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Title: A Phase 2 Clinical Trial of Rituximab and β-glucan PGG in Relapsed Indolent Non-Hodgkin Lymphoma.

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Agent(s): Rituximab (NSC#; IND#) - ; Imprime PGG (NSC#; IND#) - Biothera

SCHEMA

Definitions

CR - Complete Response

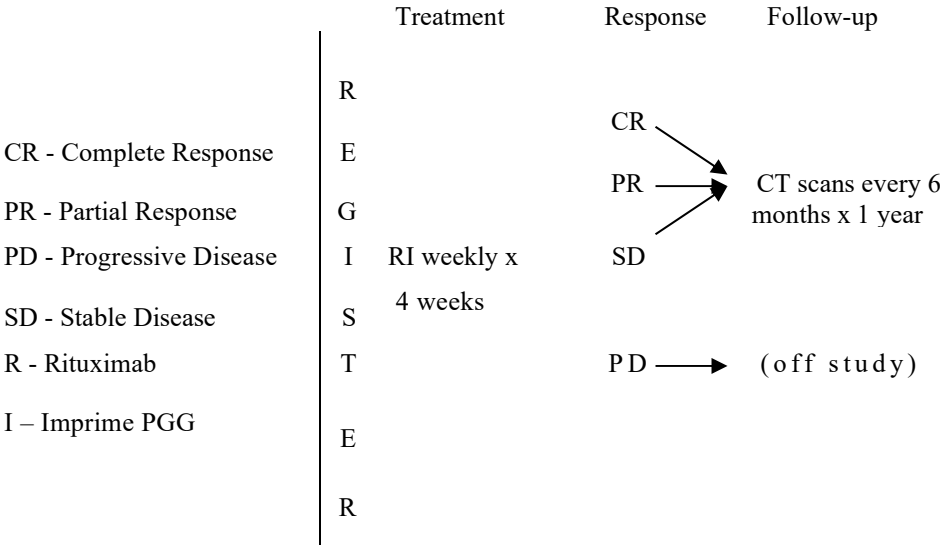
PR - Partial Response

PD - Progressive Disease

SD - Stable Disease

R - Rituximab

I – Imprime PGG



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1. OBJECTIVES

1.1 Study Design

This is a Phase 2 open label single arm study employing a single stage design to assess efficacy and safety of Imprime PGG in combination with rituximab in relapsed/refractory indolent B cell non-Hodgkin lymphomas (NHL). The study drug, Imprime PGG, will be administered intravenously at a dose of 4mg/kg weekly for 4 weeks. Rituximab will be administered intravenously by institutional standards concurrently at a dose of 375mg/m^2 weekly for 4 weeks. Response will be assessed with CT scans 10 weeks +/- 3 days following the completion of treatment.

1.2 Primary Objectives

To evaluate clinical efficacy of Imprime PGG in combination with rituximab in relapsed/refractory indolent B cell non-Hodgkin lymphoma (NHL), as measured by the overall response rate (ORR)

1.3 Secondary Objectives

- Determine progression-free survival (PFS) and duration of response. Evaluate safety of this combination in relapsed/refractory indolent NHL patients
- To perform correlative laboratory studies using on-treatment peripheral blood samples and post-treatment tumor samples to quantify the binding of Imprime PGG to neutrophils and correlate with treatment response.

2. BACKGROUND

2.1 Imprime PGG

Imprime PGG is an immunomodulator. The active ingredient is PGG Beta Glucan, an uncharged, water-soluble, beta-glucan polymer purified from the cell wall of a proprietary, nonrecombinant strain of *Saccharomyces cerevisiae.* Beta glucans are polymers of glucose that are extractable from yeasts, fungi (mushrooms), seaweed, and some cereals.[1] Beta glucans are conserved molecules that are recognized by the human innate immune system as non-self molecules. Different forms of beta glucan exist; yeast contains beta 1, 3/1, 6 glucan, which is the glucan form in Imprime PGG. In the case of yeast infection, human innate immune cells (e.g., macrophages, monocytes and neutrophils) recognize the yeast beta glucan as foreign and initiate an immune response

against the microbe. An essential step in this response is activation of the complement cascade, by antibodies that recognize the yeast as foreign. This leads to opsonization of the yeast cells with iC3b, the inactivated form of complement component 3b, a relatively early component in the complement cascade. Subsequently, the opsonized yeast bind to complement receptor 3 (CR3) on innate immune cells, and cytotoxicity follows. Such activity has been shown to require yeast cell interaction with two binding sites on CR3: one that binds iC3b on the opsonized yeast cells and a second that binds beta glucan on the cell surface of the yeast.[2] Dual ligation of the CR3 receptor triggers the innate immune effector cells, such as neutrophils, to exert cytotoxic responses against the opsonized target. This type of cytotoxicity has been referred to as CR3-dependent cell-mediated cytotoxicity (CR3-DCC) and differs from traditional ADCC and CDC.[3]

It is well understood that anti-tumor monoclonal antibodies, such as rituximab, activate the complement system, which would result in the deposition of iC3b on the surface of tumor cells. However, leukocyte effector cells would not be expected to exert CR3-DCC activity against the tumor cells in the manner that they do against yeast cells because mammalian cells do not make or contain beta glucan. Thus, even though leukocyte CR3 may recognize the iC3b-opsonized tumor cells, the mechanism of innate cell killing described above for yeast would not be activated due to the absence of the second CR3 signal, i.e., that of beta glucan binding. Thus, administration of beta glucan in combination with a monoclonal antibody (MAb) like rituximab should result in CR3-DCC against tumor cells. This is because 1) MAbs (i.e rituximab) bind to tumor-associated antigens (i.e. CD20), leading to iC3b opsonization of the tumor cell, and 2) beta-glucan binds to CR3 on innate immune effector cells, thus priming them, so that 3) the primed immune effector cell can now engage the iC3b-opsonized tumor cell for cytotoxicity (i.e., CR3-DCC).

Pre-clinical studies have demonstrated that combination treatment with beta glucan and tumor-specific MAbs induce significant antitumor responses that are superior to either agent alone in numerous animal models. [4-8]. Similar enhancement of effects have been observed in early clinical trials of Imprime PGG combined with antitumor MAbs[9]. Unpublished results from Biothera study reports of ongoing clinical trials of Imprime PGG in combination with cetuximab or bevacizumab with or without chemotherapy in colorectal and lung adenocarcinoma are detailed below. In addition, an ongoing study of the combination of Imprime PGG, rituximab and alemtuzumab in patients with high risk chronic lymphocytic leukemia (CLL) has produced a 64% complete response rate compared to the expected rate of 37% for the MAb treatment alone.[9] Imprime PGG is an investigational new drug being developed by Biothera in combination with anti-tumor MAbs for the treatment of cancer. The active ingredient in Imprime PGG is PGG Beta Glucan. The inactive ingredients of the drug product are sodium citrate and sodium chloride. The drug product, Imprime PGG, is a sterile solution for IV administration. It is supplied in 20-mL or 50-mL vials containing PGG Beta Glucan at a nominal concentration of 1 mg/mL in 0.14 M sodium chloride, 0.011 M sodium citrate, pH 5.0-7.5. In preclinical models, the combination of Imprime PGG and tumor-specific mAbs results in a dose-dependent anti-tumor and long-term survival-enhancing effect that exceed the effects of Imprime PGG or MAb alone.[5,8,10] Neutrophils have been shown to

be important effector cells of the antitumor activity seen with combination Imprime PGG and MAb therapy, and this antitumor activity requires the presence of CR3.[10] Blocking CR3 prevents Imprime PGG binding to human neutrophils and monocytes *in vitro*. This data has lead Biothera to develop protocols investigating the combination of Imprime PGG and MAbs in the treatment of colon and lung cancer.

