BrUOG 326: A Phase I Dose-Escalation Study of Vincristine Sulfate Liposome Injection (Marqibo®) in Combination with Bendamustine and Rituximab (BRiM) in Indolent non-Hodgkin Lymphoma (IIS-MAR-003)

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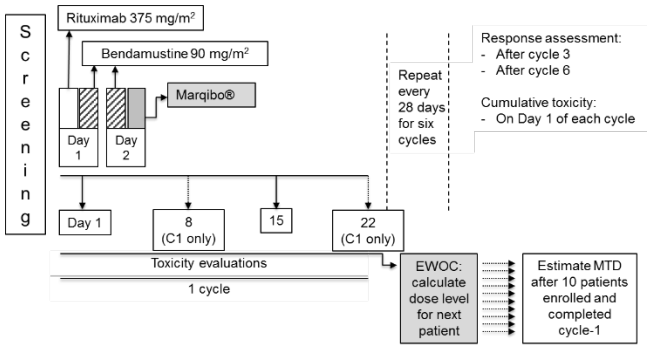
PROTOCOL SYNOPSIS Title of Study:	A Phase I Dose-Escalation Study of Vincristine Sulfate Liposome Injection (Marqibo®) in Combination with Bendamustine and Rituximab (BRiM) in Indolent non-Hodgkin Lymphoma
Sponsor:	Adam Olszewski, MD
IND Number:	Study Exempt from IND Requirements per 21 CFR 312.2(b) and IND exemption letter from the FDA.
Study Centers:	Brown University Oncology Research Group – Rhode Island Hospital
Objectives:	Primary objective: • To establish the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of vincristine sulfate liposome injection (Marqibo®) in combination with bendamustine and rituximab (BRiM). • To establish the dose-limiting toxicities (DLT) of vincristine sulfate liposome injection (Marqibo®) in combination with bendamustine and rituximab (BRiM). Secondary objectives: • To evaluate cumulative rates of non-DLT toxicities of the BRiM combination in patients with non-Hodgkin lymphoma. • To evaluate tolerability, assessed by rate of completion of the planned six cycles of BRiM chemotherapy. • To evaluate response rate (RR) and complete response rate (CR) of the BRiM regimen in the study population of indolent non-Hodgkin lymphoma patients.
Study Design:	Phase 1, single-center, open-label, single-arm trial in 10 patients with indolent B-cell non-Hodgkin lymphoma otherwise appropriate for bendamustine-rituximab as initial or subsequent line of therapy. Patients will receive the BRiM regimen, consisting of rituximab and bendamustine (standard doses) in combination with vincristine sulfate liposome injection (Marqibo®)—at a patient-specific dose determined by the Escalation With Overdose Control (EWOC) protocol, from 1.8 mg/m^2 to the ceiling dose of 2.4 mg/m^2. The treatment will continue at the same dose for up to 6 cycles. Patients will be evaluated weekly during Cycle 1 to assess toxicity and identify dose-limiting toxicities (DLT). During Cycle 2-6 patients will be followed every two weeks. The response to chemotherapy will be evaluated after Cycles 3 and 6 of treatment- see section 6. The maximum tolerated dose (MTD, recommended phase II dose) of Marqibo® in the BRiM combination will be defined upon completion of the trial as the median of the marginal posterior distribution of the MTD. **The trial will be terminated if the first three patients experience a DLT or anytime the posterior probability that the DLT rate at the minimum dose exceeds 0.33 is 0.8 or more.**
Dosing schema	

Study Treatment Assignments	• **Rituximab** at 375 mg/m^2 intravenously over 3-5 hours on Day 1 • **Bendamustine** at 90 mg/m^2 intravenously over 10 to 30 minutes on Day 1, 2 • **Marqibo®** at patient-specific dose, intravenously over 60 minutes on Day 2 —every 28 days for up to six cycles.
Number of Subjects:	Ten (10) patients will be treated.
Target Population:	Adult subjects with indolent B-cell non-Hodgkin lymphoma otherwise appropriate for therapy with bendamustine-rituximab regimen according to current National Comprehensive Cancer Network (NCCN Guidelines®). The following subtypes are allowed: • Follicular lymphoma; • Mantle cell lymphoma; • Marginal zone lymphoma, not amenable to curative therapy; • Small lymphocytic lymphoma; • Lymphoplasmacytic lymphoma; • Other indolent B-cell lymphomas (including not otherwise specified, NOS); Patients may receive the protocol therapy as the initial or subsequent line of treatment, as long as bendamustine-rituximab is an otherwise clinically appropriate treatment option.
Duration of Treatment:	In the absence of clinical or radiographic progression or prohibitive toxicity, patients will continue therapy for up to six 28-day cycles.
Discontinuation:	Patients may be discontinued from the study treatment for the following reasons: • Occurrence of a DLT in the first cycle of treatment, • Disease progression, • The need for administration of therapy for lymphoma not specified in the protocol; this includes any form of chemotherapy, radiation therapy or biologic therapy; • Intercurrent illness that prevents further administration of treatment, • Adverse event(s) deemed unacceptable by the patient or the treating physician, • Patient decides to withdraw from the study for any reason, or • General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
Diagnosis and Main Eligibility Criteria:	• **Eligibility criteria**: Patients must have histologically confirmed indolent B-cell non-Hodgkin lymphoma, CD20-positive, previously treated or untreated-for which bendamustine-rituximab chemotherapy is clinically indicated; the following subtypes are allowed: Follicular lymphoma; Mantle cell lymphoma; Marginal zone lymphoma; Small lymphocytic lymphoma; Lymphoplasmacytic lymphoma, or Indolent B-cell lymphoma, NOS. • Radiological measurable disease, defined as any measurable lesion >15 mm on the staging CT or PET/CT. Patients with blood or bone marrow involvement only are ineligible. Splenomegaly is acceptable as a measurable site if enlarged on the initial CT scan (>13 cm in the cranio-caudal dimension). • Previous treatment for lymphoma is allowed, with the exception of use of bendamustine within 180 days of the date of the consent form, or any prior use of vincristine sulfate liposome injection (Marqibo®). • Age ≥18 years. • ECOG performance status 0 or 1 (see Appendix A). • Life expectancy of greater than 6 months. • Patients must have adequate organ and marrow function as defined below:

- leukocytes ≥3,000/mm3
- absolute neutrophil count ≥1,000/mm3
- platelets ≥75,000/mm3
- total bilirubin within normal institutional limits
- AST(SGOT)/ALT(SGPT) <2.5 × institutional ULN
- creatinine <2.0 mg/mL
- AND
- creatinine clearance <50 mL/min/1.73 m2. calculated by method of Cockroft and Gault

- Prevention of pregnancy.
- The effects of bendamustine and vincristine on the developing human fetus are unknown. For this reason and because Class D agents as well as other therapeutic agents used in this trial are known to be teratogenic, women and men of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence; vasectomy) prior to study entry and up to 4 months after the last dose of study treatment.
- Women of childbearing potential must have a negative serum or urine pregnancy test within 14 days prior to first treatment on study (Cycle 1, Day 1). Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Postmenopausal women (after surgical menopause or no menses for >12 months) do not need to have a pregnancy status, but their postmenopausal status must be documented.
- Ability to understand and the willingness to sign a written informed consent document.

Exclusion criteria:

- History of any allergic reaction attributed to rituximab (with the exception of <grade 3 infusion reaction), bendamustine, vincristine sulfate, Marqibo®, mannitol, sodium phosphate injection or sphingomyelin/cholesterol liposome.
- Patients who have had any lymphoma-directed radiotherapy, chemotherapy, biologic or experimental therapy, oral or intravenous, within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier to ≤grade 1-with the exception of alopecia, which is allowed.
- Any prior treatment with vincristine sulfate liposome injection (Marqibo®).
- Prior treatment with bendamustine or vincristine sulfate within 180 days of enrollment. Prior treatment with rituximab is allowed.
- Patients who are receiving any other investigational agents or anti-cancer therapy with the exception of endocrine therapy for breast or prostate cancer.
- Patients with known central nervous system involvement (infiltration of the brain, meninges or cerebrospinal fluid) by the lymphoma are excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.
- Active peripheral sensory or motor neuropathy > grade 1. This is defined by the CTCAE as any neuropathy requiring intervention or limiting instrumental activities of daily life.
- History of demyelinating form of Charcot-Marie-Tooth syndrome, acquired demyelinating disorders, or other demyelinating condition.
- Documented positive test for the Human Anti-Chimeric Antibody (HACA).
- Patients receiving any medications or substances that are strong inhibitors or inducers of CYP3A enzyme are ineligible.

- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection (that requires antibiotic use which is not prophylactic), symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements. In cases of uncertainty, the PI will decide whether an illness is considered prohibitive. Suppressive antiviral therapy with acyclovir, famciclovir, or valacyclovir for herpes simples or herpes zoster is allowed.
- Prisoners.
- Pregnant or breast-feeding women.
- Known Human Immunodeficiency Virus (HIV) or active Hepatitis B infection (defined as presence of HBV DNA or hepatitis B S antigen in the blood).
- Any prior or active cancer, which in the opinion of the investigator would preclude safe participation in this study.

Study Procedures/ Frequency:

Patients will undergo screening and registration procedures, including staging of their lymphoma using a CT scan or a PET/CT scan and, if clinically indicated, a bone marrow biopsy.

Patients will receive the study regimen (BRiM), approximately every 28 days for up to 6 cycles. Patients will undergo clinical and laboratory evaluation on approximately Day 1, 8, 15 and 22 of Cycle-1 of therapy, and a on Day 1 and 15 of each subsequent cycle of treatment.

Patients will undergo radiographic assessment of response using a CT scan or a PET/CT scan after Cycle-3 and Cycle-6 of therapy. Bone marrow aspiration and biopsy may be performed after completion of therapy if indicated to confirm complete remission.

Test Product, Dose, and Mode of Administration:

Commercially available preparation of bendamustine and rituximab will be used in this study, and administered as in general clinical practice. The drugs will be administered as outpatient, intravenously.

VSCLI (Marqibo®) will be supplied as a single use, 3-vial kit designed to enable entrapment of vincristine in liposomes at the time of use.

Patients will receive Marqibo® at a patient-specific dose determined at the time of registration by the EWOC algorithm, from 1.8 mg/m^2 up to the ceiling dose of 2.4 mg/m^2 (maximal actual dose given to any study patient will be 2.3 mg/m^2), as an intravenous infusion over 60 minutes on Day 2 of each cycle.

Dose Escalation Schedule

Dose Level	Dose*		
	Rituximab (mg/m^2)	***Bendamustine (mg/m^2)***	***Marqibo® (mg/m^2)***
Level 1	375 (Day 1)	90 (Day 1 and 2)	1.80
Levels 2-10	375 (Day 1)	90 (Day 1 and 2)	EWOC-specified 1.8 – 2.4 mg/m^2

**Doses are stated as exact dose in units (*e.g.*, mg/m^2, mcg/kg, etc.) rather than as a percentage.*

Criteria for Evaluation:

Dose-limiting toxicity (DLT) will be defined as one of the following adverse reactions occurring during the first cycle of study therapy:

- Grade 4 neutropenia (< 500/mm3) lasting > 7 days
- Grade 3 neutropenia (<1000/mm3) with fever or infection;

- Grade 4 thrombocytopenia (<25,000/mm3);
- Grade 3 thrombocytopenia (<50,000/mm3) requiring transfusion;
- Grade 3 or 4 treatment-related non-hematologic toxicity, excluding:
  - Alopecia.
  - Grade 3 nausea or vomiting if corrected to ≤ grade 2 within 48 hours.
  - Grade 3 or 4 infusion reactions if occurring on Day 1 of Cycle 1.
- Delay of 2nd cycle of treatment for >14 days.

Safety: Adverse events and laboratory results will be summarized as proportions of patients experiencing toxicity. Toxicity will be graded according to the NCI CTCAE v4.0.

Efficacy: Response rate will be evaluated according to The Revised International Working Group Response Criteria for malignant lymphomas.

Statistical Methods and Sample Size:

The primary endpoint **(Maximum tolerated dose, MTD)** will be defined as the dose level of Marqibo® in the BRiM combination, that when administered to a patient results in a probability of 33% that a DLT will be manifest within the first cycle of treatment. For this purpose, consecutive patients will be treated with BRiM chemotherapy using escalating doses of Marqibo®. Subjects will be enrolled in cohorts of *N*=1 (i.e. the next subject will be enrolled only after the DLT status of all previous subjects have been resolved and a new dose level assigned). The dose escalation schema will use the Escalation With Overdose Control (EWOC) design and software—a Bayesian method permitting precise determination of the therapeutic working-dose while directly controlling the likelihood of an overdose. MTD will be determined after completion of the study using the EWOC algorithm. It will be calculated as the median of the marginal posterior distribution of the MTD, rounded to 0.05 mg/m2.

The Marqibo® dose will be escalated from the starting dose (1.8 mg/m^2). The maximum dose in the escalation scheme will be set at 2.4 mg/m^2, but this dose is never actually administered to any patient. The maximum actual dose that might be administered in the absence of any DLT's will be 2.3 mg/m^2.

The trial will be terminated if the first three patients experience a DLT or anytime the posterior probability that the DLT rate at the minimum dose exceeds 0.33 is 0.8 or more..

The baseline rate of serious adverse events (SAE) with BR is assumed to be equal to 19% (as derived from the STiL phase III trial, Rummel et al., Lancet. 2013;381(9873):1203-10). The sample size of 10 subjects for the current study is chosen on the basis of a simulation of *N*=100 trials, assuming the target probability of DLT (θ) of 33%, probability of exceeding target dose (α) of 25% (with variable α increment of 5%), starting Marqibo® dose of 1.8 mg/m^2, and maximal dose of 2.4 mg/m^2. The study will be able to correctly estimate the MTD in the range of 1.80 mg/m^2 to 2.20 mg/m^2 with >80% of patients treated at ±10% of the optimal dose.

A simulation of *N*=500 trials with the above parameters, with sample size varying between 10 and 30, demonstrates that for the range of true MTD from 1.85 mg/m^2 to 2.20 mg/m^2, trials with sample size of 10 will deliver a reasonably precise estimate of MTD according to the operating characteristics described in Section 16.

ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate transaminase
AUC	Area under the curve
AUC_{inf}	Area under the concentration vs. time curve extrapolated to infinity
BP	Blood pressure
BR	Bendamustine and rituximab
BRiM	Bendamustine, rituximab and Marqibo®
BSA	Body surface area
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisone
CI	Confidence interval
CNS	Central nervous system
CR	Complete remission
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CVP	Cyclophosphamide, vincristine and prednisone
CYP3A4	Cytochrome P450 3A4
DA-EPOCH	Dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
ECOG	Eastern Cooperative Oncology Group
EWOC	Escalation With Overdose Control
FDG	Fluorodeoxyglucose
FL	Follicular lymphoma
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonisation
IND	Investigational New Drug (Application)
IRB	Institutional review board
IV	Intravenous
kg	Kilogram
LDH	Lactate dehydrogenase

LPL	Lymphoplasmacytic lymphoma
MCL	Mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MTD	Maximal tolerated dose
MZL	Marginal zone lymphoma
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	Non-Hodgkin's lymphoma
nM	Nanomolar
PD	Progressive disease
PE	Physical examination
PET	Positron emission tomography
PFS	Progression-free survival
PR	Partial remission
PT	Prothrombin time
PVC	Poly vinyl chloride
RCHMP	Rituximab, cyclophosphamide, doxorubicin, Marqibo® , prednisone
RCHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
SAE	Serious adverse event
SD	Stable disease
SGOT	Serum glutamic oxalo-acetic transaminase (same as AST)
SGPT	Serum glutamic pyruvic transaminase (same as ALT)
SPD	Sum of the product of diameters
US	United States
USP	United States Pharmacopeia
vs	*versus*
VSLI	Vincristine sulfate liposome injection
WBC	White blood cell (count)

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1. OBJECTIVES

1.1 Primary Objectives

- To establish the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of vincristine sulfate liposome injection (Marqibo®) in combination with bendamustine and rituximab (BRiM).
- To establish the dose-limiting toxicities (DLT) of vincristine sulfate liposome injection (Marqibo®) in combination with bendamustine and rituximab (BRiM).

1.2 Secondary Objectives

- To evaluate cumulative rates of non-DLT toxicities during the six planned cycles of the BRiM combination in patients with indolent non-Hodgkin lymphoma.
- To evaluate tolerability, assessed by rate of completion of the planned six cycles of BRiM chemotherapy.
- To evaluate response rate (RR) and complete response rate (CR) of the BRiM regimen in the study population of indolent non-Hodgkin lymphoma patients.

2. BACKGROUND

2.1 Therapy of Mature B-Cell Non-Hodgkin Lymphomas

Mature B-cell non-Hodgkin lymphomas (NHL) are a highly heterogeneous group of lymphoid malignancies, which comprise nearly 20 subtypes according to the most recent 2008 World Health Organization classification. They range from indolent lymphomas often managed by "watchful waiting" until symptomatic phase, to highly aggressive diseases associated with poor prognosis and immediate need for aggressive chemotherapy.[1] B-cell NHL is typically treated with chemotherapy in combination with the monoclonal antibody rituximab.

The treatment in aggressive B-cell NHL, such as diffuse large B-cell lymphoma (DLBCL) is curative and most commonly involves the RCHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). In contrast, therapy in "indolent NHL", which include, among else, follicular lymphoma (FL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), lymphoplasmacytic lymphoma (LPL) and small lymphocytic lymphoma (SLL), is geared towards achieving a partial or complete remission, although most patients experience further recurrences of the disease and are not cured.

