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EA1131

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

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(Limited to U.S. sites only)

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ACTIVATION DATE

April 29, 2015
Addendum #1 – Incorporated Prior to Activation
Addendum #2 – 2/16
Addendum #3 – 6/16
Addendum #4 – 9/17
Addendum #5 – 4/2018
Addendum #6 - 11/2018
Addendum #7 – 11/2020
Addendum #8

Agents	IND#	NSC#	Supply
Cisplatin	IND exempt study	119875	Commercially available
Carboplatin	IND exempt study	241240	Commercially available
Capecitabine	IND exempt study	712807	Commercially available

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

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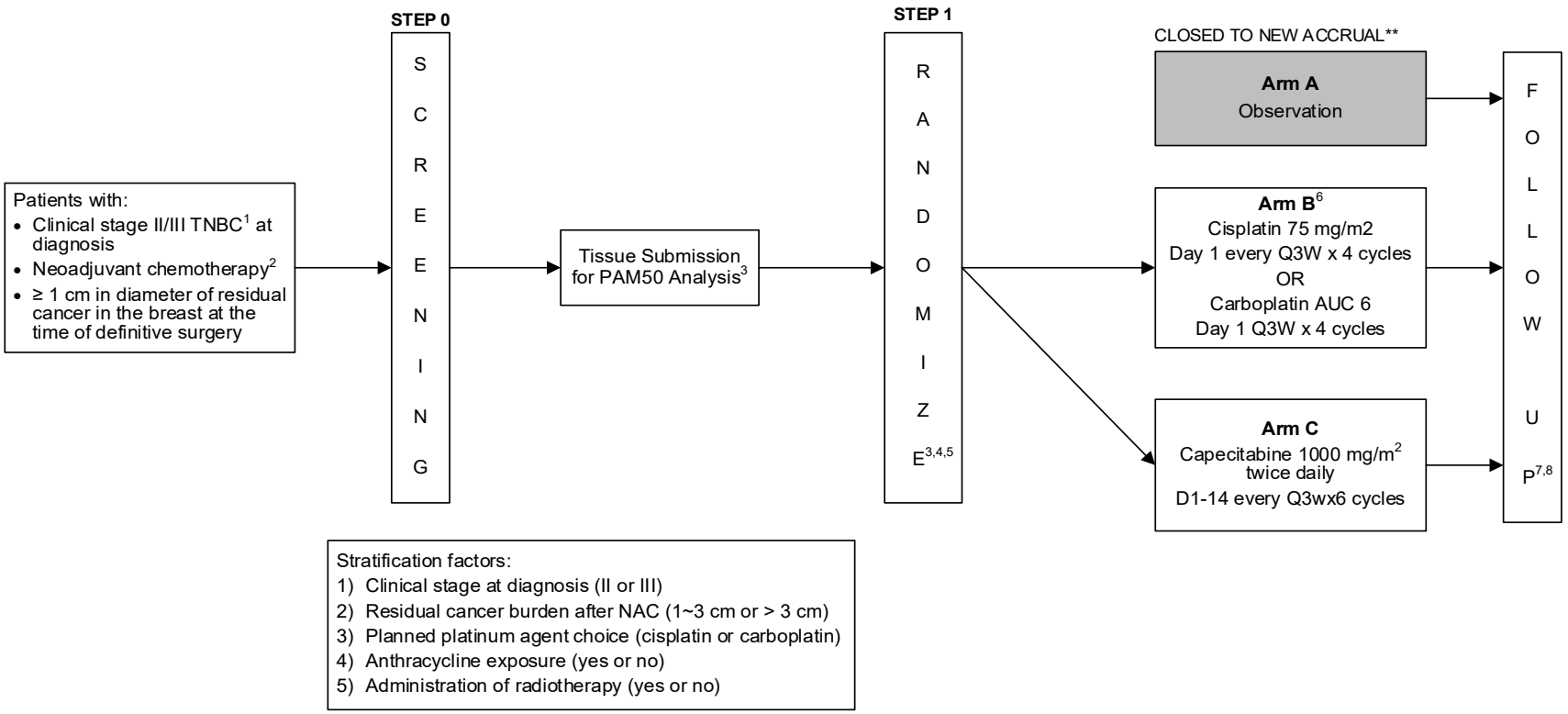
Schema



Accrual = 775
1 cycle = 3 weeks

1. TNBC: ER/PR 1 to ≤ 10% positive staining with weak intensity score, or ≤ 1% positive staining; HER2 negative per ASCO guidelines.
2. Taxane ± anthracycline based; platinum agents or capecitabine not allowed.
3. Tumor tissue from the residual disease on the definitive surgical specimen must have been received by ECOG-ACRIN Central Biorepository and Pathology Facility (EA CBPF) for PAM50 analysis/ determination of patient eligibility as outlined in Section 10. Patients cannot be randomized to treatment until institution receives confirmation of tissue receipt/ eligibility from ECOG-ACRIN.tion 10.2.
4. Females of child-bearing potential must have a blood test or urine study within 2 weeks prior to treatment initiation to rule out pregnancy.
5. Radiation therapy (when applicable) may be completed before or after protocol treatment. If performed before protocol treatment, it needs to be completed prior to randomization.
6. Choice of platinum agent will be per treating physician discretion.
7. Primary endpoint: IDFS in patient with basal-like TNBC.
8. Secondary endpoints: IDFS in patient with non-basal-like TNBC, OS and RFS.

**Arm A closed to new accrual in Addendum #3. New patients are randomized to Arm B or C

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(1). Among young women and African-American women, its prevalence is elevated(2). Patients with TNBC have an increased likelihood of distant recurrence and death compared with women with other types of breast cancer(3), 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(4). More specifically, approximately 30% of TNBC treated with anthracycline and taxane–based neoadjuvant chemotherapy (NAC) have a pCR to treatment(5), 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(6,7) (**Figures 1a and b**).

Figure 1a. Prognostic impact of various definitions of pathologic complete response on survival. Disease free survival in 5,894 patients according to postoperative tumor size (ypT stage).

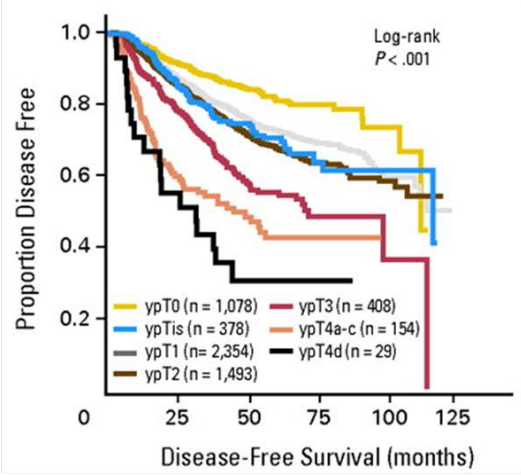
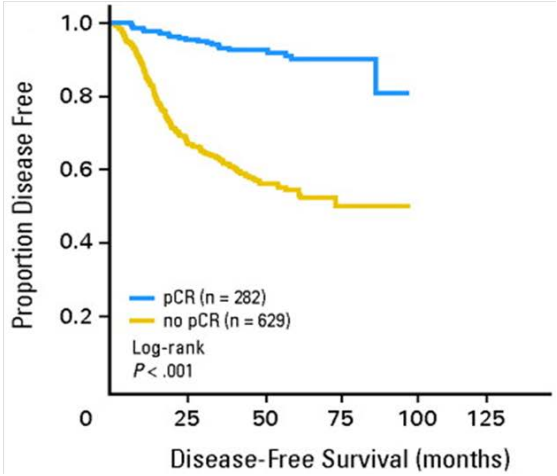
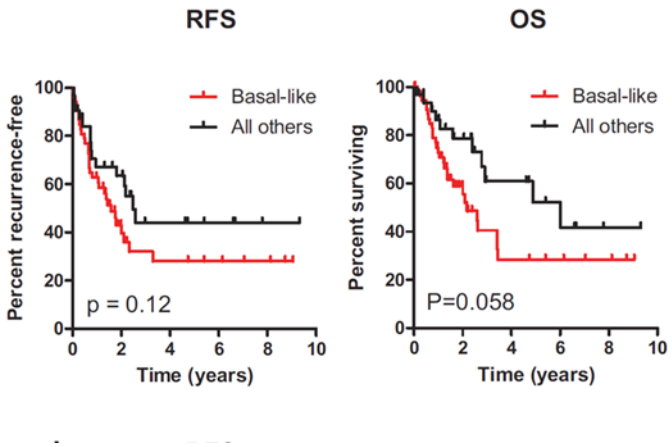


Figure 1b. Prognostic impact of pathologic complete response (pCR) on disease-free survival (DFS) in 4,193 patients according to breast cancer intrinsic subtype. Patients with triple-negative tumors.



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)(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**).

Figure 2. Clinical outcomes of 89 patients with stage II-III basal-like and non-basal-like TNBC with residual disease after treatment with neoadjuvant chemotherapy



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.

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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(9). Within TNBC, about 70% are expected to be basal-like, by gene expression profile(10). Consistent with early clinical data in TNBC, breast cancer cells and xenografts with basal-like gene expression were particularly sensitive to cisplatin (**Figure 3**).

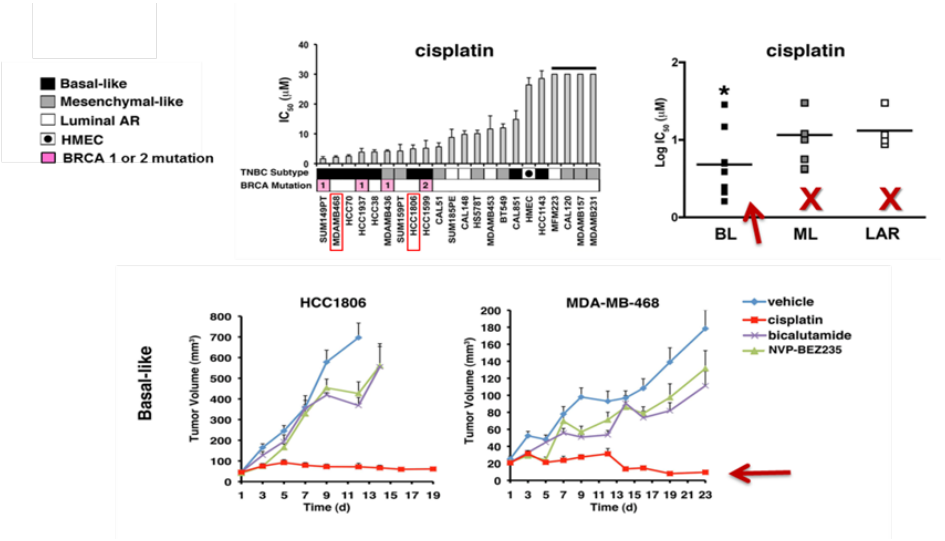

Figure 3. TNBC gene-expression subtyping and drug sensitivity in cell culture and xenograft models. Xenograft tumors established from TNBC subtypes display differential sensitivity to cisplatin. The basal-like tumors were highly sensitive to cisplatin and were significantly growth inhibited ($p<0.0001$) relative to treatment with vehicle control or other experimental treatments.

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.(11) reported a p63-dependent tumor survival pathway that directly mediates cisplatin sensitivity, specifically in TNBC. To further corroborate these findings, Rocca et al.(12) 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(13). 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(14).

Further evidence of the activity of platinum agents in TNBC comes from 2 phase II randomized trials in the neoadjuvant setting: the GeparSixto phase II randomized trial, in its TNBC subset (n=315), compared weekly neoadjuvant paclitaxel, liposomal doxorubicin, and bevacizumab to the same regimen with the addition of carboplatin. The pCR rate improved from 36.9% to 53.2% with the addition of weekly carboplatin. However, only about 50% of patients were able to complete treatment due to adverse events (possibly since all chemotherapy drugs were given concomitantly(15). The 3 year disease-free survival (DFS) for the patients that received carbo was 85.8%, compared to 76.1% for patients in the non-carbo arm [HR =0.56, 95% CI (0.33, 0.96); p=0.0350](16). CALGB 40603 (NCT00861705) is a randomized phase II trial with a 2 x 2 factorial design that explored the addition of every 3 weeks carboplatin +/- bevacizumab to neoadjuvant weekly paclitaxel followed by dose-dense AC in in 443 patients with stage II/III TNBC(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). After a median follow-up of 39

months, the 3 year DFS for the patients that received carbo was 76%, compared to 71% for patients in the non-carbo arm [HR =0.84, 95% CI (0.58, 1.22); p=0.36](18). 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, lack of precision from small sample sizes are likely responsible for the difference seen in DFS between these two trials. The chemotherapy backbone and the carboplatin dose and schedule may be critical to optimal efficacy, which could also explain some of the discrepancy seen in the results above. Long term effects of the added toxicity are also now known. Therefore, the addition of a platinum agent routinely in the neoadjuvant setting in TNBC is still an individualized decision and not yet standard of care.

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 may not be 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. Studies that are adequately powered to detect a DFS and OS are still important and needed.

1.4 Capecitabine in TNBC

Capecitabine is an orally administered prodrug of 5-fluorouracil (5-FU) that is activated to -FU preferentially in tumor tissue due to increased expression of thymidine phosphorylase in tumor tissue, which contributes to the drug's specificity and action against tumor cell proliferation (Wagstaff 2003, Drugs). Capecitabine was first approved for MBC in 1998 in patients pretreated with anthracyclines and taxanes. It was later approved in combination with docetaxel after the combination resulted in improved overall survival (OS) when compared with docetaxel alone[20,21]. Since then, capecitabine has come into wide use in MBC and is now approved both as monotherapy and in combination with docetaxel(19).

Studies on the use of capecitabine in women with metastatic TNBC are limited, partly because of a current interest in platinum compounds after anthracycline and taxane failure for this subtype. The data available so far include a non-randomized phase 2 trial of capecitabine plus bevacizumab as first-line therapy for metastatic disease which showed poor outcome in patients with TN cancers with a median overall survival (OS) of 7.5 months and progression-free survival (PFS) of 4.4 months(20), and a randomized trial of adjuvant therapy in early breast cancer in older women suggesting that those with the TN subtype had 4 times the chance of relapse and a 3 times higher risk of death if treated with capecitabine rather than with standard chemotherapy(21).

CREATE-X is a phase III randomized clinical trial conducted in Japan(22), that randomized 900 patients with HER2-negative breast cancer with lack of pCR post-neoadjuvant chemotherapy (anthracycline or taxane containing regimens; more than 80% of patients received both) to observation or capecitabine 1250mg/m^2 twice daily, 14 days on followed by 7 days off, every 3 weeks, for 24 weeks (8 cycles). About 40% of patients were able to complete 8 cycles of capecitabine, and about 60% completed 6 cycles of capecitabine. As expected, hand-foot sd, diarrhea and neutropenia were the most common side effects in the capecitabine arm. For the overall patient population (ER+ and TNBC), the addition of capecitabine provided a 5-year DFS of 74.1%, opposed to 67.7% in

the observation arm [HR=0.7 (95% CI 0.53 – 0.93, one sided p=0.00524)], and a 5 year overall survival (OS) of 89.2%, opposed to 83.9% in the observation arm [HR=0.6 (95% CI 0.4 – 0.92, one sided p < 0.01)]. Subgroup analysis for the 296 patients that had TNBC revealed a statistically significant improvement in DFS (4-year DFS of 67%) with the addition of capecitabine [HR=0.58 (95% CI 0.39 – 0.87)], whereas the patients with ER+ BC (561) did not seem to derive significant benefit [HR=0.84 (95% CI 0.57 – 1.23)].

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1.5 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. However, the significant improvement in DFS and OS provided by adjuvant capecitabine for patients with TNBC and residual disease post-neoadjuvant chemotherapy seen with CREATE-X, a single phase III trial, merits consideration, and the addition of capecitabine in the adjuvant setting is likely to be adopted by oncologists for patients with TNBC and residual disease with high risk of recurrence post completion of neoadjuvant chemotherapy.

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. While the GeparSixto(15) and CALGB40603(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 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.(23) 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. We hypothesize that for patients with basal-like TNBC, with residual disease post completion of neoadjuvant chemotherapy, the addition of a platinum agent in the adjuvant setting will provide a higher DFS benefit than capecitabine.

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.

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.

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1.6 Chemotherapy dose selection

The usual dose of cisplatin for a variety of tumors (ovarian, bladder, neuroblastoma, ostegenic 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(24) 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 for a total of 4 cycles (12 weeks) as the prescribed chemotherapy regimen in this trial.

Capecitabine was initially approved for use at a starting dosage of 1250mg/m^2 twice daily, with a dosing schedule of 14 days on followed by 7 days off despite frequent treatment-limiting toxicities, primarily hand-and-foot syndrome, stomatitis, and diarrhea at this dosage. Of note, a retrospective multivariate analysis by Haller and colleagues of data from three phase III trials of 5-FU, capecitabine and oxaliplatin for the treatment of early and advanced colorectal cancer show a significantly worse toxic-effect profile in patients recruited from the US than in those from Asia or elsewhere, for both early and advanced disease(25). Furthermore, a randomized trial of adjuvant therapy in early breast cancer in older women initially used the FDA approved capecitabine dose, but had to be amended to a lower dose due to excessive toxicity(21). This suggests that the 1250mg/m^2 twice daily dosing in the CREATE-X trial may not be reproducible in the US from a tolerance point of view. Since the approval of capecitabine, moderate dosage reductions have been studied, either retrospectively[28,29] or in small prospective trials(26-28) in order to assess both the efficacy and frequency of adverse effects (AEs) associated with lower dosages. Market research from the manufacturers of capecitabine (Roche) indicates it is relatively rare for US-based oncologists to prescribe the label-recommended

dose of capecitabine (1,250 mg/m^2 twice daily for 14 days) compared with their European colleagues. Instead, a starting dose of 1,000 mg/m^2 twice daily for 14 days is commonplace in the US. Since the majority of patients in the CREATE-X trial were only able to complete 6 cycles of capecitabine, for the purposes of our trial capecitabine will be given for a total of 1,000 mg/m^2 twice daily for 14 days every 3 weeks for a total of 6 cycles (18 weeks).

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1.7 Biomarker Correlatives

Mutational spectrum analyses suggest that TNBC has a higher mutational frequency than other subtypes(29-31), and our group has shown that profiling of TNBC post-neoadjuvant chemotherapy in a small scale is feasible and identifies gene alterations that may have a role in chemoresistance(8). We propose to perform a *prospective large-scale* genomic profiling of surgical tissue for patients enrolled in the EA1131 clinical trial. The prospective and large-scale nature of this proposal, in a homogeneous and highly selected high-risk patient population with complete clinical annotation, is a major advantage towards successful identification of factors that predict chemotherapy resistance and recurrence, which is still an overarching need in early TNBC. Early and accurate detection of patients at highest risk for overt metastasis development sets the stage for additional therapeutic interventions in the adjuvant setting. The nature of these interventions can be guided by the comprehensive genomic analysis proposed, where certain molecular alterations could be readily actionable, while others may give insight into development of novel therapeutics. Ultimately, these novel approaches (early detection and novel interventions) will significantly impact risk of recurrence and mortality in this group of patients at highest risk, which is our overall goal.

We expect that at least 400 patients (of the planned 775 to be accrued) will have a) viable tissue from the surgical specimen, b) paired blood specimens from baseline and after treatment completion, and c) have successful assay. Assuming the 400 patients with surgical specimen and blood specimens are representative of the whole study population, it is expected that about 100 RFS events will occur to the 400 patients. The prospective and large-scale nature of this proposal, in a selected high-risk patient population with complete clinical annotation, is a unique opportunity to successfully identify factors that predict chemotherapy resistance and recurrence. This would be further enriched thanks to the ability to analyze paired tissue and plasma-based molecular results, which would be invaluable to gain insights into tumor evolution and mechanisms of resistance to chemotherapy. Early and accurate detection of patients at highest risk sets the stage for additional therapeutic interventions in the adjuvant setting. The nature of these interventions can be guided by the comprehensive genomic analysis proposed, where certain molecular alterations could be readily actionable, while others may give insight into development of novel therapeutics. Ultimately, these novel approaches will significantly impact risk of recurrence and mortality in this group of patients at highest risk, which is our overall goal.

1.7.1 ***Genomic Alterations in the Surgical Tumor.*** We aim to determine if genomic alterations identified via profiling of the surgical tumor specimen of patients in the EA1131 clinical trial correlates with RFS. DNA and RNA will be extracted from the surgical specimens and subjected to whole exome sequencing (WES) and if feasible, RNA-sequencing (RNA-seq) analysis. Genomic alterations identified via profiling (i.e., mutations, CNV) will be correlated with RFS. Full

sequencing of residual TNBC in large scale will likely mirror the genomic make-up of metastatic recurrences. We expect that the large-scale identification of tissue genomic biomarkers of chemotherapy sensitivity and resistance will increase our ability to predict which patients with TNBC are at highest risk of relapse after surgery and identify clinically actionable alterations.

We hypothesize that the genomic alterations identified via genomic profiling will predict relapse-free survival (RFS) for this group of patients at high risk of recurrence. Successful completion of this comprehensive profiling will a) more accurately identify patients with TNBC at highest risk of recurrence, and b) provide novel insights into future targeted interventions that could significantly impact risk of recurrence and mortality in patients at highest risk.

