Protocol Title

A Phase II Randomized Controlled Trial of Genomically Directed Therapy After Preoperative Chemotherapy in Patients with Triple Negative Breast Cancer

HCRN BRE12-158

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PROTOCOL SIGNATURE PAGE

A Phase II Randomized Controlled Trial of Genomically Directed Therapy
After Preoperative Chemotherapy in Patients with Triple Negative Breast Cancer

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I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

Instructions to the investigator: Please **SIGN** and **DATE** this signature page. **PRINT** your name and title, the name and location of the facility in which the study will be conducted, and the expected IRB approval date. Scan and email the completed form to HCRN and keep a copy for your files.

_____ _____
Signature of Investigator Date

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Investigator Name (printed)

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Investigator Title

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Name of Facility

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Location of Facility (City and State)

_____ ❑ Not Submitting to IRB
Expected IRB Approval Date

COMPLETE AND EMAIL COPY TO HOOSIER CANCER RESEARCH NETWORK

SYNOPSIS

TITLE	A Phase II Randomized Controlled Trial of Genomically Directed Therapy After Preoperative Chemotherapy in Patients with Triple Negative Breast Cancer
STUDY PHASE	Phase II
OBJECTIVES	**Primary Objective:** To compare 2-year disease-free survival (DFS) in participants with confirmed triple negative breast cancer (TNBC) treated with a genomically directed therapy or standard of care following preoperative chemotherapy **Secondary Objectives:** • To compare overall DFS and 1-year DFS • To determine 5-year overall survival (OS) • To collect archived tumor specimens and genomic DNA to explore potential correlates of recurrence and toxicity. • To describe the toxicities associated with genomically directed therapies in this population **Exploratory Objectives:** • To describe the evolution of genomically directed therapies during the course of the study • To evaluate the drug specific effect on both efficacy outcomes (DFS and OS) and toxicity.
STUDY DESIGN	**Sequencing:** DNA from archived tumor samples collected at the time of surgery (residual disease post neoadjuvant chemotherapy) will be extracted and sequenced. The resulting sequencing data will be interrogated for known genomic drivers of sensitivity or resistance to existing FDA approved agents. **Cancer Genomics Tumor Board (CGTB):** Realizing that optimal treatment recommendations cannot be made based on sequencing data alone, the CGTB will be responsible for the final treatment recommendation. The CGTB will consider the genomic data along with the participant's prior treatment history, ongoing toxicities, and comorbidities. Preference will be given to the treatment identified by the sequencing data unless a significant clinical or safety contraindication exists for that therapy. All participants and treating investigators will be blinded to sequencing results and CGTB deliberations until the time of relapse.

STUDY DESIGN	**Participants with a CGTB treatment recommendation:** Participants with a CGTB recommendation will be randomized to Experimental Arm A (genomically directed monotherapy) or Control Arm B (standard therapy). Experimental Arm A (genomically directed monotherapy) Participants randomized to Experimental Arm A will receive an FDA approved drug at standard dose for four cycles (12-16 weeks total duration, depending on cycle length). Clinical and laboratory monitoring and dose-reductions will follow the FDA package insert guidelines. Detailed information about the drugs expected to be recommended most commonly can be found in Appendix A. Control Arm B (standard therapy) Recently, a randomized phase III trial of over 900 HER2-negative participants demonstrated an improvement in DFS and OS for the addition of 8 cycles of capecitabine in the post-neoadjuvant setting. The hazard ratios were also significant in the triple negative subgroup. Thus, capecitabine can be considered a standard option in this setting. As this represents only a single trial (with prior data not demonstrating benefit for the addition of capecitabine in the neoadjuvant nor adjuvant settings in unselected participants), observation can be considered an option as directed by the treating physician. While not recommended, other therapies can be used as deemed appropriate by the treating physician. **Participants with no CGTB recommendation:** Participants may have no CGTB recommendation either because 1) sequencing did not identify a matched drug or 2) the matched drug was contraindicated. These participants will be **assigned** to Control Arm B and treated as described above for Control Arm B. As the outcome of participants without an 'actionable' genomically directed therapy may differ, the primary analysis will include only participants **randomized** to Control Arm B.
NUMBER OF PARTICIPANTS	Total number REQUIRED to be randomized and evaluable for efficacy = 136 Estimated number with technical failure in sequencing = 5 Estimated number of participants expected to have no CGTB recommendation = 30 Estimated total number of participants to be enrolled = 192 Maximum number of participants to be enrolled = 200

ELIGIBILITY	1. Written informed consent and HIPAA authorization for release of personal health information. **NOTE:** HIPAA authorization may be included in the informed consent or may be obtained separately. **NOTE:** Central pathology review may be conducted any time after definitive surgery. Consenting participants may be pre-registered to the study and proceed with central pathology review before full eligibility has been confirmed. However, ALL of the eligibility criteria must be met and formal study registration completed prior to submission of the sample for sequencing. 2. Age ≥ 18 years at the time of consent. 3. ECOG Performance Status 0 or 1 within 14 days prior to study registration. 4. Women and men of childbearing potential must be willing to use an effective method of contraception (e.g. hormonal or barrier method of birth control; abstinence) from the time consent is signed until 4 weeks after protocol therapy discontinuation. 5. Women of childbearing potential must have a negative pregnancy test within 30 days prior to study registration. Women should be counseled regarding acceptable birth control methods to utilize from the time of screening to start of treatment. If prior to treatment after discussion with the subject it is felt by the treating physician there is a possibility the subject is pregnant a pregnancy test should be repeated. **NOTE:** Women are considered not of childbearing potential if they are surgically sterile (they have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy), or they are postmenopausal for at least 12 consecutive months. 6. Women must not be breastfeeding. 7. Must have histologically or cytologically confirmed triple negative (ER-/PR-/HER2-) invasive breast cancer, clinical stage I-III at diagnosis (AJCC 6th edition) based on initial evaluation by physical examination and/or breast imaging prior to study registration. **NOTE:** ER, PR, and HER2 status will be confirmed by central pathology review prior to randomization. ER and PR will be considered negative if ≤ 10% of cells stain weakly positive. HER2 will be considered negative if scored 0 or 1+ by immunohistochemistry (IHC) or 2+ by IHC associated with a fluorescence in situ hybridization (FISH) ratio of < 2.0 or < 6 copies per cell. 8. Must have completed preoperative (neoadjuvant) chemotherapy. **NOTE:** Acceptable preoperative regimens include an anthracycline or a taxane, or both. Participants who received preoperative therapy as part of a clinical trial may enroll. Participants may not have received adjuvant chemotherapy after surgery prior to randomization. Bisphosphonate use is allowed.

	9. Must have completed definitive resection of primary tumor. For those that do not require radiotherapy, the most recent surgery for breast cancer must have been completed at least 14 days prior, but no more than 84 days prior, to study registration. NOTE: Negative margins for both invasive and ductal carcinoma in situ (DCIS) are desirable, however participants with positive margins may enroll if the treatment team believes no further surgery is possible and participant has received radiotherapy. Participants with margins positive for lobular carcinoma in situ (LCIS) are eligible. Either mastectomy or breast conserving surgery (including lumpectomy or partial mastectomy) is acceptable. 10. Must have significant residual invasive disease at the time of definitive surgery following preoperative chemotherapy. Significant residual disease is defined as at least one of the following: • Residual Cancer Burden (RCB) classification II or III6 • Residual invasive disease in the breast measuring at least 2 cm. The presence of DCIS without invasion does not qualify as residual disease in the breast. • Residual invasive disease in the breast measuring at least 1 cm with any lymph node involvement (does not include metastases in lymph node which are only detected by immunohistochemistry). • Any lymph node involvement that results in 20% cellularity or greater regardless of primary tumor site involvement (includes no residual disease in the breast). 11. Must have an FFPE tumor block with tumor cellularity of 20% or greater. **NOTE:** Prior to registration, the tumor cellularity will be confirmed by central pathology review. Percent values will be double-checked at Paradigm (a Next Generation Sequencing Company). 12. BREAST RADIOTHERAPY • Whole breast radiotherapy is required for participants who underwent breast-conserving therapy, including lumpectomy or partial mastectomy. Participants must have completed radiotherapy at least 14 days prior (but no more than 84 days prior) to study registration. • Participants with a primary tumor > 5 cm or involvement of ≥4 lymph nodes who require a mastectomy must also have radiotherapy pre- or post-operatively at the discretion of the treating physician. For participants with primary tumors ≤ 5 cm or with < 4 involved lymph nodes, provision of post-mastectomy radiotherapy is at the discretion of the treating physician. Registration must occur within 84 days of the completion of the last local therapy. • For radiation required prior to surgery, the participant must register within 84 days of surgery. Also, participants in this

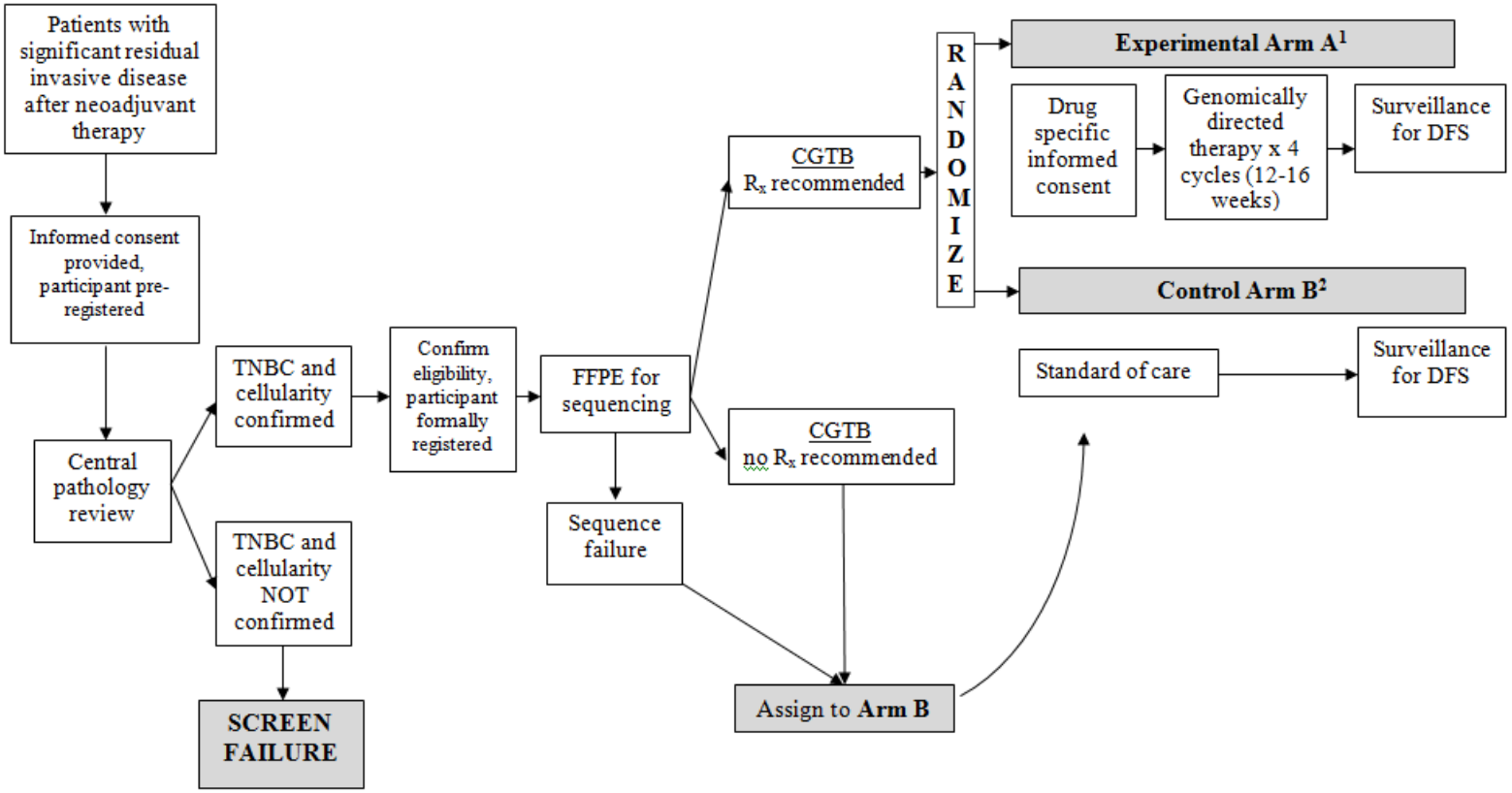
	situation would not be required to have additional post-mastectomy radiation therapy. • For those participants who do not require radiation, registration must be within 84 days of surgery. 13. No stage IV (metastatic) disease, however no specific staging studies are required in the absence of symptoms or physical exam findings that would suggest distant disease. 14. No treatment with any investigational agent within 30 days prior to study registration. 15. No history of chronic hepatitis B or untreated hepatitis C. 16. Adequate laboratory values must be obtained within 14 days prior to study registration. • Hemoglobin (Hgb) ≥ 9.0 g/dL • Platelets ≥ 100 K/mm3 • Absolute neutrophil count (ANC) ≥ 1.5 K/mm3 • Calculated creatinine clearance of ≥ 50 cc/min using the Cockcroft-Gault formula • Bilirubin ≤ 1.5 × ULN (except in participants with documented Gilbert's disease, who must have a total bilirubin ≤ 3.0 mg/dL) • Aspartate aminotransferase (AST, SGOT) ≤ 2.5 × ULN • Alanine aminotransferase (ALT, SGPT) ≤ 2.5 × ULN 17. Left ventricular ejection fraction within normal limits obtained within 30 days prior to study registration. **NOTE:** Participants with an unstable angina or myocardial infarction within 12 months of study registration are excluded. 18. No clinically significant infections as judged by the treating physician. 19. Must consent to allow submission of adequate archived tumor tissue sample from definitive surgery for genomic assessment of tumor. 20. Must consent to collection of whole blood samples for genomic analysis. 21. No clinically significant arrhythmia or baseline ECG abnormalities in the opinion of the treating physician. 22. No active second malignancy (except non-melanomatous skin cancer or incidental prostate cancer found on cystectomy): Active second malignancy is defined as a current need for cancer therapy or a high possibility (> 30%) of recurrence during the study. Previous contralateral breast cancer is allowable unless it meets "active" criteria as stated above.

