

Academic and Community Cancer Research United (ACCRU)

Double Blind, Parallel Groups, Controlled, Randomized Phase II Trial to Evaluate Vaccination with Folate Receptor Alpha Peptide Vaccine with GM-CSF as Vaccine Adjuvant Following Oral Cyclophosphamide Versus GM-CSF/Placebo to Prevent Recurrence in Patients with Triple Negative Breast Cancer

For any communications regarding this protocol, please contact the person indicated on the Protocol Resource page. This is a stand-alone document found on the ACCRU web site ([REDACTED]).

Study Chairs

ACCRU: [REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]

[REDACTED]
[REDACTED]

Study Co-chairs: [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

FDA/IND Sponsor Investigator: [REDACTED]

Statistician: [REDACTED]
[REDACTED]
[REDACTED]

Drug Availability

Commercial Agents: Oral Cyclophosphamide (Cytoxan), GM-CSF (Leukine)

Drug Company Supplied: Folate Receptor Alpha Peptide Vaccine (IND# 17133)

√ Study contributor(s) not responsible for patient care.

* Grant holder

Research Coordinating Center

[REDACTED]
[REDACTED]
[REDACTED]

Document History

Activation ACCRU

Addendum 1

Addendum 2

Addendum 3

(effective date)

March 31, 2017

June 28, 2018

September 6, 2018

October 3, 2018

Addendum 4	June 10, 2019
Addendum 5	June 19, 2020
Addendum 6	March 5, 2021
Addendum 7	December 20, 2021
Addendum 8	June 26, 2023

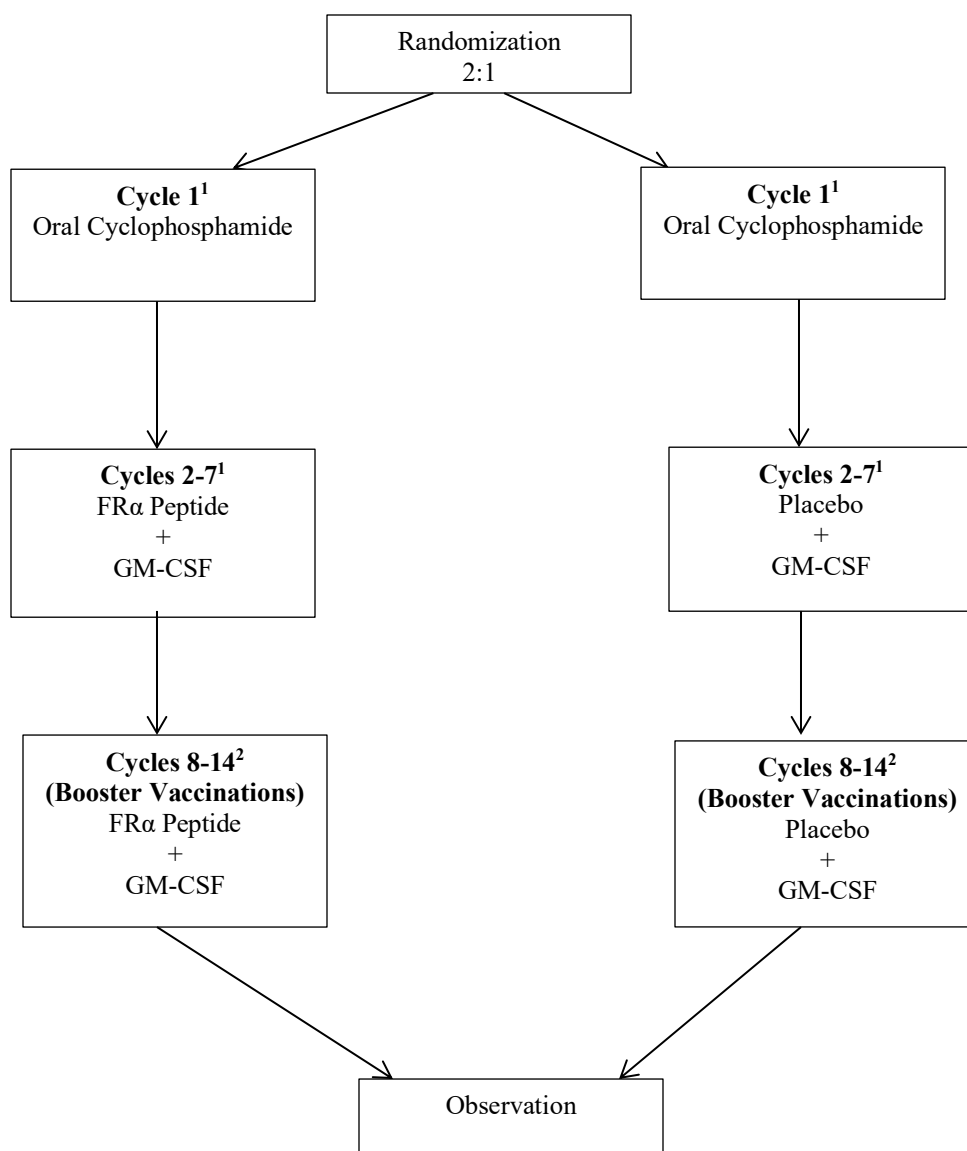
Index

Schema

- 1.0 Background
- 2.0 Goals
- 3.0 Patient Eligibility
- 4.0 Test Schedule
- 5.0 Stratification Factors
- 6.0 Registration/Randomization Procedures
- 7.0 Protocol Treatment
- 8.0 Dosage Modification Based on Adverse Events
- 9.0 Ancillary Treatment/Supportive Care
- 10.0 Adverse Event (AE) Reporting and Monitoring
- 11.0 Treatment Evaluation Using RECIST Guideline
- 12.0 Descriptive Factors
- 13.0 Treatment/Follow-up Decision at Evaluation of Patient
- 14.0 Body Fluid Biospecimens
- 15.0 Drug Information
- 16.0 Statistical Considerations and Methodology
- 17.0 Pathology Considerations/Tissue Biospecimens
- 18.0 Records and Data Collection Procedures
- 19.0 Budget
- 20.0 References

Appendix I – Neurologic Evaluation

Appendix II – Sample Cyclophosphamide Pill Diary

Schema¹ Cycle = 28 days² Cycle= 6 months

Generic name: Cyclophosphamide Brand name(s): Cytoxan Availability: McKesson Specialty Pharmacy's Clinical Research Services	Generic name: GM-CSF Brand name(s): Leukine Availability: McKesson Specialty Pharmacy's Clinical Research Services
Generic name: FRα Peptide Brand name(s): Availability: McKesson Specialty Pharmacy's Clinical Research Services	Generic name: Placebo (Normal saline) Brand name(s): Availability: Commercially Available

1.0 Background

1.1 Treatment

1.11 TRIPLE NEGATIVE BREAST CANCER (TNBCs)

Triple negative breast cancer (TNBC) is a heterogeneous group of breast cancers which lack estrogen and progesterone receptors and have low to moderate levels of HER2 [1]. TNBC occurs in approximately 15% of all patients with breast cancer and is associated with a poor prognosis [1]. Patients with TNBC derive no benefit from approved available targeted therapies (e.g. trastuzumab, pertuzumab, tamoxifen). Excluding those patients who demonstrate a pathologic complete response following neo-adjuvant chemotherapy, which is a minor fraction (i.e. ~15%), overall survival is only ~45% at 7 years; if considering patients with node negative or positive disease [2, 3]. Following standard of care, there are windows of opportunity to further and safely treat patients to prevent recurrence. We believe that stimulating the immune system to produce T cells specific for tumor antigens can significantly delay recurrence and potentially cure patients. The clinical trial outlined in the current propose will focus on vaccination of TNBC patients who have been rendered disease free following conventional therapy, to induce T cells to survey for the reemergence of TNBCs, with the goals to prevent recurrence.

The vaccine strategy that we propose is antigen-specific and will target the folate receptor alpha (FR α). FR α is an ideal target because of its generally low or negative expression in healthy tissues and its higher more frequent expression in a large proportion (70-86%) of TNBCs. Preclinical and clinical studies of our group and others have shown that it is a biologically important marker associated with poorer clinical outcome and is retained in metastatic lesions (~85%) [4, 5]. We have identified immunogenic epitopes and developed peptide pools that safely generated CD4 T cell immune responses in patients examined in an ongoing phase I clinical trial [6]. Our preliminary data from a phase I trial (described below), which includes immune responses and safety information, provide the basis to proceed with phase II testing to evaluate efficacy. The proposed research is based on good scientific and clinical research principles, as part of our overall strategy to improve outcomes of patients diagnosed with TNBC.

1.12 FOLATE RECEPTOR ALPHA (FR α) AND FOLATE

Three FR isoforms have been described, referred to as FR α , FR β and FR γ . FR α is the most widely studied FR isoform and it has restricted expression in normal cells but is highly expressed in various non-mucinous tumors of epithelial origin. FR α confers a growth advantage to the tumor by modulating folate uptake from serum or by generating regulatory signals [7]. Folate is the generic term for folic acid and structurally-related compounds that have the biochemical activity of folic acid. It is involved in essential one-carbon transfer reactions that are important in DNA synthesis and replication, cell division, and growth and survival, particularly for rapidly dividing cells [7]. The importance of folate analogues (e.g., methotrexate) to cancer treatment provides strong evidence that folate is required by rapidly proliferating tumor cells. Two functionally different

systems exist for cellular uptake of folates: (i) membrane-bound FR (FR α and FR β), which is linked to cell surfaces via a glycosyl-phosphatidylinositol (GPI) anchor and internalizes folates by receptor-mediated endocytosis and (ii) reduced folate carrier [RFC], which uses a bidirectional anion-exchange mechanism to transport folates into the cytoplasm. The RFC is the main cellular supply pathway for folate in the human body.

1.13 PATIENTS NATURALLY DEVELOP IMMUNE RESPONSES TO THE FR α

Our group has been a pioneer in developing the FR α as a tumor antigen. Using a CD4+ T cell epitope prediction algorithm, we predicted epitopes of FR α , and tested for immunity in 30 breast (n = 17) or ovarian (n = 13) cancer patients and 18 healthy donors using enzyme-linked immunospot (ELISPOT) analysis [6]. The epitopes were chosen based on degeneracy (i.e. the potential binding to more than one HLA-DR polymorph). Patients responded to an average of 3 peptides, whereas healthy donors responded to 1 peptide (P = .004), demonstrating cancer-induced immune responses [6]. Lastly, patients demonstrated elevated levels of FR α antibodies consistent with a coordinated immune response. These results demonstrate that patients with breast cancer naturally generate immunity to FR α .

1.14 PREVIOUS PHASE I TRIAL: The vaccine being used in the present protocol has been tested in a Mayo Clinic Phase I trial (MC1015) entitled: MC1015, A Phase I Trial of the Safety and Immunogenicity of a Multi-epitope Folate Receptor Alpha Peptide Vaccine Used in Combination with Cyclophosphamide in Subjects Previously Treated for Breast or Ovarian Cancer.

The objectives of MC1015 were: (1) To determine the safety of administering six monthly vaccinations with a peptide-based vaccine targeting FR α . Patients were immunized with FR α peptides following a single course of cyclophosphamide (as adjuvant) and (2) To determine the ability of this vaccination protocol to elicit an immune response as measured by activated FR α -specific T lymphocytes or high-affinity antibodies.

Cyclophosphamide and vaccine targeting FR α were administered as outlined below. Each cycle was 28 days $\pm$ 4 days in length.