For decades, regimens utilizing the alkylating agent cyclophosphamide and vincristine, such as CHOP/RCHOP and CVP/RCVP, have been the mainstay of therapy for B-cell NHL. A number of randomized studies have established RCHOP as the standard treatment for DLBCL.[2-6] In indolent B-cell NHL, the acceptable front-line regimens included rituximab alone, RCHOP, RCVP and combinations of rituximab with fludarabine ± mitoxantrone—depending on patient characteristics, comorbidities and burden of the lymphoma.[7-11] MCL is associated with poorer prognosis than other indolent NHLs and in recent trials more aggressive treatments are investigated for this disease.[12] These regimens are typically prescribed for 6 to 8 cycles, delivered every 21 days, with additional chronic maintenance therapy using single-agent rituximab in FL.[9]

2.2 Bendamustine-Rituximab: Standard Front-Line Therapy in Indolent NHL

Bendamustine is an alkylating neoplastic agent. Rituximab is a monoclonal antibody against the CD20 molecule present on mature B-cells. In 2005 the combination of bendamustine with

rituximab has shown high activity in relapsed/refractory indolent NHL (FL and MCL). In a phase II trial of 63 patients, Rummel et al. achieved an overall response rate of 90% and complete remission rate of 60%, with a median progression-free survival (PFS) of 24 months.[13] This regimen was notable for its tolerability: non-hematologic toxicities were limited to grade 1-2, with at 16% risk of grade 3/4 neutropenia, and only 3% rate of other grade 3-4 hematologic toxicities. These results were confirmed in a North American phase II study, with an overall response of 92%, CR rate of 41%, PFS of 23 months and 36% rate of grade 3-4 neutropenia and very rare non-hematologic severe adverse events: febrile neutropenia 6%, infections 10%.[14] **The BR regimen is not associated with significant rates of peripheral neuropathy or ileus.**

Two subsequent large randomized trials have compared BR with RCHOP/RCVP as a front-line therapy in indolent NHL. The German Study Group for Indolent Lymphomas (StiL) trial randomized 549 patients with FL, MCL, MZL, LPL, SLL or other low-grade B-cell NHL (not otherwise specified, NOS) to 6 cycles of RCHOP or BR.[15] At a median follow-up of 45 months, BR was associated with a significantly longer PFS (68.5 months vs 31.2 months, hazard ratio 0.58, 95% CI 0.44-0.74), and significantly improved CR rate (40% vs 30%), despite similar overall RR (93% vs 91%). The overall survival did not differ between the treatment groups. In the BRIGHT study, 487 patients with indolent NHL were randomized to RCHOP/RCVP or BR.[16] In this trial, BR was shown to be non-inferior to RCHOP/RCVP in the primary endpoint (CR, 31% vs 25%), as well as overall RR (97% vs 91%).

In both studies, the toxicity of BR was significantly more favorable than that of RCHOP, and was generally quite manageable, with very low rates of non-hematologic grade 3-4 toxicities. Moreover, BR was shown to improve patients' quality of life better than RCHOP/RCVP in the BRIGHT study.[17]

Table 1. **Rates of adverse events in phase III trials of BRin indolent NHL.**

Grade 3-4 adverse event	**Rate in StIL Rummel at al.[15]**	**Rate in BRIGHT Flinn et al.[16]**
All grade 3-4	**19%**	**Not reported**
Neutropenia	29%	39%
Anemia	3%	0%
Thrombocytopenia	5%	10%
Infection	Not reported	12%
Vomiting	0%	5%
Fatigue	0%	4%
Other (grade 1-4)		
Infection	37%	55%
Paresthesiae	7%	9%
Stomatitis	6%	3%
Skin (erythema)	16%	
Skin (allergic reaction)	15%	20%
Sepsis	<1%	

The results of those two randomized studies established BR as a standard front-line regimen in indolent B-cell lymphomas. Current US national guidelines from the National Comprehensive Cancer Network (NCCN Guidelines®) for the management of indolent NHL recommend BR as a top category 1 front-line treatment option for patients with FL (grade 1-2), MCL (for patients requiring less aggressive therapy), disseminated non-gastric MZL, and LPL.[18]

2.3 Combinations of Bendamustine (with or without Rituximab) with Other Cytotoxic Agents, Including Vincristine

Because of the excellent toxicity profile of BR, several studies have evaluated combinations of this regimen with additional chemotherapeutic agents. In a phase II study in 40 patients with MCL ineligible for more intense regimens, bendamustine (70 mg/m^2 on Day 1, 2) with rituximab (375 mg/m^2 on Day 1) and cytarabine (MTD of 800 mg/m^2 on Day 2, 3, 4) showed acceptable tolerance, with reversible myelosupression as the principal toxicity: 12% rate of febrile neutropenia, transient grade 3-4 thrombocytopenia in 87%, 35% rate of fatigue (5% grade 3), 15% rate of infection (12 % grade 2-3), 15% rate of rash, 10% rate of elevated transaminases (2% grade 3) and 40% gamma-glutamyltransferase elevation.[19] This regimen was characterized by a highly encouraging 100% RR in previously untreated patients (80% in relapsed/refractory MCL).

In relapsed/refractory indolent NHL, BR has been also combined with bortezomib—a proteasome inhibitor characterized by peripheral neuropathy and thrombocytopenia as the principal dose-limiting toxicities.[20] The regimen of bendamustine (90 mg/m^2 on Day 1 and 4), rituximab (375 mg/m^2 on Day 1) and full-dose bortezomib (1.3 mg/m^2 on Day 1, 4, 8, 11) was administered to 30 patients, and most non-hematologic adverse events were grade 1-2 only with the rates of nausea 50%, neuropathy 47%, fatigue 47%, constipation 40% and fever 40%. Eight patients (26%) experienced serious adverse effects, which included gr. 4 liver/renal failure, gr. 5 sepsis, gr.3 peripheral neuropathy, fatigue, hypotension, herpes zoster and dehydration (in 1 or 2 cases each). This toxicity was deemed acceptable to proceed with a randomized study of BR with BR+bortezomib (NCT01216683). Another US phase II study (VERTICAL trial) of bortezomib and BR in 73 patients with relapsed/refractory FL also showed limited toxicity, with dose escalation of bendamustine from 50 mg/m^2 to 90 mg/m^2 (on Day 1, 2) without reaching the MTD.[21] The overall rate of $\geq$ grade 3 toxicities was 77%, with 34% patients experiencing an SAE. The rates of grade 3-4 toxicities were: neutropenia 25%, thrombocytopenia 14%, fatigue 12%, diarrhea 12%, neuropathy 11%, vomiting 8%, nausea 7%. The overall rate of peripheral neuropathy was 44%, constipation 45% and fever 34%.

Bendamustine had been previously combined with vincristine and prednisone and compared with an analogous regimen of cyclophosphamide, vincristine and prednisone in a phase III trial conducted in Germany in 2006—as a front-line therapy for patients with indolent NHL.[22] The schedule of bendamustine in this trial differed from currently used standards (60 mg/m^2 on Day 1, 2, 3, 4 and 5—total 300 mg/m^2 per cycle). The dose of vincristine was 2 mg (Day 1) and was not weight- or BSA-adjusted. The toxicity profile of this regimen was as follows: grade 3-4 leukopenia in 19%, anemia in 10%, thrombocytopenia 4%, infection 2% (all grades: 14%), peripheral neuropathy 1.2% (all grades: 35%), constipation 0.8% (all grades: 10%). The protocol initially specified bendamustine at 70 mg/m^2 for 5 days (total dose per cycle 350 mg/m^2), which was reduced after enrollment of the first 25 patients because of significant thrombocytopenia. There were no significant differences between those two arms in the rate of RR, CR, although PFS favored the bendamustine-based combination.

Those results suggest that BR can be safely combined with other cytotoxic agents that may cause peripheral neuropathy or myelosupression, including vincristine sulfate.

2.4 Vincristine Sulfate

Vincristine sulfate (22-oxovincaleukoblastine) is an alkaloid antineoplastic agent derived from the periwinkle plant (*Vinca rosea* Linn.), with a high activity against lymphoid neoplasms. Vincristine

is a cell-cycle-specific agent which causes mitotic arrest in the M-phase by binding tubulin, a protein component of microtubules, and disrupting cell division. Vincristine sulfate is a significant component of some of the most active chemotherapy regimens for NHL, including RCVP, RCHOP or DA-EPOCH. It is also an essential component of treatment in high-grade lymphoid malignancies such as acute lymphoblastic leukemia and lymphoblastic lymphoma. Vincristine is metabolized primarily by the liver and excreted in the bile and feces. Elimination half-life in adults varies widely between 164 and 5100 minutes, depending on the assay, dose and rate of administration.[23]

The dose-limiting toxicity of vincristine sulfate is neurological.[23,24] In its most common form it is dose-dependent, symmetrical, and manifests as peripheral sensory and motor neuropathy. It can be classified as early—within 1 week of administration (decreased deep tendon reflexes, jaw or thigh pain, ileus), intermediate—within 2-3 weeks (paresthesiae, sensory loss, constipation, bladder dysfunction, hyponatremia related to the syndrome of inappropriate antidiuretic hormone), and late—beyond 3 weeks: foot/wrist drop, postural hypotension and erectile dysfunction, ophthalmoplegia, dysphagia. Cranial nerve damage or encephalopathy are rare. Distal neuropathy may progress to severe pain, weakness, gait disturbance, motor and sensory impairment. Vincristine-induced neuropathy is generally reversible although recovery may take months and is often incomplete. Because the toxicity was historically seen particularly in children treated with high doses (1.5-2.0 mg/m^2 weekly), the dose of vincristine sulfate is typically capped at total 2 mg per dose in all currently used regimens.[25]

Other toxicities associated with vincristine sulfate are rare and include alopecia, hyponatremia, constipation and colicky abdominal pain. These reflect a vincristine-induced autonomic nervous system dysfunction. Fatal adynamic ileus has been rarely observed. Vincristine sulfate is a vesicant and its extravasation can result in painful local inflammation. At conventional vincristine sulfate doses, myelosuppression is uncommon.

2.5 Vincristine Sulfate Liposome Injection (VSLI, Marqibo®)

Marqibo® (vincristine sulfate liposomes injection) is vincristine encapsulated in sphingomyelin/cholesterol liposomes. The lipid components in the liposome are sphingomyelin and cholesterol at a molar ratio of approximately 60:40 (mol:mol). Marqibo® was developed to improve activity, therapeutic index and pharmacokinetic profile of vincristine sulfate.[26,27] Clinical pharmacokinetic studies have shown it to be a long-circulating, slow release formulation, which in adults is characterized by an initial 3 to 12 hours delay in clearance after administration. This results in total vincristine levels that remain relatively constant before declining with time. It contributes significantly to the greater plasma exposure of total vincristine that is observed after administration of Marqibo® as compared to vincristine sulfate. The pharmacokinetics of total vincristine was not altered significantly after repeated dosing of Marqibo® up to 3 cycles (2.0 mg/m2 every 2 weeks=1 cycle). Liposomal encapsulation of vincristine sulfate does not alter its route of excretion from the body which is primarily biliary/fecal with urinary elimination comprising a minor pathway. Marqibo® has been administered to 809 subjects in 20 studies and 2 compassionate use programs since program initiation. It is currently approved by the US Food and Drug Administration for use at a dose of 2.25 mg/m^2 weekly in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies.

2.5.1 ***Pharmacokinetics***

The pharmacokinetics of Marqibo® was examined in a series of 7 clinical studies in adults with various solid and hematologic tumors, in hepatically impaired subjects, and in children with various tumors. The data are consistent and show that vincristine is retained in the plasma encapsulated in the liposomes for extended periods after administration of Marqibo®.[28] Released vincristine is undetectable at most time points in all patients for whom this was evaluated. Therefore, the total vincristine measured in plasma reflects liposomally encapsulated drug that may not be immediately bioavailable and may not be directly comparable to plasma levels of vincristine after administration of standard vincristine sulfate injection, which provides the drug in an immediately bioavailable form. Interpatient variability is high; however plasma clearance profiles for individual patients are consistent upon repeated exposure to Marqibo®. No drug accumulation in plasma is apparent upon repeated exposure with a 14 day interval. No consistent change in AUC or clearance was observed between Cycles 1 and 3 of treatment at 2.0 mg/m^2 every 14 days. Following IV administration of Marqibo®, urinary excretion was a minor route of elimination for vincristine and a metabolite, N-desformylvincristine. Less than 8% of the administered dose was eliminated in urine over the 96 hour observation period. Total vincristine clearance and plasma exposure (AUC_{inf}) did not appear to be influenced by gender, age, BSA, or cancer type.

2.5.2 ***Efficacy and toxicity as a single agent in NHL***

In a phase I study of 25 patients with various solid tumors, the maximum tolerated dose of Marqibo® was established at 2.4 mg/m^2 every 3 weeks and the recommended phase II dose was 2.0 mg/m^2.[29] Myalgias and constipation were the DLT at the dose of 2.8 mg/m^2. Early hypersensitivity with transient fever was reported in 60% of patients during the first infusion. Altogether in this study the rates of grade 3-4 toxicities were: constipation 12%, alopecia 8%, fatigue 8%, anemia 8%, other at 4%: nausea, neuropathy, fever, pain, myalgias, leukopenia, neutropenia (grade 4), and thrombocytopenia.

Sarris et al. studied Marqibo® as a single-agent at the dose of 2.0 mg/m^2 every 14 days in 51 patients with relapsed NHL, all of whom had pre-existing grade 1-2 neuropathy.[30] They observed no grade 3-4 nausea, vomiting, stomatitis, ileus, obstipation or hematologic toxicities. 31% of patients experienced worsening of neuropathy to grade 3, but it improved in all patients within weeks of discontinuation of Marqibo®. Febrile neutropenia occurred in 6% of patients, all of whom had a pre-existing neutropenia. Responses were seen in 41% of patients, particularly in aggressive or transformed NHL. Rodriguez et al. reported a phase II study of single-agent Marqibo® (2.0 mg/m^2 every 2 weeks) in 119 patients with refractory aggressive NHL (primarily DLBCL).[31] They observed a 25% RR, with very limited toxicities and predominantly grade 1/2 adverse events, 24% rate of dose modifications and 20% rate of dose delays. Neuropathy was the predominant reason for treatment discontinuation or dose modification. Grade 3/4 neuropathy occurred in 32%, all of whom had baseline grade 2 neuropathy. Other grade 3/4 toxicities included: gastrointestinal (11%), dyspnea (5%), fatigue (7%), fever (2%), constipation (3%), pain (7%), weakness (18%), anemia (15%), neutropenia (27%), thrombocytopenia (12%).

Single-agent Marqibo® was extensively studied as a treatment for refractory ALL. In a Phase II trial of Marqibo® at 2.0 mg/m^2 every 2 weeks, the RR was 14%.[32] The non-hematologic toxicity was minimal in that study, with two cases (12%) of grade 1 peripheral neuropathy, grade 2 orthostasis and headaches. Subsequently, 65 adults with relapsed/refractory Philadelphia-negative

ALL were treated with high-dose Marqibo® at 2.25 mg/m^2 weekly in a pivotal phase II trial, which demonstrated a 35% RR.[33] At this dose 86% of patients had a neuropathy-associated adverse effect, with 39% experiencing at least one ≥ grade 3 event, most commonly neuropathy-related (23%), constipation or abdominal pain (6%), fatigue, asthenia or fever (aggregate 8%). The rates of hematologic grade 3/4 adverse effects were: neutropenia 16%, anemia 5%, thrombocytopenia 7%, febrile neutropenia 3%.

2.5.3 *Combinations with rituximab and/or cytotoxic agents*

Marqibo® has been used in combination with rituximab and with RCHOP-like regimen in B-cell NHL, without signals of increased or unexpected toxicities. Kaplan et al. combined Marqibo® at 2.0 mg/m2 every 2 weeks with rituximab 375 mg/m2 in 22 patients with relapsed/refractory DLBCL or MCL in need of palliative therapy, reporting an overall RR of 59%, including 27% CR.[34] The toxicity profile was consistent with single-agent experience for Marqibo® (Table 2). Hagemeister et al. used Marqibo® 2.0 mg/m2 as a substitute for vincristine sulfate in the RCHOP regimen (with standard doses of rituximab, cyclophosphamide, doxorubicin and prednisone, every 21 days) for untreated DLBCL.[35] This RCHMP regimen achieved a 96% response rate with 90% CR rate. The safety profile was not different than what would be expected with RCHOP in this population (Table 2).

These two studies indicate that Marqibo® can be safely combined with rituximab and full-dose alkylating agents for the treatment of NHL, without unexpected toxicities.

Table 2. Rates of adverse events in studies combining Marqibo® with rituximab or rituximab, cyclophosphamide, doxorubicin and prednisone (R-CHMP).

	Rituximab-Marqibo®[34]			**R-CHMP[35]**		
	All grades, %	**Gr. 3, %**	**Gr. 4, %**	**All grades, %**	**Gr. 3, %**	**Gr. 4, %**
Any event	100	59	18	100	24	53
Neurologic	87	46	-	86	11	-
Headache	9	-	-	15	3	-
Numbness	9	-	-	39	3	-
Neuropathy				36	3	-
Motor	23	18	-			
Sensory	36	18	-			
NOS	23	9	-			
Weakness	18	9	-	12	3	-
Gastrointestinal	55	5	-	72	6	-
Constipation	46	5	-	15	-	-
Diarrhea	-	-	-	15	1	-
Nausea	23	-	-	53	1	-
Vomiting	-	-	-	35	1	-
Stomatitis	-	-	-	14	1	-
Hematologic	55	23	18	83	21	53
Leukopenia	27	14	5	7	1	6
Neutropenia	41	14	-	72	14	50
Anemia	18	-	-	28	4	0

	Rituximab-Marqibo®[34]			R-CHMP[35]		
Thrombocytopenia	18	5	-	18	13	1
Febrile neutropenia	9	9	-	21	18	1
Other	64	5	-	72	4	-
Fatigue	46	5	-	39	1	-
Mucosal inflammation	-	-	-	15	-	-
Pyrexia	18	-	-	31	3	-
Metabolic/nutrition	14	5	-	24	7	-
Dyspnea	-	-	-	17	0	-
Infection	23	5	-	Not reported		

2.6 Rationale for the BRiM combination

The front-line therapy of indolent B-cell NHL has shifted from combinations of cyclophosphamide and vincristine (RCHOP, RCVP) to the alkylator-only regimen (BR), which has superior efficacy, but does not benefit from synergy of alkylating and microtubule-disrupting agents which are characterized by different mechanisms of action. Although bendamustine is a superior alkylating agent compared with cyclophosphamide, it has not advanced to therapy of aggressive lymphomas because of the need to safely introduce it into multi-agent regimens necessary for the cure of DLBCL. There is thus an unmet need for a bendamustine-based multi-agent chemotherapy combination that could incrementally improve therapy of indolent NHL and provide a backbone for novel curative regimens in DLBCL. Considering non-overlapping toxicities, BR-vincristine combination is a natural choice for this goal, reflecting the synergy utilized in cyclophosphamide/vincristine combinations. Marqibo®, a novel liposomal formulation allowing for improved pharmacokinetics and efficacy of vincristine sulfate, is a promising agent that could be combined with BR, potentially enhancing the effects of this regimen without additional toxicity.

