A Randomized Phase III Post-Operative Trial of Platinum Based Chemotherapy Vs. Observation in Patients with Residual Triple-Negative Basal-Like Breast Cancer following Neoadjuvant Chemotherapy

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(Limited to U.S. sites only)

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<th>For patient enrollments:</th>
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<td>Please refer to the patient enrollment section of the protocol for detailed instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at <a href="https://www.ctsu.org/OPEN_SYSTEM/">https://www.ctsu.org/OPEN_SYSTEM/</a> or <a href="https://OPEN.ctsu.org">https://OPEN.ctsu.org</a>. Contact the CTSU Help Desk with any OPEN-related questions at <a href="mailto:ctsucontact@westat.com">ctsucontact@westat.com</a>.</td>
<td>Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.</td>
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The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members’ website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.

**For clinical questions (i.e. patient eligibility or treatment-related)** contact the Study PI of the Coordinating Group.

**For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission)** contact the CTSU Help Desk by phone or e-mail:

CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

**For detailed information on the regulatory and monitoring procedures for CTSU sites** please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members’ website https://www.ctsu.org > education and resources tab > CTSU Operations Information >CTSU Regulatory and Monitoring Policy

**The CTSU Web site is located at** https://www.ctsu.org
Patients with:
- stage II/III TNBC\(^1\)
- Neoadjuvant chemotherapy\(^2\)
- found to have = 1 cm in diameter of residual cancer in the breast at the time of definitive surgery

Stratification factors:
1) Clinical stage at diagnosis (II or III)
2) Residual cancer burden after NAC (1–3 cm or > 3 cm)
3) Planned platinum agent choice (cisplatin or carboplatin)
4) Anthracycline exposure (yes or no)
5) Administration of radiotherapy (yes or no)

Accrual = 558 1 cycle = 3 weeks

1. TNBC: ER/PR less than 10% positive staining with weak intensity score, or less than 1% positive staining with weak or intermediate intensity score.
2. Taxane ± anthracycline based; platinum agents not allowed
3. Choice of platinum agent will be per treating physician discretion
4. Primary Endpoint: IDFS in patients with basal-like TNBC
5. Secondary Endpoints: OS and RFS
6. Patients must have completed adjuvant radiotherapy (if applicable) prior to randomization
7. Tumor tissue from the residual disease on the definitive surgical specimen must be submitted within 12 weeks post surgery for PAM50 analysis for determination of patient eligibility as outlined in Section 10.2. Patients cannot be randomized to treatment until institution receives results for PAM50 analysis from the Molecular Diagnostics Laboratory performing the assessments.
8. Females of child-bearing potential must have a blood test or urine study within 2 weeks prior to treatment initiation to rule out pregnancy.
1. Introduction

1.1 Triple-Negative Breast Cancer (TNBC)

Triple negative breast cancer (TNBC) is defined as estrogen and progesterone receptor (ER/PR) negative and not amplified for HER2 (ERBB2), and accounts for approximately 15% of all invasive breast cancers. Most TNBCs are high-grade and the majority of them harbor a basal-like gene expression signature. Among young women and African-American women, its prevalence is elevated. Patients with TNBC have an increased likelihood of distant recurrence and death compared with women with other types of breast cancer, as well as a tendency to develop visceral metastases early in the course of their disease. Improved approaches to treatment of these cancers is critical, since less than 30% of women with metastatic breast cancer survive five years and virtually all women with metastatic TNBC will ultimately die of their disease despite systemic therapy. To date, not a single targeted therapy has been approved for treatment of TNBC, where cytotoxic chemotherapy remains the standard treatment.

1.2 Residual drug-resistant disease after neoadjuvant chemotherapy

It is generally established that patients with breast cancer who achieve a pathological complete remission (pCR - lack of residual cancer in both breast and axilla) after neoadjuvant therapy exhibit a good long-term outcome. More specifically, approximately 30% of TNBC treated with anthracycline and taxane-based neoadjuvant chemotherapy (NAC) have a pCR to treatment, and consistent with above data, achieving a pCR to NAC in this group of patients also has been shown to be a strongly positive prognostic factor. On the other hand, those patients with residual viable tumor following neoadjuvant therapy are at risk of metastatic recurrence and death. High residual disease burden in the post-treatment, surgically-excised cancers has been shown to correlate with a high rate of recurrence and death (Figures 1a and b).
Balko et al. recently completed a study where we profiled 89 residual tumors from patients with stage II (20%) and III (80%) TNBC treated with AC-T neoadjuvant chemotherapy (NAC)\textsuperscript{8}. Expression level for 450 genes was quantified by NanoString in RNA extracted from the surgical specimen. Molecular subtype of these residual tumors, after adjusting for HER2 amplification (i.e. upon re-testing, all HER2 FISH amplified cancers were excluded) was as follows: 70% basal-like; 15% HER2-enriched; 6% luminal A, 6% luminal B; and 5% normal-like. Basal-like status was associated with a trend toward worse recurrence free survival (RFS) and overall survival (OS) (log-rank test, \( P = 0.12 \) and 0.058, respectively). The median time to relapse among this high-risk group of patients with basal-like gene expression was only 18 months (Figure 2).

These data suggest that residual drug-resistant disease in the breast after neoadjuvant therapy is a surrogate for drug-resistant micrometastases that ultimately progress to clinically overt metastatic breast cancer. Therefore, more detailed molecular analysis of residual disease after neoadjuvant therapy may be useful to explain mechanisms of resistance and to identify potentially useful therapies.

1.3 Platinum agents in TNBC

Using gene expression, a recent study from Lehmann et al. supports the notion that TNBC is a heterogeneous group of tumors\textsuperscript{10}. Within TNBC, about 70% are expected to be basal-like, by gene expression profile\textsuperscript{11}. Consistent with early clinical data in TNBC, breast cancer cells and xenografts with basal-like gene expression were particularly sensitive to cisplatin (Figure 3).
Platinum salts, including carboplatin and cisplatin, lead to DNA cross-link strand breaks, which may be especially important in cells which are deficient in homologous recombination repair mechanisms such as BRCA mutated cells and TNBC. Leong et al.\textsuperscript{12} reported a p63-dependent tumor survival pathway that directly mediates cisplatin sensitivity, specifically in TNBC. To further corroborate these findings, Rocca et al.\textsuperscript{13} conducted a retrospective analysis of core biopsies of breast cancer patients treated with neoadjuvant chemotherapy and showed that regimens including cisplatin yield a significantly higher rate of pCR in p63-positive tumors. In a small phase II study (29 patients), Silver et al. showed activity of neoadjuvant cisplatin as a single agent in the treatment of patients with locally advanced TNBC. The observed pCR was 22%, and 50% of patients had a partial clinical response, and 14% had a complete clinical response\textsuperscript{14}. In another small study, 9 of 10 patients with stage I-III breast cancer harboring BRCA1 mutations achieved a pCR after neoadjuvant therapy with cisplatin\textsuperscript{15}.

Further evidence of the activity of platinum agents in TNBC comes from 2 large phase II randomized trials in the neoadjuvant setting: the GeparSixto phase II randomized trial, in its TNBC subset, compared neoadjuvant paclitaxel, liposomal doxorubicin, and bevacizumab to the same regimen with the addition of carboplatin. The pCR rate improved from 37.9% to 58.7% with the addition of carboplatin. However, only about 50% of patients were able to complete treatment due to adverse events (possibly since all chemotherapy drugs were given concomitantly)\textsuperscript{16}. CALGB 40603 (NCT00861705) is a randomized phase II trial with a 2 x 2 factorial design that explored the addition of carboplatin +/- bevacizumab to neoadjuvant weekly paclitaxel followed by dose-dense AC in in 443 patients with stage II/III TNBC\textsuperscript{17}. The pCR rate improved from 41% to 54% with the addition of carboplatin; bevacizumab had no added benefit. The concomitant use of platinum agents with chemo in CALGB 40603 was also associated with markedly higher toxicity, which resulted in significantly fewer patients receiving 11-12 doses of paclitaxel when carboplatin was added, compared to the control group (< 65% in PCarbo→ AC vs. > 85% in P → AC). Of note, neither of these studies was powered to address disease-free or overall survival benefit from the addition of carboplatin to neoadjuvant systemic chemotherapy.
It is important to emphasize that **there’s not yet a correlation between increases in frequency of pCR and event-free survival (EFS).** This has been shown by Cortazar et al.\(^9\) in a recent pooled analysis that included data from almost 12,000 women with primary breast cancer participating in large randomized trials of neoadjuvant chemotherapy. The association between pCR and long-term outcomes was strongest in patients with TNBC (EFS: HR 0.24, 95% CI 0.18–0.33; OS: 0.16, 0.11–0.25), however, in the trial-level analysis, they recorded little association between increases in frequency of pCR and EFS (\(R^2=0.03\), 95% CI 0.00–0.25) and OS (\(R^2=0.24\), 0.00–0.70). Ultimately, their pooled analysis could not validate pCR as a surrogate endpoint for improved EFS and OS. There are several possible reasons for this. First, the improvement in pCR could simply represent a marginally improved response in a subject already destined to do well. For example, the additional agent may primarily convert patients who would have had only minimal residual disease to a pCR. If that is the case there would be little expected impact in EFS. Second, the incremental improvement in pCR has been modest at best. As some patients who achieve a pCR go on to relapse and many with residual disease never experience a recurrence, small differences in pCR may never translate to improvements in EFS.

Ultimately, the reason to treat patients in the (neo)adjuvant setting is prevention of distant recurrence and death from breast cancer. The improvement in pCR rate is certainly encouraging; however, pCR is not a clinically meaningful endpoint. pCR is only important to the extent that it predicts EFS. Unfortunately the relationship between pCR and EFS is complicated and imperfect. None of the neoadjuvant studies incorporating platinum have reported an improvement in DFS or OS. Studies that are adequately powered to detect a DFS and OS are still important and needed.

### 1.4 Rationale for selected approach and trial design

At present, upon completion of neoadjuvant therapy, the standard of care for patients with TNBC (who have no clinical evidence of metastatic disease after surgical excision of the cancer regardless of burden of residual disease) is observation, since there are no additional therapies available with proven impact on DFS and OS.

While the GeparSixto\(^{16}\) and CALGB 40603\(^{17}\) phase II trials have clearly shown the merit of adding a platinum agent to the systemic treatment of patients with TNBC in the neoadjuvant setting, these trials were clearly underpowered to address DFS and OS. Furthermore, exposing (unselected) patients, many of whom will never relapse, to toxic therapy in the absence of known benefit would be clearly detrimental. Finally, the pooled analysis performed by Cortazar et al.\(^9\) could not validate pCR as a surrogate endpoint for improved EFS and OS. Therefore, studies that are adequately powered to detect a DFS and OS benefit are still important and needed.

Within TNBC, patients with tumors with basal-like expression are at the highest risk for recurrence. In preclinical models, the basal-like subtype of TNBC was the most sensitive to cisplatin; preliminary clinical data showed that residual cancer with basal-like subtype was associated with trend toward worse RFS and OS. Hence, the biologic rationale for this concept is strongest in the basal like subtype. Our proposed NCI-sponsored phase III study is designed to have a
large impact for patients with basal-like TNBC. The advantages of our proposed design are:

a) This design and patient population allow us to assess the magnitude of DFS and OS benefit from the addition of a platinum agent in the adjuvant setting without requiring extremely large number of patients, since we will be enriching the trial with participants that are at the highest risk for recurrence;

b) In the GeparSixto and CALGB 40603 neoadjuvant trials, only about 50-60% of patients were able to complete treatment due to adverse events (possibly since all chemotherapy drugs were given concomitantly); in our study, since the intervention occurs after standard of care treatment, we will potentially minimize toxicity from treatment and will maximize the chances that participants will complete treatment as planned;

c) If positive, this trial proposal is powered to foster a change in clinical practice worldwide for patients with a very high risk of early recurrence and death from basal-like TNBC.

In regards to the chemotherapy dosing and schedule chosen, the usual dose of cisplatin for a variety of tumors (ovarian, bladder, neuroblastoma, osteogenic sarcoma, non-small cell lung cancer, etc. ranges from 60 – 100 mg/m2 every 3-4 weeks, and for carboplatin ranges from AUC 4 – 6, every 3-4 weeks. A single arm, multi-center phase II study evaluating platinum monotherapy (cisplatin or carboplatin) in 86 patients receiving first or second line treatment of metastatic TNBC was recently reported, and utilized cisplatin at 75 mg/m2 every 3 weeks and carboplatin AUC 6 every 3 weeks. These doses were well tolerated, without extensive grade 3 and 4 events. Considering that the patient population in our clinical trial would have been recently exposed to neoadjuvant chemotherapy and (in a good proportion of patients) radiotherapy, and from a treatment point of view would be very similar to patient population enrolled in the above phase II trial, we opted to use cisplatin at 75 mg/m2 every 3 weeks and carboplatin AUC 6 every 3 weeks as the prescribed chemotherapy regimen in this trial.

