Document Coversheet

Study Title: Phase I Clinical Trial Assessing the Combination of Chemokine Modulation with Neoadjuvant Chemotherapy in Triple Negative Breast Cancer

Institution/Site:	Roswell Park Comprehensive Cancer Center
Document (Approval/Update) Date:	11/10/2020
NCT Number:	NCT04081389
IRB Number	I 73718

PROTOCOL TITLE:

Phase I Clinical Trial Assessing the Combination of Chemokine Modulation with Neoadjuvant Chemotherapy in Triple Negative Breast Cancer

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VERSION NUMBER: 12

DATE: 11/05/2020

Confidentiality Statement

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1 OBJECTIVES

1.1 Primary Objective

- To examine the safety and tolerability profile of the combination of rintatolimod, celecoxib ± interferon alpha-2b, when given as CKM along with chemotherapy in the neoadjuvant setting in early stage triple negative breast cancer
- To identify the appropriate dose level of CKM and paclitaxel for future clinical exploration.

1.2 Secondary Objectives

- Evaluate the effect of neoadjuvant CKM + paclitaxel on pathological response and breast MRI response in early stage triple negative breast cancer patients.
- Evaluate the overall and recurrence-free survival in early stage triple negative breast cancer patients that received neoadjuvant CKM + paclitaxel.

1.3 Exploratory Objectives

- To evaluate longitudinal changes of blood biomarkers such as peripheral T-cell subsets, myeloid derived suppressor cells (MDSC), expression of chemokine and other immune genes, circulating immune mediators and correlate them with the clinical course post-surgery.
- Comparison of response assessment criteria for a prospective analysis using RECIST 1.1. (Appendix F) and irRECIST (Appendix G)
- Evaluate changes in the intratumoral levels of biomarkers, such as, peripheral T-cell subsets, myeloid derived suppressor cells (MDSC), chemokines, and immune-regulatory factors (pre- vs post-CKM + paclitaxel treatment).

2 BACKGROUND

Breast cancer is one of the leading causes of cancer-related morbidity worldwide (1). Approximately 20% of women diagnosed with early breast cancer (EBC) will experience recurrence at a distant site within 10 years (2). One key challenge is that breast cancer is a heterogeneous disease that is categorized clinically by immunohistochemical (IHC) staining of the three receptors: estrogen receptor (ER), progesterone receptor (PR), and the human epidermal growth factor receptor-2 (ERBB2/HER2) (3). Seminal studies in the early 2000s demonstrated that gene expression signatures could classify breast cancers into distinct and reproducible molecular subgroups (4). In essence, breast cancer can be molecularly classified into luminal A and luminal B subgroups that are mostly comprised of hormone-receptor positive (HR+) breast cancers; a basal-like subgroup that is mostly comprised of triple-negative breast cancers (TNBC); a HER2-enriched subgroup that is mostly comprised of HER2 + breast cancers and a normal-like subgroup that has been proposed to be mostly comprised of the contaminating tumor-surrounding stroma (5).

Triple Negative Breast Cancer

Triple-negative breast cancer (TNBC) is immunohistochemically defined by the lack of estrogen receptor (ER), progesterone receptor and human epidermal growth factor receptor 2 (HER2)

expression (6). Although it is generally more chemosensitive than other types of breast cancer, it is also characterized to harbor the most aggressive behavior with the front-loaded risk of relapse within the first 3–5 years after completion of adjuvant chemotherapy and its prevalence in younger women (7). Once metastasized, TNBC has a high predisposition to involve the critical visceral organs such as lung, liver and brain, eventually leading to a significantly shorter median overall survival than in other subtypes (8). Therefore, developing optimal therapeutic strategies for the treatment of early TNBC is crucial to alleviate the burden of TNBC.

Neoadjuvant or adjuvant chemotherapy remains a key component of systemic treatment in early TNBC, which is determined primarily by its clinical or pathologic stage (9). Neoadjuvant and adjuvant chemotherapy are the standard systemic treatment for early TNBC, and anthracycline and taxane-based chemotherapy regimens comprise the current standard of care (10). In previous pivotal neoadjuvant trials, patients with TNBC showed significantly higher response rates to anthracycline and taxane-based chemotherapy than those of other subtypes. The pathological complete response (pCR) observed in triple negative breast cancer after anthracycline and taxane based chemotherapy is around 26% (11). Moreover, as pCR showed a significant correlation with therapeutic benefits, it has been established as a robust surrogate biomarker for long-term survival outcomes (8). Although the guideline for adjuvant chemotherapy is generally similar for each breast cancer subtype, adjuvant chemotherapy in TNBC is recommended for primary tumors larger than 0.5 cm due to their aggressive behavior (12). Regarding the paradox that TNBC carries both higher chemosensitivity and the risk of early relapse, efforts have been continued to develop more effective chemotherapeutic regimens for both responders and non-responders. Clinical trials of newer combinations and dose-determination studies that evaluated metronomic or dose-dense regimens suggested the feasibility of refining conventional chemotherapy (13).

More recently, patients with an initially high tumor burden or residual disease after neoadjuvant chemotherapy were identified as compelling candidates for intensive systemic treatment, as they carry higher chance of relapse and metastatic spread. The CREATE-X trial demonstrated the potential survival benefit of adding capecitabine to the standard adjuvant chemotherapy regimen in early TNBC with a residual tumor burden after neoadjuvant treatment (14). A meta-analysis also provided a rationale for adding capecitabine to either neoadjuvant or adjuvant standard chemotherapy in patients with TNBC (15). The role of platinum based chemotherapy has also been suggested in the neoadjuvant setting in early stage triple negative breast cancer. In the CALGB 40603 trial (16), the pCR rate was significantly improved from 41% to 54%, in patients who received neoadjuvant chemotherapy combining carboplatin and/or bevacizumab with paclitaxel followed by dose-dense doxorubicin and cyclophosphamide (ddAC). The GeparSixto trial (17) similarly showed significantly enhanced pCR rates from 36.9% to 53.2% by adding carboplatin to combinations of ddAC and taxane-based chemotherapy with bevacizumab. In their recent secondary analysis, treatment benefit was consistently maintained even in patients without BRCA1/2 mutations (18). There has been recent interest in immunotherapy in triple negative breast cancer. Due to its genomic instability and high mutational burden, tumour microenvironment of TNBC is considered to be 'hot' with abundant infiltrating immune cells, which are actively engaged in the process of 'immunoediting' (19). TILs, mainly the $CD8^+$ T cells, are the most famous immune-related player in breast cancer (20). In TNBC treated with neoadjuvant treatment, TILs was identified as a robust predictive biomarker of long-term survival and its significance in remnant disease was subsequently validated (21) revealing an active communication between immune system and cytotoxic agents. Correlation between TILs and

programmed cell death 1/ligand 1 (PD-1/PD-L1) expression was suggested in recent experiments, which assumed the existence of a feedback loop regulating PD-L1 expression as a means of immune homeostasis. Several retrospective studies of early TNBC demonstrated significantly worse survival outcomes in patients harboring high PD-L1 expression and a low number of TILs or a high ratio of PD-L1/CD8 expression (22). TILs play a significant role in orchestrating the immune microenvironment and vigorously interact with cytotoxic signals including both chemotherapy and immunotherapy (23).

Clinical trials have shown the efficacy of immunotherapy in the neoadjuvant setting. In early TNBC, preliminary results from the neoadjuvant I-SPY 2 trial demonstrated that pCR rates increased from 22.3% to 62.4% by adding neoadjuvant pembrolizumab to paclitaxel followed by anthracycline-based chemotherapy, which represents an approximately 40% improvement in pCR compared with standard chemotherapy alone (24). The KEYNOTE-173 trial also showed a remarkably increased pCR rate from 60% to 90% in high-risk patients by combining pembrolizumab with paclitaxel or conventional chemotherapy according to the physician's discretion (25). Since improvement in pathological CR is a surrogate marker for efficacy, hence, there is increasing interest in performing clinical trials combining novel agents in the neoadjuvant setting in triple negative breast cancer in order to attain a higher pathological complete response.

2.1 Pre-clinical Studies with Chemokine Modulation

The chemokine receptors CXCR3 and CCR5 are typically used by CTLs to enter inflamed tissues. High tumor production of CCL5/RANTES (ligand for CCR5) and CXCL9/MIG, CXCL10/IP10, and CXCL11/ITAC (three known ligands for CXCR3) is associated with high CTL infiltration in different cancer types (26-28). Our previous correlative and mechanistic studies in other cancer types (29-31) showed the critical roles of intratumoral production of CCL5, CXCL9, and CXCL10 in local infiltration with $CD8^+$ GrB^+ CTLs, while CCL22 was found responsible for the attraction of FOXP3+ Tregs.

Combinatorial adjuvants: Synergistic and selective induction of CTL-attracting chemokines and suppression of Treg attractants: In an attempt to correct the deficit in local production of CXCR3 and CCR5 ligands seen in many cancer lesions, we compared the ability of toll like receptor (TLR) ligands and cytokines to induce different classes of chemokines. Although TLR3 ligands, such as poly-I: C were relatively ineffective when used alone and induced a significant production of Treg-attracting CCL22 (MDC; CCR4 ligand; Fig. 1), the combination TLR3-L with IFNα (and especially with IFNα and COX2 blockers), resulted in a strong synergy in selective induction of CXCR3 and CCR5 ligands, with concomitant suppression of CCL22.

Figure 1

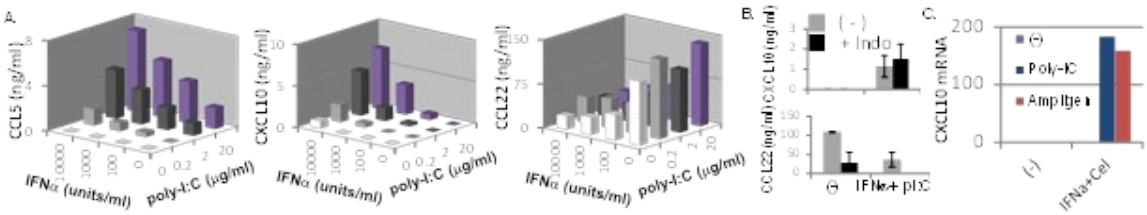


Fig. 1. Development of combinatorial adjuvants for selective induction of CTL-attracting chemokines: A. Opposite regulation of poly-IC-induced effector-type vs. suppressive chemokines by IFNα. Macrophages were used as the optimal source of CCL5 and CCL22, and fibroblasts were used as the source of CXCL10 (*see* ***Ref.***[1] *for experimental details*). **B.** COX-2 blockade selectively enhances the production of a *Teff*-attractant (CCL5) but suppresses the production of *Treg*-attracting CCL22. Chemokine levels in 48h supernatants. (ELISA). **C.** back-to back comparison of CXCL10 induction by CKM involving poly-I:C and Ampligen (Taqman). Similar data was obtained in case of CCL2 and CXCL22.

Studies completed within our NCI-funded program 1P01CA132714 "Directing Tumor-Specific T Cells to Tumors" identified TLR3 ligands, poly-I:C (double-stranded RNA; a molecular mimic of viral infections and activator TLR3 and RIG-I/MDA5 helicases) and its derivative, rintatolimod, a selective TLR3 ligand, which does not activate helicases and shows improved pattern of TME activation, with enhanced safety profile for systemic (i.v.) use, as preferred adjuvants which preferentially induce the CTL-/Th1/NK cells-attracting chemokines (29-33) and direct selective CTL accumulation in TMEs (29-31). Furthermore, the combination of rintatolimod (or poly-I: C) with IFNα and COX2 blockers (to enhance TLR3 signals and abrogate negative aspects of inflammation) are 10- to 100-fold more effective than each of these factors alone in inducing CTL attractants, and eliminates Treg attraction (29-31). Such combinatorial chemokine-modulating regimen (CKM) acts in tumor-selective fashion, avoiding activation of healthy tissues (29), and abrogates the heterogeneity of different tumor lesions (29), converting all "cold" tumors into inflamed ones (29-31).

2.2 Pre-clinical Studies with Chemokine Modulation and Chemotherapy

As discussed in the previous section, high tumor production of CCL5, CXCL9, CXCL10, and CXCL11 is associated with cytotoxic T-cell infiltration into the different cancer types. Thus, intratumoral production of CCL5, CXCL9, and CXCL10 is necessary for infiltration with CD8+ cytotoxic T cells, while, CCL22 production is responsible for attraction of FOXP3+ Tregs. Treatment of perfused liver tumors with chemotherapy (melphalan) results in production of Treg chemokines CCL22 which attracts the T regulatory cells, however, when melanoma models are treated ex-vivo with combination of celecoxib, IFN-alpha and poly-I:C, the production of CCL22 is significantly decreased, hence, supporting the hypothesis that combination of chemokine modulation with chemotherapy will result in reversal of the immunosuppressive effects of chemotherapy and potentiation of tumor infiltration with cytotoxic T-lymphocytes.

Figure 2

Chemotherapy (Melphalan) predominantly induces local production of Treg chemokines in perfused liver tumors (-MEL104t)

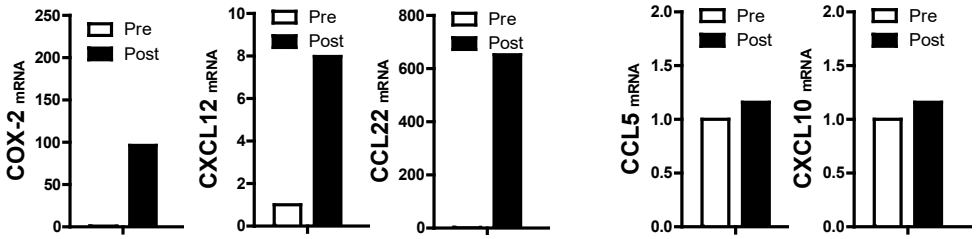
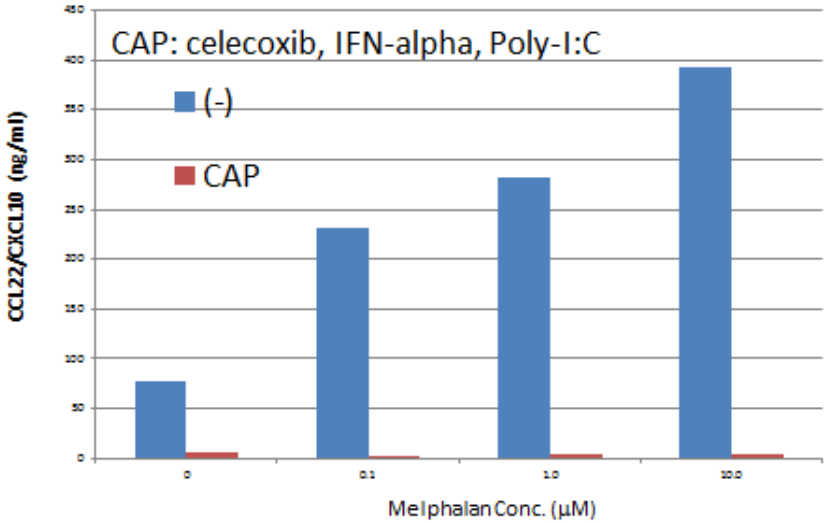


Figure 3

Ex vivo Cel+IFNa+PIC treatment reverses melphalan-induced elevation of CCL22/CXCL10 ratio in melanoma



2.3 Clinical Studies with Chemokine Modulation

Early data from our clinical trials of CKM in CRC: NCT01545141, i.v.; and ovarian cancer: NCT02432378; i.p. demonstrate safety of rintatolimod, administered alone or with IFNα, and local

efficacy in the TME of patients receiving systemic or local CKM (chemokines, immune markers, **Figure 4**).