One completed study evaluated the administration of Imprime PGG in combination with cetuximab (Erbitux®), with and without standard irinotecan therapy, in metastatic colorectal carcinoma (mCRC) subjects. In this study, subjects were enrolled into dose-escalating cohorts and dosed with 2 mg/kg, 4 mg/kg, or 6 mg/kg Imprime PGG and a standard regimen of cetuximab either with concomitant irinotecan (Arm 1; 10 subjects) or without concomitant irinotecan (Arm 2; 22 subjects). The ORR in Arm #1 was 30% and the time to progression (TTP) was 23.7 weeks; these values compared favorably to historical ORR and TTP values of 16.4%-22.9% and 17.2-17.6 weeks previously reported in mCRC subjects treated with cetuximab and irinotecan.[11] The ORR in Arm #2 was 22.7% and the TTP was 11.7 weeks, also comparing favorably to historical ORR and TTP values of 10.8% and 6.5 weeks previously reported in mCRC subjects treated with cetuximab monotherapy.[11] During the conduct of this study, the importance of tumor *KRAS* gene status in response to cetuximab therapy became known.[12] Based on this, tumor tissues from the subjects in this study were retrospectively evaluated for *KRAS* status. ORR and TTP values in the subpopulation of subjects expressing the wild type *KRAS* gene in their tumors were greater than in the overall population, again comparing favorably to historical values. In particular, in Arm #2, ORR and TTP values of 45.4% and 23.7 weeks were observed compared to previously reported ORR and TTP values of 10%-28% and 6.0-15.9 weeks in *KRAS* wild type subjects treated with cetuximab monotherapy.[13] These results supported the development of a phase 3 clinical trial in *KRAS* wild type mCRC patients. In a population of mCRC patients carrying *KRAS* mutation, a phase 2 study has been completed. A total of 18 patients were enrolled and 1 patient (5.6%) had a partial response (PR), while stable disease (SD) was observed in 9 additional subjects (50.0%), yielding a disease control rate (DCR) of 55.6%. The median overall survival was 6.6 months (range: 1.9-23.1 months). In addition, there are three additional ongoing clinical trials of Imprime PGG at a dose of 4mg/kg in combination with cetuximab in patients with *KRAS* mutant mCRC, and in combination with either cetuximab or bevacizumab and carboplatin/paclitaxel in the first line treatment of advanced non-small cell lung cancer (NSCLC).

2.1.1 Pharmacokinetics

The pharmacokinetic (PK) profile of Imprime PGG was determined based on the results of Phase 1 studies within healthy volunteers (n=36). In general, it was found that, elimination of plasma concentrations of beta glucan in healthy adult subjects fit best to a three-compartment model. The “effective” half-life (i.e., the half-life that contributes the most to beta glucan disappearance from plasma) was considered to be adequately represented by the beta phase, with $t_{1/2\beta}$ values ranging from 18.1 to 27.0 h. In a healthy volunteer study where Imprime PGG was administered daily for seven consecutive days, steady state trough concentrations of beta glucan in plasma and peripheral tissues are

observed after 4 days of dosing. Based on the observed $t_{1/2\beta}$, it was determined that a dosing interval of once every 7 days will be expected to result in negligible beta glucan accumulation in, whereas shorter dosing intervals (e.g., bi-weekly or every 48 h) would lead to noticeable accumulation. Based on these results weekly dosing of Imprime PGG was chosen for subsequent studies. PK results from the completed Phase 1b/2 study of Imprime PGG in combination with cetuximab ± irinotecan in mCRC (n=32), supported the PK results observed in the healthy volunteer studies. Additional PK data is being collected in ongoing Phase 2 studies in advanced stage NSCLC, and in the ongoing Phase 3 mCRC study, however, have not yet been analyzed.

2.1.2 Clinical Experience

The clinical experience with Imprime PGG has included three Phase 1 studies of Imprime PGG alone or in combination with G-CSF in healthy volunteers; a Phase 1b/2, a Phase 2, and an ongoing Phase 3 study of Imprime PGG in combination with cetuximab for the treatment of mCRC; and two Phase 2 studies of Imprime PGG in combination with cetuximab or bevacizumab ± chemotherapy for the treatment of NSCLC. In total 85 healthy volunteers and approximately 250 cancer patients have received at least one dose of Imprime PGG.

2.1.3 Safety

In general, Imprime PGG was very well tolerated when administered alone or in combination with G-CSF, anti-tumor MAbs, and/or chemotherapy. In studies involving healthy volunteers, while a majority of patients (84%) experienced at least 1 adverse event (AE), none of these were considered severe. Among the cancer studies, nearly all patients experienced at least one AE but the majority of these were deemed unlikely to be related to the study drug, and the number of patients who discontinued treatment due to AEs ranged from 0% to 49%. The AEs responsible for study discontinuation included most commonly allergic reactions and rash, but also pancreatitis, delayed wound healing, bilateral conjunctivitis, pleural effusion, suspected hypertrophic cardiomyopathy, and back pain.

Common adverse reactions (≥ 5% in Imprime PGG-treated subjects) in clinical trials of healthy volunteers included headache, back pain, chest pain, dyspnea, abdominal pain, arthralgia, nausea, injection site pain, musculoskeletal pain, pain in extremity, and urticaria. Fewer than 5% of patients experienced infusion reactions (dizziness, paraesthesia, rash, nausea, and flushing), fatigue, myalgia, and diarrhea.

Serious AEs (SAE) have been reported in anywhere from 25%-90% of cancer patients depending on the study, with the exception of two single-IND studies, where the respective SAE rates were 0% and 100%. In studies including a control arm, the rate of SAEs is slightly lower in the Imprime PGG arm (27.3% v 41.7% and 36.4% v 44.0%) in two of the studies, and slightly higher in the Imprime PGG arm n one study (61.7% v 40%). SAEs that have been reported in more than one patient per study include general

health decline, nausea, pneumonia, pneumothorax, diarrhea, dyspnea, lung embolism, neutropenia, pleural effusion, and pulmonary embolism. Among these, the following occurred in more than 5% of patients: general health decline (6.8%), diarrhea (6.7%), neutropenia (6.7%), and pleural effusion (6.7%). Eighteen (18) deaths have been reported in studies with Imprime PGG, including one that occurred prior to a subject receiving any study-related medications. Of these, 15 deaths occurred in the NSCLC studies: 7 in LCA0821 (Imprime PGG with bevacizumab ± chemotherapy) and 8 in LCA0822 (Imprime PGG with cetuximab ± chemotherapy). In LCA0821, deaths were the outcome of general health deterioration (N=3, investigational arm), disease progression (N=1, investigational arm), intracranial hemorrhage (N=1, investigational arm), pneumonia (N=1, investigational arm), and pneumothorax (N=1, investigational arm). In LCA0822, deaths were the outcome of sepsis following severe neutropenia and acute renal failure (N=1, investigational arm), acute cardiovascular failure (N=1, investigational arm), disease progression (N=1, control arm), hemoptysis (N=2, investigational arm), pleural effusion (N=1, investigational arm), and pulmonary hemorrhage (N=1, investigational arm). To date, three deaths have occurred in study CRC1031 (Phase 3 mCRC). The deaths were the outcome of bilateral bowel perforation (N=1, investigational arm), cardiac arrest (N=1, investigational arm), and pneumonia (N=1, investigational arm).

In dose escalation studies (2mg/kg, 4mg/kg and 6mg/kg); no maximally tolerated dose has been achieved. Biothera has opted to proceed with the 4mg/kg dose based on tolerability and efficacy data showing that this dose is more efficacious than the 2mg/kg and 6mg/kg doses.

2.2 Indolent B cell non-Hodgkin Lymphoma

There will be approximately 70,130 new cases of NHL this year in the United States, and 18,940 deaths. The indolent NHLs, including follicular lymphoma and marginal zone lymphoma, generally present at advanced stage and are incurable with conventional therapies. Though incurable, these diseases tend to be chemotherapy responsive with high rates of initial response, but they exhibit progressively lower rates of response and remission duration with subsequent lines of therapy, and always with invariable relapse. Available therapies for indolent NHLs include single-agent and combination chemotherapy, monoclonal antibody based therapy, radiotherapy, radioimmunotherapy, and stem cell transplantation in selected cases.