As for the timing of radiation therapy, we have carefully considered all options regarding the timing of platinum and radiation therapy (i.e. prior to, during, after radiation). We felt it was most appropriate not to delay initiation of radiation in view of its established DFS and OS benefit in high-risk adjuvant patients, which then allows the investigational therapy (platinum agent) to be given after completion of all standard chemotherapy and radiation. Administering the platinum agent before radiation would delay initiation of radiation in the investigational arm, introducing a variable that would complicate analysis and could negatively impact outcomes for these patients. Another practical consideration is the time necessary to conduct the PAM50 analysis as an integral biomarker/eligibility criterion. Screening all patients (and then allowing radiation to proceed when indicated) for PAM50 testing would then allow all patients to initiate protocol therapy around the same time and reduce the risk of an imbalance regarding completion of all standard loco-regional therapy before initiation of protocol therapy. Therefore, we have standardized the administration of the platinum agent after completion of any recommended radiation therapy.

This study design will lay the groundwork (i.e. the proof of concept) for additional similarly designed studies as new data and new targeted agents become available; our study is based in biology that tests a concept as much as it tests a specific drug. The information gleaned from the correlates will advance the field
irrespective of the outcome of the clinical endpoints. In addition to PAM50, this study design could allow us to explore other markers of platinum sensitivity, such as HRD (Homologous Recombination Deficiency Assay [Myriad], to identify tumors with HR deficiency), and Next Generation Sequencing in (residual) breast cancers after neoadjuvant therapy, for unbiased identification of somatic alterations (mutations, amplifications, deletions, indels) potentially associated with drug resistance, that could be targeted therapeutically in order to eradicate clinically silent micrometastases already present at the time of surgery. This type of deep molecular profiling of actionable molecular alterations could become standard of care in surgical specimens after neoadjuvant chemotherapy, where identification of these lesions in a CLIA-certified setting should be able to guide personalized adjuvant trials aimed at eradicating micrometastatic disease in the near future.
2. **Objectives**

The study hypothesis is that patients with clinical stage II-III TNBC with more than 1 cm of residual disease and basal-like subtype in their surgical specimen after neoadjuvant chemotherapy that are treated with adjuvant platinum based chemotherapy will have a longer invasive disease-free survival (IDFS) than the ones in the observation arm, which is the current standard of care.

2.1 **Primary Objective**

2.1.1 To compare the IDFS in TNBC patients with residual basal-like disease after neoadjuvant chemotherapy who are randomized to post-preoperative platinum based chemotherapy with those who are randomized to observation.

2.2 **Secondary Objectives**

2.2.1 To evaluate OS and RFS in the two arms in patients with TNBC with residual basal-like disease after neoadjuvant chemotherapy.

2.2.2 To characterize the side effects and tolerability of each platinum agent (cisplatin and carboplatin) in patients with TNBC with residual basal-like disease after neoadjuvant chemotherapy.

2.2.3 To identify the rate of basal-like gene expression using PAM50 analysis by digital mRNA quantitation amongst drug-resistant residual TNBC after neoadjuvant chemotherapy.
Selection of Patients

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

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

ECOG-ACRIN Patient No. ____________________________

Patient’s Initials (L, F, M) _______________________

Physician Signature and Date ____________________

NOTE: All questions regarding eligibility should be directed to the study chair or study chair liaison.

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

NOTE: This study involves screening and randomization. Tumor tissue specimen must be submitted for PAM50 analysis and results will determine patient’s Step 1 eligibility.

3.1 Eligibility Criteria for Screening (STEP 0)

___ 3.1.1 Age ≥ 18 years.

___ 3.1.2 ECOG Performance Status 0 or 1 within 2 weeks prior to screening.

___ 3.1.3 Female and male patients must have histologically confirmed triple negative (ER-/PR-/HER2-) invasive breast cancer, clinical stage II-III at diagnosis (AJCC 7th edition) based on initial evaluation by clinical examination and/or breast imaging.

3.1.3.1 ER- and PR- should meet one of the following criteria:

___ ≤ 10% cells stain positive, with weak intensity score (Allred score ≤ 2)

___ ≤ 1% cells stain positive, with weak or intermediate intensity score (Allred score ≤ 2)

3.1.3.2 HER2 negative (not eligible for anti-HER2 therapy) will be defined as:

___ IHC 0, 1+ without ISH HER2/neu chromosome 17 ratio OR

___ IHC 2+ and ISH HER2/neu chromosome 17 ratio non-amplified with ratio less than 2.0 and if reported average HER2 copy number < 6 signals/cells OR

___ ISH HER2/neu chromosome 17 ratio non-amplified with ratio less than 2.0 and if reported average HER2 copy number < 6 signals/cells without IHC)
NOTE: Patients that originally present with synchronous bilateral tumors are eligible provided both tumors are TNBC, and at least one of them fulfills the remainder eligibility criteria of the protocol.

3.1.4 Patients must have completed neoadjuvant taxane +/- anthracycline. Patients must NOT have received cisplatin or carboplatin as part of their neoadjuvant therapy regimen.

NOTE: Patients who received preoperative therapy as part of a clinical trial may enroll.

3.1.5 Must have completed definitive resection of primary tumor.

3.1.5.1 Negative margins for both invasive and ductal carcinoma in situ (DCIS) are desirable, however patients with positive margins may enroll if the treatment team believes no further surgery is possible and patient has received radiotherapy. Patients with margins positive for lobular carcinoma in situ (LCIS) are eligible.

3.1.5.2 Either mastectomy or breast conserving surgery (including lumpectomy or partial mastectomy) is acceptable.

3.1.5.3 Sentinel node biopsy post neoadjuvant chemotherapy (i.e. at the time of definitive surgery) is allowed. Axillary dissection is encouraged in patients with lymph node involvement, but is not mandatory.

3.1.6 Post neoadjuvant chemotherapy, patients must be found to have residual invasive cancer in the breast at the time of definitive surgery. Residual cancer is defined as a contiguous focus of residual invasive cancer, in the breast, measuring ≥ 1 cm in diameter, and with more than minimal cellularity, as per local pathologist determination.

NOTE: The presence of ductal carcinoma in situ (DCIS) without invasion does not qualify as residual invasive disease in the breast.

3.1.7 Post-mastectomy radiotherapy is required for all patients with the following:

- Primary tumor ≥ 5 cm (prior to neoadjuvant chemotherapy [clinically] or at the time of definitive surgery) or involvement of 4 or more lymph nodes at the time of definitive surgery.

- For patients with primary tumors < 5 cm or with < 4 involved lymph nodes prior to neoadjuvant chemotherapy and at the time of definitive surgery, provision of post-mastectomy radiotherapy is at the discretion of the treating physician.

NOTE: Radiation of regional nodal basins is at the discretion of the treating radiation oncologist. Patients enrolled in clinical trials addressing local therapy after neoadjuvant chemotherapy are allowed to enroll.
Whole breast radiotherapy is required for patients who underwent breast-conserving therapy, including lumpectomy or partial mastectomy.

Adequate bone marrow and organ function based on the following tests. Laboratory values must be obtained within 8 weeks prior to screening for protocol therapy.

- **Hemoglobin (Hgb) > 9.0 g/dL**
- **Platelets > 100 mm³**
- **Absolute neutrophil count (ANC) > 1500 mm³**
- **Calculated creatinine clearance of > 50 mL/min using the Cockcroft-Gault formula:**
  
  **Males:** \((140 – \text{Age in years}) \times \frac{\text{Actual Body Weight in kg}}{72} \times \text{Serum Creatinine (mg/dL)}\)
  
  **Females:** Estimated creatinine clearance for females \(\times 0.85\)

- **Bilirubin ≤ 1.5 × ULN upper limit of normal (except in patients with documented Gilbert’s disease, who must have a total bilirubin ≤ 3.0 mg/dL)**

- **Aspartate aminotransferase (AST, SGOT) ≤ 2.5 × ULN**

- **Alanine aminotransferase (ALT, SGPT) ≤ 2.5 × ULN**

No stage IV (metastatic) disease, however no specific staging studies are required in the absence of symptoms or physical exam findings that would suggest distant disease.

No clinically significant infections as judged by the treating investigator.

Patients with active ≥ CTCAE v.4 grade 2 neuropathy are ineligible.

Adjuvant chemotherapy after surgery other than that specified in this protocol is not allowed. LHRH agonists and adjuvant bisphosphonate use is allowed.

Patients must have archived formalin-fixed paraffin-embedded (FFPE) tumor tissue specimen from the residual disease on the definitive surgical specimen available for PAM50 analysis to determine patient eligibility.

Tumor tissue specimen from the definitive surgery has been collected and is ready to ship to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF) within 12 weeks post-surgery as indicated in Section 10.2.1.

The Molecular Diagnostics Laboratory (MDL) at MD Anderson Cancer Center will perform the PAM50 analysis and forward results (eligible versus non-eligible) within three (3) weeks of receipt of the tumor tissue specimen to the ordering physician via FAX and to the ECOG-ACRIN
Operations Office via secure electronic messaging to the ECOG-ACRIN database.

**NOTE:** Every effort should be made to submit the tumor tissue specimen to the ECOG-ACRIN CBPF immediately. Tumor tissue cannot be accepted after 12 weeks (post-surgery) in order to allow for PAM50 analysis.

Date of surgery: _______

Date tumor tissue sent to ECOG-ACRIN CBPF: _______

Date of receipt of PAM50 test results: _______

### 3.2 Eligibility Criteria for Randomization (Step 1):

Screened patients will remain on the study and be randomized if they meet the above and following criteria. For patients randomized to the chemotherapy arm, Cycle 1/ Day 1 must start within 1 week (5 working days) following randomization.

- **3.2.1** Must have basal-like gene expression on PAM50 analysis by digital mRNA quantitation on the formalin-fixed paraffin-embedded tumor tissue specimen (FFPE) of the residual disease in the breast or axilla resected at the time of definitive surgery.

- **3.2.2** ECOG Performance Status 0 or 1 within 2 weeks prior to randomization.

- **3.2.3** Patients must have completed adjuvant radiotherapy ≥ 2 weeks prior to randomization for protocol therapy, if applicable.

- **3.2.4** Patients must have completed treatment with any investigational agent ≥ 30 days prior to randomization for protocol therapy, if applicable.

- **3.2.5** Patients must be randomized within 15 weeks from surgery.

- **3.2.6** Women must not be pregnant or breast-feeding due to risk of teratogenicity/toxicity with platinum based therapy. All females of childbearing potential must have a blood test or urine study within 2 weeks prior to randomization to rule out pregnancy.

- **3.2.6.1** A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

- **3.2.6.2** Date of pregnancy blood test or urine study: _______

- **3.2.7** Women of childbearing potential and sexually active males must be strongly advised to use an accepted and effective method of contraception or to abstain from sexual intercourse for the duration of their participation in the study.
3.2.8 Adequate bone marrow and organ function based on the following tests. Laboratory values must be obtained within 2 weeks prior to randomization.

3.2.8.1 Hemoglobin (Hgb) > 9.0 g/dL
3.2.8.2 Platelets > 100 mm³
3.2.8.3 Absolute neutrophil count (ANC) > 1500 mm³
3.2.8.4 Calculated creatinine clearance of > 50 mL/min using the Cockcroft-Gault formula:
   Males: \( \frac{(140 - \text{Age in years}) \times \text{Actual Body Weight in kg}}{72 \times \text{Serum Creatinine (mg/dL)}} \)
   Females: Estimated creatinine clearance for females \( \times 0.85 \)
3.2.8.5 Bilirubin ≤ 1.5 x ULN (except in patients with documented Gilbert’s disease, who must have a total bilirubin ≤ 3.0 mg/dL)
3.2.8.6 Aspartate aminotransferase (AST, SGOT) ≤ 2.5 x ULN
3.2.8.7 Alanine aminotransferase (ALT, SGPT) ≤ 2.5 x ULN
4. Registration Procedures

CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed **Statement of Investigator Form** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed **Supplemental Investigator Data Form** (IDF)
- a completed **Financial Disclosure Form** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the **CTEP Investigator Registration Help Desk** by email at <pmbregpend@ctep.nci.nih.gov>.

CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members’ website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the **CTEP Associate Registration Help Desk** by email at <ctepreghelp@ctep.nci.nih.gov>.

CTSU Registration Procedures

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

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members’ web site by entering credentials at **https://www.ctsu.org**. For sites under the CIRB initiative, IRB data will automatically load to RSS.
Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. This information will be provided to the CTSU Regulatory Office from the CIRB at the time the site’s Signatory Institution accepts the CIRB approval. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on the study. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

**Downloading Site Registration Documents:**

Site registration forms may be downloaded from the EA1131 protocol page located on the CTSU members’ website.

- Go to [https://www.ctsu.org](https://www.ctsu.org) and log in to the members’ area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the ECOG-ACRIN link to expand, then select trial protocol EA1131
- Click on the Site Registration Documents link

Requirements for EA1131 site registration:

- CTSU IRB Certification (for sites not participating via the NCI CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)

**Submitting Regulatory Documents**

Submit completed forms along with a copy of your IRB Approval and *Model Informed Consent* to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office  
1818 Market Street, Suite 1100  
Philadelphia, PA 19103  
**Phone: 1-866-651-2878**  
FAX: (215) 569-0206  
E-mail: [CTSURegulatory@ctsu.coccg.org](mailto:CTSURegulatory@ctsu.coccg.org) (for regulatory document submission only)

**Required Protocol Specific Regulatory Documents**

1. CTSU Regulatory Transmittal Form.

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

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

NOTE: The above submissions must include the following details:

- Indicate all sites approved for the protocol under an assurance number.
- OHRP assurance number of reviewing IRB
- Full protocol title and number
- Version Date
- Type of review (full board vs. expedite)
- Date of review.
- Signature of IRB official

Checking Your Site’s Registration Status:

Check the status of your site’s registration packets by querying the RSS site registration status page of the members’ section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

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

Patient Enrollment

Treatment should start within five (5) working days following randomization.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at <https://eapps-ctep.nci.nih.gov/iam/index.jsp>) and a ‘Registrar’ role on either the LPO or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members’ side of the website at https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

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

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

Further instructional information is provided on the CTSU members’ web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.
4.1 Screening (STEP 0)

4.1.1 Protocol Number

4.1.2 Investigator Identification

4.1.2.1 Institution and affiliate name

4.1.2.2 Investigator’s name

4.1.3 Patient Identification

4.1.3.1 Patient’s initials (first and last)

4.1.3.2 Patient’s Hospital ID and/or Social Security number

4.1.3.3 Patient demographics

4.1.3.3.1 Gender

4.1.3.3.2 Birth date (mm/yyyy)

4.1.3.3.3 Race

4.1.3.3.4 Ethnicity

4.1.3.3.5 Nine-digit ZIP code

4.1.3.3.6 Method of payment

4.1.3.3.7 Country of residence

4.1.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.1.

