December 20, 2022

PROTOCOL AMENDMENT #1

LCCC1950: RITUXIMAB FOR MULTICENTRIC CASTLEMAN DISEASE IN MALAWI, A SINGLE-ARM PHASE II SAFETY/EFFICACY TRIAL

AMENDMENT INCORPORATES (check all that apply):

X Editorial, administrative changes
X Scientific changes (IRB approval)
X Therapy changes (IRB approval)
X Eligibility Changes (IRB approval)

The primary purpose of this protocol amendment is to update the secondary and exploratory objectives, clarify the timing of screening evaluations and assessments, amend the eligibility criteria, and clarify the determination of subject risk classification based on anemia. Specifically, the protocol now lists several secondary objectives separately for clarity. Additionally, an exploratory objective has been added to evaluate predictors of relapse or refractory disease with rituximab-based treatment. Secondary and exploratory endpoints were also added or reordered for completeness and clarity and to accompany the new exploratory objective. Furthermore, the protocol was reviewed and edited for consistency while also updating key personnel.

Editorial/Administrative

1. Mechanical edits made where appropriate.
2. Co-investigator list removed.
3. Biostatistician contact information added.
4. List of abbreviations updated.
5. Section 11.3 Honest broker language updated.
6. Appendix E (ECOG Performance Status) added.

Scientific

1. In Section 2.2:
    a. Secondary objectives for overall survival, event-free survival, and Kaposi sarcoma viral load (2.2.2, 2.2.3, and 2.2.11) were listed separately for clarity.
    b. Secondary objectives 2.2.4 and 2.2.5 were clarified by including the time at which clinical response rates and radiologic response rates, respectively, will be assessed.
2. In Section 2.3: An additional exploratory objective to evaluate for predictors of relapse or refractory disease with rituximab-based treatment was added (2.3.3).
3. Section 3.2: Secondary endpoints added or amended to ensure each secondary objective had a corresponding description of the endpoint (3.2.1 – 3.2.5, and 3.2.9. This included reordering and/or listing separately endpoints already present in the section.

4. Section 3.3: Exploratory endpoints added for all exploratory objectives (3.3.1-3.3.3).
5. Study Schema (Section 5.1) footnotes updated to clarify risk classification.
6. Statistical considerations (Section 10.1) updated to clarify risk classification.

Therapeutic

1. Prohibited medications/treatments (Section 5.5) updated to prohibit systemic therapies for other active malignancies or active infections.
2. Quality of Life assessments extended to 24 months after the end of treatment.
3. The timing of correlative testing blood sample draws was clarified in section 7.4 and the T&E table (Section 8.0).
4. T&E table updates:
    a. Adjustments were made to ensure all timepoints are calculated from the start of treatment.
    b. Follow-up visit specified at 12 weeks for consistency with objectives and endpoints.
    c. Long term follow up column added for clarity.
    d. Correlative blood draws combined into one row for clarity.
    e. Rows for tumor biopsy, survival, and treatments added for completeness.
    f. Footnotes updated to reflect other updates made throughout the protocol and to capture additional information (see #6 below).
5. CD4 count and HIV viral load long term follow up timepoints updated to 12 and 24 months for subjects that are HIV positive.
6. Sections 8.2 through 8.4.2 removed and where appropriate information moved to T&E.

Eligibility

1. Section 4.0 was clarified to specify that the allowable screening evaluation window prior to enrollment is 21 days.
2. Criterion 4.1.7 was amended to clarify qualifying anemia.
3. Criterion 4.1.9 was amended to extend the time that breastfeeding is prohibited after treatment.
4. Criterion 4.1.10 was amended to extend the time that birth control should be taken by females after treatment.
5. Criterion 4.1.11 was amended to extend the time that birth control should be taken by males after treatment.
6. Criterion 4.1.12 was added to address the conditions of corticosteroid use
7. Criterion 4.2.7 was amended to clarify the conditions of corticosteroid use and the requirement of steroid washout prior to enrollment.
8. Criterion 4.2.11 was added to ensure pregnant and/or breastfeeding women are not enrolled.

THE ATTACHED VERSION December 20, 2021 INCORPORATES THE ABOVE REVISIONS

ATTACH TO THE FRONT OF EVERY COPY OF PROTOCOL

LCCC 1950: RITUXIMAB FOR MULTICENTRIC CASTLEMAN DISEASE IN MALAWI, A SINGLE-ARM PHASE II SAFETY/EFFICACY TRIAL

Short Title: Safety and efficacy of rituximab for treatment of multicentric Castleman disease in Malawi

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LINEBERGER COMPREHENSIVE CANCER CENTER
CLINICAL ONCOLOGY RESEARCH PROGRAM
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

December 20, 2022

LCCC 1950: RITUXIMAB FOR MULTICENTRIC CASTLEMAN DISEASE IN MALAWI, A SINGLE-ARM PHASE II SAFETY/EFFICACY TRIAL

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and International Conference on Harmonization guidelines.

Principal Investigator Name: Matthew Painschab, MD

Principle Investigator Signature: _____

Date:_____

Version date/Version #: 20 December 2022/v2.0

LIST OF ABBREVIATIONS

ACTG	AIDS Clinical Trials Group
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMC	AIDS Malignancy Consortium
ANC	Absolute neutrophil count
ART	Antiretroviral therapy
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
BID	*Bis in die* (twice daily)
BSA	Body surface area
CBC	Complete blood count
CD	Cluster of differentiation
CHOP	Cyclophosphamide, vincristine, doxorubicin, and prednisone
CMP	Complete metabolic panel
CPO	Clinical Protocol Office
Cr	Creatinine
CR	Complete response
CRP	C-reactive protein
CT	Computer tomography
CTCAE	Common terminology criteria for adverse events
DALY	Disability-adjusted life year
DLBCL	Diffuse large B cell lymphoma
DSMB	Data safety monitoring board
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EFS	Event-free survival
EORTC QLQ-C30	European Organization for Research and Training in Cancer Quality of Life Questionnaire in cancer patients
GCP	Good clinical practices
G-CSF	Granulocyte colony-stimulating factor
HBs-Ag	Hepatitis B surface antigen
HBc	Hepatitis B core
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIC	High-income countries
HIV	Human immunodeficiency virus
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL	Interleukin
INF	Interferon
IRB	Institutional review board
IV	Intravenous
KS	Kaposi sarcoma
KSHV	Kaposi sarcoma herpesvirus
LANA	Latency-associated nuclear antigen
LCCC	Lineberger Comprehensive Cancer Center
LDH	Lactate dehydrogenase
LN	Lymph node
LTFU	Lost to follow-up

MCD	Multicentric Castleman disease
MCD-SS	Multicentric Castleman Disease-Symptom Score
MRI	Magnetic resonance Imaging
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NHL	Non-Hodgkin lymphoma
ORR	Overall response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression free survival
PI	Principal investigator
PO	By mouth (per os)
PR	Partial response
PRC	Protocol review committee
PRO	Patient reported outcome
PROPr	Patient reported outcomes preference
QD	*Quaque die* (once daily)
RA	Rheumatoid arthritis
RBC	Red blood cell
RES	Reticuloendothelial system
SAE	Serious adverse event
SAR	Suspected adverse reaction
s.c.	subcutaneous
SD	Stable disease
SOC	Standard of care
SOI	Start of infusion
SOP	Standard operating procedure
SPD	Sum of the product of diameters
SSA	Sub-Saharan Africa
TLS	Tumor lysis syndrome
TNFα	Tumor necrosis factor α
TPF	Tissue Procurement Facility
ULN	Upper limit of normal
UNC	University of North Carolina
WHO	World Health Organization

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1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

In sub-Saharan Africa (SSA), Kaposi sarcoma herpesvirus (KSHV)-related cancers account for 10-35% of malignancies[1-3] and >10% of cancer-related deaths.[3] Multicentric Castleman disease (MCD) is a life-threatening lymphoproliferative disorder characterized by systemic inflammation and lymphadenopathy. MCD is strongly associated with KSHV and human immunodeficiency virus (HIV). KSHV seroprevalence in SSA is >40%,[4,5] the highest of any region in the world; likewise, the prevalence of HIV is high.[6] Substantial knowledge gaps remain regarding treatment for MCD, including outcomes, safety, and cost-effectiveness, particularly in SSA.

MCD can be controlled with chemotherapy. When chemotherapy is discontinued, however, rapid relapses or development of non-Hodgkin lymphoma (NHL) occur with high mortality.[7,8] Long-term remission is achieved in most patients with rituximab, an anti-CD20 monoclonal antibody, as described in small clinical trials in high-income countries (HIC).[9-11] However, rituximab has not been evaluated for MCD in SSA, nor are there published safety data for rituximab from the region.

In this study, we aim to determine the safety and efficacy of first-line, risk-stratified rituximab-based MCD treatment in Malawi in a single-arm, phase II clinical trial. We will enroll 27 subjects with newly diagnosed or previously treated MCD (who have not previously received rituximab) requiring treatment (B symptoms or hemoglobin <10 g/dL).[12] Subjects will be treated with four weekly doses of rituximab. High-risk subjects (defined as patients with Eastern Cooperative Oncology Group (ECOG) performance status >2 or hemoglobin <8 g/dL)[9,10,13-16] will also receive etoposide chemotherapy.[9,11] Subjects will be followed for one year for toxicity and two years for survival. The primary outcome will be safety, defined as the frequency of ≥Grade 3 treatment-related Common Terminology Criteria for Adverse Events (AEs). Secondary outcomes will be event-free survival (death, progression, or development of NHL) and 1- and 2-year overall survival (OS). We also aim to compare the cost-effectiveness of first-line rituximab treatment for MCD in Malawi to chemotherapy (using our historical controls).

1.2 Multicentric Castleman Disease

MCD is a unique, life-threatening lymphoproliferative disorder characterized by systemic inflammation and lymphadenopathy that is strongly associated with KSHV and HIV. KSHV viral proteins, including a viral homolog of interleukin-6 (IL-6), are causally associated with the cytokine storm that is characteristic of MCD. HIV-infection is also a significant risk factor for MCD. In a large MCD cohort in France, 83% of MCD cases occurred in HIV-infected individuals.[17] MCD consists of two biologically-distinct subtypes: KSHV-associated and idiopathic. This proposal focuses on KSHV-associated MCD, the variant that is far more common in SSA.[18]

KSHV seroprevalence is >40% in SSA,[4,5,19] the highest of any region in the world (Figure 1). KSHV is usually transmitted through saliva with primary infection being asymptomatic. In some cases, KSHV is reactivated in a lytic state which can promote development of malignancies.[20] In Malawi, KSHV prevalence is 54% in adults and 74% in in HIV-infected adults.[21]

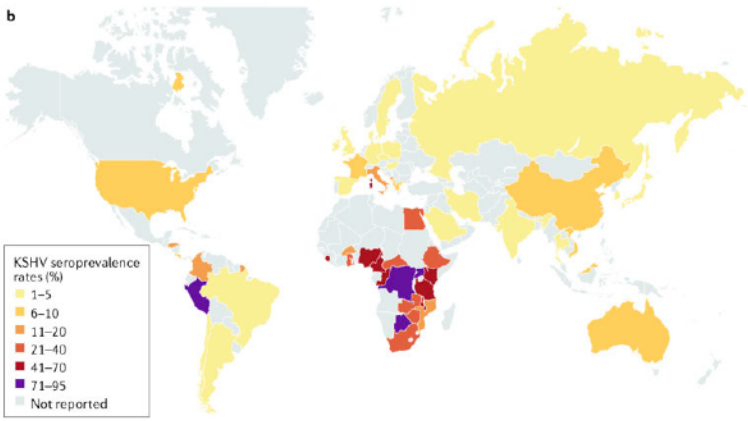

Figure 1. Seroprevalence of Kaposi sarcoma-associated herpesvirus. The prevalence in Sub-Saharan Africa generally, and Malawi specifically, are amongst the highest in the world.