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1.7.2 ***Circulating Tumor Cells (CTCs)***. Several assays are available that may detect clinically-occult tumor burden or minimal residual disease (MRD), but their clinical utility has not been established. Detection of circulating tumor DNA in the blood of cancer-free patients is one such assay, although the sensitivity, specificity, and positive/negative predictive value for predicting recurrence is currently unknown(32). Enumeration of CTCs in the blood (≥ 1 CTC in 7.5 ml blood) has also shown to be associated with recurrence when detected in patients with operable breast cancer who have not yet had surgery(33), particularly amongst those who have residual disease after neoadjuvant therapy.

In EA1131, CTC detection before protocol therapy, after protocol therapy, and change (i.e., clearance of CTCs after study therapy in those harboring these biomarkers pre-therapy) will be correlated with RFS. CTC detection after completion of chemotherapy will be coded as a binary variable (present versus absent).

Two Streck tubes for CTC analysis will be collected at the following time points: (1) baseline (prior to study therapy); 2) after completion of study therapy (e.g., capecitabine or platinum-based chemotherapy). Although the CTC enumeration must be done in real time, the results will not be provided to the clinician or patient for clinical decision-making.

Blood specimens will be forwarded to EPIC Sciences, where they will be prepared for subsequent sequencing and analyses for the corresponding mutations detected in matched primary breast tissue.

We hypothesize that:

a) patients whose specimens are negative for CTC detection at baseline will have a better RFS than patients with positive CTC detection at baseline.

b) patients whose specimens are negative for CTC detection after protocol therapy will have a better RFS than patients with positive CTC detection after protocol therapy.

We expect that the large-scale serial CTC detection will provide an important intermediate biomarker that will help identify patients with TNBC at a higher risk of relapse after surgery, identify those most

likely to benefit from additional adjuvant therapy, and identify alterations that could have clinically actionable potential.

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1.8 Patient reported outcomes (PRO)

EA1131 will randomly assign patients with residual TNBC to further treatment with platinum chemotherapy (4 cycles) or to capecitabine (6 cycles) in a high-risk group of triple negative breast cancer patients (e.g. those with residual disease after neoadjuvant anthracycline + taxane-based chemotherapy). The primary endpoint is iDFS and the trial is powered to test for non-inferiority of platinum-chemotherapy, as well as superiority of platinum-chemotherapy over capecitabine if the primary endpoint of non-inferiority is met. Whether platinum agents prove superior or non-inferior to capecitabine, it will be important for patients and treating physicians to understand how receiving adjuvant platinum agents affect overall health related quality of life (HRQL)—both short- and long-term—in order to effectively counsel patients with regards to benefit. Patient-reported medication adherence could yield additional insights into the results of EA1131, as poor adherence whether due to side effects or access could limit the impact of capecitabine on iDFS.

Further chemotherapy (whether capecitabine or platinum-based) is hypothesized to decrease the rate of cancer recurrence for this high-risk group. However, additional treatment will have *at least* short-term impact on HRQL due to the acute side effects of treatment. The CREATE-X trial examined 910 women randomized to adjuvant capecitabine vs observation. On that trial, nearly one-fifth of patients stopped treatment due to adverse events. Given the relatively shorter duration of platinum vs capecitabine chemotherapy (12 vs 18 weeks), as well as the well-characterized side effect profile, we believe that platinums will be better tolerated in the short-term, with the possible exception of neurotoxicity. Platinums are associated with a risk of long-term neurotoxocity(34, 35) that negatively affects long-term HRQL(36), while capecitabine does not carry a risk of long-term neurotoxocity. The patients enrolling on EA1131 will likely have had prior exposure to taxanes (which may also cause long-term neurotoxocity). Data exists regarding the risk for long-term neurotoxocity for combination taxane+platinums, but not for the agents given sequentially. If the platinum-chemotherapy arm proves non-inferior but not superior, it will be especially important to both oncologists and patients to be able to counsel survivors about the risks regarding the long-term neurotoxocity.

EA1131 will also offer unique access to a population of relatively young women with breast cancer. In PrECOG 0105, the median age was 48 years (range 26-73), and roughly 60% of participants were premenopausal. Patients enrolling on EA1131 may be even younger, as oncologists will preferentially elect to refer younger women and/or younger women may be the most desirous of further treatment. Thus, we expect that EA1131 will have a median age of at least 48 or possibly younger, with the majority (60% or more) being premenopausal at breast cancer diagnosis. This presents a number of unique considerations, given that these young women may live for decades after diagnosis if they do not succumb to breast cancer. These questions include: the longer-term neurotoxocity(34, 35) in the platinum and the impact of the agents in both arms on ovarian function. Little data exists regarding the effect of either capecitabine or platinum agents on ovarian function, despite increasing popularity and use. Platinum use in breast cancer includes gemcitabine + platinum [PrECOG0105] or

docetaxel + carboplatin + trastuzumab [TCH] for HER2+ breast cancer. Capecitabine use in breast or colon cancer typically occurs in the metastatic setting. In PrECOG0105, patients anecdotally reported little disruption of menses. Data for capecitabine from the colorectal world is less useful in breast cancer, due to sequencing capecitabine with agents known to disrupt ovarian functions such as anthracyclines or cyclophosphamide. Thus, due to the paucity of literature, oncologists experience difficulty counseling patients with regards to the impact of these agents on ovarian function. Ovarian function is of concern because (a) younger patients may desire to preserve fertility for child-bearing, (b) premature menopause is associated with attendant symptoms (hot flashes, sweats, vaginal dryness, decreased libido) that negatively impact HRQL.(37) and (c) premature menopause increases long term health risks (increased bone loss, possible cognitive, cardiac problems). There is an increased mortality risk with premature ovarian failure/removal in young women.(38-40)

We hypothesize that HRQL between the groups will be superior in the platinum agent arm at the start of cycle 3 and at the 15-months after start of study treatment time-points (roughly 1 year after chemotherapy ends), and we also aim to describe the rate of neurotoxicity over time in the platinum arm, the rate of medication adherence in the capecitabine arm, and the rates of amenorrhea in both arms.

To test the primary hypothesis and assess our exploratory objectives, we have selected the following measures:

HRQL Measures. **For both arms.** Measures will be assessed at baseline, and start of cycle 3, as well as 6 and 15 months after the start of study treatment. These time-points have been chosen as they allow us to capture the acute difference in side-effects following receipt of chemotherapy and follow long enough to ensure that acute differences will have resolved. Differences in symptom burden and HRQL at 15 months after the start of study chemotherapy (roughly 12 months after chemotherapy ends) would be considered persistent and be considered unlikely to improve further.

- *NCCN-Fact **FBSI-16** (16-items)* is a validated 16-item scale including all 8 items from the original FBSI and 8 additional items from Functional Assessment of Chronic Illness Therapy measures. The NFBSI-16 is formatted by subscale: Disease-Related Symptom, Treatment Side-Effect, and General Function and Well-Being.(41) Higher FBSI scores indicate better HRQL (score range, 0 to 16).

Ovarian Function Measure. **For both arms.** We will use questions used in the ATEMPT and APT studies to capture ovarian function.[37,38] Measures will be assessed at baseline and 15 months after adjuvant study chemotherapy starts (this is roughly 12 months after chemotherapy ends). Study participants will self-report menstrual history retrospectively. Only patients aged 54 years or less at time of baseline survey will complete these questions, and we will screen out those who are not premenopausal with regular menses at diagnosis.

- *Menstrual Measures (4-items).* We will use 4 measures adapted from the ATEMPT and APT studies.[38] Patients aged less than 55 will be asked about (1) absence or presence of menses in the 12 months prior to neoadjuvant chemotherapy (termination of survey if no menses), (2) did they have periods at least every 2 months prior to neoadjuvant chemotherapy (termination of survey if no), (3) did they consider themselves premenopausal prior to

neoadjuvant chemotherapy (termination of survey if no), (4) date of last menses, (5) frequency of menses over past 6 months, (6) receipt of BSO, or LHRH agonist and use of contraceptives.

Neurotoxicity Symptom Measures. **For the platinum arm only.** Measures will be assessed at baseline, and start of cycle 3, as well as 6 and 15 months after the start of study chemotherapy. These time-points have been chosen as they allow us to capture the baseline rate due to prior taxanes, acute development of neuropathy following receipt of platinum chemotherapy and to follow long enough to ensure that acute toxicity will have resolved. Neurotoxicity at 15 months (roughly 12 months after chemotherapy ends) would be considered persistent and unlikely to improve further.

- The *FACT-Gynecologic Oncology Group/Neurotoxicity (**FACT-GOG/Ntx**; 11-items*) subscale contains 11 items and is designed to assess neurotoxicity resulting from platinum and taxane-based chemotherapies.(42) Lower FACT-GOG/Ntx scores denote higher neurotoxicity (score range, 0 to 44).

Medication Adherence Measure. **For the capecitabine arm only.** This item will be assessed only for patients receiving capecitabine chemotherapy, and will be done twice while on study chemotherapy (start of cycle 3 and 6), to add to our understanding of why or why not a patient adhered to medication. This may yield additional insight into the primary endpoint results.

Rev. Add7

- *ECOG-ACRIN Medication Adherence Scale Modified from the Morisky Medication Adherence Questionnaire (8-items)*. This measures the likelihood that a patient will take prescribed medications. The Medication Adherence Scale has been validated against medication pill count methods of assessing compliance and used in a variety of settings. It is an 8-item measure with a Likert response scale. The minimal detectable change has been defined as 1.98 points. It will be administered to understand the reasons for non-adherence to protocol therapy.

1.9 Rationale for Tobacco Use Assessment

NOTE: Please refer to Appendix VI for EAQ16T references.

A significant proportion of cancer patients are current smokers at the time of cancer diagnosis,[1–5] and there are known risks associated with continued smoking following cancer diagnosis. These include decreased survival time; increased complications from surgery, radiation, and chemotherapy; and increased risk of second primary tumors.[6–11] As such, the National Comprehensive Cancer Network (NCCN), the American Association of Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO) have identified persistent smoking as a modifiable risk factor and recommend cessation counseling for cancer patients who smoke. Although evidence-based guidelines for treating tobacco dependence exist,[12] they have not yet been well-integrated into cancer care settings. Moreover, knowledge regarding the scope and patterns of tobacco use among cancer patients is limited.

Tobacco use following a cancer diagnosis compromises treatment outcomes but is not well understood. About 10% to 30% of cancer patients are smoking at the time of diagnosis,[1–4,14,15] and the majority of cancer patients who smoke at diagnosis continue to smoke following diagnosis.[3,16] Quitting smoking upon cancer diagnosis may improve cancer treatment effectiveness, reduce risk of recurrence and of developing new primary tumors,[9–11,17–21] and improve chances

of survival.[1,22–24] Conversely, continuing to smoke may result in diminished QOL,[1,25,26] treatment delays and increased treatment complications.[2,6–8,22,27–34]

Tobacco use following a cancer diagnosis may compromise patient reported outcomes. It is hypothesized that smoking may be used as a means of reducing symptom burden among cancer patients, which may be a barrier to smoking cessation. Relatedly, research has shown that cancer patients who are smoking experience more difficulty with physical and psychological symptom control, compared to nonsmokers. [35–38] Research is needed to examine how symptom levels differ, by tobacco use and exposure and how tobacco use changes may affect reported symptom burden.

National initiatives emphasize the importance of identifying tobacco use in cancer care settings. Smoking status was designated as a core objective in the 2010 federal government "Meaningful Use" electronic health record documentation.[39,40] In 2013, the American Association for Cancer Research (AACR) released guidelines emphasizing the provision of tobacco cessation services to cancer patients.[41] The American Society of Clinical Oncology (ASCO) recommends cessation counseling to all smokers by their second oncology visit as a core quality indicator.[42] The National Comprehensive Cancer Network (NCCN) published Smoking Cessation guidelines to formalize these initiatives.[43]

Integrated, evidence-based services are needed during cancer care. The USPHS Practice Guidelines recommend that evidence-based tobacco treatment be delivered to all smokers in health care settings, yet little progress has been made to integrate these guidelines into cancer care.[44] This is unfortunate, as cessation closer to the time of diagnosis results in a higher likelihood for continued abstinence,[1,45–48] effective interventions exist,[1,45–48] and many cancer patients who smoke want to quit smoking.[45,46,49,50] Little work has been done to explore the delivery and effectiveness of tobacco treatment among racial/ethnic minority cancer patients who are at elevated risk of continued smoking.[51–53]

Tobacco use is often not being assessed or intervened upon during cancer care. Recent surveys of oncologists and of clinical practices at comprehensive cancer centers and community oncology settings demonstrate that assessment of tobacco dependence is lacking.[54–57] During treatment, most cancer patients do not get assistance with smoking cessation support.[58–60] Tobacco use assessments and cessation support have not been incorporated in most cooperative group clinical trials.[61] No one has assessed cancer patients' reports of their oncology providers' assistance behaviors.

The NCI-AACR Cancer Patient Tobacco Use Assessment Task Force developed the Cancer Patient Tobacco Use [1–4,13,14] Questionnaire (C-TUQ). We propose that administering selected C-TUQ items to participants enrolling in 8 Phase II and Phase III ECOG ACRIN (EA) therapeutic trials will add value to parent trial research questions by advancing the field. Specifically, among patients with varied cancers (tobacco-related and non-tobacco-related) and cancer treatments, we will administer C-TUQ questions at EA trial enrollment and 3 and 6 months follow-up.

We have the following aims:

a) **Treatment toxicity:** To determine the effects of tobacco, operationalized as combustible tobacco (1a), other forms of tobacco (1b), and environmental

tobacco exposure (ETS) (1c) on provider-reported cancer-treatment toxicity (adverse events (both clinical and hematologic) and dose modifications).

b) **Symptom burden:** To determine the effects of tobacco on patient-reported physical symptoms and psychological symptoms.

c) **Cessation patterns and treatment:** To examine quitting behaviors and behavioral counseling/support and cessation medication utilization.

d) **Trial outcomes:** To explore the effect of tobacco use and exposure on treatment duration and relative dose intensity, and on therapeutic benefit, of 8 selected EA trials.

The findings will advance the nascent field of tobacco use in the context of cancer care by: 1) longitudinal assessment of cigarette smoking, other forms of tobacco use and secondhand smoke exposure at trial enrollment and at 3 and 6 month follow-up; 2) increase knowledge about the effects of tobacco use and exposure on treatment toxicity, physical and psychological symptoms and 3) oncology provider delivery, and 4) patient's perceptions of stigma and utilization of behavioral and pharmacological treatment of tobacco dependence. Finally, the use of this assessment would provide a unique additional value to the hypothesis of this trial, by allowing investigation of previously unanswered questions about the effects of tobacco use and exposure on trial adherence and outcomes among patients with smoking-related and non-smoking related cancers.

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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 capecitabine arm, which is an appropriate standard of care based on the Create-X trial results.

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 capecitabine.

2.2 Secondary Clinical 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) as well as capecitabine in patients with TNBC with residual 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.

2.2.4 To compare the IDFS in TNBC patients with residual non-basal-like disease after neoadjuvant chemotherapy who are randomized to post-preoperative platinum-based chemotherapy with those who are randomized to capecitabine (exploratory analysis).

2.2.5 To assess the difference in health-related quality of life (HRQL) between the platinum based and capecitabine chemotherapy arms.

2.2.6 To describe the rate of neurotoxicity over time in the platinum arm, the rate of medication adherence in the capecitabine arm and the rates of amenorrhea in both arms (exploratory).

Rev. Add7

2.3 Secondary Correlative Biomarker Objectives

2.3.1 To evaluate the association of genomic alterations identified via profiling of the surgical tumor specimen with RFS in patients with TNBC after neoadjuvant chemotherapy.

2.3.2 To explore whether any of the genomic alterations identified via profiling of the surgical tumor specimen can predict treatment benefit in patients with basal-like TNBC.

2.3.3 To determine the frequency of CTC positivity at baseline and after completion of study therapy in patients with TNBC with residual basal-like disease after neoadjuvant chemotherapy.

2.3.4 To evaluate the associations between CTC levels at baseline, and after completion of chemotherapy, with RFS

2.3.5 To evaluate the association between CTC change in status post-treatment (i.e. negative to negative, negative to positive, positive to negative, positive to positive) and RFS.

Rev. Add8

2.3.6 To explore significance of CTC number/phenotype in predicting RFS.

Rev. Add7

2.4 Exploratory Correlative Biomarker Objectives

2.4.1 To determine the frequency of plasma tumor cell-free DNA (cfDNA) positivity at baseline and after completion of study therapy in patients with TNBC with residual basal-like disease after neoadjuvant chemotherapy.

2.4.2 To evaluate the associations between plasma tumor cfDNA tumor-specific mutations (baseline and after therapy) with RFS.

2.4.3 To explore optimal biomarker combination for RFS prediction.

Rev. Add#5

2.5 Exploratory Tobacco Use Objectives

2.5.1 To determine the effects of tobacco, operationalized as combustible tobacco (1a), other forms of tobacco (1b), and environmental tobacco exposure (ETS) (1c) on provider-reported cancer-treatment toxicity (adverse events (both clinical and hematologic) and dose modifications).

2.5.2 To determine the effects of tobacco on patient-reported physical symptoms and psychological symptoms.

2.5.3 To examine quitting behaviors and behavioral counseling/support and cessation medication utilization.

2.5.4 To explore the effect of tobacco use and exposure on treatment duration, relative dose intensity, and therapeutic benefit.

NOTE: Tobacco Use objectives described above are ancillary for the Tobacco Use Assessment project approved by NCI. A combined analysis of the data from the selected ECOG-ACRIN trials is planned. Data collected from the tobacco use assessment in each parent study will not be analyzed and reported in the clinical study report.

Rev. 9/17

3. Selection of Patients

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

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

ECOG-ACRIN Patient No. _____

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

Physician Signature and Date _____

NOTE: 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.

Rev. 6/16
Rev. Add7
Rev. Add8

NOTE: This study involves screening and randomization. Tumor tissue specimen must be submitted anytime during screening for PAM50 analysis. Patients will not be randomized without notification of receipt of tumor tissue at the ECOG-ACRIN Central Biorepository and Pathology Facility.

NOTE: Patients are allowed to participate in other therapeutic clinical trials either prior (neoadjuvant setting) or after full completion of EA1131 study treatment, but not during study treatment (except for non-cancer treatment related interventions). Patients enrolled in clinical trials addressing local therapy after neoadjuvant chemotherapy are also allowed to enroll.

Rev. 6/16
Rev. Add7

3.1 Eligibility Criteria for Screening and Molecular Profiling (STEP 0)

_____ 3.1.1 Age ≥ 18 years.

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

Rev. 9/17
Rev. Add6

_____ 3.1.3 Female and male patients must have histologically confirmed invasive breast cancer that meets the following criteria:

Rev. 9/17
Rev. Add8

3.1.3.1 Clinical stage II or III (AJCC 8th edition) at diagnosis, based on initial evaluation by clinical examination and/or breast imaging; no metastatic disease (confirmed by biopsy) allowed.

Rev. 2/16

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

_____ 1 to ≤ 10% cells stain positive, with weak intensity score

_____ ≤ 1% cells stain positive

Rev. Add#5

3.1.3.3 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)

Rev. 9/17

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. Multifocal or multicentric breast cancers are eligible as long as all tumors that were tested for ER/PR/HER2 fulfill eligibility criteria (please note that tumors that were not tested already do not need to be tested for protocol eligibility).

Rev. 9/17

Rev. Add8

NOTE: Patients that have a discrepancy in ER/PR/HER2 status between original diagnosis and surgical specimen (only applicable if ER/PR/HER2 status were repeated; repeating it is not mandatory) are eligible for study participation as long as the surgical specimen's ER/PR/HER2 status fulfills eligibility criteria.

Rev. Add8

NOTE: Special histologies (i.e. metaplastic, adenoid cystic, apocrine, etc.) are eligible as long as ER/PR/HER2 testing fulfills eligibility criteria.

NOTE: Patients with inflammatory TNBC at presentation are eligible.

Rev. 6/16

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

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

Rev. 9/17

NOTE: Patients that were not able to complete their planned neoadjuvant chemotherapy for any reason (i.e. toxicities, etc.) are eligible to participate as long as no further systemic standard of care therapy is planned by the treating physician.

NOTE: Patients must have received a taxane for at least 1 cycle as part of their neoadjuvant therapy regimen.

_____ 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.

Rev. 9/17

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

Rev. 9/17
Rev. Add#5

_____ 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. Please note that in patients that have multifocal or multicentric residual tumors these lesions cannot be added up; the biggest lesion has to measure ≥ 1 cm in diameter. This is required due to constraints in DNA extraction for PAM50 analysis.

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

NOTE: Despite lymph node involvement if residual invasive cancer in the breast is < 1 cm in diameter patients are not eligible for participation.

Rev. 9/17
Rev. Add#5

_____ 3.1.7 Radiotherapy may be given before or after protocol treatment per standard of care guidelines. When radiotherapy is planned prior to protocol treatment administration, patients may be registered and screened while receiving radiation, and it has to be complete prior to randomization.

