also include nausea, vomiting, pain, headache, dizziness, dyspnea, hypotension, rash, and weakness. Re-treatment of patients who experienced severe hypersensitivity reactions has been attempted (with premedication). Some patients tolerated re-treatment, while others experienced a second severe reaction.
• Embryo-Fetal Toxicity *[see package insert for details]*
• Pulmonary Toxicity *[see package insert for details]* **US Boxed Warning:** May cause serious pulmonary toxicity (dyspnea, hypoxia, interstitial pneumonitis, pulmonary infiltrates, pleural effusion, noncardiogenic pulmonary edema, pulmonary insufficiency, acute respiratory distress syndrome [ARDS], and/or pulmonary fibrosis); discontinue for ARDS or interstitial pneumonitis. Use caution in patients with pre-existing pulmonary disease or patients with extensive pulmonary tumor involvement; these patient populations may have more severe toxicity. Pulmonary events may occur during or within 24 hours of administration; delayed reactions have occurred.
• Exacerbation of Chemotherapy-induced Neutropenia *[see package insert for details]*
• Renal toxicity: Rare cases of nephrotic syndrome with evidence of glomerulopathy have been reported, with an onset of 4-18 months from trastuzumab initiation; complications may include volume overload and HF.

Please refer to the Herceptin package insert for a detailed description of the safety profile of Herceptin.

5. Pertuzumab

Availability:
Commercially available drug will be utilized.

Supplied:
PERJETA is supplied as a 420 mg/14 mL (30 mg/mL) single-use vial containing preservative- free solution.

Preparation and administration:
Prepare the solution for infusion, using aseptic technique, as follows:
• Parenteral drug products should be inspected visually for particulates and discoloration prior to administration.
• Withdraw the appropriate volume of PERJETA solution from the vial(s).
• Dilute into a 250 mL 0.9% sodium chloride PVC or non-PVC polyolefin infusion bag.
• Mix diluted solution by gentle inversion. Do not shake.
• Administer immediately once prepared.
• If the diluted infusion solution is not used immediately, it can be stored at 2oC to 8oC for up to 24 hours.
• Dilute with 0.9% Sodium Chloride injection only. Do not use dextrose (5%) solution.

Administer as an intravenous infusion only. Do not administer as an intravenous push or bolus. Do not mix PERJETA with other drugs.

Administer dose per protocol.

Storage:
Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) until time of use.
Keep vial in the outer carton in order to protect from light.
DO NOT FREEZE. DO NOT SHAKE.

ADVERSE REACTIONS

The following adverse reactions as well as other precautions are discussed in greater detail in the package insert.

- Left Ventricular Dysfunction: Monitor LVEF and withhold dosing as appropriate
- Embryo-Fetal Toxicity
- Infusion-Related Reactions: Monitor for signs and symptoms. If a significant infusion-associated reaction occurs, slow or interrupt the infusion and administer appropriate medical therapies
- Hypersensitivity Reactions/Anaphylaxis: Monitor for signs and symptoms. If a severe hypersensitivity reaction/anaphylaxis occurs, discontinue the infusion immediately and administer appropriate medical therapies.

Appendix III: Required On-Study Data Submissions

Required for registration:

- **On study form**
- **ICF first, page patient chooses tissue storage, and last page (de-identified)**
- **Pathology report with HER2, ER, PR statuses**
    - All pathology reports for diagnosis
    - If multiple foci and histologic evaluation not done on other detected lesions, note this (otherwise send those path reports)
- **Imaging reports (source) with tumor measurements**
    - If patient had imaging studies to rule out overt metastatic disease (at physician discretion), ask physician to comment on results in clinic note or addendum
- **Treating Physician H&P**
    - **This should include mention of patient's PS, clinical stage, whether patient is considered resectable or unresectable at baseline, whether patient is a candidate for breast conservation or not and for SLN sampling or would require ALND at baseline.**
    - **Ask treating physician to comment that he or she has reviewed the study's inclusion and exclusion criteria (Sections IV. A. and B.), including baseline labs and cardiac evaluation (if performed) and that he or she certifies that the patient is eligible for the study; this can be done in a clinic note or addendum or in an email forwarded to BrUOG.**