STATISTICAL CONSIDERATIONS	**Sample Size Justification** The primary endpoint for this trial is 2-year DFS. In order to detect an improvement in the fraction of participants free from disease at 2-year from 40% in the Control Arm B to 63.2% in the genomically directed Experimental Arm A (corresponding to an HR=0.5), 136 participants will have 80% power to detect a difference in DFS using a two-side log-rank test with 0.05 level of significance (calculation done using nQuery Advisor 7.0) and assuming exponential survival. Here, we have assumed a three-year accrual time period, and each participant will subsequently be followed for two years. This three-year accrual period will ensure the ability to recruit 192 participants. Considering other factors, such as no drug calls and failed sequencing, we will ultimately register 136 participants who will be randomized into one of two Arms. **Participant Characteristics** The participant characteristics will be summarized in each treatment group for demographics, baseline disease characteristics, and medical history. The two treatment groups will be compared using standard methods such as t-tests and chi-square tests. **Analysis of Primary Objective** The comparison of DFS between the two groups will be made using an unstratified Kaplan-Meier analysis with a log-rank test to evaluate for differences. A specific comparison of 2-year DFS will be made using a two-sample test based on the complementary log-log transformation as suggested in Klein, et al. As a supportive analysis, a stratified log-rank test will be done using the stratified randomization factors: 1) neoadjuvant anthracycline versus not and 2) lymph node involvement at time of definitive surgery versus not. In addition, sensitivity analyses using Cox regression may be carried out to identify prognostic factors and provide adjusted estimates of the treatment group differences in DFS. **Analysis of Secondary Objectives** As support for the primary objective, overall DFS and 1-year DFS will be compared using the same techniques above. One-year DFS will be tested using the test described above for 2-year DFS. Toxicity variables will be tabulated separately for the two groups. Five-year OS will be compared between treatment groups using the same methodology as DFS. In addition, characteristics of tumor specimens and genomic DNA will be correlated with recurrence and toxicity. Continuous measures will be correlated with binary variables (e.g. recurrence and toxicity) using maximal chi-square tests and continuous variables using Pearson or Spearman correlations. Binary variables such as tumor and genomic characteristics will be correlated with recurrence and toxicity using chi-square or Fisher's Exact test. All of the correlative analyses are

	exploratory and are designed to complement efforts in other trials using this approach. In the secondary analysis, the participants without an actionable mutation in Control Arm B will be compared to the rest of participants in Control Arm B. Here our hypothesis is that these participants may have different disease biology. We will also compare the entire control Arm B (randomized and non-randomized) to Experimental Arm A. This analysis assumes that those participants randomized into Control Arm B and those participants without actionable mutations have similar disease biology, and thus there is no participant selection bias. The secondary analyses will look at DFS, OS, and other toxicity outcome. We will also run the drug specific analysis using frailty model. **Analysis of Exploratory Objectives** During the period required for accrual, it is expected that the ability to recommend genomically directed therapies will evolve. Changes may occur as data from ongoing correlative studies reach the level of evidence required to enter the selection algorithm and/or as new therapies are FDA approved and thus available for recommendation. To explore the impact of this evolution, sequencing data from all participants will be reanalyzed and represented along with the initial clinical information to the CGTB within 1 month of completion of the enrollment. CGTB recommendations for optimal therapy will be compared with the initial recommendations and the proportion with a change in recommendation will be reported. Another exploratory analysis will evaluate each specific drug's effect on efficacy parameters (i.e. DFS) and toxicity. Because the number of participants receiving a specific drug is expected to be relatively small, we will analyze this using a frailty model for DFS. In this model, we allow different drug effects to share the same variance estimate in order to gain power. This analysis will be implemented in R package, coxph function. The drugs' effect on toxicity will be analyzed with the generalized linear mixed effect model, implemented in SAS PROC GLIMMIX or GENMOD. The other exploratory analysis will depend on the results of sequencing. Similar to the drug specific analysis, we will use either the frailty model or the generalized linear mixed model to analyze clinical outcomes.

SCHEMA:

A Phase II Randomized Controlled Trial of Genomically Directed Therapy After Preoperative Chemotherapy in Patients with Triple Negative Breast Cancer



1: Experimental Arm A
Genomically directed therapy at FDA approved dose and schedule for 4 cycles (12-16 weeks)
2: Control Arm B
Xeloda can be considered a standard option. Observation can also be considered if deemed appropriate by the treating physician.
Other therapies are not recommended but can be administered at treating physician's discretion

1 BACKGROUND & RATIONALE

1.1 Primary (neoadjuvant) chemotherapy for breast cancer

Neoadjuvant chemotherapy has a well-established role in the management of both early-stage and locally advanced breast cancer. Providing treatment prior to definitive surgery not only improves the ability to achieve breast conservation, but also allows determination of *in vivo* sensitivity to therapy and offers an ideal platform for clinical research. Although many will experience shrinkage in tumor volume with neoadjuvant therapy, at the time of surgery only about 33% of patients will experience a pathologic complete response (pCR) with complete lack of invasive tumor tissue in the surgical specimen. Long-term follow-up of neoadjuvant studies consistently demonstrates significantly improved survival in individuals with pCR, with comparatively inferior outcomes in those with residual disease at surgery[1-4] The impact of residual disease is more striking in patients with triple negative (ER-/PR-/HER2-) disease compared to patients with other molecular phenotypes[5]. Unfortunately, patients with triple negative disease who have substantial (Miller-Payne classification[6] 1 or 2 or residual cancer burden classification II or III[7]) residual disease at the time of surgery have a dismal prognosis with only 35-40% remaining free of recurrence at 2 years[4,8]. In short, the presence of viable invasive tumor after appropriate neoadjuvant chemotherapy reflects inherent resistance and portends an exceedingly high risk of subsequent recurrence.

Recently, a phase III trial, CREATE-X[16], randomized over 900 HER2-negative patients with residual disease in the breast or lymph node involvement after completion of standard neoadjuvant therapy to 8 cycles of capecitabine at 2500 mg/m^2/day (2 out of 3 weeks) vs. no additional therapy. Approximately 64% of the population had hormone receptor positive disease and 36% had triple negative disease. The trial data was presented at the 2015 San Antonio Breast Conference (Toi et al.) after 2 years follow-up from the time of last patient randomized. The DSM committee terminated the trial early after the trial results had met a planned interim analysis of benefit for the addition of capecitabine. The capecitabine arm demonstrated an improvement in DFS from 74% in the control arm to 82% in the capecitabine arm (HR=0.70; p=0.005). The addition of capecitabine also improved OS from 89.2% to 94% (HR=0.60; p<0.01). The hazard ratios were highly significant in the triple negative subgroup (HR=0.58; 95% CI=0.39-0.87). Thus, capecitabine can be considered a standard option in this setting for triple negative breast cancer. As this represents only a single trial (with prior data not demonstrating benefit for the addition of capecitabine in the neoadjuvant nor adjuvant settings), observation can also be considered an option after discussion of risk to benefit ratio with the patient.

1.2 Rationale for genomically directed approach

Currently, many of the therapies delivered in the neo-adjuvant and adjuvant setting for breast cancer are non-specific cytotoxic agents that are not selected based on specific characteristics from the tumor. Increasingly, molecular aberrancies have opened the door for potential design and use of drugs to capitalize on dysregulated pathways. Examples of successful drugs matched to aberrancy include various categories of aberrancy: over-expression (e.g. trastuzumab for HER2 overexpression[9]), translocation (e.g. imatinib for BCR-ABL translocation[10]) and point mutation (e.g. vemurafenib for BRAF activating mutation; V600E[11]). In general, the therapeutic index for these targeted approaches has been exceptionally high. This proposal will attempt to capitalize on this basic philosophy by matching an expansive list of FDA-approved agents with molecular aberrancies determined by cutting edge assessment of the tumor using massively parallel sequencing.

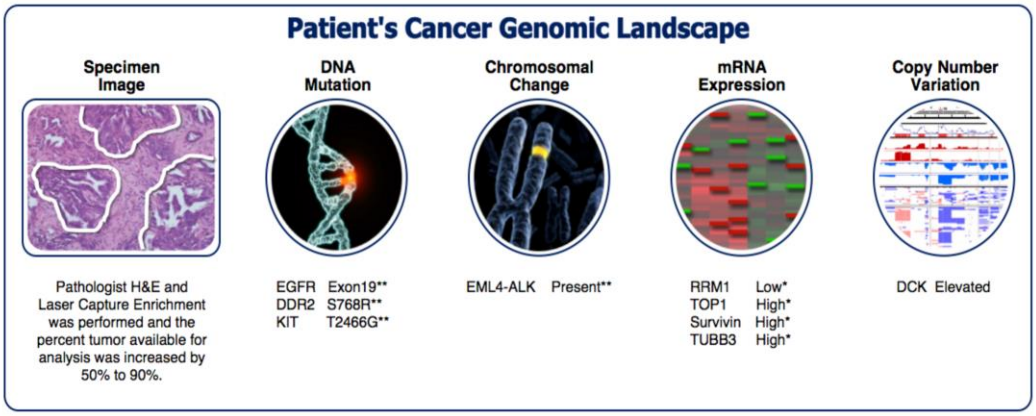
This study will capitalize on an exceptional setting to test a genomic approach and will enrich for participants who have already been exposed to standard non-specific chemotherapy in the neoadjuvant setting with substantial residual disease. This patient population, by definition, is resistant to traditional non-specific cytotoxic chemotherapy. Also, by nature of the high risk of relapse, they are clearly in need of additional (and hopefully superior) targeted therapy. Since these participants have already received standard therapy, the concern for a "high-risk" patient not receiving potentially life-saving therapy will not be an issue. Further, since all drugs used in this proposal are FDA-approved and will be used as single agents, there should be no toxicity concerns beyond those side effects that are well recognized. From a genomic standpoint, the use of these agents in a relatively early point in the tumor's life (i.e. adjuvant setting) will minimize some intrinsic concerns such as genomic drift.[12] This proposal, then, sets out to optimally test the hypothesis that a genomically directed therapy will improve outcome over standard of care in a population that needs a better standard.

1.3 Use of next generation (massively parallel) sequencing to identify therapeutic targets

Paradigm is a non-profit joint venture between the University of Michigan and the International Genomics Consortium (IGC). Paradigm's cancer diagnostic test, PCDx (which will be the platform implemented in this protocol) is a sophisticated and comprehensive CLIA next-generation sequencing cancer diagnostic test available for cancer analysis on formalin fixed paraffin sections. PCDx uses a custom analysis on the PGM Ion Torrent platform to provide patients and physicians with a blueprint of the underlying mechanisms of a patient's disease through next-generation sequencing for mutations, copy number variants (CNV), mRNA and chromosomal changes including allelic burden, potential treatment approaches, assessment of level of evidence, and comprehensive inventory of relevant clinical trials. This clinical decision support tool and analysis is run in a CLIA compliant lab and reports both paper and electronic results in approximately 4-5 working days.