Figure 4

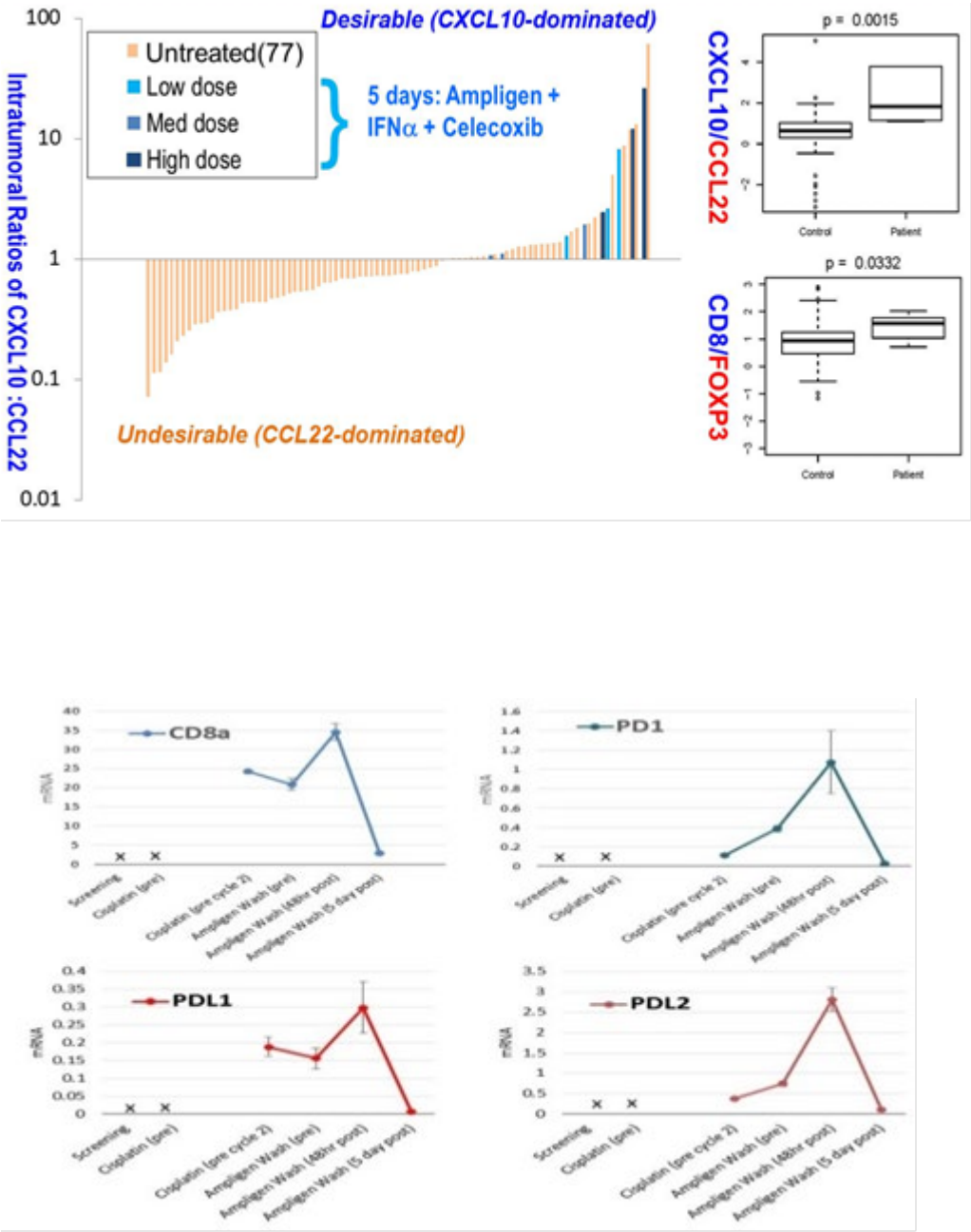


Figure 4: Safety and effectiveness of CKM in reprograming of patients' TME: Upper panel: (NCT01545141/UPCI 10-131): Increased ratios of CXCL10 (CTL-attractant) to CCL22 (Treg-

attractant), and CD8+ /FoxP3 ratios (TaqMan) in resected tumors of CRC patients receiving CKM (IFN□ doses: 5-10-20Million Units/m^2, rintatolimod (200mg/d), both.i.v., and oral celecoxib (2x200 mg/d), compared with control patients. **Bottom Panel:** (**NCT02432378/UPCI 11-128):** I.P. increases in CD8, PD1, PDL1 and PDL2 in the first patient receiving i.p. cisplatin, followed by rintatolimod (200 mg; lowest cohort, no IFNα). Two patients recently completed the second tier of i.p. CKM (rintatolimod + 2MU IFNα) without DLTs. Clinical trial at RPCI I-52917 of chemokine modulation in patients with colorectal cancer metastatic to the liver has enrolled 10 patients thus far and no DLTs have been observed. No treatment-related grade 3 or greater toxicities have been observed. The treatment has been well tolerated overall.

2.4 Clinical Studies with Chemokine Modulation and Chemotherapy

In addition to the evaluation of rintatolimod, interferon alpha-2b and celecoxib administered i.v. for one course over 5 days, as a stand-alone treatment, the same combinations (but different administration regimens) are being evaluated as a part of combinatorial regimens in additional patients with peritoneal carcinomatosis treated with HIPEC (NCT02151448 / UPCI 12-110) and recurrent ovarian cancer (NCT02432378 / UPCI 11-128). Clinical trial NCT02151448 (over 50 de-bulked and HIPEC-pretreated patients evaluated so far) involve multiple cycles of DC vaccines followed by 4 day long cycles of IFN- α /celecoxib regimen, with rintatolimod administered on days 2 and 4 of each cycle. Clinical trial NCT02432378 (5 patients evaluated so far) involve multiple cycles of intraperitoneal (i.p.) chemotherapy followed (with 1 day delay) by single i.p. doses of rintatolimod with increasing i.p. doses of IFN-α and a standard dose of celecoxib (orally).

No DLTs have been observed in any of these trials to date and, the combinations have been uniformly well tolerated.

2.5 Rationale for Neoadjuvant Chemokine Modulation

The proposed study will allow for in human proof of concept study which will serve as a basis for future combination proposals.

Currently, neoadjuvant chemotherapy is the standard of care for triple negative breast cancer, with pCR of about 30%. CKM will result in production of chemokines which would attract CD8+ T cells and decrease production of chemokines which favor immunosuppressive T regulatory cells, and hence, result in increased local infiltration of CD8+ T cells and hence, create an immunogenic environment as show in Figure 1. We hypothesize that higher number of CD8+ T-cells will result in increased efficacy of paclitaxel. Chemokine modulation, which we hypothesize from prior preclinical and clinical data, stimulates infiltration of the tumor by T-cells resulting in anti-tumor efficacy. Our hypothesis is that the combination will result in higher tumor infiltration with cytotoxic T-cells, resulting in an improvement in pCR which is considered a surrogate marker for survival.

2.6 Planned Correlative Studies

Tumor tissue, blood and serum samples will be evaluated for evidence of immune modulation and anti-cancer activity. Cytokine panel will be compared to pre-treatment samples and we will evaluate the T cell circulating component.

In addition, to identify responders vs. non-responders, we will also perform a biopsy after the patient has received 3 doses of CKM + paclitaxel combination therapy.

*specimens remaining after analyses on this study may be kept for future research, for patients who consented to the optional specimen banking.

3 INCLUSION AND EXCLUSION CRITERIA

3.1 Inclusion Criteria

To be included in this study, participants must meet the following criteria:

1 Age ≥ 18 years of age.

2 Have pathologically confirmed diagnosis of resectable triple negative breast cancer (ASCO/CAP guidelines will be used to define triple negative breast cancer).

3 Must have measurable disease. Multi-centric disease is allowed. If patient has another lesion which is biopsied with ER/PR positive it will be Physician discretion for this eligibility criteria

4 Prior therapy: No prior cytotoxic regimens are allowed for this malignancy. Participants may not have had prior chemotherapy, other targeted anticancer therapies, or prior radiation therapy to the ipsilateral breast for this malignancy. Prior bis-phosphonate therapy is allowed.

5 Patient eligible for surgery as determined by patient's surgeon.

6 Patient must have a lesion amendable to biopsy, unless inaccessible and with PI approval.

7 Have an ECOG performance status of ≤ 2. Refer to **Appendix A**.

8 Participants of child-bearing potential must agree to use adequate contraceptive methods (e.g., hormonal or barrier method of birth control; abstinence) prior to study entry. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

9 Ability to swallow and retain oral medication.

10 Ability to undergo MRI.

11 Must have adequate organ and marrow function present as defined below:

- Platelets ≥ 100,000/μL
- Hemoglobin ≥ 9 g/dL
- Absolute Neutrophil Count (ANC) ≥ 1500/μL
- Total bilirubin ≤ institutional upper limit of normal (ULN)
- AST (SGOT) and ALT (SGPT) ≤ 1.5 X institutional ULN
- Creatinine < ULN

  OR

  Creatinine clearance ≥ 50 mL/min per Cockcroft-Gault Equation for patients with creatinine levels greater than ULN-refer to **Appendix D**.

12 Left Ventricular Ejection Fraction (LVEF) ≥ 55%. If LVEF is <55% and patient is otherwise study-eligible, the PI will discuss with cardiologist if patient is eligible to receive doxorubicin and participate in study.

13 Participant or legal representative must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.

14 Participants on this study will be counseled on and are willing to use adequate contraceptive methods.

Please refer to **Appendix B** for the Investigator Study Eligibility Verification Form: Inclusion Criteria.

3.2 Exclusion Criteria

Participants will be excluded from the study for the following:

1. Patients currently treated with systemic immunosuppressive agents, including steroids, are ineligible until 3 weeks after removal from immunosuppressive treatment.
2. Patients with active autoimmune disease, requiring ongoing immunosuppressive therapy or history of transplantation.
3. Diagnosis of invasive carcinoma within the last 3 years.
4. Inflammatory breast cancer will be excluded from the study.
5. Participants who have metallic surgical implants that are not compatible with an MRI machine are not eligible.
6. Pregnant or nursing female participants.
7. Unwilling or unable to follow protocol requirements.
8. Patients with known serious mood disorders (Major depression is an exclusion). Other stable mood disorders on stable therapy for > 6 months may be allowed after consultation with PI)
9. Cardiac risk factors including:
    - Patients experiencing cardiac event(s) (acute coronary syndrome, myocardial infarction, or ischemia) within 3 months of signing consent
    - Patients with a New York Heart Association classification of III or IV (**Appendix E**)
10. History of upper gastrointestinal ulceration, upper gastrointestinal bleeding, or upper gastrointestinal perforation within the past 3 years.
11. Prior allergic reaction or hypersensitivity to NSAIDs or any drugs administered on protocol.
12. Any history of allergy to sulfonamides.
13. Any history of autoimmune hepatitis.
14. Grade 1 or higher neuropathy.

15. Any condition which in the Investigator's opinion deems the participant an unsuitable candidate to receive study drug.

Please refer to **Appendix C** for the Investigator Study Eligibility Verification Form: Exclusion Criteria.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this study.

4 LOCAL AND STUDY-WIDE NUMBER OF SUBJECTS

A total of 6-24 participants will be enrolled from Roswell Park. During the dose escalation portion of the study, a minimum of 6 subjects will be enrolled, but up to 24 patients may be required due to the unknown dose-toxicity relationship. Accrual is expected to take up to 2 years.

5 LOCAL AND STUDY-WIDE RECRUITMENT METHODS

Potential participants will be identified and recruited during scheduled visits to Roswell Park. Non-investigator Roswell Park physicians and community physicians may also refer potential subjects to the investigator for evaluation. There will be no "cold calling". Informed consent will be obtained on all subjects by the investigator prior to all study specific procedure (including screening procedures). No subject will be entered into this clinical trial without having a signed written consent form.

6 MULTI-SITE RESEARCH

Not applicable: This is a single-site study.

7 STUDY TIMELINES

Depending on the patient's clinical course, active treatment is expected to be approximately 22-27 weeks. Surgery will occur 3-6 weeks after completion of chemotherapy. An end of treatment visit will occur 2 weeks (± 3 days) after surgery and at that point the patient will come off study and be followed as per standard of care. Accrual is expected to take up to 2 years.

8 STUDY ENDPOINTS

8.1 Primary Endpoint

- To determine the safety and tolerability of CKM: rintatolimod (a selective toll-like receptor-3 agonist), celecoxib +/- IFN- α, with paclitaxel as part of standard paclitaxel and doxorubicin/cyclophosphamide neoadjuvant therapy in early stage TNBC. Safety and toxicity will be assessed using the CTEP NCI Common Terminology Criteria for Adverse Events (CTCAE Version 5.0)
- To identify the appropriate dose level of CKM and paclitaxel for future clinical exploration.

8.2 Secondary Endpoints

- Pathological response
- Complete breast MRI response after 12 weeks.

- Recurrence-free survival (RFS) and overall survival (OS) will also be assessed. RFS is defined as local/regional invasive recurrence, invasive ipsilateral breast tumor recurrence, distant recurrence, inoperable (meaning no surgery because of progression), and/or death from breast cancer (per standard of care according to physician discretion). RFS will be calculated from the time of treatment to event. OS is defined by death from breast cancer, non-breast cancer, unknown, or any other cause and will be calculated from the time of study entry to event.

8.3 Exploratory Endpoints

- To evaluate longitudinal changes of blood biomarkers such as peripheral T-cell subsets, myeloid derived suppressor cells (MDSC), expression of chemokine and other immune genes and, circulating immune mediators.
- Correlate each of the above markers and their change over treatment with the clinical course of the disease post-surgery.
- Comparison of response assessment criteria for a prospective analysis using RECIST 1.1. (Appendix F) and irRECIST (Appendix G).
- Comparing the effect of the neoadjuvant treatment (pre vs post-3 doses of CKM + paclitaxel treatment) on immune cells [tumor-infiltrating T cell subtypes, Teff/Treg ratios, CD11b+ MDSC; the expression of chemokine receptors (CCR2, CCR5, CCR4, CCR6, CXCR3, and CXCR4) and immune checkpoint molecules (PD-1, PD-L1/2, VISTA, CTLA-4, LAG3 and TIM3)] using RT-PCR, immunofluorescence (IF) and immunohistochemistry (IHC); local expression of Teff-attracting chemokines (CCR5, CXCL9, CXCL10 and CXCL11) and Treg/MDSC-favoring chemokines (CCL2, CCL22 and CXCL12) using IF and RT-PCR; RNA assays and microscopy, RT-PCR for COX-2 expression, IDO, IL-10, arginase and iNOS and, RNA signatures of groups of immune-regulatory genes that are modulated by the CKM regimen. Similar markers and additional soluble and cell-associated mediators may be evaluated in the circulating immune cells and in patients' sera. Exact scope of the above testing depends on available funding. Fresh or archival tissue from pre-, post-treatment biopsies and surgery could be used for additional correlative studies. The correlative studies would include multispectral IHC/IF analysis of the immune cell phenotypes and their activation /exhaustion status as well as gene expression based methods (using e.g., RNA seq) to define genes and pathways significantly altered upon CKM regiment and multi-gene signatures of the response and resistance.

9 DESIGN

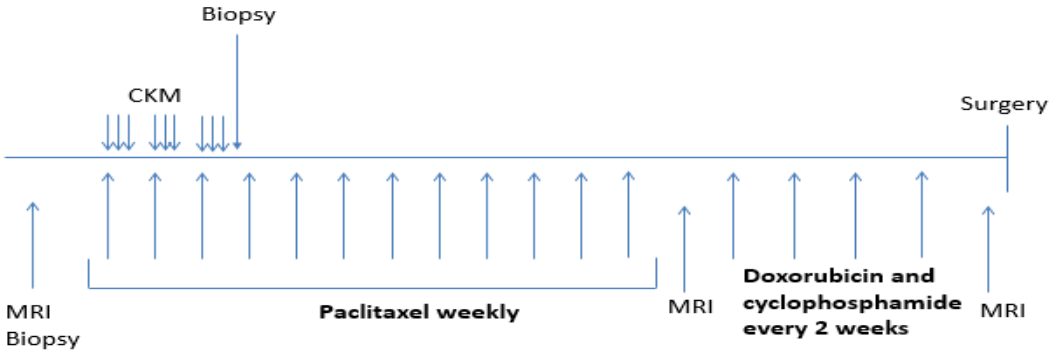
Depending on the patient's clinical course, active treatment is expected to be approximately 22-27 weeks. Based on the I-SPY (investigation of serial studies to predict your therapeutic response with imaging and molecular analysis) design where new investigational agents are studied in combination with paclitaxel in the neoadjuvant setting, in our study, patients will be treated with weekly doses of paclitaxel first.