The peptide/GM-CSF mixture was injected in 3 sites intradermally on the forearm for ovarian cancer patients. For breast cancer patients who have not had lymph node dissections on one side, the forearm on the side without node dissections was used unless the patient preferred to use the upper outer leg. For breast cancer patients with bilateral lymph node dissection, a site on the outer upper leg was used.

Cycle 1 only (priming)

Agent	Dose	Route	Day
Cyclophosphamide	50 mg	PO BID	1-7 and 15-21

Cycles 2-7 (vaccination administration)

Agent	Dose	Route	Day	Re-Treatment
Granulocyte-macrophage colony stimulating factor (GM-CSF) [adjuvant]	125 µg admixed with vaccine;	Intradermal injection	1	every 28 days (±4 days)
FR α peptide vaccine	5 peptides, 500 µg each, admixed with GM-CSF.	Intradermal injection	1	

The trial has been completed and was generally safe. Summaries of the toxicities in both the cyclophosphamide and priming phases are shown below.

Toxicities during Priming

One of the 8 patients with breast cancer was hospitalized with grade 4 sepsis during priming (attributed as unrelated to treatment) and discontinued study treatment. No severe (grade 3-5) adverse events were reported among the 14 patients with ovarian cancer. Grade 2 toxicities during priming included decreased lymphocyte count (3 pts.); decreased neutrophil count (2 pts.); decreased WBC count (2 pts.); fatigue (2 pts.); sinus pain (1 pt.) and nausea (1 pt.).

Toxicities during vaccination

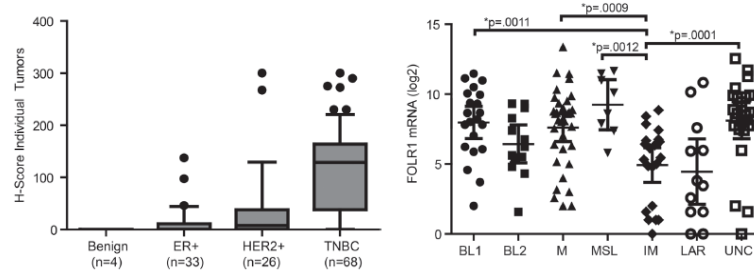
No dose limiting toxicities were reported during the first vaccination cycle among the 21 patients who completed priming and had at least one vaccination. Sixteen of these 21 patients (5 BC; 11 OC) completed all 6 vaccinations. Three OC patients discontinued due to disease progression after the 3rd (2 pts.) or 4th (1 pt.) vaccination cycle. Two participants with BC discontinued, respectively, after the 5th vaccination due to grade 2 visual changes (1 pt.) and grade 3 injection site reaction (1 pt.). No other severe toxicities were reported. The following table lists overall types of toxicities and the numbers of patients that experienced those toxicities at that grade at least once over the course of the study.

Toxicity	Number reporting grade 1	Number reporting grade 2	Number reporting grade 3	Number reporting grade 4
Alanine aminotransferase decrease	1			
Allergic reaction	3			
Alopecia	1			
Anemia	1			
Anorexia	3			
Appendicitis			1	
Aspartate aminotransferase increased	1			
Arthralgia	2	1		
Bone pain	1			
Chills	1			
Diarrhea	1			
Dysgeusia	1			
Dyspnea		1		
Erythema multiforme	2			
Eye disorder	1	2		
Fatigue	16	3		
Fever	1			
Flu-like symptoms	1			
Gastrointestinal disorders	1			
Headache	1	1		
Hot flashes	3			
Hyperthyroidism	1			
Hypothyroidism	1			
Injection site reaction	16	1	1	
Infection				1
Localized edema	1			
Lymphocyte count decrease	1	4		
Malaise	1	3		
Mucositis, oral	2			
Musculoskeletal, connective tissue disorders	、			
Myalgia	1	1		
Nausea	1	1		
Nervous system disorders		1		
Neutrophil count decrease	1	2		
Pain in extremity	2			
Peripheral motor neuropathy		2		
Postnasal drip	1			
Proteinuria	1	1		
Psychiatric disorders	1			
Skin and	6			

1.2 Correlative Research

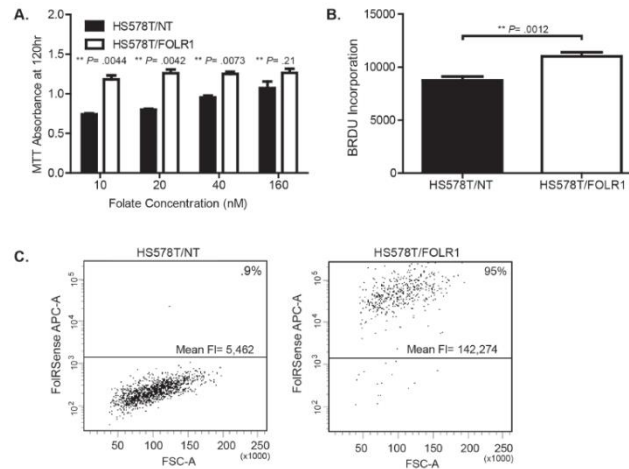
1.21 FR ALPHA IN BREAST CANCER PATHOGENESIS

Members of our collaborative group have examined its potential role in breast cancer, utilizing a tissue microarray containing samples from 63 invasive breast cancers from women with divergent clinical outcomes, grouped into poor and good outcome groups [8]. Thirty-three women comprised the poor outcome group with a median time to recurrence of 1.9 years. Thirty women, the good outcome group, were free of recurrence for a minimum of 7 years after diagnosis. The intensity of FR α staining was strongly correlated with outcome. In another recent study, in a cohort of 132 patients, FR α expression was predominantly associated with the TNBC with 86% staining positive and, importantly, was retained in metastatic lesions [4]. We also performed an analysis of FR α protein and mRNA expression in breast cancer clinical specimens, as well as functional studies [9]. These studies demonstrated that the receptor was preferentially expressed in TNBC compared to other subtypes of breast cancer and that expression was independent of genotypic subgrouping of TNBC (See Figure below).



FR α is preferentially expressed in TNBC compared to other subtypes of breast cancer. Left Panel: TMAs comprised of 131 breast cancer tumors of different subtypes from patients with classified breast cancers subtypes that include DCIS (n = 4), ER+ (n = 33), HER2+ (n = 26) and TNBC (n = 68). TMAs were evaluated using high affinity FOLR1 antibody Mab 26B3.F2 and IHC staining intensities calculated as described in the "Materials and Methods". H-score distribution of FOLR1 expression. H-scores were calculated with the formula: Hscore = 3 * (% at 3+) + 2 * (% at 2+) + 1 * (% at 1+) + 0 * (% at 0). *Statistical significance determined by Mann-Whitney test of TNBC versus benign, ER+ and HER2+. Right Panel: FR α mRNA expression from 131 TN tumors from TCGA RNA-seq dataset were plotted versus the six TNBC subtypes that include basal-like (BL1 and BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), and luminal androgen receptor (LAR) reported by Lehman et al. Tumors were assigned to an unclassified group (UNC) if they had low correlations (<0.1) for any subtype or were similar between multiple subtypes (P<.05). Statistical significance across groups was determined by ANOVA Kruskal-Wallis test followed by Dunn's Multiple Comparison Post test. *Significance at the P values shown was confirmed by Mann Whitney test of IM versus BL1, BL2, M, MSL, and LAR subtypes.

In addition, our results also suggest that FR α has a role for growth in TNBC cell lines as shown the Figure below.



Panel A: Growth of HS578T breast cancer cells engineered to stably overexpress FR α or empty vector (NT). Cells were cultured in low (0–40 nM) and super-physiological (160 nM) concentrations of folic acid and growth determined after 120 hr using the MTT assay. Error bars represent $\pm$ SD. **Statistical significance calculated by two sided unpaired t-test, assuming unequal variances. Panel B: BrdU incorporation in HS578T/NT and HS578T/FOLR1 cells grown in 10 nM folic acid. **Statistical significance calculated by two sided unpaired t-test, assuming unequal variances. Panel C: Folate uptake in HS578T/NT versus HS578T/FOLR1 cells. Briefly, flow cytometry was used to measure internalized fluorescent folate (fluorescent tagged folate agent, FolateR Sense 690) after 1 hr of exposure. Dot plots show forward scatter area (FSC-A) vs. FolateR Sense fluorescence (APC). The percent of cells with internalized fluorescent folate and the mean fluorescence per cell type are shown.

2.0 Goals

2.1 Primary

- 2.11 The primary goal of this trial is to show that FR α peptide vaccine with GM-CSF adjuvant will prolong the disease-free survival (DFS) compared to GM-CSF adjuvant treatment in patients with triple negative breast cancer.

2.2 Secondary

- 2.21 To compare the safety and tolerability of metronomic cyclophosphamide followed by FR α peptide vaccine with GM-CSF versus GM-CSF alone.

2.3 Correlative Research

- 2.31 To determine whether high level of antibody and cellular immune response toward the FR α measured at baseline is a prognostic factor for vaccine immune response and/or cancer relapse.

- 2.32 To determine whether the level of tumor expression of FR α at baseline is a prognosis factor for vaccine immune response and/or cancer relapse.

3.0 Patient Eligibility

NOTE: Waivers to eligibility criteria are not allowed per ACCRU policy

3.1 Inclusion Criteria

- 3.11 Age $\geq$ 18 years.

- 3.12 Female.

- 3.13 Resected unilateral or bilateral primary carcinoma of the breast without clinical evidence of metastatic disease (after neoadjuvant chemotherapy and/or adjuvant chemotherapy), negative for ER and PR (cut-off for positivity is $>10\%$ positive tumor cells with nuclear staining), and negative for HER2 as defined by one of the four situations delineated below:

- HER2 IHC expression of 0 or 1+ and in-situ hybridization non-amplified
- HER2 IHC expression of 0 or 1+ and in-situ hybridization not done
- HER2 IHC expression of 2+ and in-situ hybridization non-amplified
- IHC not done and in-situ hybridization non-amplified

Note: Central review is not required.

Note: If biopsy and surgical specimens are discordant from each other with regard to ER, PR, and/or Her2 status, a patient will be allowed to enroll assuming at least one of the specimens meets the above criteria and no endocrine therapy use is planned going forward.

- 3.14 Completed planned breast CANCER surgeries, any radiation therapy, and any chemotherapy, whichever is last, ≥ 90 days but not ≥ 546 days prior to randomization. Note: Reconstructive and prophylactic surgeries are allowed after randomization (during study treatment).
- 3.15 Patient had at least one of the following:
- Biopsy or surgery-proven regional node involvement by cancer
 - T1c, T2, T3 or T4 disease (with inflammatory disease allowed) identified at the time of surgery or clinically identified prior to neoadjuvant chemotherapy
 - No complete response to neoadjuvant chemotherapy (those who did achieve complete response are still eligible if a pre-chemotherapy regional nodal biopsy identified cancer or if the pre-chemotherapy tumor measured >1 cm)
- 3.16 ECOG Performance Status (PS) 0, 1. (Form is available on the ACCRU web site).

- 3.17 The following laboratory values obtained ≤ 14 days prior to randomization.
- Absolute neutrophil count (ANC) $\geq 1500/\text{mm}^3$
 - Platelet count $\geq 75,000/\text{uL}$
 - Aspartate transaminase (AST) $\leq 3 \times \text{ULN}$
 - Creatinine $\leq 1.5 \times \text{ULN}$
- 3.18 Negative serum pregnancy test done ≤ 14 days prior to randomization, for women of childbearing potential only.
- 3.19a Provide informed written consent.
- 3.19b Willing to return to enrolling institution for follow-up.
- 3.19c Willing to provide tissue and blood samples for correlative research studies (see Sections 6.0, 14.0 and 17.0).