The burden of HIV is likewise high in SSA, ranging from 3-20%.[6] The prevalence of HIV among adults in Malawi is 10%. The last decade has seen major strides in scale-up of anti-retroviral therapy (ART) in SSA, and it is now estimated that 67% of HIV-infected individuals in Malawi are on ART and 59% are virologically suppressed.[22]

Given the strong link to KSVH and HIV, and high prevalence of these viruses in SSA, MCD is likely underdiagnosed in SSA. The under-diagnosis of MCD is likely due to limited pathology services and limited awareness of MCD. However, regional centers have recently reported MCD diagnoses in SSA.[23,24] In our prospective cohort of lymphoproliferative disorders in Malawi, we have found that MCD constitutes 25/360 (7%) of all diagnoses and 25/189 (13%) of diagnoses among HIV-infected subjects.[8,25-27]

MCD burden in SSA will likely increase as ART access expands and life expectancy of HIV-infected subjects improves. MCD is associated with older age, higher CD4 count, and longer time on ART compared to KS,[9,17,28] NHL, or Hodgkin lymphoma.[26] Unlike KS, MCD is not controlled with ART alone.[29]

1.3 Rituximab

Rituximab, an anti-CD20 monoclonal antibody, induces long-term remissions and decreases the risk of NHL in small clinical trials for MCD in HIC.[9,10,16,30] Rituximab is a chimeric monoclonal antibody against CD20, a protein on the surface of B-cells which leads to B-cell depletion via complement- and antibody-mediated cytotoxicity. In two phase II trials of single-agent rituximab for MCD, the one-year event-free survival (EFS) was 92% and 71%.[10,15] After longer follow-up, five-year EFS was 78% and five-year OS was 88%.[31] Likewise, rituximab has been shown to significantly decrease the risk of NHL.[9,30,31]

Mortality often occurs in the first month of treatment with rituximab monotherapy, but this risk can be mitigated with concomitant chemotherapy. Death in the first four weeks occurs in 5% of MCD subjects treated with rituximab alone.[10,13-15,31] Risk factors for early death include ECOG performance status >2, hemophagocytic syndrome, and severe hemolytic anemia. The risk of death decreases with the addition of etoposide[9] or liposomal

doxorubicin.[16] Among subjects with MCD and pre-existing KS, the risk of KS exacerbation following rituximab monotherapy is 36-75%.[9,10] However, death from KS progression is rarely reported.

Rituximab has not been evaluated as first-line therapy for MCD in SSA. Given high opportunistic infection burden and limited supportive care infrastructure in SSA, region-specific safety and efficacy data for rituximab are needed. When added to combination chemotherapy for NHL in HIC, rituximab has been associated with an increase in treatment-related infections and mortality in HIV-infected subjects with a CD4 count <50 cells/µl, while benefiting those with higher CD4 counts.[32,33] Rituximab-based treatment +/- etoposide is likely to be less toxic than combination chemotherapy, but requires formal safety assessment. Previous studies of rituximab for MCD from HIC have found a rate of non-hematologic ≥Grade 3 AEs of around 20%.[9,10,15,16]

Even if rituximab is safe and effective, cost-effectiveness is a critical consideration. The World Health Organization (WHO) lists rituximab as a complementary medicine on the Essential Medicines list.[34] However, rituximab has not been approved for routine use by the Malawi Pharmacy, Medicines, and Poisons Board and is not routinely available in Malawi, like most public sector health systems in SSA. Cost-effectiveness analysis done in the appropriate, local context is essential to help policymakers allocate limited health resources.[35] To our knowledge, such analyses have not been published but are urgently needed. A demonstration of cost-effectiveness would support the prioritization of rituximab as a sound public health investment to treat this emerging HIV-associated comorbidity.

1.4 Etoposide

Etoposide is a topoisomerase II inhibitor that causes DNA double strand breaks and apoptosis of rapidly dividing cells, especially cancer cells. Etoposide is a common chemotherapeutic agent used in the treatment of a number of neoplasms, including lymphoma, KS, testicular cancer, Ewing sarcoma, and small cell lung cancer, among others. It is often given in combination with other chemotherapies but when given as monotherapy, etoposide is commonly associated with a number of AEs. Common AEs include alopecia, constipation, diarrhea, anemia, thrombocytopenia, leukopenia, and infusion reactions (either local site reactions or hypotension). Less common AEs include nausea, vomiting, rash, fever, and mouth sores. Rare but serious AEs include secondary malignancies, especially acute myeloid leukemia.

Etoposide pharmacokinetics

After intravenous (IV) injection, there is a biphasic pattern of clearance with a terminal $t_{1/2}$ of about 6–8 hours in patients with normal renal function. Approximately 40% of an administered dose is excreted intact in the urine. In patients with compromised renal function, dosage should be reduced in proportion to the reduction in creatinine clearance. In patients with advanced liver disease, increased toxicity may result from a low serum albumin (decreases drug binding) and elevated bilirubin (displaces etoposide from albumin); guidelines for dose reduction in this circumstance have not been defined.

Etoposide for Kaposi sarcoma in SSA

Etoposide has been used successfully as a single-agent treatment for KS, including in SSA.[36] However, other regimens have recently been shown to be superior to etoposide for KS treatment in SSA.[37] In the ACTG5264/AMC-067 trial of up-front versus as-needed etoposide for KS in SSA, the rate of ≥Grade 3 AEs was 50% in the up-front group versus 44% in the as-needed group. The majority of AEs were hematologic (47/65; 72%). There were no study-related deaths. That study was conducted with oral etoposide 50-100 mg daily days 1-7 of 14-day cycles but provides the best evidence for treatment in HIV-infected patients in SSA.

Etoposide for MCD

A more relevant study by Bower, et al[9] used a similar risk-adapted treatment for MCD and used IV etoposide at 100 mg/m^2. The study was not prospective and reported very limited data on AEs. No study-related deaths were identified in patients receiving etoposide. The rate of KS progression among those with baseline KS was 9/24 (38%) and did not differ between those who received etoposide + rituximab or rituximab alone. In this protocol, we similarly propose the use of IV etoposide at 100 mg/m^2.

1.5 Rationale for Clinical Study

MCD can be treated with chemotherapy. Many single-agent or combination chemotherapies have been utilized.[7,8,29,38] However, when chemotherapy is discontinued, rapid relapses or development of NHL often occur and are associated with high mortality.[7,8,38] Relapse after termination of chemotherapy is almost universal, and 1-year EFS is <20%.[7,8] 15-25% of subjects treated with chemotherapy develop NHL, a rate ~15x higher than HIV-infected individuals without MCD.[17,29,39] Survival for MCD subjects treated with traditional chemotherapy is also poor with 2-year OS of 42% in one study.[9]

Similarly, outcomes for MCD subjects treated with chemotherapy in Malawi are also poor. Of the 25 MCD patients in our cohort, 2 died before starting chemotherapy. Of 23 patients treated with chemotherapy, only 3 (13%) remain in remission after 5, 13, and 15 months respectively, similar to reports from HIC. First-line chemotherapy consisted of etoposide (17 patients) or cyclophosphamide, vincristine, and prednisone (six patients). Among 23 treated patients, 10 (43%) completed first-line chemotherapy without disease progression. The remaining 13 patients were switched to an alternative therapy because of poor response. Of the ten patients who completed first-line treatment, seven relapsed, after a median 29 days (range 14-147). One-year EFS was 10% (95% CI 2-26) **(Figure 2; Panel A).**

Rituximab has been successfully used by our group in Malawi as a compassionate-use intervention for patients with MCD refractory to chemotherapy, and in an ongoing clinical trial for diffuse large B cell lymphoma (DLBCL). As in most SSA public health systems, rituximab is not currently approved nor available in Malawi. With support from the University of North Carolina (UNC) Lineberger Comprehensive Cancer Center (LCCC), we are currently evaluating rituximab plus cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP) chemotherapy for DLBCL (NCT02660710), with 39 of 40 patients enrolled as of September 2019. To date, there have been 19 non-hematologic Grade 3 or worse AEs, and 1-year OS is 70%, which compares favorably to our previous work evaluating a historical cohort of patients treated with CHOP.[40]

Given high mortality, absent alternative therapies for such patients, and the availability of rituximab from this trial, we sought a compassionate use exemption from Malawi regulatory authorities to treat patients with MCD refractory to chemotherapy. As of January 2019, ten patients have received rituximab as salvage therapy for MCD. There was one Grade 3 hypersensitivity reaction but no other serious AEs. Early clinical outcomes have been encouraging. Among these 10 patients, 9 achieved remission and 7 remain in remission after a median 7 months (range 1-22). Only one patient who received rituximab died (MCD progression). One-year EFS after receiving rituximab for relapsed/refractory MCD was 78% (95% CI 37-94) **(Figure 2; Panel B)**.

1.6 Correlative Studies

Core biopsy specimens taken for routine diagnostic purposes will be used to make formalin-fixed paraffin embedded tissue blocks without any additional research biopsies. These specimens will allow for viral and genomic investigations. Gene expression

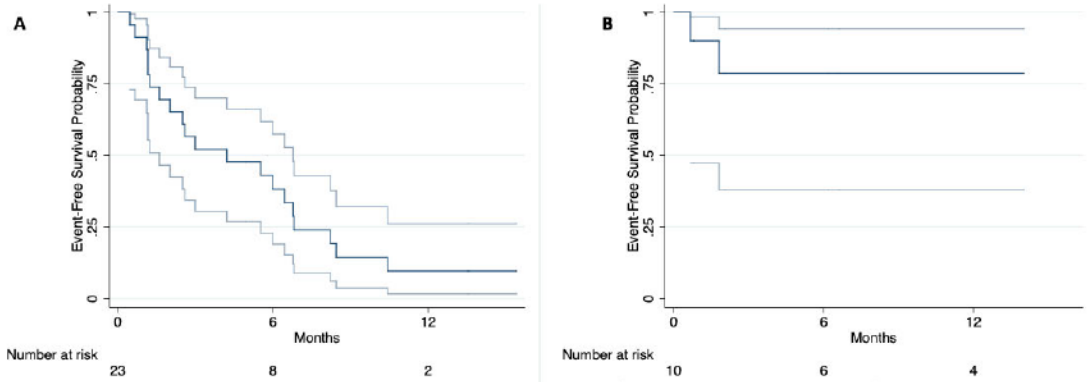

Figure 2. Event-free survival for MCD patients in Malawi treated with A) first-line chemotherapy and B) salvage rituximab.

profiling and next-generation sequencing analyses of histopathologically confirmed MCD specimens only will be conducted at the UNC Genome Analysis Facility and the UNC High-Throughput Sequencing Facility in North Carolina. Viral sequencing will be conducted by the UNC Vironomics Core. These studies will not influence treatment for enrolled patients in real time, as 'targeted' cancer therapies are not currently available in Malawi. Rather, we intend to examine the expression signature of MCD with respect to specific genes which are clearly established as influencing phenotypic clinical behavior of lymphomas, including genes involved in lymphocyte proliferation, activation, and differentiation, as has been previously extensively described in seminal papers in the field.[27,28]

Though extensive studies have been conducted in lymphoma, little is known about gene expression profiles in patients with MCD. These experiments are intended to identify mechanisms of, and risk factors for, development of MCD. Cryopreserved serum obtained at enrollment and prespecified follow-up visits only will be stored to allow basic correlative studies of predictive and prognostic biomarkers in a setting where advanced imaging for lymphoma response assessment after treatment is not available. These samples will be used for cytokine and immunologic profiling of patients with MCD. MCD is a polyclonal disease that develops in the setting of immune dysregulation but the immunologic mechanisms of this dysregulation have not been well established.

Furthermore, if certain cytokines are found to be of special significance in the pathophysiology of MCD in HIV-infected patients, cytokine-targeted therapies may be employed in future studies to treat this disease with decreased side effects, as has been completed previously in idiopathic MCD.[41] Such treatments are likely to be safer and more effective than conventional cytotoxic therapy in the Malawian context, where supportive care including hematopoietic growth factors and transfusion support are extremely limited, and where infectious burden is high.[4] Genomic data will be analyzed by study investigators including Malawian colleagues, with bioinformatics support additionally provided from UNC-Chapel Hill as necessary.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To determine the safety and treatment related mortality of a risk-adjusted treatment protocol for the treatment of MCD with rituximab with or without etoposide in Malawi.

2.2 Secondary Objectives

2.2.1 To prospectively characterize MCD presentation in Malawi.

2.2.2 To determine overall survival rate.

2.2.3 To determine event-free survival rate.

2.2.4 To describe the efficacy of the risk-adjusted treatment protocol as determined by clinical response rates at end of treatment and 12 weeks after start of treatment.

2.2.5 To describe radiologic response rates at end of treatment and 12 weeks after start of treatment.

2.2.6 To further characterize the safety by describing the frequency of all AEs with risk-adjusted treatment-protocol for MCD in Malawi.

2.2.7 To describe the rate of Kaposi sarcoma exacerbation, as defined by symptomatic or clinical (dermatologic or visceral organ) exacerbation of disease in patients receiving the risk-adjusted treatment protocol.