In this Phase I study design each eligible patient will receive breast MRI per standard of care. Eligible patients will be treated with paclitaxel, TLR3 agonist (rintatolimod) 200 mg IV for days 1-3 and COX-2 inhibitor (celecoxib) 200 mg oral twice daily for days 1-3 at fixed doses and

escalating doses of IFN-α as presented in **Table 1**. Safety will be monitored closely by the research team and the early phase clinical trials committee. At final dose, three patients will be treated for confirmation of safety and if deemed safe, this dose would be taken forward for future clinical trials to evaluate the efficacy of the combination. Patients will have a baseline biopsy prior to any study treatment. On-treatment biopsy (to evaluate the character of the local immune response) will be obtained after the combination of CKM + paclitaxel is complete (before week 4), and this will be followed by the remaining doses of paclitaxel. Research blood draws will be collected for all the patients as discussed in study calendar Appendix J **Figure 5**. The CKM regimen is expected to promote the accumulation of effector immune cells and antigen presenting cells at the sites of the chemotherapy-killed or damaged tumor and to promote local and systemic immunization to antigens released from the involuting tumor. Breast MRI assessment will be used as a non-invasive serial measurement of response during the course of treatment for Dose Level 4.MRI longest diameter and volume will be measured at each time point and will be used for early evaluation of response. This will be followed by 4 cycles of dose-dense doxorubicin/cyclophosphamide treatment every 2 weeks. The current study design to reverse the sequence of chemotherapy is based on the I-SPY trial (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis) where novel agents are studied in addition to paclitaxel followed by doxorubicin and cyclophosphamide chemotherapy. Surgery will occur 3-6 weeks after completion of chemotherapy. Pathological CR is assessed at surgery about 6 months after the treatment is initiated. Waiting until each participant's outcome has been assessed is less than ideal. Hence, to obtain earlier information about the response, MRI measurements will be performed longitudinally starting at baseline, end of treatment with paclitaxel, and end of anthracycline treatment for Dose Level 4. These measurements are not predictive of pCR, but they do correlate with it as shown in I-SPY 1.

Patients will be monitored for dose limiting toxicities (DLTs) throughout the dose –escalation portion of the study. Refer to **Section 10.5**.

Figure 5 Study Schema (Dose Escalation) Pre- and post-treatment biopsies and MRI at the completion of paclitaxel (MRI only for the patients on Dose Level 4)



10 TREATMENT

10.1 Dosing and Administration

Treatment is intended for an outpatient setting. However, at the investigator's/physician's discretion, the participant may receive treatment as an inpatient, if deemed necessary.

10.2 Dose Escalation

A dose escalation phase will be carried out to assess the safety and tolerability of CKM when given in combination with paclitaxel. During the dose escalation phase, subjects will receive paclitaxel in combination with CKM (CKM to be given during weeks 1-3), followed by treatment with doxorubicin and cyclophosphamide. Refer to **Figure 5**.

Escalation will proceed according to the rules described in Section 19.4.

Dose levels are described in **Table 1**.

Table 1 Dose Levels

	CKM Therapy				
Dose Level	**Celecoxib**	**Interferon alpha-2b**	**Rintatolimod**	**Paclitaxel**	**Number of Subjects**
1 (start)	200 mg orally BID on days 1-3 of weeks 1-3.	None	200 mg intravenous (IV) on days 1-3 of weeks 1-3.	80 mg/m^2 IV once weekly on day 1	1-6
2	200 mg orally BID on days 1-3 of weeks 1-3.	5 million units/m^2 IV on days 1-3 of weeks 1-3.	200 mg IV on days 1-3 of weeks 1-3.	80 mg/m^2 IV once weekly on day 1	1-6
3	200 mg orally BID on days 1-3 of weeks 1-3.	10 million units/m^2 IV on days 1-3 of weeks 1-3.	200 mg IV on days 1-3 of weeks 1-3.	80 mg/m^2 IV once weekly on day 1	1-6
4	200 mg orally BID on days 1-3 of weeks 1-3.	20 million units/m^2 IV on days 1-3 of weeks 1-3.	200 mg IV on days 1-3 of weeks 1-3.	80 mg/m^2 IV once weekly on day 1	3-6

10.2.1 Dose Escalation, Paclitaxel + CKM

On **day 1 of weeks 1-3**, the patient will receive paclitaxel and CKM therapy on the same day. The following medications will be given in this order:

- Celecoxib: 200 mg orally

- Pre-medications 30 minutes prior to paclitaxel: dexamethasone 12 mg IV (if patient tolerates the first dose of paclitaxel well, the dose of dexamethasone will be decreased to 4 mg IV in the subsequent cycles), diphenhydramine 50 mg IV, famotidine 20 mg IV (pre-meds may be modified according to investigator and institutional practice).
- Paclitaxel 80 mg/m^2 IV infusion over 1 hour (± 10 minutes)
- Give normal saline 250 mL over 30 minutes.
- Remainder of CKM regimen (not including morning dose of celecoxib) will start 1 hour after paclitaxel infusion is completed. If necessary due to scheduling, patient tolerance, etc., the CKM regimen may be started at least 1 but up to 24 hours post paclitaxel infusion.
    - If CKM is started on the following day, 500 ml normal saline over 60 minutes will be given with the pre-medications and celecoxib 200 mg will be repeated twice daily again, as patient will not take the evening dose of celecoxib the same day as paclitaxel if the patient does not end up receiving the CKM regimen the same day as paclitaxel.
- Pre-meds for CKM: Acetaminophen (Tylenol) 650 mg by mouth x 1 dose; Prochlorperazine (Compazine) 10 mg by mouth x 1 dose – administered 30 minutes prior to start of interferon alpha-2b. For dose level 1 in which no interferon alpha-2b is given, the Acetaminophen and Compazine pre-meds may be omitted.
- For dose levels 2-4: Interferon alpha-2b (dose according to assigned dose level) IV over 20 minutes. No Interferon alpha-2 b is given in dose level 1.
- Rintatolimod: 200 mg IV, initial administration should begin at a slow rate of infusion (approximately 20 cc/ hour) and increase to 40 cc/ hour after 30 minutes. Tubing should be flushed with 30 to 50 mL of normal saline solution upon completion. Administration will be followed by 1 hour of observation and vital signs at 30 and 60 minutes post infusion (± 5 minutes).
- Celecoxib: 200 mg orally to be taken by the patient at home approximately 12 hours following the initial dose (if patient does not end up receiving CKM the same day as paclitaxel, will need two additional doses of celecoxib the next/subsequent day when patient receives CKM regimen).

On **days 2 and 3 of weeks 1-3**, the participant will receive CKM therapy according to the dose level assigned. The medications will be given in this order:

- Pretreatment: 500 mL Normal saline over 60 minutes
- Pre-meds: Acetaminophen (Tylenol) 650 mg by mouth x 1 dose; Prochlorperazine (Compazine) 10 mg by mouth x dose – administered 30 minutes (± 5 minutes) after starting pre-treatment hydration. For dose level 1 in which no interferon alpha-2b is given, the Acetaminophen and Compazine pre-meds may be omitted.
- Celecoxib: 200 mg orally, administered along with pre-meds.
- For dose levels 2-4: Interferon Alpha-2b (dose according to assigned dose level) IV over 20 minutes. No Interferon alpha-2 b is given in dose level 1.

- Rintatolimod: 200 mg IV, initial administration should begin at a slow rate of infusion (approximately 20 cc/ hour) and increase to 40 cc/ hour after 30 minutes. Tubing should be flushed with 30 to 50 mL of normal saline solution upon completion. Administration will be followed by 1 hour of observation and vital signs at 30 and 60 minutes post infusion (± 5 minutes).
- Celecoxib: 200 mg orally to be taken by the patient at home approximately 12 hours following the initial dose.

If day 1 CKM therapy is postponed to day 2, then CKM therapy will be given on days 2-4 of that week.

10.2.2 Dose Escalation, Paclitaxel Monotherapy

After the patient has completed 3 weeks of CKM + paclitaxel combination therapy, they will continue on weekly paclitaxel alone for an additional 9 doses (weeks 4-12). Each week, paclitaxel, 80 mg/ m^2 IV, will be given over 1 hour (± 10 minutes). Patients should be pre-medicated 30 minutes prior to each paclitaxel dose with dexamethasone 4 mg-12 mg IV (depending on patient tolerance of treatment in previous infusions), diphenhydramine 50 mg IV and famotidine 20 mg IV. Pre-medications may be modified according to the investigator and/or institutional practices. If it is determined a patient is no longer deriving benefit from Paclitaxel, the paclitaxel may be discontinued and treatment may proceed using AC dosing according to the schedule of events.

Doxorubicin + Cyclophosphamide (AC)

After completion of the above, the patient will proceed with dose-dense doxorubicin in combination with cyclophosphamide every 2 weeks for 4 cycles. The first doxorubicin + cyclophosphamide dose will be given 1-3 weeks after last dose of paclitaxel.

On day 1 of every 2 week cycle, doxorubicin 60 mg/m^2 IV push over 10 minutes and cyclophosphamide 600 mg/m^2 IV over 30 minutes will be given according to institutional standards. Patients should be pre-medicated with anti-emetics to prevent nausea and vomiting (per institutional standards).

10.3 Cohort Management

During the dose escalation phase, cohort management will be performed by the Phase 1 Cohort Management Group.

10.4 Definition of Dose-Limiting Toxicity

Participants will be monitored for DLTs. The following events will be considered a DLT:

- The event occurs within 3 weeks following 1st dose of combination CKM + paclitaxel therapy and subsequent enrollment for dose-escalation will only proceed after the 3-week period has been completed.
- The toxicity has been determined by the investigator to be possibly, probably or definitely related to celecoxib, rintatolimod, interferon-α2b or paclitaxel.
- Any death not clearly due to the underlying disease or extraneous causes

- Moderate toxicity is defined as any other grade 3 or higher adverse event that is not already defined as a DLT.
- If greater than or equal to 2 out of 5 patients experience a treatment delay of > 21 days, the study will be suspended and the Roswell Park Data Safety Monitoring Committee will review the study and will make recommendations that include but not limited to; (a) continuation of the study, (b) modifications to the design (c) or termination of the study.

Table 2 DLT Definition

Toxicity	Dose Limiting Toxicity
Hematology	CTCAE grade 4 neutropenia lasting more than 7 consecutive days despite growth factor support CTCAE grade 3 thrombocytopenia lasting more than 7 consecutive days and grade 4 thrombocytopenia ≥CTCAE grade 3 thrombocytopenia with bleeding
	CTCAE grade 3 or 4 febrile neutropenia CTCAE grade 3 infection with/ without neutropenia
Cardiac	Cardiac toxicity ≥ CTCAE grade 2 Clinical signs of cardiac disease, such as unstable angina or myocardial infarction
Gastro-intestinal	≥ CTCAE grade 3 vomiting ≥48 hours despite optimal anti-emetic therapy ≥ CTCAE grade 3 diarrhea ≥48 hours despite optimal anti-diarrhea treatment ≥ CTCAE grade 3 mucositis
Hepato-biliary	≥ CTCAE grade 2 total bilirubin for more than 7 consecutive days ≥ CTCAE grade 3 total bilirubin ≥ CTCAE grade 3 ALT for > 4 consecutive days CTCAE grade 4 ALT or AST Grade 4 serum alkaline phosphatase >7 consecutive days Any AST or ALT >3 x ULN and concurrent total bilirubin > 2 x ULN without initial findings of cholestasis (elevated serum alkaline phosphatase)
Renal	≥ CTCAE grade ≥3 serum creatinine
Infusion Related Reaction	≥ CTCAE grade 3
Non-hematologic events	≥ CTCAE grade 3, except for the exclusions noted below:
Any immune-related reaction	≥ CTCAE grade 3 ≥ CTCAE grade 1 fever lasting more than 7 consecutive days

Toxicity	Dose Limiting Toxicity
Neurological	≥ CTCAE Grade 3 neurotoxicity
Exceptions to DLT criteria	Grade 3 alopecia
	< 5 days of CTCAE grade 3 fatigue

Dose escalation will proceed according to **Section 19.4**.

Participants who do not have a DLT and who do not complete 6 out of 9 doses (CKM) of combination treatment (CKM + paclitaxel) will be replaced in the study. If patient does not receive ≥ 6/9 doses of CKM during the first 3 weeks, or receives a dose modification within the first 3 weeks, it will be considered a moderate toxicity significant enough to trigger the 3+3 design.

10.5 Dose Modifications and Treatment Delays

Day 1 of each CKM dose may be delayed by 1 day for any reason (i.e. patient tolerance, etc.). In this instance, CKM doses will be moved to days 2-4 instead of days 1-3.

For patient tolerance and toxicities, if dose modifications are needed during the DLT period, this will be discussed with the study PI and the research team. With the exception of delaying day 1 of each CKM dose by 1 day, any other dose delays if needed for toxicity management will need to be discussed with the study PI and research team. After the DLT period, chemotherapy (paclitaxel, doxorubicin or cyclophosphamide) may be dose modified or delayed per physician discretion. If toxicities are observed, based on investigator discretion and the common side effects of the study drug and standard of care, attribution will be made to the study drug or paclitaxel. Dose reductions for study drugs are mentioned in Section 10.5.2. Study drug will be dose -reduced first if attribution unclear between study drug and paclitaxel. If study drugs are dose-reduced, one drug will be dose reduced first depending on which drug is most likely associated with the toxicity. We are considering DLT period as the first 3 weeks during treatment. For close monitoring for any toxicities, patients will be seen weekly for physical examination thereafter until week 6. As CKM stimulated T cell infiltration, there is a small chance for immune related toxicities past the DLT period. The toxicities for all the patients will be monitored for additional 3 months after completing the combination treatment with special attention to immune related toxicities.

If a DLT attributable to CKM causing delay in paclitaxel or AC dosing greater than 21 days or a cumulative delay of >28 days while on treatment is noted after the first 3 weeks, patients will be permanently discontinued from protocol therapy. Any of the above situations would cause a hold to the trial and reassessment of trial continuation.

10.5.1 Celecoxib Hematologic and Non-Hematologic Toxicities

Considered to be possibly, probably, or definitely related to celecoxib (interferon alpha-2b and rintatolimod will be continued). Celecoxib will be discontinued for any attributable grade ≥3 toxicity.

10.5.2 Interferon Alpha-2b and/or Rintatolimod Hematologic and Non-hematologic Toxicities

Considered to be possibly, probably, or definitely related to interferon alpha-2b and/or rintatolimod.

Any patient with persistently severe or worsening signs or symptoms of neuropsychiatric, autoimmune, ischemic, or infectious disorders will be immediately withdrawn from therapy.

Interferon alpha-2b:

- If there is a DLT at 5 million units /m^2, then the standard 3+3 design will be triggered. If 2 patients develop DLT, then patients will not receive any interferon further and in that case, we will plan to expand to 6 patients with only rintatolimod and celecoxib.
- Ophthalmologic toxicity grade ≥3: hold interferon alpha-2b dosing until toxicity is resolved to ≤ grade 1 or baseline.
- **Hematologic Toxicities**

  For Grade 3 toxicity (thrombocytopenia):

  - 1st incidence– if <7 days to resolution: Treatment to continue if toxicity resolves to ≤ grade 1 or baseline at the lower dose level as proposed in dose-escalation. The dose cannot be re-escalated.
  - If > 7 days to resolution: Treatment to continue if toxicity is resolved to ≤ grade 1 or baseline at the next study visit at the lower dose level as proposed in dose-escalation. The dose cannot be re-escalated.
  - 2nd incidence: Treatment to continue if toxicity is resolved to ≤ grade 1 or baseline at the next study visit at the second lower dose level [this is possible in case of only 20 MU/m2 but in case of 10 MU/m2 – at the second incidence of event, the protocol therapy will be discontinued]. The dose cannot be re-escalated.