The PCDx test identifies all actionable classes of genomic alterations in hundreds of cancer-related genes having a 1 or 2 level of evidence including:

- DNA Copy Number Variants (e.g. MYC)
- Base Substitutions
- Insertions
- Deletions (e.g. EGFR)
- Chromosomal Rearrangements (e.g. EML4-ALK)
- mRNA Expression
- Splice Variants
- Isoforms (e.g. ERCC1, KIT)



The Paradigm panel queries greater than 500 genetic regions of interest. This includes evaluation of tens of thousands of genomic abnormalities, driver mutations, and changes associated with clinical trials. This panel has a near-perfect ability to detect DNA mutations due to a high depth of coverage; typically over 3000×. This platform also includes a proprietary library creation technique that almost completely eliminates the risk of DNA damaged during the FFPE process from generating false mutation calls. This was validated in The Cancer Genome Atlas project (TCGA) and is the only capture enrichment technology allowed into TCGA. Copy number assays are also sequenced with high coverage, allowing excellent sensitivity; typically able to detect a change of a single chromosome copy.

The PCDx results report with recommended agent will be sent to Hoosier Cancer Research Network, Inc. (HCRN) for disbursement to the CGTB.

1.4 Expected actionable mutations/pathways with recommended agents

We have performed an *in silico* study to predict the most commonly identified and the relative diversity of compounds likely to be identified using this approach. To do this, we used 72 cases of triple-negative breast cancer from The Cancer Genome Atlas (TCGA), a publically available resource of cancer genomics data. For each of these 72 cases we collated the data regarding somatic mutations, copy number variation, and differential gene expression (compared to a panel of 20 normal breast tissues) and submitted this data through the Paradigm PCDx informatics pipeline. For each case, a comprehensive report was generated associating genomic aberrancies with potential therapeutics. The report may list any of the following: 1) FDA-approved, compendia recommended drug; 2) FDA-approved drug off compendia for breast cancer; 3) Drug that is FDA-approved, but with clinical evidence of the biomarker only sufficient to reach the level for consideration of a clinical trial; 4) Biomarker that has a high level of evidence connected with a drug that is not yet FDA approved.

Approximately 82% of the reports generated from these 72 *in silico* cases were able to either select an FDA-approved drug, or highlight a pathway for which an FDA-drug could be selected. **Table 1** provides the 14 drugs that were identified from these cases with an actionable mutation or pathway. **Appendix A** summarizes the detailed information for these 14 drugs. To maximize consistency, we have established recommended agents for the commonly identified biomarkers (**Table 1**). Specifically, there is the potential for multiple drugs to be linked to a specific genetic aberration. For example, if COX2 is upregulated, there are multiple potential NSAIDs that could

be recommended. To maximize homogeneity, we will select a preferred agent in these cases (e.g. COX2 overexpression should result in use of celecoxib if this genetic aberration is considered to be highest priority).

Table 1. Top genomic actionable biomarkers/pathways

Biomarker	Drug recommendation
1. PIK3CA, PTEN	Everolimus
2. TOP2A	Doxorubicin
3. PARP1, BRCA1	Cisplatin or Olaparib
4. VEGFA	Bevacizumab
5. TYMP	Capecitabine
6. SSTR2	Octreotide
7. MGMT	Temozolomide
8. MYC	Paclitaxel
9. EGFR	Cetuximab
10. COX2	Celecoxib
11. hENT	Gemcitabine
12. MET	Crizotinib
13. CCND1,2,3 amplifications; CDKN2A loss, CDK4/6 amplifications	Palbociclib
14. PDL1 TILS or TUMOR IHC+	Pembrolizumab
15. KIT and VEGFR2	Sunitinib
16. PIK3CA	Copanlisib

The drugs listed in **Table 1** will be dosed according to the FDA-approved package inserts (See **Appendix A**). While the drugs listed here will likely comprise a large number of our expected drug recommendations, the nature of this trial makes it impossible to anticipate the optimal genomic target for all participants. Thus, if the genomic data identifies a less common actionable mutation/pathway not included in **Appendix A**, the Sponsor investigator must obtain approval of a protocol exception from the local IRB per local institutional policy. If the same genomic changes (and drug) are recommended for a second patient, we will conclude that this represents a recurrent aberrancy rather than a sporadic event. With this knowledge, the protocol will be amended to add the mutation/pathway and resulting drug.

1.5 Cancer Genomics Tumor Board (CGTB)

Realizing that optimal treatment recommendations cannot be made based on sequencing data alone, the CGTB will be responsible for the final treatment recommendation.
The CGTB includes a diverse group of members with specific areas of expertise including:

- Sponsor Investigator (Schneider)
- Genomics/informatics expert (Radovich)
- Breast medical oncologist with clinical trial expertise (Miller)
- Director of the Indiana University Melvin and Bren Simon Cancer Center (IUSCC) Phase I Program (O'Neil)
- Ethics and supportive care (Helft)

If it becomes necessary to replace a CGTB member, a new member with similar experience and expertise will be recruited. At least three members of the CGTB will meet to review the sequencing report and relevant clinical data for each participant. If only two permanent members of the CGTB are available to meet, an *ad hoc* member (other medical oncologist with clinical trial expertise) may fill in as the third required member. Assuming there are available cases, the review will take place during a standing weekly meeting. Optimal therapy recommendations will be made by consensus. Although the participants will be de-identified during the CGTB deliberations, their underlying comorbidities and medical history may reveal the identity to the treating physician. To avoid the potential that knowledge of the sequencing data might influence the treating investigator's approach (especially if randomized to Control Arm B), any CGTB member who is also the treating physician will be recused and excluded from those discussions.

Hoosier Cancer Research Network will provide the CGTB with the Paradigm PCDx sequencing results report, recommended agent, and summary of the participant's relevant clinical data. The CGTB will consider the genomic data along with the participant's prior treatment history, ongoing toxicities, and comorbidities. Preference will be given to the treatment identified by the sequencing data unless a significant clinical or safety contraindication exists for that therapy. For example, if TOP2A is identified for a participant who previously received anthracycline-based neoadjuvant therapy, the CGTB would not recommend additional doxorubicin due to excess potential for toxicity and lack of enthusiasm for re-treatment with the same drug. Similarly, if a participant has persistent neuropathies, a drug known to cause substantial neuropathy would not be recommended.

If more than one actionable mutation/pathways drug is identified (this occurred in 30% of cases in our preliminary data set), the CGTB will make the final recommendation for a single drug based on the following criteria: 1) Strength of the data that demonstrates an association between the genomic aberration and the selected drug; 2) Participant's prior exposure to therapies; and 3) Co-morbidities or persistent toxicities.

All participants and treating investigators will be blinded to sequencing results and CGTB deliberations until the time of relapse. Reports will automatically be made available to the treating investigator at that time.

1.6 Protocol therapy

All participants for whom the CGTB recommended an optimal therapy will be randomized to Experimental Arm A or Control Arm B. If there is a technical failure in sequencing, no actionable mutations/pathways are identified, or the CGTB cannot make a treatment recommendation, participants will be assigned to Control Arm B. Based on our preliminary data; we suspect this will happen for 18% of our population. Participants who are assigned to Control Arm B will not be included in the primary analyses.

Participants in Experimental Arm A will begin protocol therapy within 10 working days of randomization.

Experimental Arm A (genomically directed monotherapy)
For participants randomized to Experimental Arm A, HCRN will send the CGTB treatment recommendation to the treating investigator in a secure email message. Drug specific details for the top 14 most commonly expected drugs can be found in **Appendix A**. After discussion of the drug specific information and expected toxicities, participants will be asked to provide additional consent to proceed with protocol therapy.

Consenting participants will receive the CGTB recommended therapy in accordance with the FDA label for 4 cycles (12-16 weeks depending on cycle length). For oral drugs administered continuously, 3 weeks will be considered one cycle. Dose reductions, modifications, or discontinuation will be in accordance with the FDA label and standard clinical practice.

Control Arm B (standard therapy)
Those randomized to Control Arm B (and those with no drug call who are assigned to Control Arm B) will follow the direction of their treating physician. Recently, a phase III trial, CREATE-X[16], randomized over 900 HER2-negative patients with residual disease in the breast or lymph node involvement after completion of standard neoadjuvant therapy to 8 cycles of capecitabine at 2500 mg/m2/day (2 out of 3 weeks) vs. no additional therapy. Approximately 64% of the population had hormone receptor positive disease and 36% had triple negative disease. The trial data was presented at the 2015 San Antonio Breast Conference (Toi et al.) after 2 years follow-up from the time of last patient randomized. The DSM committee terminated the trial early after the trial results had met a planned interim analysis of benefit for the addition of capecitabine. The capecitabine arm demonstrated an improvement in DFS from 74% in the control arm to 82% in the capecitabine arm (HR=0.70; p=0.005). The addition of capecitabine also improved OS from 89.2% to 94% (HR=0.60; p<0.01). The hazard ratios were highly significant in the triple negative subgroup (HR=0.58; 95% CI=0.39-0.87). Thus, capecitabine can be considered a standard option in this setting for triple negative breast cancer. As this represents only a single trial (with prior data not demonstrating benefit for the addition of capecitabine in the neoadjuvant nor adjuvant settings), observation can also be considered an option after discussion of risk to benefit ratio with the patient. While not recommended, other therapies can be used as deemed appropriate by the treating physician.

2 OBJECTIVES

2.1 Primary Objective:
To compare 2-year disease-free survival (DFS) in participants with confirmed triple negative breast cancer (TNBC) treated with a genomically directed therapy or standard of care following preoperative chemotherapy

2.2 Secondary Objectives:
- To compare overall DFS and 1-year DFS
- To determine 5-year overall survival (OS)
- To collect archived tumor specimens and genomic DNA to explore potential correlates of recurrence and toxicity.
- To describe the toxicities associated genomically directed therapy in this population

2.3 Exploratory Objectives:

- To describe the evolution of genomically directed therapies during the course of the study
- To evaluate the drug specific effect on both efficacy outcomes (DFS and OS) and toxicity.

3 ELIGIBILITY CRITERIA

1. Written informed consent and HIPAA authorization for release of personal health information.
   NOTE: HIPAA authorization may be included in the informed consent or may be obtained separately.
   NOTE: Central pathology review may be conducted any time after definitive surgery. Consenting participants may be pre-registered to the study and proceed with central pathology review *before* full eligibility has been confirmed. However, ALL of the eligibility criteria must be met and formal study registration completed prior to submission of the sample for sequencing.

2. Age ≥ 18 years at the time of consent.

3. ECOG Performance Status 0 or 1 within 14 days prior to study registration.

4. Women and men of childbearing potential must be willing to use an effective method of contraception (e.g. hormonal or barrier method of birth control; abstinence) from the time consent is signed until 4 weeks after protocol therapy discontinuation.

5. Women of childbearing potential must have a negative pregnancy test within 30 days prior to study registration. Women should be counseled regarding acceptable birth control methods to utilize from the time of screening to start of treatment. If prior to treatment after discussion with the subject it is felt by the treating physician there is a possibility the subject is pregnant a pregnancy test should be repeated.
   NOTE: Women are considered not of childbearing potential if they are surgically sterile (they have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy), or they are postmenopausal for at least 12 consecutive months.

6. Women must not be breastfeeding.

7. Must have histologically or cytologically confirmed triple negative (ER-/PR-/HER2-) invasive breast cancer, clinical stage I-III at diagnosis (AJCC 6th edition) based on initial evaluation by physical examination and/or breast imaging prior to study registration.
   NOTE: ER, PR, and HER2 status will be confirmed by central pathology review prior to randomization. ER and PR will be considered negative if ≤ 10% of cells stain weakly positive. HER2 will be considered negative if scored 0 or 1+ by immunohistochemistry (IHC) or 2+ by IHC associated with a fluorescence *in situ* hybridization (FISH) ratio of < 2.0 or < 6 copies per cell.

8. Must have completed preoperative (neoadjuvant) chemotherapy.
   NOTE: Acceptable preoperative regimens include an anthracycline or a taxane, or both. Participants who received preoperative therapy as part of a clinical trial may enroll. Participants may not have received adjuvant chemotherapy after surgery prior to randomization. Bisphosphonate use is allowed.

9. Must have completed definitive resection of primary tumor. For those that do not require radiotherapy, the most recent surgery for breast cancer must have been completed at least 14 days prior, but no more than 84 days prior, to study registration.
   NOTE: Negative margins for both invasive and ductal carcinoma *in situ* (DCIS) are desirable, however participants with positive margins may enroll if the study site treatment team believes no further surgery is possible and participant has received radiotherapy. Participants with margins positive for lobular carcinoma *in situ* (LCIS) are eligible. Either mastectomy or breast conserving surgery (including lumpectomy or partial mastectomy) is acceptable.

10. Must have significant residual invasive disease at the time of definitive surgery following preoperative chemotherapy. Significant residual disease is defined as at least one of the following:
    - Residual Cancer Burden (RCB) classification II or III[6]
    - Residual invasive disease in the breast measuring at least 2 cm. The presence of DCIS without invasion does not qualify as residual disease in the breast.
    - Residual invasive disease in the breast measuring at least 1 cm with any lymph node involvement (does not include metastases in lymph node which are only detected by immunohistochemistry).
    - Any lymph node involvement that results in 20% cellularity or greater regardless of primary tumor site involvement (includes no residual disease in the breast).