2.3 Rituximab

Of the many effective treatment modalities for indolent NHL, overall survival benefits have not been demonstrated favoring one treatment approach over another, with the exception of rituximab-containing chemotherapy versus chemotherapy alone. Increased intensity regimens have been shown to improve complete response rates and progression free survivals without improvement in overall survival. Choice of therapy has thus been based upon balancing efficacy and tolerability. Available treatment approaches currently

employed in chemotherapy naïve and relapsed/refractory patients include rituximab monotherapy, R-bendamustine, R-CVP (rituximab, cyclophosphamide, vincristine, prednisone), R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine, prednisone), fludarabine-based regimens, radioimmunotherapy, and occasionally single agent oral alkylator therapy. Single agent monoclonal antibodies are an attractive treatment option given excellent tolerability. Rituximab is approved as a single agent in relapsed or refractory low grade or follicular non-Hodgkin's lymphoma (NHL) and in combination with chemotherapy for first line therapy of follicular NHL and diffuse large B cell lymphoma (DLBCL).

Rituximab is a genetically engineered, chimeric, murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant pre-B and mature B cells. The antibody is an IgG$_1$ κ immunoglobulin containing murine light and heavy-chain variable region sequences and human constant region sequences. Rituximab is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids (based on cDNA analaysis) and has an approximate molecular mass of 145 kD. Rituximab has a binding affinity for the CD20 antigen of ~8.0 nM. Several mechanisms of action have been proposed in various models including complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytoxicity (ADCC), induction of apoptosis, and a "vaccinal" effect.[14] It is likely that rituximab works through a combination of these mechanisms.

The overall response rate for rituximab monotherapy in relapsed low-grade B-cell lymphoma is approximately 24-36% with complete response rates of approximately 7%.[15] Several mechanisms for rituximab resistance have been proposed including variable CD20 expression by lymphoma subtype, variability in complement activation, and polymorphisms in Fc receptors.[16-18] Novel agents that overcome these resistance mechanisms might offer similar complete response rates to combined chemotherapy and immunotherapy with improved tolerability.

2.4 Rationale for Imprime PGG combined with Rituximab in Indolent NHL

Rituximab is a highly efficacious and tolerable therapy for the treatment of indolent NHL, but response rates fall in the relapsed setting with some patients developing refractory or rituximab-resistant disease. The mechanism of this resistance is unknown but has been proposed to be related to variability in complement activation, variable CD20 expression, and polymorphisms in the Fc receptors.[16-18] Although complement activation and CDC is not absolutely necessary for rituximab-induced cytotoxicity, loss of complement has been shown to reduce its anti-tumor effect in mouse models.[19,20] Conversely, inhibition of membrane-bound inhibitory proteins of the complement cascade facilitates rituximab's effect on NHL.[20] CDC is a more potent anti-tumor mechanism when the immune target is present in higher numbers on the cell surface, and this has been shown to be true for rituximab and CD20 on the lymphoma cell surface.[21,22] Complement activation, then, can be enhanced by mechanisms that increase CD20

expression in the tumor cell, or by using immune adjuncts to enhance complement activity, or antibodies against iC3b to increase iC3b deposition.

Another way to increase anti-tumor cytotoxicity of complement depositing antibodies is to increase the recognition of tumor-bound iC3b by innate immune cells. As outlined above, Imprime PGG is the yeast-derived beta 1, 3/1, 6 glucan that is recognized by, and facilitates an immune response by, human innate immune cells (e.g., macrophages, monocytes and neutrophils) in the setting of a yeast infection. CR3-DCC, the cytotoxicity that occurs as a result of the necessary coincident binding of CR3 on innate immune cells by iC3b and beta glucan on opsonized yeast cells, differs from traditional ADCC and CDC and can be exploited to enhance tumor cell killing by antibody therapies.[3] This can be accomplished by the coadministration of a compound like Imprime PGG with an anti-tumor MAb, which allows innate immune cells to recognize iC3b opsonized tumor cells through their complement receptor 3 (CR3).[23,24] The coadministration of the two drugs takes advantage of the fact that tumor cell-MAb binding activates the complement system resulting in iC3b deposition on the tumor cells. However, leukocyte effector cells would not be expected to exert CR3-DCC activity against the tumor cells in the manner that they do against yeast cells because mammalian cells do not make or contain beta glucan, a molecule whose binding to CR3 is necessary to provide the second signal to activate the immune effector cell. The co-administration of beta glucan, however, in combination with a MAb like rituximab should result in CR3-DCC against tumor cells. This is because 1) MAbs (i.e rituximab) bind to tumor-associated antigens (i.e. CD20), leading to iC3b opsonization of the tumor cell, and 2) beta-glucan binds to CR3 on innate immune effector cells, thus priming them, so that 3) the primed immune effector cell can now engage the iC3b-opsonized tumor cell for cytotoxicity (i.e., CR3-DCC).

Clinical data from phase 1 and 2 studies in colorectal and lung cancer outlined above support this synergistic mechanism of action, and an ongoing phase 3 clinical trial of Imprime PGG and cetuximab in mCRC is underway. This has also been investigated in mouse models of NHL and Hodgkin's disease treated with (1-3),(1-4)-β-D-glucan (BG) in combination with rituximab, or BG or rituximab alone.[4] Specifically, subcutaneous and disseminated xenograft models were developed using the human Burkitt lymphoma cell line, Daudi, and the Hodgkin's disease cel lines Hs445 and RPMI 6666. Combination therapy with BG and rituximab resulted in greater suppression of tumor growth in the subcutaneous xenografts that persisted beyond treatement, and improved survival in both the subcutaneous and disseminated xenografts compared with either drug alone and no clinical toxicity was observed. Among the disseminated xenografts, approximately one quarter of the mice receiving the combination therapy were alive at one year, consistent with eradication of disease, compared to no mice who received rituximab alone. That BG interacted with effector leukocytes was confirmed by intracellular detection by immunofluorescence. Responses were greatest in Daudi xenografts, perhaps relating to the fact that Burkitt lymphoma has higher CD20 expression than Hodgkin lymphoma, although tumor progression was not associated with loss of CD20. In addition, an ongoing phase I clinical trial of alemtuzumab, rituximab,

and Imprime PGG in CLL resulted in a complete response rate of 64% (7/11) compared to a historical rate of 37% for alemtuzumab and rituximab alone.[9] In this study there were three dose cohorts for Imprime PGG (1mg/kg, 2mg/kg, and 4mg/kg) with the maximally tolerated dose being 4mg/kg and the combination being well tolerated. Taken together this data supports an exploration of Imprime PGG and rituximab in indolent B cell lymphomas that might otherwise be treated with rituximab alone.

We hypothesize that combining Imprime PGG with rituximab for the treatment of relapsed and refractory indolent B cell NHL should result in an improvement in response rates. By collecting pre- and on treatment peripheral blood samples from patients, we will be able to categorize the percentage of Imprime PGG-bound and activated neutrophils,and correlate this with responses to treatment. .

3. PATIENT SELECTION

3.1 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

3.1.1 Patients must have histologically determined indolent NHL that is relapsed or primary refractory after initial therapy. Indolent NHL includes the morphologic and clinical variants:

- Follicular lymphoma, grades 1-3a
- Marginal zone lymphoma (extranodal, nodal, or splenic)
    - All nodal marginal zone lymphomas are eligible
    - Extranodal marginal zone lymphomas of the stomach (gastric MALT lymphomas) may not be candidates for cure with antibiotics or local radiotherapy. Patients who have failed antibiotics or local therapy are eligible for the protocol as long as they have measurable disease \.
    - Splenic marginal zone lymphoma patients may have received prior splenectomy as long as they have measurable disease.
- Re-biopsy is not mandated at relapse unless there is clinical suspicion about an alternate diagnosis.