3.2 Exclusion Criteria

- 3.21 Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:
- Pregnant women
 - Nursing women
 - Women of childbearing potential who are unwilling to employ adequate contraception
- 3.22 Clinical evidence of local recurrence or distant metastases. Note: New primary tumors are allowed, both contralaterally and ipsilaterally, but a prior breast cancer must have been more than 5 years beforehand.
- 3.23 Known hypersensitivity reaction to GM-CSF.
- 3.24 Active autoimmune disease that has required systemic treatment in the ≤ 30 days (i.e., with use of disease modifying agents, corticosteroids, or immunosuppressive drugs) prior to randomization. Note: Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment. Patients with vitiligo, Graves disease, or psoriasis not requiring systemic treatment within the past 30 days are not excluded. Patients with Celiac disease controlled with diet modification are not excluded.
- 3.25 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

NOTE: Localized fungal or viral infections including of the skin, nails, mouth, and genital area are allowed.

- 3.26 History of other cancer < 5 years prior to consent (except non-melanoma skin cancer or carcinoma in situ of the uterine cervix), or current receipt of treatment

for another cancer (e.g., monoclonal antibody, small molecule pathway inhibitor).

- 3.27 Treatment with systemic corticosteroid or immune-modulators ≤ 7 days prior to randomization.
- 3.28 Concurrent treatment with other experimental drugs or any other systemic anti-cancer therapy (due to unknown drug-vaccine potential interactions). Use of experimental or other targeted therapy ≥ 3 months prior is allowed as long as it is not Her2-directed. NOTE: aspirin, NSAIDS, statins, and other medications commonly used to treat non-oncologic, non-autoimmune conditions are allowed.
- 3.29a Immunocompromised patients and patients known to be HIV positive and currently receiving antiretroviral therapy.
- 3.29b Prior or concurrent use of trastuzumab or other Her2-directed therapy.
- 3.29c Prior or concurrent use of a PD-1 or PD-L1 checkpoint inhibitor (including pembrolizumab) unless the use was ≥ 3 months prior to randomization.

4.0 Test Schedule

Tests and procedures	≤28 days prior to randomization	Active Monitoring Phase				
		Cycle 2-7 ≤ 7 days prior to each cycle ¹	24-32 days after Day 1 of Cycle 7 ¹	Cycles 8-14 ≤ 7 days prior to each cycle (Booster vaccination every 6 months +/- 30 days) ^{8, 10}	At end of final vaccination cycle or ≤30 days of study discontinuation if stops early	Observation* (Evaluation of DFS every 6 months for 3 years) ⁸
Submission of primary tumor specimen for FRα antigen expression and banking (See Section 17.0) ^{6,R}	X					
Medical history and exam ³ , weight, blood pressure ²	X	X		X	X	X
Height	X					
Adverse event assessment	X	X	X	X	X	X
Serum pregnancy test	X ⁴					
CBC/ differential	X ⁷	X ⁹	X	X ⁹	X	X
Chemistries: total bilirubin, serum creatinine, SGOT (AST), ALT	X ⁷	X ⁹	X	X ⁹	X	X
Submission of tumor specimen at recurrence ^R (See Section 17.0)		X		X	X	X
Research Blood Samples ^{5, R}	X ⁵	X ⁵	X	X ⁵	X ⁵	X ⁵

1. Cycle 2 through 7 will be 28 days ±4 days.
2. Should include review of systems (ROS) and a neurological examination. Neurologic evaluation includes assessment for cranial nerves, cerebellar and neuromuscular. See Appendix II.
3. Disease evaluation will occur at each visit throughout the study. At a minimum, this will include a history, physical examination, and hematology and chemistry group, per standard of care. Mammogram will be performed annually on remaining breast or breasts if no bilateral mastectomy has occurred.
4. Required for women of child-bearing potential only. Must be done ≤14 days prior to randomization.
5. Kits are required for this collection. See Section 14.0 for time points for; ≤14 days prior to Cycle 1 (but after randomization); prior to Cycles 2, 4, and 6 (≤ 4 days); 24-32 days after Cycle 7; prior to boosters for Cycles 8, 10, 12, and 14 (≤ 4 days); 24-32 days after Cycle 14; at the time of first relapse (not required at subsequent recurrences). Then, 1 time per year during Observation for 3 years (≤30 days).

6. ≤ 30 days after randomization.
 7. Must be done ≤ 14 days prior to randomization.
 8. The timing of each booster is relative to the vaccine administration before it (e.g., cycle 10 should be 6 months $\pm$ 30 days after the date that cycle 9 was administered).
 9. CBC/differential and chemistries to be drawn and checked prior to each vaccine administration.
 10. Cycle 8 begins 6 months $\pm$ 30 days after Cycle 7 Day 1.
 11. Patient may have labs drawn at home at a certified laboratory and results sent to the participating site if that is preferred.
- R Research funded (see Section 19.0)

*Note:

- **Observation Phase:** Part of the Active Monitoring Phase of a study. The time period following the active treatment phase when the participant continues to receive cycles of evaluation in compliance with the Test Schedule and may be required to return to the consenting site. Participants will be required to return to the consenting site for follow-up. **NOTE:** Patients are required to come once annually in person during the observation phase to collect research blood draw. However, if they prefer, the other annual visit (6 months $\pm$ 30 days later) can be performed via phone or video.. The timing of each observation visit is relative to the visit prior.

5.0 Stratification Factors

- 5.1 Prior Treatment: Adjuvant vs. neo-adjuvant chemotherapy.
NOTE: When responding to this item on the eligibility checklist, check “neo-adjuvant” if the patient received ONLY neo-adjuvant chemotherapy. Check “adjuvant” if the patient received adjuvant chemotherapy with or without neo-adjuvant chemotherapy, or if the patient did not receive any chemotherapy.
- 5.2 Stage: I/II vs. III.
NOTE: When responding to this item on the eligibility checklist, use the highest T stage and N stage to determine stage I/II vs III, whether that was based on clinical evaluations before neoadjuvant therapy or pathologic assessment at the time of surgery.

6.0 Registration/Randomization Procedures

6.1 Registration Procedures

- 6.11 To register a patient, access the ACCRU web page at [REDACTED] go to the Application section and click on “Registration” and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, email the Academic and Community Cancer Research United (ACCRU) Registration Office at [REDACTED]

The instructions for the registration/randomization application are available on the above web page under the Study Resources section, “Application Training.”

Prior to initiation of protocol study intervention, this process must be completed in its entirety and an ACCRU subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the ACCRU Registration Office . If the patient was fully registered, the ACCRU Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to “Application Training” at [REDACTED] click on “Registration, Installation & Entry Instructions”.

6.12 Correlative Research

Mandatory

A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.0, 14.0 and 17.0)

Optional

Optional correlative research components are part of this study. There will be an option to select if the patient is to be registered onto these components (see Sections 14.0 and 17.0).

- Patient has/has not given permission to provide her tissue samples to laboratories associated with ACCRU for research testing planned as part of this study.

- 6.13 Documentation of IRB approval must be on file with ACCRU before an investigator may randomize any patients. Approvals should be uploaded via the Florence.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) with ACCRU. Approvals should be uploaded via Florence. If the necessary documentation is not submitted in advance of attempting patient registration, the randomization will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

Submission of annual IRB approvals to ACCRU is necessary until the study is closed out at the site's IRB.

- 6.14 Prior to accepting the randomization, the randomization application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

- 6.15 At the time of randomization, the following will be recorded:

- Patient has/has not given permission to provide her tissue sample(s) for future research to learn about, prevent, or treat cancer.
- Patient has/has not given permission to provide her tissue sample(s) for future research to learn, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
- Patient has/has not given permission to provide her blood sample to laboratories associated with ACCRU for future research to learn about, prevent, or treat cancer.
- Patient has/has not given permission to provide her blood sample(s) for future research to learn, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
- Patient has/has not given permission to keep her leftover tissue sample(s) for research testing to learn about, prevent or treat cancer.
- Patient has/has not given permission to keep her leftover tissue sample(s) for future research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

- Patient has/has not given permission to keep her leftover blood sample(s) for future research testing to learn about, prevent or treat cancer.
- Patient has/has not given permission to keep her leftover blood sample(s) for future research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
- Patient has/has not given permission for ACCRU to give her tissue sample(s) to outside researchers.
- Patient has/has not given permission for ACCRU to give her blood sample(s) to outside researchers.

6.16 Treatment cannot begin prior to randomization and must begin ≤ 14 days after randomization.

6.17 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.18 All required baseline symptoms (see Section 10.52) must be documented and graded.

6.19a Treatment on this protocol must commence at an ACCRU institution under the supervision of a medical oncologist.

6.19b Blood draw kit is available on site.

6.2 Randomization Procedures

6.21 The factors defined in Section 5.0, together with the registering membership, will be used as stratification factors.

6.22 After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups [5].

- Oral cyclophosphamide (Cycle 1), FR α Peptide + GM-CSF (Cycles 2-7), Booster FR α Peptide + GM-CSF (Cycles 8-14)
- Oral cyclophosphamide (Cycle 1), Placebo + GM-CSF (Cycles 2-7), Booster Placebo + GM-CSF (Cycles 8-14)

6.3 Procedures for Double-Blinding the Treatment Assignment

6.31 After the treatment assignment has been ascertained by the registration/randomization application, the registration specialist will notify the designated data manager/nurse/pharmacist at the patient's institution. The name of this contact person is to be entered in the designated space on the eligibility checklist so the Registration Office personnel have it for each patient at the time of registration. Make sure this contact person will be available at the time of registration so he or she can take a call from the registration specialist if necessary. This contact person may not be involved in assessing adverse events

or any other outcome measure and should not be the same person listed on page one of the Eligibility Checklist Form as the person completing the form. The last page of the Eligibility Checklist Form should provide the sources of communication, either fax or e-mail, and the appropriate contact information. The registration specialist will then communicate the treatment assignment to the designated contact at the patient's institution.

- 6.32 The treatment assignment will be to oral cyclophosphamide (Cycle 1), FR α Peptide + GM-CSF (Cycles 2-7), Booster FR α Peptide + GM-CSF (Cycles 8-14) or oral cyclophosphamide (Cycle 1), Placebo + GM-CSF (Cycles 2-7), Booster Placebo + GM-CSF (Cycles 8-14). Marker Therapeutics, Inc. will provide the FR α Peptide supplies labeled for investigational use to McKesson Specialty Pharmacy's Clinical Research Services. McKesson Specialty Pharmacy's Clinical Research Services will procure the cyclophosphamide and GM-CSF from a wholesaler. Each participating institution will order the drug from McKesson Specialty Pharmacy's Clinical Research Services using the protocol-specific Drug Order Request Form once a patient has been randomized. Each participating institution will be responsible for monitoring drug supplies and will use the Drug Order Request Form to order additional supplies as needed. Upon receipt of orders, McKesson Specialty Pharmacy's Clinical Research Services will send bulk supply to participating institutions. The FR α Peptide /placebo solution will be prepared and labeled by the unblinded pharmacist as "FR α Peptide Vaccine/Placebo + GM-CSF" so that the contents are not discernible to the person administering the treatment.
- 6.33 The unblinded pharmacist will maintain records that indicate the identity of the patient and their corresponding treatment assignment.

7.0 Protocol Treatment

7.1 Treatment Schedule

Study Treatment will be administered as outlined in the tables below. Each cycle will be 28 days $\pm$ 4 days in length for Cycles 1-7 and every 6 months $\pm$ 30 days for Cycles 8-14.