11. Must have an FFPE tumor block with tumor cellularity of 20% or greater.
    NOTE: Prior to registration, the tumor cellularity will be confirmed by central pathology review. Percent values will be double-checked at Paradigm (a Next Generation Sequencing Company).

12. BREAST RADIOTHERAPY
    - Whole breast radiotherapy is required for participants who underwent breast-conserving therapy, including lumpectomy or partial mastectomy. Participants must have completed radiotherapy at least 14 days prior (but no more than 84 days prior) to study registration.
    - Participants with a primary tumor > 5 cm or involvement of ≥4 lymph nodes who require a mastectomy must also have radiotherapy pre- or post-operatively at the discretion of the treating physician. For participants with primary tumors ≤ 5 cm or with < 4 involved lymph nodes, provision of post-mastectomy radiotherapy is at the discretion of the treating physician. Registration must occur within 84 days of the completion of the last local therapy.
    - For radiation required prior to surgery, the participant must register within 84 days of surgery. Also, participants in this situation would not be required to have additional post-mastectomy radiation therapy.

- For those participants who do not require radiation, registration must be within 84 days of surgery.

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

14. No treatment with any investigational agent within 30 days prior to study registration.

15. No history of chronic hepatitis B or untreated hepatitis C.

16. Adequate laboratory values must be obtained within 14 days prior to study registration.
- Hemoglobin (Hgb) $\geq$ 9.0 g/dL
- Platelets $\geq$ 100 K/mm^3
- Absolute neutrophil count (ANC) $\geq$ 1.5 K/mm^3
- Calculated creatinine clearance of $\geq$ 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 $\times$ 0.85
- Bilirubin $\leq$ 1.5 $\times$ ULN (except in participants with documented Gilbert's disease, who must have a total bilirubin $\leq$ 3.0 mg/dL)
- Aspartate aminotransferase (AST, SGOT) $\leq$ 2.5 $\times$ ULN
- Alanine aminotransferase (ALT, SGPT) $\leq$ 2.5 $\times$ ULN

17. Left ventricular ejection fraction within normal limits obtained within 30 days prior to study registration.

NOTE: Participants with an unstable angina or myocardial infarction within 12 months of study registration are excluded.

18. No clinically significant infections as judged by the treating physician.

19. Must consent to allow submission of adequate archived tumor tissue sample from definitive surgery for genomic assessment of tumor.

20. Must consent to collection of whole blood samples for genomic analysis.

21. No clinically significant arrhythmia or baseline ECG abnormalities in the opinion of the treating physician.

22. No active second malignancy (except non-melanomatous skin cancer or incidental prostate cancer found on cystectomy): Active second malignancy is defined as a current need for cancer therapy or a high possibility (> 30%) of recurrence during the study. Previous contralateral breast cancer is allowable unless it meets "active" criteria as stated above.

4 PARTICIPANT REGISTRATION

All participants must be registered through HCRN's electronic data capture (EDC) system. A subject is considered registered when an "On Study" date is entered into the EDC system

Subjects must be registered prior to starting protocol therapy and begin therapy **within 10 days** of randomization.

NOTE: Central pathology review may be conducted any time after definitive surgery. Consenting participants may be pre-registered to the study and proceed with central pathology review before full eligibility has been confirmed. However, ALL of the eligibility criteria must be met and formal study registration completed prior to submission of the sample for sequencing.
Blinding: The protocol therapy is not blinded to the participant or the treating investigator. However, all participants and treating investigators will be blinded to sequencing results and CGTB deliberations until the time of relapse.

5 TREATMENT PLAN

If a subject randomizes to Arm B (control group), medications are not covered by the study and would be handled similarly to standard of care medication administration.

5.1 Pre-medication

It is strongly recommended that all participants receive adequate anti-emetics, hydration, and supportive care as directed by the FDA package insert.

5.2 Drug Administration

All drugs will be administered in accordance with the FDA-label including dose, route, and frequency. Dose modifications will be based on the FDA-label and standard clinical practice. Participants will receive four cycles of therapy. As cycle length may vary, the total duration of therapy may range from 12-16 weeks. The following conventions will be followed when considering cycle length:

Treatment administered	Cycle length
every 4 weeks	4 weeks
every 3 weeks	3 weeks
Weekly	3 weeks
continuous oral	3 weeks

See **Appendix A** for detailed information on the most commonly expected drugs.

All therapy in Experimental Arm A will be based on the participant's actual weight unless the FDA package insert recommends a fixed dose. The actual weight at screening should be used for calculating body surface area (BSA). The BSA *may* be recalculated based on the actual weight at the start of each treatment cycle but recalculation and dose adjustment is only required if a participant's weight changes by ≥ 10%.

5.3 Missed doses

In general, participants should be encouraged to comply with the FDA-recommended treatment schedule. However, if IV treatment is missed for reasons other than toxicity (e.g. participant vacation, family emergency, etc.), participants able to resume treatment within 2 weeks should receive the full planned number of cycles. If a delay of more than 2 weeks is required, the missed IV treatment should be omitted (i.e. not made up) and participants should proceed with the next cycle as originally scheduled. For those participants receiving oral agents, missed doses should not be made up and should continue for the duration planned at the outset of therapy.

5.4 Supportive Care

The use of supportive care including antibiotics, blood transfusions, etc. will be permitted as clinically indicated and according to institutional guidelines.

5.5 Concomitant Medications

Medications known to interact with the recommended drug will be considered by the CGTB at time of drug selection. If a participant is taking a drug with a significant interaction risk, and that drug is deemed important for the participant's ongoing health, the selected therapy will be considered contraindicated by the CGTB. Bisphosphonate use is allowed.

6 DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 will be used to grade adverse events.

Participants enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in section 7. Schedule of Events.

Participants will be evaluated for adverse events different in type and/or severity from what would be expected from the approved drug labeling, serious adverse events, and adverse events requiring protocol therapy interruption or discontinuation at each study visit for the duration of their participation in the study. As the agents used in this study are FDA approved with well-defined safety profiles, only serious adverse events, and adverse events resulting in dose modification and/or treatment discontinuation will be entered to the database and analyzed.

For participants in Experimental Arm A, all doses should be modified as outlined in the FDA-approved package insert (See **Appendix A**).

Participants in Experimental Arm A discontinued from the treatment phase of the study for any reason will be evaluated at least 30 days (± 7) after the last dose of protocol therapy.

7 SCHEDULE OF EVENTS

7.1 Experimental Arm A

	Pre-registration (All participants)	Screening (All participants)	Cycles 1-4[1] (Arm A only)	Treatment[2] Discontinuation (Arm A Only)	Surveillance[3] (All participants)
	Post-surgery	-30 days	D1 of each cycle (±3 days)	30 days (±7) after last dose	±1 month
REQUIRED ASSESSMENTS					
Informed consent	X		X[4]		
Complete medical history and height		X			
Complete physical examination		X	X	X	X
Weight, BP		X	X	X	X
ECOG performance status		X	X	X	X
CMP[5]		X	Repeat as needed based on FDA label and standard practice	X	
Calculated creatinine clearance		X		X	
CBC with differential		X		X	
Breast imaging (remaining native breast tissue only)					Yearly
Electrocardiogram		X	Follow FDA label and standard practice		
MUGA or Echocardiogram		X			
Urine pregnancy or serum HCG[6]		X			
Adverse event & con med assessment		X	X	X	
TREATMENT EXPOSURE					
Genomically directed therapy			X		
CORRELATIVE SAMPLES					
Tumor from initial diagnosis – Optional[7]			X		
Tumor from definitive surgery – Mandatory[7]	X[7]				
Whole blood for genomic DNA – Mandatory[8]			X[8]		
Whole blood for Plasma – Optional[9]			X[9]	X[9]	
Whole blood for CTC – Mandatory[10]			X[10]	X[10]	

1: Cycle 1 Day 1 testing need not be repeated if obtained within 14 days of starting protocol therapy.
2: Participants in Experimental Arm A discontinued from the treatment phase of the study for any reason will be evaluated 30 days (±7) after the last dose of protocol therapy.
3: Monitor for the development of either local (chest wall, axillary, or supraclavicular nodes) or distant recurrent disease, complete physical exam including weight, BP and ECOG performance status completed at least once every 3 months for the first two years, then at least every 6 months during years 3-5 after Treatment Discontinuation. At disease progression, participant should be followed for survival only.
4: Following CTGB Review, participants randomized to Experimental Arm A provide drug specific informed consent prior to initiating protocol therapy on Cycle 1 Day 1.
5: Serum chemistries (creatinine, glucose, total protein, blood urea nitrogen [BUN], total carbon dioxide [CO2], albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase [AST] and alanine transaminase [ALT]) and electrolytes (total calcium, chloride, potassium, sodium).
6: Complete only in women of childbearing potential. Screening test to be done 30 days prior registration. Women should be counseled regarding acceptable birth control methods to utilize from the time of screening to start of treatment. If prior to treatment after discussion with the subject it is felt by the treating physician there is a possibility the subject is pregnant a pregnancy test should be repeated.
7: Optional collection of tumor tissue from initial diagnosis. Subjects will be asked to consent to this collection. Mandatory complete central pathology review of tumor tissue from definitive surgery.
8: Mandatory 8.5 mL whole blood for genomic DNA will be collected at Cycle 1 Day 1 for Experimental Arm A (see Section 9.3 Samples for Future Studies).
9: Optional 10 mL whole blood for plasma will be collected at Cycle 1 Day 1 and Treatment Discontinuation for Experimental Arm A (See Section 9.3 Samples for Future Studies).
10: Mandatory 10 mL whole blood for CTC will be collected at Cycle 1 Day 1 and Treatment Discontinuation for Experimental Arm A (See Section 9.3 Samples for Future Studies).

7.2 Control Arm B

	Pre-registration (All participants)	Screening (All participants)	On Study[1] (Arm B only)	Surveillance[2] (All participants)
	Post-surgery	-30 days	D1	±1 month
REQUIRED ASSESSMENTS				
Informed consent	X			
Complete medical history and height		X		
Complete physical examination		X		X
weight, BP		X		X
ECOG performance status		X		X
CMP		X		
Calculated creatinine clearance		X		
CBC with differential		X		
Breast imaging (remaining native breast tissue only)				Yearly
Electrocardiogram		X		
MUGA or Echocardiogram		X		
Urine pregnancy or serum HCG[3]		X		
Adverse event & concomitant medication assessment		X		
TREATMENT EXPOSURE				
Capecitabine, other chemotherapy or observation[8]		X		
CORRELATIVE SAMPLES				
Tumor from initial diagnosis – Optional[4]			X	
Tumor from definitive surgery Mandatory[4]	X[4]			
Whole blood for genomic DNA Mandatory[5]			X	
Whole blood for Plasma – Optional[6]			X	
Whole blood for CTC – Mandatory[7]			X	X

1: On Study Day 1 is defined as the next available routine care visit after Randomization.
2: Monitor for the development of either local (chest wall, axillary, or supraclavicular nodes) or distant recurrent disease, complete physical exam including weight, BP and ECOG performance status completed at least once every 3 months for the first two years, then at least every 6 months during years 3-5 after Treatment Discontinuation. At disease progression, participant should be followed for survival only.
3: Complete only in women of childbearing potential. Screening test to be done 30 days prior registration. Women should be counseled regarding acceptable birth control methods to utilize from the time of screening to start of treatment. If prior to treatment after discussion with the subject it is felt by the treating physician there is a possibility the subject is pregnant a pregnancy test should be repeated.
4: Optional collection of tumor tissue from initial diagnosis. Subjects will be asked to consent to this collection. Mandatory complete central pathology review of tumor tissue from definitive surgery.
5: Mandatory 8.5 mL whole blood for genomic DNA will be collected at next available routine appointment (Day 1) (see Section 9.3 Samples for Future Studies).
6: Optional 10 mL whole blood for plasma will be collected at next available routine appointment (Day 1) (See Section 9.3 Samples for Future Studies).
7: Mandatory 10 mL whole blood for CTC will be collected at next available routine appointment (Day 1) and the 3 or 6 month visit (See Section 9.3 Samples for Future Studies).
[8]For participants where capecitabine or other chemotherapy is planned, monitoring and adjustment for toxicity should be in accordance with standard practice and the experience of the treating physician.