For grade 3 anemia: No dose modification needed and treatment can proceed at the same dose and schedule with transfusions. For grade 3 neutropenia, administer interferon at the same dose with growth factor support.

For Grade 4 toxicity (thrombocytopenia):

- 1st incidence– If <7 days to resolution: Treatment to continue if toxicity is resolved to ≤ grade 1 or baseline at the next study visit at the lower dose level. The dose cannot be re-escalated.
- 2nd incidence: Discontinue.

For grade 4 anemia: No dose modification needed and treatment can proceed at the same dose and schedule with blood transfusion. For grade 4 neutropenia, hold until toxicity resolved to ≤ grade 1 or baseline (growth factor support allowed) and then restart at same dose.

- **Non-Hematologic toxicities**

  For Grade 3 toxicity:

- 1st episode: Treatment to continue if toxicity is resolved to ≤ grade 1 or baseline at the lower dose level as proposed in dose-escalation. The dose cannot be re-escalated.
- 2nd episode: Protocol therapy discontinued.

For Grade 4 toxicity: Protocol therapy discontinued.

Rintatolimod:

- **Hematologic Toxicities**

  For Grade 3 toxicity (thrombocytopenia):

  - If < 7 days to resolution: Treatment to continue if toxicity is resolved to ≤ grade 1 or baseline at a dose reduction of 25%. The dose cannot be re-escalated.
  - If > 7 days to resolution: Treatment to continue if toxicity is resolved to ≤ grade 1 or baseline at the next study visit at a dose reduction of 25%. The dose cannot be re-escalated.
  - 2nd incidence: Treatment to continue if toxicity is resolved to ≤ grade 1 or baseline at the next study visit at a dose reduction of 25%. (total 50% reduction if the dose was not re-escalated). The dose cannot be re-escalated.

For grade 3 anemia: No dose modification needed and treatment can proceed at the same dose with transfusions. For grade 3 neutropenia, administer rintatolimod at the same dose with growth factor support.

For Grade 4 toxicity (thrombocytopenia):

- 1st incidence: If < 7 days to resolution: Treatment to continue if toxicity is resolved to ≤ grade 1 or baseline at the next study visit at a dose reduction of 25%. The dose cannot be re-escalated.
- If > 7 days to resolution: Discontinue.

For grade 4 anemia: No dose modification needed, and treatment can proceed at the same dose with blood transfusion. For grade 4 neutropenia, hold until toxicity resolved to ≤ grade 1 or baseline (growth factor support allowed) and then restart at same dose.

- **Non-Hematologic toxicities:**

For Grade 3 toxicity:

- 1st episode: Treatment to continue if toxicity is resolved to ≤ grade 1 or baseline) at a dose reduction of 25%.
- 2nd episode: Protocol therapy discontinued.

For Grade 4 toxicity:

- Protocol therapy discontinued.

10.5.3 CKM Toxicity Management

The toxicity of high dose interferon (20 million units/ m^2/d) has been established by Kirkwood et al in a number of trials. Most notable was the E1684 trial (34) where high dose interferon (20 million units/ m^2/d) was administered daily for 5 days x 4 weeks. In that trial (n=143), grade 3 toxicities were 67%, grade 4 toxicities were 9% (mainly constitutional and neurologic), and there were 2 treatment related mortalities (grade 5) due to hepatotoxicity. The proportion of Grade 3 and 4 toxicities in that trial were 48.2% for constitutional toxicities (defined as 'worst grade of any constitutional toxicity, including fever, chills, flu-like symptoms, fatigue, malaise, and diaphoresis), and 66% for non-constitutional toxicities (23.8% for myelosuppression, 13.9% for hepatotoxicity, 28% for neurological toxicity).

While the combination of high dose interferon and rintatolimod may lead to synergistic additive side effects, we will monitor subject toxicities for unexpected increases in constitutional symptoms, myelosuppression, hepatotoxicity, and neurological toxicity. Moreover, the presence of celecoxib may improve the side effect profile. Our strategy is to continuously monitor treatment related occurrences of constitutional symptoms (including fever, chills, flu-like symptoms, fatigue, malaise, or diaphoresis).

These are suggestions for specific toxicities and may be modified for institutional guidelines and treating physician preference.

Gastrointestinal Toxicity

- Nausea and/or vomiting should be controlled with adequate antiemetic therapy. Prophylactic antiemetic therapy can be used at the discretion of the investigator/sub-investigator. Subjects are encouraged to take plenty of oral fluids.

- Diarrhea should be managed with appropriate antidiarrheal therapy. Subjects should be encouraged to take plenty of oral fluids. If symptoms do not decrease to grade 1 or less with adequate antidiarrheal therapy, all protocol drugs should be held until resolved to < grade 1.

Pain/Fever/Chills/ Flu-like Symptoms

- For chills and/or fever or mild local pain, acetaminophen will be utilized at the discretion of the investigator/sub-investigator or designee. NSAIDs will be avoided.

Note: Any patient developing fever, cough, dyspnea, or other respiratory symptoms should have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient should be closely monitored, and, if appropriate, interferon alpha treatment should be discontinued.

While fever may be related to the flu-like syndrome reported commonly in patients treated with interferon, other causes of persistent fever should be ruled out.

Hypersensitivity Reactions

Caution: Subjects who had a mild to moderate hypersensitivity reaction have been successfully re-challenged, but careful attention to prophylaxis and bedside monitoring of vital signs is recommended. Hypersensitivity reactions to interferon alpha-2b and/or rintatolimod will be managed as follows:

- Mild symptoms (e.g., mild flushing, rash, pruritus): Complete infusion. Supervise at bedside. No treatment required.
- Moderate symptoms (e.g., moderate rash, flushing, mild dyspnea, chest discomfort): Stop infusion. Give intravenous diphenhydramine 50 mg and intravenous famotidine 20 mg. Resume infusion after recovery of symptoms at a 66% slower rate, then, if no further symptoms, rate can be titrated up every 5-10 min to initial rate until infusion is complete. If symptoms recur, at lowest infusion rate stop the infusion and no further interferon alpha-2b administered on that day. If symptoms recur after the rate has been increased, stop the infusion, treat reaction as per institutional guidelines, consider dexamethasone 20 mg IV and restart at 66% slower rate (over 1 hour) without up-titration. Future doses pre-treatment modifications and rate modification after discussion with the investigator. Record toxicity.
- Severe life threatening symptoms (e.g., hypotension requiring pressor therapy, angioedema, respiratory distress requiring bronchodilation therapy, generalized urticaria): Stop infusion. Treat as per institutional guidelines. Subject should be removed from further protocol therapy. Report as serious adverse event.

Ophthalmologic Disorders

Decrease or loss of vision, retinopathy including macular edema, retinal artery or vein thrombosis, retinal hemorrhages and cotton wool spots; optic neuritis, papilledema, and serous retinal detachment may be induced or aggravated by treatment with interferon alfa-2b or other alpha interferons.

- All patients should receive an eye examination at baseline. Patients with preexisting ophthalmologic disorders (e.g., diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during interferon alpha treatment.
- Any patient who develops ocular symptoms should receive a prompt and complete eye examination.

10.5.4 Paclitaxel Toxicity Management

The following are suggestions for specific toxicities and may be modified per institutional guidelines and treating physician preference:

Anaphylaxis/Hypersensitivity:

Mild symptoms (Grade 1): mild flushing, rash, pruritus.

- Complete infusion, observation in treatment area. No treatment required.

Moderate symptoms (Grade 2): moderate rash, flushing, mild dyspnea, chest discomfort.

- Stop infusion.
- Give intravenous diphenhydramine 25 mg and intravenous dexamethasone 10 mg. Methylprednisolone (60 mg IV) may be used instead of dexamethasone.
- Resume paclitaxel infusion after recovery of symptoms, at a slower rate. 10 mL/hour for 15 minutes, then 25 mL/hour for 15 minutes, then, if no further symptoms, at full dose rate until infusion is complete.
- If moderate or severe symptoms recur after rechallenge, stop paclitaxel infusion, and report as an adverse event.
- Patient may be rechallenged after premedication with dexamethasone 8 mg po or IV q 6 hrs x 4 doses (moderate symptoms) or 20 mg po or IV q 6 hrs x 4 doses (severe symptoms) and diphenhydramine 25 mg po or IV q 6 hrs x 4 doses (moderate or severe symptoms). Methylprednisolone (60 mg IV) may be used instead of dexamethasone.
- The paclitaxel should be administered at a slower rate. 10 mL/hour for 15 minutes, then 25 mL/hour for 15 minutes, then, if no further symptoms, at full dose rate until infusion is complete.

Severe life-threatening symptoms (Grade $\geq$ 3): hypotension requiring pressor therapy, angioedema, respiratory distress requiring bronchodilation therapy, generalized urticaria.

- Stop paclitaxel infusion.
- Give intravenous diphenhydramine 25 mg and intravenous dexamethasone 10 mg. Methylprednisolone (60 mg IV) may be used instead of dexamethasone.
- Add epinephrine or bronchodilators if indicated.
- Report episode as an adverse event.
- Patient will not be re-challenged and will be removed from the study.

Cardiac Arrhythmias

- Asymptomatic, EKG-documented arrhythmias:
  - Stop paclitaxel, and manage arrhythmia according to standard practice.
  - Protocol treatment will be discontinued and the episode reported as an adverse event.
- Asymptomatic sinus bradycardia or tachycardia:
  - No intervention is necessary.
- Sinus bradycardia or tachycardia associated with hypersensitivity reaction:
  - Please see above.

Hematologic Toxicity

If ANC<800 prior to paclitaxel dose

- Delay paclitaxel (consider growth factor support per standard of care).
- Check counts weekly until ANC ≥ 800 mm3
- If a delay of greater than 21 days is required, permanently discontinue protocol therapy and notify study chair.

If platelets < 100,000 prior to paclitaxel dose

- Dose-modifications per physician discretion.

Neurologic Toxicity: Neuropathy (motor and sensory)

Grade 1 or 2 Neurotoxicity:

- There will be no dose modifications for grade 1 or 2 neurotoxicity.
- Treatment does not need to be delayed and previously administered doses can be continued.
- If the patient is experiencing significant distress from grade 2 toxicity or the treating physician is uncomfortable with continuing the same doses, a dose reduction of 10 mg/m2 in the paclitaxel dose is acceptable.

Grade 3 Neurotoxicity:

- Patient should not receive additional treatment until the toxicity has resolved to ≤ Grade 2.
- The next infusion may be delayed up to 2 weeks to allow for neurologic toxicity to improve.
- If it does not resolve to ≤ Grade 2 after 2 weeks, the patient will be permanently discontinued from protocol therapy.
- Re-treatment should be initiated with a dose of paclitaxel 10 mg/m2 below the previous dose level when the toxicity resolves to Grade 2 or less. All subsequent infusions will be administered using the reduced dose.
- If Grade 3 neurotoxicity develops with additional infusions, further dose reductions may be made in increments of 10 mg/m2 to a maximum of 4 dose level reductions.

- Patients whose toxicity does not improve after 4 dose level reductions will be permanently discontinued from protocol therapy.
- Patients who develop worsening neurotoxicity with each infusion, even if it remains Grade 2, should be carefully evaluated to determine if a dose reduction would be appropriate.
- Dose reductions for neurotoxicity:
    - Full dose: 80 mg/m2
    - 1st dose reduction: 70 mg/m2
    - 2nd dose reduction: 60 mg/m2
    - 3rd dose reduction: 50 mg/m2
    - 4th dose reduction: 40 mg/m2

Grade 4 Neurotoxicity:

- Permanently discontinued from the study.

Gastrointestinal Toxicity:

- **Nausea/Vomiting**
    - Grade 0-2 Nausea/Vomiting: No change.
    - ≥Grade 3 despite maximal anti-emetic therapy: Hold paclitaxel until ≤Grade 2 then restart with 20% dose reduction in subsequent cycles.
    - If nausea/ vomiting toxicity causes a dosing delay of > 21 days, or if ≥Grade 3 nausea/ vomiting recurs despite dose reduction, permanently discontinue protocol therapy and notify study chair.

Prophylactic antiemetics should be used at the discretion of the investigator. The specific regimen must be recorded in the patient's medical record.

- **Mucositis**
    - Grade 2 Mucositis:
        - If Grade 2 mucositis is present on the day of any treatment, the treatment should be delayed until the mucositis has resolved to a Grade 1 or 0, and then resume paclitaxel at 80 mg/m^2.
    - Grade 3 or 4 Mucositis:
        - Delay treatment until mucositis has resolved to Grade 1 or 0 then the dose of paclitaxel should be reduced to 70 mg/m2.
            - If Grade 3 or 4 mucositis recurs, treatment should be delayed until mucositis has resolved to Grade 1 or 0, and the dose of paclitaxel should be reduced to 60 mg/m^2.
            - If mucositis causes a delay of > 21 days, the patient should be permanently discontinued from protocol therapy.

- Once the paclitaxel dose has been decreased, it should not be re-escalated.

- **Diarrhea**
  - Grade 2:
    - If Grade 2 diarrhea is present on the day of any treatment, the treatment should be delayed until the diarrhea has resolved to Grade 1 or 0, and then resume paclitaxel at 80 mg/m^2.
      - If diarrhea causes a delay of > 21 days, the patient should be permanently discontinued from protocol therapy.
    - Optimal use of anti-diarrheal agents is encouraged.
  - Grade 3 or 4:
    - If Grade 3 or 4 diarrhea occurs, delay treatment until the diarrhea has resolved to grade 1 or 0, then the dose of paclitaxel should be reduced to 70 mg/m2.
    - If Grade 3 or 4 diarrhea recurs, treatment should be delayed until diarrhea has resolved to grade 1 or 0, and the dose of paclitaxel should be reduced to 60 mg/m2.
    - If diarrhea causes a delay of > 21 days, the patient should be permanently discontinued from protocol therapy.
    - Once the paclitaxel dose has been decreased, it should not be re-escalated.
    - Optimal use of anti-diarrheal agents is encouraged.

- **Hepatic Dysfunction**

Because the plasma clearance of paclitaxel is reduced in patients with hepatic impairment; careful evaluation of liver enzymes in necessary before the administration of each new cycle of paclitaxel.

For elevations in total bilirubin, SGOT (AST), SGPT (ALT), the following dose modifications will be applied:

- Grade 1:
  - No dose modifications.
- Grade 2:
  - Hold paclitaxel for one week.
  - If abnormal tests return to grade 0 or 1, paclitaxel should be continued at full dose.
    - If the abnormal test does not return to grade 0 or 1 in one week, but remains at Grade 2, continue paclitaxel at 70 mg/m^2. If the abnormal test result returns to Grade 0 or 1, return to full dose, 80 mg/m^2.
- Grade 3 or 4:

- Patient should be permanently discontinued from protocol therapy.

- **Febrile Neutropenia**

Fever ≥38°C (101.3°F) in the presence of neutropenia (ANC <1000):

- Paclitaxel should be held for all instances of febrile neutropenia.
  - First episode: G-CSF or GM-CSF may be used for subsequent cycles at the discretion of the treating physician, but it is not required. There will be no dose reduction for the first episode of febrile neutropenia.
  - -Second episode: Remaining doses will be reduced to paclitaxel 70 mg/m2 given with G-CSF or GM-CSF.
  - -Three episodes: Remaining doses will be reduced to paclitaxel 60 mg/m2 given with G-CSF or GM-CSF.
  - -More than three episodes: Discontinue protocol therapy.