In front-line therapy of indolent B-cell NHL, BR provides 30-40% rate of complete remission.[16] The augmented regimen may be particularly beneficial for patients with indolent B-cell NHL who are classified as higher-risk. At present, patients with indolent NHL are treated as a homogeneous group with the standard BR regimen. However in FL significant heterogeneity in prognosis is recognized, captured by clinical prognostic scores such as FLIPI and FLIPI-2.[36-38] About 27% of patients with FL can be classified as high-risk FLIPI-2 and these patients experience a PFS rate of only about 50% at 3 years and 19% at 5 years with standard therapy.[37] An addition of a highly active agent such as Marqibo® to the front-line chemoimmunotherapy regimen may improve outcomes in this group without compromising safety.

BR has also been widely used as a front-line therapy for patients with MCL who are ineligible for more aggressive strategies.[15] However, MCL remains difficult to treat, with >50% of patients experiencing relapse within 3 years. Although the addition of cytarabine to BR may improve response rates and potentially duration of remission, it is associated with significantly increased toxicity (despite a lower dose of bendamustine, 70 mg/m^2), particularly thrombocytopenia requiring transfusion (65% of cycles) which prevented any dose escalation in the trial.[19] BRiM may offer a more tolerable alternative in this disease.

3. PATIENT ELIGIBILITY

3.1 Eligibility Criteria

3.1.1 Documentation of disease.

Patients must have histologically confirmed indolent B-cell non-Hodgkin lymphoma, CD20-positive, previously treated or untreated—for which bendamustine-rituximab chemotherapy is clinically indicated; the following subtypes are allowed:

- Follicular lymphoma
- Mantle cell lymphoma,
- Marginal zone lymphoma,
- Small lymphocytic lymphoma,
- Lymphoplasmacytic lymphoma, or
- Indolent B-cell lymphoma, NOS.

BrUOG must receive the pathology report to confirm the diagnosis and the CD20-positive status, as well as documentation from the treating physician that bendamustine-rituximab chemotherapy is clinically indicated for the subject.

3.1.2 Radiological measurable disease, defined as any measurable lesion >15 mm on the staging CT or PET/CT. Patients with blood or bone marrow involvement only are ineligible. Splenomegaly is acceptable as a measurable site if enlarged on the initial CT scan (>13 cm in the cranio-caudal dimension).

3.1.3 Previous treatment for lymphoma is allowed, with the exception of use of bendamustine within 180 days of the date of the consent form, or any prior use of vincristine sulfate liposome injection (Marqibo®).

3.1.4 Age ≥18 years.

3.1.5 ECOG performance status 0 or 1 (see **Appendix A**).

3.1.6 Life expectancy of greater than 6 months.

3.1.7 Patients must have adequate organ and marrow function as defined below:

- leukocytes ≥3,000/mm^3
- absolute neutrophil count ≥1,000/mm^3
- platelets ≥75,000/mm^3 (without a transfusion within 1 week)
  Note: if a transfusion was given, it must be documented with a date on the ConMed log
- total bilirubin within normal institutional limits
- AST(SGOT)/ALT(SGPT) <2.5 × institutional upper limit of normal
- creatinine ≤2.0 mg/mL, AND
- creatinine clearance ≥50 mL/min/1.73 m^2.

calculated by method of Cockroft and Gault, using actual weight:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age in years}) \times \text{actual weight (in kg)}}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85 \text{ (for female patients)}$$

3.1.8 Prevention of pregnancy.

The effects of bendamustine and vincristine on the developing human fetus are unknown. For this reason and because Class D agents (bendamustine, vincristine) are known to be teratogenic, women and men of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence; vasectomy) prior to study entry and up to 4 months after the last dose of study treatment.

3.1.9 Women of childbearing potential must have a negative serum or urine pregnancy test within 14 days prior to first treatment on study (Cycle 1, Day 1). Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Postmenopausal women (after surgical menopause or no menses for >12 months) do not need to have a pregnancy status, but their postmenopausal status must be documented.

3.1.10 Ability to understand and the willingness to sign a written informed consent document. The patient must be aware of the neoplastic nature of his/her disease and must willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts.

3.2 Exclusion Criteria

3.2.1 History of any allergic reaction attributed to rituximab (with the exception of <grade 3 infusion reaction), bendamustine, vincristine sulfate, Marqibo®, mannitol, sodium phosphate injection or sphingomyelin/cholesterol liposome.

3.2.2 Patients who have had any lymphoma-directed radiotherapy, chemotherapy, biologic or experimental therapy, oral or intravenous, within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier to ≤grade 1—with the exception of alopecia, which is allowed.

3.2.3 Any prior treatment with vincristine sulfate liposome injection (Marqibo®).

3.2.4 Prior treatment with bendamustine or vincristine sulfate within 180 days of enrollment. Prior treatment with rituximab is allowed.

3.2.5 Patients who are receiving any other investigational agents or anti-cancer therapy with the exception of endocrine therapy for breast or prostate cancer.

3.2.6 Patients with known central nervous system involvement (infiltration of the brain, meninges or cerebrospinal fluid) by the lymphoma are excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.7 Active peripheral sensory or motor neuropathy > grade 1. This is defined by the CTCAE as any neuropathy requiring intervention or limiting instrumental activities of daily life.

3.2.8 History of demyelinating form of Charcot-Marie-Tooth syndrome, acquired demyelinating disorders, or other demyelinating condition.

3.2.9 Documented positive test for the Human Anti-Chimeric Antibody (HACA). (Documentation must be sent to BrUOG)

3.2.10 Patients receiving any medications or substances that are strong inhibitors or inducers of CYP3A enzyme are ineligible. See Appendix B for the list of prohibited drugs.

Note: Dexamethasone use as an anti-emetic according to the protocol is allowed.

As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product. Grapefruit juice in particular has significant undesirable interactions.

3.2.11 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection (that requires antibiotic use which is not prophylactic), symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements. In cases of uncertainty, the treating physician will request a review by BrUOG to decide whether an illness is considered prohibitive (planning should be used as review can take multiple days). Suppressive antiviral therapy with acyclovir, famciclovir, or valacyclovir for herpes simples or herpes zoster is allowed.

3.2.12 Prisoners.

3.2.13 Pregnant or breast-feeding women.

Pregnant women are excluded from this study because bendamustine and vincristine are Class D agents with the potential for teratogenic or abortifacient effects. Based on its mechanism of action and findings from animal studies, Marqibo® can cause fetal harm when administered to pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with bendamustine and/or vincristine, breastfeeding should be discontinued if the mother is treated with either agent. These potential risks may also apply to other agents used in this study.

3.2.14 Known Human Immunodeficiency Virus (HIV) or active Hepatitis B infection (defined as presence of HBV DNA or hepatitis B S antigen in the blood).

HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with Marqibo®. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Patients with active hepatitis B infection are included because of high risk of disease worsening during treatment with rituximab.

3.2.15 Any prior or active cancer, which in the opinion of the investigator would preclude safe participation in this study.

3.3 Inclusion of Women and Minorities

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

4. TREATMENT

4.1 Agent Administration

Patient must start protocol treatment within 7 days of registration on the study. Treatment will be delivered in 28-day courses, for no more than 6 cycles. In case of a holiday or other extenuating circumstances, Cycle 2-6 treatment may be initiated up to 1 day before or up to 5 days after that date (ie. on Day 27 to Day 33 of the cycle), provided that all Section 4.2 criteria are met. Other delays related to toxicity as provisioned in the protocol are allowed. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Regimen description					
Agent	***Premedications; Precautions***	***Dose*** §	***Route***	***Schedule***	***Cycle***
Rituximab	Premedicate with: – Acetaminophen 650 mg orally – Diphenhydramine 25 mg IV or orally	375 mg/m^2	IV, see Section 9.1 for infusion rate	Day 1	28 days
Bendamustine	Premedicate with: Day 1: – Palonosetron 0.25 mg IV – Dexamethasone 4-20 mg IV or orally – *(optionally)* Fosaprepitant 150 mg IV Day 2: – Dexamethasone 4-20 mg IV or orally	90 mg/m^2 (each day)	IV over 10 to 30 minutes	Day 1 (after rituximab) and Day 2 (before Marqibo®)	
Marqibo®	Only administer through a secure and free-flowing venous access line Instruct the patient on the bowel regimen	** in 100mL NS as per package insert	IV over 60 minutes	Day 2 (after benda-mustine)	

§ Dose should be adjusted during each cycle only if dose recalculated with an adjusted BSA differs by more than 10% of the dose during Cycle 1

** Patient-specific dose calculated at registration, 1.8 to 2.4 mg/m^2

4.2 Criteria to initiate the next cycle

The following criteria must be met by Day 1 of a new cycle to initiate therapy:

- absolute neutrophil count≥1,000/mm^3 If ANC is <1,500/mm^3 refer to section 5.1 and hold treatment if deemed related to study treatment.
- platelets≥75,000/mm^3 (without a transfusion within 1 week)
- recovery from all non-hematologic toxicities (excluding alopecia and weight gain/loss) related to any of the agents administered on the protocol to <grade 2, or to patient's baseline grade prior to starting therapy on protocol.

Grade 2 toxicity that is continuing from baseline or is non-treatment related is allowed.

Any patient who experiences a DLT during cycle 1 must come off study.

4.3 Ancillary Therapy

4.3.1 *Hematopoietic Growth Factors*

Patients who meet criteria for primary prophylaxis of febrile neutropenia set by the American Society of Clinical Oncology may receive subcutaneous pegfilgrastim 6 mg on Day 3 or Day 4 of the treatment cycle, at least 24 hours after administration of study therapy.[39] The high-risk factors that need to be considered when evaluating patient's risk for febrile neutropenia include: age (>65 years), poor performance or poor nutritional status, history of febrile neutropenia, open wounds or active infection, extensive prior treatment, cytopenias due to bone marrow involvement by tumor and other serious comorbidities. **All patients >65 years old treated in this study protocol should receive primary prophylaxis with pegfilgrastim on Day 3, 4 or 5 of the cycle.**

Patients with neutropenic fever or infection must be hospitalized promptly for intravenous antibiotic therapy and may receive myeloid growth factors as appropriate.

Erythropoiesis-stimulating agents such as epoetin alfa or darbepoetin alfa **may not** be used during study treatment.

4.3.2 *Blood and Platelet Transfusion*

Transfusions will be used at the Investigator's clinical judgment. Red blood cell transfusions may be administered prophylactically for hemoglobin <8.0 g/dL or in case of severe symptomatic anemia. Platelet transfusions may be administered prophylactically for platelet counts ≤10,000 /mm^3 or therapeutically for low platelet counts.

4.3.3 *Infections*

Patients in this study will not receive any pre-specified infectious prophylaxis. In case of grade 4 neutropenia (ANC<500/mm^3), a prophylactic quinolone (ciprofloxacin 500 mg twice daily, levofloxacin 500 mg daily or moxifloxacin 400 mg daily) may be prescribed to prevent febrile neutropenia.

Patients with history of herpes simplex or herpes zoster on suppressive therapy with acyclovir, famciclovir or valacyclovir may (but do not need to) continue therapy during the treatment on study.

The concurrent administration of itraconazole with vincristine increases onset and severity of neuromuscular adverse effects of vincristine. If antifungal therapy is required during study treatment, alternative anti-fungals should be evaluated prior to considering any azoles.

4.4 Prior and Concomitant Medications

The Investigator will be permitted to prescribe other treatment(s) at his or her discretion. These treatments, including any transfusions or prophylactic therapies, must be recorded on the CRF. However, any other standard or investigational treatments for lymphoma are not allowed. If such treatment is deemed necessary, the patient must discontinue treatment on this study.

Medications known to interact with cytochrome P450-3A4 isoenzymes and/or P-glycoprotein are either prohibited (see **Section 3.2, Exclusion Criteria**), or should be administered with caution. A list of these medications can be found in **Appendix B**. Close monitoring is recommended for

subjects taking agents with narrow therapeutic indices and metabolized by the liver, such as warfarin, quinidine, and digoxin.

All medications and supportive therapy that are administered within 14 days prior to the start of study drug administration through 30 days after the last dose of study treatment, including the start and stop date(s), dose/amount administered, and indication, must be recorded in the source documents and in the subject's CRF. This includes any transfusions or prophylactic treatments.

4.5 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment will continue for 6 cycles or until one of the following criteria applies:

- Occurrence of a DLT in the first cycle of treatment,
- Disease progression,
- The need for administration of therapy for lymphoma not specified in the protocol; this includes any form of chemotherapy, radiation therapy or biologic therapy;
- Intercurrent illness that prevents further administration of treatment,
- Adverse event(s) deemed unacceptable by the patient or the treating physician,
- Patient decides to withdraw from the study for any reason, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5. DOSE MODIFICATIONS AND MANAGEMENT OF TOXICITY

All subjects must meet **Criteria to initiate the next cycle** according to Section 4.2 before receiving a next cycle of therapy.

If a toxicity-related treatment delay is needed, the cycle should be delayed by up to 8 days. In case of delay exceeding 14 days, the patient must discontinue the study treatment. Further therapy for the lymphoma will be at the discretion of the treating physician.

There will be no dose modifications for rituximab in this study. Dose modifications for bendamustine and Marqibo® will conform to the following dose levels:

Dose level	Dose	
	Bendamustine	**Marqibo®**
0	90 mg/m^2	100% patient-assigned dose
-1	50 mg/m^2	75% patient-assigned dose
-2	25 mg/m^2	50% patient-assigned dose

Once a dose is reduced, it may not be re-escalated during the study treatment. Patients requiring >2 dose reductions must go off protocol therapy.

The following guidelines apply **to any toxicities attributed to treatment** (understood as any agent administered on protocol)**.** Baseline or disease-related toxicities will be managed according to the treating physician's recommendations.

5.1 Neutropenia

Neutropenia	Management/Next Dose for Bendamustine	Management/Next Dose for Marqibo®
≤ Grade 1 (ANC ≥ 1500/mm^3)	No change in dose	No change in dose
Grade 2 (ANC 1000-1499/mm^3)	Hold until ≤ Grade 1. Resume at same dose level. Consider prophylactic pegfilgrastim in case of repeated delays.	Hold until ≤ Grade 1. Resume at same dose level. Consider prophylactic pegfilgrastim in case of repeated delays.
Grade 3 (ANC 500-999/mm^3)	Hold until < Grade 2. Resume at one dose level lower and consider prophylactic pegfilgrastim with the next cycle.	Hold until < Grade 2. Resume at one dose level lower and consider prophylactic pegfilgrastim with the next cycle.
Grade 4 (ANC < 500/mm^3)	Hold and consider a prophylactic antibiotic until < Grade 2. Resume at one dose level lower and/or institute prophylactic pegfilgrastim with the next cycle	Hold and consider a prophylactic antibiotic until < Grade 2. Resume at one dose level lower and/or institute prophylactic pegfilgrastim with the next cycle
Recommended management: Prophylactic antibiotics may include: ciprofloxacin 500 mg twice daily, levofloxacin 500 mg daily, or moxifloxacin 400 mg daily.		

5.2 Thrombocytopenia (CTCAE 4.0: Platelet count decreased)

Thrombocytopenia	Management/Next Dose for Bendamustine	Management/Next Dose for Marqibo®
≤ Grade 1 (≥75,000/mm^3)	No change in dose	No change in dose
Grade 2 (50-74,999/mm^3)	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3 (25-49,999/mm^3)	Hold until < Grade 2. Resume at one dose level lower, if indicated.	Hold until < Grade 2. Resume at one dose level lower, if indicated.
Grade 4 (<25,000/mm^3)	Off protocol therapy	Off protocol therapy

5.3 Nausea and Vomiting

Patients must receive prophylaxis for chemotherapy-induced nausea and vomiting (**Section 4.1)**.

Nausea or vomiting	Management/Next Dose for Bendamustine	Management/Next Dose for Marqibo®
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold until < Grade 2. Resume at one dose level lower, if indicated.	Hold until < Grade 2. Resume at one dose level lower, if indicated.
Grade 4	Off protocol therapy	Off protocol therapy
Recommended management: Administer fosaprepitant or olanzapine with the next cycle (if not given). Use breakthrough antiemetics: prochlorperazine, metoclopramide, ondansetron, lorazepam, as indicated.		

In case of grade 3 or 4 chemotherapy-induced nausea or vomiting, an aggressive outpatient or inpatient therapy with intravenous fluids, electrolyte replacement and anti-emetics should be instituted. If the nausea and/or vomiting resolve to grade 1-2 within 48 hours, such an event will not be considered a DLT.

5.4 Constipation

Severe constipation may develop in subjects who receive Marqibo®. Decreased bowel motility due to intrabdominal disease, hypercalcemia, dehydration, use of opioids can also contribute to constipation. A diet high in bulk fiber, fruits and vegetables, and adequate fluid intake may help minimize constipation. All patients treated in this study should receive education on prophylactic bowel regimen. A suggested bowel regimen is as follows:

1. Prophylactic laxatives
    a. Senna at bedtime (1-2 tablets, dose varies with the preparation), or
    b. Milk of Magnesia, 30 mL at bedtime
2. If no bowel movement with the above, add:
    a. Lactulose, 20 gram (30 mL) up to 3 times a day, or
    b. Polyethylene glycol 3350 powder (MiraLax®) 17 gram dissolved in 4-8 oz. of water, once daily by mouth, or
    c. Biscodyl, 5 to 15 mg tablet by mouth or one 10 mg suppository, at bedtime.
3. Other, more aggressive alternatives include:
    a. Magnesium Citrate, 150 mL by mouth, up to twice a day.