7.3 Pre-registration (All Participants)

- Consenting participants may be pre-registered to the study and proceed with central pathology review of tumor tissue from definitive surgery before full eligibility has been confirmed. However, ALL of the eligibility criteria must be met and formal study registration completed prior to submission of the sample for sequencing.
- Mandatory - tumor tissue from definitive surgery (See Correlatives Laboratory Manual (CLM) for collection, labeling and shipping instructions)

7.4 Screening

Within 30 days of study registration (ARMS A & B):

- Complete medical history
- Complete physical examination including: height, weight, BP, and ECOG performance status
- Complete metabolic profile (CMP) including: serum chemistries (creatinine, glucose, total protein, blood urea nitrogen [BUN], total carbon dioxide [CO_2], albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase [AST] and alanine transaminase [ALT]) and electrolytes (total calcium, chloride, potassium, sodium)
- Calculated creatinine clearance
- Complete Blood Count (CBC) with differential
- Urine pregnancy test or serum HCG (only in women of child bearing potential. Women should be counseled regarding acceptable birth control methods to utilize from the time of screening to start of treatment. If prior to treatment after discussion with the subject it is felt by the treating physician there is a possibility the subject is pregnant a pregnancy test should be repeated.
- Electrocardiogram (ECG)
- Multigated acquisition (MUGA) scan or Echocardiogram (Echo)
- Adverse event and concomitant medication assessment

7.5 On Study Day 1 (CONTROL ARM B ONLY):

On Study Day 1 is defined as the next available routine care visit after Randomization.

- Genomic and Correlative studies (See CLM for collection, labeling and shipping instructions)
    - Optional - tumor tissue from initial diagnosis
    - Mandatory - collect 8.5 mL whole blood for genomic DNA
    - Optional - collect 10 mL whole blood for plasma
    - Mandatory – collect 10 mL whole blood for Circulating Tumor Cells (CTC)

7.6 On Treatment (EXPERIMENTAL ARM A ONLY)

Following CTGB Review, participants randomized to Experimental Arm A provide drug specific informed consent prior to initiating protocol therapy on Cycle 1 Day 1.

7.6.1 Day 1 of each cycle (± 3 days) (EXPERIMENTAL ARM A ONLY):

Note: Cycle 1 Day 1 testing need not be repeated if completed within 14 days of starting protocol therapy.

- Complete physical examination including: weight, BP
- ECOG performance status
- Complete metabolic profile (CMP): Repeat as needed based on FDA label and standard practice
- Calculated creatinine clearance: Repeat as needed based on FDA label and standard practice
- CBC with differential: Repeat as needed based on FDA label and standard practice
- ECG: Repeat as needed based on FDA label and standard practice
- MUGA or Echo: Repeat as needed based on FDA label and standard practice
- Adverse event and concomitant medication assessment
- Genomic and Correlative Studies (**Cycle 1 Day 1 Only**) (See CLM for collection, labeling and shipping instructions)
    - Optional - tumor tissue from initial diagnosis
    - Mandatory - collect 8.5 mL whole blood for genomic DNA
    - Optional - collect 10 mL whole blood for plasma
    - Mandatory– collect 10 mL whole blood for CTC

7.7 Treatment Discontinuation (EXPERIMENTAL ARM A ONLY)

A participant will be discontinued from the protocol therapy under the following circumstances:

- If there is evidence of progressive disease.
- If the treating physician thinks a change of therapy would be in the best interest of the participant.
- If the participant withdraws consent to protocol treatment.
- If the drug exhibits unacceptable adverse event. (Participants will be followed until the resolution of these adverse events.)
- If a participant becomes pregnant.

NOTE: Participants can stop participating at any time. However, if they decide to stop participating in the study, they will continue to be followed for progression and survival unless the participant has also withdrawn consent for further follow-up.

7.7.1 Within 30 days (±7) after the last dose of protocol therapy (EXPERIMENTAL ARM A ONLY):

- Complete physical examination including: weight, BP
- ECOG performance status
- Adverse event and concomitant medication assessment
- Correlative Studies
    - Optional - collect 10 mL whole blood for plasma
    - Mandatory – collect 10 mL whole blood for CTC

7.8 Study Participation Discontinuation (CONTROL ARM B ONLY)

A participant will be discontinued from study participation under the following circumstances:

- If the participant requests discontinuation.

  NOTE: Participants can stop participating at any time. However, if they decide to stop participating in the study, they will continue to be followed for progression and survival unless the participant has also withdrawn consent for further follow-up.

7.9 Surveillance (ARMS A & B)

- Complete physical examination including: weight, BP
- ECOG performance status
- Participants will be monitored by their treating physicians for the development of either local (chest wall, axillary, or supraclavicular nodes) or distant recurrent disease at least once every 3 months for the first two years, then at least every 6 months during years 3-5 after Treatment Discontinuation for Experimental Arm A and for those where chemotherapy is planned in Arm B. For those on Arm B who have observation only, follow-up will begin after randomization. At progression, participants will be followed for survival only.
- Suggested guidelines for surveillance of breast cancer survivors are available through the National Comprehensive Cancer Network (www.nccn.org).
- Routine blood work or radiology in the absence of symptoms suggestive of recurrent disease is not recommended.
- Remaining breast tissue (contralateral breast and ipsilateral breast in participants treated with breast conserving surgery) should be imaged annually according to standard screening guidelines.
- Correlative Studies for Arm B only
    - Mandatory – collect 10 mL whole blood for CTC at 3 or 6 month visit

8 CRITERIA FOR DISEASE EVALUATION

DFS is defined as the duration of time from randomization to time of a DFS event, defined as local failure (invasive), regional failure, distant failure, contralateral breast cancer (invasive or non-invasive), or death from any cause. The diagnosis of local or distant recurrence should ideally be pathologically confirmed, however if biopsy if not possible, radiology confirmation by CT, MRI, or PET scan is acceptable.

9 BIOLOGICAL SAMPLES

HCRN will provide sample collection kits and shipping supplies for tissue sample submissions and for blood samples collected for genomic and correlative studies. All sample labels will only include the HCRN participant study ID#, date/time of collection and sample type. No personal identifiers will be included. Refer to the CLM associated with this protocol for collection, processing, labeling, and shipping instructions.

9.1 Central Pathology Review

Analysis by an American Society of Clinical Oncology (ASCO) and College of American Pathology (CAP) expert panel suggests that approximately 20% of ER, PR, and HER2 tests performed in community laboratories are inaccurate with a fairly equal distribution of false positive and false negative results. The ASCO/CAP guidelines seek to improve test quality and

reliability. As such, ER, PR, and HER2 status will be confirmed by central pathology review prior to randomization.

- ER and PR will be considered negative if ≤ 1% of cells stain weakly positive.
- HER2 will be considered negative if scored 0 or 1+ by immunohistochemistry (IHC) or 2+ by IHC associated with a fluorescence *in situ* hybridization (FISH) ratio of < 2.0 or < 6 copies per cell.

Additionally central pathology review will confirm the cellularity of the residual disease sample (> 20% required for eligibility). If the sample fails to meet the percent value required, a new sample (if available) will be requested from the participating site.

Formalin-fixed paraffin-embedded (FFPE) tissue from the residual disease removed at the time of definitive surgery (mandatory) is required to be submitted for central pathology review. The estimated timeframe to complete the central pathology review and provide a results report is 5-7 working days. Once the central pathology review is complete and participant eligibility is confirmed, formalin-fixed paraffin-embedded (FFPE) tissue will need to be sent to Paradigm. Paradigm will double-check the cellularity percent values and complete the genomic sequencing. Refer to the CLM for collection, labeling and shipping instructions.

NOTE: Central pathology review may be conducted any time after definitive surgery. Consenting participants may be pre-registered to the study and proceed with central pathology review before full eligibility has been confirmed. However, ALL of the eligibility criteria must be met and formal study registration completed prior to submission of the sample for sequencing.

9.2 Samples for genomic sequencing

Prior to registration, the tumor cellularity will be confirmed by central pathology review. Percent values will be double-checked at Paradigm (a Next Generation Sequencing Company). A minimum of 20% tumor cellularity is needed to initiate the next generation sequencing analysis. Paradigm will use a proprietary tumor enrichment technology called Laser Capture Enrichment (LCE) that allows the macroscopic and microscopic isolation of populations of cells such as cancer cells to be separated from the non-malignant populations. The LCE technology has been validated in The Cancer Genome Atlas project (TCGA) and is the only capture enrichment technology allowed into TCGA. Paradigm can provide the mutational next generation sequencing analysis when the cellularity is equal to or above 20% tumor nuclei. LCE will be used to enrich above the 20% tumor cellularity cut point. Above 50% tumor nuclei, the full Paradigm analysis of mutation, copy number abnormality, chromosomal aberrations, and mRNA can be performed in totality on formalin fixed paraffin sections. When the tumor cellularity is between 20% and 50% tumor nuclei than some subset of the Paradigm analysis can be performed and thus all samples above 20% will be sent.

9.3 Samples for future studies

Participant consent will be obtained for additional samples for future studies. These samples and any leftover required samples will be banked. **NOTE:** Participants will be asked to consent to allow banking of their DNA and RNA for future studies.

This includes:

- Tumor from initial diagnosis (sample collected prior to neoadjuvant chemotherapy):
  Optional for both Arms
  - Formalin-fixed paraffin embedded tissue that contains > 60% tumor cellularity will be obtained after the participant is formally registered to the trial.
- Tumor from definitive surgery:
  Mandatory for both Arms
  - Formalin-fixed paraffin embedded tissue that contains > 20% tumor cellularity will be obtained after the participant is formally registered to the trial.
- Whole blood for genomic DNA:
  Mandatory for both Arms
  - 8.5 mL whole blood will be collected on Cycle 1 Day 1 for Experimental Arm A and after Randomization at their next routine care visit (Day 1) for Control Arm B participants.
- Whole blood for Plasma:
  Optional for both Arms
  - 10 mL whole blood for plasma will be collected on Cycle 1 Day 1 and at Treatment Discontinuation for Experimental Arm A and after Randomization at their next routine care visit (Day 1) for Control Arm B.
- DNA and RNA extracted from Circulating Tumor Cells (CTC):
  Mandatory for both Arms
  - 10 mL whole blood for CTC enumeration and DNA and RNA extraction will be collected on:
    - Cycle 1 Day 1 and at Treatment Discontinuation for Experimental Arm A.
    - After Randomization at their next routine care visit (Day 1) and at the 3 or 6 month visit for Control Arm B.

Refer to the CLM associated with this protocol for collection, processing, labeling, and shipping instructions.

10 CLINICAL TRIAL MATERIAL (CTM) INFORMATION

See **Appendix A** for drug information. If treatment recommendation is an injectable drug, this will be supplied from the participating site's own pharmacy. All drugs should be stored in a securely locked area with limited access. If treatment recommendation is an oral agent other than Olaparib, the site is to obtain the drug from US Bioservices. If treatment recommendation is Olaparib, the site will obtain the drug from Biologics. Specific instructions for ordering drug are contained in the CLM. Consult the package insert for the common and serious adverse events in addition to proper storage, preparation, administration, and handling instructions. CTM is to be dispensed only by authorized personnel under the supervision of a licensed physician at the investigative site.

All drugs assigned to participants randomized to Experimental Arm A will be paid for by this study.

11 ADVERSE EVENT MANAGEMENT

Adverse events will be collected and reported as described below for the Experimental Group (Arm A) only. Arm B subjects are undergoing treatment that is considered standard of care, recording and reporting of adverse events will not be done.

11.1 Definitions of Adverse Events

11.1.1 Adverse Event (AE)

Any untoward medical occurrence in a participant or clinical trial subject administered an investigational product and which does not necessarily have a causal relationship with the treatment. An adverse event (AE) can, therefore, be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic testing.

11.1.2 Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence resulting in one or more of the following:

- Results in death
- Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

11.1.3 Unexpected Adverse Event

An adverse event not mentioned in the package insert or the specificity or severity of which is not consistent with the package insert.

11.2 Adverse Event (AE) Reporting

Adverse events will be recorded from the time of consent and for at least 30 days after final protocol treatment. As the agents used in this study are FDA-approved and have a well-defined safety profile, only serious adverse events, and adverse events resulting in dose modification and/or treatment discontinuation will be reported. All AEs considered related to trial medication

will be followed until resolution, return to baseline, or deemed clinically insignificant, even if this occurs post-trial.

11.3 Serious Adverse Event (SAE) Reporting

11.3.1 Study Center (Site) Requirements for Reporting SAEs

Treating investigators and other site personnel must report any SAEs occurring during the course of the study within 24 hours of discovery of the event. This includes events both related and unrelated to the product.

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

Table 15: Relationship of adverse event to the investigational agent

Unrelated	The Adverse Event is *clearly not related* to the agent(s)
Unlikely	The Adverse Event is *doubtfully related* to the agent(s)
Possible	The Adverse Event *may be related* to the agent(s)
Probable	The Adverse Event is *likely related* to the agent(s)
Definite	The Adverse Event is *clearly related* to the agent(s)

The completed SAE Reporting Form (see Study Procedure Manual) must be emailed to safety@hoosiercancer.org at HCRN within 24 hours of discovery of the event. The treating investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

The original copy of the SAE Reporting Form along with the email cover sheet and/or fax confirmation sheet must be kept within the study binder at the study site.