3.1.2 One or more prior lines of chemoimmunotherapy and/or monotherapy with rituximab or other anti-CD20 antibody. Patients may have had a prior autologous stem cell transplant but not prior allogeneic stem cell transplantation.

3.1.3 Measurable disease that has not been previously irradiated on CT scans of at least 2 cm, OR if the patient has had previous radiation to the marker lesion(s), there must be evidence of progression since the radiation. Imaging must be completed no greater than 6 weeks prior to study enrollment.

3.1.4 ECOG performance status 0-2 (Appendix B, Section 17.2)

3.1.5 Absolute neutrophil count $\geq$ 750 prior to treatment

3.1.6 Oxygen saturation $\geq$90%, no more than 2 LPM oxygen

3.1.7 Serum creatinine $\leq$ 1.5 X ULN

3.1.8 AST $\leq$ 3 X ULN

3.1.9 Total bilirubin $\leq$ 1.5 X ULN (unless there is lymphoma in the liver)

3.1.10 Age $\geq$18 years

3.1.11 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

3.2.1 Patients currently receiving anticancer therapies or who have received anticancer therapies within 30 days of the start of study drug (including chemotherapy, radiation therapy, antibody based therapy, etc.). Steroids for symptom palliation are allowed, but must be either discontinued or on stable doses at the time of initiation of protocol therapy.

3.2.2 Patients may not be receiving any other investigational agents, or have received investigational agents within 4 weeks of beginning treatment.

3.2.3 Patients who have previously received PGG-Betafectin (Betafectin®) or Imprime PGG.

3.2.4 Patients, who have had a major surgery or significant traumatic injury within 4 weeks of start of study drug, patients who have not recovered from the side effects of any major surgery (defined as requiring general anesthesia) or patients that may require major surgery during the course of the study.

3.2.5 Patients with known leptomeningeal or brain metastases. Imaging or spinal fluid analysis to exclude CNS involvement is not required, unless there is clinical suspicion by the treating investigator.

3.2.6 History of severe allergic or anaphylactic reactions to monoclonal antibody therapy or a known hypersensitivity to baker's yeast, unless in consultation with an allergy specialist they are deemed eligible for retreatment with desensitization.

3.2.7 Patients with known HIV infection or hepatitis B or C infection.HIV testing is not mandated and is to be performed at the discretion of the treating investigator.

3.2.8 Patients with a systemic fungal, bacterial, viral, or other infection not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment).

3.2.9 Prior history of another malignancy (except for non-melanoma skin cancer or *in situ* cervical or breast cancer) unless disease free for at least three years. Patients with prostate cancer are allowed if PSA is less than 1. Patients with indolent malignancies under control and which, in the opinion of the treating investigator, are unlikely to be clinically relevant or affect survival during the course of the study treatment and follow-up.

3.2.10 Patients should not receive immunization with attenuated live vaccine within one week of study entry or during study period.

3.2.11 Female patients who are pregnant or breast feeding, or adults of reproductive potential who are not using effective birth control methods. Women of child bearing potential (WOCBP) or male study participants of reproductive potential must agree to use double barrier birth control method of contraception during the course of the study treatment period and for 3 months after completing study treatment.

WOCBP are defined as sexually mature women who have not undergone a hysterectomy or who are not postmenopausal (no menses) for at least 12 consecutive months. WOCBP must have a negative urine or serum pregnancy test within 7 days prior to administration of treatment.

3.2.12 History of noncompliance to medical regimens.

3.2.13 Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:
- New York Heart Association Class III or IV cardiac disease, including pre-existing clinically significant arrhythmia, congestive heart failure, or cardiomyopathy
- unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction within 6 months of start of study drug, serious uncontrolled cardiac arrhythmia or any other clinically significant cardiac disease

3.2.14 Other uncontrolled intercurrent illness that would limit adherence to study requirements.

3.3 Inclusion of Women, Minorities, and other Underrepresented Populations

Women, minorities and underrepresented populations should be eligible for this trial at a similar rate to men and patients not from underrepresented populations. The inclusion and exclusion criteria should not be affected by gender or ethnicity, except for the exclusion of pregnant or lactating women.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. Registration must

occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

A member of the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. Notify the QACT Registrar of participant status changes as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. If a participant must be registered during off-hours or holidays, call the QACT registration line at 617-632-3761 and follow the instructions for registering participants after hours.

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.

2. Complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical/research record. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.**

   Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for the treatment study. Registration to both treatment and ancillary studies will not be completed if eligibility requirements are not met for all studies.

3. Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617-632-2295.

4. The QACT Registrar will (a) validate eligibility, (b) register the participant on the study, and (c) randomize the participant when applicable.
5. The QACT Registrar will send an email confirmation of the registration and/or randomization to the person initiating the registration immediately following the registration and/or randomization.

5. TREATMENT PLAN

It is expected that treatment will be administered on an outpatient basis. Therapy will consist of four weekly treatments of both Imprime PGG (4mg/kg/dose) and rituximab (375 mg/m^2/dose). Imprime PGG will be administered first, followed by a minimum waiting time of 10 to 15 minutes (but maximum of 24 hours +/- 4 hours) before the start of rituximab. Patients with bulky disease or circulating disease ≥ 15,000 circulating malignant cells/ mm3 will receive allopurinol for prophylaxis of tumor lysis syndrome. Response will be assessed 10 weeks after the completion of therapy by CT scans of the chest, abdomen, and pelvis. Expected toxicities and potential risks for Imprime PGG and rituximab are described in Section 6 (Expected Toxicities and Dosing Delays/Dose Modifications). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

5.1 Imprime PGG Administration

The study drug Imprime PGG will be administered by intravenous bolus infusion through a low protein binding 0.22-micrometer in-line filter at a dose of 4 mg/kg (actual body weight) over at least 2 hours (longer infusion times are required for subjects over 75 kg). The dosing frequency will be every 7 days for a total of 4 weeks. Participants will be pre-medicated according to institutional standards for rituximab prior to administration of either drug. Imprime PGG will be provided by Biothera. The drug product, Imprime PGG, is a sterile solution for IV administration. It is supplied in 20-mL or 50-mL vials containing PGG Beta Glucan at a nominal concentration of 1 mg/mL in 0.14 M sodium chloride, 0.011 M sodium citrate, pH 5.0-7.5.

5.2 Rituximab administration

Rituximab from a commercial supply will be administered IV at a dose of 375 mg/m2 every 7 days for 4 weeks. Actual body weight will be measured prior to each Rituximab infusion to calculate the BSA and dose for each infusion.. If the infusion cannot be completed within 1 day, the patient is allowed to receive the remainder of the infusion the following day as long as the dose is administered within 2 consecutive days.

Rituximab will be administered at DFCI per Dana-Farber Harvard Cancer Center institutional guidelines.

Dana-Farber Harvard Cancer Center institutional guidelines include:

- Participants will be pre-medicated with hydrocortisone 100 mg IV, acetaminophen 650 mg, and diphenhydramine 25 mg PO, or their equivalents, prior to each dose.
- No specific prehydration is required.
- The first infusion will begin at an initial rate of 50 mg/hour for the first hour. If hypersensitivity or infusion-related events do not occur, the rate will be increased in 50 mg/hour increments every 30 minutes until a maximal rate of 400 mg/hour.
- On subsequent infusions the initial rate in the absence of hypersensitivity will be 20 percent of the total dose over 30 minutes, followed by the remaining 80 percent of the total dose over 60 minutes.
- Vital signs should be checked approximately every 15 minutes during the first hour of infusion, then approximately once an hour or prior to any infusion rate change until completion of the infusion.
- Infusion should be temporarily discontinued for a temperature > 101.3°F, mucosal edema, or >30 mm Hg decrease in systolic blood pressure.
- An additional 25 mg of benadryl IV should be given.
- Infusion may resume after symptoms resolve a 50% of the rate infusing at the time of the event.