4.2 Additional Requirements

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

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

4.2.2 Pathological materials are required to be submitted no later than week 12 post-surgery for PAM50 analysis as indicated in Section 10.2.

NOTE: The Molecular Diagnostics Laboratory (MDL) at MD Anderson Cancer Center will notify the ordering physician via FAX and the ECOG-ACRIN Operations Office via secure electronic messaging to the ECOG-ACRIN database of the results of the PAM50 analysis (eligible versus non-eligible) within three (3) weeks of receipt of the tumor tissue specimen. Please do not call the MDL for results, as testing data cannot be provided over the telephone.

Submission of inadequate tumor tissue specimen will result in request for additional material and will delay turnaround time for reporting results.

Pathological materials will also be used for retrospective central review for confirmation of ER, PR, HER2 status.
4.3 Randomization (STEP 1)

4.3.1 Protocol Number

4.3.2 Investigator Identification

4.3.2.1 Institution and affiliate name.
4.3.2.2 Investigator’s name.

4.3.3 Patient Identification

4.3.3.1 Patient’s initials (first and last)
4.3.3.2 Patient’s Hospital ID and/or Social Security number
4.3.3.3 Patient demographics

4.3.3.3.1 Gender
4.3.3.3.2 Birth date (mm/yyyy)
4.3.3.3.3 Race
4.3.3.3.4 Ethnicity
4.3.3.3.5 Nine-digit ZIP code
4.3.3.3.6 Method of payment
4.3.3.3.7 Country of residence

4.3.4 Stratification Factors

4.3.4.1 Clinical stage at diagnosis (II or III)
4.3.4.2 Residual cancer burden after neoadjuvant chemotherapy
(1~3 cm or >3 cm)
4.3.4.3 Planned platinum agent (cisplatin or carboplatin)
4.3.4.4 Anthracycline exposure in the neoadjuvant setting (yes or no)
4.3.4.5 Administration of adjuvant radiotherapy (yes or no)

4.3.5 Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at <https://eapps-ctep.nci.nih.gov/iam/index.jsp>) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

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

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

4.4 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If after randomization a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted through Medidata Rave according to the schedule in the EA1131 Forms Completion Guidelines.
5. **Treatment Plan**

5.1 **Administration Schedule**

Doses are based on actual body weight. Repeat cycles every 3 weeks for a total of 4 cycles.

5.1.1 ARM A

Observation

5.1.2 ARM B

Cisplatin 75 mg/m\(^2\), IV infusion per institutional guidelines, day 1 every 3 weeks

OR

Carboplatin AUC 6, IV infusion per institutional guidelines, day 1 every 3 weeks

**NOTE:** CALVERT FORMULA FOR CARBOPLATIN DOSING:

Total Dose (mg) = (target AUC) x (GFR + 25)

For the purposes of this protocol, the GFR is considered to be equivalent to the creatinine clearance.

Glomerular Filtration Rate (GFR) Estimation: Calculated creatinine clearance of ≥ 50 cc/min using the Cockcroft-Gault formula:

Males: 

\[
(140 - \text{Age in years}) \times \text{Actual Body Weight in kg} \div 72 \times \text{Serum Creatinine (mg/dL)}
\]

Females: Estimated creatinine clearance for females × 0.85

With the Calvert formula, the total (final) dose of carboplatin is calculated in mg, not mg/m\(^2\).

**NOTE:** Choice of platinum agent will be per treating physician discretion. Once a platinum agent is picked, no changes are allowed.

**NOTE:** All patients (on both arms) will be followed for development of recurrences, second primary cancer and survival based on standard ECOG-ACRIN following schedules (see section 7 for details).

5.2 **Adverse Event Reporting Requirements**

5.2.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

- **Routine reporting:** Adverse events are reported in a routine manner at scheduled times during a trial using Medidata Rave.
- **Expedited reporting**: In addition to routine reporting, certain adverse events must be reported in an expedited manner for timelier monitoring of patient safety and care. The following sections provide information and instructions regarding expedited adverse event reporting.

5.2.2 Terminology

- **Adverse Event (AE)**: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

- **Attribution**: An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

<table>
<thead>
<tr>
<th>ATTRIBUTION</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrelated</td>
<td>The AE is <em>clearly NOT related</em> to treatment.</td>
</tr>
<tr>
<td>Unlikely</td>
<td>The AE is <em>doubtfully related</em> to treatment.</td>
</tr>
<tr>
<td>Possible</td>
<td>The AE <em>may be related</em> to treatment.</td>
</tr>
<tr>
<td>Probable</td>
<td>The AE is <em>likely related</em> to treatment.</td>
</tr>
<tr>
<td>Definite</td>
<td>The AE is <em>clearly related</em> to treatment.</td>
</tr>
</tbody>
</table>

- **CTCAE**: The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.

- **Expectedness**: Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes, when either the type of event or the severity of the event is NOT listed in the protocol or drug package insert.

5.2.3 Reporting Procedure


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

- the AE Team at ECOG-ACRIN (617-632-3610)
- the FDA (1-800-FDA-1088)

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

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

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

### 5.2.4 Determination of Reporting Requirements

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

- the phase (0, 1, 2, or 3) of the trial
- whether the patient has received an investigational or commercial agent or both
- the Common Terminology Criteria for Adverse Events (CTCAE) grade
- when the adverse event occurred (within 30 days of the last administration of investigational agent vs. ≥ 30 days after the last administration of investigational agent)
- the relationship to the study treatment (attribution)
- the expectedness of the adverse event

Using these factors, the instructions and tables in the following sections have been customized for protocol EA1131 and outline the specific expedited adverse event reporting requirements for study EA1131.
5.2.5 Steps to determine if an event is to be reported in an expedited manner - Arm B

Identify the **type and grade** of the event using CTCAE v4.0.

Determine if the event is related to the protocol treatment (**attribution**).

Determine the **expectedness** of the event. An unexpected event is defined as one where the type of severity of the event is not listed in the investigator's brochure, package insert or protocol.

With this information, review the chart in Section 5.2.6 to determine if event is reportable via CTEP-AERS.

Is the event reportable?

- **No**
  - Report the event via CTEP-AERS.

- **Yes**
  - Refer to footnote b in Section 5.2.6 to determine if the event meets the protocol specific reporting requirements for this study. If so, report the event via CTEP-AERS.
5.2.6 Expedited Reporting Requirements for Arm B on protocol EA1131

Commercial Agents: Cisplatin and Carboplatin

<table>
<thead>
<tr>
<th>Attribution</th>
<th>Grade 4</th>
<th>Grade 5(a)</th>
<th>ECOG-ACRIN and Protocol-Specific Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrelated or Unlikely</td>
<td></td>
<td>7 calendar days</td>
<td></td>
</tr>
<tr>
<td>Possible, Probable, Definite</td>
<td>7 calendar days</td>
<td>7 calendar days</td>
<td></td>
</tr>
</tbody>
</table>

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

*a* This includes all deaths within 30 days of the last dose of treatment regardless of attribution.  

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

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

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

5.2.7 Other recipients of adverse event reports and supplemental data

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

5.2.8 Second Primary Cancer Reporting Requirements

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

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol).** Second malignancies require ONLY routine reporting as follows:
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
  3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.
- A secondary malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
  4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

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

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

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the ECOG-ACRIN Second Primary Form.

5.3 Cisplatin or Carboplatin Dose Modifications

A patient’s protocol treatment will be discontinued if more than 2 cumulative dose reductions are necessary or if patients are unable to restart cisplatin or carboplatin within 3 weeks of interruption. Dose reductions will be permanent. Missed doses will be made up once toxicity is resolved as per guidelines below.

All toxicity grades below are described using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

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 website (http://ctep.cancer.gov).

5.3.1 Cisplatin and Carboplatin dose reduction guidelines

<table>
<thead>
<tr>
<th></th>
<th>Starting dose (100%)</th>
<th>1st dose reduction (60%)</th>
<th>2nd dose reduction (60%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>75 mg/m2</td>
<td>60 mg/m2</td>
<td>45 mg/m2</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>AUC 6</td>
<td>AUC 5</td>
<td>AUC 4</td>
</tr>
</tbody>
</table>
5.3.2 Recommended Dose Modifications

<table>
<thead>
<tr>
<th>Worst Toxicity CTCAE v4.0 Grade (unless otherwise specified)</th>
<th>Recommended Dose Modifications to cisplatin any time during a cycle of therapy</th>
<th>Recommended Dose Modifications to carboplatin any time during a cycle of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLOOD AND LYMPHATIC SYSTEM DISORDER</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anemia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 (Hgb &lt; LLN-10.0 g/dL)</td>
<td>Maintain dose level.</td>
<td>Maintain dose level.</td>
</tr>
<tr>
<td>Grade 2 (Hgb &lt; 10.0 g/dL - 8.0 g/dL)</td>
<td>Maintain dose level.</td>
<td>Maintain dose level.</td>
</tr>
<tr>
<td>Grade 3 (Hgb &lt; 8.0 g/dL); transfusion indicated</td>
<td>Maintain dose level.</td>
<td>Maintain dose level.</td>
</tr>
<tr>
<td>Grade 4 (Life threatening consequences; urgent intervention indicated); related to study drugs</td>
<td>Discontinue study treatment.</td>
<td>Discontinue study treatment.</td>
</tr>
<tr>
<td><strong>ANC decreased (Neutropenia)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 (ANC &lt; LLN - 1.5 x 10⁹/L)</td>
<td>Maintain dose level.</td>
<td>Maintain dose level.</td>
</tr>
<tr>
<td>Grade 2 (ANC &lt; 1.5 - 1.0 x 10⁹/L)</td>
<td>Maintain dose level.</td>
<td>Maintain dose level.</td>
</tr>
<tr>
<td>Grade 3 (ANC &lt; 1.0 - 0.5 x 10⁹/L)</td>
<td>Omit dose of cisplatin until resolved to CTCAE Grade ≤ 1, and no fever. Then:</td>
<td>Omit dose of carboplatin until resolved to CTCAE Grade ≤ 1, and no fever. Then:</td>
</tr>
<tr>
<td></td>
<td>- If resolved in ≤ 7 days, then maintain dose level</td>
<td>- If resolved in ≤ 7 days, then maintain dose level</td>
</tr>
<tr>
<td></td>
<td>- If resolved in &gt; 7 days, then maintain dose level and consider prophylactic growth factor support per ASCO guidelines</td>
<td>- If resolved in &gt; 7 days, then maintain dose level and initiate prophylactic growth factor support per ASCO guidelines</td>
</tr>
<tr>
<td></td>
<td>- If second occurrence, then ↓ 1 dose level for subsequent cycles.</td>
<td>- If second occurrence, then ↓ 1 dose level for subsequent cycles.</td>
</tr>
<tr>
<td>Grade 4 (ANC &lt; 0.5 x 10⁹/L)</td>
<td>Omit dose of cisplatin until resolved to CTCAE ≤ Grade 1, then ↓ 1 dose level; additionally, consider prophylactic growth factor support per ASCO guidelines.</td>
<td>Omit dose of carboplatin until resolved to CTCAE ≤ Grade 1, then ↓ 1 dose level; additionally, consider prophylactic growth factor support per ASCO guidelines.</td>
</tr>
<tr>
<td><strong>Febrile neutropenia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3 (ANC &lt; 1.0 x 10⁹/L, single temperature of &gt; 38.3°C or a sustained temperature of ≥ 38.0°C)</td>
<td>Omit dose of cisplatin, then - If resolved by ≤ 7 days, then ↓ 1 dose level and consider prophylactic growth factor support per ASCO guidelines.</td>
<td>Omit dose of carboplatin, then - If resolved by ≤ 7 days, then ↓ 1 dose level and consider prophylactic growth factor support per ASCO guidelines.</td>
</tr>
<tr>
<td></td>
<td>- If not resolved within 7 days despite appropriate management including full clinically indicated course of antibiotics, if indicated, discontinue patient from study treatment.</td>
<td>- If not resolved within 7 days despite appropriate management including full clinically indicated course of antibiotics, if indicated, discontinue patient from study treatment.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Discontinue study treatment.</td>
<td>Discontinue study treatment.</td>
</tr>
<tr>
<td><strong>Platelet count decreased (Thrombocytopenia)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 (PLT &lt; LLN - 75 x 10⁹/L)</td>
<td>Omit dose of cisplatin until resolved to CTCAE Grade ≤ 1, then maintain dose level</td>
<td>Omit dose of carboplatin until resolved to CTCAE Grade ≤ 1, then maintain dose level</td>
</tr>
<tr>
<td>Grade 2 (PLT &lt; 75 - 50 x 10⁹/L)</td>
<td>Omit dose of cisplatin until resolved to CTCAE Grade ≤ 1, then ↓ 1 dose level</td>
<td>Omit dose of carboplatin until resolved to CTCAE Grade ≤ 1, then ↓ 1 dose level</td>
</tr>
<tr>
<td>Worst Toxicity CTCAE v4.0 Grade (unless otherwise specified)</td>
<td>Recommended Dose Modifications to cisplatin any time during a cycle of therapy</td>
<td>Recommended Dose Modifications to carboplatin any time during a cycle of therapy</td>
</tr>
<tr>
<td>----------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Grade 3 (PLT &lt; 50 - 25 x 10⁹/L )</td>
<td>Omit dose of cisplatin until resolved to CTCAE Grade ≤ 1, then - If resolved in ≤ 7 days, then maintain dose level. - If resolved in &gt; 7 days, then ↓ 1 dose level.</td>
<td>Omit dose of carboplatin until resolved to CTCAE Grade ≤ 1, then - If resolved in ≤ 7 days, then ↓ 1 dose level. - If resolved in &gt; 7 days, then discontinue study treatment.</td>
</tr>
<tr>
<td>Grade 4 (PLT &lt; 25 x 10⁹/L )</td>
<td>Discontinue study treatment.</td>
<td>Discontinue study treatment</td>
</tr>
</tbody>
</table>

**Bleeding**

Any bleeding (related to cisplatin or carboplatin) resulting in a transfusion requirement

Omit dose of cisplatin until no further bleeding has been observed. Continuation of study treatment may be considered.