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

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

_____ For patients with primary tumors < 5 cm or without lymph node involvement prior to neoadjuvant chemotherapy and at the time of definitive surgery, provision of post-mastectomy radiotherapy is at the discretion of the treating physician.

Radiation of regional nodal basins is at the discretion of the treating radiation oncologist.

NOTE: Breast radiotherapy (whole breast or partial) is required for patients who underwent breast-conserving therapy, including lumpectomy or partial mastectomy.

_____ 3.1.8 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.

Rev. 2/16

_____ 3.1.8.1 Hemoglobin (Hgb) > 9.0 g/dL

Hgb: _____ Date of Test: _____

_____ 3.1.8.2 Platelets > 100,000 cells/mm^3

Platelets: _____ Date of Test: _____

_____ 3.1.8.3 Absolute neutrophil count (ANC) > 1500 cells/mm^3

ANC: _____ Date of Test: _____

_____ 3.1.8.4 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 × 0.85

Creatinine Clearance: _____ Date of Test: _____

_____ 3.1.8.5 Bilirubin ≤ 1.5 x ULN upper limit of normal (except in patients with documented Gilbert's disease, who must have a total bilirubin ≤ 3.0 mg/dL)

Bilirubin: _____ ULN:_____ Date of Test: _____

Gilberts disease?_____(Yes or No)

_____ 3.1.8.6 Aspartate aminotransferase (AST, SGOT) ≤ 2.5 × ULN

AST: _____ ULN:_____ Date of Test: _____

_____ 3.1.8.7 Alanine aminotransferase (ALT, SGPT) ≤ 2.5 × ULN

ALT: _____ ULN:_____ Date of Test: _____

Rev. 9/17 _____ 3.1.9 No history of TNBC invasive breast cancer within 5 years of enrollment, no concurrent invasive malignancies except for synchronous bilateral tumors that are TNBC, skin, thyroid, or hematologic cancers with low metastatic/death potential (i.e. squamous cell or basal cell skin cancers, DCIS, CLL, etc.). Patients are eligible if they had any other cancers that were treated prior to screening and are without evidence of recurrence.

Rev. Add8

_____ 3.1.10 No clinically significant infections, cardiac, pulmonary, or hepatic dysfunction as judged by the treating investigator. Concurrent illnesses that are well controlled with medical management are allowed.

Rev. Add8

_____ 3.1.11 Patients with active ≥ CTCAE v.4 grade 2 neuropathy are ineligible.

Rev. 6/16 _____ 3.1.12 Adjuvant chemotherapy after surgery other than that specified in this protocol is not allowed. LHRH agonists for fertility preservation or non-cancer indications and adjuvant bisphosphonate or denosumab use is allowed.

Rev. Add8

Rev. 6/16 _____ 3.1.13 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.

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Rev. 9/17
Rev. Add#5

3.1.13.1 Tumor tissue specimen from the definitive surgery has been collected and is ready to ship to the ECOG-ACRIN Central Biorepository and Pathology Facility (EA CBPF) within 21 weeks post-surgery as indicated in Section 10.2.1.

Rev. Add7

The EA CBPF will notify the ECOG-ACRIN Operations Office and submitting institution of receipt of the tumor tissue specimen.

NOTE: Tumor tissue must and can be submitted any time during screening period, even if patient is getting radiation.

NOTE: Every effort should be made to submit the tumor tissue specimen to the EA CBPF immediately.

Rev. Add8

Date of main surgery (i.e. subsequent surgeries for re-excision of margins or lymph nodes or reconstruction do not apply): _____

Date tumor tissue sent to EA CBPF: _____

Rev. 6/16
Rev. Add7

3.2 Eligibility Criteria for Randomization (Step 1):

Screened patients will remain on the study and be randomized if they meet the above and below following criteria. No specific timeframe between registration and randomization needs to be observed, as long as:

- After assignment of randomization patients must begin Cycle 1/ Day 1 (platinum based or capecitabine chemotherapy) within 6 weeks (30 working days) of the **randomization date**.

Rev. Add8

- Randomization occurs no more than 24 weeks from main surgery date (i.e. subsequent surgeries for re-excision of margins or lymph nodes or reconstruction do not apply)

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Rev. 9/17
Rev. Add8
Rev. Add#5

_____ 3.2.1 Must have confirmation from EA CBPF of receipt of formalin-fixed paraffin-embedded tumor tissue specimen (FFPE) of the residual disease in the breast resected at the time of definitive surgery.

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

Rev. 9/17

_____ 3.2.3 Radiotherapy, if applicable, may be given before or after protocol treatment. When radiotherapy is planned prior to protocol treatment administration, 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 initiation (Cycle 1/ day 1).

Rev. 2/16
Rev. Add8

_____ 3.2.5 Patients must be randomized within 24 weeks from main surgery date (i.e. subsequent surgeries for re-excision of margins or lymph nodes or reconstruction do not apply).

Rev. 6/16

_____ 3.2.6 Women must not be pregnant or breast-feeding due to risk of teratogenicity/ toxicity with capecitabine or 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 defined as any woman that has achieved menarche at some point, 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).

Female of child bearing potential?____(Yes or No)

3.2.6.2 Date of pregnancy blood test or urine study (if not applicable, write N/A instead of date): _____

_____ 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.

Rev. 2/16

_____3.2.8 Adequate bone marrow and organ function based on the following tests. Laboratory values must be obtained within 4 weeks prior to randomization.

_____ 3.2.8.1 Hemoglobin (Hgb) > 9.0 g/dL

Hgb: _____ Date of Test: _____

_____ 3.2.8.2 Platelets > 100,000 cells/mm^3

Platelets: _____ Date of Test: _____

_____ 3.2.8.3 Absolute neutrophil count (ANC) > 1500 cells/mm^3

ANC: _____ Date of Test: _____

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Rev. 9/17

_____ 3.2.8.4 INR ≤ 3 (to be done/tested only for subjects on warfarin)

Patient on warfarin?_____(Yes or No)

INR:_____ Date of Test:_____

_____ 3.2.8.5 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 × 0.85

Creatinine Clearance: _____ Date of Test: _____

_____ 3.2.8.6 Bilirubin ≤ 1.5 x ULN (except in patients with documented Gilbert's disease, who must have a total bilirubin ≤ 3.0 mg/dL)

Bilirubin: _____ ULN:_____ Date of Test: _____

Gilberts disease?_____(Yes or No)

_____ 3.2.8.7 Aspartate aminotransferase (AST, SGOT) ≤ 2.5 × ULN

AST: _____ ULN:_____ Date of Test: _____

_____ 3.2.8.8 Alanine aminotransferase (ALT, SGPT) ≤ 2.5 × ULN

ALT: _____ ULN:_____ Date of Test: _____

Rev. Add8

NOTE: Live vaccines are not permitted during study treatment period (but are permitted after study treatment completion), but all others (inactivated, mRNA-based, adenovirus, etc.) including COVID vaccine are permitted before, during and after study treatment.

NOTE: Use of (any) anti-coagulants are allowed during study.

Rev. 9/17
Rev. Add#5

4. Registration Procedures

CTEP Registration Procedures

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

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RCR utilizes five person registration types.

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

RCR requires the following registration documents:

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

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

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

Additional information can be found on the CTEP website at <https://ctep.cancer.gov/investigatorResources/default.htm>. For questions, please contact the RCR Help Desk by email at <RCRHelpDesk@nih.gov>.

CTSU Registration Procedures

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

IRB Approval:

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

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

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

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

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

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Additional Requirements

Additional requirements to obtain an approved site registration status include:

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

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Downloading Site Registration Documents:

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Protocol Organization (PO) on the protocol. One way to search for a protocol is listed below.

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on the *Protocols* in the upper left of your screen
- Either enter the protocol number in the search field at the top of the protocol tree
- Click on the By Lead Organization folder to expand
- Click on the **ECOG-ACRIN** link to expand, then select trial protocol **EA1131**
- Click on *Documents*, select the *Site Registration* documents link, and download and complete the forms provided.

(Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

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Submitting Regulatory Documents

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

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

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

Required Protocol Specific Regulatory Documents

1. Copy of IRB Informed Consent Document.

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

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

   NOTE: The above submissions must include the following details:

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

- Signature of IRB official

Rev. Add8 **Checking Your Site's Registration Status:**

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

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

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

Patient Enrollment

Rev. 9/17
Rev. Add7 **Treatment should start within 6 weeks (thirty [30] working days) following randomization date.**

Rev. Add8 The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- Have an approved site registration for the protocol prior to patient enrollment.

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

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

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

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

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

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.

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4.2.2 Pathological materials are required to be submitted no later than 21 weeks post-surgery for PAM50 analysis as indicated in Section 10.2.

NOTE: The EA CBPF will notify the ECOG-ACRIN Operations Office and submitting institution of receipt of the tumor tissue specimen. PAM50 results will not be reported to the submitting institution.

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Patients cannot proceed with randomization to STEP 1 until the EA CBPF confirms receipt of tumor tissue for PAM50 analysis.

Pathological materials will also be used for retrospective central review for confirmation of ER, PR, and 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

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4.3.4 Additional Requirements

4.3.4.1 Peripheral blood specimens are required to be submitted for defined laboratory research studies as outlined in Section 10.

4.3.4.2 Peripheral blood specimens are to be submitted for future undefined research studies per patient consent as outlined in Section 10.

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4.3.5 Stratification Factors

4.3.5.1 Clinical stage at diagnosis (II or III)

4.3.5.2 Residual cancer burden after neoadjuvant chemotherapy (1~3 cm or >3 cm)

4.3.5.3 Planned platinum agent (cisplatin or carboplatin)

4.3.5.4 Anthracycline exposure in the neoadjuvant setting (yes or no)

4.3.5.5 Administration of adjuvant radiotherapy (yes or no)

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Rev. Add8

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

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;

- Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

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

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

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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.

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4.3.7 ECOG-ACRIN Systems for Easy Entry of Patient Reported Outcomes (EASEE-PRO) System:

When patients consent to participate, they will be asked to provide a contact email address and that address along with their registration information will be sent directly from the parent trial's registration system to EASEE-PRO, and the patient will be automatically registered into EASEE-PRO for participation. To activate their account for self-directed web entry of surveys, the system will send an activation message to the contact email address that will explain how to activate their account for self-directed web entry of surveys. After their account is activated, the patient will be able to complete questionnaires using a secure browser interface from any web enabled computer, tablet, or mobile device.

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4.4 Data Quality Portal

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

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

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

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

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

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4.5 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 and EASEE-PRO according to the schedule in the EA1131 Forms Completion Guidelines.

5. Treatment Plan

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5.1 Administration Schedule

Doses are based on actual body weight.

Arm A Observation closed to accrual in Addendum #3

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5.1.1 ARM B

Cisplatin 75 mg/m^2, IV infusion per institutional guidelines, day 1 every 3 weeks for a total of 4 cycles (12 weeks)

OR

Carboplatin AUC 6, IV infusion per institutional guidelines, day 1 every 3 weeks for a total of 4 cycles (12 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: $$\frac{(140 - \text{Age in years}) \times \text{Actual Body Weight in kg}}{72 \times \text{Serum Creatinine (mg/dL)}}$$

Females: Estimated creatinine clearance for females × 0.85

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

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NOTE: Carboplatin maximum dose is based on a GFR estimate that is capped at 125 mL/min for patients with normal renal function. Based on Calvert formula, the recommended maximum AUC- based carboplatin dose is (or not to exceed or cap at):

AUC 6 →900 mg (max)

AUC 5→750 mg (max)

AUC 4 → 600 mg (max)

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

NOTE: In case of an event that causes a patient to reschedule appointments, treatment cycles should be no less than 19 days apart.

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).

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5.1.2 ARM C

Capecitabine 1,000 mg/m^2, PO twice daily, on days 1 - 14 every 3 weeks for a total of 6 cycles (18 weeks)

NOTE: In case of an event that causes a patient to reschedule appointments, treatment cycles should be no less than 19 days apart.

NOTE: Table below provides guidance on rounding the calculated dose of capecitabine as **only 500 mg tablets should be utilized**. **Please prescribe capecitabine based on the "number of 500 mg tablets" column as per table below, not based on the "total daily dose in mg" column**. Adjustments to capecitabine dose based on weight changes are not necessary unless there is ≥ 10% change in weight compared to baseline. Capecitabine tablets are to be swallowed whole, with water, 30 minutes after a meal. Tablets should not be cut or crushed. Dose escalations of capecitabine after dose reductions for safety are not permitted. Missed capecitabine doses beyond 3 hours of regular intake time should not be taken. In case of vomiting after capecitabine ingestion, dose should not be replaced. Please see Section 5.3 for additional information on capecitabine dose modifications.

Guidelines for Capecitabine Dose Calculation According to Body Surface Area									
BSA (m^2)	100% Dose Level of Capecitabine			75% Dose Level of Capecitabine			50% Dose Level of Capecitabine		
	1000 mg/m2 (BID)	**Number of 500 mg Tablets**		750 mg/m2 (BID)	**Number of 500 mg Tablets**		500 mg/m2 (BID)	**Number of 500 mg Tablets**	
	Total Daily Dose (mg)	**Morning Number of Tablets**	**Evening Number of Tablets**	Total Daily Dose (mg)	**Morning Number of Tablets**	**Evening Number of Tablets**	Total Daily Dose (mg)	**Morning Number of Tablets**	**Evening Number of Tablets**
≤ 1.25	2000	**2**	**2**	1600	**2**	**1**	1000	**1**	**1**
1.26 – 1.37	2600	**3**	**2**	2000	**2**	**2**	1300	**2**	**1**
1.38 – 1.51	2900	**3**	**3**	2300	**2**	**2**	1600	**2**	**1**
1.52 – 1.65	3300	**3**	**3**	2300	**2**	**2**	1600	**2**	**1**
1.66 – 1.77	3600	**4**	**3**	2600	**3**	**2**	1900	**2**	**2**
1.78 – 1.91	3800	**4**	**3**	2600	**3**	**2**	1900	**2**	**2**
1.92 – 2.05	4000	**4**	**4**	3000	**3**	**3**	2000	**2**	**2**
2.06 – 2.17	4300	**4**	**4**	3300	**3**	**3**	2300	**3**	**2**
≥ 2.18	4600	**5**	**4**	3600	**4**	**3**	2600	**3**	**2**

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5.2 Adverse Event Reporting Requirements

NOTE: Effective April 1, 2018 all expedited adverse event reporting done via CTEP-AERS will use CTCAE version 5.0 terminology and grading. Routine adverse event reporting and dose modifications guidelines for this study will continue to be based on CTCAE version 4.0 terminology and grading.

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.

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

- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.
- **Expectedness:** Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes, when either the type of event or the severity of the event is NOT listed in the protocol or drug package insert.

5.2.3 Reporting Procedure

This study requires that expedited adverse event reporting use CTEP's Adverse Event Reporting System (CTEP-AERS). The CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted electronically to ECOG-ACRIN and the appropriate regulatory agencies via the CTEP-AERS Web-based application located at http://ctep.cancer.gov.

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 ncictephelp@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.

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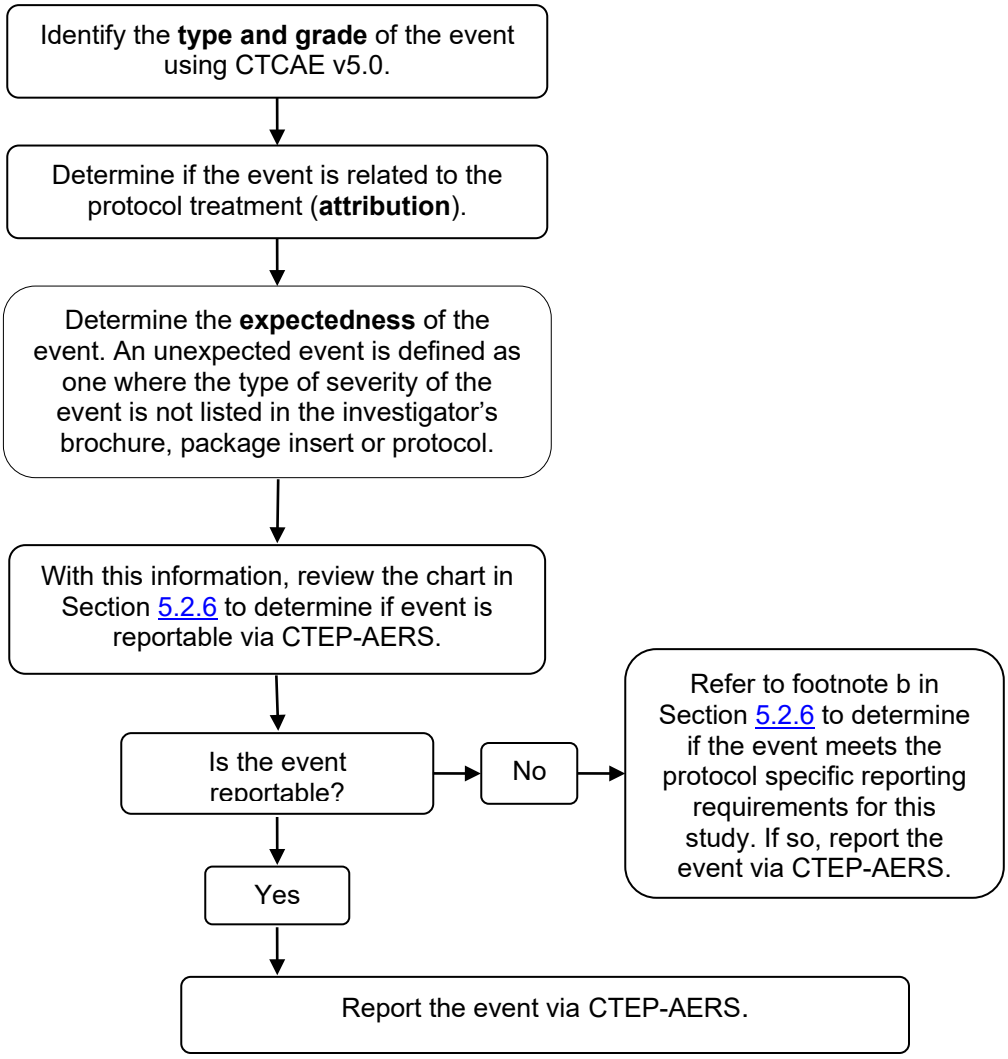
5.2.5 Steps to determine if an event is to be reported in an expedited manner – Arms B and C



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5.2.6 Expedited Reporting Requirements for Arms B and C on protocol EA1131

Commercial Agents: Capecitabine, Cisplatin and Carboplatin

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

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

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

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

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

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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 <u>secondary malignancy</u> is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov
     Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy
  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.