The peptide/GM-CSF or placebo/GM-CSF mixture will be injected intra-dermally (See Section 15.13 and 15.21 for mixing instructions). Administration is recommended on the upper arm or leg, 10 cm below the shoulder or groin, to create 3 blebs about 2 cm apart; sites should be rotated with subsequent doses. For patients who have not had lymph node dissections on one side, the forearm on the side without node dissections is preferred. For breast cancer patients with bilateral lymph node dissection, a site on the outer upper leg should be used. The upper leg site is also an option for injections per patient/provider preference otherwise.

Cycle 1 Only (Priming)

Agent	Dose Level	Route	Schedule	Days of cycle
Cyclophosphamide	50 mg (1 capsule)	PO	BID ¹	Days 1-7 and Days 15-21
Rest Days Days 8-14 and Days 22-28				

¹Doses of cyclophosphamide should be 12 hours (+/- 4 hours) apart. Missed or vomited doses should not be repeated.

Cycles 2-7 (Vaccination Administration)

Agent	Dose Level	Route	Day	ReRx
FR α peptide vaccine + Adjuvant (GM-CSF)	5 peptides, 500 μ g each, admixed with 125 μ g of GM-CSF	Intradermal injection	1	Every 28 days (+/- 4 days)
Placebo + Adjuvant (GM-CSF)	Normal saline, admixed with 125 μ g of GM-CSF	Intradermal injection	1	Every 28 days (+/- 4 days)

Cycles 8-14 (Booster Vaccinations)

Agent	Dose Level	Route	Day	ReRx ¹
FR α peptide vaccine + adjuvant (GM-CSF)	5 peptides, 500 μ g each, admixed with 125 μ g of GM-CSF	Intradermal injection	1	Every 6 months (+/- 30 days)
Placebo + Adjuvant (GM-CSF)	Normal saline, admixed with 125 μ g of GM-CSF	Intradermal injection	1	Every 6 months (+/-30 days)

1. Cycle 8 begins 6 months +/- 30 days after Cycle 7 Day 1.

- 7.2 Cycle 1 only: Patients can be instructed in administration techniques and granted treatment for independence with nursing staff approval.
- 7.3 For this protocol, the patient must return to the consenting ACCRU institution for evaluation at least every 28 days (+/- 4 days) during treatment and every 6 months +/- 30 days during observation (Active Monitoring Phase).

NOTE: Delay of treatment for reasons other than adverse events will be allowed up to 120 days. Delays longer than 120 days will require patient to come off study treatment.

- 7.4 Treatment by a local medical doctor (LMD) is not allowed.
- 7.5 Breaking Codes in Double-Blinded Studies

- 7.51 In the event of an emergency, call the ACCRU Registration Office at [REDACTED] to break the code on Monday through Friday, 8:00 a.m. to 4:30 p.m. Central Time. If the code must be broken after hours, assume the patient was assigned to active treatment and treat accordingly. Place a call to the ACCRU Registration Office and leave a message informing them of the need to un-blind a patient. Provide your contact information so that ACCRU Registration Office personnel can return the call the next business day.
- 7.52 If, in the judgment of the attending physician, it would be helpful for the future clinical care of the individual patient, the code may be broken *after* the patient has completed the study. That is, after the patient has been fully evaluated and all evaluation information has been recorded by the attending physician and the patient (if appropriate), the ACCRU Registration Office may be called [REDACTED] or emailed [REDACTED] to find out which study therapy the patient was receiving.

After the study is completed for all patients, if a patient desires to know which arm they were assigned, the information may be provided.

NOTE: It is recommended (not required) that elective procedures be scheduled at least one month before or after a booster vaccines during cycles 8-14.

8.0 Dosage Modification Based on Adverse Events

Allowable schedule modification: If a patient presents with an acute illness (cold, influenza, etc.), vaccination will be withheld until the illness has resolved. Subsequent cycles will be timed to the actual date the last vaccination was administered rather than according to the schedule established prior to the illness-induced delay.

There will not be any modifications to the dose of vaccine used. There may be allowances for the timing of the administration of vaccine to accommodate patient schedules or special circumstances.

ALERT: *ADR reporting may be required for some adverse events (See Section 10)*

8.1 Dose Modifications for Cycle 1

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified			
CTCAE System/Organ/ Class (SOC)	ADVERSE EVENT	Follow-up AGENT	ACTION
<i>AT TIME OF RETREATMENT</i>			
All adverse events	Hematologic ≥ Grade 3 OR Nonhematologic (excluding alopecia) ≥ Grade 3	Cyclophosphamide	Delay use of any study drug by at least one week and until all AEs have recovered to grade 2 or less. If the same patient experiences a second grade 3 AE of the same type during any subsequent cycle, the patient must stop all study treatment permanently and begin observation phase.

8.2 Dose Modifications for Cycles 2-7 and 8-14 (boosters): FR α Peptides/Placebo + GM-CSF

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified*			
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION
AT TIME OF RETREATMENT			
General disorders and administration site conditions	Injection site reaction manifesting as an ulceration- $\geq$ Grade 3	GM-CSF; FR α Peptides /Placebo	Discontinue vaccination and go to observation phase
Immune system disorders	Allergic reaction $\geq$ Grade 3		Discontinue vaccination and go to observation phase
Nervous system disorders	Peripheral motor neuropathy $\geq$ Grade 2 and at least possibly related to study drug Peripheral sensory neuropathy $\geq$ Grade 2 and at least possibly related to study drug		Discontinue vaccination and go to observation phase
All other adverse events	Hematologic $\geq$ Grade 3 and at least possibly related to study drug Nonhematologic (excluding alopecia) $\geq$ Grade 3 and at least possibly related to study drug		Delay use of any study drug until all AEs have recovered to grade 2 or less. If the same patient experiences a second grade 3 AE of the same type during any subsequent cycle, the patient must stop all study treatment permanently and begin observation phase.

* Located at [REDACTED]

** Use the following to describe actions in the Action column:

- Omit = Treatment is not given for this cycle
- Hold/Delay = Treatment can be made up as part of this cycle
- Discontinue = Treatment is totally stopped

8.3 If treatment is delayed >4 weeks from the planned administration date, patient will discontinue study treatment and go to observation.

9.0 Ancillary Treatment/Supportive Care

- 9.1 Antiemetics may be used at the discretion of the attending physician.
- 9.2 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions.
- 9.3 If local injection reaction is noted, investigators may use their discretion to use anti-histamine (e.g. oral diphenhydramine) and/or topical steroid (e.g. hydrocortisone).

10.0 Adverse Event (AE) Reporting and Monitoring

The site principal investigator is responsible for reporting any/all serious adverse events to the sponsor as described within the protocol, regardless of attribution to study agent or treatment procedure. The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug.
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Definitions

Adverse Event

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction

Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting

Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting

Events reported to sponsor via case report forms

Events of Interest

Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site:

- a. Adverse event monitoring and reporting is a routine part of every clinical trial.
- b. Identify the grade and severity of the event using the CTCAE version 4.0.
- c. Determine whether the event is expected or unexpected (see Section 10.2).
- d. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).
- e. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).
- f. Determine if other reporting is required (see Section 10.5).
- g. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT).

NOTE: A severe AE, as defined by the above grading scale, is NOT the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

Unanticipated Adverse Device Event (UADE)

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

- Definite - The adverse event *is clearly related* to the agent(s).
- Probable - The adverse event *is likely related* to the agent(s).
- Possible - The adverse event *may be related* to the agent(s).
- Unlikely - The adverse event *is doubtfully related* to the agent(s).
- Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug/device and the adverse event.

10.31 AEs Experienced Utilizing Investigational Agent(s) and Commercial Agent(s) on SEPARATE Arms

- An AE that occurs on an arm using an investigational agent /intervention under an IND/IDE must be assessed in accordance with the guidelines in the appropriate **IND/IDE** Reporting Table in Section 10.4.
- An AE that occurs on an arm using a commercial agent on a separate treatment arm must be assessed as specified in the protocol. **Refer to Commercial** Reporting Table in Section 10.4.

10.32 AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the SAME (Combination) Arm

When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the **entire combination (arm) is then considered an investigational intervention for reporting**. These AEs should be assessed as specified in the appropriate **IND/IDE** reporting guidelines in Section 10.4

10.33 EXPECTED Serious Adverse Events: Protocol Specific Exceptions to Expedited Reporting

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting, regardless of hospitalization. These events must still be reported via Routine Reporting (see Section 10.5). *

System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be expeditiously reported.
General disorders and administrations site conditions	Injection site reaction	≤Grade 3

Any hospitalization for breast reconstruction or any adverse event regardless of grade related to breast reconstruction does not require expedited reporting.

*Report any clinically important increase in the **rate** of a serious suspected adverse reaction (at your study) site over that which is listed in the protocol or investigator brochure as an expedited event.

*Report an expected event that is greater in severity or specificity than expected as an expedited event

*An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.

A list of known/expected AEs is reported in the investigator brochure, package insert or the literature, including AEs resulting from a drug overdose.

10.331 Death

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.
- Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.
- Reportable categories of Death**
 - Death attributable to a CTCAE term.
 - Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
 - Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
 - Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an

unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

- Death due to progressive disease should be reported as **Grade 5 “Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease)”** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.332 Secondary Malignancy

- A **secondary malignancy** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND/IDE to be reported. Three options are available to describe the event:
 - Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
 - Myelodysplastic syndrome (MDS)
 - Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.333 Second Malignancy

- A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting.

10.334 Pregnancy

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion the mother is the patient.

In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting ACCRU Adverse Event Report reports for “Pregnancy”, “Pregnancy loss”, or “Neonatal loss”, the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the “Description of Event” section. Include any available medical documentation.

10.4 Expedited Adverse Event Reporting Requirements for IND/IDE Agents 10.41 Phase 1 and Early Phase 2 Studies: Expedited Reporting via the **ACCRU Adverse Event Expedited Report Form** for Adverse Events That Occur Within 30 Days¹ of the Last Dose of the Investigational Agent

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

- 1) Death
- 2) A life-threatening adverse event
- 3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
- 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- 5) A congenital anomaly/birth defect.
- 6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the sponsor within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days	24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- “24-Hour; 3 Calendar Days” - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- “7 Calendar Days” - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

¹Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

² For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote “1” above applies after this reporting period.

Effective Date: May 5, 2011

Follow site-specific reporting guidelines.

Submit the ACCRU Adverse Event Expedited Report Form to the ACCRU SAE Coordinator via email at [REDACTED]. The ACCRU SAE Coordinator will forward to [REDACTED].

The ACCRU IND Coordinator will assist the sponsor-investigator in notifying the FDA if required.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

If the event meets the criteria for an UPIRTSO, submit to your IRB as required by your institutional policies.

10.52 Baseline and Adverse Events Evaluations

Pre-treatment symptoms/conditions to be graded at baseline and adverse events to be graded at each evaluation per the CTCAE v4.0 grading unless otherwise stated in the table below:

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Blood and lymphatic system disorders	Anemia	X	X
General disorders and administration site conditions	Fatigue	X	X
	Fever	X	X
	Injection site reaction		X
Immune system disorders	Allergic reaction		X
Investigations	White blood cell decreased	X	X
Musculoskeletal and connective tissue disorders	Arthralgia	X	X
	Myalgia	X	X
Nervous system disorders	Peripheral motor neuropathy	X	X
	Peripheral sensory neuropathy	X	X

10.53 Submit via appropriate Academic and Community Cancer Research United (ACCRU) Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.5:

10.531 Grade 1 and 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.532 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure

10.533 Grade 5 AEs (Deaths)

10.5331 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.5332 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.54 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

11.0 Treatment Evaluation Using RECIST Guideline

At the time of reevaluation, patients will be classified in the following manner:

- No evidence of disease (NED).
- Breast cancer recurrence (REC).