5.3 General Concomitant Medication and Supportive Care Guidelines

5.3.1 Pre-medications

Participants will be premedicated with hydrocortisone 100 mg IV, acetaminophen 650 mg, and diphenhydramine 25 mg PO, or their equivalents, prior to each dose. No specific prehydration is required.

5.3.2 Antibiotics

Prophylactic antibiotics or anti-virals are not required on this trial.

5.3.3 Hydration

No pre-hydration or hydration is required with this regimen.

5.3.4 Tumor lysis prevention and management

Participants with bulky disease and/or circulating disease ≥ 15,000 circulating malignant cells/ mm^3 may receive allopurinol 300mg orally daily for 7-10 days starting with the first dose of Imprime PGG and rituximab. Participants deemed at risk for tumor lysis syndrome (TLS) should have their labs monitored per standard practice. The management of established TLs should also follow standard practice.

5.3.5 Other

Blood product transfusions and the use of bisphosphonates are permitted at the discretion of the treating physician.

5.4 Duration of Therapy

Duration of therapy will be for four weeks but will be stopped in the event of any of the following:

- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates and inability or unwillingness to comply with the medication regimen and/or documentation requirements
- Participant decides to withdraw from the study
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator

5.5 Duration of Follow-up

Participants who have received at least one dose of Imprime PGG and Rituximab will be followed for 1 year after the completion of combination therapy or until death, whichever comes first.. Participants removed from the study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. The post-treatment visit (Section 9) will occur 10 weeks +/- 3 days from the last day of treatment.

5.6 Criteria for Removal from Study Treatment

Participants will be removed from study when any of the criteria listed in Section 5.4 applies. The reason for study removal and the date the participant was removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator, Caron Jacobson, M.D. at 617-632-3352.

6. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modification will be made using the recommendations in Section 6.3. Toxicity assessments will be done using the Version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) which is identified and located on the

CTEP website at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc).

All adverse events experienced by participants will be collected from the time of the first dose of the study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

6.1 Anticipated Toxicities from Imprime PGG

A list of the adverse events and potential risks associated with Imprime PGG appear below and will determine whether dose delays and modifications will be made or whether the event requires expedited reporting **in addition** to routine reporting.

- Less likely toxicities (5-20%)
    - Increase in Aspartate Aminotransferase (AST) and Alkaline phosphate (ALK) levels in the blood
    - Skin rash or dry skin
    - Diarrhea
    - Electrolyte disturbances: decrease in potassium, magnesium, and/or phosphate levels in the blood
    - Hair loss
    - Anemia
    - Decreased appetite
    - Increase in amylase levels in the blood
    - Headache
    - Allergic reaction
    - Hypertension
    - Dyspnea
    - Conjunctivitis
    - Increased or decreased number of white blood cells
    - Mouth sores
    - Nausea or vomiting
    - Swelling around finger nails
    - Arthralgia
    - Fever

- Rare but serious toxicities (<5%)
    - Dehydration
    - Fluid around the lungs
    - Blood clot that travels to the lungs
    - Death (refer to Section 2.1.1.3)

6.2 Anticipated Toxicities from Rituximab

A list of the adverse events and potential risks associated with rituximab appear below and will determine whether dose delays and modifications will be made or whether the event requires expedited reporting **in addition** to routine reporting.

- Infusion reactions: including fever, chills, headache, nausea, vomiting, throat irritation, flushing, rash, pruritis, urticaria, dyspnea, increased cough, rhinitis, asthenia, and hypotension, primarily during rituximab infusions which typically respond to an interruption of the infusion and resumption at a slower rate.
    - Fatal Infusion Reactions**:** Severe and fatal cardiopulmonary events, including angioedema, hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, and cardiogenic shock, have been reported. These severe reactions typically occurred during the first infusion with time to onset of 30-120 minutes.
- Night sweats
- Abominal pain, pain, back pain
- Sinusitis
- Diarrhea
- Myalgia
- Arthralgia
- Hypertension
- Dizziness
- Anxiety
- Tumor Lysis Syndrome: tumor lysis syndrome has been reported and is characterized in patients with a high number of circulating malignant cells (≥25,000 ul) by rapid reduction in tumor volume, renal insufficiency, hyperkalemia, hypocalcemia, hyperuricemia, and hyperphosphatemia.
- Mucocutaneous Reactions: Severe bullous skin reactions, including fatal cases of toxic epidermal necrolysis and paraneoplastic pemphigus, have been reported. The onset of reaction has varied from 1 to 13 weeks following rituximab exposure.
- Metabolic Events: Hyperglycemia, peripheral edema, LDH increase
- Hematologic Events: including lymphopenia, neutropenia, leukopenia, thrombocytopenia with a median duration of approximately 14 days. Transient aplastic anemia (pure red cell aplasia) and hemolytic anemia have been reported.

Late onset neutropenia, marrow hypoplasia, and prolonged pancytopenia have also been reported.

- Infectious Events: B cell depletion and decreased serum immunoglobulins have been associated with an increased risk of bacterial and viral infections. Serious infections (grade 3 or 4) are rare, occurring in approximately 2% of patients.
    - Hepatitis B Reactivation**:** Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death has been reported in some patients with hematologic malignancies treated with rituximab. The majority of patients received rituximab in combination with chemotherapy. The median time to the diagnosis of hepatitis was approximately four months after the initiation of rituximab and approximately one month after the last dose.
    - Other Serious Viral Infections: including JC virus (progressive multifocal leukoencephalopathy [PML]), cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C. In some cases, the viral infections occurred up to one year following discontinuation of Rituximab and have resulted in death.
- Progressive multifocal leukoencephalopathy (PML): PML is a rare and demyelinating disease of the brain caused by infection with the JC virus that usually leads to death or severe disability. JC virus infection resulting in PML and death has been reported rarely in patients with hematologic malignancies receiving rituximab. The majority of these patients had received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant.
- The following serious adverse events have been reported to occur in patients following completion of rituximab infusions: arthritis, disorders of blood vessels (vasculitis, serum sickness and lupus-like syndrome), eye disorders (uveitis and optic neuritis), lung disorders including pleuritis and scarring of the lung (bronchiolitis obliterans), that may result in fatal outcomes, and fatal cardiac failure.

6.3 Toxicity Management

Toxicity management should follow standard clinical practice. Specific recommendations that apply to both Imprime PGG and rituximab follow:

6.3.1 Infusion toxicity

Infusion should be temporarily discontinued for a temperature > 101.3F, mucosal edema, or >30 mm Hg decrease in systolic blood pressure. Hypersensitivity reactions should be treated per DFCI institutional guidelines (See Appendix A). If hypersensitivity occurs, an additional 25 mg of diphenhydramine IV should be given. Participants with hypersensitivity should also receive methylprednisolone 50 mg IVB and ranitidine 50 mg IVB. Participant with bronchospasm should be

treated with supplemental oxygen and nebulizers as needed. Infusion may resume after symptoms resolve at 50% of the rate infusing at the time of the event.

Participants with life threatening infusional reactions including cardiac arrhythmia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, cardiogenic shock, or anaphylactoid events should not be re-challenged and should be removed from study. No dose reductions will be made for infusional reactions. Section 6.4 outlines the protocol for dose delays in the setting of an infusion reaction to either agent.

6.3.2 Hematologic toxicities

The only hematologic parameter that must be met on each treatment day is an ANC $\geq$1000. Hematologic toxicities should be managed by standard use of transfusions and growth factors. In particular, white blood cell growth factor use (e.g., neupogen) is acceptable on this study. A dose delay of up to 1 week for recovery of neutropenia to an ANC $\geq$1000 is acceptable on this study.

6.3.3 Non-hematologic toxicities

In the case of asymptomatic laboratory abnormalities (e.g., LFT abnormalities), no intervention is required. Symptomatic abnormalities should be managed using standard clinical guidelines.