Omit dose of carboplatin until no further bleeding has been observed. Continuation of study treatment may be considered.

**INVESTIGATIONS – RENAL**

**Serum creatinine**

<table>
<thead>
<tr>
<th>Grade 1 (&gt; ULN - 1.5 x ULN)</th>
<th>Maintain dose level.</th>
<th>Maintain dose level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2 (&gt; 1.5 - 3.0 x ULN)</td>
<td>Omit dose of cisplatin until resolved to CTCAE Grade ≤ 1 or baseline, then - If resolved in ≤ 7 days, then maintain dose level. - If resolved in &gt; 7 days, then ↓ 1 dose level.</td>
<td>Omit dose of carboplatin until resolved to CTCAE Grade ≤ 1 or baseline, then - If resolved in ≤ 7 days, then maintain dose level. - If resolved in &gt; 7 days, then ↓ 1 dose level.</td>
</tr>
<tr>
<td>Grade ≥ 3 (&gt; 3.0 x ULN)</td>
<td>Discontinue study treatment.</td>
<td>Discontinue study treatment</td>
</tr>
</tbody>
</table>

**INVESTIGATIONS – HEPATIC**

**Blood Bilirubin** (for patients with Gilbert Syndrome these dose modifications apply to changes in direct bilirubin only)

For patients with total bilirubin ≥ grade 3, a CT scan or equivalent imaging procedure to exclude disease progression or potential other liver disease should be performed.

<table>
<thead>
<tr>
<th>Grade 1 (&gt; ULN – 1.5 x ULN)</th>
<th>Maintain dose level.</th>
<th>Maintain dose level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2 (&gt;1.5 – 3.0 x ULN)</td>
<td>Omit dose of cisplatin until resolved to CTCAE Grade ≤ 1, then - If resolved in ≤ 7 days, then maintain dose level. - If resolved in &gt; 7 days, then ↓ 1 dose level.</td>
<td>Omit dose of carboplatin until resolved to CTCAE Grade ≤ 1, then - If resolved in ≤ 7 days, then maintain dose level. - If resolved in &gt; 7 days, then ↓ 1 dose level.</td>
</tr>
<tr>
<td>Grade 3 (&gt; 3.0 – 10 x ULN) or higher</td>
<td>Discontinue study treatment. <strong>Note:</strong> If CTCAE Grade 3 or 4 hyper-bilirubinemia is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the Investigator.</td>
<td>Discontinue study treatment. <strong>Note:</strong> If Grade 3 or Grade 4 hyperbilirubinemia is due to the indirect (unconjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the investigator.</td>
</tr>
</tbody>
</table>

**AST or ALT**

<p>| Grade 1 and 2 (up to 5.0 x ULN) | Maintain dose level. | Maintain dose level. |</p>
<table>
<thead>
<tr>
<th>Worst Toxicity CTCAE v4.0 Grade (unless otherwise specified)</th>
<th>Recommended Dose Modifications to cisplatin any time during a cycle of therapy</th>
<th>Recommended Dose Modifications to carboplatin any time during a cycle of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 (&gt; 5.0 - 20.0 x ULN)</td>
<td>Omit dose of cisplatin until resolved to CTCAE Grade ≤ 1, then - If resolved in ≤ 7 days, then maintain dose level. - If resolved in &gt; 7 days, then ↓ 1 dose level.</td>
<td>Omit dose of carboplatin until resolved to Grade ≤ 1, then - If resolved in ≤ 7 days, then maintain dose level. - If resolved in &gt; 7 days, then ↓ 1 dose level</td>
</tr>
<tr>
<td>Grade 4 (&gt; 20.0 x ULN)</td>
<td>Discontinue study treatment.</td>
<td>Discontinue study treatment.</td>
</tr>
</tbody>
</table>

**NERVOUS SYSTEM DISORDERS**

**Neurotoxicity**

| Grade 1 | Maintain dose level. | Maintain dose level. |
| Transient Grade 2 that improves to grade 1 on the day of planned therapy | Maintain dose level. | Maintain dose level. |
| Grade 2 | Omit dose of cisplatin until resolved to CTCAE Grade ≤ 1, then ↓ 1 dose level. | Omit dose of carboplatin until resolved to CTCAE Grade ≤ 1, then ↓ 1 dose level. |
| Grade ≥ 3 or second occurrence of Grade 2 | Discontinue study treatment. | Discontinue study treatment. |

**GI DISORDERS**

**Diarrhea**

| Grade 1 | Maintain dose level, but initiate anti-diarrhea treatment as clinically indicated | Maintain dose level, but initiate anti-diarrhea treatment as clinically indicated |
| Grade 2 | Omit dose of cisplatin until resolved to CTCAE Grade ≤ 1, including with appropriate management, then maintain dose level. | Omit dose of carboplatin until resolved to CTCAE Grade ≤ 1, including with appropriate management, then maintain dose level. |
| Grade 3 | Omit dose of cisplatin until resolved to CTCAE Grade ≤ 1, initiate anti-diarrhea treatment, then - If resolved in ≤ 48 hours, maintain dose level. - If resolved in > 48 hours, then ↓ 1 dose level. For 2nd occurrence of diarrhea CTCAE Grade 3 for > 48 hours despite the use of anti-diarrhea treatment, discontinue study treatment. | Omit dose of carboplatin until resolved to CTCAE Grade ≤ 1, initiate anti-diarrhea treatment, then - If resolved in ≤ 48 hours, maintain dose level. - If resolved in > 48 hours, then ↓ 1 dose level. For 2nd occurrence of diarrhea CTCAE Grade 3 for > 48 hours despite the use of anti-diarrhea treatment, discontinue study treatment. |
| Grade 4 | Discontinue study treatment. | Discontinue study treatment. |

**Nausea/Vomiting**

<p>| Grade 1 | Maintain dose level, but initiate anti-emetic treatment. | Maintain dose level, but initiate anti-emetic treatment. |
| Transient Grade 2 that improves to grade 1 on the day of planned therapy | Maintain dose level. | Maintain dose level. |
| Grade 2 | Omit dose of cisplatin until resolved to CTCAE Grade ≤ 1, initiate anti-emetic treatment, then maintain dose level. | Omit dose of carboplatin until resolved to CTCAE Grade ≤ 1, initiate anti-emetic treatment, then maintain dose level. |</p>
<table>
<thead>
<tr>
<th>Worst Toxicity CTCAE v4.0 Grade (unless otherwise specified)</th>
<th>Recommended Dose Modifications to cisplatin any time during a cycle of therapy</th>
<th>Recommended Dose Modifications to carboplatin any time during a cycle of therapy</th>
</tr>
</thead>
</table>
| Grade 3                                                     | Omit dose of cisplatin until resolved to CTCAE Grade ≤ 1, initiate anti-emetic treatment, then:  
- If resolved in ≤ 48 hours, maintain dose level.  
- If resolved in > 48 hours, then ↓ 1 dose level. | Omit dose of carboplatin until resolved to CTCAE Grade ≤ 1, initiate anti-emetic treatment, then:  
- If resolved in ≤ 48 hours, maintain dose level.  
- If resolved in > 48 hours, then ↓ 1 dose level. |
| Grade 4                                                     | Discontinue study treatment.                                                   | Discontinue study treatment.                                                   |

**GENERAL DISORDERS**

**Fatigue**

<table>
<thead>
<tr>
<th>Grade 1 or 2</th>
<th>Maintain dose level.</th>
<th>Maintain dose level.</th>
</tr>
</thead>
</table>
| Grade 3                                          | Omit dose of cisplatin until resolved to CTCAE Grade ≤ 1, then  
- If resolved in ≤ 7 days, maintain dose level.  
- If resolved in > 7 days, discontinue patient from study treatment. | Omit dose of carboplatin until resolved to CTCAE Grade ≤ 1, then  
- If resolved in ≤ 7 days, maintain dose level.  
- If resolved in > 7 days, discontinue patient from study treatment. |
| Grade 4                                          | Discontinue study treatment.     | Discontinue study treatment.     |

**INFUSION REACTIONS**

**Infusion reactions**

| Grade 1 (Transient flushing or rash, fever < 38 °C [<100.4 °F]; intervention not indicated) | - Stop infusion  
- Treat per institutional guidelines.  
- May resume infusion (within 4 hours of initial start of infusion) at 50% of previous under continuous observation. Ensure that there is a minimum observation period of 1 hour prior to restarting the infusion.  
- Maintain dose level.  
- If the AE recurs at the reinitiated slow rate of infusion, and despite oral pre-medication, then do not resume infusion. | - Stop infusion  
- Treat per institutional guidelines.  
- May resume infusion (within 4 hours of initial start of infusion) at 50% of previous under continuous observation. Ensure that there is a minimum observation period of 1 hour prior to restarting the infusion.  
- Maintain dose level.  
- If the AE recurs at the reinitiated slow rate of infusion, and despite oral pre-medication, then do not resume infusion. |
<table>
<thead>
<tr>
<th>Worst Toxicity CTCAE v4.0 Grade (unless otherwise specified)</th>
<th>Recommended Dose Modifications to cisplatin any time during a cycle of therapy</th>
<th>Recommended Dose Modifications to carboplatin any time during a cycle of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2</td>
<td>- Stop infusion</td>
<td>- Stop infusion</td>
</tr>
<tr>
<td></td>
<td>- Treat per institutional guidelines.</td>
<td>- Treat per institutional guidelines.</td>
</tr>
<tr>
<td></td>
<td>- May resume infusion (within 4 hours of initial start of infusion) at 50% of previous under continuous observation. Ensure that there is a minimum observation period of 1 hour prior to restarting the infusion.</td>
<td>- May resume infusion (within 4 hours of initial start of infusion) at 50% of previous under continuous observation. Ensure that there is a minimum observation period of 1 hour prior to restarting the infusion.</td>
</tr>
<tr>
<td></td>
<td>- Maintain dose level.</td>
<td>- Maintain dose level.</td>
</tr>
<tr>
<td></td>
<td>- If the AE recurs at the reinitiated slow rate of infusion, and despite oral pre-medication, then do not resume infusion.</td>
<td>- If the AE recurs at the reinitiated slow rate of infusion, and despite oral pre-medication, then do not resume infusion.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>- Discontinue infusion immediately</td>
<td>- Discontinue infusion immediately</td>
</tr>
<tr>
<td></td>
<td>- Treat per institutional guidelines.</td>
<td>- Treat per institutional guidelines.</td>
</tr>
<tr>
<td></td>
<td>- Discontinue patient from study.</td>
<td>- Discontinue patient from study.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>- Discontinue infusion immediately</td>
<td>- Discontinue infusion immediately</td>
</tr>
<tr>
<td></td>
<td>- Treat per institutional guidelines.</td>
<td>- Treat per institutional guidelines.</td>
</tr>
<tr>
<td></td>
<td>- Discontinue patient from study.</td>
<td>- Discontinue patient from study.</td>
</tr>
</tbody>
</table>

**OTHER ADVERSE EVENTS**

- **Grade 1 or 2**
  - Maintain dose level of cisplatin or carboplatin. For intolerable grade 2 toxicity, may omit dose of cisplatin or carboplatin until resolved.

- **Grade 3**
  - Omit dose of cisplatin or carboplatin until resolved to CTCAE Grade ≤ 1, then ↓ dose level of cisplatin or carboplatin.

- **Grade 4**
  - Discontinue study treatment.

**NOTE:** All of the above are general guidelines. The investigator may omit dose of drug, decrease dose level of drug, or remove any patient from study for any toxicity, if he/she believes that it is in the best interest of the patient.