2.2.8 To describe the quality of life of patients with MCD before, during and after treatment with a rituximab-based, risk-adjusted treatment protocol, as assessed by the MCD symptom score and PROs.[42]

2.2.9 To describe the trends in hemoglobin, platelet count, C-reactive protein (CRP), and IL-6 before, during, and after a risk-adjusted, rituximab-based treatment protocol

for MCD in Malawi and describe the utility of these markers as a predictor of relapse.

2.2.10 To evaluate for predictors of relapse or refractory disease with a risk-adjusted, rituximab-based treatment protocol.

2.2.11 To evaluate changes in Kaposi sarcoma viral load as a result of treatment.

2.3 Exploratory Objectives

2.3.1 [redacted]

3.0 STUDY ENDPOINTS

3.1 Primary Endpoint

Safety will be classified and graded by non-hematologic Grade ≥3 AEs (CTCAE v5.0) and treatment-related mortality through twelve weeks from the start of rituximab with or without etoposide therapy.

3.2 Secondary Endpoints

3.2.1 At study entry, basic demographics and baseline laboratory values will be summarized using descriptive statistics (i.e., means, medians, and variability measures for continuous variable; rates and proportions for binary variables). Screening assessments to be completed within 21 days prior to study enrollment.

3.2.2 Overall survival will be assessed at 12 weeks, one year, and two years from the start of treatment.

3.2.3 Event-free survival will be defined as the rate of refractory disease, relapse (same definition of active disease as in the inclusion criteria in section 4.1), non-Hodgkin lymphoma development or death and will be assessed at 12 weeks, one year, and two years from the start of treatment.

3.2.4 Clinical response rate at end of treatment and 12 weeks from treatment initiation (clinical response defined as resolution of presenting signs/symptoms that defined

the Multicentric Castleman disease (MCD) attack) without relapse at 12 weeks. MCD attack/flare is defined in Section 4.1.1.

3.2.5 Radiologic response rate is the percentage of patients without relapse at end of treatment and 12 weeks from treatment initiation. Chest radiography and abdominal sonography will be used for staging. Per Revised response criteria for gross lymphadenopathy, response will be evaluated via complete survey of lymph nodes with measurements and physical assessment of other palpable masses with measurements.

Response criteria for lymph node response will be as follows: Complete response (CR)- disappearance of all evident disease; Partial response (PR)-at least 50% decrease in target lesions with no increase in non-target lesions, Stable disease (SD)- Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD); PD- appearance of a new lesion or at least a 50% increase in lesion size.

3.2.6 Additional safety assessment will be graded by CTCAE v 5.0 through 12 weeks from the start of therapy.

3.2.7 Kaposi sarcoma exacerbation will be defined as new symptoms attributed to KS or clinically evident exacerbation of dermatologic or visceral disease. All disease flares will be biopsy confirmed whenever possible.

3.2.8 Quality of life will be assessed by the MCD symptom score, a patient-reported outcomes questionnaire, and PROMIS Global 10, at baseline (week 1), 15 days (week 3), end of treatment (week 5), 12 weeks, 6 months, and 24 months after treatment, and at the time of any relapse.

3.2.9 Hemoglobin (grams per deciliter (g/dL)), platelet count (microliters (µl)), and C-reactive protein (CRP; milligrams per milliliter (mg/mL)) will be measured at baseline, day 15, and end-of-treatment.

3.2.10 Change in Kaposi sarcoma herpesvirus viral load will be measured in copies per milliliter at baseline, day 15, and end of treatment.

3.3 Exploratory Endpoints

3.3.1 [redacted]

3.3.2 [redacted]

3.3.3 [redacted]

[redacted]

4.0 SUBJECT ELIGIBILITY

In order to participate in this study a subject must meet ALL of the eligibility criteria outlined below. All study screening evaluations must be completed within 21 days of subject enrollment.

4.1 Inclusion Criteria

4.1.1 Newly diagnosed or previously treated subjects with KSHV-associated MCD that is pathologically confirmed by characteristic histologic features and latency-associated nuclear antigen (LANA) positivity by IHC.

4.1.2 Age ≥18 at time of consent.

4.1.3 Can provide informed consent.

4.1.4 HIV-infected or HIV-uninfected.

4.1.5 If HIV-infected, must be on or willing to start antiretroviral therapy including lamivudine or tenofovir.

4.1.6 Willing to comply with study visits.

4.1.7 MCD treatment indicated based on the presence of a symptomatic MCD flare, defined as the presence of each of the following three criteria:

1. Fever (subjective or objective)
2. Lymphadenopathy or hepatosplenomegaly
3. At least one of the following signs or symptoms attributable to MCD by the local study investigator:
    - Weight loss >5%
    - Malaise
    - Anemia (Hemoglobin <10 g/dL) within the past 4 weeks
    - Thrombocytopenia (Platelets <100 x $10^3/\mu L$)

- Note that if only two of the three criteria are present, but the provider feels treatment is indicated for a symptomatic MCD flare, this will be allowed after communication with the study principle investigator (PI).

- Note that subjects with low hemoglobin within the past 4 weeks that have since received a blood transfusion are still eligible for participation. The subject's

pre-transfusion hemoglobin value will be considered when determining risk classification.

4.1.8 Females of childbearing potential must have a negative urine pregnancy test within three days prior to registration.

- Note that females are considered of childbearing potential unless they are surgically sterile (have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are naturally postmenopausal for at least 12 consecutive months. Documentation of postmenopausal status must be provided.

4.1.9 Females must agree to abstain from breast-feeding during therapy and for 6 months after the completion of therapy.

4.1.10 Females of childbearing potential must be willing to abstain from heterosexual activity or to use two forms of effective methods of contraception from the time of informed consent until 12 months after treatment discontinuation. The two contraception methods can be comprised of two barrier methods, or a barrier method plus a hormonal method, or an intrauterine device that meets <1% failure rate for protection from pregnancy in the product label.

4.1.11 Male subjects with female partners must have had a prior vasectomy or agree to use an adequate method of contraception (i.e., double barrier method: condom plus spermicidal agent) starting with the first dose of study therapy through 6 months after the last dose of study therapy.

4.1.12 At least 7 days without corticosteroid use prior to start of treatment.

4.2 Exclusion Criteria

All subjects meeting any of the following exclusion criteria at time of enrollment will be excluded from study participation.

4.2.1 Symptomatic, extensive-stage KS (T1 by the ACTG staging system; T1 includes ulceration or edema from KS, raised or non-hard palate oral lesions, or any visceral

involvement) requiring urgent treatment, to avoid potential rituximab-induced KS worsening.

4.2.2 Previous rituximab use for MCD.

4.2.3 Second active malignancy requiring systemic therapy.

4.2.4 If HIV negative and a) hepatitis B virus surface antigen positive or unless on tenofovir or lamivudine. All HIV-infected patients must be on tenofovir or lamivudine as part of the inclusion criteria.

4.2.5 Active infection requiring systemic therapy.

4.2.6 Treatment with any investigational drug within 28 days prior to registration.

4.2.7 More than 7 days of corticosteroids immediately prior to enrollment. If subject is taking corticosteroids for more than 7 days, they require a 7 day washout period before enrollment.

4.2.8 Bilirubin >3 mg/dL.

4.2.9 Creatinine clearance <30 ml/min by Cockcroft-Gault formula.

4.2.10 ECOG performance status >3.

4.2.11 Pregnant or breastfeeding (NOTE: breast milk cannot be stored for future use while the mother is being treated on study).

5.0 TREATMENT PLAN

5.1 Schema

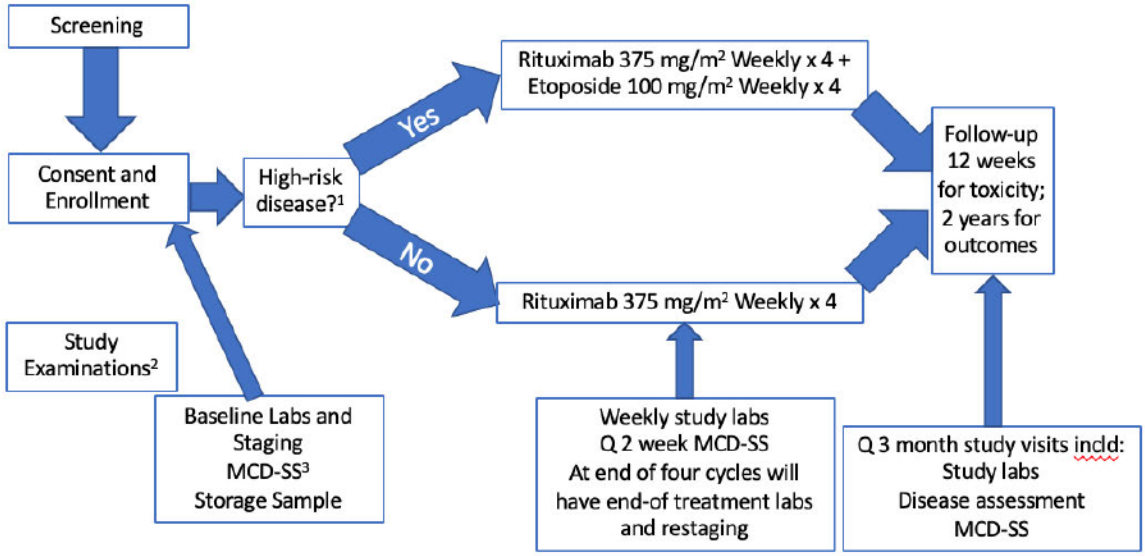

Figure 4. Clinical trial schema for newly diagnosed patients with MCD requiring treatment. "High-risk disease" defined as ECOG performance status >2 or hemoglobin <8 g/dL.

Clinical trial schema for newly diagnosed patients with MCD requiring treatment.
[1] "High-risk disease" defined as ECOG performance status >2 or hemoglobin <8 g/dL at the time of screening or enrollment labs. Note that a patient receiving a blood transfusion due to hemoglobin <8 g/dL within 1 month of enrollment will be considered high-risk.
[2] See Time and Events Table (8.1) for detailed study visit components.
[3] MCD-SS=MCD symptom score

We will conduct a single arm, phase II clinical trial for safety and efficacy of risk-stratified treatment with rituximab +/- chemotherapy for MCD. Eligible patients will be enrolled and treated according to the study schema**.** High-risk patients (defined as patients with ECOG performance status >2 or hemoglobin <8 g/dL at the the time of screening or enrollment labs)[9,10,13-16] will receive four weekly doses of rituximab (375 mg/m^2) and etoposide (100 mg/m^2) as in Bower, et al.[9] Low-risk patients will receive the same dose of rituximab alone.

The planned sample size is 27 patients and the primary outcome is safety. Secondary outcomes include one- and two-year EFS (combination of relapse, development of NHL, or death), OS, and KS exacerbation rates.

We will also collect clinical, laboratory, virologic data, and stored samples at baseline and end-of-treatment to both describe the presentation of MCD in our population and to evaluate risk factors for death or relapse.

Finally, we will conduct comprehensive microcosting analysis and a Markov model cost-effectiveness analysis.

5.2 Treatment Dosage and Administration

Treatment will be administered on an outpatient basis in the Kamuzu Central Hospital cancer clinic, as per **Table 1,** where chemotherapy is currently administered.

Table 1: REGIMEN DESCRIPTION			
Agent	**Premedications**	**Dose and Route**	**Schedule**
Rituximab	Premedicate with diphenhydramine 50 mg IV and acetaminophen 650 mg PO 1 hour prior to rituximab.	375 mg/m^2 rounded to the nearest 100 mg to avoid vial waste (dilute in normal saline or 5% dextrose to a final concentration of 1-4 mg/ml. Administer via slow IV infusion, starting at 50mg/hr and increasing by 50mg/hr every 30 minutes to a maximum infusion rate of 400mg/hr. **CAUTION**: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. IV pumps such as the IMED 960 may be used with the rituximab infusion. DO NOT INFUSE CONCOMITANTLY with another IV solution or IV medications. Prime the line with the rituximab solution such that approximately 30 mL are delivered. This will saturate the filter and tubing.	Days 1, 8, 15, 22
Etoposide	n/a	100 mg/m^2 (dilute to final concentration 0.2-0.4 mg/mL in either normal saline of 5% dextrose) IV over 1 hour after completion of rituximab	Days 1, 8, 15, 22

5.3 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed periodically for the development of any toxicity according to the Time and Events table (Section 8.1). Toxicity will be assessed according to the National Cancer Institute (NCI) CTCAE, v5.0. Dose adjustments should be made according to the system showing the greatest degree of toxicity. See **Tables 2-4** below for recommended dose delays/dose modifications.