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5.3 Capecitabine 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 capecitabine **within 3 weeks of interruption (from the time of due scheduled cycle initiation; i.e. within 6 weeks from previous cycle initiation)**. Dose reductions will be permanent. Missed doses will not be made up once toxicity is resolved as per guidelines below. **Only 500 mg tablets should be utilized. Please prescribe capecitabine based on the "number of 500 mg tablets" column as per table below, not based on the "total daily dose in mg" column. Adjustments to capecitabine dose based on weight changes are not necessary unless there is ≥ 10% change in weight compared to baseline.**

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 Standardized, initial capecitabine dosing schedule

Guidelines for Capecitabine Dose Calculation According to Body Surface Area									
BSA (m^2)	100% Dose Level of Capecitabine			75% Dose Level of Capecitabine			50% Dose Level of Capecitabine		
	1000 mg/m2 (BID)	**Number of 500 mg Tablets**		750 mg/m2 (BID)	**Number of 500 mg Tablets**		500 mg/m2 (BID)	**Number of 500 mg Tablets**	
	Total Daily Dose (mg)	**Morning Number of Tablets**	**Evening Number of Tablets**	Total Daily Dose (mg)	**Morning Number of Tablets**	**Evening Number of Tablets**	Total Daily Dose (mg)	**Morning Number of Tablets**	**Evening Number of Tablets**
≤ 1.25	2000	**2**	**2**	1600	**2**	**1**	1000	**1**	**1**
1.26 – 1.37	2600	**3**	**2**	2000	**2**	**2**	1300	**2**	**1**
1.38 – 1.51	2900	**3**	**3**	2300	**2**	**2**	1600	**2**	**1**
1.52 – 1.65	3300	**3**	**3**	2300	**2**	**2**	1600	**2**	**1**
1.66 – 1.77	3600	**4**	**3**	2600	**3**	**2**	1900	**2**	**2**
1.78 – 1.91	3800	**4**	**3**	2600	**3**	**2**	1900	**2**	**2**
1.92 – 2.05	4000	**4**	**4**	3000	**3**	**3**	2000	**2**	**2**
2.06 – 2.17	4300	**4**	**4**	3300	**3**	**3**	2300	**3**	**2**
≥ 2.18	4600	**5**	**4**	3600	**4**	**3**	2600	**3**	**2**

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5.3.2 Recommended Dose Modifications

Worst Toxicity CTCAE v4.0 Grade (unless otherwise specified)	Recommended Dose Modifications to capecitabine any time during a cycle of therapy
BLOOD AND LYMPHATIC SYSTEM DISORDER	
Anemia	
Grade 1 (Hgb < LLN-10.0 g/dL)	Maintain dose level.
Grade 2 (Hgb < 10.0 g/dL - 8.0 g/dL)	Maintain dose level.
Grade 3 (Hgb < 8.0 g/dL); transfusion indicated	Maintain dose level.
Grade 4 (Life threatening consequences; urgent intervention indicated); related to study drugs	Discontinue study treatment.
ANC decreased (Neutropenia)	
Grade 1 (ANC < LLN - 1.5 x 10^9/L)	Maintain dose level.
Grade 2 (ANC < 1.5 - 1.0 x 10^9/L)	Maintain dose level.
Grade 3 (ANC < 1.0 - 0.5 x 10^9/L)	Omit capecitabine until resolved to CTCAE Grade ≤ 2, then: - If resolved in ≤ 7 days, then maintain dose level. - If resolved in > 7 days, then reduce by 25%. - If second occurrence, then reduce by 25%
Grade 4 (ANC < 0.5 x 10^9/L)	Omit capecitabine until resolved to CTCAE ≤ Grade 2, then reduce by 25%.
Febrile neutropenia	
Grade 3 (ANC < 1.0 x 10^9/L, single temperature of > 38.3°C or a sustained temperature of ≥ 38.0°C)	Omit capecitabine until resolved to CTCAE Grade ≤ 2, and no fever, then: - If resolved by ≤ 7 days, then reduce by 25%. - If not resolved within 7 days despite appropriate management including full clinically indicated course of antibiotics, if indicated, discontinue patient from study treatment.
Grade 4	Discontinue study treatment.
Platelet count decreased (Thrombocytopenia)	
Grade 1 (PLT < LLN - 75 x 10^9/L)	Maintain dose level
Grade 2 (PLT < 75 - 50 x 10^9/L)	Omit capecitabine until resolved to CTCAE Grade ≤ 1, then reduce by 25%.
Grade 3 (PLT < 50 - 25 x 10^9/L)	Omit capecitabine until resolved to CTCAE Grade ≤ 1, then - If resolved in ≤ 7 days, then reduce by 25%. - If resolved in > 7 days, then discontinue study treatment.
Grade 4 (PLT < 25 x 10^9/L)	Discontinue study treatment.
Bleeding	
Any bleeding (related to cisplatin or carboplatin) resulting in a transfusion requirement	Omit capecitabine until no further bleeding has been observed. Continuation of study treatment may be considered.
INVESTIGATIONS – RENAL	
Serum creatinine	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level.
Grade 2 (> 1.5 - 3.0 x ULN)	Omit capecitabine until resolved to CTCAE Grade ≤ 1 or baseline, then - If resolved in ≤ 7 days, then maintain dose level. - If resolved in > 7 days, then reduce by 25%.

Worst Toxicity CTCAE v4.0 Grade (unless otherwise specified)	Recommended Dose Modifications to capecitabine any time during a cycle of therapy
Grade ≥ 3 (> 3.0 x ULN)	Discontinue study treatment.
INVESTIGATIONS – HEPATIC	
Blood Bilirubin [b] (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.	
Grade 1 (> ULN – 1.5 x ULN)	Maintain dose level.
Grade 2 (>1.5 – 3.0 x ULN)	Omit capecitabine until resolved to CTCAE Grade ≤ 1, then - If resolved in ≤ 7 days, then maintain dose level. - If resolved in > 7 days, then reduce by 25%.
Grade 3 (> 3.0 – 10 x ULN) or higher	Discontinue study treatment. **NOTE:** 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 reduce by 25% and continue treatment at the discretion of the Investigator.
AST or ALT	
Grade 1 and 2 (up to 5.0 x ULN)	Maintain dose level.
Grade 3 (> 5.0 - 20.0 x ULN)	Omit capecitabine until resolved to CTCAE Grade ≤ 1, then - If resolved in ≤ 7 days, then maintain dose level. - If resolved in > 7 days, then reduce by 25%.
Grade 4 (> 20.0 x ULN)	Discontinue study treatment.
NERVOUS SYSTEM DISORDERS	
Neurotoxicity	
Grade 1	Maintain dose level.
Transient Grade 2 that improves to grade ≤ 1 on the day of planned therapy	Maintain dose level.
Grade 2	Omit capecitabine until resolved to CTCAE Grade ≤ 1, then reduce by 25%.
Grade ≥ 3 or second occurrence of Grade 2	Discontinue study treatment.
GI DISORDERS	
Diarrhea	
Grade 1	Maintain dose level, but initiate anti-diarrhea treatment as clinically indicated
Grade 2	Omit capecitabine until resolved to CTCAE Grade ≤ 1, including with appropriate management, then maintain dose level.
Grade 3	Omit capecitabine 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 reduce by 25%. 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.

Worst Toxicity CTCAE v4.0 Grade (unless otherwise specified)	Recommended Dose Modifications to capecitabine any time during a cycle of therapy
Nausea/Vomiting	
Grade 1	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.
Grade 2	Omit capecitabine until resolved to CTCAE Grade ≤ 1, initiate anti-emetic treatment, then maintain dose level.
Grade 3	Omit capecitabine 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 reduce by 25%.
Grade 4	Discontinue study treatment.
GENERAL DISORDERS	
Fatigue	
Grade 1 or 2	Maintain dose level.
Grade 3	Omit capecitabine 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.
Dehydration	
Grade 1	Maintain dose level.
≥ Grade 2	Interrupt capecitabine until dehydration is corrected. Once resolved, may resume at same level.
MUCOCUTANEOUS AND DERMATOLOGIC	
Hand-Foot Syndrome	
Grade 1 or 2	Maintain capecitabine. For intolerable grade 2 toxicity, may omit dose of capecitabine until resolved to CTCAE Grade ≤ 1, consideration of 25% dose reduction at investigator's discretion.
Grade 3	Omit capecitabine until resolved to CTCAE Grade ≤ 1, then reduce by 25%.
Grade 4	Discontinue study treatment.
Stomatitis/ Mucosal Inflammation	
Grade 1 or 2	Maintain capecitabine. For intolerable grade 2 toxicity, may omit dose of capecitabine until resolved to CTCAE Grade ≤ 1, consideration of 25% dose reduction at investigator's discretion.
Grade 3	Omit capecitabine until resolved to CTCAE Grade ≤ 1, then reduce by 25%.
Grade 4	Discontinue study treatment.

Worst Toxicity CTCAE v4.0 Grade (unless otherwise specified)	Recommended Dose Modifications to capecitabine any time during a cycle of therapy
OTHER ADVERSE EVENTS	
Grade 1 or 2	Maintain capecitabine. For intolerable grade 2 toxicity, may omit dose of capecitabine until resolved to CTCAE Grade ≤ 1, consideration of 25% dose reduction at investigator's discretion.
Grade 3	Omit capecitabine until resolved to CTCAE Grade ≤ 1, then reduce by 25%.
Grade 4	Discontinue study treatment.

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NOTE: All of the above are general guidelines. **The investigator may omit a 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.**

NOTE: If a patient requires a dose delay of > 21 consecutive days (from the time of due scheduled cycle initiation; i.e. > 42 days from previous cycle initiation) of capecitabine then the patient must be discontinued from the study treatment.

NOTE: Patients who discontinue from the study for a study-related adverse event or an abnormal laboratory value must be followed approximately once a week for 3 weeks and subsequently approximately at 3-week intervals, until resolution or stabilization of the event, whichever comes first, unless stated otherwise.

5.3.3 Supportive Care

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

5.3.3.2 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.

5.3.3.3 Appropriate supportive measures for diarrhea should include Loperamide and/or Diphenoxilate/atropine, and should be implemented immediately to prevent dehydration.

5.3.3.4 A specific antiemetic regimen is at the discretion of the treating physician, provided adequate control is achieved.

5.3.3.5 Patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy should have their anticoagulant response (INR or prothrombin time) monitored closely with great frequency and the anticoagulant dose should be adjusted accordingly.

5.3.3.6 Patients with certain homozygous or certain compound heterozygous mutations in the DPD gene that result in complete or near complete absence of DPD activity are at increased risk for acute early-onset of toxicity and severe, life-threatening, or fatal adverse reactions caused by

capecitabine (e.g., mucositis, diarrhea, neutropenia, and neurotoxicity). Patients with partial DPD activity may also have increased risk of severe, life threatening, or fatal adverse reactions caused by capecitabine. Withhold or permanently discontinue capecitabine based on clinical assessment of the onset, duration and severity of the observed toxicities in patients with evidence of acute early-onset or unusually severe toxicity, which may indicate near complete or total absence of DPD activity. No capecitabine dose has been proven safe for patients with complete absence of DPD activity. There is insufficient data to recommend a specific dose in patients with partial DPD activity as measured by any specific test.

5.3.3.7 Capecitabine tablets are to be swallowed whole, with water, 30 minutes after a meal. Tablets should not be cut or crushed. Dose escalations of capecitabine after dose reductions for safety are not permitted. Missed capecitabine doses beyond 3 hours of regular intake time should not be taken. In case of vomiting after capecitabine ingestion, dose should not be replaced.

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5.4 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 (from the time of due scheduled cycle initiation; i.e. within 6 weeks from previous cycle initiation). 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).

5.4.1 Cisplatin and Carboplatin dose reduction guidelines

	Starting dose (100%)	**1st dose reduction (80%)**	**2nd dose reduction (60%)**
Cisplatin	75 mg/m2	60 mg/m2	45 mg/m2
Carboplatin	AUC 6	AUC 5	AUC 4

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5.4.2 Recommended Dose Modifications

Worst Toxicity CTCAE v4.0 Grade (unless otherwise specified)	**Recommended Dose Modifications to cisplatin any time during a cycle of therapy**	**Recommended Dose Modifications to carboplatin any time during a cycle of therapy**
BLOOD AND LYMPHATIC SYSTEM DISORDER		
Anemia		
Grade 1 (Hgb < LLN-10.0 g/dL)	Maintain dose level.	Maintain dose level.
Grade 2 (Hgb < 10.0 g/dL - 8.0 g/dL)	Maintain dose level.	Maintain dose level.
Grade 3 (Hgb < 8.0 g/dL); transfusion	Maintain dose level.	Maintain dose level.

Worst Toxicity CTCAE v4.0 Grade (unless otherwise specified)	Recommended Dose Modifications to cisplatin any time during a cycle of therapy	Recommended Dose Modifications to carboplatin any time during a cycle of therapy
indicated		
Grade 4 (Life threatening consequences; urgent intervention indicated); related to study drugs	Discontinue study treatment.	Discontinue study treatment.
ANC decreased (Neutropenia)		
Grade 1 (ANC < LLN - 1.5 x 10^9/L)	Maintain dose level.	Maintain dose level
Grade 2 (ANC < 1.5 - 1.0 x 10^9/L)	Maintain dose level.	Maintain dose level
Grade 3 (ANC < 1.0 - 0.5 x 10^9/L)	Omit dose of cisplatin until resolved to CTCAE Grade ≤ 2. Then: - If resolved in ≤ 7 days, then maintain dose level - If resolved in > 7 days, then maintain dose level and consider prophylactic growth factor support per ASCO guidelines - If second occurrence, then ↓ 1 dose level for subsequent cycles.	Omit dose of carboplatin until resolved to CTCAE Grade ≤ 2. Then: - If resolved in ≤ 7 days, then maintain dose level - If resolved in > 7 days, then maintain dose level and initiate prophylactic growth factor support per ASCO guidelines - If second occurrence, then ↓ 1 dose level for subsequent cycles.
Grade 4 (ANC < 0.5 x 10^9/L)	Omit dose of cisplatin until resolved to CTCAE ≤ Grade 2, then ↓ 1 dose level; additionally, consider prophylactic growth factor support per ASCO guidelines.	Omit dose of carboplatin until resolved to CTCAE ≤ Grade 2, then ↓ 1 dose level; additionally, consider prophylactic growth factor support per ASCO guidelines.
Febrile neutropenia		
Grade 3 (ANC < 1.0 x 10^9/L, single temperature of > 38.3°C or a sustained temperature of ≥ 38.0°C)	Omit dose of cisplatin until resolved to CTCAE Grade ≤ 2, and no fever, then: - If resolved by ≤ 7 days, then ↓ 1 dose level and consider prophylactic growth factor support per ASCO guidelines. - If not resolved within 7 days despite appropriate management including full clinically indicated course of antibiotics, if indicated, discontinue patient from study treatment.	Omit dose of carboplatin until resolved to CTCAE Grade ≤ 2, and no fever, then: - If resolved by ≤ 7 days, then ↓ 1 dose level and consider prophylactic growth factor support per ASCO guidelines. - If not resolved within 7 days despite appropriate management including full clinically indicated course of antibiotics, if indicated, discontinue patient from study treatment.
Grade 4	Discontinue study treatment.	Discontinue study treatment.
Platelet count decreased (Thrombocytopenia)		
Grade 1 (PLT < LLN - 75 x 10^9/L)	Maintain dose level	Maintain dose level
Grade 2 (PLT < 75 - 50 x 10^9/L)	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 (PLT < 50 - 25 x 10^9/L)	Omit dose of cisplatin until resolved to CTCAE Grade ≤ 1, then - If resolved in ≤ 7 days, then then ↓ 1 dose level. - If resolved in > 7 days, then discontinue study treatment.	Omit dose of carboplatin until resolved to CTCAE Grade ≤ 1, then - If resolved in ≤ 7 days, then then ↓ 1 dose level. - If resolved in > 7 days, then discontinue study treatment.
Grade 4 (PLT < 25 x 10^9/L)	Discontinue study treatment.	Discontinue study treatment
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	Omit dose of carboplatin until no further bleeding has been observed. Continuation of study

Worst Toxicity CTCAE v4.0 Grade (unless otherwise specified)	Recommended Dose Modifications to cisplatin any time during a cycle of therapy	Recommended Dose Modifications to carboplatin any time during a cycle of therapy
	treatment may be considered.	treatment may be considered.
INVESTIGATIONS – RENAL		
Serum creatinine		
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level.	Maintain dose level
Grade 2 (> 1.5 - 3.0 x ULN)	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 > 7 days, then ↓ 1 dose level.	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 > 7 days, then ↓ 1 dose level.
Grade ≥ 3 (> 3.0 x ULN)	Discontinue study treatment.	Discontinue study treatment
INVESTIGATIONS – HEPATIC		
Blood Bilirubin [b] (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.		
Grade 1 (> ULN – 1.5 x ULN)	Maintain dose level.	Maintain dose level
Grade 2 (>1.5 – 3.0 x ULN)	Omit dose of cisplatin until resolved to CTCAE Grade ≤ 1, then - If resolved in ≤ 7 days, then maintain dose level. - If resolved in > 7 days, then ↓ 1 dose level.	Omit dose of carboplatin until resolved to CTCAE Grade ≤ 1, then - If resolved in ≤ 7 days, then maintain dose level. - If resolved in > 7 days, then ↓ 1 dose level.
Grade 3 (> 3.0 – 10 x ULN) or higher	Discontinue study treatment. **NOTE:** 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.	Discontinue study treatment. **NOTE:** 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.
AST or ALT		
Grade 1 and 2 (up to 5.0 x ULN)	Maintain dose level.	Maintain dose level.
Grade 3 (> 5.0 - 20.0 x ULN)	Omit dose of cisplatin until resolved to CTCAE Grade ≤ 1, then - If resolved in ≤ 7 days, then maintain dose level. - If resolved in > 7 days, then ↓ 1 dose level.	Omit dose of carboplatin until resolved to Grade ≤1, then - If resolved in ≤ 7 days, then maintain dose level - If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (> 20.0 x ULN)	Discontinue study treatment.	Discontinue study treatment

Worst Toxicity CTCAE v4.0 Grade (unless otherwise specified)	Recommended Dose Modifications to cisplatin any time during a cycle of therapy	Recommended Dose Modifications to carboplatin any time during a cycle of therapy
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		
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.
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.

Worst Toxicity CTCAE v4.0 Grade (unless otherwise specified)	Recommended Dose Modifications to cisplatin any time during a cycle of therapy	Recommended Dose Modifications to carboplatin any time during a cycle of therapy
Grade 4	Discontinue study treatment.	Discontinue study treatment.
GENERAL DISORDERS		
Fatigue		
Grade 1 or 2	Maintain dose level.	Maintain dose level.
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.
Grade 2 (Intervention or infusion interruption indicated; responds promptly to symptomatic treatment [e.g., antihistamines, NSAIDS, narcotics]; prophylactic medications indicated for ≤24 hrs)	- 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.
Grade 3 Prolonged [e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae [e.g., renal impairment, pulmonary infiltrates])	- Discontinue infusion immediately - Treat per institutional guidelines. - Discontinue patient from study.	- Discontinue infusion immediately - Treat per institutional guidelines. - Discontinue patient from study.

Worst Toxicity CTCAE v4.0 Grade (unless otherwise specified)	Recommended Dose Modifications to cisplatin any time during a cycle of therapy	Recommended Dose Modifications to carboplatin any time during a cycle of therapy
Grade 4 (Life-threatening; urgent intervention indicated)	- Discontinue infusion immediately - Treat per institutional guidelines. - Discontinue patient from study.	- Discontinue infusion immediately - Treat per institutional guidelines. - Discontinue patient from study.
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 to CTCAE Grade ≤ 1.	
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 a 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.**		
NOTE: If a patient requires a dose delay of > 21 consecutive days (from the time of due scheduled cycle initiation; i.e. > 42 days from previous cycle initiation) of platinum agent then the patient must be discontinued from the study treatment.		
NOTE: Patients who discontinue from the study for a study-related adverse event or an abnormal laboratory value must be followed approximately once a week for 3 weeks and subsequently approximately at 3-week intervals, until resolution or stabilization of the event, whichever comes first, unless stated otherwise.		

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5.4.3 Supportive Care

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

5.4.3.2 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.

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

5.4.3.4 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.

5.4.3.5 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.

5.4.3.6 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 anti-emetic such as metoclorpramide 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

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5.5 PRO Administration

The PRO assessment includes health-related quality of life (HRQL), neurotoxicity, ovarian function, and adherence. The PROs assessment will be administered at the following time points:

FBSI (Arms B and C), NTx (Arm B) will be assessed at:

- Baseline,
- Day 1, Cycle 3,
- 6 months after start of study chemotherapy
- 15 months after the start of chemotherapy.

Ovarian function (Arms B and C) will be assessed at:

- Baseline
- 15-months post study chemotherapy start

Medication Adherence Scale (Arm C) will be assessed at:

- Day 1, Cycle 3,
- Day 1, Cycle 6

The timing of these assessments corresponds to standard clinic office visits of routine care, and assessments will be made prior to clinician visits when possible. It is estimated that the overall attrition rate is about 10% by the end of chemotherapy, 12% by 6 months after the start of chemotherapy and 20% by 15 months after the start of chemotherapy for the PROs assessment in both arms.

All participants (*n*=775) enrolled on the main study are potentially eligible for the HRQL PRO assessments, although only *n* = 362 are required to power the primary PRO objective. Thus, 362 participants will be recruited for the PRO assessments Any participants who take the PROs surveys at more than 1 time-point will be eligible for analysis.

Participants who develop recurrent disease during the follow-up period will be assessed (although they would likely go on to further therapy and/or have different concerns, these can be better addressed statistically if we have data on which to base assumptions.)

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5.5.1 Instruments to be Administered

We would anticipate these survey items would require between 10-20 minutes per time-point, for a maximum of 1 hour(s) of participant time over the entire course of the study.

Table 5.5.1. Overall TIMELINE and NUMBER OF QUESTIONS on Patient PRO Questionnaires

Timing of Assessment	**Measure**			
	Medication Adherence Scale^	NTx[&]/FBSI	Ov. Function*	Total
Baseline/On Study	0	27	8	33
Before Cycle 3 chemotherapy (Day 1, Cycle 3)	8	27	0	37
Before Cycle 6 chemotherapy (Day 1, Cycle 6)	8	0	0	8[^]
6 months after the start chemotherapy	0	27	0	27
15 months after the start of chemotherapy	0	27	5	33

^ Only patients on the capecitabine arm.
& Only patients on the platinum arm
*Women age < 55 yo only would answer 4 menstrual questions.

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5.5.2 Survey Administration Instructions

PRO assessment time-points correspond to the standard clinic office visits for routine care. Assessments will be done prior to the clinician visit when possible. The questionnaires should be administered at the time points listed above. The patient should be instructed to respond to the questionnaires in terms of her experience during the timeframe specified on each questionnaire. The patient should be asked to read

the instructions at the beginning of each questionnaire and complete all the items. It is permissible to assist the patient with the completion of the questionnaires as long as the staff person does not influence the patient's responses.

The questionnaires should be reviewed by the protocol nurse or research coordinator as soon as the patient completes them to ensure all items were marked appropriately. If more than one answer was marked, the patient should be asked to choose the answer which best reflects how she is feeling. If a question was not answered, the patient should be asked if she would like to answer it. The patient should always have the option to refuse. If the patient refuses, it should be indicated on the questionnaire that she declined to answer the item. If the patient cannot complete a questionnaire, or if the patient refuses to complete the questionnaire, the reason should be noted according to the instructions in the **EA1131** Forms Completion Guidelines.