Follow-up information should be emailed to safety@hoosiercancer.org at HCRN, using a new SAE Reporting Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the participant continued or withdrew from study participation.

11.3.2 Death and Immediately Life-Threatening Events

Any death and immediately life-threatening event from any cause while a participant is receiving protocol therapy or up to 30 days after the last dose of protocol therapy, or any death and immediately life-threatening event occurring more than 30 days after protocol therapy has ended but which is felt to be treatment related must be reported within 24 hours of discovery of event. All deaths must be reported primarily for the purposes of SAE reporting; however, deaths due unequivocally to progression are not SAEs.

Your local IRB should be notified and their reporting procedure followed. The completed SAE Reporting Form should be emailed to safety@hoosiercancer.org at HCRN **within 24 hours of discovery** of the event.

11.3.3 HCRN Requirements for Reporting SAEs

HCRN will voluntarily report to the FDA, regardless of the study site of occurrence, any SAE that is reasonably related (i.e. possible, probable, definite) to the protocol therapy and different in type and/or severity from what would be expected from the approved drug labeling (unexpected). Unexpected fatal or life-threatening experiences associated with the protocol therapy will be voluntarily reported to the FDA as soon as possible but in no event later than 7 calendar days after initial receipt of the information by HCRN. All other serious unexpected experiences associated with the use of the protocol therapy will be voluntarily reported to the FDA no later than 15 calendar days after initial receipt of the information by HCRN.

For Guidelines and MedWatch Form FDA 3500, refer to the FDA Voluntary Reporting for Consumers and Healthcare Professionals Guidelines webpage:
http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm

12 STATISTICAL CONSIDERATIONS

Table 16: Data Sets for Protocol Endpoints

Data Set/Endpoint	Criteria
Disposition	All participants registered into the study
General safety	All participants in Experimental Arm A receiving at least one dose of any protocol therapy
Efficacy	All participants (Experimental Arm A receiving at least one dose of any protocol therapy and Control Arm B) with at least one post-Randomization disease evaluation

Participants will be included in the analysis for the treatment to which they were randomized.

12.1 Sample Size Justification

The primary endpoint for this trial is 2 year DFS. In order to detect an improvement in the fraction of participants free from disease at 2-year from 40% in the Control Arm B to 63.2% in the genomically directed Experimental Arm A (corresponding to an HR=0.5), 136 participants will have 80% power to detect a difference in DFS using a two-side log-rank test with 0.05 level of significance. The power calculation was calculated and validated by SAS, R, and nQuery and based on SAS (**Table 17**).

Table 17.

2 Year Survival		HR Arm A/B*	Power R		Power SAS	Power nQuery
Arm A	Arm B*		Log rank	Cox	Log rank	Log rank
0.682	0.40	2.40	0.93	0.92	0.92	0.92
0.632	0.40	2.00	0.80	0.80	0.80	0.80
0.582	0.40	1.70	0.58	0.58	0.58	0.57

**Randomized participants (excludes participants assigned to Control Arm B)*

Here, we have assumed a three-year accrual time, and each participant will subsequently be followed for two years. This three-year accrual period will ensure the ability to recruit 192 participants. Considering other factors, such as no drug calls and failed sequencing, we will enroll 136 eligible participants who will be randomized into one of two Arms.

12.2 Participant Characteristics

Participant characteristics will be summarized by treatment group for demographics, baseline disease characteristics, and medical history. The two treatment groups will be compared using standard methods such as t-tests and chi-square tests.

12.3 Analysis of Primary Objective

The comparison of DFS between the two groups will be made using an unstratified Kaplan-Meier analysis with a log-rank test to evaluate for differences. A specific comparison of 2-year DFS will be made using a two-sample test based on the complementary log-log transformation as suggested in Klein, et al[15]. As a supportive analysis, a stratified log-rank test will be done using the stratified randomization factors: 1) neoadjuvant anthracycline versus not and 2) lymph node involvement at time of definitive surgery versus not. In addition, sensitivity analyses using Cox regression may be carried out to identify prognostic factors and provide adjusted estimates of the treatment group differences in DFS.

Participants who are assigned to Control Arm B will not be included in the primary analyses.

12.4 Analysis of Secondary Objectives

As support for the primary objective, overall DFS and 1-year DFS will be compared using the same techniques above. One-year DFS will be tested using the test described above for 2-year DFS. Toxicity variables will be tabulated separately for the two groups. Five-year OS will be compared between treatment groups using the same methodology as DFS. In addition, clinical and demographic characteristics of tumor specimens and genomic DNA will be correlated with recurrence and toxicity. Continuous measures will be correlated with binary variables (e.g. recurrence and toxicity) using maximal chi-square tests and continuous variables using Pearson or Spearman correlations. Binary variables such as tumor and genomic characteristics will be correlated with recurrence and toxicity using chi-square or Fisher's exact test. All of the correlative analyses are exploratory and are designed to complement efforts in other trials using this approach.

In the secondary analysis, the participants without an actionable mutation in Control Arm B will be compared to the rest of participants in Control Arm B. Here our hypothesis is that these participants may have different disease biology. We will also compare the entire control Arm B (randomized and non-randomized) to Experimental Arm A. This analysis assumes that those participants randomized into Control Arm B and those participants without actionable mutations have similar disease biology, and thus there is no participant selection bias. The secondary analyses will look at DFS, OS, and other toxicity outcome. We will also run the drug specific analysis using frailty model.

12.5 Analysis of Exploratory Objectives

During the period required for accrual, it is expected that the ability to recommend genomically directed therapies will evolve. Changes may occur as data from ongoing correlative studies reach the level of evidence required to enter the selection algorithm and/or as new therapies are FDA approved and thus available for recommendation. To explore the impact of this evolution, sequencing data from all participants will be reanalyzed and represented along with the initial clinical information to the CGTB within 1 month of completion of the study enrollment. CGTB recommendations for optimal therapy will be compared with the initial recommendations and the proportion with a change in recommendation will be reported.

Another exploratory analysis will evaluate each specific drug's effect on the participant efficacy outcome (i.e. DFS) and toxicity. Because the number of participants receiving a specific drug treatment is expected to be relatively small, we will analyze using a frailty model for DFS. In this model, we allow different drug effects to share the same variance estimate, in order to gain power. This analysis will be implemented in R package, coxph function. The drug effects on the toxicity will be analyzed with the generalized linear mixed effect model, implemented in SAS PROC GLMMIX or GENMOD.

The other exploratory analysis will depend on the results of sequencing. Similar to the drug specific analysis, we will use either the frailty model or the generalized linear mixed model to analyze clinical outcomes.

13 TRIAL MANAGEMENT

13.1 Quality Controls and Quality Assurance

13.1.1 Data and Safety Monitoring Board

This study will have a Data and Safety Monitoring Board (DSMB) that will review and monitor study progress, toxicity, safety and other data from this trial. The DSMB is separate from the IUSCC Data and Safety Monitoring Committee (DSMC) referred to below. The board is chaired by an independent medical oncologist external to this trial. Questions about participant safety or protocol performance will be addressed with the Sponsor investigator, statistician, and study team members. Should any major concerns arise; the DSMB will offer recommendations regarding whether or not to suspend the trial.

The DSMB will meet twice a year to review accrual, toxicity, response, and reporting information. The DSMB will meet annually after the last participant is off treatment and has completed the end of treatment evaluation. Information to be provided to the DSMB may include: participant accrual, treatment regimen information, adverse events, and serious adverse events reported by category, summary of any deaths on study, audit, and/or monitoring results.

The DSMB will provide a recommendation to the team after all information is reviewed. This information should also be provided to the IRB at the time of continuing review for the trial.

13.1.2 Data Safety Monitoring Committee

HCRN will provide the DSMC with data summary reports as requested. The DSMC will also review DSMB reports regarding this study.

13.1.3 HCRN Oversight Activities

This trial is subject to auditing and/or monitoring. The HCRN data management team provides safety oversight for all HCRN trials. Specific data and safety monitoring tasks conducted by HCRN include:

- Review all adverse events requiring expedited reporting as defined in the protocol
- Notify participating sites of adverse events requiring expedited reporting
- Provide trial accrual progress and safety information to the sponsor-investigator
- Provide data summary reports to the sponsor-investigator
- Submit data summary reports to the Data Safety Monitoring Board per their Charter.

13.1.4 Study Monitoring

For-cause monitoring visits to the trial sites may be made periodically during the trial. Source documents will be reviewed for verification of agreement with data as submitted via the data collection system. The treating investigator/institution guarantee access to source documents by HCRN or its designee and appropriate regulatory agencies.

The trial site may also be subject to quality assurance audit by appropriate regulatory agencies.

It is important for the treating investigators and their relevant personnel to be available during the monitoring visits and possible audits and for sufficient time to be devoted to the process.

13.2 Data Handling and Record Keeping

13.2.1 Case Report Forms and Submission

This study will utilize electronic case report form (eCRF) in the Electronic Database Capture (EDC) system. The EDC system is a comprehensive database used by HCRN and, properly used, is compliant with Title 21 CFR Part 11. Access to the data through the EDC system is restricted by user accounts and assigned roles. Once logged into the EDC system with a user ID and password, EDC defines roles for each user, which limits access to appropriate data. User information and passwords can be obtained by contacting HCRN at 317-921-2050.

Generally, clinical data will be electronically captured in the EDC system and correlative results will be captured in the EDC system or other secure database. If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in the EDC system, according to study-specific objectives. Detailed guidelines for eCRF completion can be found in the eCRF Instructions.

The completed dataset is the sole property of HCRN and should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from HCRN.

13.2.2 Record Retention

To enable evaluations and/or audits from Health Authorities/HCRN, the treating investigator agrees to keep records, including the identity of all participants (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all eCRFs, and detailed records of drug disposition. To comply with international regulations, the records should be retained by the treating investigator in compliance with regulations.

During data entry, range and missing data checks will be performed on-line. The checks to be performed will be documented in the Data Management Plan for the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRFs will be generated for each site and transmitted to the site and the site monitor. Corrections will be made by the study site personnel. This will be done on an ongoing basis.

13.3 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the participant will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study team. Samples that are collected will be identified by a participant study number assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the participant study number.

Participants will be informed in writing that some organizations including the treating investigator and his/her research associates, HCRN, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the participant's identity will remain confidential.

13.4 Changes to the Protocol

Study procedures will not be changed without the mutual agreement of the sponsor-investigator and HCRN.

If it is necessary for the study protocol to be amended, a new version of the study protocol (amended protocol) will be generated by HCRN and must be approved by each participating site IRB, and if applicable, local regulatory authority. Local requirements must be followed.

If a protocol amendment requires a change to the Informed Consent Form, then the IRB must be notified. Approval of the revised Written Informed Consent Form by the IRB is required before the revised form is used.

The Sponsor investigator is responsible for the distribution of these documents to his or her IRB, and to the staff at his or her center. The distribution of these documents to the regulatory authority will be handled according to local practice.

13.5 Ethics

13.5.1 Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved by an IRB. The treating investigator must submit written approval to the HCRN office before he or she can enroll any participant into the study.

The treating investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit participants for the study. The protocol must be re-approved by the IRB annually, as local regulations require.

Progress reports and notifications of serious unexpected adverse drug reactions will be provided to the IRB according to local regulations and guidelines.

These reports will be reviewed by the Sponsor investigator, and those considered unexpected and possibly related to protocol therapy, and all deaths within 30 days of discontinuing treatment, will be forwarded to participating sites for submission to their Institutional Review Boards per their guidelines. All other events will be held and submitted to the sites for continuing review.

13.5.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki, which are consistent with ICH Good Clinical Practice, and applicable regulatory requirements.

13.5.3 Informed Consent

The treating investigator will ensure the participant is given full and adequate oral and written information about the nature, purpose, possible risks, and benefits of the study. Participants must also be notified they are free to discontinue from the study at any time. The participant should be given the opportunity to ask questions and allowed time to consider the information provided. The participant's signed and dated informed consent must be obtained before conducting any procedure specifically for the study.

Following CTGB Review and Randomization, Experimental Arm A participant's signed and dated drug specific informed consent form must be obtained before initiating protocol therapy on Cycle 1 Day 1.

The treating investigator must store all original, signed Informed Consent Forms. A copy of the signed Informed Consent Form must be given to the participant.

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HCRN BRE12-158 Appendix A.

Chemotherapy dosing, monitoring and dose adjustments.