Assigning cause of death is often difficult in Malawi because diagnostic capabilities are limited and deaths frequently occur outside of health facilities. To address this challenge, two senior non-study clinicians will be enlisted to review all study data for deceased patients and assign cause of death as either likely treatment-related, MCD-related, related to another cause, or unable to determine. In the event of discordant conclusions, a third senior clinician will serve as a tiebreaker.

Table 2: Hematological toxicity dose reductions		
ANC	**Platelets**	**Action**
$\geq 0.5 \times 10^3/\mu L$	$\geq 50 \times 10^3/\mu L$	None.

$< 0.5 \times 10^3/\mu L$	$< 50 \times 10^3/\mu L$	FIRST EPISODE: Hold current etoposide dose until ANC $\geq 0.5 \times 10^3/\mu L$ and platelets $\geq 50 \times 10^3/\mu L$. Restart next treatment at 75 mg/m^2. Do NOT hold or reduce rituximab dose. SECOND EPISODE: Hold current etoposide dose until ANC $\geq 0.5 \times 10^3/\mu L$ and platelets $\geq 50 \times 10^3/\mu L$. Restart next treatment at 50 mg/m^2. Do NOT hold or reduce rituximab dose. Goal is to replace doses and complete full course of four doses of both etoposide and rituximab.

Table 3: Non-hematological toxicity dose reductions for rituximab	
NCI CTC Grade	
0-2	No change from original dose.
3-4	Wait until resolved to $\leq$ Grade 2, no dose reduction.
Second episode of Grade 3 or 4 toxicity	Hold until resolved to $\leq$ Grade 2, no dose reduction.
Third episode of Grade 3 or 4 toxicity	Remove subject from trial

Table 4: Hepatic and renal dysfunction dose adjustment for etoposide	
Event	**Action**
Renal dysfunction	
Cr clearance >50 ml/min	None
Cr clearance 15-50 ml/min	Decrease dose to 75 mg/m^2
Cr clearance <15 ml/min	Decrease dose to 50 mg/m^2
Hepatic dysfunction	
Bilirubin <1.5 mg/dl	None
Bilirubin 1.5-3.0 mg/dl	Decrease dose to 50 mg/m^2
Bilirubin >3.0 mg/dl	Hold until bilirubin <3.0 mg/dl

5.4 Concomitant Medications/Treatments/Supportive Care Allowed

5.4.1 Hematopoietic growth factors

- Recombinant granulocyte colony-stimulating factor (G-CSF) and recombinant erythropoietin will not be routinely available, as is typical of current public sector standards of care in Malawi and most SSA settings.

5.4.2 Transfusions and bleeding

- RBC transfusions can be given per treating provider discretion. Blood for transfusion is not universally available in Malawi and study treatment will not be held awaiting transfusions as anemia is a primary manifestation of MCD. For patients receiving active etoposide therapy, transfusion for a hemoglobin <7 g/dL is generally recommended. For those receiving rituximab only, transfusion is generally recommended for a hemoglobin <6 g/dL, but in both scenarios provider discretion will be the primary driver for transfusion decisions.
- Platelet transfusions will be recommended for platelet count <20,000/µl, or <50,000/µl with bleeding or per treating provider discretion.

- Tranexamic acid will be recommended for bleeding and platelet count <50,000/ µl, or per treating provider discretion, when available locally. The standard dose is 1300 mg PO three times daily for the duration of bleeding episode and 24 hours after bleeding stops.

5.4.3 Anti-infective prophylaxis

- HIV-infected individuals will receive daily cotrimoxazole throughout treatment per Malawi national HIV treatment guidelines

5.4.4 Antiretroviral therapy

Antiretroviral therapy (ART) is not prescribed by the study protocol and, according to Malawi national guidelines, is left to the discretion of treating HIV clinicians. Study clinicians will collaborate with HIV clinicians to ensure receipt of ART concurrently with chemotherapy. Zidovudine-based treatment will be strongly discouraged to avoid additional myelosuppression.

5.4.5 Infections

Febrile neutropenia to be treated per UNC Project Malawi febrile neutropenia standard operating protocol (SOP) (Appendix A. Febrile Neutropenia SOP).

5.4.6 Nausea and vomiting

Antiemetic prophylaxis for etoposide is per UNC Project Malawi antiemetic SOP (Appendix B. UNC Project Malawi Antiemetic SOP). American Society of Clinical Oncology (ASCO) considers etoposide a low emetogenic agent. All patients will receive the following as antiemetic prophylaxis:

- 5-HT3 antagonist
  - Granisetron 2 mg PO or 1 mg IV
  - OR Ondansetron 8 mg PO Q6 hours x 2 doses or 8 mg IV x 1 dose
- AND dexamethasone 8 mg PO or IV

5.4.7 Extravasation

If there is evidence of chemotherapy leakage or swelling during or following chemotherapy administration, local care will be provided per UNC Project Malawi extravasation SOP (Appendix C. UNC Project Malawi Extravasation SOP). The extravasation SOP is appended to this protocol and includes surgical consultation.

5.4.8 Etoposide anaphylaxis

Anaphylaxis has been reported extremely rarely during etoposide infusion. In the case of such a reaction, patients will be treated per standard hypersensitivity reaction protocol (Appendix D. UNC Project Malawi Hypersensitivity/Infusion Reaction SOP).

5.4.9 Hypersensitivity reactions from rituximab

- Patients may experience hypersensitivity reactions during infusion of rituximab. Rituximab will be administered via slowly titrated infusion as

per instructions in section 5.2 to minimize the risk of hypersensitivity reactions.

- If hypersensitivity symptoms occur during rituximab infusion, the infusion will be stopped, and a local study investigator will be notified to evaluate the patient immediately. For patients receiving their first rituximab infusion, a local study investigator will directly supervise the entire infusion until completion.
- Initial suggested management of hypersensitivity symptoms is based on severity per Appendix D. UNC Project Malawi Hypersensitivity/Infusion Reaction SOP. Other treatments and resuscitation will be administered as clinically indicated.
- If hypersensitivity symptoms occur during rituximab infusion, the patient will be observed for at least two hours after completion of the infusion, and until all symptoms resolve. If symptoms persist without resolution for more than two hours after the infusion, the patient will be admitted to the hospital for continued observation.

5.5 Prohibited Medications/Treatments

Systemic therapies for other active malignancies or active infections.

5.6 Other Modalities or Procedures

No other treatment modalities (i.e., radiation or surgery) will be part of MCD treatment included in this protocol as they are not standard of care therapies for MCD.

5.7 Duration of Therapy

In the absence of treatment delays due to AEs, treatment may continue for **4 weekly doses** or until one or more of the following occur:

- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable AE(s)
- Pregnancy
- Subject decides to withdraw from study treatment
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator

5.8 Duration of Follow Up

For determination of study endpoints, all subjects will be followed for up to 24 months or until death, whichever occurs first after removal from study treatment.

Subjects removed from study treatment for unacceptable AEs will be followed for resolution or stabilization of the AE(s). All subjects (including those withdrawn for AEs) should be followed after removal from study treatment as stipulated in the protocol.

Although study follow-up is for 24 months, patients will be consented to be contacted at 30, 36, 42, 48, 54, and 60 months simply to assess vital status after completion of study procedures.

5.9 Study Withdrawal

Subjects will be removed from the study, removed from protocol mandated therapy (i.e. further therapy will be at discretion of the treating provider), and the study PI notified when any of the criteria listed in section 5.7 apply. The reason for discontinuation of protocol therapy will be documented in the electronic case report form (eCRF).

If a subject decides to withdraw from the study (and not just from protocol therapy) an effort will be made to complete and report study assessments as thoroughly as possible. At the time of withdrawal, the investigator will attempt to establish as completely as possible the reason for the study withdrawal.

- The subject will be asked if they are willing to allow for the abstraction of relevant information from their medical record in order to meet long-term follow-up objectives (e.g., survival) outlined in the protocol.
- A complete final evaluation at the time of the subject's study withdrawal will be obtained with an explanation of why the subject is withdrawing from the study.
- If the subject is noncompliant and does not return for an end of study follow up assessment, this will be documented in the eCRF.
- If the reason for removal of a subject from the study is an AE, the principal specific event will be recorded in the eCRF.

Excessive subject withdrawals from protocol therapy or from the study can render the study un-interpretable; therefore, unnecessary withdrawal of subjects should be avoided.

6.0 DRUG INFORMATION

6.1 Rituximab

Rituximab for this study will be supplied as Reditux (Dr. Reddy's Laboratories, India). For extensive product information, preparation instructions, and AEs information, please refer to the United States Food and Drug Administration roduct guidelines here: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103705s5311lbl.pdf

Rituximab is the standard therapy for MCD in HIC, but published data is missing on the safety of rituximab in SSA. Rituximab will be provided free of charge to all study participants.

6.1.1 Description

Rituximab is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen. Rituximab has an approximate

molecular weight of 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM. It is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

6.1.2 Storage and Handling

Rituximab should be stored at 2-8°C. Do NOT freeze or store at room temperature. The product is a protein. HANDLE GENTLY AND AVOID FOAMING. The avoidance of foaming during product handling, preparation and administration is important, as foaming may lead to the denaturing of the product proteins.

6.1.3 Pharmacology

Pharmacokinetics: In prior studies patients treated at the 375 mg/m2 dose levels exhibited detectable antibody concentrations throughout the treatment period. Most patients exhibited increasing pre-infusion antibody concentrations with each subsequent infusion. In nine patients, the T1/2 following the first antibody infusion was 59.8 hours (11.1-104.6 hr) with a Cmax of 271mcg/mL. Following the fourth antibody infusion when circulating B cells had been depleted and antigenic sites coated, the T1/2 was 174 hr (26.4-442.3 hr) and Cmax 496.7 mcg/mL.

Duration: Detectable in serum 3-6 months after treatment completion; B-cell recovery begins almost 6 months following treatment completion; median B-cell levels return to normal by 12 months following treatment completion.

Absorption: Intravenous: Immediate and results in a rapid and sustained depletion of circulating and tissue-based B cells.

Half-life elimination: Median terminal half-life: 22 days (range: 6-52 days)

Excretion: Uncertain; may undergo phagocytosis and catabolism in the reticuloendothelial system (RES).

6.1.4 Formulation

100 mg (10 mL) and 500 mg (50 ml) pharmaceutical grade vials at a concentration of 10 mg of protein per mL (actual concentration should be noted on the product label).

6.1.5 Return and Retention of Study Drug

Return and retention of rituximab will be done per UNC Project Malawi drug destruction SOP used in support of ongoing and completed clinical trials.

6.1.6 Adverse Events Associated with Investigational Drug

Human Toxicology: Single doses of up to 2275 mg/m2 and weekly x 4 doses of 375 mg/m2 have been administered without dose limiting toxicity. AEs are most common during the initial antibody infusion and usually consist of Grade 1 or 2 fever (73%), asthenia (16%), chills (38%), nausea (19%), vomiting (11%), rash (14%) and tumor site pain (3%). Grade 1 or 2 hypotension (8%) may be treated

with IV fluids. Hematologic toxicity is usually mild and reversible. Transient decreases in the WBC or platelet count have been observed - especially in patients with high levels of circulating tumor cells or bone marrow involvement. Two patients have had late-onset Grade 4 neutropenia at four and ten months that was attributed to an unknown cause, was transient, and resolved. Infections (Grade 1 and 2) have not been related to dose level. Symptoms are generally associated with the initial antibody infusions and diminish in frequency with each successive infusion. A report in the literature described an increase in fatal infection in HIV-related lymphoma patients when rituximab was used in combination with CHOP chemotherapy as compared to CHOP alone.

Severe Infusion and Hypersensitivity Reactions: Rituximab has caused severe infusion reactions. In some cases, these reactions were fatal. An infusion-related symptom complex consisting of fever and chills/rigors has occurred in many patients during the first rituximab infusion. Signs and symptoms of severe infusion reactions may include urticaria, hypotension, angioedema, hypoxia, or bronchospasm. The most severe manifestations and sequelae include pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, and anaphylactic and anaphylactoid events. These reactions generally occurred within 30 minutes to 2 hours of beginning the first infusion, and resolved with slowing or interruption of the rituximab infusion and with supportive care (including, but not limited to IV saline, diphenhydramine, and acetaminophen).