Constipation	Management/Next Dose for Bendamustine	Management/Next Dose for Marqibo®
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold until < Grade 2. Resume at one dose level lower, if indicated.**	Hold until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy	Off protocol therapy
Recommended management: See above.		

5.5 Diarrhea

Diarrhea	Management/Next Dose for Bendamustine	Management/Next Dose for Marqibo®
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold until < Grade 2. Resume at one dose level lower, if indicated	Hold until < Grade 2. Resume at one dose level lower, if indicated.
Grade 4	Off protocol therapy	Off protocol therapy
Recommended management: Rule out infectious diarrhea. Loperamide antidiarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours). Use flouroquinolones and/or octreotide according to the ASCO Guidelines for the Treatment of Cancer Treatment-Induced Diarrhea.[40]		

5.6 Rituximab infusion and hypersensitivity reactions

- Interrupt rituximab for infusion reactions ≥ grade 1. Resume infusion when symptoms improve to < grade 1 at 50% of the previous infusion rate.
- For grade 1 or 2 hypersensitivity reactions, interrupt rituximab infusion and manage according to institutional procedures. Resume infusion when symptoms improve to < grade 1 at 50% of the previous infusion rate.
- For grade 3 or 4 hypersensitivity reactions, discontinue rituximab.

5.7 Other non-hematologic, treatment-related toxicities (excluding alopecia, weight gain/loss)

Toxicity	Management/Next Dose for Bendamustine	Management/Next Dose for Marqibo®
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold until < Grade 2. Resume at one dose level lower, if indicated.	Hold* until < Grade 2. Resume at one dose level lower, if indicated.
Grade 4	Off protocol therapy	Off protocol therapy

6. SCHEDULE OF EVALUATIONS / STUDY CALENDAR

Evaluation	Pre-Treatment Period		Treatment Period Cycle 1				Treatment Period Cycle 2-6		Off Study[e]
	≤ 42 days before registration	≤ 14 days before first treatment	D1[a]	D8[d]	D15[d]	D22[d]	D1[a,f]	D15[d]	
Clinical evaluation									
Signed informed consent	X[g]								
History and physical examination		X	X[a]				X		X
Vital signs: BP, pulse, respiratory rate, temperature		X	X[a]	X	X	X	X	X	X
ECOG performance status		X	X[a]	X	X	X	X	X	X
Height (baseline only), weight, BSA		X	X[a]	X	X	X	X	X	X
Tumor measurements	X						X[b]		X
Toxicity assessment		X	X[a]	X	X	X	X	X	X
Concomitant medication log		X	X[a]				X		X
DLT determination				X	X	X	X(C2)		
Laboratory studies									
CBC with differential		X	X[a]	X	X		X[a]		X
Electrolytes (Na, K, Cl, CO2. Ca, Mg, phosphorus), BUN, and creatinine		X	X[a]	X	X		X[a]		X
Creatinine clearance (calculated)		X	X[a]	X	X		X[a]		X
Bilirubin total, ALP, AST, ALT		X	X[a]	X	X		X[a]		X
PT, APTT		X	X[a]						
Serum or urine pregnancy test (women of child bearing potential only)		X	X[a]				X[a]		
LDH		X	X[a]	X	X		X[a]		
Uric acid		X	X[a]	X	X				
12-lead electrocardiogram	X								
Urinalysis (WBC, blood, protein)		X	X[a]				X[a]		
HIV, Hepatitis B S Ag		X							
Disease assessment [b]									
CT (chest-abomen-pelvis) or PET-CT	X						X[b]		X[b]
Bone marrow aspirate / biopsy [c]	X[c]								X[c]
Treatment									
BRiM chemotherapy			X[h]				X[h]		

a. Laboratory values and clinical assessments may be obtained within 72 hours prior to Day 1 of each cycle. Pre-registration assessments may be used for Cycle 1/Day 1 assessment if obtained within 7 days before treatment. **Treatment must start within 7 days of registration.**

b. CT must be with IV contrast unless there is a documented contraindication. Imaging studies and tumor measurements should be obtained:
- After Cycle 3: between Day 22 and Day 28 of Cycle 3 and
- After Cycle 6: within 28-42 days after the last treatment

Ct scan at "off study" is not required for patients who terminate study therapy early and have received fewer than 3 cycles of treatment, or had a restaging CT scan within 1 month prior to discontinuation of study therapy.

c. Bone marrow aspirate and biopsy is not required, unless it is clinically necessary for staging in the judgment of the investigator, within ≤42 days of the first treatment and within 28-42 days after the last administered study treatment, if needed to document a complete remission.

d. ± 1 day

e. Off Study Assessment visit should occur between Day 30 and Day 42 of the last treatment cycle.

f. Cycle 2 to 6 may be delivered up to 1 calendar day before (Day 28 of the previous cycle), to 5 days after the scheduled date in case of holidays or other extenuating circumstances, and not accounting for delays as mandated by toxicity.

g. Consent must be signed within 30 days of Day 1 of treatment. Otherwise the subject must be reconsented.

h. Including chemotherapy administration on Day 2 per protocol.

6.1 Dose-Limiting Toxicity (Definition)

Dose-limiting toxicity (DLT) will be defined as one of the following AEs occurring during Cycle 1 of study therapy (with a final determination on Day 1 of Cycle 2), after administration of any study medication listed in **Section 4.1**:

- Grade 4 neutropenia (< 500/mm3) lasting > 7 days
- Grade 3 neutropenia (<1000/mm3) with fever or infection;
- Grade 4 thrombocytopenia (<25,000/mm3);
- Grade 3 thrombocytopenia (<50,000/mm3) requiring transfusion;
- Grade 3 or 4 treatment-related non-hematologic toxicity, excluding:
  - Alopecia.
  - Grade 3 nausea or vomiting if corrected to ≤ grade 2 within 48 hours.
  - Grade 3 or 4 infusion reactions if occurring on Day 1 of the first cycle.
  - Grade 3 or 4 electrolyte (sodium, potassium, magnesium, calcium, chloride, phosphorus) abnormality, unless corrected to <grade 2 within 48 hours.
- Delay of 2nd cycle of treatment for >14 days.

Any patient who experiences a DLT must come off study. The trial will be terminated if the first three patients experience a DLT or anytime the posterior probability that the DLT rate at the minimum dose exceeds 0.33 is 0.8 or more. Toxicities occurring prior to administration of any study medications will not be considered DLT.

6.2 Disease Assessments

For the purpose of the study, the disease will be assessed and tumor measurements performed at three time points:

- During pre-treatment period, within 42 days prior to registration (**Section 8.1**)
- After Cycle-3 chemotherapy, between Day-22 and Day-28 of the cycle
- After Cycle-6 chemotherapy (or the last treatment, if therapy is discontinued earlier).

CT scan is not required for patients who terminate study therapy early and have received fewer than 3 cycles of treatment, or had restaging CT scan within 1 month prior to discontinuation of study therapy.

For patients who undergo a pre-treatment staging bone marrow evaluation, the procedure must be repeated if complete remission (CR) is assigned as the final tumor response. A repeat procedure is not necessary otherwise. Any assessment for disease that is performed between the date of informed consent signature and off-study assessment date must be submitted to BrUOG.

6.3 Off Study Assessment

The patient will undergo Off Study Assessment during a visit scheduled between Day 30 and Day 42 of the last cycle of study treatment they receive. The visit will entail the following evaluations:

- History and physical examination, including vital signs, ECOG performance status, weight, BSA, and concomitant medication log.
- Toxicity grading assessment, including determination of all cumulative toxicities for the purpose of the study.

- Assessment of final response to treatment using the International Working Group Revised Response Criteria for Malignant Lymphoma (see **Section 7.1**)[41]. This assessment should be finalized after the results of disease assessment tests become available.

7. RESPONSE ASSESSMENT

Although response is not the primary endpoint of this trial, patients with measurable disease will be assessed by standard International Working Group criteria for Malignant Lymphomas, as revised in 2007.[41]

Patients will be assessed for response to treatment after Cycle 3 and Cycle 6 of therapy on study (see Section 6.2). Earlier assessment may be performed in case of suspected clinical progression of disease. A CT scan or a PET-CT scan can be used for response assessment in this study, according to Investigator's preference guided by the histologic subtype of the lymphoma. For the purpose of study evaluation, all relevant measurable nodal and extranodal sites of disease ≥1 cm in size should be recorded in the baseline scan and followed until resolution. If CT is utilized for response assessment, it should be performed with IV contrast unless there is a documented contraindication (such as chronic kidney disease or hypersensitivity to contrast agent).

7.1 Definitions of response

7.1.1 ***Complete remission***

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.
2. FDG-avid lymphoma: in patients with no pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.
3. Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to ≤ 1.0 cm in their short axis after treatment.
4. The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.
5. If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR.

7.1.2 ***Partial remission***

1. At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2. No increase should be observed in the size of other nodes, liver, or spleen.
3. Splenic and hepatic nodules must regress by ≥ 50% in their SPD or, for single nodules, in the greatest transverse diameter.
4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.
5. Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (eg, large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders.
6. When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.
7. No new sites of disease should be observed.
8. Typically FDG-avid lymphoma: for patients with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.
9. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT criteria should be used.
10. In patients with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with one or at most two residual masses that have regressed by more than 50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.

7.1.3 ***Stable disease***

1. A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease.
2. Typically FGD-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.
3. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

7.1.4 ***Progressive disease***

Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes ≤ 1.0 × ≤ 1.0 cm will not be considered as abnormal

for progressive disease.

1. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.
2. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (eg, splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥ 50% and to a size of 1.5 × 1.5 cm or more than 1.5 cm in the long axis.
3. At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.

Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

Table 4: **International Working Group Criteria for response to therapy in NHL**

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

8. REGISTRATION PROCEDURES

8.1 General Guidelines

All patients will be registered through the Brown University Oncology Research Group Central Office. The following documents must be faxed to the BrUOG Central Office, Fax: (401) 863-3820, at the time of registration and prior to patient treatment:

- Eligibility checklist with supporting original source documentation
- On-study form
- Signed patient consent form.

Details of patient's study participation will be documented in the institutional electronic medical record. The Brown University Oncology Research Group will provide case report forms, included in the appendix, for the recording and collection of data. In the event of corrections, each correction will be initialed and dated by the person making the correction. The investigator will sign the case reports to indicate that, to his/her knowledge, they are complete and accurate. Case report forms, flow sheets, off-study forms and follow-up forms should be mailed / faxed to:

Brown University Oncology Research Group,
Brown University
Box G-R 001
Providence, RI 02912
Fax: 401-863-3820
Phone: 401-863-3000

BrUOG@brown.edu

All supporting data must be sent in with the corresponding BrUOG forms. It is the treating physician's responsibility to review all data submitted to the BrUOG Central Office for accuracy and completeness and he/she must sign the on-study form. It is required that source documentation be submitted to support all eligibility criteria (inclusion and exclusion) and also the schedule of evaluations table for prior to registration.

A next subject can be registered for this study only after the DLT status of all prior subjects have been resolved and a new dose level is assigned according to the procedures outlined in Section 16.

9. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the agents administered in this study can be found in **Section 11.1.**

The Investigator and the trial site are responsible for the investigational product accountability. All clinical trial supplies will be delivered to and be the responsibility of a suitably qualified and authorized person such as a hospital pharmacist, who will document study drug disposition and accountability for the duration of the trial.

Acrotech Biopharma, LLC will provide Marqibo® as the investigational agent. Patients will receive commercially available preparations of bendamustine (Treanda®, Belrapzo®, or Bendeka®) and rituximab (Rituxan®).

9.1 Rituximab (IDEC-C2B8)

9.1.1 *Product description*

Rituximab is a CD20-directed chimeric monoclonal antibody. It is indicated for treatment of: relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent; previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and as single-agent maintenance therapy; non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line CVP chemotherapy; and previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens.
A comprehensive product information and list of adverse effects is available in the Rituxan® package insert, available at:

http://www.gene.com/download/pdf/rituxan_prescribing.pdf

9.1.2 *Availability*

The commercial, FDA-approved formulation of rituximab (Rituxan®, Genentech, Inc, South San Francisco, CA) will be used in this study. Rituximab is available in 10 mL and 50 mL single-use vials containing 100 mg or 500 mg of rituximab solution, respectively, at a concentration of 10 mg/mL.

9.1.3 *Storage and stability*

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

9.1.4 *Preparation*

The desired dose of rituximab should be diluted in 0.9% NaCl or D5W to a final concentration of 1-4 mg/mL. Mix by inverting the bag gently.

9.1.5 *Dosage and Administration*

Rituximab will be administered by IV infusion at the dose of 375 mg/m2 on Day 1 of each study treatment. Patients must be pretreated with acetaminophen and diphenhydramine on each day of antibody treatment.
Do not administer rituximab IV push or bolus. For the initial infusion, start at a rate of 50 mg/hour; if there is no reaction, increase the rate by 50 mg/hour increments every 30 minutes, to a maximum rate of 400 mg/hour. For subsequent infusions, if the patient tolerated the initial infusion, start at a rate of 100 mg/hour; if there is no reaction, increase the rate by 100 mg/hour increments every 30 minutes, to a rate of 400 mg/hour. If the patient did not tolerate the initial infusion, follow the initial infusion guidelines. If a reaction occurs, slow or stop the infusion. If the reaction abates, restart infusion at 50% of the previous rate.

If the subject did not experience a Grade 3 or 4 infusion-related adverse event during Cycle 1, a 90-minute infusion can be administered during Cycle 2. Initiate at a rate of 20% of the total dose to be given in the first 30 minutes and the remaining 80% of the total dose over the next 60 minutes. If the 90-minute infusion is tolerated during Cycle 2, the same rate can be used during all subsequent cycles. Patients who have clinically significant cardiovascular disease or who have a circulating lymphocyte count ≥5000/mm3 before Cycle 2 should not be administered the 90-minute infusion.

9.1.6 ***Toxicity***

The most serious adverse events associated with rituximab include severe infusion reactions, tumor lysis syndrome, and severe mucocutaneous reactions. Severe infusion reactions consisting of hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation or cardiogenic shock may be fatal. Most reported fatal reactions occurred within 24 hours of the first dose of rituximab. Because severe infusion reactions have been noted more frequently in patients with high leukocyte counts, such patients should be observed closely.

Tumor lysis syndrome resulting in renal failure has been described, and occasional fatalities noted. Tumor lysis syndrome is more likely in patients with high numbers of circulating malignant cells.

Severe mucocutaneous reactions associated with rituximab include Stevens-Johnson syndrome and toxic epidermal necrolysis. The onset of these reactions has been from 1-3 weeks.

Less severe infusion reactions are common with rituximab. These include fever, chills, and dyspnea. The mechanism of rituximab infusion reactions is thought to be the release of cytokines.

Hepatitis B reactivation with fulminant hepatitis, hepatic failure and death in some patients with hematologic malignancies treated with rituximab have been reported. The majority of these patients received rituximab in combination with chemotherapy. The median time to diagnosis of hepatitis was approximately 4 months after starting rituximab and approximately 1 month after the last dose.

Exacerbation or reactivation of other viral infections has also been reported with rituximab. JC virus reactivation leading to progressive multifocal leukoencephalopathy in patients who were receiving rituximab has been reported. Patients presenting with new neurologic findings (e.g., major changes in vision, unusual eye movements, loss of balance or coordination, confusion) should be evaluated for progressive multifocal leukoencephalopathy. An increase in fatal infection in HIV-related lymphoma patients when rituximab was used in combination with CHOP chemotherapy, as compared to CHOP alone has been reported.

For a comprehensive list of adverse events, refer to the Rituxan® package insert.

9.1.7 ***Drug interactions***

Rituximab does not have any known clinically significant interactions with other study drugs.

9.2 Bendamustine hydrochloride

9.2.1 ***Product description***

Bendamustine hydrochloride is an alkylating antineoplastic drug which is a bifunctional mechlorethamine derivative containing a purine-like benzimidazole ring. It is indicated for treatment of patients with CLL or with an indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

Bendamustine is available as two formulations: Treanda® and Bendeka®. Both are acceptable for this study. A comprehensive product information and list of adverse effects is available in the Treanda® and Bendeka® package inserts, available at:

http://www.treandahcp.com/pdf/TREANDA_final_PI.pdf and

http://bendeka.com/Pdf/PrescribingInformation.PDF

9.2.2 ***Availability***

Treanda® (Cephalon, Inc. Frazer, PA) is supplied as a single-use vial containing 100 mg bendamustine HCL as white to off-white lyophilized powder. Bendeka® (Teva Oncology, North Wales, PA) is supplied in individual cartons of 5 mL clear multiple-dose vials containing 100 mg of bendamustine hydrochloride as a clear, and colorless to yellow ready-to-dilute solution.

9.2.3 ***Storage and stability***

Treanda® may be stored up to 25° C (77°F) with excursions permitted up to 30°C (86°F). Bendeka® should be stored in a refrigerator, 2°-8°C (36°- 46°F). Retain in original package until time of use to protect from light.

9.2.4 ***Preparation***

9.2.4.1 *Treanda®*

- Aseptically reconstitute each 100 mg bendamustine HCl (Treanda®) vial with 20 mL of only Sterile Water for Injection, USP. Shake well to yield a clear, colorless to a pale yellow solution with a bendamustine HCl concentration of 5 mg/mL. The lyophilized powder should completely dissolve in 5 minutes. If particulate matter is observed, the reconstituted product should not be used.
- Aseptically withdraw the volume needed for the required dose (based on 5 mg/mL concentration) and immediately transfer to a 500 mL infusion bag of 0.9% Sodium Chloride Injection, USP (normal saline). As an alternative to 0.9% Sodium Chloride Injection, USP (normal saline), a 500 mL infusion bag of 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, may be considered. The resulting final concentration of bendamustine HCl in the infusion bag should be within 0.2 – 0.6 mg/mL. The reconstituted solution must be transferred to the infusion bag within 30 minutes of reconstitution. After transferring, thoroughly mix the contents of the infusion bag. The admixture should be a clear and colorless to slightly yellow solution.

Use Sterile Water for Injection, USP, for reconstitution and then either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, for dilution, as outlined above. No other diluents have been shown to be compatible.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Any unused solution should be discarded according to institutional procedures for antineoplastics.