If a patient requires a dose delay of > 21 consecutive days of cisplatin or carboplatin then the patient must be discontinued from the study treatment. Patients who discontinue from the study for a study-related adverse event or an abnormal laboratory value must be followed at least once a week for 3 weeks and subsequently at 3-week intervals, until resolution or stabilization of the event, whichever comes first, unless stated otherwise.
5.4 Supportive Care

5.4.1 All supportive measures consistent with optimal patient care will be given throughout the study.

5.4.2 The clinical tolerance of the patients, and the medical judgment of the investigator will determine if it is in the patient’s best interest to continue or discontinue treatment. If treatment is discontinued due to any toxicity, the patient must be followed to monitor duration of toxicity, response and time to progression (even if non-protocol therapy is initiated). Suggested supportive care medications may be substituted at the discretion of the investigator based on drug availability.

5.4.3 Growth factor support (filgastrim or peg-filgastrim) may be used in accordance with the American Society of Clinical Oncology (ASCO) guidelines.

5.4.4 Diarrhea may occur on Arm B. Appropriate supportive measures for diarrhea should include Loperamide and/or Diphenoxilate/atropine, and should be implemented immediately to prevent dehydration.

5.4.5 Hydration guidelines may be modified at the discretion of the treating physician provided adequate pre and post cisplatin hydration is achieved and renal function remains adequate. One suggested regimen consists of administering cisplatin in 250 cc to 1000 cc of IV fluids following adequate hydration and the establishment of adequate urinary output. It is suggested the pre-cisplatin hydration consist of NS at 500 cc/hr x 1 liter and post-cisplatin hydration consist of 1/2 NS + 10 meq KCl/liter + 1 gram magnesium sulfate/liter + 25 grams mannitol/liter at 500 cc/hr for at least one hour, followed by additional hydration at the discretion of the investigator.

5.4.6 Antiemetic therapy is critical for proper administration of cisplatin/carboplatin. The specific antiemetic regimen is at the discretion of the treating physician, provided adequate control is achieved. However, on the day of cisplatin therapy the investigator should consider use of a steroid medication and a 5HT3 antagonist. One such regimen consists of 20 mg of dexamethasone and a high dose of a 5HT3 antagonist (such as 1 mg oral of 10 mcg/kg IV granisetron or 8 mg ondansetron or equivalent) and continuing with 4 days of dexamethasone or equivalent steroid and 4 days of scheduled antiemetic such as metoclopramide or a 5HT3 antagonist. If this regimen is ineffective, consideration of the long-acting 5HT3 antagonist palonosetron and the agent aprepitant or fosaprepitant should be considered at the discretion of the investigator.

**NOTE:** Aprepitant or fosaprepitant should be used with caution in patients receiving concomitant medicinal products, including chemotherapy agents that are primarily metabolized through CYP3A4. Inhibition of CYP3A4 by aprepitant or fosaprepitant could result in elevated plasma concentrations of these concomitant medicinal products. The effect of aprepitant or fosaprepitant on the pharmacokinetics of orally administered CYP3A4
substrates is expected to be greater than the effect of aprepitant or fosaprepitant on the pharmacokinetics of intravenously administered CYP3A4 substrates.

NOTE: Dexamethasone dose should be reduced by 50% when administered with aprepitant or fosaprepitant.

5.5 Duration of Therapy

Patients will receive protocol therapy unless:
- Patient develops a local-regional or distant recurrence.
- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the EA1131 Forms Packet.
- Intercurrent illness that prevents further administration of therapy per protocol
- Patient becomes pregnant
- Patient withdraws consent.
- Patient experiences unacceptable toxicity.
- Non-protocol anti-cancer therapies are administered.

5.6 Duration of Follow-up

For this protocol, all patients (on both arms A and B), including those who discontinue protocol therapy early, will be followed for recurrence and second primary cancer, even if non-protocol anti-cancer therapy is initiated, and for survival for 10 years from the date of registration. All patients must also be followed through completion of all protocol therapy.
6. **Measurement of Effect**

6.1 **Local, Regional Recurrence**

6.1.1 The development of a local or regional recurrence of breast cancer:

Local-regional recurrence of the disease (ipsilateral or regional invasive breast cancer) should be cytologically/histologically confirmed, whenever possible. A CT scan of the chest/abdomen/pelvis or any other area as clinically indicated should be performed at the time of local recurrence to exclude further spread of the disease. Patients who develop loco-regional recurrence should discontinue study treatment (if recurrence during treatment period) and will continue to be followed for distant recurrence, new cancers, subsequent anti-cancer therapies and survival as per study schedule.

6.2 **Distant Recurrence**

6.2.1 The development of a distant recurrence of breast cancer:

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

6.3 **Invasive Disease-Free Survival**

6.3.1 Date of randomization to the date of first treatment failure (local/regional or distant recurrence, second invasive primary cancer or death before recurrence):

Disease free survival should be initially assessed by regular physical examination and clinical assessment. Recurrence event should be confirmed via radiological and/or cytological/histological assessment.

**NOTE:** a subsequent diagnosis of non-invasive cancer (DCIS) would not be considered an IDFS event.

6.4 **Survival**

6.4.1 Date of randomization to date of death from any cause.
# Study Parameters

## 7.1 Therapeutic Parameters

<table>
<thead>
<tr>
<th></th>
<th>STEP 0-Screening</th>
<th>STEP 1-Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All patients</td>
<td>All Patients</td>
</tr>
<tr>
<td></td>
<td>Within 8 weeks</td>
<td>Up to 1 week</td>
</tr>
<tr>
<td></td>
<td>prior to Screening</td>
<td>after Randomization</td>
</tr>
<tr>
<td>Demographics</td>
<td>X</td>
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</tr>
<tr>
<td>History and Physical</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Vital Signs and Weight</td>
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<tr>
<td>Height</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>ECOG Performance Status</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Toxicity Assessments</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Concomitant Medications Assessments</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Non Protocol Anti-Cancer Medications Assessments</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

### CLINICAL EVALUATIONS

- Serum or Urine Pregnancy Test
- CBC with Differential
- Complete Metabolic Panel (CMP)
- Imaging Tests
- Chemotherapy administration

### LABORATORY/RADIOLOGICAL ASSESSMENTS

- X
- X
- X
- X
- X

### TREATMENT ADMINISTRATION

- X

### BIOLOGICAL SAMPLE SUBMISSIONS

- MANDATORY: Tumor Tissue

---

1. Each cycle is a 3-week period of time. Total number of treatment cycles is 4. A window of +/- 3 days is allowed for above procedures, to account for holidays, vacation, and scheduling issues.
2. Pre-study CBC (with differential and platelet count) which includes WBC, ANC, Platelets, Hgb, and Hct or PCV should be done ≤ 8 weeks prior to screening, ≤ 2 weeks prior to randomization, and during treatment, it should be done within 3 days prior to each treatment cycle.

3. All required pre-study chemistries (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, total bilirubin, calcium, magnesium, total protein, albumin, AST, ALT, and alkaline phosphatase), should be done ≤ 8 weeks before screening, ≤ 2 weeks prior to randomization, and during treatment, it should be done within 3 days prior to each treatment cycle.

4. For women of childbearing potential; should be done within 2 weeks prior to randomization.

5. Cisplatin or Carboplatin; per treating physician’s discretion. Chemotherapy must be initiated within 5 working days following randomization.

6. Tumor tissue is required to be submitted for PAM50 analysis as outlined in Section 10.2. Submit to the ECOG-ACRIN Central Biorepository and Pathology Facility at MD Anderson Cancer Center within 12 weeks post surgery. The PAM50 analysis is mandatory for participation in this study. Results (eligible versus non-eligible) will be forwarded to the ordering physician via FAX and to the ECOG-ACRIN Operations Office via secure electronic messaging to the ECOG-ACRIN database within three (3) weeks of receipt of tumor tissue. The CLIA Laboratory Sample Submission Form (Appendix IV) must be submitted with the tumor tissue.

7. Every 3 months if patient is < 2 years from study entry, every 6 months if patient is 2-5 years from study entry, every 12 months if patient is 5-10 years from study entry. No specific requirements if patient is more than 10 years from study entry. A window of +/− 3 weeks is allowed for these procedures, to account for holidays, vacation and scheduling issues.

8. All specimens submitted must be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS) as outlined in Section 10.4.

9. In case of a local recurrence or clinical suspicion of distant recurrence, imaging tests to exclude presence of recurrent disease are strongly recommended, but should be performed at the investigator’s discretion.

10. If Baseline CBC and CMP were performed within 3 days of Day 1 Cycle 1 of treatment initiation, there’s no need to repeat them on Day 1 Cycle 1

11. Determination if any anti-cancer treatment is being administered beyond 3 months from randomization, which was not specified in the protocol.
8. Drug Formulation and Procurement

Both cisplatin and carboplatin will be obtained commercially. For additional information, please refer to the FDA approved package insert for each drug.

8.1 Cisplatin

8.1.1 Other Names: Platinol®

8.1.2 Classification: Cisplatin (cisplatin injection) (cis-diamminedichloroplatinum) is an anti-neoplastic agent – alkylating agent. It consists of a heavy metal complex containing a central atom of platinum surrounded by two chloride atoms and two ammonia molecules in the cis position. It is a white powder with the molecular formula PtCl2H6N2, and a molecular weight of 300.05. It is soluble in water or saline at 1 mg/mL and in dimethylformamide at 24 mg/mL. It has a melting point of 207°C.

8.1.3 Mode of Action: Its cytotoxic mode of action is mediated by its interaction with DNA to form DNA adducts, primarily intra-strand crosslink adducts, which activate several signal transduction pathways, including those involving ATR, p53, p73, and MAPK, and culminate in the activation of apoptosis.

8.1.4 Storage and Stability: Aqueous cisplatin should be stored at 15 – 25°C and protected from light. Do not refrigerate. It is supplied in a multi-dose vial without preservatives. Once the vial has been entered, the remaining cisplatin is stable for 28 days protected from light or for 7 days if under fluorescent light at room temperature.

8.1.5 Dose Specifics: Cisplatin will be administer at 75 mg/m² IV on day 1 every 21 days, for a total of 4 doses (3 week-cycles).

8.1.6 Preparation: Cisplatin 10 mg/vial and 50 mg/vial of lyophilized powder formulation should be reconstituted with 10 and 50 ml of sterile water, respectively, resulting in a 1 mg/ml solution. The desired dose of cisplatin is often further diluted with 250 ml or more of 0.45%-0.9% NaCl and 5% dextrose, normal saline or 0.3% sodium chloride.

8.1.7 Route of Administration: Cisplatin will be administered as an intravenous infusion. It should be administered in 250 – 1000 mL NaCl, following intravenous hydration with at least 1000 mL NaCl. Needles, syringes, catheters or IV administration sets containing aluminum parts should not be used as contact with cisplatin yields a black precipitate.

8.1.8 Incompatibilities: Plasma levels of anticonvulsant agents may become sub-therapeutic during cisplatin (cisplatin injection) therapy. In a randomized trial in advanced ovarian cancer, response duration was adversely affected when pyridoxine was used in combination with altretamine (hexamethylmelamine) and cisplatin (cisplatin injection). Other drugs that are incompatible with cisplatin include amifostine, amphotericin B sulfate complex, cefepime, gallium nitrate, piperacillin/tazobactam, and thiotepa. Needles, syringes, catheters or
IV administration sets containing aluminum parts should not be used as contact with cisplatin yields a black precipitate.

8.1.9 Availability: Cisplatin (Bristol-Myers Oncology Division) is commercially available as a lyophilized powder for injection (10 and 50 mg/vial) and as a 1 mg/ml solution (50 and 100 mg/vial).

8.1.10 Side Effects:

8.1.10.1 Hematologic: Leukopenia and thrombocytopenia occur, but are rarely dose-limiting; anemia.

8.1.10.2 Dermatologic: Alopecia (uncommon).

8.1.10.3 Gastrointestinal: Nausea and vomiting are common and may persist for up to 24-96 hours; anorexia.

8.1.10.4 Renal: Nephrotoxicity is dose-related and relatively uncommon with adequate hydration and diuresis; elevated serum creatinine and BUN.

8.1.10.5 Hepatic: Elevated AST and ALT.

8.1.10.6 Neurologic: Peripheral neuropathy (paresthesias), common and dose-limiting when the cumulative cisplatin dose exceeds 400 mg/m²; rarely seizures; ototoxicity manifested initially by high frequency hearing loss; vestibular toxicity (dizziness) uncommon; tetany (caused by hypomagnesemia); rarely Lhermitte’s sign.

8.1.10.7 Other: Hypomagnesemia, hypocalcemia, hyponatremia, vein irritation, papilledema, rarely retrobulbar neuritis, rarely anaphylaxis, fatigue.

8.1.11 Nursing/Patient Implications

- Assess labs prior to administration (esp. CBC, platelet count, BUN, Cr.).
- Assess urine output prior to each dose. Maintain hydration. Urine output should be 100-150 ml/hr. Diuretics may be ordered.
- Administer antiemetics before cisplatin. Post-treatment antiemetics should be given as per institutional guidelines
- Observe carefully for signs of anaphylaxis.
- Monitor for signs of neurotoxicity, hearing loss

8.1.12 References


8.2 Carboplatin

8.2.1 Other Names: Paraplatin®

8.2.2 Classification: Carboplatin (carboplatin injection) (platinum, diammine[1,1-cyclobutanedicarboxylato(2-)-O,O′]-, (SP-4-2)) is a platinum coordination compound, used as an antineoplastic agent. It is a second-generation tetravalent organic platinum compound. It is a crystalline powder with the molecular formula of C6H12N2O4Pt and a molecular weight of 371.25. It is soluble in water at a rate of approximately 14 mg/mL, and the pH of a 1% solution is 5 to 7. It is virtually insoluble in ethanol, acetone, and dimethylacetamide.