6.4 Dose Modifications/Delays

No dose reductions will be made. Participants unable to tolerate the specified dose of either Imprime PGG or rituximab will be removed from study. Imprime PGG and/or rituximab infusion should be interrupted for severe reactions, e.g., rapid tumor lysis. Treatment of infusion-related symptoms with diphenhydramine and acetaminophen is recommended. Additional treatment with bronchodilators or IV saline may be indicated. Epinephrine, antihistamines, and corticosteroids should be available for immediate use in the event of a hypersensitivity reaction to rituximab (e.g., anaphylaxis). In most cases, the infusion can be resumed at a 50% reduction in rate from the last known rate (e.g., from 100mg/hr to 50mg/hr) when symptoms and laboratory abnormalities have completely resolved. Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias. Subjects who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions. Whether to discontinue the infusion and when to restart the infusion of either agent following a non-life threatening infusion reaction is up to the discretion of the treating physician. In the event of a non-life threatening infusion reaction to Imprime PGG, patients must be rechallenged within one week, and rituximab may be delayed by up to 24 hours following the successful infusion of Imprime PGG. In the event of a non-life threatening infusion

reaction to rituximab, dosing of Imprime PGG and rituximab may be delayed by up to one week.

A temporary delay of all study dosing may occur if the subject's health precludes study drug administration (i.e., subject is experiencing an adverse event that requires hospitalization; ANC <750.) Subjects that require permanent discontinuation of rituximab, or fail to receive any rituximab for ≥7 consecutive days from the missed dose, or ≥ 14 consecutive days in total, should discontinue all study drug administration.

Participants will be removed from study when any of the criteria listed in Section 5.4 apply. The reason for study removal and the date the participant was removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with the participant.

7. DRUG FORMULATION AND ADMINISTRATION

7.1 Imprime PGG

7.1.1 Drug product formulation

Imprime PGG is supplied in 20-mL and 50-mL Type I clear borosilicate glass vials. Each vial contains PGG Beta Glucan at a nominal concentration of 1 mg/mL in a citrate-buffered saline solution (pH 5.0-7.5). Vials are filled to a target volume of 21.2 mL to ensure a deliverable amount of 20 mL per vial.

The active ingredient of the drug product is the beta glucan polymer, PGG Beta Glucan. The inactive ingredients of the drug product are sodium citrate and sodium chloride.

7.1.2 Storage

Imprime PGG should be stored between 15°C and 27°C.

7.1.3 Compatibility

Imprime PGG, is a sterile solution for IV. infusion. The appropriate dose based on body weight will be diluted by the site pharmacist in 0.9% Sodium Chloride so that the total volume of Imprime PGG and 0.9% Sodium Chloride equals the volumes specified below for strata of body weight in Section 7.1.6 Preparation and Route of Administration.

7.1.4 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

7.1.5 Availability

Imprime PGG is an investigational agent and will be supplied free-of-charge from Biothera.

7.1.6 Preparation and Route of Administration

Imprime PGG, is a sterile solution for IV infusion. The appropriate dose based on body weight will be diluted by the site pharmacist in 0.9% Sodium Chloride so that the total volume of Imprime PGG and 0.9% Sodium Chloride equals the volumes specified below for strata of body weight.

Subject Weight in Kilograms	Imprime PGG Dose (mg/kg)	Total Infusion Volume (mLs)	Total Infusion Time (hours)	Rate of Infusion (mL/min)
≤75 kgs	4 mg/kg	500 mLs	2 hours (+/- 10 min)	4.2 mLs/min
>75 to ≤150kgs	4 mg/kg	750 mLs	3 hours (+/- 10 min)	4.2 mLs/min
>150 kgs	4 mg/kg	1000 mLs	4 hours (+/- 10 min)	4.2 mLs/min

The final volume will be administered by IV infusion at a rate of 4.2mL/min (total time to be determined by the total infusion volume) with a +/- 10 minute window. An infusion pump will be used to assure accurate and consistent dosing. Imprime PGG is supplied in 20-mL or 50-mL vials containing 20mg or 50mg, respectively, of Imprime PGG (1 mg/mL). The total storage time of Imprime PGG diluted in the IV bags, inclusive of administration, cannot exceed 8 hours at room temperature or 24 hours at 2-8^{0}C.

7.1.7 Ordering

Imprime PGG for this study will be ordered from Biothera. Ordering can be done with a templated reorder form from Biothera, sent to Email: kbreuer@biothera.com or Fax: (651) 675-0400; Attn: Kelly Breuer.

7.1.8 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form. (See the CTEP website at http://ctep.cancer.gov/protocolDevelopment for the "Policy and Guidelines for

Accountability and Storage of Investigational Agents" or to obtain a copy of the drug accountability form.)

7.1.9 Destruction and Return

At the end of the study, unused supplies of [agent] should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

7.2 Rituximab

7.2.1 Drug Product Information

Rituximab is commercially available and will be provided as an infusion prepared by a site pharmacist. Please refer to the FDA-approved package insert for rituximab for product information.

7.2.2 Storage

Intact vials should be stored under refrigeration. Dilute solutions for infusion (1-4 mg/mL) are stable for 24 hours under refrigeration, and for an additional 24 hours at room temperature.

7.2.3 Availability

Rituximab is commercially available in 10 mL and 50 mL single-use vials containing 100 or 500 mg of rituximab solution, respectively, at a concentration of 10 mg/mL. Please refer to the agent's package insert for additional information.

7.2.4 Preparation and Route of Administration

The desired dose of rituximab should be diluted in 0.9% NaCl or D5W to a final concentration of 1-4 mg/mL. Mix by inverting the bag gently. Rituximab will be administered by IV infusion. Participants must be premedicated with hydrocortisone 100 mg IV, acetaminophen 650 mg, and diphenhydramine 25 mg PO, or their equivalents, prior to each dose. No specific prehydration is required.

7.2.5 Destruction and Return

At the end of the study, unused supplies of [agent] should be destroyed according to institutional policies. Destruction will be documented and drug accountability for rituximab will not be documented since this drug will be charged to patients insurance.

8. CORRELATIVE/SPECIAL STUDIES

Participants will have one pretreatment peripheral blood sample collected within one week of starting treatment, 4 post-treatment peripheral blood samples collected approximately one hour following the completion of both infusions (one on each infusion day), and 3 pre-treatment blood samples collected at the time of routine lab collection on days 8, 15, and 22. Fresh whole blood samples will be processed in the laboratory of Dr. Jerome Ritz and Biothera will provide the funding necessary to complete this work. Using reagants and a flow cytometric protocol provided by Biothera, we will quantify the percentage of Imprime PGG-bound and unbound neutrophils following each weekly treatment. Preclinical evaluation of healthy subjects, and cancer patients participating in Imprime PGG studies, demonstrate that based on the ability of Imprime PGG to bind to neutrophils and monocytes, subjects can be categorized into (i) binders- in which Imprime PGG bound to 5% or more of the total neutrophil population and (ii) low or non-binders- in which Imprime PGG bound to less than 5% of total neutrophils. We will correlate the percentage of Imprime PGG bound neutrophils with treatment response. Flow cytometric analysis of pre- and post-treatment changes in neutrophil activation marker expression using antibodies against CD11a, CD11b, CD63, CD87 and CBRM1/5 will also be performed.[25] This flow cytometric profile was used to quantify the proportion of activated neutrophils in whole blood before and after immunotherapy with an anti-tumor monoclonal antibody and GM-CSF in patients with neuroblastoma. All five markers of neutrophil activation were upregulated following treatment, and the degree to which they were upregulated correlated with outcome as reflected by progression-free survival. We will use this profile to quantify the proportion of activated neutrophils pre- and post-therapy on our study and correlate this with treatment response.

Finally, more recently it has been appreciated that one factor that distinguishes Imprime PGG “binders” from “non-binders” is whether a patients has a high level of endogenous anti-beta glucan antibodies. Preliminary clinical data indicate superior clinical response to beta-glucan therapy in biomarker positive (i.e. high binder, high anti-beta glucan level) patients (internal Biothera data). To investigate this further, Biothera has developed an in-house ELISA assay for the detection and quantification of IgG and IgM antibodies against beta glucan. Pre- and post-treatment serum samples obtained at the timepoints outlined above will be shipped to Biothera for analysis of anti-beta glucan antibody levels. Exploratory analysis of baseline beta glucan levels and binding capacity, and changes during therapy will be assessed and correlated with clinical outcomes.