Tumor Lysis Syndrome: Rituximab rapidly decreases benign and malignant CD20 positive cells. Tumor lysis syndrome has been reported to occur within 12 to 24 hours after the first rituximab infusion in patients with high numbers of circulating malignant lymphocytes. Patients with high tumor burden (bulky lesions) may also be at risk. Patients at risk for developing tumor lysis syndrome should be followed closely and appropriate laboratory monitoring performed.

Hepatitis B Reactivation with Related Fulminant Hepatitis and Other Viral Infections: 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 diagnosis of hepatitis was approximately four months after the initiation of rituximab and approximately one month after the last dose. Persons at high risk of HBV infection should be screened before initiation of rituximab. Carriers of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis during and for up to several months following rituximab therapy. In patients who develop viral hepatitis, rituximab and any concomitant chemotherapy should be discontinued and appropriate treatment, including antiviral therapy, initiated. There are insufficient data regarding the safety of resuming rituximab therapy in patients who develop hepatitis subsequent to HBV reactivation. The following additional serious viral infections, either new, reactivated or exacerbated, have been identified

in clinical studies or postmarketing reports. The majority of patients received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. These viral infections included John Cunningham virus, which is associated with progressive multifocal leukoencephalopathy, 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.

Severe Mucocutaneous Reactions: Mucocutaneous reactions, some with fatal outcome, have been reported in patients treated with rituximab. These reports included paraneoplastic pemphigus (an uncommon disorder which is a manifestation of the patient's underlying malignancy), Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of the reaction in reported cases have varied from 1-13 weeks following rituximab exposure. Patients experiencing a severe mucocutaneous reaction should not receive any further infusions and seek prompt medical evaluation. Skin biopsy may help to distinguish among different mucocutaneous reactions and guide subsequent treatment. The safety of readministration of rituximab to patients with any of these mucocutaneous reactions has not been determined.

Bowel Obstruction and Perforation: Abdominal pain and bowel obstruction and perforation (in some cases leading to death) were observed in patients receiving rituximab in combination with chemotherapy for DLBCL. In post-marketing reports, which included patients with both low-grade or follicular NHL and DLBCL, the mean time to onset of symptoms was 6 days (range 1-77) in patients with documented gastrointestinal perforation. Complaints of abdominal pain, especially early in the course of treatment, should prompt a thorough diagnostic evaluation and appropriate treatment.

Cardiovascular: The incidence of serious cardiovascular events in the double-blind clinical trial for rheumatoid arthritis (RA) patients was 1.7% and 1.3% in rituximab and placebo groups, respectively. Three cardiovascular deaths occurred during the double-blind period of the RA studies, including all rituximab regimens (3/759 = 0.4%) as compared to none in the placebo group (0/389).
Since patients with RA are at increased risk for cardiovascular events compared to the general population, patients with RA should be monitored throughout the infusion and rituximab should be discontinued in the event of a serious or life-threatening cardiac event. Rituximab infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias. Patients who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions of rituximab. Patients with pre-existing cardiac conditions including arrhythmias and angina have had recurrences of these events during rituximab therapy and should be monitored throughout the infusion and immediate post-infusion period.

Renal: Rituximab administration has been associated with severe renal toxicity including acute renal failure requiring dialysis and, in some cases, has led to fatal outcomes in hematologic malignancy patients. Renal toxicity has occurred in patients with high numbers of circulating malignant cells (> 25,000/μL) or high tumor burden who experience tumor lysis syndrome and in patients with NHL administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and rituximab is not an approved treatment regimen. If this combination is used in clinical trials *extreme caution* should be exercised; patients should be monitored closely for signs of renal failure. Discontinuation of rituximab should be considered for those with rising serum creatinine or oliguria.

Immunization: The safety of immunization with live viral vaccines following rituximab therapy has not been studied and vaccination with live virus vaccines is not recommended. The ability to generate a primary or anamnestic humoral response to vaccination is currently being studied. For patients with NHL, the benefits of primary and/or booster vaccinations should be weighed against the risks of delay in initiation of rituximab therapy.

Carcinogenesis, Impairment of Fertility, Pregnancy, and Nursing: No long-term animal studies have been performed to establish the carcinogenic potential of rituximab. Studies also have not been completed to assess mutagenic potential of rituximab, or to determine potential effects on fertility in males or females. Individuals of childbearing potential should use effective contraceptive methods during treatment and for up to 12 months following rituximab therapy. It is not known whether rituximab is excreted in human milk. Because human IgG is excreted in human milk and the potential for absorption and immunosuppression in infants is unknown, women should be advised to discontinue nursing until circulating drug levels are no longer detectable.

6.2 Etoposide Description and Management

Brief Description: Etoposide is a topoisomerase II inhibitor that causes DNA double strand breaks and apoptosis of rapidly dividing cells, especially cancer cells. Etoposide is a common chemotherapeutic agent used in the treatment of a number of neoplasms, including lymphoma, Kaposi sarcoma, testicular cancer, Ewing sarcoma, and small cell lung cancer, among others.

Etoposide (also known as VP-16) is sold by Pfizer (New York, USA).

Full prescribing information for etoposide is available at:
https://www.pfizer.com/files/products/uspi_toposar.pdf

Dosage and Administration:
Etoposide will be administered at 100 mg/m^2 intravenous over one hour.

Storage and Stability:

Unopened vials are stable for 24 months at room temperature. Vials diluted at recommended concentration of 0.2 or 0.4 mg/ml are stable for 96 or 24 hours, respectively, at room temperature.

Handling and Disposal: Local requirements for disposal of hazardous drugs should be followed at each participating clinical site.

Please see UNC policy on hazardous drugs:
http://intranet.unchealthcare.org/intranet/hospitaldepartments/safetynet/policies/hazardousdrugs.pdf

6.2.1 Etoposide pharmacokinetics

After IV injection, there is a biphasic pattern of clearance with a terminal $t_{1/2}$ of about 6–8 h in patients with normal renal function. Approximately 40% of an administered dose is excreted intact in the urine. In patients with compromised renal function, dosage should be reduced in proportion to the reduction in creatinine clearance. In patients with advanced liver disease, increased toxicity may result from a low serum albumin (decreased drug binding) and elevated bilirubin (which displaces etoposide from albumin); guidelines for dose reduction in this circumstance have not been defined.

6.2.1 Adverse events associated with etoposide

The following data on adverse reactions are based on both oral and IV administration of etoposide as a single agent, using several different dose schedules for treatment of a wide variety of malignancies.

Hematologic Toxicity: Myelosuppression is dose related and dose limiting with granulocyte nadirs occurring 7 to 14 days after drug administration and platelet nadirs occurring 9 to 16 days after drug administration. Bone marrow recovery is usually complete by day 20, and no cumulative toxicity has been reported. The occurrence of acute leukemia with or without a preleukemic phase has been reported rarely in patients treated with etoposide in association with other antineoplastic agents.

Gastrointestinal Toxicity: Nausea and vomiting are the major gastrointestinal toxicities. The severity of such nausea and vomiting is generally mild to moderate with treatment discontinuation required in 1% of patients. Nausea and vomiting can usually be controlled with standard antiemetic therapy. Gastrointestinal toxicities are slightly more frequent after oral administration than after IV infusion.

Hypotension: Transient hypotension following rapid IV administration has been reported in 1% to 2% of patients. It has not been associated with cardiac toxicity or electrocardiographic changes. No delayed hypotension has been noted. To prevent this rare occurrence, it is recommended that etoposide be administered by slow IV infusion over a 30- to 60-minute period. If hypotension occurs, it usually responds to cessation of the infusion and administration of fluids or other supportive therapy

as appropriate. When restarting the infusion, a slower administration rate should be used.

Allergic Reactions: Anaphylactic-like reactions characterized by chills, fever, tachycardia, bronchospasm, dyspnea, and hypotension have been reported in 0.7% to 2% of patients receiving IV etoposide and in less than 1% of the patients treated with oral capsules. Although these reactions can be fatal, they usually respond promptly to cessation of the infusion and administration of pressor agents, corticosteroids, antihistamines, or volume expanders as appropriate. Hypertension and flushing have also been reported. Blood pressure usually normalizes within a few hours after cessation of the infusion. Anaphylactic-like reactions have occurred during the initial infusion of etoposide. Facial/tongue swelling, coughing, diaphoresis, cyanosis, tightness in throat, laryngospasm, back pain, and/or loss of consciousness have sometimes occurred in association with the above reactions. In addition, an apparent hypersensitivity-associated apnea has been reported rarely. Rash, urticaria, and/or pruritus have infrequently been reported at recommended doses. At investigational doses, a generalized pruritic erythematous maculopapular rash, consistent with perivasculitis, has been reported.

Alopecia: Reversible alopecia, sometimes progressing to total baldness, was observed in up to 66% of patients.

Other Toxicities: The following adverse reactions have been infrequently reported: aftertaste, fever, pigmentation, abdominal pain, constipation, dysphagia, transient cortical blindness, and a single report of radiation recall dermatitis. Hepatic toxicity, generally in patients receiving higher than recommended doses of the drug, has been reported with etoposide. Metabolic acidosis has also been reported in patients receiving these higher doses. The incidences of adverse reactions in **Table 6** are derived from multiple databases from studies in 2,081 patients when etoposide was used either orally or by injection as a single agent.

Table 6: Incidence of adverse events in patients receiving etoposide across multiple studies for multiple cancer types.

ADVERSE DRUG EFFECT	PERCENT RANGE OF REPORTED INCIDENCE
Hematologic toxicity	
Leukopenia (less than 1,000 WBC/mm^3)	3–17
Leukopenia (less than 4,000 WBC/mm^3)	60–91
Thrombocytopenia (less than 50,000 platelets/mm^3)	1–20
Thrombocytopenia (less than 100,000 platelets/mm^3)	22–41
Anemia	0–33
Gastrointestinal toxicity	
Nausea and vomiting	31–43
Abdominal pain	0–2
Anorexia	10–13
Diarrhea	1–13
Stomatitis	1–6
Hepatic	0–3
Alopecia	8–66
Peripheral neurotoxicity	1–2
Hypotension	1–2
Allergic reaction	1–2

7.0 CLINICAL ASSESSMENTS

Clinical assessments will be performed as outlined in the Time and Events Table in Section 8.0.

7.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at baseline/screening and throughout the study as summarized in the Time and Events Table in Section 8.0. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

7.1.2 Demographics

Demographic information (i.e., date of birth, gender, race) will be recorded at screening.

7.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history (e.g., tobacco use), and information regarding underlying diseases will be recorded at screening and a focused medical history of symptoms/toxicity will be performed thereafter.

7.1.4 Physical Examination

A complete physical examination including height (at screening only), weight, ECOG Performance status, lymph node assessment, and vital signs (i.e., temperature and blood pressure) will be performed by either the investigator or a sub-investigator at screening and each treatment visit.

New abnormal physical exam findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

7.1.5 Adverse Events

Events should be assessed per NCI-CTCAE criteria v5.0. Information regarding occurrence of AEs will be captured throughout the study. Duration (start and stop dates), severity/grade, outcome, treatment, and relation to study drug will be recorded in the eCRF. PRO-CTCAE has recently been translated and validated in Malawi and will be used to capture patient reported adverse events.

7.1.6 Clinical Disease Assessment

Response assessment varies across MCD studies, but our clinical response will be defined as follows:

Event-free survival will be defined by the absence of an event. An event includes either: relapse of symptomatic MCD requiring re-initiation of treatment as in the previous study by Bower, et al, death, or progression to non-Hodgkin lymphoma.[10] Definition of symptomatic MCD for purposes of this study are the same as in the "Inclusion Criteria" (Section 4.1).

7.1.7 Radiologic Disease Assessment (Revised response criteria for gross lymphadenopathy)

All patients will undergo baseline on-study chest radiography and abdominal sonography for staging. Response will be evaluated via complete survey of lymph nodes with measurements and physical assessment of other palpable masses with measurements (using a flexible metric ruler in two dimensions). Chest radiography and abdominal sonography will be repeated at completion of treatment.

Measurable disease will be defined as the presence of at least one measurable pathologic lymph node or other mass that can be accurately measured by physical exam in at least one dimension with the longest diameter a minimum size of 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable). All measurements should be recorded in metric notation using calipers. All baseline evaluations should be performed as close as possible to the treatment start and never more than four weeks before the beginning of 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. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers.