Bevacizumab

Recommended dosing for bevacizumab

Drug	Dose	Frequency of administration	Route of administration	Number of cycles
Bevacizumab	15 mg/kg	Every 3 weeks Cycle=3 weeks	IV	4 cycles (12 weeks)

Recommended monitoring for bevacizumab

1. Urine protein every cycle
    a. -hold if urine protein $\geq$ 2+
2. Blood pressure every cycle
    a. -if BP>150/100 add anti-hypertensive
    b. -If BP>180/110 hold
3. Sign/Symptoms of bleeding or thrombosis, every cycle
4. Dose adjustments:
    a. hypertension, severe, not controlled: temporarily suspend bevacizumab; discontinue with hypertensive crisis or hypertensive encephalopathy.
    b. proteinuria, moderate to severe: temporarily suspend bevacizumab; discontinue for nephrotic syndrome.
    c. surgery: suspend treatment with bevacizumab at least 28 days prior to elective surgery; do not restart until the surgical incision has completely healed; do not give for at least 28 days following major surgery; discontinue if wound healing complications require medical intervention.

The National Cancer Institute Common Terminology Criteria for Adverse events v4.0 (CTCAE) will be used for adverse event reporting and grading. For any toxicity that is Grade 2, the dose will be held and reduced per package insert guidelines for the given medication. For any toxicity that is grade 3 or higher, the treatment will be discontinued and re-evaluated at the resolution of the adverse event.

The package insert will be consulted and followed for the recommended manufacturer monitoring or dose adjustments required based on complete blood counts and metabolic panel. The current package insert can be found at http://www.accessdata.fda.gov/scripts/cder/daf/

Capecitabine

Recommended dosing for Capecitabine

Drug	Dose	Frequency of administration	Route of administration	Number of cycles
Capecitabine	1250 mg/m^2 (round for tablet)	Twice daily for 2 weeks then 1 week off Cycle=3 weeks	orally	4 cycles (12 weeks)

Recommended monitoring for capecitabine

1. Complete metabolic panel, prior to each cycle
2. Complete blood counts, prior to each cycle
3. Dose adjustments:
    a. renal impairment: CrCl 30 to 50 mL/min, decrease starting dose to 75% of the original dose
    b. hepatic impairment: mild to moderate, no initial dosage adjustment necessary
    c. monotherapy, grade 2 adverse event: first appearance, hold capecitabine dose until resolved to grade 0 to 1; second appearance, hold capecitabine dose until resolved to grade 0 to 1 and give 75% of the original capecitabine dose at the start of the next cycle; third appearance, hold capecitabine dose until resolved to grade 0 to 1 and give 50% of the original capecitabine dose at the start of the next cycle; fourth appearance, discontinue treatment
    d. monotherapy, grade 3 adverse event: first appearance, hold capecitabine dose until resolved to grade 0 to 1 and give 75% of the original capecitabine dose at the start of the next cycle; second appearance, hold capecitabine dose until resolved to grade 0 to 1 and give 50% of the original capecitabine dose at the start of the next cycle; third appearance, discontinue permanently
    e. monotherapy, grade 4 adverse event: first appearance, discontinue permanently or continue if the physician considers it to be in the best interest of the participant; give 50% of the starting capecitabine dose at the start of the next cycle

The National Cancer Institute Common Terminology Criteria for Adverse events v4.0 (CTCAE) will be used for adverse event reporting and grading. For any toxicity that is Grade 2, the dose will be held and reduced per package insert guidelines for the given medication. For any toxicity that is grade 3 or higher, the treatment will be discontinued and re-evaluated at the resolution of the adverse event.

The package insert will be consulted and followed for the recommended manufacturer monitoring or dose adjustments required based on complete blood counts and metabolic panel. The current package insert can be found at http://www.accessdata.fda.gov/scripts/cder/daf/

Celecoxib

Recommended dosing for Celecoxib

Drug	Dose	Frequency of administration	Route of administration	Number of cycles
Celecoxib	200 mg	Daily Cycle = 3 weeks	Orally	4 cycles (12 weeks)

Recommended monitoring for celecoxib

1. Signs/symptoms of skin reaction
2. Complete blood counts and complete metabolic panel at the discretion of the physician.
3. Dose adjustments
    a. Discontinue in severe renal (CrCl < 30 ml/min) and hepatic (Child-Pugh Class C) impairment

The National Cancer Institute Common Terminology Criteria for Adverse events v4.0 (CTCAE) will be used for adverse event reporting and grading. For any toxicity that is Grade 2, the dose will be held and reduced per package insert guidelines for the given medication. For any toxicity that is grade 3 or higher, the treatment will be discontinued and re-evaluated at the resolution of the adverse event.

The package insert will be consulted and followed for the recommended manufacturer monitoring or dose adjustments required based on complete blood counts and metabolic panel. The current package insert can be found at http://www.accessdata.fda.gov/scripts/cder/daf/

Cetuximab

Recommended dosing for Cetuximab

Drug	Dose	Frequency of administration	Route of administration	Number of cycles
Cetuximab	400 mg/m^2 week 1 loading dose, then, 250 mg/m^2 weekly thereafter	Weekly Cycle = 3 weeks	IV	4 cycles (12 weeks)

Recommended monitoring for cetuximab

1. Signs/symptoms of dermatologic toxicity
2. Signs/symptoms of infusion reactions
3. BMP plus magnesium, monthly
4. Premedicate with a H1 antagonist prior to first dose; premedication should be administered for subsequent doses based upon clinical judgement and presence/severity of prior infusion reactions.
5. Dose adjustments:
    a. dermatologic toxicities (severe, grade 3 or 4 acneiform rash): delay for 1 to 2 weeks; if improved, restart at 250 mg/m(2) after the first occurrence, 200 mg/m(2) after the second occurrence, and 150 mg/m(2) after the third occurrence; cetuximab should be discontinued if a participant does not improve from a previous episode or has a fourth occurrence
    b. infusion-related toxicities: decrease infusion rate by 50% for grade 1 or 2 infusion-related reactions and non-serious grade 3 infusion reactions; immediately and permanently discontinue cetuximab in participants experiencing a serious reaction that requires medical intervention and/or hospitalization
    c. pulmonary toxicities: interrupt for acute onset or worsening of pulmonary symptoms; permanently discontinue cetuximab in participants if interstitial pulmonary lung disease is confirmed.

The National Cancer Institute Common Terminology Criteria for Adverse events v4.0 (CTCAE) will be used for adverse event reporting and grading. For any toxicity that is Grade 2, the dose will be held and reduced per package insert guidelines for the given medication. For any toxicity that is grade 3 or higher, the treatment will be discontinued and re-evaluated at the resolution of the adverse event.

The package insert will be consulted and followed for the recommended manufacturer monitoring or dose adjustments required based on complete blood counts and metabolic panel. The current package insert can be found at http://www.accessdata.fda.gov/scripts/cder/daf/

Cisplatin

Recommended dosing for Cisplatin

Drug	Dose	Frequency of administration	Route of administration	Number of cycles
Cisplatin	75 mg/m^2	Every 3 weeks Cycle = 3 weeks	IV	4 cycles (12 weeks)

Recommended monitoring for cisplatin

1. Complete metabolic panel, prior to each cycle
2. Complete blood counts, prior to each cycle
3. Dose adjustments:
    a. renal impairment: repeat courses should not be given until serum creatinine is less than 1.5 mg/100 mL and/or BUN is less than 25 mg/100 mL
    b. absolute neutrophil count (ANC) 1.0 K/mm^3 to 1.5 K/mm^{3}or platelets 50 to 100K/mm^3): hold therapy until ANC is greater than 1.5 K/mm^3 and platelets greater than 100 K/mm^3; maintain initial dose.

The National Cancer Institute Common Terminology Criteria for Adverse events v4.0 (CTCAE) will be used for adverse event reporting and grading. For any toxicity that is Grade 2, the dose will be held and reduced per package insert guidelines for the given medication. For any toxicity that is grade 3 or higher, the treatment will be discontinued and re-evaluated at the resolution of the adverse event.

The package insert will be consulted and followed for the recommended manufacturer monitoring or dose adjustments required based on complete blood counts and metabolic panel. The current package insert can be found at http://www.accessdata.fda.gov/scripts/cder/daf/

Copanlisib
Recommended dosing for Copanlisib

Drug	Dose	Frequency of administration	Route of administration	Number of cycles
Copanlisib	60 mg	Days 1, 8 and 15 of a 28 day cycle Cycle = 4 weeks	IV over 60 minutes	4 cycles (16 weeks)

Recommended monitoring for copanlisib

1. Complete blood counts with differential, baseline then weekly
2. Dose adjustments:
    a. Withhold treatment until ANC $\geq 0.5 \times 10^3$ cells/mm^3
    b. Withhold treatment if platelet count $< 25 \times 10^9$ and utilize dose reduction guidelines per PI.
    b. Withhold treatment in patients until both the systolic blood pressure (BP) is less than 150 mmHg and the diastolic BP is less than 90 mmHg. Consider reducing dose if anti-hypertensive treatment is required. Discontinue in patients with BP that is uncontrolled or with life-threatening consequences. Monitor for signs and symptoms of congestive heart failure and abnormal arrhythmia
    b. Monitor urine protein
    c. Monitor serum glucose
    d. Monitor for severe cutaneous reactions

The National Cancer Institute Common Terminology Criteria for Adverse events v4.0 (CTCAE) will be used for adverse event reporting and grading. The dose of copanlisib will be held and reduced per package insert guidelines for the given medication. For any toxicity that is grade 3 or higher, the treatment will be discontinued and re-evaluated at the resolution of the adverse event.

The package insert will be consulted and followed for the recommended manufacturer monitoring or dose adjustments required based on complete blood counts and metabolic panel. The current package insert can be found at http://www.accessdata.fda.gov/scripts/cder/daf/

Crizotinib

Recommended dosing for Crizotinib

Drug	Dose	Frequency of administration	Route of administration	Number of cycles
Crizotinib	250 mg	Twice daily Cycle = 3 weeks	Orally	4 cycles (12 weeks)

Recommended monitoring for crizotinib

1. Complete blood counts, baseline then monthly
2. liver function tests, including ALT and total bilirubin; monthly
3. BMP plus magnesium monthly
4. Electrocardiograms in participants with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, and participants taking concomitant QT-prolonging drugs
5. Evaluate for CYP3A4 drug interactions.
6. Dose adjustments:
    a. hepatic impairment, grade 3 or 4 ALT or AST elevation with concurrent grade 1 or lower elevation of total bilirubin: withhold crizotinib until recovery to grade 1 or lower or to baseline, then resume at 200 mg orally twice a day; if toxicity recurs withhold until recovery to grade 1 or lower, then resume at 250 mg orally once a day; permanently discontinue in case of grade 3 or 4 recurrence.
    b. renal impairment: no dosage adjustments required in mild (CrCl 60 to 90 mL/min) or moderate renal impairment (CrCl 30 to 60 mL/min).
    c. hematologic toxicity, grade 3: except lymphopenia unless associated with clinical events (e.g., opportunistic infections), withhold crizotinib until recovery to grade 2 or lower, and then resume at the same dose schedule.
    d. hematologic toxicity, grade 4: except lymphopenia unless associated with clinical events (e.g., opportunistic infections), withhold crizotinib until recovery to grade 2 or lower, then resume at 200 mg orally twice a day; if grade 4 hematologic toxicity recurs withhold until recovery to grade 2 or lower, then resume at 250 mg orally once a day; permanently discontinue in case of grade 4 recurrence.

The National Cancer Institute Common Terminology Criteria for Adverse events v4.0 (CTCAE) will be used for adverse event reporting and grading. For any toxicity that is Grade 2, the dose will be held and reduced per package insert guidelines for the given medication. For any toxicity that is grade 3 or higher, the treatment will be discontinued and re-evaluated at the resolution of the adverse event.

The package insert will be consulted and followed for the recommended manufacturer monitoring or dose adjustments required based on complete blood counts and metabolic panel. The current package insert can be found at http://www.accessdata.fda.gov/scripts/cder/daf/

Doxorubicin

Recommended dosing for Doxorubicin

Drug	Dose	Frequency of administration	Route of administration	Number of cycles
Doxorubicin	60 mg/m^2	Every 3 weeks Cycle=3 weeks	IV	4 cycles (12 weeks)

Recommended monitoring for Doxorubicin

1. LVEF (via MUGA or ECHO) at baseline then periodically if cardiac risk factors present
2. Complete blood count, prior to each dose
3. Complete metabolic panel, prior to each dose
4. Dose adjustments:
    a. neutropenic fever/infection (adjuvant treatment of axillary node-positive breast cancer) administer 75% of the starting doses of doxorubicin; delay next cycle until the absolute neutrophil count is at least 1.0 K/mm^3 the platelet count is at least 100 K/mm^3), and non-hematologic toxicities have resolved.
    b. hepatic impairment: 50% dose reduction for serum bilirubin of 1.2 to 3 mg/dL; 75% dose reduction for serum bilirubin of 3.1 to 5 mg/dL

The National Cancer Institute Common Terminology Criteria for Adverse events v4.0 (CTCAE) will be used for adverse event reporting and grading. For any toxicity that is Grade 2, the dose will be held and reduced per package insert guidelines for the given medication. For any toxicity that is grade 3 or higher, the treatment will be discontinued and re-evaluated at the resolution of the adverse event.