Local/regional breast cancer recurrence is defined as the development of invasive or DCIS tumor (LCIS not included as event) in the ipsilateral breast (after lumpectomy); in the soft tissue/chest wall and/or skin of the ipsilateral chest wall; or tumor in the ipsilateral internal mammary, infraclavicular, or axillary nodes or soft tissue of ipsilateral axilla. Suspected tumor recurrence in the ipsilateral breast, chest wall structures or lower (level I $\pm$ II) axillary nodal areas must be confirmed by biopsy or cytology. Histologic or cytologic confirmation of tumor is recommended for internal mammary or infraclavicular/high axillary nodal recurrence.

A distant recurrence is defined as development of tumor in areas other than the local/regional area that is documented by a positive cytology aspirate, biopsy, or imaging studies.

- New primary (NEWP): A new primary is defined as the development of contralateral invasive or DCIS breast cancer or a second primary invasive cancer (non-breast and does not include squamous or basal cell carcinoma of the skin or new in situ carcinomas of any non-breast site) that is histologically confirmed.

Further treatment after the documentation of a breast cancer recurrence or second primary cancer is left to the discretion of the treating physician.

12.0 Descriptive Factors: None

13.0 Treatment/Follow-up Decision at Evaluation of Patient

- 13.1 A patient who has not developed tumor recurrence at the time of reassessment and has not experienced intolerable toxicity will be eligible for re-treatment until disease progression, unacceptable toxicity, refusal or a maximum of 14 cycles.
- 13.2 Criteria for discontinuation of protocol therapy include:
 - Tumor progression
 - Request by the patient to discontinue study treatment
 - Treatment intolerability
 - Treatment delay of > 28 days
 - Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree or require discontinuation of drug
 - Administration of radiotherapy, non-protocol chemotherapy, or an experimental drug during the trial.
- 13.3 Patients who complete all 14 cycles will go to the observation phase of the study.

- 13.4 Patients who develop recurrent disease during treatment or during observation will go to observation phase. Future treatments of the recurrent disease will be at the discretion of the patient's treating physician.
- 13.5 Any patient who withdraws treatment, refuses treatment, or discontinues due to intolerability will go to the observation phase and if willing, to donate research bloods.
- 13.6 If patient withdraws consent from all follow-up, withdrawal of consent forms must be submitted as well as all data collected prior to withdrawal of consent. No further data submission is necessary.
- 13.7 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry.
- If the patient received any treatment, the patient will discontinue treatment and go to the observation phase of the study.
 - If the patient never received treatment, on-study material (excluding research bloods) and the Off Treatment/ Off Study form must be submitted. No further follow up is required.
- 13.8 A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated such that evaluability for the primary endpoint is questionable. The patient will discontinue treatment and go directly to the observation phase of the study.
- 13.9 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the Off Treatment Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens**14.1 Summary Table of Research Blood/Blood Products to Be Collected for This Protocol**

*When a patient is scheduled please notify the lab via outlook calendar at [REDACTED] In this notification you will need to include patient study ID and visit description. Once the tracking number is obtained this notice will need to be updated with the tracking number

Correlative Study (Section for more information)	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	After randomization, but ≤ 14 days prior to Cycle 1 ¹	Prior to Vaccination Cycles 2, 4, 6 and 24-32 days after Cycle 7 ^{1,2}	Prior to boosters every 6 months for Cycles 8, 10, 12, 14 ¹ and 24-32 days after Cycle 14 ²	Yearly during observation for 3 years ³	At time of first relapse if between scheduled visits	Process at site? (Yes or No)	Temperature Conditions for Storage/Shipping ⁴
Immunologic	Mandatory	Blood	Red	10mL (1)	X			X		No	Refrigerate
Immunologic	Mandatory	Blood	Red	10mL (1)		X	X			No	Refrigerate
Immunologic	Mandatory	Blood	Red	10mL (1)					X	No	Refrigerate
Immunologic	Mandatory	Blood	Green	10mL (3)	X			X		No	Ambient
Immunologic	Mandatory	Blood	Green	10mL (6)		X	X			No	Ambient
Immunologic	Optional (Banking)	Blood	Green	10mL (6)					X	No	Ambient

¹ Samples can be collected ≤ 4 days prior to each cycle.

² Samples to be collected one time during the range of 24-32 days (≤ 4 days) after the last vaccination or booster.

³ Samples can be collected ≤ 30 days prior to each cycle.

⁴ Ship samples according to shipping instructions (see Section 14.12 for detailed shipping instructions.)

14.11 Kits are required for this study

- 14.111 The kit contains supplies and instructions for collecting, processing and shipping specimens.
- 14.112 Participating institutions may obtain kits by completing and faxing the Supply Order Form (found on the ACCRU web site) to the number listed on the form. Fill out the site address to where the kits will be shipped on the Fax Supply Order Form. Because we are now being charged for all outgoing kits, a small, but sufficient, supply of the specimen collection kits should be ordered prior to patient entry. Do not send the unused kits back to Biospecimen Accessioning and Processing (BAP) Receiving or the BAP Shared Resource.
- 14.113 Kits will be sent via FedEx® Ground at no additional cost to the participating institutions. **Allow at least two weeks to receive the kits.**
- 14.114 Kits will not be sent via rush delivery service unless the participating institution provides their own FedEx® account number or alternate billing number for express service. **ACCRU will not cover the cost for rush delivery of kits.**
- 14.115 All samples must be collected Monday – Thursday only. **Do not collect samples on weekends or just prior to federal holidays.**
- 14.116 Label specimen tubes(s) with the protocol number, ACCRU patient ID number, and time and date blood is drawn.
- 14.117 Collect and process all blood/blood products according to specific kit instructions.

14.12 Shipping

- 14.121 Verify ALL sections of the Specimen Submission: Blood form (See CRF Packet), BAP Requisition Form (provided in kit) and specimen collection labels are completed and filled in correctly.
- 14.122 Specimens must be shipped the same day they are drawn.
- 14.123 Email to notify [REDACTED] PRIOR to shipping along with tracking number.
- 14.124 **Ship Na Heparin ambient temperature. Red Top serum tubes should be shipped refrigerated.**
- 14.125 Ship specimens via Priority Overnight service, **Monday-Thursday ONLY**, to BAP Receiving according to kit instructions. **Do not send samples on weekends or just prior to federal holidays.**
- 14.126 The BAP kits will include a smart shipper label (3x5 white barcoded label) affixed to the shipping boxes. The smart shipper label is a pre-addressed return label, which replaces the need for an airbill. Shipping costs will be covered by

ACCRU if the shipping box provided with the BAP kit is used for shipping specimens to BAP receiving.

14.127 BAP Freezer will receive the samples and immediately forward specimens to the BAP Florida Shared Resource, Attention: BAP Supervisor.

14.2 Study Methodology and Storage Information

14.21 Blood/blood product samples will be collected for the following research

14.211 A portion of the peripheral blood will be processed to isolate serum in the BAP laboratory using standard laboratory protocols. According to patient consent information (see Section 6.0), serum/plasma will be stored frozen at -70°C by BAP. A portion of the serum will be tested for folate receptor antibodies in [REDACTED] laboratory. The remaining serum will be stored until additional specific analyses are identified. As protocols are developed, they will be presented for ACCRU and IRB review and approval. (This collection is part of a general strategy of investigation for the majority of ACCRU studies.)

14.212 A portion of the peripheral blood will be processed to isolate Peripheral Blood Mononucleocytes (PBMC's) by BAP. PBMC's will be stored frozen in liquid nitrogen by BAP. PBMC's will be assayed for immune response in [REDACTED] laboratory.

14.213 1ml of the peripheral blood will be processed to extract genomic DNA in the BAP laboratory using standard laboratory protocols. Genomic DNA will be assayed for high resolution human leukocyte antigen (HLA) genotype.

14.214 As part of ongoing ACCRU research, we will collect serum/plasma and PBMC's for future research studies, according to patient consent information (see Section 6.0), on molecular determinants of efficacy and tolerability. Serum/plasma samples will be stored frozen at -70°C and PBMC's will be stored in liquid nitrogen by BAP until specific analyses are identified. As protocols are developed, they will be presented for ACCRU and IRB review and approval.

15.0 Drug Information

IND #17133

15.1 TPIV200 (FR α vaccine, HuFR-1) IND #14546

- Investigator brochure
Available on the ACCRU website.

15.11 **Background:** The tumor antigen targeted by the vaccine is folate receptor alpha (FR α), a high affinity folate-binding protein that is overexpressed on over 70-90% of ovarian tumors and ~ 50% of breast tumors. The vaccine contains five peptides ranging in length from 15-18 amino acids derived from the human FR α

protein sequence starting at positions: FR30, FR56, FR76, FR113, and FR238.

- 15.12 **Formulation:** The five lyophilized API peptides are resolubilized in an acetic acid solution, admixed with mannitol, sterile-filtered through a 0.2 micron filter, and aseptically filled into single-dose, sterile, pyrogen-free glass vials for lyophilization, stoppering, and crimp-sealing at an FDA-inspected facility under cGMP conditions. Each single-dose vial contains a 2.50 mg nominal dose of TPIV200 (0.5 mg of each of the 5 peptides) plus a 0.25 mg overage as well as mannitol as a lyophilization excipient.

- 15.13 **Preparation and storage:** TPIV200 peptide vials are stored and shipped at $-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$.

If frozen, thaw peptide vials in the refrigerator overnight or at room temperature for 1-2 hours. Bring vaccine to room temperature before preparing the dose. When reconstituting, mix the solution in the vial by vigorously swirling; do not shake.

Do not refreeze vaccine peptides after thawing

- Remove the ‘Hu-FR-alpha Vaccine for Injectable Suspension’ vial from the freezer and equilibrate to room temperature for 1 to 2 hours. Also, remove a vial of GM-CSF from the refrigerator and equilibrate to room temperature.
 - Add 0.5 mL of Bacteriostatic WFI or sterile WFI (SWFI) to reconstitute the lyophilized GM-CSF to a concentration of 500 $\mu\text{g/mL}$. If liquid GM-CSF product is used, there is no need to reconstitute; the concentration should already be 500 $\mu\text{g/mL}$. If liquid GM-CSF product is used, there is no need to reconstitute; the concentration should already be 500 $\mu\text{g/mL}$.
 - Add 1.1 mL of SWFI water to reconstitute the peptide vial. Swirl vigorously to mix; do not shake. Allow the reconstituted vial to sit upright for a minute.
 - Withdraw 0.275 mL of the reconstituted GM-CSF and add to the 1.1 mL of the reconstituted TPIV200 vial (1.375 mL total). Swirl to mix. This product can now be called the human FR α vaccine or TPIV200
 - Load 3 tuberculin syringes with ~ 0.41 mL of the peptide/GM-CSF mixture.
- 15.14 **Administration:** Administer the vaccine intradermally (ID) to the patient as soon as possible (within a maximum of 6 hours) after preparation, labeling and dose confirmation by a second pharmacist. Administration is recommended on the upper arm or leg, 10 cm below the shoulder or groin, to create 3 blebs about 2 cm apart; sites should be rotated with subsequent doses.
- 15.15 **Potential Drug Interactions:** There are no known drug interactions.
- 15.16 **Known potential toxicities:** Patients receiving ID peptide vaccines with

GM-CSF may experience local injection site reactions that can include temporary pain, redness, and/or swelling.