10.6 General Concomitant Medication and Supportive Care

Additional cancer directed chemo-, immune-, and radiotherapies are not permitted during the active treatment period of this trial. Any supportive care deemed necessary by the investigator (i.e. blood transfusions, anti-emetics, etc.) are allowed. Growth factor support may be given as standard of care.

10.7 Compliance

On days that CKM regimen is given, the morning dose of celecoxib will be administered in the Clinical Research Center (or other clinical area) and documented by the nurse on the Medication Administration Record. The evening dose of celecoxib will be self-administered at home and documented by the participant on the patient diary. The participant will be asked to bring the diary with him/her to each clinical visit.

11 PROCEDURES INVOLVED

The study-specific assessments are outlined in Study Calendar (**Appendix J**).

Unless otherwise defined in the written protocol text, all procedures/assessments will be conducted in accordance with Roswell Park Clinical Research Services Standard Operating Procedures.

Eligibility of each participant will be established prior to start of treatment.

Informed consent ***MUST*** be completed prior to receiving any study related procedures.

11.1 Correlative Studies

Blood samples (60 cc) will be collected at the time points specified on the study calendar (Appendix J). At each time point, (1) 10 mL red top tube and (5) 10 mL sodium heparin green top tubes will be collected. Collection tubes are to be labeled with the participant's MR number, participant's initials, participant's study number, time of collection, and protocol day. Specimens will be sent at room temperature to the attention of the Correlative Science Pathology Office (Pneumatic Station 19) where they will get accessioned for tracking in the source document. Once

specimen receipt has been documented, the specimens will be sent at ambient temperature to pneumatic station 641 (located in CCC LOB-4th floor). The Kalinski Laboratory will be notified via telephone *and* e-mail (all contacts to be copied with each e-mail-see contact information below) prior to sample shipment and, the samples will be held in CSPO until a response is received acknowledging that personnel are available to procure the samples from the pneumatic tube station. Samples will be processed in the Kalinski Laboratory for future analysis.

Roswell Park Comprehensive Cancer Center
Kalinski Laboratory
CCC Bldg. 5th Floor, Rm. 502F
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Elm & Carlton Streets
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Per.Basse@RoswellPark.org
Pawel.Kalinski@roswellpark.org

Note: All investigator or analyzing research laboratories housing research samples need to maintain current **Temperature Logs** and study-specific **Sample Tracking and Shipping Logs**. The Principal Investigator/Laboratory Manager **must** ensure that the stated lab(s) have a process in place to document the receipt/processing/storage/shipping of study-related samples/specimens. This is required for both observational and interventional clinical studies collecting clinical samples.

11.2 Pathology

11.2.1 Fresh Biopsies

As per amendment 10, a fresh biopsy is required at baseline for all patients (standard of care). An additional biopsy to assess the intratumoral biomarkers will be required for the patients:

After completion of 3 doses of CKM + paclitaxel combination therapy patients will have fresh biopsy collected (prior to 4th dose).

If patients develop disease progression during the DLT period, tumor biopsy can be performed (if patient agrees, not mandatory) and will be analyzed for exploratory endpoints as discussed but will not be considered for efficacy analysis as these patients have already developed disease progression on treatment.

4 tumor and 2 surrounding tissue cores will be obtained at each time point. 1 tumor core will be fixed in formalin for 8 to 24 hours and processed as a paraffin embedded block (FFPE block). Upon completion of processing, the FFPE block will be QC'd and stored ambient at the Correlative Sciences Pathology Office (GBSB S-636) until requested. The rest of the core biopsy samples will be placed in separate 10-mL cold sterile DPBS (supplied by the Kalinski lab). Label the samples as "tumor" or "non-tumor" with study-specific subject ID number, clinical study number, protocol time point, and protocol day. Samples will be sent to Dr. Pawel Kalinski's lab via pneumatic tube station #641 (located in CCC-LOB 4th floor) upon completion of processing (preferably ASAP

within 2 hours of collection, but within 4 hours of collection is allowed). In case of any delays, the samples should be refrigerated (4° C) or kept on ice, but not frozen.

Roswell Park Comprehensive Cancer Center
Kalinski Laboratory
CCC Bldg. 5th Floor, Rm. 502F
Attn: Study Number – I 73718
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Note: All investigator or analyzing research laboratories housing research samples need to maintain current **Temperature Logs** and study-specific **Sample Tracking and Shipping Logs**. The Principal Investigator/Laboratory Manager **must** ensure that the stated lab(s) have a process in place to document the receipt/processing/storage/shipping of study-related samples/specimens. This is required for both observational and interventional clinical studies collecting clinical samples.

12 WITHDRAWAL OF SUBJECTS

12.1 Treatment Discontinuation

Upon treatment discontinuation, all end of treatment evaluations and tests will be conducted. The reason for treatment discontinuation will be documented in the electronic case report form (eCRF). All participants who discontinue due to an AE must be followed until the event resolves or stabilizes. Appropriate medical care should be provided until signs and symptoms have abated, stabilized, or until abnormal laboratory findings have returned to acceptable or pre-study limits. The final status of the AE will be reported in the participant's medical records and the appropriate eCRF.

Reasons for treatment discontinuation should be classified as follows:

- Death
- Toxicity; treatment related or unrelated
- Investigator judgment
    - The Investigator may discontinue a participant if, in his/her judgment, it is in the best interest of the participant to do so.
- Noncompliance
- Participant voluntary withdrawal
    - A participant may withdraw from the study at any time, for any reason. If a participant discontinues treatment, an attempt should be made to obtain information regarding the reason for withdrawal.

- Sponsor (Roswell Park) decision.

13 RISKS TO SUBJECTS

13.1 Paclitaxel

Common adverse events: alopecia; diarrhea; inflammatory disease of mucous membrane, nausea and vomiting; anemia; leukopenia; neutropenia; thrombocytopenia; hypersensitivity reaction; arthralgia; myalgia; peripheral neuropathy.

Serious adverse effects include: Atrial fibrillation; cardiac dysrhythmia; cardiotoxicity; congestive heart failure; myocardial infarction; supraventricular tachycardia; Stevens-Johnson syndrome; Toxic epidermal necrolysis, gastrointestinal perforation; Grade 3 or higher nausea and vomiting, Grade 3 or higher anemia; deep vein thrombosis; febrile neutropenia; Grade 4 neutropenia; Grade 3 or greater thrombocytopenia; anaphylaxis; opportunistic infection; sepsis; Grade 3 or higher peripheral neuropathy; seizure; tonic-clonic seizure; pulmonary embolism; respiratory failure.

Paclitaxel is commercially available. Please refer to the package insert for a complete list of adverse effects.

13.2 Doxorubicin

Common adverse effects: alopecia; nausea; vomiting.

Serious adverse effects include: cardiomyopathy; congestive heart failure, late onset; left ventricular failure, acute; myocardial infarction; pericarditis; tachyarrhythmia, injection site extravasation, radiation recall syndrome, tissue necrosis, pancreatitis, acute myeloid leukemia, Grade 3 or 4 leukopenia, myelodysplastic syndrome, myelosuppression, neutropenia, Grade 3 or 4 thrombocytopenia, hepatitis, Veno-occlusive disease of the liver, anaphylaxis, septic shock, radiation pneumonitis, tumor lysis syndrome.

Doxorubicin is commercially available. Please refer to the package insert for a complete list of adverse effects.

13.3 Cyclophosphamide

Common adverse effects: alopecia; disorder of skin pigmentation; nail damage; rash; abdominal discomfort; diarrhea; loss of appetite; nausea and vomiting; leukopenia; neutropenia; amenorrhea.

Serious adverse effects include: cardiac tamponade; cardiotoxicity; congestive heart failure; pericardial effusion; erythema multiforme; malignant tumor of dermis; Stevens-Johnson syndrome; Toxic epidermal necrolysis; Acute myeloid leukemia; chronic myeloid leukemia; malignant tumor of lymphoid hemopoietic and related tissue; myelodysplastic syndrome, angiosarcoma of liver; anaphylaxis; acquired contracture of bladder neck; bladder cancer; fibrosis of urinary bladder; hemorrhagic cystitis; pyelitis; renal hematuria; secondary malignant neoplasm of renal pelvis; azoospermia; oligozoospermia; interstitial pneumonia; pulmonary fibrosis; infectious disease.

Cyclophosphamide is commercially available. Please refer to the package insert for a complete list of adverse effects.

13.4 Celecoxib

Prolonged use of celecoxib may cause dyspepsia, headaches (including migraines) and borderline elevated liver function tests (which could indicate liver damage). Recently, information from three long-term studies of celecoxib has become available. In the first study, a cancer prevention study, an increased risk of heart attacks, strokes, and/or deaths resulting from heart or blood vessel disease was reported among people taking celecoxib. Approximately 1 in 100 subjects enrolled in this study receiving the placebo treatment had one of these serious events. In contrast, between 2 and 3 in 100 subjects taking celecoxib (between 400 and 800 mg daily) had one of these serious events. Another clinical cancer prevention study found no increased risks in subjects taking celecoxib 400 mg daily. The third study, an Alzheimer's disease prevention study, did not find increased risks with celecoxib. Dosing has been suspended in all three of these studies based on the findings of the first cancer prevention study. As a result, the FDA is now evaluating the possibility that celecoxib increases the risk of heart attack, stroke, and or death resulting from heart or blood vessel disease. Known infrequent side effects of celecoxib include nausea and/or vomiting, diarrhea, flatulence, abdominal and stomach pain, bleeding ulcer, upper respiratory tract infection, pharyngitis, rhinitis, sinusitis, peripheral edema, back pain, dizziness, insomnia, and skin rash. Rare risks include sudden death (unexpected or instant death that occurs within minutes or hours from any cause other than violence), vasculitis, hepatitis, liver failure, kidney failure, blood dyscrasia, hypoglycemia, hyponatremia, viral meningitis, severe allergic reaction, visual changes, and transient ischemic attack. Warnings/Precautions: Stomach problems may be more likely to occur if patients drink alcoholic beverages while taking this medicine. Taking two or more of the nonsteroidal anti-inflammatory drugs together on a regular basis may increase the chance of unwanted effects. Also, taking acetaminophen, aspirin or other salicylates, or ketorolac (e.g., Toradol) regularly while taking a nonsteroidal anti-inflammatory drug may increase the chance of unwanted effects. The risk will depend on how much of each medicine is taken every day and how long the medicines are taken together. Therefore, patients should not take acetaminophen or aspirin or other salicylates or ketorolac (e.g., Toradol). Clinical studies with celecoxib have identified potentially significant interactions with fluconazole and lithium. Experience with nonsteroidal anti-inflammatory drugs (NSAIDs) suggests the potential for interactions with furosemide and ACE inhibitors. Celecoxib is contraindicated in patients with known hypersensitivity to celecoxib. Celecoxib should not be given to patients who have demonstrated allergic-type reactions to sulfonamides. Celecoxib should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients.

For more risk information reference the Investigator's Brochure or package insert.

13.5 Interferon-α2b

Interferon alpha-2b may cause fever, chills and flu-like symptoms; loss of appetite; nausea; vomiting, diarrhea and abdominal pain; fatigue; lowered white blood count may increase risk of infection; lowered platelets may lead to an increase in bruising or bleeding; hair loss. Other risks which may be common in cases of prolonged administration of interferon alpha-2b include drowsiness; temporary confusion; anxiety, amnesia, irritability, confusion, delusions and depression which can be severe; numbness and/or tingling in the hands and/or feet, skin rashes and inflammation of the pancreas. Inflammation of the pancreas is swelling or irritation of the pancreas

which may result in tenderness or pain in the stomach and/or back. When the pancreas is inflamed, the body is not able to absorb all the nutrients it needs.

For more risk information reference the Investigator's Brochure or package insert.

13.6 Rintatolimod

Clinical experience with rintatolimod totals over 800 patients with more than 400 patients receiving rintatolimod for at least six (6) months, greater than 200 patients for one (1) year, over 50 patients up to two (2) years, and with 20 or more patients over two (2) years at doses as high as 1200 mg i.v. twice weekly. No evidence of dose-limiting organ toxicity, including hematologic, liver, or renal toxicity, has been observed.

Adverse events related to infusion such as mild flu-like symptoms, transient headache, fever, myalgia, arthralgia, and fatigue/malaise which were seen, usually occur during the initial weeks of treatment and tend to subside on repeated administration. These side events were seen in Chronic Fatigue Syndrome patients, cancer patients, chronic hepatitis B infected patients and individuals infected with HIV at doses of 200 and 400 mg and higher. Patients that experience these minor side effects can continue on rintatolimod and as noted, these signs and symptoms typically subside after several weeks of continued treatment. Specific symptoms of note include a flushing reaction, characterized by at least one occurrence of erythema of the face, neck and chest, which has been observed in approximately 10% of patients treated in various studies. Usually the flushing is both mild and transient and disappears with repeated dosing. Occasionally, it can be accompanied by a tightness of the chest, tachycardia, anxiety, shortness of breath, subjective reports of "feeling hot", diaphoresis and nausea. The reaction is usually infusion-rate dependent and may generally be controlled by slowing the infusion rate. An antihistamine (diphenhydramine hydrochloride) can be helpful in controlling and reducing the response in the occasional patient for whom the symptom persists. Other less frequently occurring adverse effects include nausea, diarrhea, itching, urticaria, bronchospasm, transient hypotension, photophobia, rash, bradycardia and transient visual disturbances. A severe unexpected local reaction to extravasation of rintatolimod (Ampligen®, Poly I: Poly $C_{12}U$) at the infusion site in the dorsum of the left hand was reported in a Chronic Fatigue Syndrome patient with chilblains. Several patients experienced liver enzyme level elevations while receiving rintatolimod associated with chronic dosing over many weeks.

Rintatolimod has been dosed in combination with alpha interferon in investigator initiated studies under investigator IND applications during the period between December 1985 and April 1994. A total of 24 patients received combination treatments. Clinical conditions included renal cell carcinoma, chronic myelogenous leukemia, melanoma, and ovarian cancer. Rintatolimod was given as an IV infusion at a dose of 300 mg twice weekly. The starting dose was sometimes as low as 1-10 mg. The interferons were administered at a dose of 3 million units daily, with some doses of 0.75 million units at the low side and up to 6 million units at the higher side.

The therapy with rintatolimod in combination with alpha interferon was generally well tolerated without evidence of dose-limiting or cumulative toxicities. The most frequent adverse reactions were considered minor in severity and duration. Most of them were flu-like symptoms such as chills, cold feeling, fatigue, decreased appetite, fever, muscular aches. Also shortness of breath has been seen as well as hypotension, nausea, anemia, dyspnea, numbness, itching and blurred vision. These adverse events were judged possibly related to the condition of the patients, but also possibly related to the administration of rintatolimod or interferon. In some cases worsening of the patient's

condition has been seen due to tumor progression, but in general favorable clinical patterns were observed in these patients with advanced disease. Such combinations were not intended to be immune modulating and were evaluated in the context of clinical cancer care.

For more risk information reference the Investigator's Brochure or package insert.

14 POTENTIAL BENEFITS TO SUBJECTS

Our hypothesis is that CKM in addition to chemotherapy will potentiate the anti-tumor activity of the latter and result in a higher pathological complete response. By conducting a biopsy at the end of 3 doses of CKM + paclitaxel combination therapy, we will be able to identify early responders vs. non-responders (and correlate these findings with the final pathology at the time of surgery).

15 DATA AND SPECIMEN BANKING

All samples for correlative analysis will be sent to Dr. Kalinski's Laboratory for processing (CCC-502F). Samples will be used for planned study assays as well as for future analysis for other yet to be identified biomarkers that may be related to the clinical outcome of the study population. Any clinical data that is associated with the samples, will be stored on a secure server in the Department of Medicine, will be accessible only by the PI, Co-Investigators and PI designated data manager and, will be password protected. All computer entry and networking programs will be done using PIDs only. Any clinical data and/or specimens that are used for future studies will be de-identified before being released.