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5.6 Patient Reported Outcome Measures: Tobacco Use Assessment

5.6.1 Assessments

Assessments will be captured directly from the participants using the EASEE-PRO portal. When patients consent to participate, they will be asked to provide a contact email address and that address along with their registration information will be sent directly from the parent trial's registration system to EASEE-PRO, and the patient will be automatically registered into EASEE-PRO for participation. To activate their account for self-directed web entry of surveys, the system will send an activation message to the contact email address that will explain how to activate their account for self-directed web entry of surveys. After their account is activated, the patient will be able to complete questionnaires using a secure browser interface from any web enabled computer, tablet, or mobile device.

The Core and Extension C-TUQ items will be assessed, together with patient-reported physical and psychological symptoms (See Table 2). Specifically, these items will be administered using the EASEE-PRO system described in the companion EA NCORP application. The advantage of our virtual electronic data capture system is that our proposed assessments will not be limited to, or dependent upon, patient trial visits. Confidential and potentially stigmatizing information can be provided without requiring direct contact with the care team.

The selected Core and Extension C-TUQ items (from categories of Basic Tobacco Use Information, Tobacco Use in Relation to Cancer Diagnosis and Treatment, Smoking Cessation/Cessation Products/Assistance Methods, Use of Other Products, and Second-Hand Smoke Exposure) will be assessed. The 4-item Short Form PROMIS® for anxiety and depression, the Lung Cancer Stigma Scale, and six symptom items (general pain, fatigue, nausea, cough, sleep difficulties, shortness of breath) from FACIT (Functional Assessment of Chronic Illness Therapy) together with modifications of these same six questions to address the degree of bother associated with each symptom will be administered as well. Additionally, we will ask

participants' perceptions of how smoking improves or worsens each of the six-symptom experience. All these items will be compiled into Survey of Tobacco Use (STU). Detailed information on various measures is outlined in Appendix VI.

Contents and Corresponding Questions in Survey of Tobacco Use (STU)

Dimension	Source of Measures	Baseline STU	Follow-up STU
Basic Tobacco Use Information	C-TUQ	Q1 – Q5	Q1 – Q2
Tobacco Use in Relation to Cancer Diagnosis and Treatment	C-TUQ	Q6 – Q7	Q3
Smoking Cessation, Cessation Products, and Assistance Methods	C-TUQ	Q8 – Q13	Q4 – Q9
Use of Other Products	C-TUQ	Q14	Q10
Second-Hand Smoke Exposure	C-TUQ	Q15 – Q16	Q11 – Q12
Psychological Symptoms	PROMIS Lung Cancer Stigma Scale	Q17 – Q18	Q13 – Q14
Physical Symptoms	FACIT	Q19	Q15
Sociodemographics		Q20 – 21	

NOTE: In order to minimize ambiguity and assure that patients are oriented to answer appropriately, the specific phrasing of items may vary depending specific cancer type and treatment.

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5.6.2 Assessment Schedule

Survey of Tobacco Use will be administered at the following time points:

- at baseline (trial enrollment)
- at 3 months follow-up from study registration
- at 6 months follow-up from study registration

5.7 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.
- Concurrent 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.

5.8 Duration of Follow-up

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For this protocol, all patients (on all arms A, B, and C), 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

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

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

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

Date of randomization to date of death from any cause.

7. Study Parameters

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7.1 Therapeutic Parameters

NOTE: A window of +/- 3 working days is allowed for all below procedures **unless otherwise specified in the calendar itself**, to account for holidays, vacation, and scheduling issues.

	STEP 0-Screening	STEP 1-Randomization								
	All Patients		For Arms B and C							All Patients
	Within 8 weeks prior to Screening	Within 2 weeks prior to Randomization	Day 1 of Each Treatment Cycle[1]	Day 1 Cycle 1	Day 1 Cycle 3	Day 1 Cycle 6	End of Treatment (28 ±7 working days) post treatment discontinuation)[13]	6 months (±4 weeks) after chemotherapy initiation	15 months (±6 weeks) after chemotherapy initiation	Arm A: post randomization to 10 years Arm B and C: 6 months to 10 years from chemotherapy initiation[7]
CLINICAL EVALUATIONS										
Demographics	X									
History and Physical	X[1]	X[1]	X				X			X
Vital Signs and Weight		X[1]	X				X			
Height		X								
ECOG Performance Status	X[1]	X[1]	X				X			
Toxicity Assessments			X				X			
Concomitant Medications Assessments			X				X			
Non-Protocol Anti-Cancer Medications Assessments			X							X[11]
FBSI PRO				X	X			X	X	
Medication Adherence Scale PRO[15]					X	X				
NTx PRO[14]				X	X			X	X	
Ov Function PRO[16]				X					X	

	STEP 0-Screening	STEP 1-Randomization							
	All Patients		For Arms B and C						All Patients
	Within 8 weeks prior to Screening	Within 2 weeks prior to Randomization	Day 1 of Each Treatment Cycle[1]	Day 1 Cycle 1	Day 1 Cycle 3	Day 1 Cycle 6	End of Treatment (28 ±7 working days) post treatment discontinuation)[13]	6 months (±4 weeks) after chemotherapy initiation	15 months (±6 weeks) after chemotherapy initiation	Arm A: post randomization to 10 years Arm B and C: 6 months to 10 years from chemotherapy initiation[7]
Tobacco Use Assessment PROs[17]	See Section 5.6									
LABORATORY/ RADIOLOGICAL ASSESSMENTS										
Serum or Urine Pregnancy Test[4]		X								
CBC with Differential[1, 2]	X	X	X[10]				X			
Complete Metabolic Panel (CMP)[1, 3]	X	X	X[10]				X			
INR[1,12,15]	X	X	X[10,12,15]							
Imaging Tests[9]	Not mandatory, but recommended at any time as a standard of care procedure, at the investigator's discretion if clinical concerns, to rule out a locoregional or distant recurrence									
TREATMENT ADMINISTRATION										
Platinum chemotherapy administration[5,14]			X[5,14]							
Capecitabine administration[15]			X[15]							
MANDATORY BIOLOGICAL SAMPLE SUBMISSIONS[6,8,18]										
Tumor Tissue – submit to EA CBPF	X									
Peripheral Blood (two 10mL Streck Cell-Free DNA tubes) – submit to Epic Sciences				X				X		

	STEP 0-Screening	STEP 1-Randomization							
	All Patients		For Arms B and C						All Patients
	Within 8 weeks prior to Screening	Within 2 weeks prior to Randomization	Day 1 of Each Treatment Cycle[1]	Day 1 Cycle 1	Day 1 Cycle 3	Day 1 Cycle 6	End of Treatment (28 ±7 working days) post treatment discontinuation)[13]	6 months (±4 weeks) after chemotherapy initiation	15 months (±6 weeks) after chemotherapy initiation	Arm A: post randomization to 10 years Arm B and C: 6 months to 10 years from chemotherapy initiation[7]
OPTIONAL BIOLOGICAL SAMPLE SUBMISSIONS[8,18,19]										
Peripheral Blood (two 10mL Streck Cell-Free DNA tubes) – submit to EA CBPF				X				X		

Rev. 6/16 1. Each cycle is a 3-week period of time. Total number of treatment cycles is 6 for the capecitabine arm and 4 for the platinum agents. Chemotherapy must be initiated within 6 weeks (30 working days) following randomization. CBC, chemistries and INR (**INR is only necessary for patients on warfarin that are on Arm C**) should be done ≤ 8 weeks prior to screening, ≤ 2 weeks prior to randomization, and during
Rev. Add8 treatment, it should be done within 3 days prior to each treatment cycle. Telehealth visits are acceptable as long as ECOG status, vital signs, height and weight are current (i.e. performed within 8 weeks) on Day 1 of each cycle. Additionally, treatment initiation may be delayed for up to 10 days without requiring repeat labs/ clinic visit/ clinic assessments in the following special circumstances: inclement weather, holidays, COVID-related issues, delay in drug delivery from specialty pharmacies for patients on Arm C (capecitabine), and insurance approval delays.

Rev. 6/16 2. Pre-study CBC (with differential and platelet count) includes WBC, ANC, Platelets, Hgb, and Hct or PCV

Rev. 6/16 3. All required chemistries include sodium, potassium, chloride, bicarbonate (also known as CO2 or carbon dioxide), BUN, creatinine, glucose, total bilirubin, calcium, magnesium, total protein, albumin, AST, ALT, and alkaline phosphatase.

Rev. Add8 4. For patients of childbearing potential; must be done within 2 weeks prior to randomization.

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Rev. Add8 5. Cisplatin or Carboplatin (Arm B only); per treating physician's discretion. Growth factor use is allowed per ASCO guidelines.

Rev. 2/16 6. Tumor tissue collection is mandatory and required to be submitted to the ECOG-ACRIN Central Biorepository and Pathology Facility (EA CBPF) as outlined in Section 10.2. Confirmation of receipt of tumor tissue will be forwarded to the ECOG-ACRIN Operations Office and submitting institution. The CLIA Laboratory Sample Submission Form (Appendix IV) must be submitted with the tumor tissue. Results of PAM50 analysis will not be reported to the submitting institution. Two Streck tubes of peripheral blood must be collected on all patients at the following two time points: on or before cycle 1 day 1 of protocol chemotherapy and around 6 months after protocol chemotherapy initiation.

7. Every 3 months (± 2 weeks) if patient is < 2 years from study randomization, every 6 months (± 4 weeks) if patient is 2-5 years from study randomization, every 12 months (± 6 weeks) if patient is 5-10 years from study randomization. No other specific requirements are needed if
Rev. Add8 patient is more than 10 years from study randomization. If a recurrence (locoregional or distant) occurs prior to 10 years from randomization, patient will be followed for survival (until year 10) but no other protocol procedures (clinic visits, blood collections, etc.) will be necessary.

8. All specimens submitted must be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS) as outlined in Section 10.3.

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

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10. If Baseline CBC, INR (**INR is only necessary for patients on warfarin that are on Arm C**) 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.
12. Only for patients on warfarin therapy and Arm C

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13. End of treatment visit should be scheduled 28 (+/- 7 working days) from Day 1 of last administration of platinum agent in Arm B, and 28 (+/- 7 days) from the last administered treatment dose for Arm C; regardless if patients completed treatment or if treatment was interrupted due to toxicities or other causes.
14. For Arm B (platinum chemotherapy) only
15. For Arm C (capecitabine) only
16. Women age < 55 years old only would answer 8 questions on Day 1 Cycle 1, and 5 questions 15 months after the initiation of chemotherapy.
17. Tobacco use assessment PROs will be collected using EASEE-PRO; no other EA1131 study PRO will be collected using EASEE-PRO.
18. Kits will be provided for the collection and shipment of peripheral blood specimens. See Section 10 for instructions.
19. Submit from patients who answer 'Yes' to 'I agree to provide additional samples for research' in the informed consent.

8. Drug Formulation and Procurement

Rev. 6/16 Capecitabine, cisplatin and carboplatin will be obtained commercially. For additional information, please refer to the FDA approved package insert for each drug.

Rev. 6/16 8.1 Capecitabine

8.1.1 Other Names: Xeloda®

8.1.2 Classification: capecitabine) is a fluoropyrimidine carbamate with antineoplastic activity. It is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR) which is converted to 5-fluorouracil. Capecitabine is a white to off-white crystalline powder with an aqueous solubility of 26 mg/mL at 20ºC.

8.1.3 Mode of Action: Enzymes convert capecitabine to 5-fluorouracil (5-FU) in vivo. Both normal and tumor cells metabolize 5-FU to 5-fluoro-2'-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). These metabolites cause cell injury by two different mechanisms. First, FdUMP and the folate cofactor, N5-10-methylenetetrahydrofolate, bind to thymidylate synthase (TS) to form a covalently bound ternary complex. This binding inhibits the formation of thymidylate from 2'-deoxyuridylate. Thymidylate is the necessary precursor of thymidine triphosphate, which is essential for the synthesis of DNA, so that a deficiency of this compound can inhibit cell division. Second, nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uridine triphosphate (UTP) during the synthesis of RNA. This metabolic error can interfere with RNA processing and protein synthesis.

8.1.4 Storage and Stability: Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature]. KEEP TIGHTLY CLOSED. Care should be exercised in the handling of capecitabine. Capecitabine tablets should not be cut or crushed. Procedures for the proper handling and disposal of anticancer drugs should be considered. Any unused product should be disposed of in accordance with local requirements, or drug take back programs.

8.1.5 Dose Specifics: Capecitabine will be administered at 1000 mg/m^2 twice a day, PO, on days 1 - 14 every 21 days, for a total of 6 cycles.

8.1.6 Route of Administration: oral, 30 minutes after a meal.

8.1.7 Incompatibilities: anticoagulants (warfarin), phenytoin, leucovorin, CYP2C9 substrates

8.1.8 Availability: Capecitabine is supplied as biconvex, oblong film-coated tablets for oral administration. Each light peach-colored tablet contains 150 mg capecitabine and each peach-colored tablet contains 500 mg capecitabine.

8.1.9 Side Effects:

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

8.1.9.2 Dermatologic: Hand-foot sd, dermatitis, nail disorders.

8.1.9.3 Gastrointestinal: Diarrhea, nausea, vomiting, dyspepsia, anorexia.

8.1.9.4 General: fatigue, myalgias

8.1.9.5 Cardiac: edema.

8.1.9.6 Hepatic: Elevated AST and ALT, hyperbilirrubinemia.

8.1.9.7 Neurologic: paresthesia, headache, dizziness, insomnia.

8.1.9.8 Other: eye irritation

8.1.10 Nursing/Patient Implications

- Assess labs prior to administration (esp. CBC, platelet count, BUN, Cr.).
- Observe carefully for signs of severe diarrhea, mucocutaneous toxicities, neurotoxicities, cardiotoxicities.

8.1.11 References

- NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.
- OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html
- American Society of Health-System Pharmacists. ASHP Guidelines on Handling Hazardous Drugs: Am J Health-Syst Pharm. 2006;63:1172-1193.
- Polovich M., White JM, Kelleher LO (eds). Chemotherapy and biotherapy guidelines and recommendations for practice (2nd ed.) 2005. Pittsburgh, PA: Oncology Nursing Society

8.2 Cisplatin

8.2.1 Other Names: Platinol®

8.2.2 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.

8.2.3 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.

8.2.4 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.

8.2.5 Dose Specifics: Cisplatin will be administered at 75 mg/m^2 IV on day 1 every 21 days, for a total of 4 doses (3 week-cycles).

8.2.6 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.

8.2.7 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.

8.2.8 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, pipercallin/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.

8.2.9 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).

8.2.10 Side Effects:

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

8.2.10.2 Dermatologic: Alopecia (uncommon).

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

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

8.2.10.5 Hepatic: Elevated AST and ALT.

8.2.10.6 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.

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

8.2.11 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.

8.2.12 References

- Ries F, Klastersky J. Nephrotoxicity induced by cancer chemotherapy with special emphasis on cisplatin toxicity. Am J Kidney Dis 1986; 8: 368-379.
- Hutchison FN, et al. Renal salt wasting in patients treated with cisplatin. Ann Intern Med 1988; 108: 21-25.
- Hansen SW, et al. Long-term neurotoxicity in patients treated with cisplatin, vinblastine and bleomycin for metastatic germ cell cancer. J Clin Oncol 1989; 7:1457-1461.
- Eeles R, et al. Lhermitte's sign as a complication of cisplatin-containing chemotherapy for testicular cancer. Cancer Treat Rep 1986; 70: 905-907.
- Schilsky RL, et al. Persistent hypomagnesemia following cisplatin chemotherapy for testicular cancer. Cancer Treat Rep 1982; 66: 1767-1769.
- Schaefer SD, Post JD, Close LG, et al. Ototoxicity of low- and moderate-dose cisplatin. Cancer 1985; 56: 1934-1939.
- Wilding G, et al. Retinal toxicity after high-dose cisplatin therapy. J Clin Oncol 1985; 3: 1683-1689.

8.3 Carboplatin

8.3.1 Other Names: Paraplatin®

8.3.2 Classification: Carboplatin (carboplatin injection) (platinum, diammine[1,1-cyclobutanedicarboxylato(2-)-O,O′]-, (SP-4-2)) is platinum coordination compound, used as an anti-neoplastic 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.

8.3.3 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.

8.3.4 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 D_5W. Stability has also been demonstrated for dilutions in D_5W 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.

8.3.5 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: $$\frac{140 - \text{Age in years}) \times \text{Actual Body Weight in kg}}{72 \times \text{Serum Creatinine (mg/dL)}}$$

Females: Estimated creatinine clearance for males × 0.85

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

8.3.6 Preparation: Manufacturer's labeling states solution can be further diluted to concentrations as low as 0.5 mg/mL in NS or D_5W; however, most clinicians generally dilute dose in either 100 mL or 250 mL of NS or D_5W. 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.

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

8.3.8 Incompatibilities: Amphotericin B chloesteryl 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.

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

8.3.10 Side Effects:

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

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

8.3.10.3 Dermatologic: Rash, urticaria.

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

8.3.10.5 Neurologic: rarely Peripheral neuropathy.

8.3.10.6 Renal: Elevations in serum creatinine, BUN; electrolyte loss (Na, Mg, K, Ca).

8.3.10.7 Other: Pain, asthenia.

8.3.11 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.

8.3.12 References

- Calvert AH, et al. Carboplatin dosage: Prospective evaluation of a simple formula based on renal function. J Clin Oncol 1989; 7: 1748-1756.
- Woloschuk DMM, Pruemer JM, Cluxton RJ. Carboplatin: A new cisplatin analog. Drug Intell Clin Pharm 1988; 22: 843-849.
- Christian MC. Carboplatin. In: Principles and Practice of Oncology, PPO Updates 1989; 3(11): 1-16.

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9. Statistical Considerations

Three changes are made to the study design in the Amendment #7:

- Basal-like subtype is no longer a stratification factor: Current data (ongoing monitoring) suggest that > 75% of the residual tumors tested thus far are basal subtype. Removing basal-like subtype as a stratification factor will speed up randomization and therefore will improve accrual, also allowing investigators who wish to pursue RT *after* chemotherapy completion to do so (this is particularly important for patients that wish to subsequently enroll in the phase III S1418 protocol). Patients will be randomized to arm B or arm C as long as meeting all eligibility criteria listed in Section 3 and the EA Operations Office receives confirmation of receipt of tumor tissue from EA CBPF. The basal-like subtype status will be identified after randomization, and some patients may have assay failure and their basal-like subtype status will be unknown. We expect about 7% of patients will have assay failure based on data available as of June 24, 2019 (24 out of 365 patients screened have had assay failure). This subgroup of patients with unknown disease subtype will be randomized to arm B or arm C, and they will be analyzed separately from patients with known disease subtypes (basal-like vs. non-basal like) as an exploratory objective of the study. The total sample size is updated (775 vs 750) to reflect the impact of removing basal-like subtype from the stratification factor list (i.e.., about 7% of patients randomized will have assay failure) and the observed slightly higher proportion of basal-like disease in the patients (observed vs expected: 78% vs 75%).
- The futility monitoring rule based on Jennison and Turnbull repeated confidence interval (RCI) method is changed to be more conservative: The rule now is that if the lower boundary of the two-sided 95% RCI for the observed hazard ratio is greater than 0.754 (i.e., the alternative hypothesis) for arm B/arm C and the conditional power of rejecting HR>=1.154 (Ho) when HR=0.754 (Ha) is less than 10%, then the trial would be stopped due to futility.
- Correlative biomarker blood studies about CTC (secondary correlative objective) added to the protocol.

9.1 Study Objectives

The primary objective of this multi-institutional, open-label, randomized phase III study is to compare the two treatment arms, platinum and capecitabine, with respect to invasive disease-free survival (IDFS) 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), toxicity profile and PRO. 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.

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9.2 Study Design

Based on the literature, the benefit of platinum agent therapy in TNBC after NAC, if any, is expected to be predominantly in the basal-like subtype. Hence, the primary population for the primary endpoint is the basal-like subtype in this trial. After screening, tumor tissue will be sent to EA CBPF for molecular profile via PAM50 analysis by digital mRNA quantitation (NanoString) in the residual surgical specimen to identify its molecular subtype. At the time when the trial was developed, we expected at least 75% of the residual post-NAC TNBC screened to fall within the basal-like subtype. Based on data available as of the 2019 Spring DSMC meeting, about 78% of the patients randomized to arms B and C fall in the basal-like subtype. We will use this proportion in the below sample size calculation. In addition, about 7% of patients screened had assay failure and their intrinsic subtype is unknown. We assume 7% of patients will have assay failure in the remaining patients as well.

After EA CBPF sending the confirmation of receipt of tumor tissue to EA Operations Office, all eligible patients will then be randomized according to the permuted block algorithm with a 1:1 randomization ratio to platinum and capecitabine 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).