In the event that either funding and/or blood/serum samples are limited, these studies will be prioritized as follows: 1) flow cytometric analysis for quantification of Imprime PGG bound neutrophils 2) ELISA assay for detection and quantification of anti-beta glucan antibodies and 3) flow cytometric analysis for the quantification of activated neutrophils.

9. STUDY CALENDAR

Baseline evaluations are to be conducted within 2 weeks prior to the start of protocol therapy. Scans must be done $\leq$ 6 weeks prior to the start of therapy. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

All assessments must be performed prior to administration of any study medication. All study assessments and medications should be administered within $\pm$ 3 days of the protocol-specified date, unless otherwise noted.

The follow-up schedule will be at the discretion of the treating clinician, as long as the required study visits (see Table below) are met.

Study Calendar

Study Assessment	**Baseline**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Post Treatment** [6]	**Follow-up visits (6mo and 1 year +/- 4 weeks)** [4]
Study Days	-14 to -1	1	8	15	22	92	
Study Drug: *Imprime PGG*		x	x	x	x		
Rituximab		x	x	x	x		
Medical History, Medication Review, Physical Exam, Weight	x	x	x	x	x	x	X[7]
Toxicity Assessment		x	x	x	x	x	x

ECOG Performance Status[1]	x	x	x	x	x	x	x
ECG	x						
CBC, Differential, Blood Chemistries[2]	x	x	x	x	x	x	x
Hep B/C serology, pregnancy testing[8]	x						
Tumor restaging[3]	x[4]					x[4]	x[4]
Peripheral blood collection for neutrophil studies[5]	x[5]	x[5]	x[5]	x[5]	x[5]		

[1]Should be obtained at baseline and at the start of every cycle; see Appendix B for additional information.

[2]Blood chemistries to include complete metabolic panel, LDH. Labs on C1D1 do not have to re-meet eligibility other than the ANC must be >1000 as required for all treatment days.

[3]Tumor restaging will be with CT scans of the chest, abdomen, and pelvis.

[4]Tumor restaging should be performed within the 6 weeks prior to 1st administration of treatment, and 10 weeks +/- 3 days after week 4 of treatment. Surveillance during the one year +/- 4 weeks follow-up will include CT scans of the chest, abdomen and pelvis every 6 months from the end of treatment.

[5] One pretreatment peripheral blood sample(s) will be collected for correlative studies (Section 8) within the 1 week prior to the first administration of treatment. Sampling will also be collected 1 hour following the end of both infusions and on each infusion day and pre-infusion with routine labs on days 8, 15, and 22 for all of the studies outlined in section 8.

[6]End of study visit to be performed 10 weeks +/- 3 days after the end of treatment with tumor restaging performed at this time.

[7]At follow up visits, only medication review is required.

[8]Hepatitis B/C serology should include Hep B core, Hep B surface anti-body and antigen, Hep C anti-body, Hep B and Hep C viral loads.

9.1 Required data

The following must be obtained within 14 days prior to the 1st day of treatment:

- Medical history, medication review, physical exam, height and weight, ECOG performance status (see Appendix B)
- CBC with manual differential, blood chemistries including complete metabolic panel, LDH, quantitative immunoglobulins and β2-microglobulin
- Hepatitis B and C serologies
- Serum or urine β-HCG for females of childbearing potential
- Electrocardiogram
- Tumor restaging (within 6 weeks). This will consist of CT scans of the chest, abdomen, and pelvis.
- Peripheral blood sample for neutrophil studies (within 1 week prior to the 1st of treatment; Section 8)

9.2 Required data during study

The following must be obtained during the study:

- Medical history, medication review, physical exam, and weight, ECOG performance status (see Appendix B)
- Toxicity assessment
- CBC with manual differential, blood chemistries including complete metabolic panel and LDH – day 1 of week 1-4
- Peripheral blood sample for neutrophil studies 1 hour after treatment on day 1 of weeks 1-4 of treatment and serum for evaluation of anti-beta glucan antibody levels

9.3 Required at post-treatment visit (10 weeks +/- 3 days from end of treatment)

The following must be obtained at post-treatment visit (10 weeks+/- 3 days from the last day of treatment).

- Medical history, medication review, physical exam, height and weight, ECOG performance status (see Appendix B)
- Toxicity assessment
- CBC with manual differential, blood chemistries including complete metabolic panel and LDH
- Tumor restaging, which will consist of CT scans of the chest, abdomen, and pelvis
- Surveillance during the six month and 1 year (+/- 4 weeks) follow-up period (from the end of treatment) will include physician visits with routine laboratory evaluation, physical exam, and CT scans of the chest, abdomen, and pelvis every 6 months. Additional physician visits with routine laboratory assessment and physical exam will be left up to the discretion of the treating physician.

10. MEASUREMENT OF EFFECT

Response criteria will follow the International Harmonization Project for Lymphoma criteria[26] (see Appendix C) using CT scans of the chest, abdomen, and pelvis.

11. ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Definitions

11.1.1 Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

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

11.1.2 Serious adverse event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.

- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

11.1.3 Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

11.1.3.1 Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected

when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Refer to Section 6.1 for a listing of expected adverse events associated with the study agent(s).

11.1.3.2 Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

11.1.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment.

11.2 Procedures for AE and SAE Recording and Reporting

Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms.

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

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

11.3 Reporting Requirements

The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to the study sponsor and/or others as described below.

11.4 Reporting to the Study Sponsor

11.4.2 Serious Adverse Event Reporting

All serious adverse events that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the DF/HCC Overall Principal Investigator on the local institutional SAE form. This includes events meeting the criteria outlined in Section 11.1.2, as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) Events – Only events that are unexpected and possibly, probably or definitely related/associated with the intervention.

- All Grade 4 (life-threatening or disabling) Events – Unless expected AND specifically listed in the protocol as not requiring reporting.

- All Grade 5 (fatal) Events – When the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Note: If the participant is in long term follow up, report the death at the time of continuing review.

Participating investigators must report each serious adverse event to the DF/HCC Overall Principal Investigator within 24 hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Caron Jacobson, MD

617 582 7591 (phone)
cajacobson@partners.org
617 632 5168 (fax)

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

To ensure patient safety, every SAE, regardless of suspected causality, occurring in the following circumstances must be reported to Biothera within 24 hours of learning of its occurrence.

- After the patient has provided informed consent and until the patient has stopped study treatment/participation
- After protocol-specified procedures begin (e.g. placebo run-in, washout period, double-blind treatment) and until at least 28 days after the patient has stopped study treatment
- After the start of any period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication) and until at least 28 days after the patient has stopped study treatment

Any SAEs experienced after this 28-day period should only be reported to Biothera if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information.

An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Med Watch 3500A Form. The investigator must assess and record the relationship of each SAE to each specific study drug, complete the Med Watch Form in English, and fax the completed form within 24 hours to Caron Jacobson at 617-632-3470.

All SAEs will have to be submitted to Apcer to be included in our safety database. SAEs need to be transmitted to APCER via email to **safety.biothera@apcerpharma.com** or via fax to **+1 (609) 531-0154**

11.4.3 Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the DF/HCC Overall Principal Investigator on the toxicity Case Report Forms.

11.5 Reporting to the Institutional Review Board (IRB)

Investigative sites within DF/HCC will report all serious adverse events directly to the DFCI Office for Human Research Studies (OHRS).

A copy of the submitted institutional SAE form should be forwarded to:

Caron Jacobson, MD
617 582 7591 (phone)
cajacobson@partners.org
617 632 5168 (fax)

11.6 Reporting to the Food and Drug Administration (FDA)

The DF/HCC Overall Principal Investigator, as holder of the IND, will be responsible for all communication with the FDA. The DF/HCC Overall Principal Investigator will report to the FDA, regardless of the site of occurrence, any adverse event that is serious, unexpected and reasonably related (i.e., possible, probable, definite) to the study treatment.