Note: All investigator or analyzing research laboratories housing research samples need to maintain current Temperature Logs and study-specific Sample Tracking and Shipping Logs. The Principal Investigator/Laboratory Manager must ensure that the stated lab(s) have a process in place to document the receipt/processing/storage/shipping of study-related samples/specimens. This is required for both observational and interventional clinical studies collecting clinical samples.

16 MEASUREMENT OF EFFECT

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

For the purposes of this study, patients should be re-evaluated by MRI for response at the following time points:

- Prior to start of doxorubicin and cyclophosphamide combination, after completion of last paclitaxel treatment (MRI at the completion of paclitaxel only for patients at Dose Level 4).
- Prior to surgery, after completion of last dose of doxorubicin/cyclophosphamide

16.1 Continuation of Treatment Post-Disease Progression

Progressive disease: If there is evidence of disease progression per RECIST v1.1 but it is determined the patient is receiving clinical benefit while on the trial, the patient may continue at the discretion of the Principal Investigator.

17 SAFETY EVALUATION

17.1 Adverse Events

An adverse event or adverse experience (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be ANY unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of 'unrelated', 'unlikely', 'possible', 'probable', or 'definite').

An AE is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan in other study-related documents.

- **Diagnosis Versus Signs and Symptoms**

  If known, a diagnosis should be recorded on the CRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be clinically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the CRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

- **Adverse Events Occurring Secondary to Other Events**

  In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the CRF.

  However, clinically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the CRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the CRF.

- **Abnormal Laboratory Values**

  Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the CRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

  If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 x the upper limit of normal associated with

cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event CRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the CRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7 mEq/L should be recorded as "hyperkalemia".

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the CRF, unless their severity, seriousness, or etiology changes.

- **Preexisting Medical Conditions (Baseline Conditions)**

  A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an Adverse Event CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

17.2 Grading and Reporting Adverse Events

- **Grading and Relationship to Drug**

  The descriptions and grading scales found in the CTEP Version 5 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. CTEP Version 5 of the CTCAE is identified and located at:

  http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

  AEs not covered by specific terminology listed should be reported with common medical terminology, and documented according to the grading scales provided in the CTCAE Version 5.

  The relationship of event to study drug will be documented by the Investigator as follows:

  Unrelated: The event is clearly related to other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs administered to the participant.

  Unlikely: The event is doubtfully related to investigational agent(s). The event was most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.

  Possible: The event follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs.

  Probable: The event follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the study drug. The event cannot be reasonably explained by other factors such as the participant's clinical state, therapeutic interventions or concomitant drugs.

Definite: The event follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern to the study drug, cannot be reasonably explained by other factors such as the participant's condition, therapeutic interventions or concomitant drugs; AND occurs immediately following study drug administration, improves upon stopping the drug, or reappears on re-exposure.

- **Reporting Adverse Events:**

  Routine AEs occurring between the start date of intervention until 30 days after the last intervention, or until the event has resolved, the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible, will be reported. New information will be reported after it is received.

Guidelines for Routine Adverse Event Reporting for Phase 1 Studies (Regardless of Expectedness)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4
Unrelated	X	X	X	X
Unlikely	X	X	X	X
Possible	X	X	X	X
Probable	X	X	X	X
Definite	X	X	X	X

17.3 Serious Adverse Events

A serious adverse event (SAE) is any adverse event (experience) that in the opinion of either the investigator or sponsor results in ANY of the following:

- Death.
- A life-threatening adverse event (experience). Any AE that places a participant or participants, in the view of the Investigator or sponsor, at immediate risk of death from the reaction as it occurred. It does NOT include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours).
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly or birth defect.
- Important Medical Event (IME) that, based upon medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Reporting Serious Adverse Events

All new SAEs occurring from the date the participant signs the study consent until 30 days after the last intervention or a new treatment is started, whichever comes first, will be reported. The

Roswell Park SAE Source Form is to be completed with all available information, including a brief narrative describing the SAE and any other relevant information.

SAEs occurring after the 30 day follow-up period that the investigator determines to be possibly, probably or definitely related to the study intervention should be reported.

SAEs identified as an Unanticipated Problem by the Investigator must be reported. Please refer to Section 17.5 for details on reporting Unanticipated Problems.

17.4 Follow-Up for Serious Adverse Events

All related SAEs should be followed to their resolution, until the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible. New information will be reported when it is received.

17.5 Unanticipated Problems

An Unanticipated Problem (UP) is any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given:
    - The research procedures that are described in the study-related documents, including study deviations, as well as issues related to compromise of participant privacy or confidentiality of data.
    - The characteristics of the participant population being studied.
- Related or possibly related to participation in the research (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).
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized and if in relation to an AE is also deemed Serious per **Section 17.3.**

Reporting Unanticipated Problems:

The Reportable New Information (RNI) Form will be submitted to the CRS Quality Assurance (QA) Office within 1 business day of becoming aware of the Unanticipated Problem. After review, CRS QA Office will submit the RNI to the IRB.

When becoming aware of new information about an Unanticipated Problem, submit the updated information to CRS QA Office with an updated Reportable New Information Form. The site Investigator or designated research personnel will report all unanticipated problems to the IRB in accordance with their local institutional guidelines.

17.6 FDA Reporting

When Roswell Park is the IND holder the following describes the FDA reporting requirements by timeline for AEs and new safety findings that meet the criteria outlined below:

Within 7 Calendar Days

Any adverse event that meets **ALL** the following criteria:

- Related or possibly related to the use of the study drug;
- Unexpected; and
- Fatal or life-threatening.

Within 15 Calendar Days

Any adverse event that meets **ALL** the following criteria:

- Related or possibly related to the use of the study drug;
- Unexpected; and
- Serious but not fatal or life-threatening;

Or, meets **ANY** of the following criteria:

- A previous adverse event that is not initially deemed reportable but is later found to fit the criteria for reporting (report within 15 days from when event was deemed reportable).
- Any findings from other studies, including epidemiological studies, pooled analysis of multiple studies, or other clinical studies conducted with the study drug that suggest a significant risk in humans exposed to the drug.
- Any findings from animal or in vitro testing that suggest a significant risk for human participants including reports of mutagenicity, teratogenicity, or carcinogenicity or reports of significant organ toxicity at or near the expected human exposure.
- Any clinically important increase in the rate of occurrence of a serious, related or possibly related adverse event over that listed in the protocol or investigator brochure.

Sponsors are also required to identify in IND safety reports, all previous reports concerning similar adverse events and to analyze the significance of the current event in the light of the previous reports.

Reporting Process

The principal investigator or designee will complete and submit a FDA Form 3500A MedWatch for any event that meets the above criteria. Forms will be submitted to the CRS QA Office via email to CRSQA@RoswellPark.org.

18 DATA MANAGEMENT AND CONFIDENTIALITY

18.1 Data Collection

Full build studies are managed by Roswell Park CRS Data Management for analysis by Roswell Park Biostatisticians. All electronic case report form (eCRF) data are captured for these studies.

Data management activities are performed using a CTMS system that enables the collection, cleaning and viewing of clinical trial data. CRS data management designs the study-specific database and facilitates development by the Information Technology team. Once the database design is approved by the Investigator, Statistician, and Clinical Research Coordinator, the database is put into production and data entry can begin. Data can be entered and changed only by those with the rights to do so into the eCRFs.

18.2 Maintenance of Study Documents

Essential documents will be retained per Roswell Park's policy for 6 years from the study termination date. These documents could be retained for a longer period, however, if required by the applicable local regulatory requirements or by an agreement with Roswell Park.

18.3 Revisions to the Protocol

Roswell Park may make such changes to the protocol as it deems necessary for safety reasons or as may be required by the U.S. FDA or other regulatory agencies. Revisions will be submitted to the IRB/ERC for written approval before implementation.

18.4 Termination of the Study

It is agreed that, for reasonable cause, either the Roswell Park Investigators or the Sponsor, may terminate this study, provided a written notice is submitted within the time period provided for in the Clinical Trial Agreement. In addition, Roswell Park may terminate the study at any time upon immediate notice if it believes termination is necessary for the safety of participants enrolled in the study. Any deaths on the clinical trial deemed related to the study drugs will necessitate trial suspension, review and possible termination.

18.5 Confidentiality

Refer to section 25.0 "Provisions to Protect the Privacy Interests of Subjects".

19 STATISTICAL PLAN

This is a Phase I safety and tolerability trial evaluating the combination of chemokine modulation with neoadjuvant chemotherapy in triple negative breast cancer.

Statistical analysis will be performed by the Roswell Park Biostatistics & Bioinformatics Department.

19.1 Demographics and Baseline Characteristics

Descriptive statistics (as appropriate: n, percent, mean, median, min and max) will be used to summarize demographic and baseline characteristics.

19.2 Analysis Cohorts

Analysis Cohorts:

Safety Cohort: All subjects that receive any study treatment will be included in the safety summary.

Dose Escalation Cohort: Any subjects who receive study treatment and complete the DLT period (or fail to complete the DLT period due to toxicity) will be included in the dose escalation cohort.

Patient Replacement: Patients who are unevaluable for DLT (i.e. disease progression prior to completion of CKM or patient refusal will be replaced for the primary safety analysis (i.e. identification of the MTD) and efficacy analyses. Patients who fail to complete at least 6 out of the 9 planned CKM doses (due to non-DLT related reasons) are not considered evaluable for the primary safety analysis and will be replaced. Data from patients who received only a part of the experimental regimen (<6 doses of CKM) may be evaluated in the exploratory manner for secondary/exploratory outcomes.

19.3 Sample Size Determination

The sample size determination is based on the primary analysis; which evaluates the safety of the treatment combination using an accelerated titration design. The exact sample size depends on the unknown dose-toxicity relationship. However, based on the number of dose-levels and decision rules, no more than 24 subjects will be required. Based on prior experience and the specified dose levels, we expect no more than 6-9 evaluable subjects to be enrolled.

19.4 Primary Analysis: Dose Escalation

The primary objective of this study is to evaluate safety and identify the appropriate dose level of Interferon alpha-2b in combination with celecoxib, rintatolimod, and paclitaxel.

An accelerated titration design will be utilized to identify the appropriate dose-level for a future study. A single patient will be enrolled at dose level 1 (no Interferon alpha-2b). If a DLT is observed, then the standard 3+3 design will be triggered. If no DLT is observed, then a single patient will be enrolled at dose level 2.

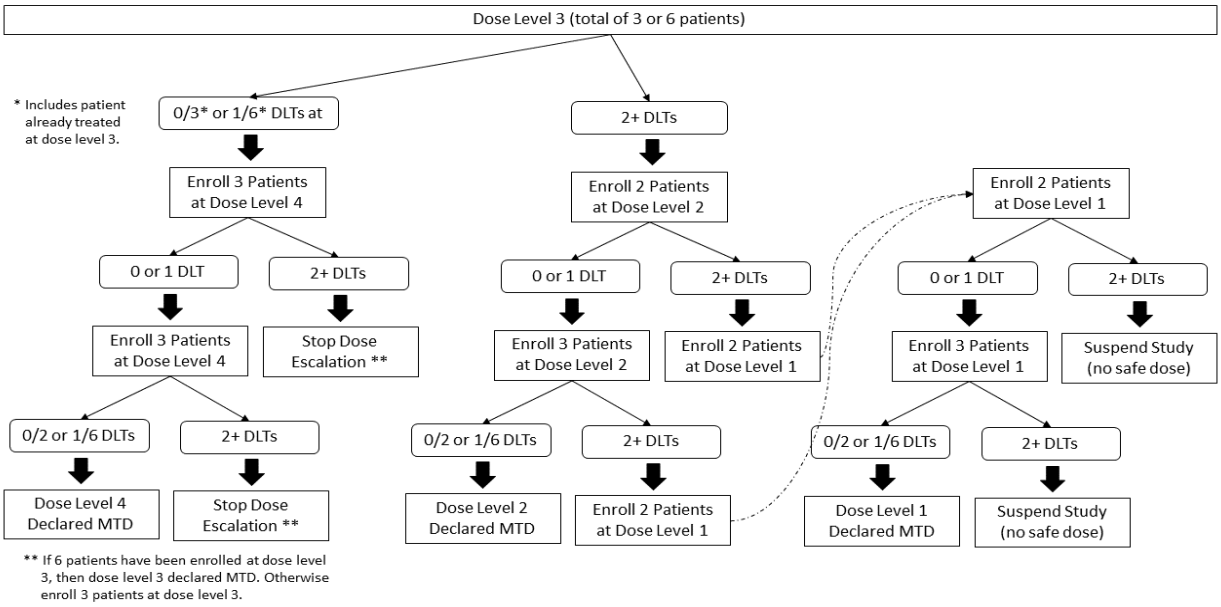
If a DLT or 2 cumulative moderate toxicities are observed at dose level 2, then the standard 3+3 design will be triggered. Otherwise, a single patient will be enrolled at dose level 3.

If a DLT or 2 cumulative moderate toxicities are observed at dose level 3, then the standard 3+3 design will be triggered. Otherwise, 3 patients will be enrolled at dose level 4.

If a DLT or 2 cumulative moderate toxicities are observed at dose level 4, then the standard 3+3 design will be triggered. Otherwise, the study will be deemed complete.

3+3 Dose Escalation

As of Amendment 10, the 3+3 dose escalation design has been triggered at dose level 3 due to a treatment delay and dose reduction. An additional n=2 patients will be enrolled at dose level 3. If 1 DLT is observed, then an additional n=3 patients will be enrolled at dose level 3. If DLTs are observed in 0 of 2 or 1 of 5, then n=3 patients will be enrolled at dose level 4 (and standard 3+3 rules will apply). If 2 or more DLTs are observed, then n=2 patients will be enrolled at dose level 2 (and standard 3+3 rules will apply).



19.5 Secondary and Exploratory Analysis

The secondary objectives are to evaluate: 1) the immunomodulatory effect of CKM and paclitaxel in the tumor microenvironment; 2) safety of the combination, 3) complete pathological response (pCR) and complete breast MRI response after 12 weeks and, 4) overall and recurrence-free survival. The safety and response outcomes are treated as dichotomous variables.

Immunomodulatory effect of CKM

The tumor infiltrating CD8+ CTLs, which are treated as continuous variables and will be summarized by time-point using the mean and standard deviation; and graphically using box- or dot-plots. The mean change in tumor infiltrating CD8+ CTLs (baseline to post-treatment) will be evaluated using a one-sided, permutation paired t-test about the following hypotheses:

$$H_0: \mu_d = 0 \text{ versus } H_A: \mu_d > 0,$$

where μ_d is the true mean change in tumor infiltrating CD8+ CTLs. A 90% confidence interval about the mean change will be obtained using standard methods. Transformations or non-parametric methods (i.e. sig test) will be used as appropriate.

Safety

All adverse events (AEs), serious AEs (SAEs), and toxicities will be summarized by attribution (overall and related/ unrelated to treatment) and grade using frequencies and relative frequencies.

Response Assessments

The response data will be summarized using frequencies and relative frequencies. A 90% confidence interval about the true pCR rate will be obtained using Jeffrey's prior method. The pCR rate will be compared to the historic pCR for standard neoadjuvant chemotherapy alone (approximately 0.26) using a one-sided binomial exact test

Survival Outcomes

Overall and recurrence-free survival will be summarized using standard Kaplan-Meier methods; where estimates of the median and 3years rates will be estimated with 90% confidence intervals.

19.6 Interim Analysis and Criteria for Early Termination

There are no formal interim analyses or rules for early termination based on efficacy. The study is monitored for safety, with rules allowing for study suspension.

The study will be monitored by the Roswell Park Data Safety and Monitoring Committee, who may make recommendations about study continuation and termination.

20 PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF SUBJECTS

All Roswell Park Phase I studies are reviewed at the scheduled Early Phase Clinical Trial Committee meetings and the minutes are forwarded to the IRB for review.