8.2.3 Mode of Action: Like cisplatin, carboplatin binds to DNA, thereby inhibiting DNA synthesis, in a cell cycle nonspecific manner. Carboplatin must first undergo activation to produce antineoplastic activity. Bidentate carboxylate ligands of carboplatin are displaced by water forming (aquation) positively charged platinum complexes which bind to nucleophilic sites in DNA, such as the O-6 position on guanine. Carboplatin produces predominantly interstrand DNA crosslinks rather than DNA-protein crosslinks. Intrastrand crosslinks result from the formation of adducts between the activated platinum complexes of the drug and the N-7 atom (not exclusively) atom on guanine to produce 1,2 intrastrand links between adjacent guanine molecules, between neighboring guanine and adenosine molecules, or between neighboring guanine molecules. Interstrand cross-linking within the DNA helix also occurs. Platinum adducts may inhibit DNA replication, transcription and ultimately cell division.

8.2.4 Storage and Stability: Store intact vials at room temperature at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light. Further dilution to a concentration as low as 0.5 mg/mL is stable at room temperature (25°C) for 8 hours in NS or D5W. Stability has also been demonstrated for dilutions in D5W in PVC bags at room temperature for 9 days; however, the manufacturer recommends use within 8 hours due to lack of preservative. Multidose vials are stable for up to 14 days after opening when stored at 25°C (77°F) following multiple needle entries.

8.2.5 Dose Specifics: Carboplatin will be administered at AUC 6 IV on day 1 every 21 days, for a total of 4 doses (3 week-cycles).
Calvert Formula for Carboplatin (AUC) Dosing

Total dose (mg) = target AUC (in mg/mL/minute) * [GFR (in L/minute) + 25]

For the purposes of this protocol, the GFR is considered to be equivalent to the creatinine clearance.

Glomerular Filtration Rate (GFR) Estimation: Calculated creatinine clearance of ≥ 50 cc/min using the Cockcroft-Gault formula:

Males: 140 – Age in years) × Actual Body Weight in kg
42 × Serum Creatinine (mg/dL)

Females: Estimated creatinine clearance for males × 0.85

With the Calvert formula, the total (final) dose of carboplatin is calculated in mg, not mg/m².

8.2.6 Preparation: Manufacturer’s labeling states solution can be further diluted to concentrations as low as 0.5 mg/mL in NS or D₅W; however, most clinicians generally dilute dose in either 100 mL or 250 mL of NS or D₅W. Concentrations used for desensitization vary based on protocol. Hazardous agent; use appropriate precautions for handling and disposal. Needles or I.V. administration sets that contain aluminum should not be used in the preparation or administration of carboplatin; aluminum can react with carboplatin resulting in precipitate formation and loss of potency.

8.2.7 Route of Administration: Carboplatin will be administered as an intravenous infusion.

8.2.8 Incompatibilities: Amphotericin B cholesteryl sulfate complex. 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.

8.2.9 Availability: Carboplatin (Bristol-Myers Oncology Division) is commercially available in 50, 150, and 450 mg vials.

8.2.10 Side Effects:

8.2.10.1 Hematologic: Thrombocytopenia, neutropenia, leukopenia, more pronounced in patients with compromised renal function and heavily pretreated patients; may be cumulative.

8.2.10.2 Gastrointestinal: Nausea and vomiting, treatable with moderate doses of antiemetics.

8.2.10.3 Dermatologic: Rash, urticaria.

8.2.10.4 Hepatic: Abnormal liver function tests, usually reversible with standard doses.

8.2.10.5 Neurologic: rarely Peripheral neuropathy.

8.2.10.6 Renal: Elevations in serum creatinine, BUN; electrolyte loss (Na, Mg, K, Ca).
8.2.10.7 Other: Pain, asthenia.

8.2.11 Nursing/Patient Implications

- Monitor CBC and platelet count; nadir occurs at approximately day 21 with recovery by day 28-30.
- Premedicate with antiemetics - evaluate effectiveness.
- Monitor fluid status - maintain adequate hydration.
- Assess skin/mucous membranes.
- Assess for signs of peripheral neuropathy - coordination, sensory loss.

8.2.12 References

9. **Statistical Considerations**

9.1 **Study Objectives**

The primary objective of this multi-institutional, open-label, randomized phase III study is to determine whether a platinum agent improves invasive disease-free survival (IDFS) compared to observation (current standard of care) in patients with triple-negative breast cancer (TNBC) treated with taxane +/− anthracycline-based neoadjuvant chemotherapy (NAC) who do not achieve a pathologic complete response (pCR) with a residual disease of more than 1.0 cm and with basal-like gene expression via PAM50 analysis by digital mRNA quantitation (NanoString) in the residual surgical specimen. IDFS is the primary endpoint, which is defined to be time from randomization to the earliest of documented disease recurrence (local, regional and/or distant), invasive contralateral breast cancer, invasive any other second primary cancer, or death. Cases with incomplete follow up or without adequate disease evaluations will be censored at the date last documented to be free of IDFS events. Secondary endpoints include overall survival (OS), recurrence-free survival (RFS) and toxicity. Overall survival is defined as time from randomization to death from any cause. Cases still alive will be censored at the last date of known alive.

9.2 **Study Design**

Based on the literature, the benefit of platinum agent therapy in TNBC after NAC, if any, is expected to be exclusively or predominantly in the basal-like subtype. Hence, the patient population is restricted to the basal-like subtype only in this trial. After screening, molecular profile will be evaluated via PAM50 analysis by digital mRNA quantitation (NanoString) in the residual surgical specimen to identify its molecular subtype. We expect at least 75% of the residual post-NAC TNBC screened to fall within the basal-like subtype.

Patients with basal-like TNBC will then be randomized according to the permuted block algorithm with a 1:1 randomization ratio to platinum based chemotherapy and observation arms. Stratification factors include 1) clinical stage at diagnosis (II or III), 2) residual cancer burden after NAC (1~3 cm or >3 cm), 3) planned platinum agent (cisplatin or carboplatin), 4) anthracycline exposure in the neoadjuvant setting (yes or no), and 5) administration of radiotherapy (yes or no).

Based on the review (by Von Minckwicz et al.\textsuperscript{5}) of patients with TNBC (basal-like and non-basal-like) that do not achieve a pCR after neoadjuvant chemotherapy, the outcome contingent on tumor size in the residual disease show no difference between patients with pT1 and pT2; i.e. 50% of those patients recur in ~ 60 months. Of note, that would support the reasoning behind allowing patients with residual tumors ≥ 1 cm. The ones with pT3 and pT4 mimic the cohort of patients with basal-like TNBC in the analysis by Balko et al.\textsuperscript{8}; where 50% of them recur in 18 months. The patients with pT3 and pT4 represented ~ 20% of the whole number of patients (in the review by Von Minckwicz et al.\textsuperscript{5}) that did not achieve a pCR. We would expect that 20% of the patients that would potentially be accrued in our current trial would have a median IDFS of ~ 18 months and 80% would have a median DFS of ~60 months. Therefore, it would be reasonable to assume that a conservative estimate of the actual median DFS for the observation arm in this trial would be 48 months, with a median OS of 60 months.
Based on the accrual rate of the CALGB 40603 trial (NCT00861705, accrued 445 patients from 6/2010 to 8/2012), we anticipate an accrual rate of approximately 12 basal-like TNBC patients per month in our study.

9.2.1 Sample Size and Accrual

The null hypothesis of the study is HR=1 for comparison of IDFS in the two arms, and the alternative hypothesis is HR=0.667 for chemotherapy/observation in the basal-like TNBC patients. The primary analysis of IDFS will be performed using stratified log-rank test, with an overall one-sided type I error of 2.5%, stratifying on the randomization stratification factors (clinical stage at diagnosis, residual cancer burden after NAC, planned platinum agent and anthracycline exposure in the neoadjuvant setting, and administration of radiotherapy). The primary comparisons will be intention-to-treat (ITT) analysis (defining groups by assigned treatment regardless of treatment received) among all basal-like patients regardless of eligibility status. A total accrual of 432 basal-like patients (216 on each arm) and total information of 206 IDFS failures is planned, to give 80% power to detect a 33.3% reduction in the IDFS failure hazard rate, and this reduction in IDFS failure hazard rate corresponds to an improvement in median IDFS from 48 months on observation arm to 72 months on chemotherapy arm, under the assumption of exponential distribution of IDFS.

However, it is likely that some patients who are assigned to observation arm will opt to be treated with cisplatin or carboplatin anyway. If it happens, we expect that these patients will start chemotherapy shortly after randomization. Non-adherence to chemotherapy will not be considered in the trial design. Since the primary analysis will compare the randomized treatment groups, treatment non-adherence will dilute the treatment effect and reduce the power of this study. The total information and sample size need to be adjusted to account for this effect. At the time of the study design, the total non-adherence rate is about 12% in the RxPonder trial (personal communication). For the purpose of study design, we assume a similar level of non-adherence rate in our trial, and expect that about 12% of patients assigned to the observation arm will start chemotherapy after the trial is activated. This assumption will be closely monitored throughout the trial. Appropriate procedures will be put in place as well to ensure treatment adherence. If there are significant deviations from the assumption, then design will be modified by the ECOG-ACRIN Data Safety Monitoring Committee (DSMC) to ensure that adequate power will be available at the final analysis. Based on the Lachin-Foulkes correction method assuming non-compliers on the observation arm will have the same exponential hazard as the chemotherapy group, the total information needs to be increased by about 29% compared to that under 100% adherence rate to ensure the same level of power for the primary analysis.

Under the assumption of 12% non-adherence rate, a total accrual of 558 basal-like patients and total information of 269 (=206*1.29) IDFS failures will be planned to give 80% power to detect a 33.3% reduction
in the IDFS failure hazard rate with the interim analysis plan as described later (Table 1). Assuming an accrual rate of 12 patients with basal-like TNBC per month, about 46.5 months of accrual will be needed with an additional 33.5 months of follow up to reach the expected number of IDFS failures. The final analysis for IDFS comparison in the basal-like patients is expected to be conducted at about 86 months (46.5 months of accrual + 33.5 months of follow up + 6 months of data collection and cleaning) after study activation.

We expect at least 75% of the residual post-NAC TNBC screened to fall within the basal-like subtype. Hence, at least 744 patients (=558/0.75) with residual TNBC at the time of surgery will be screened to obtain the 558 patients with basal-like TNBC.

1.2.2 Interim analysis plan

The study will be monitored for early stopping for efficacy by the ECOG-ACRIN DSMC according to the principals of group-sequential methods. The first interim efficacy analysis will be performed at the first DSMC meeting when at least 25% of the total information has been reported. Since 269 IDFS failures are required as the total information under the alternative hypothesis, the first efficacy interim analysis is estimated to take place after 67 IDFS failures have occurred, which corresponds to 32 months after activation of the study in calendar time, under the accrual and failure rate assumptions mentioned above. Efficacy interim analysis will be performed for each subsequent DSMC meeting until either the criteria for early stopping (described below) are met or the total planned number of IDFS failures has been reported. In total, this design is expected to incorporate 8 interim analyses and one final analysis for IDFS comparisons. Table 1 shows expected timing of interim analyses and critical values for early stopping monitoring (discussed below).

Because interim analyses are timed to coincide with the semi-annual ECOG-ACRIN DSMC meetings, these boundaries may change depending on the number of observed IDFS failures at that time. Also, because of delays in data submission and processing, it is likely that actual analysis times will be 6-12 months later.

At each interim analysis, the stratified log-rank test statistic will be computed, stratified on the randomization stratification factors. To preserve the overall type I error rate, critical values for rejecting null hypothesis at the interim analyses will be determined using a truncated version of the Lan-DeMets spending function corresponding to the O'Brien-Fleming boundary. Boundary values at a nominal significance less than 0.0005 will be truncated at 0.0005, with the boundary also adjusted to preserve the overall one-sided type I error rate of 2.5%. If the boundary is crossed at an interim analysis or at the final analysis, then the null hypothesis will be rejected, and the platinum agent therapy is superior to observation in terms of IDFS. If the criteria for rejecting the null hypothesis are not met, then it will be concluded that this trial fails to show superiority of platinum agent therapy over observation on IDFS.
Table 1: Operating characteristics of the study design

<table>
<thead>
<tr>
<th>Repeated analysis</th>
<th>Time from study activation (months)</th>
<th>Information time (%)</th>
<th>Number of Failures under alternative</th>
<th>Nominal significance</th>
<th>Upper boundary</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32</td>
<td>25</td>
<td>67</td>
<td>0.0005</td>
<td>3.2905</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>34</td>
<td>92</td>
<td>0.0005</td>
<td>3.2905</td>
</tr>
<tr>
<td>3</td>
<td>44</td>
<td>45</td>
<td>120</td>
<td>0.0005</td>
<td>3.2905</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>56</td>
<td>150</td>
<td>0.0020</td>
<td>2.8750</td>
</tr>
<tr>
<td>5</td>
<td>56</td>
<td>66</td>
<td>178</td>
<td>0.0048</td>
<td>2.5850</td>
</tr>
<tr>
<td>6</td>
<td>62</td>
<td>76</td>
<td>204</td>
<td>0.0080</td>
<td>2.4111</td>
</tr>
<tr>
<td>7</td>
<td>68</td>
<td>85</td>
<td>228</td>
<td>0.0113</td>
<td>2.2811</td>
</tr>
<tr>
<td>8</td>
<td>74</td>
<td>93</td>
<td>249</td>
<td>0.0146</td>
<td>2.1810</td>
</tr>
<tr>
<td>Final</td>
<td>80</td>
<td>100</td>
<td>269</td>
<td>0.0178</td>
<td>2.1015</td>
</tr>
</tbody>
</table>

In addition to efficacy interim monitoring, this study will also be monitored for early stopping in favor of the null hypothesis (i.e., futility) using the Linear 20% Inefficacy Boundary (LIB20) method\textsuperscript{23}. This method generally results in less than 1% loss of power, there will be no sample size increase to account for the futility interim monitoring in the study.