All measurable lesions by physical exam or maximum of five lesions should be identified as target lesions and will be recorded and measured in two dimensions at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameters) and should also be those that lend themselves to reproducible

repeated measurements. A sum of the product of diameters (SPD, as in the International Harmonization Product criteria) for all target lesions will be calculated and reported as the baseline SPD. The baseline SPD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

All other lesions (or sites of disease), including lesions evident only by chest x-ray or ultrasound given difficulties with reproducibility of radiographic studies in our setting, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as 'present' or 'absent', or in rare cases 'unequivocal progression.'

A similar strategy for response assessment based on target lesions documented by physical exam alone is currently being utilized at UNC Project Malawi for a clinical trial for lymphoma.

Response criteria for lymph node response will be as follows.

- Complete response (CR): Disappearance of all evident disease. Any pathological lymph node (LN), whether target or non-target, must have decreased to <10mm in diameter. Any non-target lesion evident by chest x-ray or ultrasound must also be documented to have resolved by repeat evaluation.
- Partial response (PR): At least a 50% decrease in SPD of up to six target lesions without any increase in size of non-target lesions.
- Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
- Progressive disease (PD): Appearance of a new lesion(s) >15mm in diameter, at least a 50% increase in SPD of more than one node, OR at least a 50% increase in diameter of a previously identified node >1cm. Given numerous causes of adenopathy in Malawi (particularly among HIV-infected individuals) and in order to exclude alternative non-lymphoma diagnoses, a concerted attempt to re-biopsy at the time of relapse or progression will be made unless patients refuse or the site is not amenable using locally available resources.

7.2 Clinical Laboratory Assessments

7.2.1 Hematology

Blood will be obtained and sent to the clinical site hematology lab for complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, white blood cell differential, and platelet count) and C-reactive protein (CRP) as per time and events table (section 8.0).

7.2.2 Blood Chemistry Profile

Blood will be obtained and sent to the clinical site chemistry lab for determination of serum creatinine, total bilirubin, albumin, lactate dehydrogenase, and the following as deemed necessary per SOC: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase.

7.2.3 HIV viral load and CD4 count

Will be assessed for all HIV-infected subjects.

7.2.4 Hepatitis B serologies

Hepatitis B surface antigen will be assessed for all HIV negative subjects at baseline.

7.2.5 Pregnancy Test

A urine pregnancy test will be obtained from female subjects who are of childbearing age prior to their participation in the study.

7.3 Quality of life assessment

Symptoms and quality of life will be assessed by the MCD symptom score and PROMIS-Preference, as adapted for UNC Project Malawi previously.

7.4 Correlative Studies

We plan to conduct correlative studies, including viral and host genomics (of the tumor sample only), cytokine studies, and KSHV viral load. Host genomic studies will be completed in the Vironomic core at UNC Chapel Hill from formalin-fixed paraffin-embedded biopsy specimens and will focus on both the malignant plasmablasts as well as the surrounding tumor microenvironment, but no specific germline mutation testing will be completed. This biopsy is standard of care and is required for diagnosis and entry into this study. If insufficient tissue is available, subjects can still participate in the clinical trial. Viral genomic studies will be conducted from the same biopsy specimen or from plasma samples taken for cytokine studies as outlined below.

Cytokine studies will require blood draws of 10 mL (2 heparin tubes separated into plasma and PBMCs) and 1 tube (5 mL) with citrate at baseline, mid-treatment (day 15), end-of-treatment (day 29), first follow-up (12 weeks)after start of treatment, and at all long term follow up visits. Samples will be stored at -80 °C.

8.0 EVALUATIONS AND ASSESSMENTS

8.1 Time and Events Table (Table 7)

Table 7: Time and Events Table.	Initial Visit or Relapse[1]	Treatment days 1, 8, 15, and 22[2]	End-of-treatment (Week 5)	Follow-up (12 weeks)	Long term follow up[4]
Informed consent	Initial visit only				
History & physical exam[5]	X	X	X	X	X
Concomitant medications[6]	X	X	X		
ECOG performance status[7]	X	X	X		
Toxicity evaluation[8]	X	X	X	X	X[8]
Tumor biopsy[9]	X				
Survival[10]		X	X	X	X
Treatments[11]		X			
Lymph node measurements	X	Day 15 only	X	X	X
MCD-SS and Quality of life assessment[12]	X	Day 15 only	X	X	X[12]
Chest X-ray and abdominal ultrasound	X		X[13]		
Hematology & blood chemistries[14]	X[15]	X[16]	X	CBC only	CBC only
Correlative blood samples[17]	X	Day 15 only	X	X	X[19]
Lactate dehydrogenase	X	Day 15 only	X		

Viral and host genotyping	X	
Urine pregnancy test	X[18]	
Hepatitis B (for HIV-negative patients)	X	
CD4 and HIV RNA (if HIV positive)	X	X[19]

[1] Screening assessments must be completed within 21 days prior to study enrollment.

[2] A window of +/- 7 days will apply to all study visits; however, lymph node measurements must take place prior to that cycle's treatment.

[3] End-of-treatment visit should occur 7-14 days from final dose of chemotherapy. A subject who is being withdrawn for disease progression or for other reasons (e.g. unacceptable toxicity, etc.) should complete an end of treatment visit.

[4] Long term follow-up will occur every 3 months until 24 months after the start of treatment unless otherwise noted.

[5] After the initial visit (comprehensive history and physical exam) subsequent visits will address a focused history and physical exam.

[6] All concomitant medications will be recorded.

[7] See Appendix E. ECOG Performance Status

[8]per NCI CTCAEv5.0 for notation of baseline toxicity. Assess from initial visit through first follow-up visit (12 weeks) and again at the final follow up visit visit (24 months).

[9] Archival and/or fresh sample.

[10] Survival will be assessed at each visit through out the duration of treatment, follow up, and long term follow up.

[11] Subjects with low risk disease will receive rituximab at 375 mg/m^2 weekly for 4 weeks. High risk subjects will receive rituximab at 375 mg/m^2 and etoposide at 100 mg/m^2 weekly for 4 weeks.

[12]Quality of life assessment includes PROMIS Global 10, MCD-SS and QoL will be assessed through follow up, and at 24 months during long term follow up. QoL will also be assessed at the time of any relapse.

[13] Omitted if no baseline abnormalities on chest x-ray and abdominal ultrasound.

[14] Hematology assessments include hemoglobin, white blood cell count, white blood cell differential, and platelet count. Blood chemistry assessments include serum creatinine, total bilirubin, albumin, and the following as deemed necessary per SOC: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase. See the T&E table for when lactate dehydrogenase is measured.

[15] If a patient has been tested for hemoglobin within 1 month of enrollment and received and blood transfusion due to low hemoglobin, then the original test will dictate treatment group (high vs low risk).

[16] Hemoglobin and platelet count will be assessed per SOC during treatment.

[17] Blood sample for correlatives will include assessments of C-reactive protein, KSHV viral load from plasma and PBMCs, and cytokine levels (IL-6, IL-10, IL-2, TNFα, INFγ). KSHC genotyping will occur on the first draw only. Blood draws will be two 10 mL tubes (2 heparin tubes separated into plasma and PBMCs) and 1 tube (5 mL) with citrate). Correlative blood samples collected during long term follow up will be stored and analyzed

[18] In women under 60 years of age, required within 3 days of start of treatment.

[19] At 12 and 24 month long term follow up visits.

8.2 Handling of Biospecimens Collected for Correlative Research

Biospecimens collected for this study will be stored in the LCCC Tissue Procurement Facility (TPF), or if needed, in a secure off-site storage facility. All biospecimen samples will be obtained in accordance with procedures outlined in the LCCC 1950 Study Laboratory Manual and stored in containers with controlled access. Each sample will be assigned a unique code number and no identifiable personal health information ill be on the specimen label. Information about the subject's disease will be linked to the specimens stored in the repository database. TPF-associated research staff, LCCC Bioinformatics staff who support the TPF database and the LCCC Data Warehouse, and researchers with IRB-approval for access to PHI for each subject in this study will be able to link specimens to relevant medical information. Some results from laboratory analyses that occurred during the subject's participation in the clinical study may also be included. This information may be important for understanding how the subject's cancer developed and responded to treatment.

Storage Time:

- The biospecimen will be used first and foremost for research purposes outlined within the confines of this protocol. Samples will be discarded/destroyed after relevant data are collected for this study, unless consent was obtained from the subject to use tissue for other research purposes (e.g., TPF consent form was signed by the subject). In this circumstance, there is no time limit on how long biospecimens may be stored.

- The investigator must agree to abide by policies and procedures of the TPF facility and sign a letter of research agreement for ethical and appropriate conduct of their research that utilizes specimens obtained from the TPF facility (e.g., use of leftover specimens will require a protocol outlining the research plan for biospecimen use).

Compliance Statement

Biospecimen collection for this study will be conducted in full accordance to all applicable UNC research policies and procedures and all applicable federal and state laws and regulations, including 45 CFR 46 and the Health Insurance Portability and Accountability Act Privacy Rule. Any episode of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent (unless a waiver is granted), and will report unexpected problems in accordance with UNC IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

8.3 Assessment of Safety

Any subject who receives at least one dose of study therapy on this protocol will be evaluable for toxicity. Each subject will be assessed periodically for the development of any toxicity according to the Time and Events table. Toxicity will be assessed according to the NCI CTCAEv5.0.

8.4 Assessment of Efficacy

All patients with measurable disease who have received at least one dose of treatment and have their disease re-evaluated will be evaluable for assessment of efficacy endpoints. The planned disease measurements are to occur at baseline, day 15, end-of-treatment, and on long-term follow-up.

8.4.1 Tumor Measurement

See 7.1.7 for details of tumor measurement and response assessment.

9.0 ADVERSE EVENTS

9.1 Definitions

9.1.1 Adverse Event (AE)

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

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of a central line) need not be considered AEs and should not be recorded as such. Disease progression should not be recorded as an AE unless the investigator deems it attributable to the study therapy.

9.1.2 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any AE for which there is a *reasonable possibility* that the investigational product is the cause. *Reasonable possibility* means that there is evidence to suggest a causal relationship between the drug and the AE. An SAR implies a lesser degree of certainty about causality than an adverse reaction, which means any AE caused by an investigational product.

Causality assessment to a study drug is a medical judgment made in consideration of the following factors: temporal relationship of the AE to study investigational product exposure, known mechanism of action or side effect profile of study treatment, other recent or concomitant drug exposures, normal clinical course of the disease under investigation,

and any other underlying or concurrent medical conditions. Other factors to consider in determining if a study drug caused the AE include:

- Single occurrence of an uncommon event known to be strongly associated with investigational product exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome).
- One or more occurrences of an event not commonly associated with investigational product exposure, but otherwise uncommon in the population (e.g., tendon rupture). Often more than one occurrence from one or multiple studies would be needed before the sponsor could determine that there is *reasonable possibility* that the investigational product caused the event.
- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the investigational product treatment group than in a concurrent or historical control group.

9.1.3 Unexpected AE or SAR

An AE or SAR is considered unexpected if the specificity or severity of it is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Unexpected also refers to AEs or SARs that are mentioned in the Investigator's Brochure as occurring with a class of drugs/investigational product or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug product under investigation.

9.1.4 Serious AE or SAR

An AE or SAR is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Requires inpatient hospitalization (>24 hours) or prolongation of existing hospitalization (hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered a serious AE/SAR)
- Results in congenital anomaly/birth defect
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious study treatment-related AE/SAR when, based upon appropriate medical judgment, they may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in the definition (for reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event)

Pregnancy that occurs during the study must also be reported as a serious AE/SAR.

9.2 Documentation of non-serious AEs or SARs

For non-serious AEs or SARs, documentation must begin from day 1 of study treatment and continue through the 30-day follow-up period after treatment is discontinued.

Collected information should be recorded in the eCRF for that subject. Please include a description of the event, its severity or toxicity grade, onset and resolved dates (if applicable), and the relationship to the study drug. Documentation should occur at least monthly.

9.3 SAEs or Serious SARs

9.3.1 Timing

After informed consent but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g. SAEs related to invasive procedures such as biopsies, medication washout).

For any other experience or condition that meets the definition of an SAE or a serious SAR, recording of the event must begin from day 1 of study treatment and continue through the 30-day follow-up period after treatment is discontinued.

9.3.2 Documentation and Notification

SAEs or Serious SARs must be documented and the NCCN project manager notified of the event/reaction via email within 24 hours of learning of its occurrence.

9.4 Adverse Event Reporting

9.4.1 IRB Reporting Requirements:

UNC:

- The UNC IRB will be notified of all SAEs that qualify as an Unanticipated Problem as per UNC IRB policy using the IRB's web-based reporting system within 7 days of the Investigator becoming aware of the problem. Please note, these events must be reported to the sponsor within 24 hours of learning of the occurrence.