Since platinum is considered less toxic than capecitabine and also platinum is expected to be better than capecitabine on improvement of IDFS in patients with basal-like TNBC, a non-inferiority design with superiority alternative (a hybrid design[33] is preferred for this trial). The primary analysis for the primary endpoint will test the null hypothesis of inferiority of platinum. The sample size would be calculated based on a modest superiority alternative hypothesis. If the hypothesis of inferiority of platinum is rejected in the primary analysis, the secondary hypothesis of no difference vs. superiority of platinum will be tested. Due to the closed testing procedure, no multiple-comparison adjustment is required for the two hypothesis tests[34]

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 16 TNBC patients (16*0.93*0.78=12 patients with basal-like subtype) per month in our study.

9.2.1 Non-inferiority test of platinum

9.2.1.1 Sample Size and Accrual

Based on the review (by Von Minckwicz et al.(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.(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.(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 would be 48 months (i.e., 4-year DFS rate of 50%) for the study patients if receiving no chemotherapy after surgery, with a median OS of 60 months (i.e., 5-year OS rate of 50%). Based on the CREATE-X trial, the 4-year DFS rate was 67% in the 296 TNBC patients when receiving capecitabine (HR=0.58, 95% CI 0.39 – 0.87). Therefore, a conservative estimate of the 4-year IDFS rate would be 67% (0.5^0.58=0.67) for the capecitabine arm in patients with basal-like TNBC disease in this trial.

The null hypothesis for testing non-inferiority of platinum is defined as that the hazard ratio (HR) for platinum/capecitabine ≥ 1.154 (i.e., HR of 1.154 is used as the non-inferiority margin). This corresponds to a 4-year IDFS rate of ≤63% on platinum if the 4-year IDFS rate is 67% on capecitabine arm. With a total accrual of 562 patients (281 on each arm) and full information of 196 IDFS events, this non-inferiority test would have about 83% power, with a one-sided 0.025 significance level, to reject the null hypothesis of inferiority of platinum under the alternative hypothesis of HR=0.754 for platinum/capecitabine, i.e., the 4-year IDFS rate for platinum is expected to be 73.9%.

With an average annual accrual rate of 144 patients with basal-like TNBC, about 3.9 years of accrual will be needed with an additional 3 years of follow up to reach the expected number of IDFS failures. The final analysis for IDFS comparison in the basal-like TNBC patients is expected to be conducted at about 7.5 years (3.9 years of accrual + 3 years of follow up + 0.5 years of data collection and cleaning) after study activation.

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We expect at least 78% of the residual post-NAC TNBC screened to fall within the basal-like subtype within the patients with successful assay, and about 7% of patients will have assay failure. Hence, at least 775 patients (=562/0.78/0.93) with residual TNBC at the time of surgery will be enrolled to obtain the 562 patients with basal-like TNBC.

9.2.1.2 Interim analysis plan

The study will be monitored by the ECOG-ACRIN Data and Safety Monitoring Committee (DSMC) according to the principals of group-sequential methods. The first interim analysis will be performed at the first DSMC meeting when

at least 25% of the total information has been reported. Since 196 IDFS failures are required as the total information under the alternative hypothesis, the first interim analysis is estimated to take place after 49 IDFS failures have occurred, which corresponds to 2.9 years after activation of the study in calendar time, under the accrual and failure rate assumptions mentioned above. 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.

The Jennison and Turnbull repeated confidence interval (RCI) methodology[35] will be used to monitor the trial in favor of non-inferiority. At each interim analysis, a two-sided 95% RCI on the log hazard ratio (logHR) for platinum/capecitabine will be computed using partial likelihood estimation method, and the critical value for each interim analysis (see Table 1) will be based on Lan-DeMets error spending rate function(43) corresponding to the truncated version of O'Brien-Fleming boundaries(44) with an overall one-sided type I error rate of 0.025. The partial likelihood estimator of logHR and its standard error will be derived from stratified Cox proportional hazard model, where the patients will be stratified using the same factors as the randomization (i.e., clinical stage at diagnosis, residual cancer burden after NAC, planned platinum agent, anthracycline exposure I the neoadjuvant setting, and administration of radiotherapy). The confidence interval for the HR will be reported by exponentiating the logHR intervals. When the upper confidence limit for the HR is less than 1.154 (the pre-defined non-inferiority margin) at any interim analysis or final analysis, then the null hypothesis of inferiority of platinum will be rejected, and we would conclude that the platinum therapy is non-inferior to capecitabine in terms of IDFS. The primary hypothesis of the trial (i.e., non-inferiority of platinum) is then answered, and superiority test of platinum (i.e., secondary hypothesis of the trial) would be then performed (see Section 9.2.2). If this occurs at an interim analysis, accrual to the study will continue to allow a definitive answer to the secondary hypothesis test (superiority of platinum), i.e., the rejection of null hypothesis for the non-inferiority test of platinum will not result in early termination of the trial.

Table 1 shows expected timing of interim analyses and critical values for early stopping monitoring under the alternative hypothesis of HR=0.754 for platinum/capecitabine. 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.

Table 1: Expected timing of interim analyses and critical values under the alternative hypothesis of HR=0.754 (i.e., 4-year IDFS rate of 67% on capecitabine vs. 73.9% on platinum)

Repeated analysis	Time from study activation (years)	Information time (%)	Number of Failures under alternative	Upper boundary (critical value for two-sided 95% RCIs)
1	2.9	0.25	49	3.2905
2	3.4	0.34	67	3.2905
3	3.9	0.44	87	3.2905
4	4.4	0.55	107	2.9084
5	4.9	0.65	126	2.6218
6	5.4	0.74	145	2.4376
7	5.9	0.83	162	2.2980
8	6.4	0.92	179	2.1870
Final	6.9	1.00	196	2.0962

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In addition to efficacy monitoring for the non-inferiority test, the trial will be monitored to allow early stopping for inferiority of platinum based on conditional power and the above RCI methods. At each interim analysis, the conditional power of the log rank test for the primary comparison at a one-sided type I error rate of 0.025 will be computed using simulation, and if the conditional power of the assigned treatment analysis is < 10% and the lower boundary of the above two-sided 95% RCI is greater than 0.754 for arm B/arm C (the alternative hypothesis), then the trial would be stopped due to futility unless there is other supporting evidence for non-inferiority of platinum at the time. We would conclude that the trial fail to reject the null hypothesis of inferiority of platinum, and platinum is inferior to capecitabine. If the conditional power is > 10% or the lower boundary of the 95% RCI is below 0.754, the trial would continue.

9.2.2 Superiority test of platinum

If inferiority of platinum is rejected at an interim analysis or the final analysis, the primary hypothesis is answered, and a superiority test of platinum (i.e., the secondary hypothesis) is then performed at an overall one-sided type I error rate of 0.025, using the same RCIs used for the above non-inferiority test. For the superiority test, the null hypothesis is that HR=1 for platinum/capecitabine. Assuming the alternative hypothesis is HR=0.653 for platinum/capecitabine for the superiority test, with 562 basal-like TNBC patients and total information of 196 IDFS events, there would be at least 82% power to detect a 34.7% reduction in the IDFS failure hazard rate using stratified log rank test with an overall one-sided type I error rate of 0.025, if the trial continues regardless of the results of non-inferiority test. This reduction in IDFS failure hazard rate corresponds to an

improvement in 4-year IDFS rate from 67% on the capecitabine arm[5,38] to 77% on the platinum arm, under the assumption of exponential distribution of IDFS.

At any interim analysis or the final analysis, when the upper confidence limit for the HR is less than 1, the null hypothesis of no difference between the two arms would be rejected and we would conclude that platinum is superior to capecitabine in improving IDFS in patients with basal-like TNBC. If this occurs at an interim analysis, DSMC may consider stopping the trial early for efficacy. If the RCI for the HR does not include the target alternative HR of 0.653 for platinum/capecitabine, the study may be stopped early for lack of benefit (i.e., fail to reject the null hypothesis for the superiority test of platinum).

In summary, if, at any of the interim analyses, the null hypotheses for both non-inferiority test of platinum (i.e., HR ≥ 1.154) and superiority test of platinum (i.e., HR=1) are rejected, the DSMC may consider stopping the trial early. If only the inferiority of platinum is rejected and the superiority test of platinum dose not cross the stopping boundary, the trial will continue. In this case, RCIs would be computed using the same upper boundary listed in Table 1, but the stopping rules would be shifted to the equality vs. superiority difference. If criteria for early stopping (either for efficacy or for futility) are not met for the non-inferiority test, the final analysis for the non-inferiority test will be performed when IDFS event has occurred in 196 patients. If inferiority of platinum is rejected at the final analysis, superiority test would then be performed at the final analysis.

For the IDFS endpoint, the primary analysis will compare treatment groups defined by the randomized treatment assignment (intent-to-treat analysis, ITT). A secondary analysis will be performed comparing groups defined by treatment received. The results will be creditable only if the two analyses are reasonably consistent.

Although one-sided type I error rate of 0.025 is used for hypothesis test in the study design, two-sided 95% RCIs will be used in the DSMC and final reports for reporting purpose.

9.3 Secondary Endpoints

9.3.1 Overall Survival

Overall survival (OS) is an important secondary endpoint in the study, and only superiority test of platinum is planned for OS. With a total accrual of 562 basal-like patients, total information of 240 deaths is needed to give about 80% power to detect a 30% reduction (i.e., HR=0.7 for platinum/ capecitabine 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 5-year OS from 66% on capecitabine arm to 75% on platinum arm, under the assumption of exponential distribution of OS. The final analysis for OS is expected to occur at about 10.5 years after study activation (3.9 years of accrual + 6.1 years of follow up+0.5 years of

data collection and cleaning, i.e., 3 years after IDFS final analysis) to reach the expected number of OS failures. The OS comparison will be intent-to-treat analysis of all randomized patients regardless of eligibility status. A secondary analysis of OS will be conducted in eligible patients.

9.3.2 Toxicity

Another secondary endpoint of the study is to evaluate toxicities in patients with basal-like TNBC. All patients who start protocol therapy (i.e., receive at least one dose of protocol treatment) will be included in toxicity analysis. Assuming 14 basal-like TNBC patients (14/281=5%) will not start protocol therapy in each arm, with 267 evaluable patients, the binomial exact 95% confidence interval for toxicity rate would be no wider than 0.12, and there would be at least 83% power to detect a 13% difference in grades 3 or higher toxicity rate, using Fisher exact test with one-sided type I error rate of 0.025. For each individual platinum agent (carboplatin or cisplatin), the binomial exact 95% confidence interval for toxicity rate would be no wider than 0.17 if about the same number of patients (n=133) 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 in basal-like TNBC. The final analysis of IDFS and all secondary endpoints except for OS will be conducted at about 7.5 years after study activation (3.9 years of accrual + 3 years of follow up + 0.5 years of data submission and processing). The final analysis for OS will be conducted at about 10.5 years after study activation (3.9 years of accrual + 6.1 years of follow up + 0.5 years of data collection and cleaning).

The distributions of IDFS, RFS and OS will be estimated using the Kaplan- Meier method(45). For the non-inferiority test, the primary analysis for IDFS will be performed using the RCI method with HR being estimated via stratified Cox proportional hazard model, stratifying on the randomization stratification factors. For the superiority tests of IDFS, OS and RFS, the primary analysis will be performed using stratified log-rank tests, and stratified Cox proportional-hazard models will also be built to estimate the HRs for treatment effect for these efficacy endpoints as a supportive analysis. IDFS, OS and RFS in non-basal like TNBC patients (n=158) and in patients with assay failure (n=35) would be analyzed as an exploratory analysis to examine whether the treatment effect appears similar between the three subsets (basal-like and non-basal like subtype TNBC, and patients with unknown subtype). The treatment-by-basal like subtype interaction would be explored using Cox proportional hazard model in the overall study population. 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 basal-like TNBC 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 each arm. The incidence of deaths and treatment-emergent serious adverse events will be calculated along with exact 95% CI based on binomial distribution and compared between treatment arms using Fisher exact test. Also, the incidence of adverse events leading to discontinuation of chemotherapy and/or withdrawal from the study will be summarized and listed. Toxicity in all patients (including both basal-like and non-basal like patients) will be summarized and compared between treatment arms as well.

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

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9.5 Biomarker Correlative Study

For this correlative biomarker study, we will combine all the patients on all the arms since we don't expect the prognostic value of the biomarkers of interest (i.e., tumor genomic alterations, CTCs) will differ by type of chemotherapy patients received and the intrinsic subtype. The total sample size is 775 patients for EA1131 (562 basal-like patients, 158 non-basal-like patients and 35 patients with unknown subtype). As of June 2019, about 260 patients have enrolled to the study. Taking into consideration of various factors (continuous enrollment in the upcoming months, assay failure, etc.), we expect to have successful genomic profiling of the surgical specimens from at least 400 patients at the end of the study. Per the study protocol, the final analysis of the primary endpoint of the EA1131 trial will take place at 3 years after accrual completion. At the final analyses time (6.9 years after study activation), 196 IDFS events (including recurrence, contralateral breast cancer, second invasive primary cancer, and death) are expected to have occurred to the 562 basal-like TNBC patients based on the alternative hypothesis of the EA1131 study. Of the 196 IDFS events, it is expected that approximately 75% will be recurrence or death, i.e., relapse-free survival (RFS) events. Assuming the same distribution of RFS in the 158 non-basal-like patients and in the 35 patients with unknown subtype, there will be approximately 100 RFS events occurred to the 400 patients with successful genomic profiling, assuming success of genomic profiling is independent of risk of recurrence and basal-like subtype.

9.5.1 Genomic alterations in the surgical specimen

We hypothesize that genomic alternations identified via genomic profiling will predict RFS for patients with TNBC at high risk of recurrence. The frequency of genomic alterations identified will be assessed via genomic profiling in TNBC patients with high risk of recurrence, and associations between genomic alterations and RFS will be assessed; we expect that we can identify some genomic alterations that can predict RFS in TNBC at high risk of recurrence.

With 400 patients and 100 RFS events, for a binary genomic alteration (i.e., the genomic alteration is coded as a binary variable), the minimal hazard ratio (HR) that could be detected with 80% power at two-sided type I error of 0.05 will be 1.78 assuming 50% of the patients have the genomic alteration and the genomic alteration increases risk of recurrence. The minimal HR will be 1.85, 1.75, 1.87 and 2.06 if the proportion of genomic alteration is 20%, 40%, 60% and 70%, respectively.

Frequency of genomic alterations will be summarized using binomial proportions and 95% exact confidence interval. Association of genomic alterations with RFS (i.e., prognostic value of genomic alterations) will be analyzed using log rank test and Cox proportional hazard models. Available potential confounding variables will be adjusted in the Cox model. Due to the exploratory nature of the study, no adjustment will be made for multiple comparisons. All testes will be two-sided with significance level of 0.05. In addition to the prognostic value of genomic alterations, the predictive value of genomic alterations will also be explored via a treatment-by-biomarker interaction test in multivariable Cox proportional hazard models. These analyses will have limited statistical power without prior hypothesis, and they will be considered exploratory and hypothesis generating.

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9.5.2 Peripheral Blood CTCs

We hypothesize that the detection of CTCs at baseline after completion of protocol therapy will predict RFS for patients with TNBC at high risk of recurrence. Further, we predict that the percent change in CTC from pre to post-therapy will also predict RFS, with lower RFS in those who turn from positive to negative over the course of treatment than those who remain positive or turn positive after treatment.

We will determine the proportion of, and factors associated with CTC detection at baseline in early stage TNBC. We will also assess the proportions of patients whose CTCs disappear or persist after chemotherapy. We will evaluate the association between detection of CTC after completion of chemotherapy and RFS and see whether persistence of CTC after chemotherapy can predict disease recurrence. We will also evaluate the association between change in CTC and RFS to see whether lack of decrease in CTC can predict higher risk of recurrence.

In order to test the hypothesis about CTC and RFS, research blood is mandatory for all patients enrolled in the trial, and all patients with research blood and successful assay results about CTC will be included in the analysis. Of the 400 patients with successful CTC detection at baseline and after completion of chemotherapy, we expect that about 35% of them will have detectable CTCs after completion of adjuvant chemotherapy. CTC detection will be coded as a binary variable (positive versus negative), and presence of CTC is defined as any detectable CTC, e.g., >=1 CTC in 7.5 ml blood. With 100 RFS events at the analysis time (assuming no RFS event before

completion of chemotherapy), the minimal HR for presence of CTC versus absence of CTC that could be detected with 80% power at two-sided type I error of 0.05 will be 1.75. The minimal HR that can be detected with 80% power will be 1.85, 1.80, 1.77, and 1.76 if the proportion of CTC is 20%, 25%, 30% and 45%, respectively.

Associations between detection of CTC at completion of chemotherapy as well as change over the course of therapy and RFS will be analyzed using Cox proportional hazard models. Available potential confounding variables will be adjusted in the Cox models. Landmark method will be used for these analyses with landmark time point at 5 months (i.e., completion of chemotherapy in both arms). Factors associated with CTC detection at baseline will be analyzed using Chi square test and Logistic regression models. Due to the exploratory nature of the study, no adjustment will be made for multiple comparisons. All testes will be two-sided with significance level of 0.05.

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9.5.3 To-be-defined Exploratory Correlative Objectives

The association of detection of plasma tumor cell-free DNA tumor-specific mutations prior and after study therapy, its change over time and long-term outcome (RFS) will be explored. An amendment or proposal for this and any additional correlative science studies to be performed on biological samples will be submitted to CTEP, NCI for review and approval according to NCTN guidelines. Amendments to the protocol and/or proposals for use of biological samples will include the appropriate background, experimental plans with assay details, and a detailed statistical section. Samples for testing will not be released for testing until the appropriate NCI approvals have been obtained.

9.6 PRO Study

The study will assess the difference in health-related quality of life (HRQL) between two chemotherapy arms and to describe the rate of neurotoxicity over time in the platinum arm, the rate of medication adherence in the capecitabine arm and the rates of amenorrhea in both arms.

All participants enrolled on the main study are potentially eligible for the PRO assessments after its activation in addendum #4. Patients (regardless of molecular subtype) will be enrolled consecutively for the PRO study until reaching the target sample size for the PRO primary endpoint (i.e., 362 patients with baseline PROs assessments, see Section 9.5.1). PROs assessment for HRQL, neurotoxicity or ovarian function will not be administered in the rest of the patients enrolled for the assessment of the clinical outcomes. The adherence measure (Medication Adherence Scale) for capecitabine will be descriptive and administered to all patients in this cohort.

Rev. Add#5

9.6.1 Statistical Consideration for PRO Endpoints

The primary objective of the PRO study is to compare HRQL between the chemotherapy arms. HRQL measures will be assessed at baseline, and at day 1 of cycle 3 (at 6 weeks), and 6 and 15 months after the start of study chemotherapy (dated at Day 1 of Cycle 1).

These time-points have been chosen as they will allow us to capture the acute difference in side-effects following receipt of chemotherapy, while following long enough to ensure that acute differences in side effects have resolved. Differences in symptom burden and HRQL at 15 months would be considered persistent and unlikely to improve significantly with further follow up. The study hypothesis is that HRQL between the two arms will differ significantly at all time points after baseline (i.e. the platinum chemotherapy group will report higher HRQL at all time-points). The null hypothesis is that patients on the two arms have same overall HRQL at these time points.

The primary endpoints for the PRO objective are HRQL at 6 months and 15 months after the start of study chemotherapy. The type I error rate is split between the two primary endpoints to control the overall one-sided type I error rate at 2.5% for the PROs analysis. Specifically, the one-sided type I error rate is 1.0% for HRQL test at 6 months after the start of chemotherapy and 1.5% for HRQL test at 15 months after the start of chemotherapy.

HRQL will be measured by the FBSI Treatment Side Effects (TSE) subscale score in the study, an aggregate score of 4 items from the NCCN-FACT FBSI-16 scale. Higher score represents better HRQL (score range 0-16). Based on Garcia's study (Value in Health 2012), the minimally important difference (MID) for the FBSI-TSE is 1.5 points, and the standard deviation (SD) for the score is about 3.7. A total of 326 patients will be needed to provide a 90% power to detect an effect size (i.e., MID/SD) of 0.4 at 6-months post baseline, using two-sample t test with one-sided type I error rate of 0.01. For HRQL comparison at 15 months, 290 patients would be needed for this test with one-sided type I error rate of 0.015 and 90% power. Assuming an overall attrition rate of approximately 12% by 6 months after the start of chemotherapy and 20% by 15 months after the start of chemotherapy for the PROs assessment in both arms, it is expected that about 362 patients will be needed for the primary analysis for HRQL in the study to provide the 326 patients for the HRQL test at 6 months after the start of chemotherapy and the 290 patients for HRQL test at 15 months after the start of chemotherapy.

Rev. 9/17
Rev. Add#5

9.6.2 Analysis Plan for PRO Endpoints

PROs endpoints will be analyzed at the final analysis time for the primary endpoint. Any participants who take the PROs surveys at more than 1 time-point will be eligible for analysis. The primary endpoint for HRQL is FBSI TSE subscale score at 6 and 15 months after the start of chemotherapy. The primary endpoint of ovarian function is rate of amenorrhea at 15 months. Amenorrhea is defined as the absence of menses without secondary reason (e.g., pregnancy, oophorectomy or receipt of LHRH agonist, etc.) for the whole 6 months prior to the 15-month survey (i.e., no menses between 9 and 15 months). The primary analysis of HRQL will be assessed in all eligible patients. The primary analysis of rate of amenorrhea will be assessed in women aged 18-49 at enrollment who are premenopausal at cancer diagnosis.