- 15.17 **Drug procurement:** The drug will be purchased from Marker Therapeutics, Inc. and supplied to McKesson Specialty Pharmacy's Clinical Research Services. Each participating ACCRU treating location will order the drug from McKesson Specialty Pharmacy's Clinical Research Services. Fax the Drug Order Request Form (found in the forms packet) to:

[REDACTED]
[REDACTED]
[REDACTED]

Each participating ACCRU treating location will be responsible for monitoring the supply of folate receptor alpha peptide and will use the Drug Order Request Form to order additional supplies as needed.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.18 **Nursing guidelines**

- 15.181 Patients should be monitored for 30 minutes after injection for acute toxicity.
- 15.182 Anaphylaxis is a possibility, monitor patients for signs or symptoms of allergic reaction, including hives, swelling, generalized urticaria, or bronchospasm.
- 15.183 Instruct patients that they may experience mild myalgia/arthralgia and bone pain.
- 15.184 Warn patients of injection site reactions which may include redness, swelling, and discomfort.
- 15.185 FR α DC vaccine should only be administered intradermally according to the protocol, by nurses who have been trained in the administration of the vaccine.
- 15.186 See Section 15.14 for recommended sites of administration.

15.2 Matching Placebo admixed with GM-CSF

The placebo will be normal saline (NS, 0.9% sodium chloride) mixed with GM-CSF.

15.21 **Preparation:**

- Retrieve a placebo vial and bring to room temperature.
- Remove a vial of lyophilized GM-CSF (250 mcg/vial) from the refrigerator and allow to reach room temperature.

- To the placebo vial, add 1.1 mls of NS, 0.9% sodium chloride.
- Allow the vial to sit upright for a minute.
- Add 0.5 ml of SWFI or Bacteriostatic SWFI to reconstitute lyophilized GM-CSF to achieve a concentration of 0.5 mg/ml.
- Withdraw 0.275 ml of the GM-CSF vial and add to the peptide vial. Swirl to mix. Load three tuberculin syringes with ~0.41 mL of the peptide/GM-CSF mixture.
- Label each syringe with the Patient Study Number and the Time of Preparation. Each syringe should be labeled by the unblinded pharmacist as “FR α Peptide Vaccine/Placebo + GM-CSF” so that the contents are not discernible to the person administering the treatment. Have the labeling and randomization confirmed by a second pharmacy personnel.
- Deliver the 3 syringes immediately for injection to the patient.
- Discard unused GM-CSF and peptide/placebo solution.

- 15.22 **Administration:** Administer the placebo intradermally (ID) to the patient as soon as possible (within a maximum of 6 hours) after preparation, labeling and dose confirmation by a second pharmacist. Administration is recommended on the upper arm or leg, 10 cm below the shoulder or groin, to create 3 blebs about 2 cm apart; sites should be rotated with subsequent doses. For patients who have not had lymph node dissections on one side, the forearm on the side without node dissections is preferred. For breast cancer patients with bilateral lymph node dissection, a site on the outer upper leg should be used. The upper leg site is also an option for injections per patient/provider preference otherwise.

Vaccine/placebo administration is initiated after completion of one cycle of cyclophosphamide for a total of 6 vaccination cycles followed by 7 booster vaccinations.

15.3 Sargramostim (Leukine®, GM-CSF)

- 15.31 **Background:** Sargramostim stimulates proliferation, differentiation and functional activity of neutrophils, eosinophils, monocytes, and macrophages.
- 15.32 **Formulation:** Commercially available
Injection, powder for reconstitution: 250 mcg [contains mannitol 40 mg/mL and sucrose 10 mg/mL]
Liquid injection: 500 mcg/mL [contains mannitol, tromethamine, benzyl alcohol]
- 15.33 **Preparation, storage, and stability:** Refer to package insert for complete preparation and dispensing instructions. Store intact vials under refrigeration at 2°C to 8°C (36°F to 46°F), do not freeze. Do not shake. Sargramostim powder for injection may be reconstituted with 0.5mL preservative free Sterile Water for Injection (SWFI) or bacteriostatic water for injection (with benzyl alcohol 0.9%) for a final concentration of 500 mcg/mL. Preparations made with SWFI should be administered as soon as possible, and discarded within 6 hours of reconstitution. Preparations made

with bacteriostatic water may be stored for up to 20 days at 2°C to 8°C.
Gently swirl to reconstitute; do not shake.

- 15.34 **Administration:** Refer to the treatment section and/or supportive care section of the protocol.
- 15.35 **Pharmacokinetic information:**
Onset of action: Increase in WBC: 7-14 days
Duration: WBCs return to baseline within 1 week of discontinuing drug
Half-life elimination: Subcutaneous administration: 2.7 hours
- 15.36 **Potential Drug Interactions:** Simultaneous administration, or administration 24 hours preceding/following cytotoxic chemotherapy or radiotherapy is not recommended.
- 15.37 **Known potential adverse events:** Consult the package insert for the most current and complete information.
Common known potential toxicities, > 10%:
Cardiovascular: Hypertension, pericardial effusion, edema, chest pain, peripheral edema, tachycardia
Central nervous system: Fever, malaise, headache, chills, anxiety, insomnia
Dermatologic: Rash, pruritus
Endocrine & metabolic: Hyperglycemia, hypercholesterolemia
Gastrointestinal: Diarrhea, nausea, vomiting, abdominal pain, weight loss, hematemesis, dysphagia, gastrointestinal hemorrhage
Neuromuscular & skeletal: Weakness, bone pain, arthralgia, myalgia
Ocular: Eye hemorrhage
Renal: BUN increased, serum creatinine increased
Respiratory: Pharyngitis, epistaxis, dyspnea

Less common known potential toxicities, 1% - 10%:
Respiratory: Pleural effusion

Rare known potential toxicities, <1% (limited to important or life-threatening): Allergic reaction, anaphylaxis, anorexia, arrhythmia, capillary leak syndrome, constipation, eosinophilia, fever, first-dose effect (syndrome with respiratory distress, hypoxia, flushing, hypotension, syncope, and/or tachycardia occurring with the first dose of a treatment cycle); injection site reaction, lethargy, leukocytosis, malaise, pain, pericarditis, rigors, sore throat, supraventricular arrhythmia (transient), thrombocytosis, thrombophlebitis, thrombosis.
- 15.38 **Drug procurement:** The drug will be purchased from Cardinal Health and supplied to McKesson Specialty Pharmacy's Clinical Research Services. Each participating ACCRU treating location will order the drug McKesson Specialty Pharmacy's Clinical Research Services. Fax the Drug Order Request Form (found in the forms packet) to:

[REDACTED]

Each participating ACCRU treating location will be responsible for monitoring the supply of GM-CSF and will use the Drug Order Request Form to order additional supplies as needed.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.39 Nursing guidelines:

- 15.391 Patient may experience fever or flulike symptoms (myalgias, chills, rigors, fatigue, and headache) associated with drug. Premedication with Tylenol may alleviate this. Instruct in other comfort measures.
- 15.392 Assess baseline pulmonary and fluid status. Monitor for fluid retention or pulmonary edema.
- 15.393 Rash or local irritation may occur. Instruct patient to report rash to health care team.
- 15.394 Assess for mild-moderate transient bone pain and advise patient in comfort measures.
- 15.395 Acetaminophen is the recommended analgesic for mild bone pain. It sometimes helps when taken at the time of injection.

15.4 Cyclophosphamide for Oral Administration (Cytoxan®, Neosar®, CTX)

- 15.41 **Background:** Cyclophosphamide is an alkylating agent that prevents cell division by cross-linking DNA strands and decreasing DNA synthesis. It is a cell cycle phase nonspecific agent. Cyclophosphamide also possesses potent immunosuppressive activity. Cyclophosphamide is a prodrug that must be metabolized to active metabolites in the liver.
- 15.42 **Formulation:** Commercially available for oral administration as:
Capsules: 25 mg, 50 mg
- 15.43 **Preparation, storage, and stability:** Refer to package insert for complete preparation and dispensing instructions. Store oral capsules at room temperature preferably below 25°C (77°F). This product will withstand brief exposure to temperatures up to 30°C (86°F), but should be protected from temperatures above 30°C (86°F). Dispense in a tight container as defined in the USP/NF. Refer to labeling on the bottle for expiration date of the commercial capsules.
- 15.44 **Administration:** Refer to the treatment section for specific administration instructions. To minimize the risk of bladder irritation, do not administer tablets at bedtime.

15.45 **Pharmacokinetic information:**

Distribution: V_d : 0.30-0.50 L/kg; crosses placenta; crosses into CSF (not in high enough concentrations to treat meningeal leukemia)

Protein binding: 20% to 60%

Bioavailability: >75%

Time to peak, serum: Oral: ~1 hour

Metabolism: Hepatic to active metabolites acrolein, 4-aldophosphamide, 4-hydroperoxycyclophosphamide, and nor-nitrogen mustard

Half-life elimination: 3-12 hours

Excretion: Urine (<30% as unchanged drug, 85% to 90% as metabolites)

15.46 **Potential Drug Interactions:**

Cytochrome P450 Effect: **Substrate** of CYP2A6 (minor), 2B6 (major), 2C9 (minor), 2C19 (minor), 3A4 (minor); **Inhibits** CYP3A4 (weak);

Induces CYP2B6 (weak), 2C8 (weak), 2C9 (weak)

Increased Effect/Toxicity: Allopurinol may cause an increase in bone marrow depression and may result in significant elevations of cyclophosphamide cytotoxic metabolites. CYP2B6 and CYP3A4 inducers may increase the levels/effects of acrolein (the active metabolite of cyclophosphamide); see package insert for example inducers. Etanercept may enhance the adverse effects of cyclophosphamide. Cyclophosphamide reduces serum pseudocholinesterase concentrations and may prolong the neuromuscular blocking activity of succinylcholine and mivacurium.

Decreased Effect: Cyclophosphamide may decrease the absorption of digoxin capsules. CYP2B6 and CYP3A4 inhibitors may decrease the levels/effects of acrolein (the active metabolite of cyclophosphamide); see package insert for example inhibitors.

Herb/Nutraceutical Interactions: Avoid black cohosh, dong quai in estrogen-dependent tumors.

15.47 **Known potential adverse events:** Consult the package insert for the most current and complete information. Please note that this study uses a low dose and short course of cyclophosphamide such that the toxicities described below likely overestimate risks from treatment on this study because they are based on data from studies of higher doses and longer duration of cyclophosphamide.**Frequent potential toxicities, 10-50%:**

Gastrointestinal: Slight nausea

Respiratory: Stuffy nose

Occasional potential toxicities, 1% - 10%:

Dermatologic: Slight hair loss (alopecia), darkening of the skin or fingernails, rash, facial flushing.

Gastrointestinal: Stomach cramps, decreased appetite, mouth sores

Hematologic: Low red blood cell count, low white blood cell count, low platelet count

Urinary: Blood in the urine (hemorrhagic cystitis).

Central nervous system: Headache, dizziness

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

Cyclophosphamide may increase the cardiac toxicity of anthracyclines. Other adverse reactions include severe allergic reactions (anaphylaxis), liver damage, low potassium or sodium level, severe immunosuppression leading to serious infection, and secondary malignancy (e.g., bladder carcinoma).