Unexpected fatal or life-threatening experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 7 calendar days after initial receipt of the information.

All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

Events will be reported to the FDA by telephone (1-800-FDA-1088) or by fax (1-800-FDA-0178) using Form FDA 3500A (Mandatory Reporting Form for investigational agents). Forms are available at http://www.fda.gov/medwatch/getforms.htm.

11.7 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

11.8 Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 28 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the DF/HCC Overall Principal Investigator and their respective IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

12. DATA AND SAFETY MONITORING

12.1 Data Reporting

12.1.1 Method

The QACT will collect, manage, and monitor data for this study.

12.1.2 Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the QACT is as follows:

12. Form	13. Submission Timeline
Eligibility Checklist	Complete prior to registration with QACT
On Study Form	Within 14 days of registration
Baseline Assessment Form	Within 14 days of registration
Treatment Form	Within 10 days of the last day of the cycle
Adverse Event Report Form	Within 10 days of the last day of the cycle
Response Assessment Form	Within 10 days of the completion of the cycle required for response evaluation
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

12.2 Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMC will meet quarterly and/or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days for Phase 1 or 2 protocols; for gene transfer protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the DF/HCC Overall Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

13. REGULATORY CONSIDERATIONS

13.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The DF/HCC Overall Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

13.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining

the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

13.3 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
    - Title 21 Part 50 – Protection of Human Subjects www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
    - Title 21 Part 54 – Financial Disclosure by Clinical Investigators www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
    - Title 21 Part 56 – Institutional Review Boards www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
    - Title 21 Part 312 – Investigational New Drug Application www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html
- State laws
- DF/HCC research policies and procedures http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

13.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records,

recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

13.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

14. STATISTICAL CONSIDERATIONS

14.1 Study Design/Endpoints

This is an open-label, single-arm, phase II clinical trial of Imprime PGG in combination with rituximab in patients with relapsed/refractory indolent B cell non-Hodgkin lymphomas. The primary endpoint is efficacy as measured by overall response rate. Secondary endpoints will include response duration, progression free survival at 1 year, , and rate of grade III and IV adverse events or discontinuation due to toxicity. We will estimate the proportion of patients alive without progression at 12 months after study entry. All patients must be followed for a minimum 12 months and must have scans at 6 and 12 months. No patients will be censored for this assessment. The one-year rate of being alive without progression will be estimated as a binomial proportion, and an exact binomial 90% confidence interval will be provided.

Patients will be accrued in a single stage design, with a goal accrual of 25 patients. Assuming a 30% response rate with rituximab alone, if the true but unknown rate of CR or PR is 50% with the addition of Imprime PGG, the probability of observing 11 or more patients with a response is 0.79. Therefore a study with 25 patients, in which an observed response rate of 11/25 (44%) would be considered worthy of further consideration.

We propose correlative studies quantifying Imprime PGG-bound and activated neutrophils, comparing both to the number and activation of unbound neutrophils from the same patient. We can examine the association between response to therapy (CR/PR vs. SD/Progression as best response).

14.2 Early Stopping- Toxicity

If 3 or more participants experience a grade 4 non-hematologic toxicity, the study will be suspended and the data will be reviewed by the data monitoring committee.

Additionally, if at any point in the study any participant experiences a grade 5 toxicity, the study will be suspended and the toxicity data including attribution will be carefully reviewed. If these toxicity events are determined to be at least possibly related then the study will close.

Dr. Caron Jacobson reserves the right to discontinue the study at any time.

14.3 Sample Size/Accrual Rate

The planned sample size is 25 patients. Based on historical rates, accrual will be complete in 24 months. The total anticipated duration of the study, after the first patient is enrolled, will be approximately 36 months.

14.4 Reporting and Exclusions

The primary analysis will be performed on all evaluable patients.

14.5 Disclosures and Confidentiality

The investigator requests strict confidentiality from his/her staff and the IRB. Study documents provided by Biothera (protocols, investigators' brochures, case report forms, and other material) will be stored appropriately to ensure their confidentiality. The information provided by Biothera to the investigator may not be disclosed to others without direct written authorization from Biothera, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

15. PUBLICATION PLAN

The results of this study will be submitted for presentation at national meetings and for publication in appropriate journals within 24 months of the completion of the study. The first analysis and submission will be conducted when all patients have reached the End of Study visit (or been taken off study).

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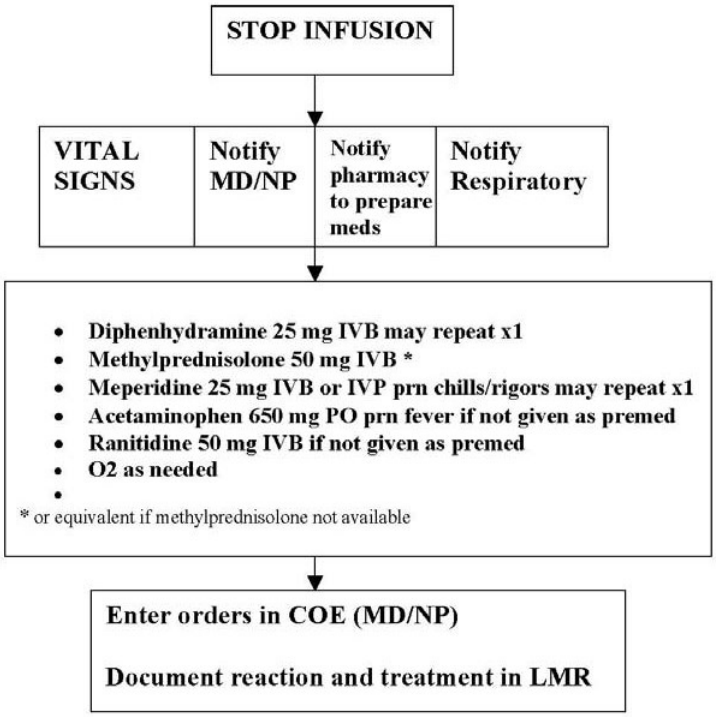
17. APPENDICES

17.1 APPENDIX A: HYPERSENSITIVITY ALGORITHM

CHEMOTHERAPY-INDUCED REACTION TREATMENT ALGORITHM



CHEMOTHERAPY AGENTS THAT MAY CAUSE HYPERSENSITIVITY REACTIONS		
TAXANES Paclitaxel (Taxol ®) Docetaxel (Taxotere®) **Most Common Symptoms** Flushing Dyspnea Back pain Urticaria Hypotension Rash	**MAB'S** Rituximab (Rituxan®) Alemtuzumab(Campath®) Trastuzumab (Herceptin ®) Gemtuzumab (Mylotarg®) Bevacuzimab (Avastin®) Cetuximab (Erbitux®) **Most Common Symptoms** Fever Chills Rigors Hypotension Dyspnea pruritis Rash Nausea/vomiting Arthralgias/myalgias	**OTHER** Carboplatin Doxil® Aspariginase Etoposide Bleomycin Ontak®

17.2 APPENDIX B: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Description	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. 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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

17.3 APPENDIX C: RESPONSE CRITERIA FOR LYMPHOMA

(adapted from the International Harmonization Project for Lymphoma Criteria[26])

Response	Definition	Nodal masses	Spleen/liver	Bone Marrow
Complete Response (CR)	Disappearance of all evidence of disease	(a) For FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) For variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
Partial Response (PR)	Regression of measurable disease and no new sites	≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
Stable Disease (SD)	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed or Progressive Disease (PD)	Any new lesion or increase by ≥50% of previously involved sites from nadir	Appearance of a new lesion(s)>1.5cm in any axis, ≥50% increase in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node >1cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	>50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: PET, positron emission tomography; CT, computed tomography; SPD, sum of the product of the diameters.