Subscale scores for HRQL endpoint will be prorated by multiplying the sum of the subscale by the number of items in the subscale, then dividing by the number of items actually answered: Prorated subscale score= (sum of items cores) * (number of items in subscale) /(number of items answered). When there are missing data, prorating by subscale in this way is acceptable as long as more than 50% of the items are answered in each subscale. Standard descriptive and graphical analyses will be used initially to examine missing data patterns, and to understand the relationship between variables for HRQL scores. The assessment scores for the HRQL will be compared between the two treatment arms at all time points, using two samples t test (or Wilcoxon rank sum test if the distribution of the score is not symmetric). Change in the HRQL scores between all other time points and the baseline visits will be compared between the two arms using two sample t tests. Similar analyses will be conducted for each NCCT-FACT FBSI subscales. The mean score and proportion of moderate/severe symptoms will be compared between treatment arms for each individual FBSI item at 6 months after the start of chemotherapy using Wilcoxon rank sum test and Fisher exact test, respectively, as an exploratory analysis. Mixed effect models will be constructed as another exploratory analysis to estimate the time profile of HRQL in the two treatment arms and to evaluate treatment-by-time interactions. Time will be included as a continuous variable if there is a linear trend in HRQL over time or a set of dummy variables if non-linear trend exits for HRQL. Likelihood ratio test will be used for model selection. Adjusted covariates in the mixed effect models will include patient demographic and disease characteristics, such as age, ECOG PS, clinical stage at diagnosis, residual cancer burden, prior therapy, et al.

Fisher exact test will be used to examine the difference in rates of amenorrhea between the arms at 15 months. Logistic models will be used for regression analysis for amenorrhea. Adjusted covariates in the logistic models will include patient demographic and disease characteristics, such as age, ECOG PS, clinical stage at diagnosis, residual cancer burden, prior therapy, et al.

In all analyses, P-values will be two-sided. A level of 2.0% will be considered statistically significant for HRQL comparison at 6 months after the start of chemotherapy between two arms. A level of 3.0% will be considered statistically significant for HRQL comparison at 15 months after the start of chemotherapy between two arms. For all other analysis, a level of 5% will be considered statistically significant. No adjustment will be made for multiple comparisons for secondary and exploratory endpoints.

For neurotoxicity (platinum arm) and adherence (capecitabine arm), it will be descriptive only. Neurotoxicity is measured by the FACT-GOG/NTx 11-item subscale score at each time point. The FACT-GOG/NTx subscale score is calculated in a similar way as that for HRQL endpoint. Mixed effect model will be constructed as an exploratory analysis to estimate the time profile of neurotoxicity in the platinum arm. For adherence for capecitabine, the distribution of the

adherence score will be displayed via box-and-whisker plot. The proportion of high, medium and low adherence will be calculated along with the binomial exact 95% confidence interval. The adherence score for each cycle will be calculated. The reasons for non-adherence will be summarized.

9.6.3 Tobacco Use Assessment

Detailed statistical considerations are outlined in Appendix VI.

Rev. Add7

9.7 Gender and Ethnicity

Rev. Add#5

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 7 male patients with TNBC could enroll out of a sample size of 775, and all of them are expected to be non-Hispanic White patients. For the 768 female patients, based on previous data from SWOG S0226 and ECOG E2100 studies, the anticipated accrual in subgroups defined by gender and race is:

Racial Categories	Ethnic Categories				
	Hispanic or Latino		Not Hispanic or Latino		
	Females	Males	Females	Males	Total
American Indian or Alaskan Native	0	0	0	0	0
Asian	0	0	15	0	15
Native Hawaiian or other Pacific Islander	0	0	0	0	0
Black or African American	0	0	65	0	65
White	53	0	635	7	695
Total	53	0	715	7	775

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.

9.8 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.

Rev. 2/16, 6/16
Rev. 9/17
Rev. Add6
Rev. Add7
Rev. Add8

10. Biological Sample Submissions

Tumor tissue from the residual disease on the definitive surgical specimen must be submitted for PAM50 analysis as defined in Section 11. The PAM50 analysis will be performed by the Molecular Diagnostics Laboratory (MDL) at MD Anderson Cancer Center and receipt of tumor tissue will be forwarded to the ECOG-ACRIN Operations Office and submitting institution. Results of the PAM50 analysis will not be reported to the submitting institution.

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, as patients need to be randomized within 24 weeks from surgery.

Rev. Add8

Patients cannot proceed to STEP 1/ randomization before the EA CBPF acknowledges receipt of tumor tissue for PAM50 analysis.

Peripheral blood specimens must be submitted for defined laboratory research studies described in Section 11.

Rev. Add8

Peripheral blood specimen are to be submitted per patient consent for undefined future research studies.

It is required that all specimens submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (see Section 10.3). An STS shipping manifest form is to be included with every submission.

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

Rev. Add6

10.1 Submissions to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF)

Rev. Add7

10.1.1 Tumor Tissue Submission **(Mandatory)**

Pathology specimens must be submitted as soon as possible as not to delay randomization, as patients need to be randomized within 24 weeks from surgery.

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

Rev. Add8

The tumor tissue specimens and pathology report are to be labeled with the Pathology accession ID number and as well as the information above.

10.1.1.1 Required Materials

Rev. Add8

Forms: Must be submitted with all tumor tissue submissions.

- STS generated shipping manifest form
- Copy of the institutional surgical pathology report

- CLIA Laboratory Sample Submission Form (Appendix IV)

10.1.1.2 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.

10.1.1.3 Notification of Tumor Tissue Receipt

The MDL will notify the ECOG-ACRIN Operations Office and submitting institution of receipt of the tumor tissue specimen.

CRA's will receive an email notification when patients can proceed to Step 1 randomization.

Rev. Add8

Randomization cannot occur until receipt of the tumor tissue specimen is acknowledged.

Rev. Add6

10.1.2 Optional Peripheral Blood Submissions for Future ctDNA Analysis

Submit from patients who answer 'Yes' to 'I agree to provide additional samples for research' on the informed consent document.

Kits for the collection and shipment of the peripheral blood specimens are ordered on-line from Cenetron Central Laboratories. Instructions are provided in Appendix VII. Questions regarding kits can be directed to projectmanagement@cenetron.com or call the Cenetron Clinical Trials Group at (512) 439-2000. Kits must be ordered after the patient has been randomized to the trial and will generally arrive within three (3) business days from when the order was placed.

Peripheral blood specimens are to be collected at the following time points:

- Prior to Start of Treatment [Cycle 1, Day 1]
- Six (6) Months from Chemotherapy Initiation [+/- 2 weeks]

Blood specimens are to be shipped at ambient temperature **on the day of collection** (Cycle 1/ Day 1 and 6 months [+/- 2 weeks] from chemotherapy initiation).

10.1.2.1 Specimen Preparation Guidelines

- Confirm blood tube is not expired. Expired tubes should not be used for blood collection.
- Draw two (2) 10mL Streck Cell-Free DNA BCT tubes of whole blood at each time point. Fill each tube completely.

NOTE: The first 5mL of blood collected from the fresh venipuncture cannot be used for the collection into the Streck tubes due to

possibility of contaminating epithelial cells during venipuncture. Please ensure that at least one (1) blood tube of 5mL or more is collected prior to collection.

- Ensure at least 10mL of blood is drawn in each tube. Avoid low volume to minimize agitation during shipping.
- Immediately after collection, gently invert tubes 180 degrees and back 10 times to ensure adequate mixing.
- Label the tube with ECOG-ACRIN protocol number (EA1131), ECOG-ACRIN five-digit patient sequence number and date and time of blood draw. Unlabeled blood tubes may not be processed.
- Maintain blood at room temperature (6ºC to 37ºC) until shipping. **Do Not** place tubes in refrigerator
- Ship on day of collection in shipper provided at ambient temperature.

NOTE: Prevention of Backflow:

Since Streck Cell-Free DNA tubes contain chemical additives, it is important to avoid possible backflow from the tube. To guard against backflow, observe the following precautions:

- Keep patient's arm in the downward position during the collection procedure
- Hold the tube with the stopper uppermost
- Release tourniquet once the blood starts to flow into the tube, or within two minutes of application
- Tube contents should not touch stopper or the end of the needle during the collection procedure

Rev. Add6

10.1.3 Specimen Shipping Procedures

Pathology specimens are to be shipped at ambient temperature within 21 weeks post-surgery.

Peripheral blood specimens are to be shipped at ambient temperature Monday-Thursday via overnight courier.

Friday shipments are ill advised, similarly shipping before holidays is often problematic. The laboratory is closed Saturday, Sunday, and holidays.

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 G1.3598
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 to have an account created, please contact the CBPF by email at eacbpf@mdanderson.org.

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

Rev. Add7

10.2 Mandatory Submission of Peripheral Blood for CTCs to Epic Sciences

If you have any questions concerning specimen collection and shipment, please contact Epic Sciences at (858) 356-6610 or partners@epicsciences.com.

Peripheral blood specimens are to be collected at the following time points:

- Prior to Start of Treatment [Cycle 1, Day 1]
- Six (6) Months from Chemotherapy Initiation [+/- 2 weeks]

Epic Sciences will be providing collection and shipping kits to include Streck Cell-Free DNA BCT tubes, shipping containers. Please email partners@epicsciences.com to order kits and provide the shipping address. Indicate 'EA1131/EP-001' in the subject line of the email. Kits will generally arrive within seven (7) days from when the order was placed.

Please use FedEx account number: 680817251 when shipping specimens to Epic Sciences for this trial only.

10.2.1 Specimen Preparation Guidelines

- Confirm blood tube is not expired. Expired tubes should not be used for blood collection.
- Draw two (2) 10mL Streck Cell-Free DNA BCT tubes of whole blood at each time point. Fill each tube completely. NOTE: The first 5mL of blood collected from the fresh venipuncture cannot be used for the collection into the Streck tubes due to possibility of contaminating epithelial cells during venipuncture. Please ensure that at least one (1) blood tube of 5mL or more is collected prior to collection of the CTC specimen to avoid adversely affecting the test results.
- Ensure at least 10mL of blood is drawn in each tube. Avoid low volume to minimize agitation during shipping.

  NOTE: Epic requires minimum of 4mL of blood per time point, but a full 10mL tube of blood should be provided when possible.

- **Immediately after collection, gently invert tubes 180 degrees and back 10 times to ensure adequate mixing.**
- Label the tube with ECOG-ACRIN protocol number (EA1131), ECOG-ACRIN five-digit patient sequence number and date and time of blood draw. Unlabeled blood tubes may not be processed.
- Maintain blood at room temperature (6ºC to 37ºC) until shipping. Do Not place tubes in refrigerator
- Ship on day of collection in shipper provided at ambient temperature.

NOTE: Prevention of Backflow:

Since Streck Cell-Free DNA tubes contain chemical additives, it is important to avoid possible backflow from the tube. To guard against backflow, observe the following precautions:

- Keep patient's arm in the downward position during the collection procedure
- Hold the tube with the stopper uppermost
- Release tourniquet once the blood starts to flow into the tube, or within two minutes of application
- Tube contents should not touch stopper or the end of the needle during the collection procedure

10.2.2 Specimen Shipment Procedures

Please use FedEx account number: 680817251 when shipping specimens to Epic Sciences for this trial only.

The lab is open for specimen receipt and processing Mondays-Saturdays. Please mark courier slip with 'Saturday Delivery' if shipping on Thursdays and Fridays.

Rev. Add8

Clinical sites should provide email notification of specimen shipment to Epic Sciences on the day of collection, send notification to: partners@epicsciences.com

The email should contain:

- Trial Code (EA1131/EP-001)
- ECOG-ACRIN 5-Digit Patient Sequence Number
- Collection Date and Time
- Time Point/Visit
- Tracking Information

Do not place 'Infectious Substance' sticker on shipper, as this can result in a delay of shipment.

Ship specimens to:

Epic Sciences
Attn: EA1131 / EP-001
9381 Judicial Drive, Suite 200
San Diego, CA 92121

Phone: (858) 356-6610
Fax: (858) 356-5852

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

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

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

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

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

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

Study Specific Notes

Generic Specimen Submission Form (#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 (EA CBPF)
- EPIC Sciences

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

Rev. Add6

10.4 Use of Specimens in Research

Tumor tissue specimens will be sent directly to the MDL at MDA for PAM50 analysis and residual tumor tissue will be distributed to Vanderbilt University for laboratory research studies outlined in Section 11. Peripheral blood specimens will be sent directly to Epic Sciences for CTC Detection analysis as outlined in Section 11.

Use of banked specimens will not occur until an amendment to this protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies. The proposed future studies are:

- Rate of ctDNA Detection and Significance of ctDNA-detected Mutations

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). DNA, RNA, serum, and plasma (if appropriate) will be isolated from the submitted peripheral blood specimens.

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.

Rev. Add6

10.5 Sample Inventory Submission Guidelines

Inventories of all specimens submitted from institutions will be tracked via the ECOG-ACRIN STS and receipt and usability verified by the receiving laboratory. Inventories of specimens 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.

Rev. Add6

11. Biomarker Studies

11.1 Rate of basal-like gene expression using PAM50 analysis by digital mRNA quantitation – Integral Biomarker Study

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[1,41]. Among young women and African-American women, its prevalence is elevated(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)[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(9). 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(10)) 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 capecitabine arm.

Rev. 6/16

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(46-49). The PAM50 test provides additional information about the tumor biology and quantitative data on biomarkers already used for treatment

decisions[46,47]. Along with a categorical classification of breast cancer subtype, the clinical PAM50 test also determines a quantitative value for proliferation(50). 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.

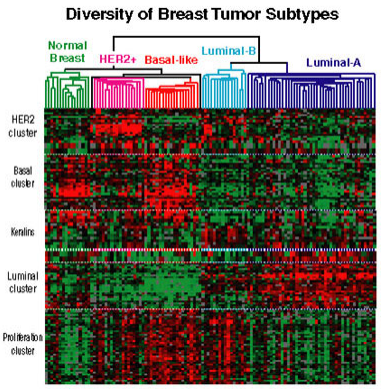
Within this study, we expect at least 75% of the residual post-NAC TNBC screened to fall within the basal-like subtype by gene expression profile(10). Hence, at least 750 patients (=562/0.75) with residual TNBC at the time of surgery will be screened to obtain the 562 patients with basal-like TNBC.

Rev. 6/16

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(51). The MDL will have a custom software configuration that is intended

for investigational use within this clinical trial and will output intrinsic subtype.

Rev. Add7

11.2 Genomic alterations identified via whole exome sequencing (WES) and RNA sequencing – Biomarker Study

11.2.1 Rationale and Background for WES and RNA-seq in Surgical Residual Tumor

Mutational spectrum analyses suggest that TNBC has a higher mutational frequency than other subtypes(29-31), and our group has shown that profiling of TNBC post-neoadjuvant chemotherapy in a small scale is feasible and identifies gene alterations that may have a role in chemoresistance(8). We propose to perform a *prospective large-scale* genomic profiling of surgical tissue from patients enrolled in the EA1131 clinical trial; we hypothesize that the genomic alterations identified via genomic profiling will predict relapse-free survival for this group of patients at high risk of recurrence. Successful completion of this comprehensive profiling will a) more accurately identify patients with TNBC at highest risk of recurrence, and b) provide novel insights into future targeted interventions that could significantly impact risk of recurrence and mortality in patients at highest risk.

We will assess the frequency of genomic alterations (VAFs, copy number, and patterns of mutant allele expression) identified via genomic profiling in TNBC patients with high risk of recurrence, and assess associations between genomic alterations and clinical outcome; we expect that we can identify some genomic alterations that can predict relapse free survival in TNBC at high risk of recurrence. We will use the WES methods developed by Griffith(52), which will deliver ~100x average coverage of targeted regions. We will use established RNA-seq methods(53), and enrich WES data by assessing expression and relevance of mutations identified by WES. Missense mutations expressed at RNA level are more likely to be relevant than those not expressed. We will also be able to identify expressed gene fusions through RNA-seq; which would be more sensitive/specific than WES for detecting gene fusions and novel cryptic fusions. Gene's normalized expression level will be assessed.

11.2.2 Specimens and Processing

The surgical tumor specimens will be subjected to whole genome sequencing (WES) and RNA-seq. Future analysis will be performed on the DNA and RNA extracted from the formalin-fixed paraffin-embedded (FFPE) tumor specimens submitted from patients who:

- Registered prior to activation of Addendum #6 and answered "Yes" to "My samples and related information may be kept in a Biobank for use in future health research."

OR

- Registered following activation of Addendum #6 and answered "Yes" to "I agree that my samples and related information may be used for the laboratory studies described above."

Rev. Add7

11.3 Blood-Based Biomarkers – Rate of CTC Detection

11.3.1 Rationale and Background

We hypothesize that the detection of CTC after completion of adjuvant chemotherapy and change in CTC prior to and after completion of adjuvant chemotherapy will predict RFS for patients with TNBC at high risk of recurrence.

In 2004, the seminal work by Cristofanilli et al. demonstrated that CTC count was an independent prognostic factor for progression-free survival (PFS) and OS in metastatic BC(54). In a large study involving 2,026 primary BC patients, CTCs have been detected in the peripheral blood of approximately 22% of patients after surgery and before adjuvant therapy(55). In adjuvant setting, CTC detection (≥ 1 CTC in 7.5 mL of blood) before chemotherapy has shown to be an independent predictor of disease-free survival (DFS) and OS and, not only the presence but also the quantity of CTCs has proven to be associated with worse outcome. Moreover, the persistence of CTCs after adjuvant treatment significantly correlates with a decreased DFS(33, 55). CTCs evaluation in patients with early-stage BC could provide useful information for adjuvant treatment decision-making. However, in this particular context, CTCs are observed with low frequency thus, CTC detection methods with higher sensitivity could be necessary for their clinical use. Moreover, further studies are needed to better define its efficacy in both the prediction of outcome and monitoring the effect of therapy.

The Epic Sciences CTC detection and characterization platform enables enumeration of CTCs as well as evaluation of protein biomarker expression and subcellular localization when used with their 1) 4 or 5-color immunofluorescence assays, 2) gene amplifications, deletions or rearrangements by DNA FISH and 3) genomic aberrations via mutation or copy number variation (CNV) analysis via next-generation sequencing (NGS).

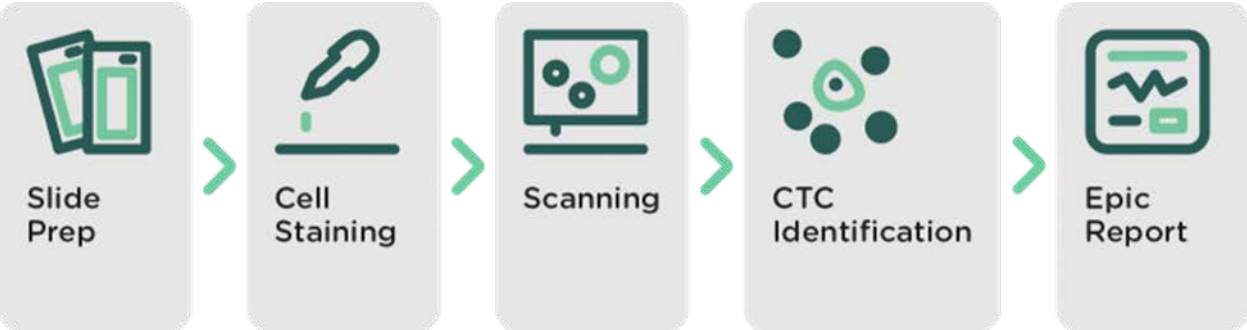
Analytical validation in terms of assay performance, accuracy, linearity, specificity and precision of CTC enumeration was published in by Werner et al(56). An excerpt of data that highlights the performance of key parameters is shown below.

Performance Characteristics	Assessment Parameter	Spike-In CLCs	Measured Parameter
Accuracy	Recovery of nucleated cells	0 to 300 CLSs/slide (7 serial dilutions)	% Recovery of Nucleated Cells
Linearity (Reportable Range)	Assay Linearity	0 to 300 CLCs/Slide (7 serial dilutions)	Linear Regression of CLC Count
Specificity	False Positive CLC Detection	Unspiked healthy donor slides	CLC Count

Performance Characteristics	Assessment Parameter	Spike-In CLCs	Measured Parameter
Precision/Repeatability	Intra-Assay (n=3 replicate tests / run) Inter-Assay (n=5 runs / 3 operators) Intra-Operator (n=3 runs / operator) Inter-Operator (n=3 runs / 3 operators)	(i) 25 CLCs/slide (ii) 300 CLCs/slide	% CV CLC Count

These are the analytical characteristics assessed to benchmark the performance of the Epic Sciences CTC detection and characterization platform. Varying concentrations of COLO-205 cell line cells (CLCs) were spiked into healthy donor blood, red blood cells were lysed, and 3 x 106 nucleated cells were deposited onto slides, ranging from 0-300 CLCs/slide. Slides were stained with a cocktail of CK, CD45 and DAPI antibodies. Assay accuracy, linearity, specificity and precision were determined as described in the methods. For each analysis, a "run" is comprised of three tests, with each test consisting of two replicate slides.