Pregnancy:

- Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study, or within 30 days of the subject's last dose of study drug should be recorded as SAEs. The subject is to be discontinued immediately from the study.
- The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

- The Investigator will follow the female subject until completion of the pregnancy and must document the outcome of the pregnancy (either normal or abnormal outcome) and report the condition of the fetus or newborn to the UNC study coordinator. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE.

9.5 Data and Safety Monitoring Plan

The study PI will provide continuous monitoring of subject safety in this trial with periodic reporting to the Data and Safety Monitoring Board (DSMB).

Meetings/teleconferences will be held at a frequency dependent on study accrual, and in consultation with the study Biostatistician. These meetings will include the investigators as well as protocol nurses, clinical research associates, regulatory associates, data managers, biostatisticians, and any other relevant personnel the study PI may deem appropriate. At these meetings, the research team will discuss all issues relevant to study progress, including enrollment, safety, regulatory, data collection, etc.

The team will produce summaries or minutes of these meetings. These summaries will be available for inspection when requested by any of the regulatory bodies charged with the safety of human subjects and the integrity of data including, but not limited to, the oversight Office of Human Research Ethics Biomedical IRB, the Oncology Protocol Review Committee (PRC) or the North Carolina TraCS Institute DSMB.

The UNC LCCC DSMB will review the study on a regular (quarterly to annually) basis, with the frequency of review based on risk and complexity as determined by UNC PRC. The study PI will be responsible for submitting the following information for review:

1. Safety and accrual data including the number of subjects treated
2. Significant developments reported in the literature that may affect the safety of participants or the ethics of the study
3. Preliminary response data
4. Summaries of team meetings that have occurred since the last report

Findings from the DSMB review will be disseminated by memo to the study PI, UNC PRC, and UNC IRB.

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

This is a single arm, prospective, phase II clinical trial for safety and efficacy of risk-stratified treatment with rituximab +/- chemotherapy for MCD. Eligible patients will be enrolled and treated according to the study schema. High-risk patients (defined as patients with ECOG performance status >2 or hemoglobin <8 g/dL during screening or enrollment)[9,10,13-16] will receive four weekly doses of rituximab (375 mg/m^2) and etoposide

(100 mg/m^2) as in Bower, et al.[9] Note that patients with low hemoglobin within the last month that receive a blood transfusion as treatment will be considered high risk if their pre-tranfusion hemoglobin was <8 g/dL. Low-risk patients will receive the same dose of rituximab alone. The planned sample size is 27 patients and the primary outcome is safety. Secondary outcomes include one- and two-year EFS (relapse, development of NHL, or death), OS, and KS exacerbation rates. We will also collect clinical, laboratory, virologic data, and stored samples at baseline and end-of-treatment to both describe the presentation of MCD in our population and to evaluate risk factors for death or relapse. Finally, we will conduct comprehensive microcosting analysis and a Markov model cost-effectiveness analysis.

10.2 Sample Size, Accrual and Duration of Accrual

To assess safety, toxicities will be monitored, graded, and documented by investigators at each clinic visit. Rituximab-based treatment will be considered safe in this population provided <40% non-hematologic AEs; we hypothesize that the true rate will be around 20%, based on previous studies.[9,10,15,16] With a sample size of 24 patients, we reach 80% power to reject (if we observe $\leq 6 \geq$ Grade 3 AEs) the null hypothesis (H_0: toxicity rate >40%) using a one-sided exact test at α=0.1. To account for 10% possible loss to follow-up during the toxicity-monitoring period, we will plan to enroll 27 patients. We plan to enroll approximately 10 patients annually and therefore expect to accrue patients for a total of three years.

10.3 Safety monitoring

Sequential boundaries will be used to monitor the rate of treatment-related mortality and non-hematologic AEs. Accrual to the study will be suspended until the study PI, co-investigators and the DSMC can review the data, and determine if the study should continue, be amended, or be closed to further accrual if excessive numbers of these events are seen (i.e., the number of deaths or the number of non-hematologic AEs is equal to or exceeds b_n out of n patients with full follow-up (**Table 8**)). The boundaries for treatment-related mortality rate are Pocock-type stopping boundaries that yield the probability of crossing the boundary at most 0.05 when the death rate is equal to the acceptable rate (0.10). The boundaries for the rate non-hematologic AEs are Pocock-type stopping boundaries that yield the probability of crossing the boundary at most 0.05 when the death rate is equal to the acceptable rate (0.40). The bounds are non-binding, and provide a guideline that may result in study modification or closure.

Table 8: Pocock-stopping bounds for deaths and adverse events.

Number of Patients, n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Boundary Treatment-related mortality, b_n	-	2	2	2	2	3	3	3	3	3	3	4	4	4	4	4	4	4	5	5	5	5	5	5
Boundary Grade ≥3 non-hematologic adverse events b_n	-	-	-	-	5	6	6	7	8	8	9	9	10	10	11	11	12	13	13	14	14	15	15	16

10.4 Data Analysis Plans

10.4.1 Primary Objective: To describe the safety, as determined by the rate of Grade ≥3 non-hematologic AEs and treatment-related mortality, of a risk-adjusted approach to the treatment of MCD with rituximab (375 mg/m^2 weekly for four weeks) +/- etoposide (100 mg/m^2 weekly for four weeks) in Malawi.

The rate will be estimated for individual AEs and a summation of Grade ≥3 non-hematologic AEs will be estimated along with a 95% confidence interval.

The rate of treatment-related mortality will be estimated along with a 95% confidence interval around the point estimate.

10.5 Secondary Objectives

10.5.1 To better characterize MCD presentation in Malawi.

Basic demographics and baseline laboratory values will be summarized using descriptive statistics (i.e., means, medians, and variability measures for continuous variable; rates and proportions for binary variables).

10.5.2 To describe the efficacy of the risk-adjusted approach as determined by clinical and radiologic response rates, 90-day, one-year, and two-year EFS and OS.

An event for EFS is either relapse (defined as "MCD attack" in the Inclusion Criteria (section 4.1)), refractory disease, lost-to-follow-up (LTFU), or death. We will consider patients LTFU if they cannot be contacted by phone for three months. Given the high mortality associated with MCD and previously published literature supporting a strong association between LTFU and mortality in SSA, we will consider LTFU as a failure event for both EFS and OS.[43] Relapse for purposes of this study will be defined as recurrence of an "MCD attack" (Inclusion Criteria; section 4.1) requiring re-initiation of treatment, with a strong preference for biopsy-proven recurrence whenever possible. We will conduct survival analysis using Kaplan-Meier methods. Radiologic response will be assessed in parallel with clinical response with response criteria defined in section 7.1.7. We will assess the prognostic value of radiologic response for EFS and OS in Cox proportional hazards model.[10,15,16]

10.5.3 To describe the safety, as determined by the rate of all AEs during a risk-adjusted approach to treatment of MCD in Malawi.

All AEs will be described up to 30 days after final dose of MCD-directed treatment.

10.5.4 To describe the rate of KS exacerbation, as defined by symptomatic or clinical (dermatologic or visceral organ) exacerbation of disease.

The rate of KS exacerbation will be reported as the number of KS cases requiring KS-specific treatment divided by the number of patients with pre-existing KS (as defined by personal history of KS, baseline presence of KS, or KS in lymph node biopsy). This will be estimated along with a 95% confidence interval for the proportion.

10.5.5 To describe the quality of life of patients with MCD before, during and after treatment with a rituximab-based, risk-adjusted treatment approach, as assessed by the MCD symptom score[42] and PROPr instrument.[44]

The MCD symptom score will be summed and differences across treatment will be compared using a paired t-test. We hypothesize that quality of life will be significantly improved from baseline to end of treatment with rituximab-based treatment (the MCD symptom score will be lower and PRO-Pr will be higher in utility).

10.5.6 To describe the trends in hemoglobin, platelet count, CRP, IL-6, IL-10, and KSHV viral load before, during, and after treatment with a risk-adjusted, rituximab-based treatment for MCD in Malawi, and to describe the utility of these markers as a predictor of relapse.

Hemoglobin, platelet count, CRP, IL-6, IL-10, and KSHV viral load will be measured at baseline, day 15, and end-of-treatment. Differences will be compared by paired t-test. We hypothesize that hemoglobin, platelet count, CRP, and plasma KSHV viral load will be strongly associated with disease activity (hemoglobin and platelet count will increase in remission and CRP and KSHV viral load will decrease in remission).

10.6 Exploratory Objectives

10.6.1 [redacted]

[redacted]

11.0 STUDY MANAGEMENT

11.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment into this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all relevant elements currently required by FDA and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

11.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Protocol Office (CPO) at UNC.

- A copy of the official IRB approval letter for the protocol and informed consent form(s)
- IRB membership list
- CVs and medical licensure for the study PI and any sub-investigators who will be involved in the study.
- The study PI's signature documenting understanding of the protocol and providing commitment that this trial will be conducted according to all stipulations of the protocol is sufficient to ensure compliance
- College of American Pathologists and Clinical Laboratory Improvement Amendments certification numbers and institution laboratory normal values
- Executed clinical research contract

11.3 Data Management and Monitoring/Auditing

The CPO at UNC LCCC will serve as the coordinating center for this trial. All data will be collected and entered into eCRFs by research coordinators.

The sponsor will provide direct access to source data/documents for trial-related monitoring, audits, Independent Ethics Committee and IRB review, and regulatory inspection. As an investigator-initiated study, this trial will also be audited by the LCCC compliance committee every 6 or 12 months.

Provision of Data to Correlative Scientists

Identification and Role of the Study Coordinator (or other named role) as the Honest Broker

The study coordinator (or other named role) will be in charge of collecting and maintaining all data points and data management. The study coordinator should have adequate training to enter, manage, and deidentify data. The study coordinator will provide a unique study number to each enrolled subject. All documentation and samples will be labeled with the unique study number. The correlative teams will only be provided this unique study ID number as opposed to any other patient identifiers. The clinical team will be the only people able to access identifiable data and the study coordinator will be a conduit to provide the de-identified data to the correlative team.

Requests for a data

Identifiable data will not be given out to any correlative investigators at any time. UNC correlative Investigators may ask the study coordinator for a specific data set, and the study coordinator will return a deidentified data set. This data may only be used for purposes of the study. Any use other than directly related to the study must be approved by the IRB of record. If there is a need for an investigator to access identifiable data during the study, then a new IRB application will need to be submitted from that investigator detailing the reasons needed to access that data. The study coordinator will also ensure that correlative results are not returned from the correlative team to the clinical team to dictate treatment or follow-up decisions unless this is specifically approved by the IRB of record and delineated in the clinical protocol.

11.4 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.4.1 Emergency Modifications

UNC may implement a deviation from or change of the protocol to eliminate immediate hazard(s) to trial subjects without prior approval/favorable opinion from UNC or their respective institution's IRB.

For any such emergency modification implemented, a UNC IRB modification form must be completed by UNC research personnel within five business days of making the change.

11.4.2 Single Patient/Subject Exceptions

Eligibility single subject exceptions are not permitted for LCCC investigator-initiated trials under any circumstances. Other types of single subject exceptions may be allowed if proper regulatory review has been completed in accordance with LCCC Single Subject Exceptions Policy.

11.4.3 Other Protocol Deviations/Violations

According to UNC IRB, a protocol deviation is any unplanned variance from an IRB-approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s)

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants
- Has damaged the scientific integrity of the data collected for the study
- Results from willful or knowing misconduct on the part of the investigator(s)
- Demonstrates serious or continuing noncompliance with federal regulations, state laws, or university policies

If a deviation or violation occurs, please follow the guidelines below:

Protocol Deviations: UNC will record the deviation in OnCore® and report to any sponsor(s) or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Violations should be reported by UNC personnel within one week of the investigator becoming aware of the event using the same IRB online mechanism used to report unanticipated problems.

Unanticipated Problems:
Any events that meet the criteria for "Unanticipated Problems" as defined by UNC IRB must be reported by the study personnel using the IRB's web-based reporting system.

11.5 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the study PI at UNC. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the subject, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to UNC IRB for approval prior to implementation.

11.6 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, sponsor correspondence to investigators, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed subject consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug/investigational product seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization region. In all other cases, study documents should be kept on file until three years after completion and final study report of this investigational study.