In addition, the Roswell Park Data Safety Monitoring Committee will assess the progress of the study, the safety data, and critical efficacy endpoints (Phase I studies will be reviewed quarterly; Phase II, III and pilot investigator-initiated studies will be reviewed semi-annually). The DSMC will review the study and will make recommendations that include but not limited to; (a) continuation of the study, (b) modifications to the design (c) or termination of the study.

21 VULNERABLE POPULATIONS

Not applicable.

22 COMMUNITY-BASED PARTICIPATORY RESEARCH

Not applicable.

23 SHARING OF RESULTS WITH SUBJECTS

Individual response data is shared with the participant as a part of their clinical care.

24 SETTING

Potential subjects with breast cancer will be identified and recruited during scheduled visits to Roswell Park. Potential subjects, who are referred by their Roswell Park or community physicians, will be scheduled with an investigator in the clinic for evaluation. All participant related research procedures will be conducted at Roswell Park.

25 PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF SUBJECTS

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a limited access environment. All computer entry and networking programs will be done using PIDs only. Information will not be released without written authorization of the participant.

26 RESOURCES AVAILABLE

Not applicable.

27 PRIOR APPROVALS

Not applicable.

28 COMPENSATION FOR RESEARCH-RELATED INJURY

If the subject believes they have been injured as a direct result of their participation in this research study, they will be advised to notify the Roswell Park Patient Advocate at (716) 845-1365 or the Study Doctor at (716) 845-1486.

Medical diagnosis and treatment for the injury will be offered, and a determination will be made regarding appropriate billing for the diagnosis and treatment of the injury. A financial counselor (716-845-3161) will be able to provide an explanation of coverage and to answer questions the subject may have regarding study related billing.

The subject is not prevented from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

29 ECONOMIC BURDEN TO SUBJECTS

The participants will not be subject to any economic burden.

30 CONSENT PROCESS

This study will not be initiated until the protocol and informed consent document(s) have been reviewed and approved by a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Each participant (or legal guardian) shall read, understand, and sign an instrument of informed consent prior to performance of any study-specific procedure. It is the responsibility of the investigator to ensure that the participant is made aware of the investigational nature of the treatment and that informed consent is given.

The Investigator is responsible for the retention of the participant log and participant records; although personal information may be reviewed by authorized persons, that information will be treated as strictly confidential and will not be made publicly available. The investigator is also responsible for obtaining participant authorization to access medical records and other applicable study specific information according to Health Insurance Portability and Accountability Act regulations (where applicable).

This study will be conducted in compliance with all applicable laws and regulations of the state and/or country and institution where the participant is treated. The clinical trial should be conducted in accordance with the ethical principles embodied in the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, consistent with good clinical practice and the applicable regulatory requirements and according to the guidelines in this protocol, including attached appendices.

Informed consent will be obtained according to SOP: Informed Consent Process for Research (HRP-090).

31 PROCESS TO DOCUMENT CONSENT IN WRITING

The Investigator (or IRB specified designee) is responsible for obtaining written consent from each participant or the participant's legally authorized representative in accordance with GCP guidelines using the approved informed consent form, before any study specific procedures (including screening procedures) are performed. The informed consent form acknowledges all information that must be given to the participant according to applicable GCP guidelines, including the purpose and nature of the study, the expected efficacy and possible side effects of the treatment(s), and specifying that refusal to participate will not influence further options for therapy. Any additional information that is applicable to the study must also be included. Additional national or institutionally mandated requirements for informed consent must also be adhered to. The participant should also be made aware that by signing the consent form, processing of sensitive clinical trial data and transfer to other countries for further processing is allowed.

The Investigator shall provide a copy of the signed consent form to the participant and the signed original shall be maintained in the Investigator File. A copy of the signed consent form must be filed in the participant file. At any stage, the participant may withdraw from the study and such a decision will not affect any further treatment options.

SOP: Written Documentation of Consent (HRP-091) will be followed.

32 DRUGS OR DEVICES

Roswell Park will hold the IND for this study.

32.1 Doxorubicin, Cyclophosphamide and Paclitaxel

Doxorubicin, cyclophosphamide and paclitaxel are commercially available and will be dispensed per standard of care. These drugs will not be provided by the study and will be paid for by the patient's insurance carrier as part of standard of care treatment.

32.2 Celecoxib

A sulfa non-steroidal anti-inflammatory drug (NSAID) used in the treatment of osteoarthritis, rheumatoid arthritis, acute pain, painful menstruation and menstrual symptoms, and to reduce numbers of colon and rectum polyps in patients with familial adenomatous polyposis.

32.2.1 Other Names

Celebrex, Celebra or Onsenal (commercially available)

32.2.2 Formulation and Packaging

Celecoxib as capsules in the following dosages: 100 mg and 200 mg.

32.2.3 Drug Shipment

Celecoxib will be provided by Roswell Park.

32.2.4 Drug Administration

Celecoxib 200 mg will be administered orally twice a day approximately 12 hours apart on the days the patient receives the CKM regimen. The morning dose will be given to the participant at the same time as the other pre-medications for the CKM regimen. The evening dose of celecoxib will be self-administered by the participant at home and documented on the patient diary. Refer to **Appendix H**.

32.2.5 Drug Storage and accountability

The Investigator or designate will be responsible for ensuring that the investigational product is securely maintained in a locked, limited access facility in accordance with the applicable regulatory requirements.

Store celecoxib at room temperature (77°F/ 25°C) away from light and moisture. Brief storage between 59-86 °F (15-30 °C) is permitted.

Drug storage temperature will be maintained and recorded, as applicable.

32.3 Interferon Alpha-2b

A drug approved around the world for the treatment of chronic hepatitis C, chronic hepatitis B, hairy cell leukemia, chronic myelogenous leukemia, multiple myeloma, follicular lymphoma, carcinoid tumor, and malignant melanoma. Interferon alpha-2b has many drug classifications including anti-infective, anti-neoplastic, antiproliferative, antiviral and immunological agent.

32.3.1 Formulation and packaging

50 million units/ mL, lyophilized powder, which must be reconstituted prior to administration.

- Vial size:10 million units/vial
- Diluent: Compatible with normal saline, Ringer's injection, lactated Ringer's, and 5% sodium bicarbonate injection. Interferon alpha-2b should be reconstituted with 1 mL to reach a final concentration of 10:1. IV dose should be diluted in sodium chloride 0.9%/100 mL and given over 20 minutes. The final concentration of INTRON A should not be less than 10 million International Units/100 mL
- Source: Schering Plough Corp.

32.3.2 Drug Shipment

Interferon alpha-2b will be provided by Roswell Park.

32.3.3 Preparing and Dispensing

The lyophilized product is reconstituted as directed by the manufacturer. Investigational Drug Service Pharmacy (IDS) will prepare and dispense.

32.3.4 Drug Administration

Interferon alpha-2b will be administered intravenously over 20 minutes.

32.3.5 Drug Storage and Accountability

The Investigator or designate will be responsible for ensuring that the investigational product is securely maintained in a locked, limited-access facility in accordance with the applicable regulatory requirements.

Powder for injection should be stored at 2 to 8°C (36-46°F). After reconstitution, the solution should be used immediately but may be stored up to 24 hours at 2-8°C (36-46°F).

Drug storage temperature will be maintained and recorded, as applicable.

32.3.6 Concomitant Medications

Interactions between interferon alpha-2b and other drugs have not been fully evaluated (see Appendix I). Caution should be exercised when administering interferon alpha-2b therapy in combination with other potentially myelosuppressive agents such as zidovudine. Concomitant use of interferon alpha-2b and theophylline decreases theophylline clearance, resulting in a 100% increase in serum theophylline levels. Concomitant interferon alpha-2b and REBETOL (Ribavirin) use is contraindicated.

32.4 Rintatolimod (poly IC analog)

A substituted double stranded polyribonucleic acid (polyI: polyC12U), rintatolimod preserves activity of polyIC with a much improved systemic toxicity profile. The product has been studied extensively for use as a vaccine adjuvant and for its direct antiviral activity, as well in several cancer studies as a monotherapy, but most extensively in chronic fatigue syndrome (CFS).

32.4.1 Other Names

polyIC12U, Ampligen®, poly I: polyC12U; Polyinosinic: polycytidylic-polyuridylic acid; polyriboinosinic/polyribocytidylic (uridylic) acid

32.4.2 Formulation and Packaging

Rintatolimod is supplied as a liquid solution in glass bottles containing 200 mg (100 mg in case of toxicity) per 80 mL. Rintatolimod is a colorless solution containing 2.5 mg/mL in physiological salts (0.15 M NaCl, 0.01 M phosphate, 0.001 M Mg++). The product does not contain preservatives or antioxidants.

32.4.3 Drug Shipment

Rintatolimod will be provided by Hemispherix and shipped to the participating site.

The date of receipt and the amount of drug received will be documented. Drug shipment records will be retained by the investigational pharmacist or designee.

32.4.4 Preparing and Dispensing

A vial of rintatolimod is suitable for direct IV infusion. IDS will prepare and dispense. Each vial should be taken from the refrigerator and allowed to equilibrate to room temperature.

32.4.5 Drug Administration

Rintatolimod 200 mg will be administered by intravenous infusion after Interferon alpha-2b. Additional details on the procedures for receiving, storing and using rintatolimod (Ampligen®) can be found in a separate document entitled "Procedures for Receiving, Storing, and Using Ampligen® (Poly I:Poly C12U) Liquid Solution".

The initial administration should begin at a slow rate of infusion (approximately 20 cc/ hour) and increase to 40 cc/hour after 30 minutes. Tubing should be flushed with 30 to 50 mL of normal saline solution upon completion.

32.4.6 Drug Storage and accountability

Rintatolimod should be stored at 2 to 8°C (36-46°F).

Drug storage temperature will be maintained and recorded, as applicable.

32.4.7 Handling and Disposal

The Investigator or designee will be responsible for dispensing and accounting for all investigational drug provided by Hemispherix exercising accepted medical and pharmaceutical practices. Study drugs must be handled as cytotoxic agents and appropriate precautions taken per the institution's environmentally safe handling procedures. All investigational drugs will be dispensed in accordance with the Investigator's prescription or written order.

All products dispensed will be recorded on a product accountability record. Records of product lot numbers and dates received will be entered on a product accountability form. This record will be reviewed by the Sponsor's staff or representative during periodic monitoring visits. It is the Investigator's responsibility to ensure that an accurate record of investigational drug issued and returned is maintained.

Used vials (excess drug) will be destroyed according to standard practices after properly accounting for the dispensing. Partially used vials of study drug will not be re-used for other participants.

Under no circumstances will the Investigator supply investigational drug to a third party or allow the investigational drug to be used in a manner other than as directed by this protocol.

In regards to drug receipt, accountability and storage, SOP IDS-601 will be followed.

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34 APPENDICES/SUPPLEMENTS

Appendix A ECOG Performance Status Scores

Description	Status
Fully active, able to carry on all pre-disease performance without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	1
Ambulatory and capable of all self-care but unable to carry out any work activities.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4
Dead	5

Appendix B INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM: INCLUSION CRITERIA

Participant Name: _____

Medical Record No.: _____

Title: Phase I Clinical Trial Assessing the Combination of Chemokine Modulation with Neoadjuvant Chemotherapy in Triple Negative Breast Cancer

INCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "Yes" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. Age ≥ 18 years of age.	
☐	☐	☐	2. Have pathologically confirmed diagnosis of resectable triple negative breast cancer (ASCO/CAP guidelines will be used to define triple negative breast cancer).	
☐	☐	☐	3. Must have measurable disease. Multi-centric disease is allowed. If patient has another lesion which is biopsied with ER/PR positive it will be Physician discretion for this eligibility criteria	
☐	☐	☐	4. Prior therapy: No prior cytotoxic regimens are allowed for this malignancy. Participants may not have had prior chemotherapy, other targeted anticancer therapies, or prior radiation therapy to the ipsilateral breast for this malignancy. Prior bis-phosphonate therapy is allowed.	
☐	☐	☐	5. Patient eligible for surgery as determined by patient's surgeon.	
☐	☐	☐	6. Patient must have a lesion amendable to biopsy, unless inaccessible and with PI approval.	
☐	☐	☐	7. Have an ECOG performance status of ≤ 2. Refer to Appendix A.	
☐	☐	☐	8. Participants of child-bearing potential must agree to use adequate contraceptive methods (e.g., hormonal or barrier method of birth control; abstinence) prior to study entry. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.	
☐	☐	☐	9. Ability to swallow and retain oral medication.	
☐	☐	☐	10. Ability to undergo MRI.	

INCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "Yes" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	11. Must have adequate organ and marrow function present as defined below: -Platelets ≥ 100,000/µL -Hemoglobin ≥ 9 g/dL -Absolute Neutrophil Count (ANC) ≥ 1500/µL -Total bilirubin ≤ institutional upper limit of normal (ULN) -AST (SGOT) and ALT (SGPT) ≤ 1.5 X institutional ULN -Creatinine < ULN OR -Creatinine clearance ≥ 50 mL/min per Cockcroft-Gault Equation for patients with creatinine levels greater than ULN-refer to Appendix D.	
☐	☐	☐	12. Left Ventricular Ejection Fraction (LVEF) ≥ 55%. If LVEF is <55% and patient is otherwise study-eligible, the PI will discuss with cardiologist if patient is eligible to receive doxorubicin and participate in study.	
☐	☐	☐	13. Participant or legal representative must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.	
☐	☐	☐	14. Participants on this study will be counselled on and are willing to use adequate contraceptive methods.	

Investigator Signature: _____ Date: _____

Printed Name of Investigator: _____

Appendix C INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM: EXCLUSION CRITERIA

Participant Name: _____

Medical Record No.: _____

Title: Phase I Clinical Trial Assessing the Combination of Chemokine Modulation with Neoadjuvant Chemotherapy in Triple Negative Breast Cancer

EXCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "No" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. Patients currently treated with systemic immunosuppressive agents, including steroids, are ineligible until 3 weeks after removal from immunosuppressive treatment.	
☐	☐	☐	2. Patients with active autoimmune disease, requiring ongoing immunosuppressive therapy or history of transplantation.	
☐	☐	☐	3. Diagnosis of invasive carcinoma within last 3 years.	
☐	☐	☐	4. Inflammatory breast cancer will be excluded from the study.	
☐	☐	☐	5. Participants who have metallic surgical implants that are not compatible with an MRI machine are not eligible.	
☐	☐	☐	6. Pregnant or nursing female participants.	
☐	☐	☐	7. Unwilling or unable to follow protocol requirements.	
☐	☐	☐	8. Patients with known serious mood disorders (major depression is an exclusion). Other stable mood disorders on stable therapy for > 6 months may be allowed after consultation with PI)	
☐	☐	☐	9. Cardiac risk factors including: -Patients experiencing cardiac event(s) (acute coronary syndrome, myocardial infarction, or ischemia) within 3 months of signing consent. -Patients with a New York Heart Association classification of III or IV (Appendix E).	
☐	☐	☐	10. History of upper gastrointestinal ulceration, upper gastrointestinal bleeding, or upper gastrointestinal perforation within the past 3 years.	

EXCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "No" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	11. Prior allergic reaction or hypersensitivity to NSAIDs or any drugs administered on protocol.	
☐	☐	☐	12. Any history of allergy to sulfonamides.	
☐	☐	☐	13. Any history of autoimmune hepatitis	
☐	☐	☐	14. Grade 1 or higher neuropathy	
☐	☐	☐	15. Any condition which in the Investigator's opinion deems the participant an unsuitable candidate to receive study drug.	

Participant meets all entry criteria: ☐ **Yes** ☐ **No**

If "NO", do not enroll participant in study.