CTC enumeration on the Epic Sciences platform consists of:



1. **Slide Prep:** Upon receipt of patient blood specimen, whole blood is lysed and nucleated cells are deposited on up to 12 microscope slides that are frozen at -80 ºC until analysis.
2. **Cell Staining and Scanning:** Slides are immunofluorescently stained and scanned by Epic's rapid fluorescent scanning method, which images each nucleated cell.
3. **CTC Identification and Biomarker Analysis:** A digital pathology algorithm, which includes protein expression and morphology, differentiates candidate CTCs from surrounding white blood cells (WBCs). CTCs are confirmed and classified into one of the following categories (1) Traditional CTCs, (2) CTC clusters, (3) CK(-) CTCs and (4) Apoptotic CTCs (see CTC basics to review these different classes of CTCs).

   The Epic Sciences' platform analyzes all nucleated cells within a blood specimen at single cell resolution. Cells from a patient's

blood specimen are deposited on replicate glass slides and compared for morphological features, expression of biomarkers and nuclear integrity, using immunofluorescent staining. Guided by cell phenotype and marker expression, CTCs are individually recovered from the slide surface. Their genomes are amplified (WGA) and analyzed by next-generation sequencing (NGS) for the presence of point mutations, copy number alterations, genome wide chromosomal instability, ploidy or genome wide scarring.

1. **Slide Prep:** Upon patient blood specimen receipt at Epic Sciences, whole blood is lysed and nucleated cells are deposited onto microscope slides.
2. **Cell Staining and CTC Identification:** Cells are stained for immunofluorescence to identify CTCs and other biomarkers in the study. Coordinates of all CTCs on the slide are preserved.
3. **Genomics Analysis:** Coverslips are removed and cell coordinates are used to relocate CTCs. Once relocated, cells are picked and placed into individual wells of an assay-ready 96 well plate.

11.4 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.

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12. Electronic Data Capture

Please refer to the EA1131 Forms Completion Guidelines for the forms submission schedule. Data collection will be performed in Medidata Rave and EASEE-PRO (for tobacco use assessment).

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis, either by FTP burst of data or via the CDS web application. Reports are due January 31, April 30, July 31, and October 31.

13. Patient Consent and Peer Judgment

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

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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 (#2981v3)

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

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The following materials must be submitted within 21 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.

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2. Forms and Reports:
   - Copy of institutional surgical pathology report.
   - STS generated shipping manifest form.
   - CLIA Laboratory Sample Submission Form (Appendix IV)

   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:

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ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN
Room G1.3598
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.

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

Robert L. Comis, MD, and Mitchell D. Schnall, MD, PhD
Group Co-Chairs

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. capecitabine 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, central review, and defined laboratory research studies.

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 materials 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.

Please note: Since blocks are being used for laboratory studies, in some cases the material may be depleted, and, therefore, the block may not be returned.

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.

ECOG-ACRIN Generic Specimen Submission Form

Form No. 2981v3

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

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

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

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

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

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

Fields to be completed if requested per protocol. Refer to the protocol-specific sample submissions for additional fields that may be required.

Leukemia/Myeloma Studies:	**Diagnosis**	**Intended Treatment Trial**	**Peripheral WBC Count (x1000)**	**Peripheral Blasts %**	**Lymphocytes %**
Study Drug Information:	**Therapy Drug Name**	**Date Drug Administered**	**Start Time 24 HR**	**Stop Time 24HR**	
Caloric Intake:	**Date of Last Caloric Intake**		**Time of Last Caloric Intake 24HR**		

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

Comments

9/12/14

A Randomized Phase III Post-Operative Trial of Platinum Based Chemotherapy Vs. Capecitabine 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] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we 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. Capecitabine in Patients with Residual Triple-Negative Basal-Like Breast Cancer following Neoadjuvant Chemotherapy

Appendix III

ECOG Performance Status

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

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

Appendix IV

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CLIA Laboratory Sample Submission Form

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Department of Pathology
Tissue Qualification Laboratory
T 713-745-4901 F 713-745-4925
T 844-744-2420 (Toll Free)
Unit 0085
1515 Holcombe Blvd
Room G1.3597
Houston, Texas 77030

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	
ECOG-ACRIN TRIAL NUMBER: _____	ECOG-ACRIN Patient ID: _____
Section II. SITE'S TIME ZONE INFORMATION	
Time Zone: ☐ Atlantic ☐ Eastern ☐ Central ☐ Mountain ☐ Pacific ☐ Alaska ☐ Hawaii-Aleutian ☐ Other: _____ Is Daylight Saving Time observed: ☐ Yes ☐ No	
Section III. PATIENT INFORMATION	
Last Name: _____	First Name: _____
Date of Birth (MM/DD/YYYY): _____	Gender: ☐ Female ☐ Male
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	Section B Site CRA or Research Contact	Section C Pathology Group
Last Name:	Last Name:	Last Name (optional):
First Name:	First Name:	First Name (optional):
NPI:		
Phone:	Phone:	Phone:
Fax:	Fax:	Fax (optional):
Institution:	Institution:	Institution:
Department:	Department:	Department:
Street Address Line 1:	Street Address Line 1:	Street Address Line 1:
Street Address Line 2:	Street Address Line 2:	Street Address Line 2:
City:	City:	City:
State: / Zip Code:	State: / Zip Code:	State: / Zip Code:
Physician E-mail (optional):	Research Contact E-mail (optional):	Pathologist E-mail (optional):
Office Contact Name (optional):	Office Contact Name (optional):	Office Contact Name (optional):
Office Contact E-mail (optional):	Office Contact E-mail (optional):	Office Contact E-mail (optional):

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Appendix V

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Patient Pill Calendar

NOTE: This pill calendar is for patients randomized to Arm C ONLY.

Pill Calendar Directions

1. Take your schedule dose of pill
2. If you forget, the missed pills will not be taken later.
3. Please bring the empty bottle or any leftover pills and your pill calendar to your next clinic visit.
4. When taking Capecitabine:
   - Capecitabine pills are to be swallowed whole with water within 30 minutes after a meal
   - Do not crush or cut capecitabine pills

Patient Pill Calendar

This is a calendar on which you are to record the time and number of pills you take each day. You should take your schedule dose of each pill. **Note the times and the number of pills that you take each day.** If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided.

Cycle: _____

Prescribed dosage: _____

Bring any unused pills and your completed pill calendar to your doctor's visits.

CYCLE DAY	**Date**			**Times Pills Taken**		**Number of Pills Taken**		**Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)**
	(Month / Day / Year)			AM	PM	AM	PM	
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								
14								

Patient Signature: _____ Date: _____

Number of pills returned: _____

Administrator Signature: _____ Date: _____

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

Rev. Add#5

Appendix VI

Ancillary for Tobacco Use Assessment: EAQ16T

Study Co-Chairs: Elyse Park, Ilana Gareen, Lynne Wagner, Jamie Ostroff, Ben Herman

Patients registered to selected ECOG-ACRIN trials are eligible to participate in this ancillary study, once the appropriate amendment incorporating the study is activated.

The Ancillary for Tobacco Use Assessment is a project that seeks to address questions about patient-reported tobacco use and smoking behaviors that may span several studies and/or diseases. The tobacco use ancillary is embedded into parent protocols, with participation in the ancillary informed in the parent consent form and participation determined via providing email address to the sites. The general objectives of the tobacco use ancillary are not specific to any single parent protocol; however, specific objectives may be included in the parent or related parent protocols.

A significant proportion of cancer patients are current smokers at the time of cancer diagnosis,[1–5] and there are known risks associated with continued smoking following cancer diagnosis. These include decreased survival time; increased complications from surgery, radiation, and chemotherapy; and increased risk of second primary tumors.[6–11] As such, the National Comprehensive Cancer Network (NCCN), the American Association of Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO) have identified persistent smoking as a modifiable risk factor and recommend cessation counseling for cancer patients who smoke. Although evidence-based guidelines for treating tobacco dependence exist,[12] they have not yet been well-integrated into cancer care settings. Moreover, knowledge regarding the scope and patterns of tobacco use among cancer patients is limited. As a critical step in closing this knowledge gap, the NCI-AACR Cancer Patient Tobacco Use Asssessment Task Force developed the Cancer Patient Tobacco Use [1–4,13,14] Questionnaire (C-TUQ). Through this ancillary, the modified C-TUQ measures will be administered to participants enrolling in selected Phase II and Phase III ECOG ACRIN (EA) therapeutic trials.

The major questions may be summarized:

1. What is the smoking status of cancer patients enrolled on EA clinical trials?
2. Do patients quit smoking or try to quit smoking after receiving a cancer diagnosis?
3. What forms of tobacco use do patients engage in?
4. What assistance do patients use or receive to try to quit?
5. How does tobacco use, other forms of tobacco use, and/or environmental tobacco exposure affect patient's treatment toxicity, patient-reported physical and psychological symptoms, trial adherence, and therapeutic outcomes?

When patients consent to participate, they will be asked to provide a contact email address and that address along with their registration information will be sent directly from the parent trial's registration system to ECOG-ACRIN Systems for Easy Entry of Patient Reported Outcomes (EASEE-PRO), and the patient will be automatically registered into EASEE-PRO for participation. To activate their account for self-directed web entry of surveys, the system will send an activation message to the contact email address that will explain how to activate their account for self-directed web entry of surveys. After their account is activated, the patient will be

able to complete questionnaires using a secure browser interface from any web enabled computer, tablet, or mobile device.

Measures

The selected Core and Extension C-TUQ items will be assessed. The 4-item Short Form PROMIS® for anxiety and depression, the Lung Cancer Stigma Scale, and six symptom items (general pain, fatigue, nausea, cough, insomnia, shortness of breath) from FACIT (Functional Assessment of Chronic Illness Therapy)) together with modifications of these same six questions to address the degree of bother associated with each symptom will be administered as well. Additionally, we will ask participants' perceptions of how smoking improves or worsens each of the six symptom experience. All these items will be compiled into Survey of Tobacco Use (STU) (baseline and follow-up).

Contents and Corresponding Questions in Survey of Tobacco Use (STU)

Dimension	Source of Measures	Baseline STU	Follow-up STU
Basic Tobacco Use Information	C-TUQ	Q1 – Q5	Q1 – Q2
Tobacco Use in Relation to Cancer Diagnosis and Treatment	C-TUQ	Q6 – Q7	Q3
Smoking Cessation, Cessation Products, and Assistance Methods	C-TUQ	Q8 – Q13	Q4 – Q9
Use of Other Products	C-TUQ	Q14	Q10
Second-Hand Smoke Exposure	C-TUQ	Q15 – Q16	Q11 – Q12
Psychological Symptoms	PROMIS Lung Cancer Stigma Scale	Q17 – Q18	Q13 – Q14
Physical Symptoms	FACIT	Q19	Q15
Sociodemographics		Q20 – 21	

NOTE: In order to minimize ambiguity and assure that patients are oriented to answer appropriately, the specific phrasing of items may vary depending specific cancer type and treatment.

Tobacco Use. The selected Core and Extension C-TUQ items (from categories of Basic Tobacco Use Information, Tobacco Use in Relation to Cancer Diagnosis and Treatment, Smoking Cessation/Cessation Products/Assistance Methods, Use of Other Products, and Second-Hand Smoke Exposure) will be assessed in the baseline and follow-up Survey of Tobacco Use.

Oncology Provider Assistance. C-TUQ Question 13 assesses "cancer doctors" Advise. We will add 4 As to assess participants' reported 5As (Ask (Q12a), Advise (Q12b), Assess (Q12c), Assist (Q12d-Q12f), and Arrange follow-up (Q12g), as in Baseline STU).[80]

Psychological Symptom Assessment. Anxiety & Depression: *(The Patient Reported Outcomes Measurement Information System (PROMIS®)).* We will administer the 4-item Short Form PROMIS® for anxiety and depression (Q17 in Baseline STU). Stigma: The Lung Cancer Stigma scale measures the extent to which shame is internalized (Q18 in Baseline STU).[81]

Physical Symptom Assessment *Physical Symptom Assessment (Functional Assessment of Chronic Illness Therapy (FACIT)). FACIT, a measurement system with a collection of quality-of-life questionnaires, expands the more familiar FACT (Functional Assessment of Cancer Therapy) questionnaires into other chronic illness and conditions. FACIT consists of many*

individual questions to assess various symptoms from the patient perspective. We will use 6 FACIT items, selected based on the therapeutic regimens, expected toxicity, and malignancy type of the parent trials. In addition, we have created modifications of these same six questions to address the degree of bother associated with each symptom" The symptoms of general pain, fatigue, nausea, cough, sleep difficulty, and shortness of breath will be assessed, first using the standard and validated FACT item, and then asking the degree of "bother" imposed by each symptom, on the same 5-point scale. These clusters of symptoms were specifically chosen based on potential interactions between tobacco use and longitudinal symptoms.

Sociodemographic Variables. Sociodemographic variables, including age, sex, zip code, and race/ethnicity are collected for all NCTN trial participants at registration. At baseline, participants will provide information on marital status (Q20 in Baseline STU) and education level (Q21 in Baseline STU) as part of the tobacco supplemental assessment.

Cancer Treatment Variables. Clinical variables including date of diagnosis, malignancy type (smoking related vs. non-smoking related, cancer stage), and treatment details (i.e. types and dates of surgery, chemotherapy, and/or radiation received), along with disease status and survival, will be captured in Medidata Rave via the parent protocol and will be available for analysis of the ancillary. Provider-assessed adverse events will also be captured via the parent protocol in Medidata Rave, using case report forms commonly used across the NCTN and using standard data elements.

Assessments

All items in Survey of Tobacco Use will be administered using the EASEE-PRO system. The advantage of our virtual electronic data capture system is that our proposed assessments will not be limited to, or dependent upon, patient trial visits. Confidential and potentially stigmatizing information can be provided without requiring direct contact with the care team.

Timing of Assessments

Given the critical questions that remain[13] about the timing of conducting tobacco use assessments, we have carefully chosen to collect tobacco assessment data at trial enrollment, 3 and 6 month follow-up. For tobacco treatment trials, 6 month follow-up is the recommended primary outcome time point. By 6 month follow-up, most cancer treatment-related quitting activity[62], cancer treatment initiation of therapy, and FDA-approved smoking cessation medication regimens will be completed. Adverse events during treatment will have been observed.

Statistical Considerations and Analysis Plans

The analysis plans described below are planned for a combined analysis of the data from the 8 selected ECOG-ACRIN trials. Consistency in the effects over the studies would be examined in this analysis.

1. CHANGES IN SMOKING STATUS AND EXPOSURE. At baseline, combustible tobacco use (1a) will be characterized by smoking status (never smoker, former smoker, and current smoker based on Baseline STU Qs 1 and 5), other forms of tobacco use (1b) will be a composite variable determined by non-cigarette items (based on Baseline STU Q7 and Q14), and environmental tobacco smoke (ETS) level (1c) will be determined by current household and work exposure (Baseline STU Qs 15-16). At follow-up, combustible tobacco use (1a) will be examined by smoking status (Follow-up STU Qs 1 and 2), other forms of tobacco use (1b) will be determined by Follow-up STU Q10, and ETS level (1c) will be determined by 30 day household and work exposure (Follow-up STU Qs 11-12). We will examine tobacco use at baseline, 3 and 6 month follow-up, and change in status (abstinence in combustible tobacco, abstinence of other forms of tobacco use, and change

in exposure to smoke-free home and work) using summary statistics (frequency and proportion). We will explore the effects of sociodemographic and cancer treatment factors on smoking status using logistic regression (comparing smokers and non-smokers). We will also evaluate factors associated with changes in smoking status.

2. TREATMENT TOXICITY. The selected trials capture information about adverse events during treatment using NCI's Common Terminology Criteria for Adverse Events, Version 4. Toxicities are measured at each treatment visit and graded according to severity, with grade 1 corresponding to mild toxicity and grade 5 signifying a lethal adverse event. We will determine each patient's worst degree toxicity across all event types and treatment visits and will compare the distribution of worst degree grades between smokers and non-smokers and between patients with environmental tobacco exposure and those without exposure using exact tests. We will also examine the distribution of worst degree grades between users with different form of tobacco use. In addition, we will explore the effects of tobacco use on dose modifications (yes vs. no) using logistic regression, with each patient's dose modification status determined across all treatment visits.
3. SYMPTOM BURDEN. Tobacco variables will be conceptualized as described in the section of CHANGES IN SMOKING STATUS AND EXPOSURE. Tobacco use status (as measured at baseline, 3 and 6 months follow-up) will be compared to physical and psychological symptom burden (as measured at each corresponding time points). At 3 and 6 months follow-up, we will also examine the association between tobacco use changes and changes in symptom burden. We will explore the effects of sociodemographic and cancer treatment factors on symptom burden using repeated measures mixed effects models. As an example of statistical power, we consider the PROMIS SF-4 depression measure. We assume that 1500 patients will be enrolled across the 8 parent studies over 13 months, and that 20% are smokers. We assume that 85% of patients will have assessments at 6 months. Given groups of these sizes (26 quitters and 230 still-smokers) and standard deviation of 4.08 for the PROMIS SF-4 depression scale, there will be 83% power to detect a difference in change scores of 2.5 between groups using a two-sample t-test with Type I error of 5%. The minimally important difference for this instrument is 2.2.[79]
4. CESSATION PATTERNS AND TREATMENT. At baseline we will explore pre-treatment combustible tobacco use patterns (STU Q6a and Q6b), quitting behaviors (STU Q13), behavioral program utilization (STU Q11) and oncology provider support (5As, STU Q12), and smoking cessation medication use (STU Q10). At follow-up we will explore post-treatment combustible tobacco use patterns (STU Q3a-Q3e), quitting behaviors (STU Q9), behavioral program utilization (STU, Q7) and oncology provider support (5As, STU Q8), and smoking cessation medication use (STU Q6). We will explore the effects of sociodemographic and cancer treatment factors on these variables. We will examine associations of quitting behaviors and behavioral and medication utilization with tobacco use status (as outlined in the section of CHANGES IN SMOKING STATUS AND EXPOSURE) at baseline and on respective 3 and 6 month tobacco outcomes. These analyses will be descriptive in nature. Summary statistics (frequency, proportions, and 95% confidence intervals) will be used.
5. TRIAL OUTCOMES. We will compare treatment duration between smokers and non-smokers and between patients with environmental tobacco exposure and those without exposure. Cumulative incidence/competing risk methods will be used to estimate time to treatment discontinuation for adverse events, disease progression, completion per protocol, or other causes. Gray's test will be used to test for differences in the cumulative incidence distributions.[78] Differences in the distribution of reasons for discontinuation of treatment will be examined using exact tests. Relative dose intensity is defined as the ratio of actually delivered dose intensity to the planned dose intensity. The effects of tobacco use and

exposure on relative dose intensity (≥ 90% vs. < 90%) will be explored using logistic regression. Differences in the primary endpoint and important secondary endpoints will be examined using log rank test and exact test (as appropriate).

Data collected in the tobacco use project will support a range of analyses. Precise estimates of power will depend on the prevalence of smoking at baseline among study participants, the proportion whose smoking status changes, and the duration and adequacy of follow-up.

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Rev. Add6

Appendix VII

EA1131 Collection and Shipping Kit Order Instructions

Specimen Collection/Shipping Kits are being provided by CENETRON CENTRAL LABORATORIES and are to be ordered ONLINE.

Rev. Add8

Starter kits are not available. Kit requests are to be made AFTER patient randomization (preferred) but can be ordered after patient consent.

Questions regarding kits can be directed to projectmanagement@cenetron.com or call the Cenetron Clinical Trials Group at (512) 439-2000.

Ordering Process:

- Following randomization of the patient to the trial, go to the website www.cenetron.com and click on the 'Order Kits' button at the top right. It is recommended that kits be ordered same day as patient randomization.
- The order form is not study specific and can be used for any study. Complete the online form as follows:
  - **Sponsor (REQUIRED):** ECOG-ACRIN
  - **Contact Name (REQUIRED):** Name of the institution kit contact.
  - **Protocol Number (REQUIRED):** EA1131
  - **Phone Number (REQUIRED):** Phone number of the kit contact. Please ensure that this is a number that can be reached from an external caller.
  - **Site Number (REQUIRED):** Institution NCI Site ID
  - **FAX Number:** Fax number of the kit contact
  - **Investigator:** Last name of the kit contact is adequate
  - **Email (REQUIRED):** Email of the institution kit contact. Must be entered twice to confirm.
  - **Date Supplies Needed (REQUIRED):** Add three (3) business days or more to order date. (Reminder that weekends and holidays must also be considered in this timeline)
  - **KIT NAME (REQUIRED):** EA1131 Collection Kit
  - **Quantity:** 1
  - **Comments:** Provide EA1131 Patient Case ID# and full shipping address
- 'Patient Case ID =' #####
- *'Ship Kit to'* name of the individual to whom the kit is being shipped. (May be different than the kit contact provided above)
- Full street address, town, state and zip code
  - Answer the security question

Please complete this form correctly, including the valid ECOG-ACRIN patient case number and complete shipping address. If information is missing the kit processing will be delayed.