- 15.48 Drug procurement: The drug will be purchased from Cardinal Health and supplied to McKesson Specialty Pharmacy's Clinical Research Services. Each participating ACCRU treating location will order the drug from McKesson Specialty Pharmacy's Clinical Research Services. Fax the Drug Order Request Form (found in the forms packet) to:

[REDACTED]
[REDACTED]
[REDACTED]

Each participating ACCRU treating location will be responsible for monitoring the supply of cyclophosphamide and will use the Drug Order Request Form to order additional supplies as needed.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.49 Nursing Guidelines:

- 15.491 Myelosuppression is common. Monitor CBC including platelets. Instruct patient on signs/symptoms of infection and to inform health care team of any unusual bruising, or signs of bleeding.
- 15.492 Instruct patient to drink 2-3 liters of fluid per day for 2-3 days following treatment and to void frequently, not greater than every three hours to facilitate keeping the bladder clear of drug.
- 15.493 Instruct patient to report any urinary urgency, frequency, dysuria, or hematuria.
- 15.494 Advise patient in possible strong metallic taste associated with Cytosan and suggest hard candy with a strong flavor (cinnamon, peppermint) to alleviate it.
- 15.495 Administer antiemetics as necessary to minimize nausea and vomiting, which usually occurs 6-8 hours after administration.
- 15.496 Report and record any complaint of lightheadedness, facial "heat sensation," diaphoresis during administration.

- 15.497 Corticosteroids, phenothiazine, imipramine, vitamin A succinylcholine, digoxin, thiazide diuretics, warfarin and allopurinol may inhibit Cytosan metabolism and modify its' effect. They may also increase bone marrow suppression.
- 15.498 Advise female patients of possible menstrual changes or amenorrhea.
- 15.499a Patients on anticoagulant therapy should have INR levels carefully monitored as cytosan increases their effect.
- 15.499b Monitor digoxin levels closely as cytosan may decrease these levels.
- 15.499c Cytosan may potentiate doxorubicin-induced cardiomyopathy. Instruct patient to report any chest pain.

16.0 Statistical Considerations and Methodology

16.1 Overview of the statistical design

This is a double blind, randomized Phase II trial in triple negative patients with adjuvant breast cancer. The primary endpoint is disease-free survival (DFS), and the objective is to test for the superiority of Folate Receptor Alpha vaccine with GM-CSF (experimental arm) over placebo + GM-CSF (control arm) for disease-free survival. Patients will be randomized between the experimental and control arm with a 2:1 allocation within strata as defined by previous line of therapy (neoadjuvant vs adjuvant; stage I/II vs stage III). Subjects will continue protocol directed therapy until completion of treatment, documentation of disease progression, development of unacceptable toxicity, or withdrawal of consent. All subjects who begin treatment will be followed until death, withdrawal of consent, or study termination and will be included in the final analysis.

The target accrual is 280 patients. With an anticipated monthly accrual of approximately 18 patients, it will require 15 months of patient accession to reach 280 patients. The final analysis would occur after approximately 30 months of additional follow-up, and the anticipated total length of this trial is 4.5 years.

16.2 Endpoints

The primary endpoint is the duration of disease-free survival (DFS). DFS is the time from registration to first recurrence, where a recurrence is defined as any local, regional, or distant recurrence of breast cancer; the development of a contralateral breast cancer or second primary other than squamous or basal cell carcinoma of the skin, carcinoma in situ of the cervix, or lobular carcinoma in situ of the breast; or death from any cause without the documentation of one of these recurrences. Patients who are lost to follow-up and subjects who are alive at the date of data cut-off will be censored at the date the subject was last known alive.

Secondary endpoints include assessment of safety and tolerability of treatment and overall survival (OS), defined as the time from randomization to death due to any cause. The assessment of safety will be according to CTCAE 4.0. Time-to-treatment failure and treatment-related toxicity will be assessed. The primary correlative endpoint of this trial is vaccine induced FR α -specific T cell responses defined as: (1) a 2-fold or greater

increase in FR α -specific antibody concentration from pretreatment levels at any point during treatment or (2) FR α -specific antibodies above the lower limit of detection at any point during treatment if pre-treatment levels were non-detectable.

16.3 Sample size and power calculations

The primary objective of this trial is to show that folate receptor peptide vaccine with GM-CSF adjuvant will prolong the disease-free survival (DFS) compared to GM-CSF adjuvant treatment in patients with triple negative breast cancer. Folate receptor peptide vaccine will be allocated in a 2:1 fashion to the vaccine. The sample size of 280 patients provides a 78% power to detect a difference of 14% between groups assuming a 3.5 year DFS rate of 70% in the control group and 50% reduction in the hazard ratio.

16.31 Randomization allocation error

From February 24, 2020 through September 8, 2020, the dynamic randomization algorithm randomized patients to folate receptor peptide vaccine at a higher than 2:1 ratio. When the algorithm was corrected on September 8, 2020, there were 107 patients enrolled and the folate receptor peptide vaccine to placebo randomization allocation ratio was 2.68:1. The dynamic randomization process was re-started with the original 2:1 ratio to be used on the remaining 193 patients to be enrolled. The anticipated final allocation ratio over the entire 280 patient cohort is 2.22:1. This change in the allocation ratio from the original 2:1 to new 2.22:1 will result in a modest loss of power from 78% to 76%.

16.4 Data analysis

Analyses of all efficacy endpoints will be intention-to-treat, such that patients will be included in the arm to which they were randomized irrespective of treatment received. Further, patients who withdraw for toxicity, who withdraw consent for continued treatment, or who start off-protocol therapy will continue to be followed for recurrence and overall survival. Patients who withdraw consent to be followed will be censored. Analyses of toxicity will be conducted in the subset of patients who receive vaccine and placebo, respectively. All tests of endpoint will use a two-sided Type I alpha of 0.05, and point estimates will be reported with 95% confidence intervals.

16.41 Disease Status:

Disease-free survival is defined as the time from registration to documentation of disease recurrence, second primary, or death without disease recurrence or second primary. Overall survival time is defined as the time from registration to death due to any cause. The distribution of disease-free and overall survival times will be estimated using the method of Kaplan-Meier. The primary analysis will use the stratified log-rank tests, as described for DFS and OS. As a secondary analysis we will use a multivariable Cox proportional hazard model to estimate adjusted hazard ratios for vaccine over placebo, study stratification factors, and covariates for known prognostic factors. Baseline FR alpha levels will also be investigated as a potential prognostic factor.

16.42 Safety Profile:

As per CTEP Version 4.0 of the NCI CTCAE, the term toxicity is defined as adverse events that are classified as either unrelated, unlikely to be related, possibly, probably, or definitely related to the study treatment. The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed by primary disease site to determine toxicity patterns. For treatment-related toxicity, the primary analysis will use the Cochran-Mantel-Haenszel chi-squared test with study stratification factors. Secondary analyses will use logistic regression to test differences in proportions while controlling for the known covariates.

16.43 FR α -specific T cell immune response:

For FR alpha response, the proportion of patients with at least a 2-fold increase in the number of cells/plasma concentration (marker specific response) after the first cycle of treatment as well as anytime during treatment will be determined along with its corresponding 95% confidence interval. Among vaccinated patients, the proportion of responses will be compared between those who experience a DFS event and those who did not progress.

It is hypothesized that patients who have no folate receptor alpha expression may not benefit from the vaccine. Thus, a subgroup analysis will be performed only among those patients who express FR alpha to assess whether the vaccine prolongs DFS. In addition, FR alpha levels at baseline will be examined as a prognostic factor in the vaccine immune response. A multivariable Cox proportional hazard model will be used to assess baseline FR alpha levels as a potential prognostic factor for immune response.

16.5 Stopping rules

The stopping rule specified below is based on safety profile reported from an ongoing FR alpha clinical trial. The stopping rule was determined by taking the observed adverse event rates in this trial and calculating the 90% upper bound. The 90% upper bound was used as the cut point in the stopping rule.

We note that the adverse event stopping rule may be adjusted at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may also choose to suspend accrual because of unexpected adverse events that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (*i.e.*, an adverse event with attribution specified as “possible”, “probable”, or “definite”) and that satisfy any of the following:

- If 5 or more patients in the first 20 treated patients on either arm experience a grade 3 or higher hematologic adverse event, OR
- If 5 or more patients in the first 20 patients on either arm experience a grade 3 or higher non-hematologic adverse event, OR

- After the first 20 patients have been treated: if more than 25% of the treated patients on either arm experience a grade 3 or higher hematologic adverse event, OR
- After the first 20 patients have been treated: if more than 25% of the treated patients on either arm experience a grade 3 or higher non-hematologic adverse event.

In addition, we will review grade 4 and 5 adverse events deemed “unrelated” or “unlikely to be related”, to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.6 Study monitoring

The efficacy and toxicity data for this study will be reviewed at least semiannually by the Mayo Clinic Data Safety Monitoring Board (DSMB). Early termination of accrual will be considered if there is evidence of unacceptable toxicity.

17.0 Pathology Considerations/Tissue Biospecimens**17.1 Tissue Biospecimen Submission**

NOTE: Patients must have consented to submission of the optional tissue(s) listed in the following table.

17.11 Summary Table of Tissue Biospecimens for This Protocol

Type of tissue biospecimen to submit	Mandatory or optional	When to submit	Reason for submission (background/methodology section)	Where to find specific details for biospecimen submission
Formalin-fixed paraffin-embedded (FFPE) tissue blocks from primary diagnosis with corresponding H&E (OR 5 unstained slides with corresponding H&E)	Mandatory	≤30 days after randomization	Correlative studies (Section 17.5)	Section 17.2
3 unstained slides with corresponding H&E Formalin fixed paraffin tissue	Optional	At first recurrence only	Correlative studies (Section 17.5)	Section 17.3
5 unstained slides from primary diagnosis with corresponding H&E Formalin fixed paraffin tissue	Optional	≤30 days after randomization	Banking	Section 17.4

17.2 Paraffin Embedded Tissue Blocks/Slides

17.21 Submit one formalin fixed paraffin-embedded (FFPE) tumor tissue block with corresponding H&E with at least 1 cm of tumor from primary diagnosis according to patient's treatment below (and from recurrence for optional tissue submission if applicable).

- In patients who did not receive neoadjuvant chemotherapy, surgical sample should be submitted.

- In patients who received neoadjuvant chemotherapy and achieved complete pathological response (pCR) after neoadjuvant chemotherapy, only diagnostic biopsy prior to neoadjuvant chemotherapy should be submitted.
 - In patients who received neoadjuvant chemotherapy and still had residual disease after neoadjuvant chemotherapy, both diagnostic biopsy prior to neoadjuvant chemotherapy and surgical sample after neoadjuvant chemotherapy should be submitted.
- 17.22 The FFPE tissue block is preferred; however, **if an institution is unable to provide a tissue block**, cut 5 unstained slides with corresponding H&E cut at five micron sections and mount on charged glass slides. **Label the slides with ACCRU patient ID number, accession number, and order of sections.** The unstained slides will be processed as described in 17.3. For samples containing less than 900 square millimeters of tumor tissue, multiple sections should be mounted onto each slide to ensure that the appropriate amount of tumor tissue is available. Ideally, each slide must have a minimum of 75% tumor tissue on the slide to be deemed adequate for study. **Do not bake or place covers slips on the slides.**
- 17.23 The following materials below are mandatory (unless indicated otherwise) and required for shipment:
- Paraffin embedded tissue blocks with corresponding H&E slide (OR 5 unstained slides with corresponding H&E(s)).
 - Specimen Submission: Tissue form
 - Surgical Pathology Report
 - Operative Report (*optional*)
 - **Note: Please include the ACCRU patient ID number on all materials listed above.**
- 17.24 The block/slides must be appropriately packed to prevent damage (e.g., slides should be placed in appropriate slide container) and placed in an individual plastic bag. Label the bag with the protocol number, ACCRU patient ID number, and patient initials.
- 17.25 Tissue specimens must be shipped ≤ 30 days after randomization.
- 17.26 Verify that the appropriate sections of the Tissue Specimen Submission Form are completed and filled in correctly. Enter information from the Tissue Specimen Submission Form into the remote data entry system on the same day the specimen is submitted (see Forms Packet).
- 17.27 Ship all block/slide tissue specimens and accompanying materials to the BAP/PRC Core Laboratory Facility:



17.3 Optional Submission of Recurrent Tissue Samples (Staining for FR α expression as well

17.31 Please submit formalin-fixed paraffin-embedded (FFPE) tissue block with corresponding H&E (or 3 unstained slides with corresponding H&E cut at five micron sections). Please follow submission instructions in Section 17.2.