11.7 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The study PI is responsible for personally overseeing the treatment of all study subjects. The study PI must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The study PI will be responsible for assuring that all required data will be collected and entered in the eCRFs. Periodic auditing and monitoring of trials will be conducted and the study PI will provide access to his/her original records to permit verification of proper data entry. At study completion, all eCRFs will be reviewed by the study PI and will require their final signature to verify accuracy of the data.

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13.0 APPENDICES

13.1.1 Appendix A. Febrile Neutropenia SOP

PURPOSE

To standardize the management of neutropenic fever among cancer patients receiving chemotherapy at UNC Project Malawi.

DEFINITION

Patients with neutropenic fever must have both of the following:

1. **Fever** (= Temperature $\geq$ 38.0°C)*
2. **Neutropenia** (= Neutrophil # $\leq$ 0.5 x $10^3/\mu L$)

*Rectal temperatures must be AVOIDED in neutropenic patients.

All patients receiving chemotherapy should be informed of increased risk for infection and the importance of routine preventive measures (hand washing, avoid sick contacts, food and water hygiene, etc.)

Patients should also be instructed about the importance of returning promptly to Tidziwe for evaluation if any fever develops during receipt of chemotherapy.

INITIAL DIAGNOSTIC EVALUATION

The initial evaluation of a patient with neutropenic fever should include a complete history and physical exam in search of a potential source of infection. Importantly, signs of infection may be less evident in neutropenic patients due to the absence of a typical immune response. The evaluation should include the following components ***at a minimum***, and others as clinically indicated:

Review of symptoms	Physical exam	Laboratory/ radiology
Upper respiratory symptoms	Blood pressure (orthostatics if possible)	Full blood count with differential
Sinus tenderness/ drainage	Sinus/ nasopharynx	Electrolytes
Pain with swallowing, nausea, Vomiting	Oropharynx/ mucositis	Liver and renal function tests
Cough, shortness of breath	Lungs, pulse oximetry	Blood culture
Abdominal pain, diarrhea	Abdomen	Urinalysis
Perirectal tenderness	Perineum (NO routine digital rectal exam)	Chest x-ray
New skin lesions	Skin (nodules, rash)	Malaria blood smear

Stiff neck, confusion	Mental status	
	Lymph nodes	

MANAGEMENT

Inpatient versus Outpatient Care

*Clinical judgment is MORE important than any algorithm.

MASCC predictive model: calculate total score

Burden of illness	Score
No or mild symptoms	5
Moderate symptoms	3
No hypotension	5
No lung disease	4
Solid tumor (not hematologic malignancy)	4
Outpatient status	3
No dehydration	3
Age <60 years	2
Total	

Persons who may be candidates for outpatient oral therapy:

- MASCC score $\geq$ 21
- Will be closely observed in the home (does not live alone)
- Can return to Tidziwe promptly if clinical worsening
- No identified focus of bacterial infection
- No signs or symptoms suggestive of systemic infection (rigors, hypotension)
- Easy outpatient follow-up in 3-5 days
- Not taking other oral antimicrobials

If HIV-infected, no CD4 count specifically prohibits outpatient oral therapy, but caution regarding this approach is advised if pre-chemotherapy CD4 count <100 cells/μL.

Initial Empiric Antibiotics

Please also refer to UNC Project Malawi antibiogram attached to the end of this document as needed.

If appropriate for outpatient oral therapy (and not allergic to fluoroquinolones or beta-lactams):

- **Ciprofloxacin 750mg PO BD + Amoxicillin-clavulanate (Augmentin) 500-125mg PO TDS***

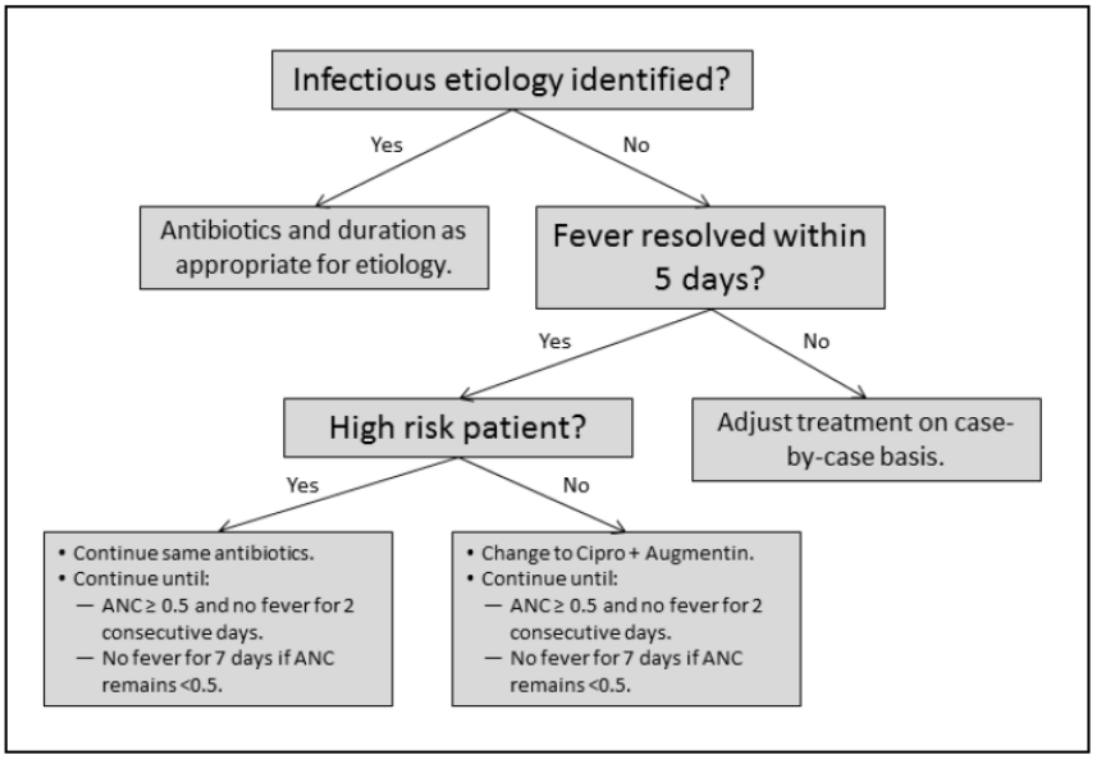
*Not recommended if patient is already on Ciprofloxacin prophylaxis or cannot take oral medicines reliably.

If not appropriate for outpatient oral therapy:

- **Ceftriaxone 2g IV OD + Ciprofloxacin 750mg PO BD* OR**
- **Ceftriaxone 2g IV OD + Gentamicin 5mg/kg IV OD****
- **Add Metronidazole 400mg PO TDS for anaerobic coverage if suspected abdominal or perineal infection**

*Not recommended if patient is already on Ciprofloxacin prophylaxis or cannot take oral medicines reliably.
**Assumes normal renal function. Dose adjustment required if creatinine is abnormal.

Subsequent Care



All subsequent care should be in collaboration with consultants.

Consider the following for non-resolving fever:

- **Additional diagnostic workup.**
- **Antibiotic escalation.**
    - **Piperacillin-Tazobactam 4.5g IV TDS OR Meropenem 1g IV TDS (depending on availability).**
- **Adding antifungal therapy (i.e. Fluconazole 400mg OD).**

Chemotherapy dose should be modified with next chemotherapy cycle if required by study protocol.

Consider antibiotic prophylaxis to prevent neutropenic fever with subsequent chemotherapy cycles:

- **Ciprofloxacin 500mg PO BD.**

Monitoring of serum creatinine should be repeated after 5 days in patients receiving gentamicin.

13.1.2 Appendix B. UNC Project Malawi Antiemetic SOP

***Antiemetic risk derived from most recent ASCO Clinical Practice Guidelines on Antiemetics**

See table: https://www.asco.org/sites/new-www.asco.org/files/content-files/2017-Emetic-Risk-Antineoplastic-Agents-chart.pdf

Prophylaxis and as-needed antiemetic recommendations for UNC Project Malawi.

Antiemetic Risk	Treatment	Dose on day 1	Dose others
High (Doxorubicin + Cyclophophamide combo)	Granisetron OR Ondansetron	2 mg PO or 1 mg IV 8 mg PO Q6 hours x 2 doses or 8 mg IV x1	
	Dexamethasone	12 mg PO or IV	
	+/- Olanzapine	10 mg PO	10 mg PO days 2-4
High (all others)	Granisetron OR Ondansetron	2 mg PO or 1 mg IV 8 mg PO Q6 hours x 2 doses or 8 mg IV x1	
	Dexamethasone	12 mg PO or IV	8 mg PO or IV days 2-4
	+/- Olanzapine	10 mg PO	10 mg PO days 2-4
Moderate	Granisetron OR Ondansetron	2 mg PO or 1 mg IV 8 mg PO Q6 hours x 2 doses or 8 mg IV x1	
	Dexamethasone	8 mg PO or IV	8 mg PO or IV days 2,3
Low	Granisetron OR Ondansetron	2 mg PO or 1 mg IV 8 mg PO Q6 hours x 2 doses or 8 mg IV x1	
	Dexamethasone	8 mg PO or IV	

13.1.3 Appendix C. UNC Project Malawi Extravasation SOP

I. Purpose

Extravasation occurs when some or all the chemotherapy infusion flows into the tissues of the surrounding area of cannula insertion. The degree of extravasation will depend on the site and amount infiltrated concentration and nature of the agent. Necrosis, damage to tendons, nerves and joints may occur. The purpose of this SOP is to standardize the recognition, prevention, and management of extravasation among cancer patients receiving chemotherapy at UNC Project Malawi.

II. Scope

This SOP applies to UNC Project Malawi staff involved in participant management of extravastion. Staff include research nurses, research clinicians, and medical officers. This procedure applies to all NIH sponsored Network studies (AMC, HPTN, HVTN, ACTG, IMPAACT, MTN) and non-network studies.

III. Allowable Exceptions

This SOP is meant to be followed without deviation. However, it is an allowable exception to follow procedures specified in a protocol or Study Specific Procedure Manual (SSP) that may deviate from this SOP.

IV. Procedure

A. Clinical Features of Extravasation

- Immediate swelling
- Pain
- Burning
- Stinging
- Erythema or swelling around the cannula site
- Signs of poor flow via the cannula (ex. resistance, poor flow rate, and/or inadequate back flow of blood)
- Severe pain or burning, redness with ulceration 48-96 hours after infusion

B. Risk Factors for Extravasation

- Multiple cannulation/venipuncture sites. Avoid needle insertion distal to recent (<24hrs) venipuncture site.
- Avoid positioning siting cannula in antecubital fossa, crossing joints, overlying vital structures (e.g. nerves or tendons, in previously irradiated areas)
- Fragile veins
- Swollen arms

Note: If you cannot find a good vein get help. Do not administer chemotherapy if in doubt.

C. Prevention of Extravasation

- Safe positioning of cannula
- Frequent checks on cannula site and flow during chemotherapy administration
- Administer vesicants first
- Administer bolus vesicant through fast running drip
- Educating the patient on how to keep the cannula patent like proper positioning of the hand

D. Management of Extravasation

- Stop the infusion
- Aspirate as much of the drug as possible from the extravasation site via the cannula
- Inform the doctor immediately
- Mark the area
- Remove the cannula
- Make use of the extravasation kit if available
- Apply cold pack regularly for 24 hours (with the exception of vinca alkaloids, oxaliplatin which need a warm pack)
- Elevate the limb
- Apply 1% hydrocortisone cream
- Review frequently
- Use the other limb if chemo is to be continued
- Consult plastics team if it's a vesicant drug that's extravasated

13.1.4 Appendix D. UNC Project Malawi Hypersensitivity/Infusion Reaction SOP

Management of rituximab hypersensitivity reactions				
Grade	Symptoms	Medications	Nursing Care	Reinfusion
1 (mild)	Itching Flushing Rash Fevers Rigors	Diphenhydramine 25 mg IV	Vital signs every 10 minutes until resolution of symptoms	Resume at half the previous rate once symptoms completely resolve
2 (moderate)	Dyspnea Chest tightness	Diphenhydramine 25 mg IV Ranitidine 50 mg IV Dexamethasone 20 mg IV		
3 (severe)	Stridor Wheezing Respiratory distress Generalized hives Angioedema Hypotension not responsive to fluids Decreased responsiveness	Diphenhydramine 25 mg IV Ranitidine 50 mg IV Dexamethasone 20 mg IV Normal saline 1 L bolus Epinephrine 0.3 mg IM Bronchodilators		Do not resume

13.1.5 Appendix E. ECOG Performance Status

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
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).
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.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.