9.2.4.2 *Bendeka®*

Follow the procedure according to FDA-approved Prescribing Information:

- Aseptically withdraw the volume needed for the required dose from the 25 mg/mL solution and immediately transfer the solution to a 50 mL infusion bag of one of the following diluents: − 0.9% Sodium Chloride Injection, USP; or − 2.5% Dextrose/0.45% Sodium Chloride Injection, USP; or − 5% Dextrose Injection, USP. The resulting final concentration of bendamustine hydrochloride in the infusion bag should be within 1.85 mg/mL – 5.6 mg/mL. After transferring, thoroughly mix the contents of the infusion bag. The admixture should be a clear, and colorless to yellow solution.

- Bendeka® injection contains no antimicrobial preservative. The admixture should be prepared as close as possible to the time of patient administration. If diluted with 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, the final admixture is stable for 24 hours when stored refrigerated (2-8°C or 36-46°F) or for 6 hours when stored at room temperature (15-30°C or 59-86°F) and room light. Administration of diluted Bendeka® injection must be completed within this period of time. In the event that 5% Dextrose Injection, USP is utilized, the final admixture is stable for 24 hours when stored refrigerated (2-8°C or 36-46°F) or for only 3 hours when stored at room temperature (15-30°C or 59-86°F) and room light. Administration of diluted BENDEKA must be completed within this period of time.

9.2.5 *Dosage and Administration*

Treanda® is administered by intravenous route over 30 minutes in 500 mL of 0.9% Sodium Chloride (or 2.5% Dextrose/0.45% Sodium Chloride). Bendeka® is administered by intravenous route over 10 minutes in 50 mL of 0.9% Sodium Chloride, or 0.45% Sodium Chloride /2.5% Dextrose or 5% Dextrose .

Bendamustine will be administered in this study at the dose of 90 mg/m^2 each day on Days 1 and 2 of each cycle.

9.2.6 *Toxicity*

The most common side effect is bone marrow suppression. Most common non-hematologic adverse reactions for NHL (frequency ≥15%) are nausea, fatigue, vomiting, diarrhea, pyrexia, constipation, anorexia, cough, headache, weight decreased, dyspnea, rash, and stomatitis. Most common hematologic abnormalities (frequency ≥15%) are lymphopenia, anemia, leukopenia, thrombocytopenia, and neutropenia. For a comprehensive list of adverse events, refer to Treanda® or Bendeka® package insert.

9.2.7 *Drug interactions*

Concomitant CYP1A2 inducers or inhibitors have the potential to affect the exposure of bendamustine. Inhibitors of CYP1A2 (e.g., fluvoxamine, ciprofloxacin) have potential to increase plasma concentrations of bendamustine and decrease plasma concentrations of active metabolites. Inducers of CYP1A2 (e.g., omeprazole, smoking) have potential to decrease plasma concentrations of bendamustine and increase plasma concentrations of its active metabolites. Caution should be used, or alternative treatments considered if concomitant treatment with CYP1A2 inhibitors or inducers is needed.

9.3 Vincristine sulfate liposomal injection (Marqibo®)

9.3.1 *Product description*

Marqibo® is a vinca alkaloid indicated for the treatment of adult patients with Philadelphia chromosome-negative acute lymphoblastic leukemia in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies. The drug substance and active ingredient is the chemotherapeutic agent, vincristine sulfate. Vincristine Sulfate is supplied as Vincristine Sulfate Injection, USP which is a component of the Vincristine Sulfate Liposome Injection (0.16 mg/mL) (Marqibo®) kit. Vincristine Sulfate Liposome Injection (Marqibo®) binds to microtubular protein of the mitotic spindle causing metaphase arrest.

A comprehensive product information and list of adverse effects is available in the Marqibo® package insert, available at:

http://marqibo.com/pi

Additional information about VSLI is provided in **Section 2.5**.

9.3.2 *Availability*

Marqibo® is supplied as a single-use, 3-vial kit designed to enable entrapment of vincristine in sphingomyelin/cholesterol liposomes at the time of use. The active agent consists of vincristine sulfate as an aqueous solution and the vehicle consists of sphingomyelin/cholesterol liposomes with a sodium phosphate buffer as described in the 3-vial kit component table below.

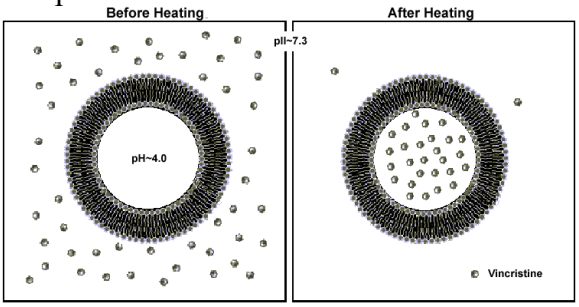
Table 5: **Vincristine Sulfate Liposomes Injection (0.16 mg/mL) 3-vial Kit Components[1]**

Component	No. of Vials/Kit	Description
Active	1	Vincristine Sulfate Injection, USP (1 mg/mL, 5 mL)
Liposomes	1	Sphingomyelin/Cholesterol Liposomes Injection (103 mg/mL, 1 mL)
Buffer	1	Sodium Phosphate Injection (14.2 mg/mL, 25 mL)

[1]Kit also includes: 1) 1 floatation ring, 2) 1 infusion bag label, 3) 1 Marqibo® overlabel, 4) 1 set of constitution instructions.

Vincristine is encapsulated into the sphingomyelin/cholesterol liposomes during the constitution procedure. Vincristine sulfate injection, sphingomyelin/cholesterol liposomes, and buffer are combined and warmed to 65 ± 2° C for 10 minutes. The sphingomyelin/cholesterol liposomes have an internal pH of ~4.0. When the sodium phosphate buffer and vincristine sulfate injection are added, the solution outside the liposomes has a pH of ~7.3. The pH gradient induces vincristine to migrate across the sphingomyelin/cholesterol liposome membrane, which becomes more permeable upon heating. Returning to room temperature, the sphingomyelin/cholesterol liposome membrane loses its permeability with the vincristine encapsulated inside.

Figure 1:
Marqibo® Encapsulation Process



9.3.3 *Storage and stability*

Marqibo® kits are to be stored in a controlled refrigerator (2-8ºC; 36-46ºF) until the time of constitution; refrigeration temperature logs (or equivalent records) should be maintained. Retain vials in carton until time of use. **DO NOT FREEZE**.

Constitution should take place under strict aseptic conditions following detailed instructions included in the kit. After constitution of Marqibo, the constituted product should be stored in the constitution vial or diluted, according to the instructions, in the infusion bag.

The constituted product should be stored at controlled room temperature (15-30ºC; 59-86ºF) and must be administered within 12 hours of the constitution start time.

All unused Marqibo® kits will be returned to the drug manufacturer or delegate at the end of the study or destroyed at the site as per local pharmacy's cytotoxic agent destruction procedures and according to applicable regulations. Destruction on site should only occur with prior drug manufacturer's authorization. Documentation of local Marqibo® destruction must be provided to the drug manufacturer. Marqibo® is an investigational drug. Drugs supplied for clinical investigation should be given by or under the supervision of the Investigators throughout this study.

9.3.4 ***Preparation and Constitution***

The illustrated constitution procedure for the 3-vial Marqibo® kit is located in the study procedures manual**.**

One Marqibo® kit will adequately supply sufficient constituted Marqibo® at a dose of 2.25 mg/m^2 for a BSA of ≤ 2.1 m^2. A BSA of > 2.1 m^2 will require two Marqibo® kits.

The reliability of the preparation procedure for Marqibo® from the 3-vial kit can be performed in a high degree of confidence with small variations having minimal or no effect on product quality and performance.

9.3.4.1 *Items Required by the Pharmacy to Prepare Marqibo®*

Either water bath or block heater can be used for preparation of the Marqibo® infusion:

- Marqibo® Kit
- Water bath (for water bath processing) or Dri-Block heater (for block heater processing)
- Calibrated thermometer (0°C to 100°C)
- Calibrated electronic timer
- Sterile venting needle or other suitable device equipped with a sterile 0.2 micron filter
- 1 mL or 3 mL sterile syringe with needle, and
- 5 mL sterile syringe with needle.
- Tongs

9.3.4.2 *Preparation Instructions for Marqibo® (vinCRIStine sulfate LIPOSOME injection), 5 mg/31 mL (0.16 mg/mL)*

Procedures for handling and disposal of anticancer drugs should be followed.

Call 1-888-292-9617 if you have questions about the preparation of Marqibo®. Marqibo® takes approximately 60 to 90 minutes to prepare. The preparer should have dedicated uninterrupted time to prepare Marqibo® due to the extensive monitoring of temperature and time required for the preparation.

Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is present in Marqibo®. The preparation steps of Marqibo® that involve mixing the Sodium Phosphate Injection, Sphingomyelin/Cholesterol Liposome Injection, and Vincristine Sulfate Injection must be done in a biological safety cabinet or by established pharmacy safety procedures for the preparation of sterile injectable formulations and hazardous drugs. If using the water bath, the preparation steps that involve placement of the vial in the water bath must be done outside of the sterile area.

Do not use with in-line filters. Do not mix with other drugs.

Please note the kit instructions will include details on the use of the water bath and the heat block.

Water bath:

1. Fill a water bath with water to a level of at least 8 cm (3.2 inches) measured from the bottom and maintain this minimum water level throughout the procedure. The water bath must remain outside of the sterile area.
2. Place a calibrated thermometer in the water bath to monitor water temperature and leave it in the water bath until the procedure has been completed.
3. Preheat water bath to 63°C to 67°C. Maintain this water temperature until completion of the procedure using the calibrated thermometer.
4. Visually inspect each vial in the Marqibo® Kit for particulate matter and discoloration prior to preparation, whenever solution and container permit. Do not use if a precipitate or foreign matter is present.
5. Remove all the caps on the vials and swab the vials with sterile alcohol pads.
6. Vent the Sodium Phosphate Injection vial with a sterile venting needle equipped with a sterile 0.2 micron filter or other suitable venting device in the biological safety cabinet. Always position venting needle point well above liquid level before adding Sphingomyelin/Cholesterol Liposome Injection and VinCRIStine Sulfate Injection.
7. Withdraw 1 mL of Sphingomyelin/Cholesterol Liposome Injection.
8. Inject 1 mL of Sphingomyelin/Cholesterol Liposome Injection into the Sodium Phosphate Injection vial.
9. Withdraw 5 mL of VinCRIStine Sulfate Injection.
10. Inject 5 mL of VinCRIStine Sulfate Injection into the Sodium Phosphate Injection vial.
11. Remove the venting needle and gently invert the Sodium Phosphate Injection vial 5 times to mix. DO NOT SHAKE.
12. Fit Flotation Ring around the neck of the Sodium Phosphate Injection vial.
13. Confirm that the water bath temperature is at 63°C to 67°C using the calibrated thermometer. Remove the Sodium Phosphate Injection vial containing VinCRIStine Sulfate Injection, Sphingomyelin/Cholesterol Liposome Injection, and Sodium Phosphate Injection from the biological safety cabinet and place into the water bath for 10 minutes using the calibrated electronic timer. Monitor the temperature to ensure the temperature is maintained at 63°C to 67°C.
14. IMMEDIATELY after placing the Sodium Phosphate Injection vial into the water bath, record the constitution start time and water temperature on the Marqibo® Overlabel.
15. At the end of the 10 minutes, confirm that the water temperature is 63°C to 67°C using the calibrated thermometer. Remove the vial from the water bath (use tongs to prevent burns) and remove the Flotation Ring.
16. Record the final constitution time and the water temperature on the Marqibo® Overlabel.
17. Dry the exterior of the Sodium Phosphate Injection vial with a clean paper towel, affix Marqibo® (vinCRIStine sulfate LIPOSOME injection) Overlabel, and gently invert 5 times to mix. DO NOT SHAKE.
18. Permit the constituted vial contents to equilibrate for at least 30 minutes to controlled room temperature (15°C to 30°C, 59°F to 86°F).
19. Marqibo® (vinCRIStine sulfate LIPOSOME injection) contains 5 mg/31 mL (0.16 mg/mL) vincristine sulfate. One prepared, store at controlled room temperature (15°C to 30°C, 59°F to 86°F) for no more than 12 hours.
20. Swab the top of the vial now containing Marqibo® with a sterile alcohol pad and return the vial back into the biological safety cabinet.
21. Calculate the patient's Marqibo® dose based on the patient's actual body surface area (BSA) and remove the volume corresponding to the patient's Marqibo® dose from an infusion bag containing 100 mL of 5% Dextrose Injection or 0.9% Sodium Chloride Injection.
22. Inject the dose of Marqibo® into the infusion bag to result in a final volume of 100 mL.
23. Complete the information required on the Infusion Bag Label and apply to the infusion bag.
24. Finish administration of the diluted product within 12 hours of the initiation of Marqibo® preparation.
25. Empty, clean, and dry the water bath after each use.
26. Deviations in temperature, time, and preparation procedures may fail to ensure proper encapsulation of vincristine sulfate into the liposomes. In the event that the preparation deviates from the instructions in the above steps, the components of the kit should be discarded and a new kit should be used to prepare the dose.

Block Heater:

1. Arrange the three heater blocks in the Block Heater such that the block holding the constitution vial is centered between the two other blank heater blocks.
2. Place a calibrated thermometer in the block opening adjacent to the vial well to monitor the temperature. Leave the thermometer in the block opening until the procedure has been completed.
3. Turn on the Block Heater and set the controller to 75°C. Verify the block temperature by checking that the thermometer inserted in the block reads 75 ±2°C. Equilibrate the heating block at 75 ±2°C for 15 minutes. Maintain this block temperature until completion of the procedure using the calibrated thermometer.
4. Visually inspect each vial in the MARQIBO Kit for particulate matter and discoloration prior to preparation, whenever solution and container permit. Do not use if a precipitate or foreign matter is present. Note that Sphingomyelin/cholesterol

liposomes are a white to off-white homogeneous suspension, essentially free of visible foreign matter and aggregates.
5. Remove all the caps on the vials and swab the vials with sterile alcohol pads.
6. Vent the Sodium Phosphate Injection vial with a sterile venting needle equipped with a sterile 0.2-micron filter or other suitable venting device in the biological safety cabinet. Always position venting needle point well above liquid level before adding Sphingomyelin/Cholesterol Liposome Injection and VinCRIStine Sulfate Injection.
7. Withdraw 1 mL of Sphingomyelin/Cholesterol Liposome Injection.
8. Inject 1 mL of Sphingomyelin/Cholesterol Liposome Injection into the Sodium Phosphate Injection vial.
9. Withdraw 5 mL of VinCRIStine Sulfate Injection.
10. Inject 5 mL of VinCRIStine Sulfate Injection into the Sodium PhosphateInjection vial.
11. Remove the venting needle and gently invert Sodium Phosphate Injection vial 5 times to mix. DO NOT SHAKE.
12. Confirm that the Block Heater temperature is at 73°C to 77°C using the calibrated thermometer. Remove the Sodium Phosphate Injection vial containing VinCRIStine
Sulfate Injection, Sphingomyelin/Cholesterol Liposome Injection, and Sodium Phosphate Injection from the biological safety cabinet and place into the Block
Heater for 18 minutes using the calibrated electronic timer. Monitor the temperature to ensure the temperature is maintained at 73°C to 77°C.
13. IMMEDIATELY after placing the Sodium Phosphate Injection vial into the Block
Heater, record the constitution start time and Block Heater temperature on the MARQIBO Overlabel. Use only the calibrated thermometer inserted in the block to monitor temperature.
14. At the end of the 18 minutes using the Block Heater, confirm that the Block Heater temperature is 73°C to 77°C using the calibrated thermometer. Remove the vial from the Block Heater (use tongs to prevent burns).
15. Record the final constitution time and the Block Heater temperature on the MARQIBO Overlabel.
16. Affix MARQIBO (vinCRIStine sulfate LIPOSOME injection) Overlabel, and gently invert 5 times to mix. DO NOT SHAKE.
17. Permit the constituted vial contents to equilibrate for at least 30 minutes to controlled room temperature (15°C to 30°C, 59°F to 86°F).
18. MARQIBO (vinCRIStine sulfate LIPOSOME injection) contains 5 mg/31 mL (0.16 mg/mL) vincristine sulfate. ONCE PREPARED, STORE AT CONTROLLED ROOM
TEMPERATURE (15°C to 30°C, 59°F to 86°F) FOR NO MORE THAN 12 HOURS.
19. Swab the top of the vial now containing MARQIBO with a sterile alcohol pad and
return the vial back into the biological safety cabinet.
20. Calculate the patient's MARQIBO dose based on the patient's actual body surface area (BSA) and remove the volume corresponding to the patient's Marqibo dose from an
infusion bag containing 100 mL of 5% Dextrose Injection or 0.9% Sodium Chloride Injection.
21. Inject the dose of MARQIBO into the infusion bag to result in a final volume of 100 mL.
22. Complete the information required on the Infusion Bag Label and applyto the infusion bag.
23. Finish administration of the diluted product within 12 hours of the initiation of MARQIBO preparation.
24. Deviations in temperature, time, and preparation procedures may fail to ensure proper encapsulation of vincristine sulfate into the liposomes. In the event that the preparation deviates from the instructions in the above steps, the components of the kit should be discarded and a new kit should be used to prepare the dose.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if a precipitate or foreign matter is present.

9.3.5 *Dosage and Administration*

Marqibo® will be administered at a patient-specific dose established for each patient at the time of registration (see **Section 4.3** and **Section 5.1**). The dose will be given intravenously over 60 minutes (±10 minutes) on Day 2 of each treatment cycle.

Marqibo® may be infused through a free running peripheral or central venous catheter, without the use of an inline filter, using an infusion pump. For peripheral venous access, a minimum 21-gauge catheter or butterfly should be used. It is extremely important that the intravenous needle or catheter be properly positioned before any Marqibo® is administered. Leakage into surrounding tissue during intravenous administration of Marqibo® may cause local irritation. If extravasation occurs, the injection should be discontinued immediately and managed per institutional

procedures. Any remaining portion of the dose should be introduced into another vein.