Please submit formalin-fixed paraffin-embedded (FFPE) tissue block with corresponding H&E from primary diagnosis (OR 5 unstained slides with corresponding H&E). Please follow submission instructions in Section 17.5.

17.51 Submitted tissue samples will be analyzed as follows: We will measure folate receptor alpha protein expression level by immunohistochemistry (IHC), using the folate receptor alpha antibody supplied by Morphotek.

17.53 Banking of tumor tissue, according to the patient consent permission (see Section 6.15), is for future research. Banked tumor tissue will be stored in the BAP/PRC Core Laboratory Facility, Jacksonville, Florida (Attn.: Laura Pacheco-Spann) for future research according to the patient consent permission (see Section 6.15). As protocols are developed, they will be presented for ACCRU and IRB review and approval. (This collection is part of a general strategy of investigation for ACCRU studies).

17.54 The institutional pathologist (Aziza Nassar, M.D.) will be notified by the BAP/PRC Manager if the block may be depleted.

17.55 Blocks requested to accommodate individual patient management will be returned promptly upon request.

17.56 Return of Genetic Testing Research Results: No genetic specimens will be collected from tissue biospecimens for this study. If future genetic testing is being requested for stored tissue, patient reconsent is required.

All data must be entered by Remote Data Entry (RDE) and completed by qualified and authorized personnel. Access the RAVE RDE system through the iMedidata portal at

██████████ All data on the CRF must reflect the corresponding source document. Please refer to the ACCRU website for instructions ██████████

18.1 Submission Timetable

Initial Material(s) -

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)
Institutional Contacts	≤2 weeks after registration
On-Study	
On-Study: Prior Systemic Therapy ²	
Adverse Events: Baseline	
Supporting Documentation: Baseline	
Laboratory Tests and Results	
Specimen Submission: Tissue (Baseline) (See Section 17.0)	
Specimen Submission: Blood (Baseline) (see Section 14.0)	
Baseline Research Tissue Submission Form (see Section 17.0)	
Patient Status: Baseline	
OP and Path Reports (see Section 17.0) ¹	
Off Treatment	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy

1. Upload Op and Path Reports via the Supporting Documentation: Baseline form. This is in addition to the pathology material requirements for tissue submission (Section 17.0).
2. Submit only if applicable.

Test Schedule Material(s)

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)		
	At each evaluation during treatment	At end of treatment	Observation
Treatment (Intervention)	X	X	
Treatment (Intervention): Dose Modifications, Omissions and Delays	X ²		
Adverse Events: Solicited	X	X	X
Adverse Events: Other	X	X	X
Supporting Documentation	X ¹	X ¹	X ¹
Laboratory Tests and Results	X	X	X
Specimen Submission: Blood (See Section 14.0)	X ²	X ²	X ²
Specimen Submission: Tissue (See Section 17.0)	X ²	X ²	X ²
Patient Status: Treatment (Intervention)	X	X	
Off Treatment		X	
Patient Status: Clinical Follow-Up/Observation			X
Notice of New Primary ²	X ²	X ²	X ²
Consent Withdrawal (choose appropriate form) ² • Consent Withdrawal: Specimens Only • Consent Withdrawal: Clinical Follow-Up Only • Consent Withdrawal: All Follow-Up	X	X	X
Lost to Follow-Up ²	X	X	X
Deviation Form ²	X	X	X
SAE Coordinator Only: Expedited Reporting/Hospitalizations ²	X	X	X

1. Upload a copy of documentation of progression in RAVE on the Supporting Documentation Form.
2. Submit only if applicable.

19.0 Budget

- 19.1 Each site should review the test schedule (Section 4.0), taking into account local and regional coverage policies, to determine which items are standard of care and which are research at their site. Refer to the payment synopsis for funding provided per accrual for covering study costs, as well as any additional invoiceables that may be allowed.
- 19.2 Tests to be research funded: Refer to the payment synopsis. Blood collection kits will be provided.
- 19.3 Other budget concerns: Cyclophosphamide, GM-CSF and FR α Peptide will be provided. The placebo for the FR α Peptide will be supplied by each site.

20.0 References

20. References

1. Bianchini, G., J.M. Balko, I.A. Mayer, M.E. Sanders, and L. Gianni, *Triple-negative breast cancer: challenges and opportunities of a heterogeneous disease*. Nat Rev Clin Oncol, 2016 <http://www.ncbi.nlm.nih.gov/pubmed/27184417>.
2. Liedtke, C., C. Mazouni, K.R. Hess, F. Andre, A. Tordai, J.A. Mejia, W.F. Symmans, A.M. Gonzalez-Angulo, B. Hennessy, M. Green, M. Cristofanilli, G.N. Hortobagyi, and L. Pusztai, *Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer*. J Clin Oncol, 2008. **26**(8): p. 1275-81
<http://www.ncbi.nlm.nih.gov/pubmed/18250347>.
3. Dent, R., M. Trudeau, K.I. Pritchard, W.M. Hanna, H.K. Kahn, C.A. Sawka, L.A. Lickley, E. Rawlinson, P. Sun, and S.A. Narod, *Triple-negative breast cancer: clinical features and patterns of recurrence*. Clin Cancer Res, 2007. **13**(15 Pt 1): p. 4429-34
<http://www.ncbi.nlm.nih.gov/pubmed/17671126>.
4. O'Shannessy, D.J., E.B. Somers, J. Maltzman, R. Smale, and Y.S. Fu, *Folate receptor alpha (FRA) expression in breast cancer: identification of a new molecular subtype and association with triple negative disease*. Springerplus, 2012. **1**: p. 22
<http://www.ncbi.nlm.nih.gov/pubmed/23961352>.
5. Zhang, Z., J. Wang, D.E. Tacha, P. Li, R.E. Bremer, H. Chen, B. Wei, X. Xiao, J. Da, K. Skinner, D.G. Hicks, H. Bu, and P. Tang, *Folate receptor alpha associated with triple-negative breast cancer and poor prognosis*. Arch Pathol Lab Med, 2014. **138**(7): p. 890-5
<http://www.ncbi.nlm.nih.gov/pubmed/24028341>.
6. Knutson, K.L., C.J. Krco, C.L. Erskine, K. Goodman, L.E. Kelemen, P.J. Wettstein, P.S. Low, L.C. Hartmann, and K.R. Kalli, *T-cell immunity to the folate receptor alpha is prevalent in women with breast or ovarian cancer*. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2006. **24**(26): p. 4254-61
<http://www.ncbi.nlm.nih.gov/pubmed/16908932>.
7. Kelemen, L.E., *The role of folate receptor alpha in cancer development, progression and treatment: cause, consequence or innocent bystander?* Int J Cancer, 2006. **119**(2): p. 243-50
<http://www.ncbi.nlm.nih.gov/pubmed/16453285>.
8. Hartmann, L.C., G.L. Keeney, W.L. Lingle, T.J. Christianson, B. Varghese, D. Hillman, A.L. Oberg, and P.S. Low, *Folate receptor overexpression is associated with poor outcome in breast cancer*. International journal of cancer. Journal international du cancer, 2007. **121**(5): p. 938-42
<http://www.ncbi.nlm.nih.gov/pubmed/17487842>.
9. Necela, B.M., J.A. Crozier, C.A. Andorfer, L. Lewis-Tuffin, J.M. Kachergus, X.J. Geiger, K.R. Kalari, D.J. Serie, Z. Sun, A. Moreno-Aspitia, D.J. O'Shannessy, J.D. Maltzman, A.E. McCullough, B.A. Pockaj, H.E. Cunliffe, K.V. Ballman, E.A. Thompson, and E.A. Perez, *Folate receptor-alpha (FOLR1) expression and function in triple negative tumors*. PLoS One, 2015. **10**(3): p. e0122209
<http://www.ncbi.nlm.nih.gov/pubmed/25816016>.

Appendix I
RU011501I Neurologic Evaluation
(Evaluator to document neurologic examination in clinical note)

<u>Exam component</u>	<u>Status (circle one)</u>	
Cranial nerves II-XII	Normal	Abnormal*
Cerebellar function	Normal	Abnormal*
Neuromuscular function	Normal	Abnormal*

*Abnormalities must be documents in the medical recor

Appendix II
Sample Cyclophosphamide Pill Diary
(Cycle 1 Only)

Name _____

Study Name/Number RU011501I

Patient ID Number _____

Patient Instructions:

- Your dose of cyclophosphamide is 50 mg (1 capsule) twice a day at the same time each day (approximately 12 hours apart, +/- 4 hours) on days 1-7 and 15-21.
- Do not administer capsules at bedtime.
- If you miss your dose of cyclophosphamide, take your next dose as scheduled. Do not take another dose to replace the dose you missed.
- If you vomit your dose of cyclophosphamide, take your next dose as scheduled. Do not take another dose to replace the one after vomiting.
- Cyclophosphamide should not be crushed, chewed or dissolved in water.
- Cyclophosphamide can be taken with or without food and water.
- You should bring this drug diary with your pill bottles to you next visit (Cycle 2 Day 1).
- Cyclophosphamide should be stored at room temperature.
- Record the date, time, number of pills taken and any comments immediately following each dose.

	Date	Time	Number of Cyclophosphamide Capsule Taken	Comments
Day 1		__ : __ ☐ AM		
		__ : __ ☐ PM		
Day 2		__ : __ ☐ AM		
		__ : __ ☐ PM		
Day 3		__ : __ ☐ AM		
		__ : __ ☐ PM		
Day 4		__ : __ ☐ AM		
		__ : __ ☐ PM		
Day 5		__ : __ ☐ AM		
		__ : __ ☐ PM		
Day 6		__ : __ ☐ AM		
		__ : __ ☐ PM		
Day 7		__ : __ ☐ AM		
		__ : __ ☐ PM		
Day 8		REST DAYS NO CYCLOPHOSPHAMIDE		
Day 9				
Day 10				
Day 11				
Day 12				
Day 13				
Day 14				
Day 15		__ : __ ☐ AM		
		__ : __ ☐ PM		
Day 16		__ : __ ☐ AM		
		__ : __ ☐ PM		

Day 17		__ : __ ☐ AM		
		__ : __ ☐ PM		
Day 18		__ : __ ☐ AM		
		__ : __ ☐ PM		
Day 19		__ : __ ☐ AM		
		__ : __ ☐ PM		
Day 20		__ : __ ☐ AM		
		__ : __ ☐ PM		
Day 21		__ : __ ☐ AM		
		__ : __ ☐ PM		
Day 22		REST DAYS NO CYCLOPHOSPHAMIDE		
Day 23				
Day 24				
Day 25				
Day 26				
Day 27				
Day 28				

Participant Signature: _____ Date: _____

Area Below To Be Completed By Study Staff Only

Number of pills returned: _____
Date: _____

Study Coordinator initials: _____
Discrepancy: Yes ___ No ___