Investigator Signature: _____ Date: _____

Printed Name of Investigator: _____

Appendix D Cockcroft-Gault Equation

Cockcroft-Gault Equation*

Men: CrCl = [(140-YR) x IBW] / (PCr x 72)

Women: CrCl = 0.85 x [(140-YR) x IBW] / (PCr x 72)

Where:

CrCl is creatine clearance (mL/min)

IBW is ideal body weight (kg)

PCr is plasma creatinine (mg/dL)

YR is age (years)

Appendix E NYHA CLASSIFICATION

NEW YORK HEART ASSOCIATION CLASSIFICATION OF CARDIAC DISEASE

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Appendix F RECIST 1.1 Criteria

Objective Tumor Response

All protocol-defined imaging studies must be performed at the investigative site or sponsor-approved facility using protocol-defined parameters. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. RECIST 1.1 will be used to assess objective tumor response.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, will be identified as target lesions and recorded and measured at baseline. Target lesions will be selected on the basis of their size. Lesions with the longest diameter (short axis for lymph nodes) and are ≥ 10 mm (CT and MRI), ≥ 15 mm lymph nodes, > 20 mm CXR and are for accurate repetitive measurements (either by imaging techniques or clinically) will be chosen. A sum of the longest diameter (short axis for lymph nodes) of all target lesions will be calculated and reported as the baseline sum diameters. This will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

Complete Response (CR): Disappearance of all target lesions. Any lymph nodes must have a reduction in short axis to < 10 mm. **Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Changes in tumor measurements must be confirmed by repeat studies performed no less than 6 weeks after the criteria for response are first met.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as references the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.

Stable Disease (SD): Neither a sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameter while on study. Participants having a documented response with no confirmation of the response will be listed with stable disease.

Non-Target Lesions

All other small lesions (longest diameter < 10 mm or lymph nodes ≥ 10 mm to < 15 mm short axis) and non-measurable lesions (i.e., leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, blastic bone lesions, or abdominal masses / abdominal organomegaly identified by physical exam that is not measurable by imaging) should be identified as non-target lesions and indicated as present in the source documents at baseline. The general location will also be documented on the images drawing a regularly-shaped Region of Interest. Measurements of the non-target lesions will not be performed, but the presence or absence of each should be noted throughout follow-up and evaluation.

Complete Response: Disappearance of all non-target lesions and normalization of tumor marker level, if applicable. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-Complete Response/Non-Progressive Disease: Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the upper limits of normal.

Progressive Disease: Appearance of 1 or more new lesions or the unequivocal progression of existing non-target lesions. Although a clear progression of non-target lesions is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed at a later time.

Cytology and Histology

These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors), where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

Evaluation of Response

Response assessments will be performed at the following time points:

- Prior to start of doxorubicin and cyclophosphamide combination, after completion of last paclitaxel treatment
- Prior to surgery, after completion of last dose of doxorubicin/cyclophosphamide

To determine time point response, refer to tables below:

Time Point Response Criteria: target (± non-target lesion)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Time Point Response Criteria: non-target disease only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[1]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

1 Non-CR/non-PD is preferred over SD for non-target disease since SD is used as endpoint for assessment of efficacy in trials so to assign this category when no lesions can be measured is not advised.

The best overall response is the best response recorded from the start of study treatment until the end of treatment or disease progression/recurrence, whichever occurs earlier, taking into account any requirement for confirmation. In general, the participant's best response assignment will depend on the achievement of both measurement and confirmation criteria and will be determined by combining the participant's status of target lesions, non-target lesions, and new lesions.

- Symptomatic Deterioration: Participants with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not related to study treatment or other medical conditions should be reported as progressive disease due to "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment due to

symptomatic deterioration. Symptomatic deterioration that may lead to discontinuation of treatment include, but is not limited to, symptoms such as:

- Weight loss > 10% of body weight.
- Worsening of disease-related symptoms (e.g., worsening dyspnea, increasing pain/increasing requirement for narcotic analgesics).
- Decline in performance status of > 1 level on ECOG scale.

Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical Lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study,

confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor Markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response.

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG PET imaging can be identified according to the following algorithm:

Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Appendix G Adaption of Immune-Related Response Criteria (irRECIST)

The following is taken from Bohnsack et al, 2014, 1070P-Adaptation of the Immune Related Response Criteria: irRECIST, Ann Oncol, 25 (suppl 4): iv369 doi:10.1093/annonc/mdu342.23 [35].

1. Baseline

A. Measurable Lesion Definitions and Target Lesion Selection

- Follow the definitions from RECIST 1.1
- Measurable lesions must be accurately measured in at least one dimension with a minimum size of:
    - 10 mm in the longest diameter by CT or MRI scan (or no less than double the slice thickness) for non- nodal lesions and ≥ 15 mm in short axis for nodal lesions
    - 10 mm caliper measurement by clinical exam
    - 20 mm by chest X-ray

B. Non-measurable Lesion Definitions

- Follow the definitions from RECIST 1.1
- Non-target lesions will include
    - Measurable lesions not selected as target lesions
    - All sites of non-measurable disease, such as neoplastic masses that are too small to measure because their longest uninterrupted diameter is < 10 mm (or < two times the axial slice thickness), i.e., the longest perpendicular diameter is ≥ 10 and < 15 mm.
    - Other types of lesions that are confidently felt to represent neoplastic tissue, but are difficult to measure in a reproducible manner. These include bone metastases, leptomeningeal metastases, malignant ascites, pleural or pericardial effusions, ascites, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, ill-defined abdominal masses, skin lesions, etc.

C. Target and Non-target Lymph Node Lesion Definitions

- Follow the definitions from RECIST 1.1

D. Non-target Lesion Selection

- All lesions or sites of disease not recorded as target lesions should be recorded as non-target lesions at baseline. There is no limit to the number of non-target lesions that can be recorded at baseline.

E. Bone Lesions

- Follow the definitions from RECIST 1.1
- Regardless of the imaging modality blastic bone lesions will not be selected as target lesions. Lytic or mixed lytic-blastic lesions with a measurable soft tissue component ≥ 10 mm can be selected as target lesions.

F. Brain Lesions

- Brain Lesions detected on brain scans can be considered as both target or non-target lesions.

G. Cystic and Necrotic Lesions as Target Lesions

- Lesions that are partially cystic or necrotic can be selected as target lesions.
- The longest diameter of such a lesion will be added to the Total Measured Tumor Burden (TMTB) of all target lesions at baseline.
- If other lesions with a non-liquid/non-necrotic component are present, those should be preferred.

H. Lesions with Prior Local Treatment

- During target lesion selection the radiologist will consider information on the anatomical sites of previous intervention (e.g. previous irradiation, RF-ablation, TACE, surgery, etc.).
- Lesions undergoing prior intervention will not be selected as target lesions unless there has been a demonstration of progress in the lesion.

I. No Disease at Baseline

- If a patient has no measurable and no non-measurable disease at baseline the radiologist will assign 'No Disease' (irND) as the overall tumor assessment for any available follow-up time-points unless new measurable lesions are identified and contribute to the TMTB.

2. <u>Follow-Up</u>

A. Recording of Target and New Measurable Lesion Measurements

- The longest diameters of non-nodal target and new non-nodal measurable lesions, and short axes of nodal target and new nodal measurable lesions will be recorded. Together they determine the Total Measured Tumor Burden (TMTB) at follow-up.

B. Definition of New Measurable Lesions

- In order to be selected as new measurable lesions (≤ 2 lesions per organ, ≤ 5 lesions total, per time-point), new lesions must meet criteria as defined for baseline target lesion selection and meet the same minimum size requirements of 10 mm in long diameter and minimum 15 mm in short axis for new measurable lymph nodes. New measurable lesions shall be prioritized according to size, and the largest lesions shall be selected as new measured lesions.

C. Non-target Lesion Assessment

- The RECIST 1.1 definitions for the assessment of non-target lesions apply.
- The response of non-target lesions primarily contributes to the overall response assessments of irCR and irNon-CR/Non-PD (irNN).
- Non-target lesions do not affect irPR and irSD assessments.
- Only a massive and unequivocal worsening of non-target lesions alone, even without progress in the TMTB is indicative of irPD.

D. New Non-Measurable Lesions Definition and Assessment

- All new lesions not selected as new measurable lesions are considered new non-measurable lesions and are followed qualitatively.
- Only a massive and unequivocal progression of new non-measurable lesions leads to an overall assessment of irPD for the time-point.
- Persisting new non- measurable lesions prevent irCR.

3. irRECIST Overall Tumor Assessments

- **irCR**: complete disappearance of all measurable and non-measurable lesions. Lymph nodes must decrease to < 10 mm in short axis. Confirmation of response is not mandatory.
- **irPR**: decrease of ≥ 30% in TMTB relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions.
- **irSD**: failure to meet criteria for irCR or irPR in the absence of irPD.
- **irNN**: no target disease was identified at baseline and at follow-up the patient fails to meet criteria for irCR or irPD.

- **irPD**: minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions. Confirmation of progression is recommended minimum 4 weeks after the first irPD assessment.
- **irNE**: used in exceptional cases where insufficient data exists.
- **irND**: in adjuvant setting when no disease is detected.

For additional information, refer to the following article and online supplemental information:
Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, Lin NU, Litiere S, Dancey J, Chen A, Hodi FS, Therasse P, Hoekstra OS, Shankar LK, Wolchok JD, Ballinger M, Caramella C, de Vries EG, group Rw. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017;18(3):e143-e52. doi: 10.1016/S1470-2045(17)30074-8. PubMed PMID: 28271869.
(36)

Appendix H Celecoxib Patient Diary

Protocol # _____ Patient Name: _____
Drug Name: Celecoxib

Med. Record #: ___ ___ ___ ___ ___ ___

Study Medication Calendar

You are participating in a study that requires Celecoxib 200 mg to be given twice daily, approximately 12 hours (+/- 1 hour) apart on certain days. Your morning dose of Celecoxib will be given to you along with your pre-medications while you are in clinic. Please complete this calendar to document your evening doses of Celecoxib. Your nurse will let you know what time you receive your morning dose of Celecoxib so you can take your evening dose approximately 12 hours after.

Pre-treatment Regimen #_____:

Date			
Time that morning dose was taken (to be completed by the nurse in clinic)			
Evening Dose			
Time			
Patient's Initials			

Please remember to bring this calendar and your pill bottle (including any unused pills) with you to your next study appointment.

Coordinator use only
Date of return: _____
# of pills
(dispensed: _____ -- returned: _____)
_____ x 100 = % adherence: _____
# of pills scheduled _____

Patient signature: _____ Date: _____

Investigator signature: _____ Date: _____

Appendix I Description of Interferon Alpha-2b Potential Interactions

Aldesleukin: Interferons (Alfa) may enhance the adverse/toxic effect of Aldesleukin. In particular, risks of myocardial and renal toxicity may be increased by this combination. *Risk D: Consider therapy modification*

Methadone: Interferons (Alfa) may increase the serum concentration of Methadone. *Risk C: Monitor therapy*

Ribavirin: Interferons (Alfa) may enhance the adverse/toxic effect of Ribavirin. Hemolytic anemia has been observed. *Risk C: Monitor therapy*

Telbivudine: Interferon Alfa-2b may enhance the adverse/toxic effect of Telbivudine. Specifically, the risk for peripheral neuropathy may be increased. *Risk X: Avoid combination*

Theophylline Derivatives: Interferons may decrease the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Zidovudine: Interferons may enhance the adverse/toxic effect of Zidovudine. Interferons may decrease the metabolism of Zidovudine. *Risk C: Monitor therapy*

Appendix J Dose Escalation Cohort Study Calendar

Evaluation	Baseline[#]	Paclitaxel + CKM combination Weeks 1-3			Paclitaxel monotherapy Day 1 of weeks 4 through 12	Doxorubicin + Cyclophosphamide Every 2 weeks on Day 1 (4 cycles)	Pre-Surgical Visit	Surgery	End of Treatment[13]
		D1	D2	D3					
Informed Consent	X								
Concomitant Medications	X[1]	X	X	X	X	X			X
Adverse Events		X	X	X	X	X			X
Medical and surgical history	X								
Physical examination (including breast exam and measurement of breast lesion)	X[2]	X[2a]			X[2a]	X[2]	X		X
Vital Signs[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]		X[3]
Height/Weight[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]		
ECOG PS	X	X			X	X	X		X
Hematology[5]	X	X			X	X	X		X
Chemistry[6]	X	X			X	X	X		X
TSH	X								
Serum HCG	X[7]								

Evaluation	**Baseline#**	**Paclitaxel + CKM combination Weeks 1-3**			**Paclitaxel monotherapy Day 1 of weeks 4 through 12**	**Doxorubicin + Cyclophosphamide Every 2 weeks on Day 1 (4 cycles)**	**Pre-Surgical Visit**	**Surgery**	**End of Treatment[13]**
		D1	**D2**	**D3**					
Correlative Studies		X[8]							
MRI Breast	X[9]				X[9]	X[9a]			
ECHO/MUGA	X								
Surgery								X[10]	
Biopsy[11]	X			X					
Study Drug Administration									
Paclitaxel[14]		X[14]			X[14]				
CKM		X[12]	X	X					
Doxorubicin						X[14]			
Cyclophosphamide						X[14]			

Baseline assessments to be completed within 28 days of treatment start unless otherwise stated.

1 Medications ongoing, or discontinued, within 1 week prior to first dose of study drug.

2 Physical exam (including breast exam and measurement of breast lesions) is required prior to dosing on weeks +/- 3 days 1,2,3, 4,5,6, 7, 10 and 12. During doxorubicin/cyclophosphamide treatment, physical exam will be performed every 2 weeks on day of treatment, prior to dosing.

2a: During the DLT period (Day 1 of Week 1 through Week 6, physical exam to include assessment of head/ears/eyes/nose/throat (HEENT), skin, chest/lungs, heart, neck/lymph nodes, abdomen, extremities. Ophthalmologic evaluation to be performed after week 6 if symptoms develop.

3 Vital Signs include blood pressure, pulse, temperature and respiratory rate. On days that rintatolimod is given, vital signs will be obtained pre-treatment, 30 and 60 minutes post rintatolimod (± 5 minutes)

4 Weight is required prior to dosing on each dosing day. CKM dose will be recalculated if weight changes greater than 10%. Height is required at baseline only.

5 CBC with automated differential+/- 1 day

6 CMP+/- 1 day

7 Within 7 days of first dose of study drug in women of child-bearing potential.

8 60 cc of blood (five 10 cc green tops and one 10 cc red top) will be collected pre-chemotherapy dose on day 1 of week 1; 30 minutes after completion of Rintatolimod on day 1 of week 1.

9 MRI breast will be done within 6 weeks +/- 3 days of baseline evaluations for study participants per standard of care.

a. Only for the cohort at dose level 4: prior to start of doxorubicin/cyclophosphamide combination at least 1 day after last paclitaxel dose; and prior to surgery (standard of care) at least 2-3 weeks after last dose of doxorubicin/cyclophosphamide combination

10 Lumpectomy/ mastectomy done 3-6 weeks after the last dose of chemotherapy. Surgical outcome data collected.

11 All patients will be required to receive a paired biopsy on study. Biopsies will be performed at screening, and between Week 3 Day 3, and prior to infusion of Paclitaxel on Week 4 Day 1.

12 Day 1, 2, or 3 of each CKM dose may be delayed by 1 day for any reason (i.e. patient tolerance, etc.) In this instance, all CKM doses and corresponding assessments will be moved to days 2-4 instead of days 1-3. In the event that an assessment or labs was already performed on day 1 of that week, it does not need to be repeated on day 2 unless specifically indicated by the investigator. For example, if physical exam or labs was completed on day 1 and CKM start was delayed to day 2, the physical exam or labs does not need to be repeated.

13 End of treatment visit to occur 2 week (± 3 days) after surgery. After this visit, the patient will be followed as per standard of care if no drug related toxicity is observed. Survival status will be assessed by telephone contact or chart review every 6 months from surgery for a max of 3 years, and then taken off study. Additionally (if applicable), the patient can be contacted by telephone until resolution of any drug-related toxicity.

14 Treatment can be administered +/- 3 days on the 1st day of every cycle