Marqibo® should be administered only by intravenous infusion and by individuals experienced with the administration of vincristine sulfate.

Marqibo® should not be mixed with or diluted with other drugs or solutions for infusion. It is recommended that the infusion bag and tubing be constructed from medical grade PVC. There is currently no compatibility data available for material other than medical grade PVC. It is not required that the Marqibo® dose be corrected for obese subjects.

9.3.6 ***Toxicity***

Marqibo® has a safety profile comparable to conventional vincristine. Neurotoxicity is the dose limiting toxicity of Marqibo, mostly peripheral sensory neuropathy. The severity of neuropathy worsens with cumulative dose but this occurs gradually. Myelosuppression is evident from Marqibo® treatment but significant myelotoxicity occurs infrequently and can be managed with the concomitant use of colony stimulating factors. Fatigue was commonly observed but severe infections, infusion-related pyrexia, severe gastrointestinal symptoms, and alopecia were seen infrequently. Other common or important adverse effects reported in clinical experience with Marqibo® include:

- General: chills, pain, mucosal inflammation and infusion site leakage
- Hematologic: neutropenia, febrile neutropenia and thrombocytopenia
- Gastrointestinal: abdominal pain, hemorrhage, weight loss, vomiting, ulceration, swelling in mouth/colon/stomach
- Metabolism: dehydration, change in chemistries, elevation of liver enzymes
- Musculoskeletal: weakness, jaw pain- notes as common
- Neurologic: peripheral neuropathy, urinary retention
- Respiratory: shortness of breath with potential for respiratory failure
- Cutaneous: alopecia, rash
- Cardiovascular: hypertension, hypotension

For a comprehensive list of adverse events, refer to Marqibo® package insert.

9.3.7 ***Drug Accountability***

All study drug supplies must be kept in a locked limited access room. The study drug must not be used outside the context of the protocol. Under no circumstances should the Investigator or other site personnel supply study drug to other Investigators, subjects, or clinics, or allow supplies to be used other than directed by this protocol without prior authorization from the Sponsor and the drug manufacturer.

The pharmacist will maintain complete drug accountability records as described in **Section 12.3.6**. Periodically throughout the study, and again at the end of the study, BrUOG will require submission of the drug accountability record providing a complete accounting of the receipt and disposition of each vial of study drug and the total number of vials dispensed to each subject. This will occur again at the closure of the study.

9.3.8 ***Drug Handling***

As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions with Marqibo®. The use of gloves and protective garments is

recommended during Marqibo® preparation. Preparation should occur in a vertical laminar flow biological hood using proper aseptic technique. Disinfect vertical laminar flow biological hood by wiping surfaces with 70% isopropyl alcohol or by established pharmacy procedures. If a solution of Marqibo® contacts the skin, wash immediately and thoroughly with soap and water. If Marqibo® contacts the mucous membranes, flush thoroughly with water. Dispose of all anticancer agents according to institutional policy.

9.3.9 ***Spillage/Contamination***

Wear gloves, mask, and protective clothing. Treat spilled liquid with sodium hypochlorite solution. Carefully absorb solution with gauze pads or towels, wash area with water and absorb with gauze or towels again.

Place the gauze pads or towels in a plastic bag, seal, double bag and mark as hazardous waste. Dispose of waste by incineration or by other methods approved for hazardous materials.

Personnel involved in clean up should wash with soap and water.

9.3.10 ***Disposal***

Avoid contact with skin by using gloves. All needles, syringes, vials, and other materials that have come in contact with vincristine sulfate should be segregated in plastic bags, sealed, and marked as hazardous waste. Incinerate at 1000°C or higher. Sealed containers may explode if a tight seal exists.

If incineration is not available, sodium hypochlorite (household bleach) may be added to the vial(s) to detoxify the vincristine sulfate. Care must be taken to vent the vial(s) to avoid a pressure build-up of chlorine gas generated. Decomposition occurs within 10 minutes. Dispose of detoxified vials in a safe manner.

Dispose all components of the Vincristine Sulfate Liposomes Injection Marqibo® Kit that did not come into contact with vincristine sulfate as per established pharmacy procedures for non-biohazardous waste.

The water bath can be destroyed on site, per institutional policy.
The destruction of all materials is required to be documented via the drug accountability log, except for used vials. Prior to destroying drug or any materials (such as the water bath etc), BrUOG must be made aware and obtain approval from Acrotech Biopharma, LLC. Once approved by Acrotech Biopharma, LLC, BrUOG will then approve site destruction of all materials including drug, before destruction occurs. This does not include the destruction of used vials.

10. AGENT ACCOUNTABILITY

10.1 Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from manufacturer using a Drug Accountability Record Form. Sites must submit to BrUOG accountability logs during the study and prior to destruction. To be able to destroy drug, sites must contact BrUOG who will obtain approval from Acrotech Biopharma, LLC prior to destruction.

10.2 Treatment Compliance

Records of study medication used, dosages administered, and intervals between visits will be recorded during the study. Drug accountability will be noted.
All drugs will be administered to eligible patients under the supervision of the investigator or identified sub-investigator(s). The pharmacist will maintain records of drug receipt drug preparation, and dispensing, including the applicable lot numbers. Any discrepancy between the calculated dose and dose administered and the reason for the discrepancy must be recorded in the source documents.

11. ADVERSE DRUG REACTION REPORTING

11.1 Adverse Events and Potential Risks List

11.1.1 *Adverse event (definition)*

An **adverse event (AE)** will be defined as any untoward medical occurrence in a patient enrolled in the study, which may or may not have a causal relationship with this treatment. AEs will include:

- any unfavorable and unintended sign, symptom, or disease, whether or not considered related to the study therapy;
- pre-existing events or illnesses which increase in frequency or severity or change in nature during or as a consequence of study treatment;
- pre- or post-treatment complications that occur as a result of protocol-mandated procedures.

Any AE with an onset date between the **date the subject signs the informed consent for this trial** and the date of End-of-study Assessment should be recorded as an AE in the patient files.

AEs do **not** include disease progression. Any events that are unequivocally due to progression of disease must not be reported as AEs, unless they result in the death of the patient.

11.1.2 *Serious adverse events*

A **serious adverse event (SAE)** will be any AE occurring during the time on study that results in any of the following outcomes:

- Death;
- Life-threatening adverse event;
- An AE that results in an inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Congenital anomaly/birth defect in the offspring of a subject who received study drug;
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

"Life-threatening" means that the patient is at immediate risk of death from the event as it occurred. This definition does not encompass an event that *might* have led to death, *if* it had occurred with greater severity. Complications that occur during hospitalizations are AEs. If a complication prolongs hospitalization, it is an SAE.

11.1.3 *Lists of adverse events associated with study agents*

For comprehensive lists of potential risks and adverse events for each of the study agents refer to the FDA-approved package inserts, available at:

Rituximab: **http://www.gene.com/download/pdf/rituxan_prescribing.pdf**

Bendamustine: **http://treanda.com/PDF/TREANDA_final_PI.pdf or http://www.treandahcp.com/pdf/TREANDA_final_PI.pdf**

Vincristine sulfate liposome injection (Marqibo®): **http://marqibo.com/**

The most commonly encountered and most significant adverse effects associated with each agent are listed below.

Drug	Adverse effects
Rituximab	**Common:** **Cardiovascular**: Hypotension (non-Hodgkin lymphoma, 10%; chronic lymphocytic leukemia, 2%), Peripheral edema (Wegener granulomatosis or microscopic polyangiitis, 16%) **Dermatologic**: Night sweats (non-Hodgkin lymphoma, 15%), Pruritus (non-Hodgkin lymphoma, 14%), Rash (non-Hodgkin lymphoma, 15%; Wegener granulomatosis or microscopic polyangiitis, 10%) **Gastrointestinal**: Abdominal pain (non-Hodgkin lymphoma, 14%; rheumatoid arthritis, 2%), Diarrhea (non-Hodgkin lymphoma, 10%; Wegener granulomatosis and microscopic polyangiitis, 17%), Nausea (non-Hodgkin lymphoma, 23%; Wegener granulomatosis and microscopic polyangiitis, 18%), Vomiting (non-Hodgkin lymphoma, 10%) **Hematologic**: Anemia, All grades (non-Hodgkin lymphoma, 8% to 35%; Wegener granulomatosis or microscopic polyangiitis, 16%) **Musculoskeletal**: Arthralgia (non-Hodgkin lymphoma, 10%; Wegener granulomatosis or microscopic polyangiitis 13%), Backache (non-Hodgkin lymphoma, 10%), Myalgia (non-Hodgkin lymphoma, 10%) **Neurologic**: Asthenia (non-Hodgkin lymphoma, 26%; rheumatoid arthritis, 2%), Dizziness (non-Hodgkin lymphoma, 10%), Headache (non-Hodgkin lymphoma, 19%; Wegener granulomatosis and microscopic polyangiitis, 17%), Sensory neuropathy (non-Hodgkin lymphoma, 30%) **Respiratory**: Increasing frequency of cough (non-Hodgkin lymphoma, 13%), Rhinitis (non-Hodgkin lymphoma, 12%) **Other**: Fever (non-Hodgkin lymphoma, 53%), Infectious disease (non-Hodgkin lymphoma, 31%; rheumatoid arthritis, 39%; Wegener granulomatosis or microscopic polyangiitis, 62%), Pain (non-Hodgkin lymphoma, 12%), Shivering (non-Hodgkin lymphoma, 33%; rheumatoid arthritis, 3%) **Rare but serious:** **Cardiovascular**: Cardiac dysrhythmia, Cardiogenic shock, Heart failure, Myocardial infarction, Supraventricular arrhythmia, Supraventricular tachycardia **Dermatologic**: Lichenoid dermatitis, Pemphigus paraneoplastica, Stevens-Johnson syndrome, Toxic epidermal necrolysis

	Gastrointestinal: Bowel obstruction, Gastrointestinal perforation, Regional ileocolitis **Hematologic**: Anemia, Grade 3 and 4 (non-Hodgkin lymphoma, 3%), Aplastic anemia, Transient, Cytopenia, Grade 3 and 4 (non-Hodgkin lymphoma, 48%), Febrile neutropenia, Grade 3 and 4 (chronic lymphocytic leukemia, 9% to 15%), Hemolytic anemia, Leukopenia, Grade 3 and 4 (non-Hodgkin lymphoma, 4%; chronic lymphocytic leukemia, 23%), Lymphocytopenia, Grade 3 and 4 (non-Hodgkin lymphoma, 40%), Neutropenia, All grades (non-Hodgkin lymphoma, 8% to 14%), Neutropenia, Grade 3 and 4 (non-Hodgkin lymphoma, 4% to 6%; chronic lymphocytic leukemia, 8.5% to 49%), Thrombocytopenia (non-Hodgkin lymphoma, all grades, 12%; grades 3 and 4, 2% to 9%; chronic lymphocytic leukemia, 11%) **Hepatic**: Fulminating type B viral hepatitis, acute, Hepatitis B, Liver failure, Relapsing type B viral hepatitis **Immunologic**: Infusion reaction, All grades (non-Hodgkin lymphoma, 77%; rheumatoid arthritis, 32%; Wegener granulomatosis or microscopic polyangiitis, 12%), Infusion reaction, Grade 3 and 4 (non-Hodgkin lymphoma, 1.1% to 3.5%; chronic lymphocytic leukemia, 7% to 9%) **Neurologic**: Progressive multifocal leukoencephalopathy (rheumatoid arthritis, rare) **Ophthalmic**: Peripheral ulcerative keratitis **Renal**: Nephrotoxicity **Respiratory**: Dyspnea (Wegener granulomatosis or microscopic polyangiitis, 10%), Obliterative bronchiolitis, Pneumocystis pneumonia, Pneumonitis, Pulmonary fibrosis **Other**: Angioedema (non-Hodgkin lymphoma, 11%), Infectious disease, Serious (non-Hodgkin lymphoma, 4%; rheumatoid arthritis, 2%; Wegener granulomatosis or microscopic polyangiitis, 11%), Tumor lysis syndrome
Bendamustine	**<u>Common:</u>** **Dermatologic**: Injection site pain (6%), Pruritus (5% to 6%), Rash (all grades, 8% to 16%; grade 3 or 4, less than 1% to 3%) **Endocrine metabolic**: Weight loss (all grades, 7% to 18%; grade 3 or 4, 2%) **Gastrointestinal**: Constipation (all grades, 29%; grade 3 or 4 less than 1%), Diarrhea (all grades, 9% to 37%; grade 3 or 4, 1% to 3%), Loss of appetite (all grades, 23%; grade 3 or 4, 2%), Nausea (all grades, 20% to 75%; grade 3 or 4, less than 1% to 4%), Stomatitis (all grades, 15%; grade 3 or 4, less than 1%), Vomiting (all grades, 16% to 40% ; grade 3 or 4, less than 1% to 3%) **Neurologic**: Headache (21%) **Respiratory**: Cough (all grades, 4% to 22%; grade 3 or 4, less than 1%), Dyspnea (all grades, 16%; grade 3 or 4, 2%) **Other**: Dehydration (all grades, 14%; grade 3 or 4, 5%), Fatigue (all grades, 9% to 57%; grade 3 or 4, 1% to 11%), Fever (all grades, 24% to 34%; grade 3 or 4, 2% to 4%) **<u>Rare but serious:</u>** **Cardiovascular:** Hypertensive crisis **Dermatologic**: Dermatologic toxicity, Injection site extravasation, Stevens-Johnson syndrome, Toxic epidermal necrolysis **Endocrine metabolic**: Hyperuricemia (all grades, 7%; grade 3 or 4, 2%)

	Hematologic: Acute myeloid leukemia, Anemia (all grades, 88% to 89%; grade 3 or 4, 11% to 13%), Febrile neutropenia (6%), Leukopenia (all grades, 61% to 94%; grade 3 or 4, 28% to 56%), Lymphocytopenia (all grades, 68% to 99%; grade 3 or 4, 47% to 94%), Myelodysplastic syndrome, Myeloproliferative disorder, Myelosuppression, grade 3 and 4 (98%), Neutropenia (all grades, 75% to 86%; grade 3 or 4, 43% to 60%), Thrombocytopenia (all grades, 77% to 86%; grade 3 or 4, 11% to 25%) **Immunologic**: Anaphylaxis, Hypersensitivity reaction (all grades, 5%; grade 3 or 4, 1%), Infectious disease, Sepsis, Septic shock **Renal**: Renal failure **Respiratory**: Squamous cell carcinoma of bronchus **Other**: Myelodysplastic syndrome, Tumor lysis syndrome
Vincristine sulfate liposome injection (Marqibo®)	**Common:** **Gastrointestinal**: Constipation (57%), Decrease in appetite (33%), Diarrhea (37%), Nausea (52%) **Hematologic**: Anemia (34%), Febrile neutropenia (38%) **Neurologic**: Insomnia (32%), Peripheral nerve disease (39%) **Other**: Fatigue (41%), Fever (43%) **Rare but serious:** **Cardiovascular**: Cardiac arrest (6%), Hypotension, Grade 3 or greater (6%) **Gastrointestinal**: Constipation, Grade 3 or greater (4.8%), Pseudo-obstruction of gastrointestinal tract, Grade 3 or greater **Hematologic**: Anemia, Grade 3 or greater (16.9%), Febrile neutropenia, Grade 3 or greater (31.3%), Neutropenia, Grade 3 or greater (18.1%), Thrombocytopenia, Grade 3 or greater (16.9%) **Hepatic**: AST/SGOT level raised, Grade 3 or greater (6% to 11%), Hepatotoxicity **Immunologic**: Immune hypersensitivity reaction, Septic shock, Grade 3 or greater (6%), Staphylococcal infectious disease, Grade 3 or greater (6%) **Neurologic**: Peripheral motor neuropathy, Grade 3 or greater (16.7% to 31%) **Respiratory**: Pneumonia, Grade 3 or greater (8.4%), Respiratory distress, Grade 3 or greater (6%), Respiratory failure, Grade 3 or greater (4.8%) **Other**: Fever, Grade 3 or greater (14.5%), Tumor lysis syndrome

11.2 Routine Adverse Event Reporting

All AEs, whether serious or non-serious, related or unrelated, will be reported **from the time the signed and dated informed consent form is obtained** until **the date of Off Study Assessment**, or until the subject withdraws consent from study participation, or at the time the patient is deemed ineligible for the study, whichever occurs first. AEs will be graded, assessed by the Investigator, and recorded on the CRF. All AEs **must** be reported in routine study data submissions. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. These are available at:

http://evs.nci.nih.gov/ftp1/CTCAE/About.html and

https://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx

AEs occurring during Cycle 1 of study treatment will be used for DLT designation if they meet the DLT definition (**Section 6.3**). AEs occurring during Cycle 1 through 6 will be recorded and used for determination of secondary outcomes (cumulative toxicity).

During each study assessment, all new AEs as well as previously occurred, unresolved AEs will be recorded. For each AE, the following items will be recorded:

11.3 Serious Adverse Event Reporting

All SAEs and deaths occurring within the AE reporting timeframe must be reported to BrUOG, the drug manufacturer and the IRB. The process of reporting is initiated by the Investigator according to the guideline below.

11.3.1 ***Investigator's responsibilities.***

11.3.1.1 *Telephone/email report to BrUOG:*

Investigator (or designee at the site) must notify BrUOG within 24 hours of learning of the event by phone: 401-863-3000 or email. Investigator (or designee at the site) must provide 24-hour notification prior to submitting SAE to BrUOG (unless event is a death, for which site is to provide notification more expeditiously).

11.3.1.2 *Written report to BrUOG.*

Investigator (or designee at the site) must provide a written signed report using the **MedWatch 3500A form**, within 4 calendar days of the event (or as soon as they are aware of the event), to the BrUOG Central Office by email or fax:

Brown University Oncology Research Group	
Phone: (401) 863-3000	**Fax**: (401) 863-3820
Email: BrUOG@brown.edu	

All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 4 calendar days or as soon as the investigator is made aware of the event. If the death is thought to be related to the study drug, deaths must be reported within 24 hours of the investigator being made aware of the event.

The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product, if available. Information not available at the time of the initial report must be documented on a follow-up report.