The package insert will be consulted and followed for the recommended manufacturer monitoring or dose adjustments required based on complete blood counts and metabolic panel. The current package insert can be found at http://www.accessdata.fda.gov/scripts/cder/daf/

Everolimus

Recommended dosing for Everolimus

Drug	Dose	Frequency of administration	Route of administration	Number of cycles
Everolimus	10 mg	Daily Cycle = 3 weeks	Orally	4 cycles (12 weeks)

Recommended monitoring for Everolimus

1. Complete blood counts, baseline then monthly
2. Complete metabolic panel, baseline then monthly
3. Fasting serum glucose, baseline then every 3 months
4. Fasting lipid panel, baseline then every 3 months. Treatment of dyslipidemia in accordance with National institute of health guidelines.
    a. metabolic events (e.g., hyperglycemia, dyslipidemia): if dose reduction below the lowest available strength is necessary, consider alternate-day dosing; grade 3, temporarily interrupt therapy and consider reinitiating at approximately 50% the previous dose; grade 4, discontinue Everolimus.
5. Non-hematologic toxicities (not metabolic events): if dose reduction below the lowest available strength is necessary, consider alternate-day dosing; grade 2 and intolerable symptoms, interrupt therapy until recovery to grade 1 or less and reinitiate at the same dose, if symptoms recur again at grade 2, interrupt therapy again until symptoms improve to grade 1 or less and reinitiate at approximately 50% the previous dose; grade 3, interrupt therapy until symptoms improve to grade 1 or less and consider reinitiating at approximately 50% the previous dose, consider discontinuation if toxicity recurs at grade 3; grade 4, discontinue Everolimus.
6. Evaluate for CYP3A4 drug interactions.

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The package insert will be consulted and followed for the recommended manufacturer monitoring or dose adjustments required based on complete blood counts and metabolic panel. The current package insert can be found at http://www.accessdata.fda.gov/scripts/cder/daf/

Gemcitabine

Recommended dosing for Gemcitabine

Drug	Dose	Frequency of administration	Route of administration	Number of cycles
Gemcitabine	1250 mg/m^2	Days 1, 8 every 21 days Cycle = 3 weeks	IV	4 cycles (12 weeks)

Recommended monitoring for gemcitabine

1. Complete blood counts with differential, prior to each dose
2. Complete metabolic panel, baseline then periodically as needed
3. Dose adjustments:
    a. non-hematologic toxicity (grade 3 or 4) (except alopecia, nausea, or vomiting): hold dose or decrease by 50%.
    b. On Day 1 of gemcitabine; if the absolute neutrophil count (ANC) is 1500 × 10^6/L or greater and the platelets are 100 K/mm^3 or greater, give the full dose; if the ANC is less than 1.5 K/mm^3 or the platelets are less than 100 K/mm^3, hold the dose. On Day 8 of treatment; if the ANC is 1.0-1.199 K/mm^3 or platelets are 50 - 75 K/mm^3, give 75% of the dose; if the ANC is 0.7 – 0.999 K/mm^3 and platelets are > 50 K/mm^3, give 50% of the dose; if the ANC is < 0.7 K/mm^3 and platelets are < 50 K/mm^3, hold the dose.

The National Cancer Institute Common Terminology Criteria for Adverse events v4.0 (CTCAE) will be used for adverse event reporting and grading. For any toxicity that is Grade 2, the dose will be held and reduced per package insert guidelines for the given medication. For any toxicity that is grade 3 or higher, the treatment will be discontinued and re-evaluated at the resolution of the adverse event.

The package insert will be consulted and followed for the recommended manufacturer monitoring or dose adjustments required based on complete blood counts and metabolic panel. The current package insert can be found at http://www.accessdata.fda.gov/scripts/cder/daf/

Octreotide

Recommended dosing for Octreotide

Drug	Dose	Frequency of administration	Route of administration	Number of cycles
Octreotide	20 mg	Every 4 weeks Cycle = 4 weeks	IM, intragluteally	4 cycles (16 weeks)

Recommended monitoring for octreotide

1. Thyroid function, baseline and prior to last dose
2. BMP prior to each dose
3. Electrocardiogram baseline

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The package insert will be consulted and followed for the recommended manufacturer monitoring or dose adjustments required based on complete blood counts and metabolic panel. The current package insert can be found at http://www.accessdata.fda.gov/scripts/cder/daf/

Olaparib

Recommended dosing for Olaparib

Drug	Dose	Frequency of administration	Route of administration	Number of cycles
Olaparib	400 mg	Twice daily Cycle = 4 weeks	PO	4 cycles (16 weeks)

Recommended monitoring for Olaparib

2. Basic metabolic panel, prior to each cycle
3. Complete blood counts, prior to each cycle
4. Dose adjustments:
    a. Renal impairment, mild (CrCl 50 to 80 mL/min): No dose adjustment is required, although monitoring is recommended. No data is available for participants on dialysis or with moderate to severe impairment (CrCl less than 50mL/min).
    b. Absolute neutrophil count (ANC) 1.0 to 1.5 K/mm^3 or platelets 50 to 100 K/mm^3): hold therapy until ANC is greater than 1.5 K/mm^3 and platelets greater than 100 K/mm^3; maintain initial dose. If participant experiences toxicity again, reduce dose to 200 mg BID.

The National Cancer Institute Common Terminology Criteria for Adverse events v4.0 (CTCAE) will be used for adverse event reporting and grading. For any toxicity that is Grade 2, the dose will be held and reduced per package insert guidelines for the given medication. For any toxicity that is grade 3 or higher, the treatment will be discontinued and re-evaluated at the resolution of the adverse event.

The package insert will be consulted and followed for the recommended manufacturer monitoring or dose adjustments required based on complete blood counts and metabolic panel. The current package insert can be found at http://www.accessdata.fda.gov/scripts/cder/daf/

Paclitaxel

Recommended dosing for Paclitaxel

Drug	Dose	Frequency of administration	Route of administration	Number of cycles
Paclitaxel	80 mg/m^2	Weekly Cycle = 3 weeks	IV	4 cycles (12 weeks)

Recommended monitoring for paclitaxel

2. Complete blood counts, prior to each dose
3. Complete metabolic panel, monthly
4. Sign/symptoms of infusion reaction
5. Premedication for paclitaxel included diphenhydramine 50 mg and an H_2 blocker approximately 30 minutes prior to each paclitaxel infusion plus dexamethasone 10 mg prior to weekly paclitaxel.
6. Dose adjustments:
    a. do not initiate therapy if baseline neutrophils are less than 1.5 K/mm^3; do not administer a subsequent cycle until neutrophils are greater than 1.5 K/mm^3 and platelets are greater than 100 K/mm^3; if neutrophil count drops below 0.5 K/mm^3 for one week or longer, decrease dose by 20% on subsequent cycles.
    b. peripheral neuropathy: decrease dose by 20% on subsequent cycles

The National Cancer Institute Common Terminology Criteria for Adverse events v4.0 (CTCAE) will be used for adverse event reporting and grading. For any toxicity that is Grade 2, the dose will be held and reduced per package insert guidelines for the given medication. For any toxicity that is grade 3 or higher, the treatment will be discontinued and re-evaluated at the resolution of the adverse event.

The package insert will be consulted and followed for the recommended manufacturer monitoring or dose adjustments required based on complete blood counts and metabolic panel. The current package insert can be found at http://www.accessdata.fda.gov/scripts/cder/daf/

Palbociclib

Recommended dosing for Palbociclib

Drug	Dose	Frequency of administration	Route of administration	Number of cycles
Palbociclib	125 mg	Daily for 21 days of a 28 day cycle Cycle = 4 weeks	Orally	4 cycles (16 weeks)

Recommended monitoring for palbociclib

1. Complete blood counts with differential, baseline then on day 14 (14 days after the first dose) of 28-day treatment cycle and weekly until recovery if the absolute neutrophil count falls below 150 K/mm^3
2. Dose adjustments or dose reductions per package insert guidelines

The National Cancer Institute Common Terminology Criteria for Adverse events v4.0 (CTCAE) will be used for adverse event reporting and grading. For certain Grade 3 toxicities or higher, the dose will be held and possibly reduced per package insert guidelines for the given medication.

The package insert will be consulted and followed for the recommended manufacturer monitoring or dose adjustments required based on complete blood counts and metabolic panel. The current package insert can be found at http://www.accessdata.fda.gov/scripts/cder/daf/

Pembrolizumab

Recommended dosing for pembrolizumab

Drug	Dose	Frequency of administration	Route of administration	Number of cycles
Pembrolizumab	200 mg	Every 3 weeks Cycle = 3 weeks	IV	4 cycles (12 weeks)

Recommended monitoring for pembrolizumab

1. Signs/symptoms of immune mediated problems
    - Pneumonitis
    - Colitis
    - Hepatitis
    - Endocrinopathies
    - Rash (Steven Johnson's Syndrome)
    - Changes in eyesight
    - Muscle pain or weakness
    - Myocarditis
2. Signs/symptoms of infusion reactions
5. CBC and CMP before each dose. Thyroid function at baseline then as clinically needed.
6. No pre-medications required
7. Withhold pembrolizumab for any of the following:
    - Grade 2 pneumonitis
    - Grade 2 or 3 colitis
    - Grade 3 or 4 endocrinopathies
    - Grade 2 nephritis
    - Grade 2 hypophysitis
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 and up to 5 times upper limit of normal (ULN) or total bilirubin greater than 1.5 and up to 3 times ULN
    - Any other severe or Grade 3 treatment-related adverse reaction

The National Cancer Institute Common Terminology Criteria for Adverse events v4.0 (CTCAE) will be used for adverse event reporting and grading.

The package insert will be consulted and followed for the recommended manufacturer monitoring or dose adjustments required. The current package insert can be found at http://www.accessdata.fda.gov/scripts/cder/daf/

Sunitinib

Recommended dosing for Sunitinib

Drug	Dose	Frequency of administration	Route of administration	Number of cycles
Sunitinib	37.5 mg	Daily for 21 days of a 21 day cycle Cycle = 3 weeks	Orally	4 cycles (12 weeks)

Recommended monitoring for sunitini

1. Complete blood counts with differential, baseline then on day 1 of each cycle
2. Dose adjustments:
    a. SUTENT should be interrupted for Grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution. Do not restart SUTENT if patients subsequently experience severe changes in liver function tests or have other signs and symptoms of liver failure.
    b. Monitor for signs and symptoms of congestive heart failure and abnormal arrythmia
    c. Monitor for high blood pressure
    d. Monitor urine protein
    e. Monitor serum glucose

The National Cancer Institute Common Terminology Criteria for Adverse events v4.0 (CTCAE) will be used for adverse event reporting and grading. For any toxicity that is Grade 2, the dose will be held and reduced per package insert guidelines for the given medication. For any toxicity that is grade 3 or higher, the treatment will be discontinued and re-evaluated at the resolution of the adverse event.

The package insert will be consulted and followed for the recommended manufacturer monitoring or dose adjustments required based on complete blood counts and metabolic panel. The current package insert can be found at http://www.accessdata.fda.gov/scripts/cder/daf/

Temozolomide

Recommended dosing for Temozolomide

Drug	Dose	Frequency of administration	Route of administration	Number of cycles
Temozolomide	150 mg/m^2 (round for tablet)	Daily for 5 days of a 28 day cycle Cycle = 4 weeks	Orally	4 cycles (16 weeks)

Recommended monitoring for temozolomide

1. Complete blood counts with differential, baseline then on day 22 (21 days after the first dose) of 28-day treatment cycle and weekly until recovery if the absolute neutrophil count and platelet count fall below 150 K/mm^3 and 100 K/mm^3, respectively
2. Dose adjustments:
    a. absolute neutrophil count (ANC) 1.0 to 1.5 K/mm^3 or platelets 50 to 100 K/mm^3): hold therapy until ANC is greater than 1.5 K/mm^3 and platelets greater than 100 K/mm^3; maintain initial dose.

The National Cancer Institute Common Terminology Criteria for Adverse events v4.0 (CTCAE) will be used for adverse event reporting and grading. For any toxicity that is Grade 2, the dose will be held and reduced per package insert guidelines for the given medication. For any toxicity that is grade 3 or higher, the treatment will be discontinued and re-evaluated at the resolution of the adverse event.

The package insert will be consulted and followed for the recommended manufacturer monitoring or dose adjustments required based on complete blood counts and metabolic panel. The current package insert can be found at http://www.accessdata.fda.gov/scripts/cder/daf/