Before futility interim analysis using the Linear 20% Inefficacy Boundary method, we will first perform a “harm” look at 25% information (about 32 months after study activation), using the rule that stops the trial for harm if the one-sided lower 95% unadjusted confidence bound for the observed hazard ratio (HR for chemotherapy/observation) is above 1 (i.e., HR > 1.49). This is the same as one-sided 0.05 level test of the null hypothesis in the direction of harm. If the trial does not stop at the “harm” look, the study will be monitored by formal futility interim analysis via the Linear 20% Inefficacy Boundary method as described below. If the study stops at the “harm” look, the whole trial stops for lack of efficacy.

The one-sided type I error is 2.5% and the power is 80% for the IDFS test in the study, the first futility interim analysis could take place at as early as 49% information time per the Linear 20% Inefficacy Boundary method, at which the observed HR > 1 would imply that the two-sided 95% confidence interval for log hazard ratio would not contain the log alternative hypothesis log(0.667). The information time is about 45% at the third DSMC meeting and 56% at the fourth DSMC meeting, the first futility interim analysis will be performed at the fourth DSMC meeting (50 months after study activation) when the information time is ≥ 49%. Futility interim analysis will be performed for each subsequent DSMC meeting until either the criteria for early stopping (described below) are met or the total planned number of IDFS events has been reported. In total, this design is expected to incorporate 5 futility interim analyses for IDFS comparisons. The cut-off values for HRs and lower two-sided 95% confidence interval bound (unadjusted)
are given in Table 2. If at any time point, the observed HR (chemotherapy/observation) is larger than the cut off values, the trial will stop for lack of efficacy.

In each interim analysis, the observed HR will be calculated using stratified Cox proportional-hazards model, stratified on randomization stratification factors, without any other covariates.

Because futility interim analyses are timed to coincide with the semi-annual ECOG-ACRIN DSMC meetings, and the observed non-adherence rate might be different from 12% as well, the boundaries for HRs may change depending on the number of observed IDFS events and non-adherence rate at that time. Also, because of delays in data submission and processing, it is likely that actual analysis times will be 6-12 months later.

**Table 2: Inefficacy stopping boundaries for IDFS endpoint**
(Alternative HR=0.667, Full information=269 IDFS events, One-sided type I error=2.5%, Power=80%)

<table>
<thead>
<tr>
<th>Repeated interim analysis for futility</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information time</td>
<td>56%</td>
<td>66%</td>
<td>76%</td>
<td>85%</td>
<td>93%</td>
</tr>
<tr>
<td>Calendar time (months after study activation)</td>
<td>50</td>
<td>56</td>
<td>62</td>
<td>68</td>
<td>74</td>
</tr>
<tr>
<td>Hazard ratio (stopping boundaries)</td>
<td>0.990</td>
<td>0.976</td>
<td>0.962</td>
<td>0.950</td>
<td>0.939</td>
</tr>
<tr>
<td>Lower two-sided 95% confidence bound (unadjusted, Z=1.96 at all interim looks)</td>
<td>0.719</td>
<td>0.727</td>
<td>0.731</td>
<td>0.733</td>
<td>0.733</td>
</tr>
</tbody>
</table>

In addition to monitoring the trial for early stopping for efficacy and futility, ECOG-ACRIN will closely monitor the non-adherence rate and drop-out rate for both arms of the study, and rate of patients on the no-treatment arm who receive post neoadjuvant chemotherapy. If there is large deviation from the assumed compliance rate, i.e., more than 12% of patients assigned to observation arm cross over to the platinum arm or receive post neoadjuvant chemotherapy, the design modification will be discussed with CTEP. If a design modification is proposed and approved by CTEP, the proposed protocol amendment will then be presented to the ECOG-ACRIN DSMC for approval. If the non-adherence rate is greater than 20% after 200 patients have been enrolled and randomized to the observation arm, the trial will be terminated. Moreover, the CTEP will also consider terminating the trial if the drop-out rate (official loss to follow up per ECOG-ACRIN standards) is greater than 20% after the 200 patients are followed for ≥ 1 year on the observation arm (at about 45 months after study activation, i.e., the third efficacy interim analysis time). Appropriate procedures will be put in place to minimize non-adherence and loss to follow-up in the trial.
9.3 Secondary Endpoints

9.3.1 Overall Survival

Overall survival (OS) is an important secondary endpoint in the study. With the above design (a total accrual of 432 basal-like patients without non-adherence), total information of 243 deaths is needed to give about 80% power to detect a 30% reduction (i.e., HR=0.7 for chemotherapy/observation under alternative hypothesis) in the OS failure hazard rate using stratified log-rank test with one-sided type I error rate of 0.025, without any interim analysis plan. This reduction in OS failure hazard rate corresponds to an improvement in median OS from 60 months on observation arm to 86 months on chemotherapy arm, under the assumption of exponential distribution of OS. Under the assumption of 12% non-adherence rate (which requires 29% increase in total information to remain 80% power) and a total accrual of 558 basal-like patients (12 patients/month * 46.5 months of accrual), the final analysis for OS is expected to occur at about 116 months after study activation (46.5 months of accrual + 33.5 months of follow up + 6 months of data collection and cleaning, i.e., 2.5 years after IDFS final analysis) to reach the expected number of OS failures (243*1.29=314 deaths).

9.3.2 Toxicity

Another secondary endpoint of the study is to evaluate toxicities. All patients who start protocol therapy (i.e., receive at least one dose of protocol treatment) will be included in toxicity analysis. Assuming 14 patients (14/279=5%) will not start protocol therapy in the chemotherapy arm, with 265 evaluable patients, the binomial exact 95% confidence interval for toxicity rate would be no wider than 0.13. For each individual platinum agent (carboplatin or cisplatin), the binomial exact 95% confidence interval for toxicity rate would be no wider than 0.18 if about the same number of patients (n=132) take each agent.

9.4 Analysis Plan for Primary and Secondary Endpoints

The primary endpoint is invasive disease-free survival (IDFS) in patient with basal-like TNBC, which is defined to be time from randomization to the earliest of documented disease recurrence (local, regional and/or distant), invasive contralateral breast cancer, invasive any other second cancer, or death. Cases with incomplete follow up or without adequate disease evaluations will be censored at the date last documented to be free of IDFS events. The secondary endpoints include overall survival (OS), recurrence-free survival (RFS), and incidence of toxicity. The final analysis of IDFS and all secondary endpoints except for OS will be conducted at about 86 months after study activation (46.5 months of accrual + 33.5 months of follow up + 6 months of data submission and processing). The final analysis for OS will be conducted at about 116 months after study activation (46.5 months of accrual + 63.5 months of follow up + 6 months of data collection and cleaning).

All primary analyses regarding efficacy (IDFS, RFS, and OS) will be based on intention-to-treat population regardless of eligibility status. A secondary analysis for efficacy outcomes will be conducted in eligible patients. The distributions of
IDFS, RFS and OS will be estimated using the Kaplan-Meier method, with 95% confidence intervals calculated using Greenwood’s formula. The primary analysis of IDFS, RFS and OS comparisons between two treatment arms will be performed using stratified log-rank tests, stratifying on the randomization stratification factors (clinical stage, residual cancer burden, planned platinum agent, and anthracycline exposure in the neoadjuvant setting, and administration of radiotherapy). Stratified Cox proportional-hazard models will also be built to estimate the hazard ratios (HRs) for treatment effect for DFS as a supportive analysis, stratifying on the randomization stratification factors. In the multivariable Cox models, known prognostic factors will be included as covariates when appropriate, such as age, race/ethnicity, ECOG performance status, et al. Patients with missing values for covariates will be excluded from modeling when the proportion of missingness is less than 5% and will be imputed appropriately if the proportion of missingness is ≥ 5%.

Toxicity analysis will be conducted in all cases receiving at least one dose of chemotherapy (i.e., all treated population). Adverse events will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All treatment-emergent and baseline adverse events and hematological/biochemical toxicities based on laboratory measurements will be summarized for patients on platinum agent. The incidence of deaths and treatment-emergent serious adverse events will be calculated along with exact 95% CI based on binomial distribution. Also, the incidence of adverse events leading to discontinuation of chemotherapy and/or withdrawal from the study will be summarized and listed as well.

The proportion of basal-like TNBC in all screened TNBC patients will be calculated with exact 95% CI based on binomial distribution.

In all analyses, P-values will be two-sided. A level of 5% will be considered statistically significant for all analyses.
9.5 Gender and Ethnicity

Male breast cancer accounts for approximately 1% of all breast cancers. Meanwhile, some elderly male patients may not be eligible or consider trials. We could anticipate that about 5 male patients with basal-like TNBC could enroll out of a sample size of 558, and all of them are expected to be non-Hispanic White patients. For the 553 female patients, based on previous data from SWOG S0226 and ECOG E2100 studies, the anticipated accrual in subgroups defined by gender and race is:

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Gender</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
<td>Males</td>
<td>Total</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>41</td>
<td>0</td>
<td>41</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>512</td>
<td>5</td>
<td>517</td>
</tr>
<tr>
<td><strong>Ethnic Category: Total of all subjects</strong></td>
<td><strong>553</strong></td>
<td><strong>5</strong></td>
<td><strong>558</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Racial Category</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian or Alaskan Native</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Asian</td>
<td>7</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Black or African American</td>
<td>46</td>
<td>0</td>
<td>46</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td>500</td>
<td>5</td>
<td>500</td>
</tr>
<tr>
<td><strong>Racial Category: Total of all subjects</strong></td>
<td><strong>553</strong></td>
<td><strong>5</strong></td>
<td><strong>558</strong></td>
</tr>
</tbody>
</table>

The accrual targets in individual cells are not large enough for definitive treatment comparisons to be made within these subgroups. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

9.6 Study Monitoring

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

Tumor tissue from the residual disease on the definitive surgical specimen must be submitted for PAM50 analysis to determine patient eligibility as defined in Section 11. The PAM50 analysis will be performed by the Molecular Diagnostics laboratory (MDL) at MD Anderson Cancer Center and results forwarded to the ordering physician via FAX and to the ECOG-ACRIN Operations Office via secure electronic messaging to the ECOG-ACRIN database within three (3) weeks of receipt of the tumor tissue specimen.

Tumor tissue will also be assessed by central review of immunohistochemistry (IHC) expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor (HER2) FISH to rule out conversion of these clinical markers following chemotherapy.

Every effort should be made to submit tumor tissue specimen to the MDL immediately. Tumor tissue cannot be accepted after week 12 (post-surgery) in order to allow for PAM50 analysis.

Submission of inadequate tumor tissue will result in request for additional material and will delay turnaround time for reporting results to the submitting institution.

It is required that all samples submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (see Section 10.4). An STS shipping manifest form is to be included with every submission.

All samples must be labeled clearly with the ECOG-ACRIN protocol number (EA1131), ECOG-ACRIN patient sequence number, patient’s initials, date of collection and sample type.

10.1 Sample Collection and Submission Schedule

Samples are to be submitted as follows:

- Pathology samples are mandatory and must be submitted within 12 weeks post-surgery as outlined in Section 10.2.

10.2 Submission to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF)

10.2.1 Tumor Tissue Submission (Mandatory)

Submitting pathologist and clinical research associate may refer to Appendix I, which outlines the Pathology Submission Guidelines. Submission of pathology samples from all patients is mandatory.

The tissue samples are to be labeled with the Pathology ID as well as the information above.

10.2.1.1 Required Materials

Forms: Must be submitted with all tissue submissions.

- STS generated shipping manifest form
- Copy of the institutional surgical pathology report
- CLIA Laboratory Sample Submission Form (Appendix IV) [gender does not need to be completed]
10.2.1.2 Pathological Material Submission:
- FFPE tumor tissue block – breast primary specimen from definitive surgery (≥ 1 cm in diameter, > minimal cellularity as per local pathologist determination).

**NOTE:** If these criteria cannot be met, please contact the ECOG-ACRIN CBPF (eacbpf@mdanderson.org) to obtain alternative submission requirements.

10.2.1.3 Notification to the Submitting Institution of PAM50 Analysis Results

The MDL will notify the ordering physician via FAX and the ECOG-ACRIN Operations Office via secure electronic messaging to the ECOG-ACRIN database of the results of the PAM50 analysis (eligible versus non-eligible) within three (3) weeks of receipt of the tumor tissue specimen.