MedWatch 3500A reporting guideline: In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description and number: **BrUOG 326 and IIS-MAR-003**
- Description of event, severity, treatment, and outcome, if known
- Expectedness (determined by investigator based on Investigator Brochure, protocol and consent)

- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to investigational product (Marqibo®), bendamustine, rituximab, disease, or any suspect medication.

Additional follow-up information:
For any follow-up SAE report, submit a new MedWatch 3500A report; do not resubmit the initial report with any additions. The follow-up report must be submitted to BrUOG with subject identifiers (subject number, initials, and date of birth), protocol description and number (BrUOG 326 and IIS-MAR-003), suspect drug, a brief summary of previously reported SAE information, and any new information, including modification of prior events, causality, new serious events, discharge date, etc.

A final report documenting discharge date from the hospital is required.

11.3.1.3 *Investigator's report to the IRB*

The Investigator is required to notify his/her Institutional Review Board (IRB) of a serious adverse event according to institutional policy.

11.3.2 ***BrUOG responsibilities.***

BrUOG must inform:
- the FDA, Fax: 1-800-FDA-0178 (1-800-332-0178)
- the Principal Investigator (via email),
- all participating sites (via email), and
- Acrotech Biopharma, LLC at:
    - Email: DrugSafety@acrotechbiopharma.com

of any SAE, in writing using a signed MedWatch 3500A form submitted by the Investigator (or designee at the site), no later than 1 business day after BrUOG's receipt of the information (signed form) from the site. A copy of the email transmission of the SAE report to Acrotech Biopharma, LLC will be attached to the SAE and retained with the study records at BrUOG.

11.4 Overdosage

There are currently no data available regarding overdosage of Marqibo® or rituximab. The treatment of AEs associated with overdosage should be supportive for the underlying adverse symptoms. Management of overdosage of bendamustine should include general supportive measures, including monitoring of hematologic parameters and electrocardiogram. Signs and symptoms of an overdose that meet the criteria of serious should be reported as a SAE and be documented as clinical sequelae to an overdose.

11.5 Procedures in the Event of Pregnancy

Marqibo® can cause fetal harm when administered to a pregnant woman. There are no adequate and controlled studies of Marqibo® or vincristine sulfate conducted in pregnant women. Vincristine sulfate is a known teratogen in animals. Therefore women and men of child bearing potential must use adequate methods of birth control while participating in the study, from the registration through 4 months after the last dose of study treatment.

Pre-menopausal women of childbearing potential must inform the Investigator immediately if they become pregnant during the study, and must be immediately removed from the protocol if a pregnancy occurs. The Investigator will counsel the patient and discuss the risk and the possible

effects on the fetus. Monitoring of the patient will continue until conclusion of the pregnancy.

If a female partner of a male subject on the study product becomes pregnant, the male subject should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately.

Treatment on study must be discontinued immediately in the event of a pregnancy. The pregnancy must be reported to BrUOG by the investigator within 1 working day of learning about it on the Medwatch 3500A form, and BrUOG will in turn report it to Acrotech Biopharma, LLC within 1 working day of receiving the documentation from the investigator. Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or state of the disease) of a female subject occurring within the AE reporting window are considered immediately reportable.

12. REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

Patients will be removed from study when any of the criteria listed in **Section 4.5** applies. The reason for study removal and the date the patient was removed must be documented in the CRF.

Patients who discontinue the study treatment should undergo the End-of-study Assessment within 30 to 42 days after their last treatment. Documentation of all SAEs and AEs are to be collected up to the date of the End-of-study Assessment.

13. REGULATORY CONSIDERATIONS

This research study is sponsored by the Principal Investigator, Dr. Adam J. Olszewski, in collaboration with Brown University Oncology Research Group (BrUOG), which will serve as the central coordinating office for the study.

14. DATA MONITORING, QUALITY ASSURANCE AND RECORD RETENTION

14.1 Rationale for the study and subject selection

Most indolent B-cell lymphomas, including the follicular, mantle cell, marginal zone, and lymphoplasmacytic subtypes, are at present incurable in the majority of patients. The goals of treatment include relief (palliation) of symptoms and achievement of remission from the lymphoma. Currently available standard regimens, such as bendamustine-rituximab (BR), have a limited potential to achieve these goals, and are associated with recurrences of the disease in a majority of patients. Development of more active regimens, which would provide improved response rates and duration of remission, without compromising the toxicity profile and patients' quality of life, is an important research goal. For example, current NCCN guidelines® for treatment of follicular lymphoma recommend consideration of investigational therapy as first line of treatment given incurability with conventional therapy.[18]

Patients eligible for this study must be otherwise good candidates for the standard BR regimen as would be administered in routine clinical practice and supported by current NCCN guidelines®. All patients must read, comprehend, and sign the IRB-approved Informed Consent prior to engaging in any study-related procedures.

14.2 Data and Safety Monitoring Plan

This study will treat 10 subjects. Patients who experience a DLT during the first cycle of therapy will be removed from the study and their further treatment will be at the managing physician's discretion. If the first three patients experience a DLT or anytime the posterior probability that the

DLT rate at the minimum dose exceeds 0.33 is 0.8 or more, the study regimen will be considered too toxic and the study will be terminated.

All AEs occurring during the study treatment will be recorded in the study data files (**Section 11**), All SAEs will be immediately reported to BrUOG, who will then report them to Acrotech Biopharma, LLC (**Section 11.3**). The Principal Investigator will be responsible for reviewing the toxicities in all study participants, identifying, reporting and resolving any potential issues related to the study conduct, observed AEs and data management and safety.

Protocol deviations and violations will be managed and reported according to BrUOG's Standard Operating Procedures.

14.3 Investigator Responsibilities

14.3.1 *Good Clinical Practice*

The Investigator will ensure that this study is conducted in full compliance with the principles of the Declaration of Helsinki (as amended in Tokyo, Venice, Hong Kong, and South Africa), ICH guidelines, and with the United States laws and regulations, whichever affords the greater protection to the study subject. The Investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998, are adhered to. The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice.

14.3.2 *Institutional Review Board (IRB) Approval*

This protocol and any accompanying material to be provided to the subject (such as advertisements, information sheets, or descriptions of the study used to obtain informed consent) will be submitted, by the Investigator, to the IRB. The IRB's approval opinion must be obtained before starting the study and should be documented in a letter to the Investigator.

Any modifications made to the protocol after receipt of IRB approval must also be submitted to the IRB for approval/favorable opinion prior to implementation.

14.3.3 *Informed Consent*

It is the responsibility of the Investigator to obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and prior to undertaking any study-related procedures. The Investigator must utilize a current IRB consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject and the person obtaining consent.

Subjects will be treated and/or compensated for any study-related illness/injury pursuant to the information provided in the Compensation for Injury section of the Sample Informed Consent.

BrUOG must receive and approve all consent forms, including the initial form, prior to IRB submission, and throughout the duration of the study, any time the consent document is amended.

14.3.4 *Confidentiality*

The Investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials and an identification code

(i.e., not names) should be recorded on any form submitted to the drug manufacturer and IRB. The Investigator must keep a subject identification code list showing codes, names, and addresses for all subjects enrolled in the trial.

The Investigator agrees that all information received from Acrotech Biopharma, LLC or agent, including but not limited to the Investigator's Brochure, the investigational new drug, and any other study information are and remain the sole and exclusive property of Acrotech Biopharma, LLC. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Acrotech Biopharma, LLC. The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

14.3.5 ***Study Files and Retention of Records***

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

The Brown University Oncology Research Group, as coordinator of this study, is responsible for ensuring proper conduct of the study with regard to protocol adherence and the validity of the data recorded on the case report forms. The Principal Investigator (Adam J. Olszewski, M.D.) and Brown University Oncology Research Group will monitor this study. The case report forms will be monitored for accuracy, completeness, adherence to the protocol and regulatory compliance.

U.S. FDA (21CFR§312.62[c]) states that an Investigator shall retain the required records:
a) for a period of two years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or
b) if no application is to be filed or if the marketing application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.
If neither a) or b) applies, then the Investigator shall retain the required records for a minimum of fifteen (15) years after the completion or discontinuation of the study.

14.3.6 ***Drug Accountability***

The Investigator or designee (i.e., pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), and subject dispensing records. Dispensing records will document quantities received from Acrotech Biopharma, LLC and quantities dispensed to subjects, including lot number, date dispensed, subject identifier number, subject initials, and the initials of the person dispensing the study drug.

In addition, for each dose of Marqibo® constituted, the study drug records must include:
- the start time of the constitution of each dose of Marqibo, and
- the name(s) of the responsible pharmacy staff who performed the constitution.

14.3.7 ***Protocol Compliance and Revisions***

The Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

All revisions to the protocol must be created and provided by BrUOG to the participating Investigators. The Investigators will not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from BrUOG, except where

necessary to eliminate an immediate hazard(s) to study patients. When applicable, documentation of approval signed by the chairperson or designee of the IRB must be sent to BrUOG. If the revision is an Administrative Letter, Investigator must inform the IRB.

14.4 Drug Manufacturer's Responsibilities

14.4.1 *Drug provision*

This study is conducted with support of Acrotech Biopharma, LLC, the manufacturer of Marqibo®. The drug manufacturer will provide Marqibo® for the current study, with a sufficient number of reconstitution kits to treat each enrolled patient for all cycles of study therapy, and allowing for timely administration of treatment according to this protocol. In case of damage or expiry of a kit, a replacement kit will be provided.

15. DATA SAFETY AND MONITORING BOARDS

This BrUOG study is subject to oversight by the Data Safety Monitoring Board (DSMB). The BrUOG DSMB meets two times per year with additional meetings scheduled when needed. The DSMB responsibilities are as follows:

- Familiarize the DSMB members with the research protocol.
- Review trial performance information including accrual information.
- Review interim analyses of outcome data and cumulative toxicity data summaries to determine whether the trial should continue as originally designed, should be changed, or should be terminated based on these data.
- Determine whether and to whom outcome results should be released prior to the reporting of study results.
- All adverse events are reviewed by the committee, with assurances that these have been in fact sent for review to all pertinent IRBs.
- Review of reports of related studies to determine whether the monitored study needs to be changed or terminated.
- Review major proposed modifications to the study prior to their implementation (e.g., termination, dropping an arm based on toxicity results or other reported trial outcomes, increasing target sample size).
- Following each DSMB meeting, provide the study leadership with written information concerning findings for the trial as a whole related to cumulative toxicities observed and any relevant recommendations related to continuing, changing, or terminating the trial.

The DSMB leadership will provide information on cumulative toxicities and relevant recommendations to the local principal investigators to be shared with their IRB's.

16. STATISTICAL CONSIDERATIONS

16.1 Study Design/Endpoints

This is a Phase 1, single-center, open-label, single-arm trial evaluating escalating doses of Marqibo® in combination with standard doses of bendamustine-rituximab (BRiM) in adult patients with indolent B-cell non-Hodgkin lymphoma, for whom bendamustine-rituximab is otherwise clinically indicated as initial or subsequent line of therapy.

16.1.1 *Primary endpoint*

The primary endpoint in this study is the **Maximum Tolerated Dose (MTD)** of Marqibo® in the BRiM combination.

MTD is defined to be the dose level of Marqibo® that when administered to a patient in the BRiM combination results in a probability of $\theta = 33\%$ that a DLT will be manifest within the first cycle of treatment. It will be synonymous with the recommended phase II dose for this regimen.

Upon completion of the trial, the primary endpoint will be calculated as the median of the marginal posterior distribution of the MTD, rounded to 0.05 mg/m2. The MTD and the 95% highest posterior density credible interval estimate of the MTD will be reported, as calculated by the Investigator in cooperation with the study statistician. Data from all enrolled patients will be used for the calculation.

The computation of the dose to be administered to each patient and the 95% highest posterior density credible interval estimate of the MTD will be carried out by the Investigator in cooperation with statistician consultant, using the Web-EWOC computer software, available at:[42]

http://biostatistics.csmc.edu/ewoc/

In case of unavailability of the Web-EWOC interface, the stand-alone EWOC Version 3.1 will be used. The results of all simulations, calculations and dose determinations will be recorded in the study files and signed by the Investigator.

The DLT will be described as the CTCAE terms for the recorded DLT's, and the dose level at which they occurred. **The trial will be terminated after ten patients are evaluated, or if the first three patients experience a DLT or anytime the posterior probability that the DLT rate at the minimum dose exceeds 0.33 is 0.8 or more.**

16.1.2 *Secondary endpoints*

The secondary endpoints of the study include:

- Tolerability of the BRiM regimen, assessed by proportion of enrolled patients completing 6 cycles of study treatment.
- Proportions of patients experiencing cumulative toxicities with the BRiM combination during the study treatment.
- Proportion of patient achieving partial remission (PR) or complete remission (CR) after completion of the study treatment

The secondary endpoints will be calculated using data from Off Study Assessments for all enrolled patients. Proportions of patients with cumulative toxicities will be calculated as the total numbers of patients experiencing each of the recorded toxicities at each grade. Each AE will be counted once per patient, at the worst grade experienced during treatment.

16.1.3 *Analysis population*

The endpoints will be assessed in the population of all registered patients.

16.1.4 *Treatment regimen*

The dose of Marqibo® will be determined specifically for each patient at the time of registration, from the starting dose of 1.8 mg/m2, up to the convergence ceiling dose of 2.4 mg/m2. The computation of the dose to be administered to each patient and the 95% highest posterior density

credible interval estimate of the MTD will be carried out by the Principal Investigator with the EWOC-Web software. The Principal Investigator will provide BrUOG with the dose-assignment trees (as in Figure 3 below) for the first 5 patients before the first patient is registered on the study. The Principal Investigator will then generate a dose-assignment tree for 4 subsequent patients when subject #4 is registered (see Section 16.4 for details).

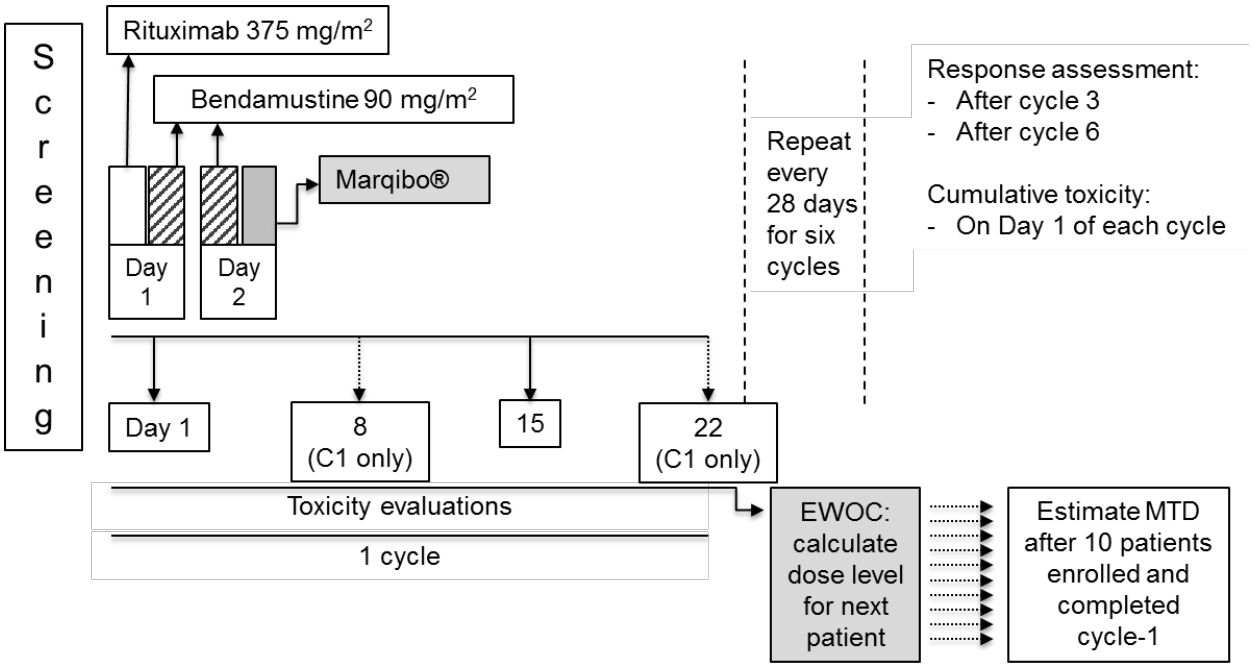
Patients will be evaluated weekly during the **first** cycle to assess clinical and laboratory toxicity and to identify any DLT. Patients will be followed every two weeks during **subsequent** cycles, until completion of six cycles of therapy or discontinuation of treatment.

The response to chemotherapy will be evaluated after 3 cycles and 6 cycles of treatment. The cumulative toxicities will be evaluated at each visit. The radiographic responses will be assessed according to the International Working Group criteria.[41]

16.2 EWOC Phase I design

The dose escalation will follow a Bayesian method permitting precise determination of the therapeutic working-dose while directly controlling the likelihood of an overdose. The method, known as EWOC (Escalation With Overdose Control), has been used to design many dose finding clinical trials.[43-50] Babb et al. provided a comparison of EWOC with alternative phase I design

Figure 2: **Treatment schema.**



methods.[51] They showed that up-and-down designs treated only 35% of patients at optimal dose levels, versus 55% for EWOC, i.e., more patients are treated with doses outside the therapeutic window by up-and-down than by EWOC designs. Babb and Rogatko provide a summary of Bayesian phase I design methods and Tighiouart et al. studied the performance of EWOC under a rich class of prior distributions for the MTD.[52,53] Tighiouart and Rogatko showed that EWOC is coherent.[54]

EWOC was the first dose-finding procedure to directly incorporate the ethical constraint of

minimizing the chance of treating patients at unacceptably high doses. Its defining property is that the expected proportion of patients treated at doses above the MTD is equal to a specified value α, the *feasibility bound*. This value is selected by the clinician and reflects his/her level of concern about overdosing. Zacks et al. showed that among designs with this defining property, EWOC minimizes the average amount by which patients are under-dosed.[55] This means that EWOC approaches the MTD as rapidly as possible, while keeping the expected proportion of patients overdosed less than the value α. Zacks et al. also showed that, as a trial progresses, the dose sequence defined by EWOC approaches the MTD (i.e., the sequence of recommended doses converges in probability to the MTD). Eventually, all patients beyond a certain time would be treated at doses sufficiently close to the MTD.