CRA’s will receive an email notification once results have been faxed to the ordering physician in order for them to retrieve the report for randomization (step 1).

Submission of inadequate tumor tissue specimen will result in request for additional material and will delay turnaround time for reporting results.

Do not call the MDL for results, as testing data cannot be provided over the telephone.

Randomization cannot occur until results are released.

Only basal-like patients are eligible to be randomized to treatment.

10.2.2 Shipping Procedures

Pathology samples are to be shipped at ambient temperature within 12 weeks post surgery.

Ship using the CBPF’s FedEx account using the FedEx on-line Ship Manager.

Ship to:

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
1515 Holcombe Boulevard
Houston, TX 77030
Toll Free Phone: (844) 744-2420 (713-745-4440 Local or International Sites)
Fax: (713) 563-6506
Email: eacbpf@mdanderson.org

Access to the shipping account for shipments to the CBPF can only be obtained by logging into fedex.com with an account issued by the CBPF. For security reasons, the account number will no longer be given out in protocols, over the phone, or via email. If your site needs
10.3 **ECOG-ACRIN Sample Tracking System**

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

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

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

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

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

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

**Study Specific Notes**

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

- ECOG-ACRIN Central Biorepository and Pathology Facility

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

10.4 **Use of Specimens in Research**

Specimens from patients who consented to allow their specimens to be used for future ECOG-ACRIN approved research studies will be retained in an ECOG-ACRIN designated central repository.

For this trial, specimens will be retained at the ECOG-ACRIN Central Biorepository and Pathology Facility.

Specimens submitted will be processed to maximize their utility for current and future research projects. Tissue processing may include, but not limited to, extraction of DNA and RNA and construction of tissue microarrays (TMAs).

Any residual blocks will be available for purposes of individual patient management on specific written request.

If future use is denied or withdrawn by the patient, the specimens will be removed from consideration for use in any future research study. Pathology materials may be retained for documentation purposes or returned to the site. All other specimens will be destroyed per guidelines of the respective repository.
10.5 Sample Inventory Submission Guidelines

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

11.1 **Rate of basal-like gene expression using PAM50 analysis by digital mRNA quantitation**

11.1.1 **Rationale for PAM50 analysis in surgical residual tumor**

Most TNBCs are high-grade and the majority of them harbor a basal-like gene expression signature\textsuperscript{1,41}. Among young women and African-American women, its prevalence is elevated\textsuperscript{2}. We recently completed a study where we profiled 89 residual tumors from patients with stage II (20%) and III (80%) TNBC treated with AC-T neoadjuvant chemotherapy (NAC)\textsuperscript{8}. Expression level for 450 genes was quantified by NanoString in **RNA extracted from the surgical specimen**. Molecular subtype of these residual tumors, after adjusting for HER2 amplification (i.e. upon re-testing, all HER2 FISH amplified cancers were excluded) was as follows: 70% basal-like; 15% HER2-enriched; 6% luminal A, 6% luminal B; and 5% normal-like. **Basal-like status was associated with a trend toward worse RFS and OS** (log-rank test, $P = 0.12$ and 0.058, respectively). The median time to relapse among this high-risk group of patients with basal-like gene expression was only 18 months. Consistent with early clinical data in TNBC, breast cancer cells and xenografts with basal-like gene expression are particularly sensitive to cisplatin\textsuperscript{10}. In summary, within TNBC, patients with tumors with basal-like expression are at the highest risk for recurrence. Hence the biologic rationale for this concept is strongest in the basal subtype. At present, patients with TNBC (of which about 70% are expected to be basal-like by gene expression profile\textsuperscript{11}) that complete neoadjuvant therapy and have no clinical evidence of metastatic disease after surgical excision of the cancer, regardless of residual disease burden, are usually observed. This conduct might not be appropriate for patients at a very high risk of early recurrence such as those with a high residual disease burden in the residual drug-resistant tumor. Based on all the above data, we hypothesized that patients with clinical stage II-III basal-like triple-negative breast cancer (TNBC) with more than 1 cm of residual disease in their surgical specimen after neoadjuvant chemotherapy that are treated with adjuvant platinum based chemotherapy will have a longer disease-free survival (DFS) than the ones in the observation arm, which is the current standard of care.

11.1.2 **PAM50 background**

In 2009, a 50-gene set (PAM50) was proposed for standardizing subtype classification. The PAM50 Breast Cancer Intrinsic Classifier is the clinical manifestation of this gene set using a digital gene expression assay on the NanoString nCounter Dx Analysis System that has been validated on formalin-fixed, paraffin-embedded tissues. Multivariable analyses using the PAM50 subtypes and other clinical data (e.g., node status, grade, ER-status) show that the PAM50 is an independent predictor of survival in breast cancer\textsuperscript{42-45}. The PAM50 test provides additional information about the tumor biology and quantitative data on biomarkers already used for treatment.
decisions. Along with a categorical classification of breast cancer subtype, the clinical PAM50 test also determines a quantitative value for proliferation. The PAM50 gene set testing will be performed using an Investigational Use Only (IUO) PAM50 Assay on the nCounter Dx Analysis System produced by NanoString Technologies. The IUO PAM50 assay uses the same reagents, procedures and algorithm as the Prosigna Gene Expression Assay, which have all been analytically validated and cleared for use by the FDA as a prognostic test in ER+ breast cancer patients who are treated with endocrine therapy alone.

Within this study, we expect at least 75% of the residual post-NAC TNBC screened to fall within the basal-like subtype by gene expression profile. Hence, at least 744 patients (=558/0.75) with residual TNBC at the time of surgery will be screened to obtain the 558 patients with basal-like TNBC.

11.1.3 Assay description

Used together, the PAM50 and nCounter Dx Analysis System are a nucleic acid hybridization, visualization and image analysis system based upon coded probes designed to detect the messenger RNA transcribed from 58 genes. The test input is purified RNA from FFPE breast tumor specimens. The PAM50 assay uses gene-specific probe-pairs that hybridize directly to the mRNA transcripts in solution. The nCounter Dx Analysis System delivers direct, multiplexed measurements of gene expression through digital readouts of the relative abundance of the mRNA transcripts.

Specifications are included to control for sample quality, RNA quality, and process quality. The PAM50 assay utilizes prototypical expression profiles (centroids) which are associated with and define each of the four intrinsic subtypes of breast cancer. Patients are categorized into one of the four subtypes based upon how close their gene expression pattern is to each of the centroids (Luminal A, Luminal B, Her2-Enriched, and Basal-Like).

11.1.4 Specimens and Processing:

Formalin-fixed paraffin-embedded (FFPE) tumor block from the residual disease on the definitive surgical specimen will be collected and submitted to the Molecular Diagnostics Laboratory (MDL) at MD Anderson Cancer Center, where H&E stain will be performed to assess tumor area and cellularity. After central processing, the tumor areas will be transposed to unstained slides. Adjacent non-tumor tissue will be macrodissected and RNA will be extracted with a manual kit and subjected to PAM50 analysis, as described above. Results will be available within ≤ 3 weeks. The MDL will have a
custom software configuration that is intended for investigational use within this clinical trial and will output intrinsic subtype.

11.2 Lab Data Transfer Guidelines

The data collected on the above mentioned laboratory research study will be submitted electronically using a secure data transfer to the ECOG-ACRIN Operations Office – Boston by the investigating laboratories on a quarterly basis or per joint agreement between ECOG-ACRIN and the investigator.
12. **Electronic Data Capture**

Please refer to the EA1131 Forms Completion Guidelines for the forms submission schedule. Data collection will be performed exclusively in Medidata Rave.

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

13. **Patient Consent and Peer Judgment**

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

14. **References**


Appendix I

Pathology Submission Guidelines

The following items are included in Appendix I:

1. Guidelines for Submission of Pathology Materials
   (instructional sheet for Clinical Research Associates [CRAs])
2. Instructional memo to submitting pathologists
3. ECOG-ACRIN Generic Specimen Submission Form (#2981)
Guidelines for Submission of Pathology Materials

EA1131  A randomized phase III post-operative trial of platinum based chemotherapy vs. observation in patients with residual basal-like triple-negative breast cancer following neoadjuvant chemotherapy

The following materials must be submitted within 12 weeks post surgery.

1. **Pathology Submission:**
   - FFPE tumor tissue block (≥ 1 cm in diameter, > minimal cellularity as per local pathologist determination) from the residual disease on the definitive surgical specimen – submission is **mandatory**.

   **NOTE:**  If these criteria cannot be met, please contact the ECOG-ACRIN CBPF(eacbpf@mdanderson.org) to obtain alternative submission requirements.

The following items are to be included with the pathology materials.

2. **Forms and Reports:**
   - Copy of institutional surgical pathology report.
   - STS generated shipping manifest form.
   - CLIA Laboratory Sample Submission Form (Appendix IV) [gender does not need to be completed]

   **NOTE:**  Adequate patient identifying information must be included with every submission. It is strongly recommended that full patient names be provided. The information will be used only to identify patient materials, for interactions between the ECOG-ACRIN CBPF, the central testing laboratory and the site, and will help to expedite any required communications with the institution (including site pathologists).

3. **Mail pathology materials to:**
   
   ECOG-ACRIN Central Biorepository and Pathology Facility  
   Anderson Cancer Center  
   Department of Pathology, Unit 085  
   Tissue Qualification Laboratory for ECOG-ACRIN  
   Room G1.3586  
   1515 Holcombe Boulevard  
   Houston, TX 77030

   If you have any questions concerning the above instructions or if you anticipate any problems in submitting the required pathology material, contact the Pathology Coordinator at the ECOG-ACRIN CBPF by telephone: (844) 744-2420, by fax: (713) 563-6506, or by email: eacbpf@mdanderson.org.
MEMORANDUM

TO: ____________________________________________________
    (Submitting Pathologist)

FROM: Stanley Hamilton, M.D., Chair
       ECOG-ACRIN Laboratory Science and Pathology Committee

DATE: ____________________________

SUBJECT: Submission of Pathology Materials for EA1131: A randomized phase
         III post-operative trial of platinum based chemotherapy vs. observation
         in patients with residual basal-like triple-negative breast cancer
         following neoadjuvant chemotherapy

A patient has been entered onto an ECOG-ACRIN protocol by
__________________________________________ (ECOG-ACRIN Investigator). This protocol requires the
submission of pathology materials for PAM50 analysis and central review.

Return the surgical pathology report(s), the slides and/or blocks and any other required
material to the Clinical Research Associate (CRA). The CRA will forward all required
pathology material to the ECOG-ACRIN Central Biorepository and Pathology Facility
(CBPF).

Blocks and/or slides submitted for this study will be retained at the ECOG-ACRIN CBPF
for future undefined research studies. Paraffin blocks will be returned upon written
request for purposes of patient management.

If you have any questions regarding this request, please contact the ECOG-ACRIN
CBPF at (844) 744-2420 or Fax (713) 563-6506.

The ECOG-ACRIN CRA at your institution is:

Name: ____________________________________________
Address: __________________________________________
Phone: ____________________________________________

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

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<th>Patient ID</th>
<th>Patient Initials</th>
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Shipped To (Laboratory Name) Date CRA will log into STS

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

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### Completed by Receiving Lab

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

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### Completed by Receiving Lab

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**Study Drug Information:**

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**Caloric Intake:**

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CRA Name ___________________________ CRA Phone ________________________ CRA Email ________________________

Comments ____________________________________________________________

9/12/14
A Randomized Phase III Post-Operative Trial of Platinum Based Chemotherapy Vs. Observation in Patients with Residual Triple-Negative Basal-Like Breast Cancer following Neoadjuvant Chemotherapy

Appendix II

Patient Thank You Letter

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

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

_____________________________________________________________________________________

[ PATIENT NAME] [ PATIENT ADDRESS]

[DATE]

Dear [PATIENT SALUTATION],

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

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

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

Sincerely,

[PHYSICIAN NAME]
A Randomized Phase III Post-Operative Trial of Platinum Based Chemotherapy Vs. Observation in Patients with Residual Triple-Negative Basal-Like Breast Cancer following Neoadjuvant Chemotherapy

Appendix III

ECOG Performance Status

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<th>Fully active, able to carry on all pre-disease performance without restriction</th>
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<td>PS 1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light house work, office work.</td>
</tr>
<tr>
<td>PS 2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.</td>
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<tr>
<td>PS 3</td>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.</td>
</tr>
<tr>
<td>PS 4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.</td>
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</table>
A Randomized Phase III Post-Operative Trial of Platinum Based Chemotherapy Vs. Observation in Patients with Residual Triple-Negative Basal-Like Breast Cancer following Neoadjuvant Chemotherapy

Appendix IV

CLIA Laboratory Sample Submission Form
# CLIA Laboratory Sample Submission Form

The information on this form is required for results reporting from the CLIA laboratory. This form MUST be completed and submitted with all specimens. Failure to submit this form will result in a delay in specimen processing and a delay in the reporting of results to the ordering physician.

## SECTION I. TRIAL INFORMATION

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## Section II. PATIENT INFORMATION

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## Section IV. SITE CONTACTS

Sections A and B must be completed.

If applicable, has or will the tissue submitted be reviewed by a local pathologist? [ ] Yes [ ] No

If yes, Section C must be completed and a copy of the local pathology report must be uploaded into Medidata Rave within 5 days of submission of the tissue or per protocol instructions.

### Section A Ordering Physician

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### Section B Site CRA or Research Contact

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### Section C Pathology Group

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