16.3 Dose Escalation Procedure

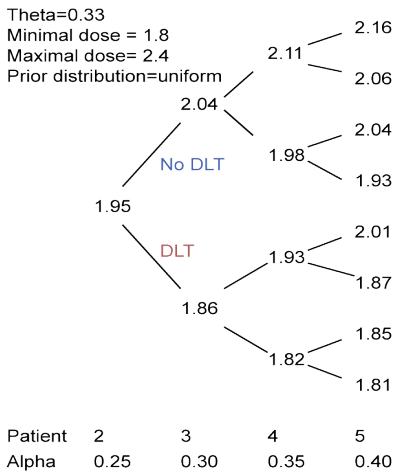
The dose of Marqibo® for the first patient in this trial will be 1.8 mg/m^2, which is considered to be safe in view of feasibility of 2.0 mg/m^2 dose in the R-CHMP combination with full-dose rituximab and cyclophosphamide.[35] The dose for each subsequent patient will be determined so that, on the basis of all available data, the probability that it exceeds the MTD is equal to a pre-specified value α. In this trial, we set α = 25%, with an increase α in small increments of 5% until α = 50%, this value being a compromise between the therapeutic aspect of the agent and its toxic side effects.

The dose selected for every patient in the trial will be between the minimum dose of 1.8 mg/m^2 and the maximum allowable dose 2.4 mg/m^2. This maximum dose serves only as a convergence value for the algorithm and will never be actually administered to any patient. The maximum dose that could be administered to a patient during the dose escalation portion, in the absence of any DLT, would be 2.3 mg/m^2. **The trial will be terminated if the first three patients experience a DLT or anytime the posterior probability that the DLT rate at the minimum dose exceeds 0.33 is 0.8 or more.** Figure 3 shows all the possible dose sequences that could be realized for the first 5 patients, assuming that the first patient is treated at dose level 1.8 mg/m^2 and does not experience a DLT.

16.4 Assignment of Marqibo® Dose Level

The determination of the patient-specific dose of Marqibo® to be delivered as part of the study regimen will be performed solely by the BrUOG central office using the pre-populated dose-

Figure 3. **Distribution of doses (in mg/m^2) for patients 2-5 in the study according to the EWOC protocol (assuming the first patient is treated at dose 1.8 mg/m^2 and does not experience a DLT).**



assignment trees generated by the Principal Investigator. The doses will be calculated using the EWOC-web software, available at:[42]

http://biostatistics.csmc.edu/ewoc/

When creating the dose-assignment trees, the Investigator will input a data matrix containing information about all study patients for whom DLT information is available at the time of calculation. The following parameters will be set for the software:

- Target Probability of Dose Limiting Toxicity = 0.33
- Probability of Exceeding Target Dose = 0.25
- Minimum Dose = 1.8
- Maximum Dose = 2.4
- Minimum Dose Increment = 0.01
- Bayesian Confidence Interval Percentage = 95
- Number of Patients = 1
- Variable Alpha Increment = 0.05
- Prior Distribution = Uniform
- Uniform Lower = 0
- Uniform Upper = 0.33

Only *N*=1 patient per cohort is allowed, i.e. a new subject may be registered for the study only after all previous subjects resolve their DLT assessment period.
At no time will there be more than one subject on the study with unresolved DLT status.

The calculated dose will be patient-specific and will not be adjusted during subsequent cycles (except for toxicity, as delineated in **Section 5**).

16.5 Sample Size/Accrual Rate

The planned sample size for this study is 10 treated patients with a planned accrual rate of 5 patients per year.

Procedure for determining the number of patients needed in a dose finding trial using a Bayesian framework depends on the investigators, goal and sets of criteria such as precision of the estimate of the MTD and frequency of DLTs. The investigators conducted extensive simulations under several scenarios, with true values of the MTD ranging from 1.85 mg/m^2 to 2.20 mg/m^2, and probability of toxicity at the initial dose (20%) and target probability of DLT (θ = 33%) set at the levels assumed for the study using prior literature. Table 3 presents results of simulations of *N*=100 trials consisting of 10 patients, assuming different levels of true MTD. The results indicate that the study will estimate reasonably precise MTD within a range of MTD 1.80 mg/m^2 to 2.20 mg/m^2.

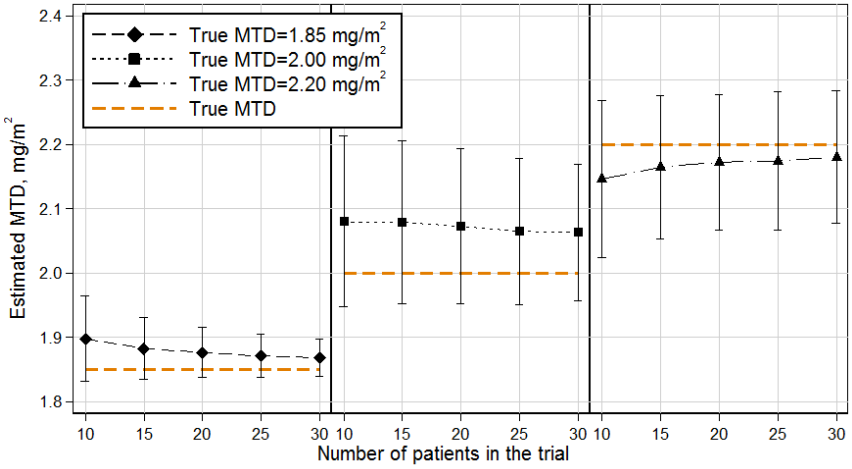
Table 3. Results of simulation of N=100 trials of 10 patients with true MTD ranging from 1.81 mg/m2 to 2.25 mg/m2, conducted according to the current trial's design.

True MTD level (mg/m^2)	Estimated MTD (mg/m^2)	Estimated root mean standard error (mg/m^2)	Patients treated at ±10% of the optimal dose, %	Patients overdosed, %	DLT's observed, %
1.81	1.82	0.01	100	0	58
1.90	1.98	0.08	88	12	43
2.00	2.08	0.13	83	17	33

2.10	2.12	0.11	98	0	28
2.20	2.15	0.12	89	0	26
2.25	2.15	0.15	87	0	25

Figure 4 shows the results of a simulation of N=500 trials with varying sample size (10 to 30) and true MTD (1.80, 2.00, and 2.25 mg/m^2), with resulting estimated MTD and mean root standard errors. The simulation indicates acceptable performance and precision of the estimates even with the smallest sample size, if the MTD is rounded to 0.05 mg/m^2.

Figure 4. **Simulation of *N*=500 trials with varying sample size conducted according to the current study design, with a true MTD of 1.85, 2.00 or 2.20 mg/m^2**



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APPENDIX A PERFORMANCE STATUS CRITERIA

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.

APPENDIX B LIST OF CONCOMITANT MEDICATIONS KNOWN TO INTERACT WITH CYTOCHROME P450-3A4 ISOENZYMES AND/OR P-GLYCOPROTEIN (TO BE USED WITH CAUTION)+

Generic Name	Trade Name	Generic Name	Trade Name
Amiodarone	Cordarone	Miconazole (systemic)	Lotrimin, Monistat
Atazanavir§	Reyataz	Modafinil§	Provigil
Atorvastatin	Lipitor	Nefazodone§	Serzone
Azithromycin	Zithromax	Nelfinavir§	Viracept
Barbiturates§ (including phenobarbital)	Amytal, Fioricet, Fiorinal, Illocalm, Mebaral, Brietal, Nembutal, Seconal, Pentothal	Nevirapine§	Viramune
Bromocriptine	Parlodel	Nicardipine	Cardene
Buprenorphine/naloxone§	Suboxone	Norfloxacin	Noroxin
Carbamazepine§	Tegretol, Tegretol-XR	Omeprazole	Prilosec
Cerivastatin	Baycol	Orphenadrine	Norflex
Chlorpheniramine	Chlor-Trimeton	Oxcarbazepine§	Trileptal
Cimetidine	Tagamet	Paroxetine	Paxil
		Phenytoin§	Dilantin
Ciprofloxacin	Cipro	Posaconazole	Noxafil
Clarithromycin§	Biaxin	Progesterone	Progestasert, Prometrium, Crinone, Corluvite
Clotrimazole*	Mycelex, Lotrimin*	Quinine	Legatrin, Quinamm Quinine sulfate
Cyclosporine	Neoral, Sandimmune	Ranitidine	Zantac, Tritec
Danazol*	Danocrine*	Rapamycin	Rapamune
Delavirdine	Rescriptor	Rifabutin§	Mycobutin
Dexamethasone§	Decadron	Rifampin§	Rifadin, Rimactane
Diltiazem	Cardizem	Rifapentine	Priftin
Digoxin	Lanoxin	Ritonavir§	Novir, Kaletra
Efavirenz§	Sustiva	Rosiglitazone	Avandia
Ergotamine	Ergomar, Ergostat	Saquinavir§	Invirase, Fortovase
Erythromycin	E-Mycin, EES, Ilosone, Pediazole	Sertraline	Zoloft
Fluconazole*	Diflucan*	Simvastatin	Zocor
Grapfruit juice	NA	St. John's Wort§	NA
Haloperidol	Halodol	Tacrolimus	Prograf
Indinavir§	Crixivan	Tamoxifen	Nolvadex
Isoniazid	INH, Nydrazid, PMS-Isoniazid	Telithromycin§	Ketek
Itraconazole§	Sporanox*	Toremifene	Fareston
Ketoconazole§	Nizoral*	Trazodone	Desyrel
		Troglitazone§	Rezulin, Resulin, Romozin, Noscal
Lidocaine	Xylocaine	Troleadomycin	TAO
Lovastatin	Mevacor	Verapamil	Calan
Methadone	Dolophine, Diskets	Voriconazole	Vfend
Metronidazole*	Flagyl*	Zafirlukast	Accolate

+ Not a comprehensive listing

* Must have Sponsor's and drug manufacturer's approval prior to use

§ Prohibited in his protocol. Patients taking this medication are not eligible for participation. Dexamethasone use as an anti-emetic according to the protocol is allowed.

APPENDIX C REGISTRATION CHECKLIST

Inclusion Criteria

___ **Yes** Histologically confirmed indolent B-cell non-Hodgkin lymphoma, CD20-positive, previously treated or untreated—for which bendamustine-rituximab chemotherapy is clinically indicated; the following subtypes are allowed (check or circle applicable):

- Follicular lymphoma
- Mantle cell lymphoma,
- Marginal zone lymphoma,
- Small lymphocytic lymphoma,
- Lymphoplasmacytic lymphoma, or
- Indolent B-cell lymphoma, NOS.

*Note: BrUOG must receive the **pathology report** to confirm the diagnosis and the CD20-positive status, as well as **documentation from the treating physician that bendamustine-rituximab chemotherapy is clinically indicated** for the subject.*

___ **Yes** Radiological measurable disease, defined as any measurable lesion >15 mm
Patients with blood or bone marrow involvement only are ineligible.
Splenomegaly is acceptable as a measurable site if enlarged on the initial CT scan (>13 cm in the cranio-caudal dimension).

___ **Yes** Previous treatment for lymphoma is allowed, with the exception of use of bendamustine within 180 days of the date of the consent form, or any prior use of vincristine sulfate liposome injection (Marqibo®).

___ **Yes** Age ≥18 years.

___ **Yes** ECOG performance status 0 or 1

___ **Yes** Life expectancy of greater than 6 months.

___ **Yes**	White blood cell count	≥3,000/mm^3	Date _____
___ **Yes**	Absolute neutrophil count	≥1,000/mm^3	Date _____
___ **Yes**	Platelets *Note: platelet transfusion within 1 week before registration is not allowed; note the date of a prior platelet transfusion on the ConMed log*	≥75,000/mm^3	Date _____
___ **Yes**	Total bilirubin within normal institutional limit		Date _____
___ **Yes**	AST(SGOT)/ALT(SGPT) <2.5x normal institutional limit		Date _____
___ **Yes**	Creatinine	≤2.0 mg/mL	Date_____
___ **Yes**	Creatinine clearance *Note: calculate by Cockroft-Gault equation, using actual weight*	≥50 mL/min/1.73 m2.	Date_____

___ **Yes** Subject is a women of child-bearing potential or a man, and agrees to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and up to 4 months after the last dose of study treatment.

___ **Yes** Subject is a woman of childbearing potential and has a negative serum or urine pregnancy test. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she agrees to inform her treating physician immediately.

___ **Yes** Postmenopausal women (after surgical menopause or no menses for >12 months) do not need to have a pregnancy status, but their postmenopausal status must be documented. Males with a vasectomy also must be documented.

___ **Yes** Subject is able to understand and the willingness to sign a written informed consent document.

Exclusion criteria

___ **No** History of any allergic reaction attributed to rituximab (with the exception of <grade 3 infusion reaction), bendamustine, vincristine sulfate, Marqibo®, mannitol, sodium phosphate injection or sphingomyelin/cholesterol liposome.

___ **No** Any lymphoma-directed radiotherapy, chemotherapy, biologic or experimental therapy, oral or intravenous, within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study, or subject has not recovered from adverse events due to agents administered more than 4 weeks earlier to ≤grade 1—with the exception of alopecia, which is allowed.

___ **No** Any prior treatment with vincristine sulfate liposome injection (Marqibo®).

___ **No** Prior treatment with bendamustine or vincristine sulfate within 180 days of enrollment.
Prior treatment with rituximab is allowed.

___ **No** Subject is receiving any other investigational agents or anti-cancer therapy with the exception of endocrine therapy for breast or prostate cancer.

___ **No** Known central nervous system involvement (infiltration of the brain, meninges or cerebrospinal fluid) by the lymphoma

___ **No** Active peripheral sensory or motor neuropathy > grade 1. This is defined by the CTCAE as any neuropathy requiring intervention or limiting instrumental activities of daily life.

___ **No** History of demyelinating form of Charcot-Marie-Tooth syndrome, acquired demyelinating disorders, or other demyelinating condition.

___ **No** Documented positive test for the Human Anti-Chimeric Antibody (HACA).

___ **No** Subject is receiving any medications or substances that are strong inhibitors or inducers of CYP3A enzyme are ineligible.

___ **No** Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection (that requires antibiotic use), symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
Note: Suppressive anti-HSV/VZV therapy with acyclovir, famciclovir, or valacyclovir is allowed.

___ **No** Prisoner.

___ **No** Pregnant or breast-feeding woman.

___ **No** Known Human Immunodeficiency Virus (HIV) or active Hepatitis B infection (defined as presence of HBV DNA or hepatitis B S antigen in the blood).

___ **No** Any prior or active cancer, which in the opinion of the investigator would preclude safe participation in this study.

Signed informed consent:

___ **Yes** The patient is aware of the neoplastic nature of his/her disease and willingly consents after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts.

Support documentation enclosed: (*NOTE: all must be faxed to BrUOG for registration*)

___ **Yes**	Demographics Form	___ **Yes**	Pathology Report	___ **Yes**	CT or PET-CT report(s)
___ **Yes**	Treating oncologist's note (documenting that bendamustine-rituximab is clinically indicated)				
___ **Yes**	Lab Source Document	___ **Yes**	ICF signature page	___ **Yes**	Others, please list:

IRB approval date of protocol: _____ Hospital where patient will be treated: _____
Date patient will begin treatment: _____ Treating oncologist: _____

Your signature: _____ Date: _____

*The **support documentation**, **consent form**, and **this checklist**, must be faxed to BrUOG at the time of registration. **Source documents** to support each inclusion and prove the subject does not meet each exclusion criteria are required. Source document for each element in Section 6 must also be sent.*

APPENDIX D MODEL INFORMED CONSENT FORM

AGREEMENT TO PARTICIPATE IN A RESEARCH STUDY AND AUTHORIZATION FOR USE AND DISCLOSURE OF INFORMATION

BrUOG 326: A Phase I Dose-Escalation Study of Vincristine Sulfate Liposome Injection (Marqibo®) in Combination with Bendamustine and Rituximab (BRiM) in Indolent non-Hodgkin Lymphoma

You are being asked to take part in a research study. All research studies carried out at <INSERT HOSPTIAL NAME> are covered by rules of the Federal government as well as rules of the State and <INSERT HOSPTIAL NAME>. Under these rules, the researcher will first explain the study, and then he or she will ask you to participate. You will be asked to sign this agreement that states that the study has been explained, that your questions have been answered, and that you agree to participate.

The researcher will explain the purpose of the study. He or she will explain how the study will be carried out and what you will be expected to do. The researcher will also explain the possible risks and possible benefits of being in the study. You should ask the researcher any questions you have about any of these things before you decide whether you wish to take part in the study. This process is called informed consent.

This form also explains the research study. Please read the form and talk to the researcher about any questions you may have. Then, if you decide to be in the study, please sign and date this form in front of the person who explained the study to you. You will be given a copy of this form to keep.

Nature and Purpose of the **Study**

Your doctors are participating in this research study sponsored by the Principal Investigator, Dr. Adam Olszewski, in collaboration with Brown University Oncology Research Group (BrUOG), which will serve as the central coordinating office for the study

You have been asked to participate in this study, because you have been diagnosed with a lymphoma for which your doctor has recommended treatment with rituximab and bendamustine chemotherapy.

The combination of rituximab and bendamustine is one of the treatment options for patients with indolent (slow-growing) lymphomas. Although other chemotherapy regimens exist, rituximab/bendamustine is often used because it is both effective (works well) and is well tolerated by patients when compared with other combinations. Many patients with indolent lymphomas who receive rituximab/bendamustine chemotherapy for the first time experience shrinking of their lymphoma. However, some patients with indolent lymphomas do not respond to this treatment, and while over half of the patients who do respond are alive and have not had recurrence of their lymphoma more than 5 years after this treatment, in most patients the lymphoma does eventually regrow. Also, about 1 in 5 patients treated with rituximab/bendamustine experience a serious side effect (toxicity) during therapy. New treatments are needed to see if new combinations of treatments are well tolerated and might work better.

The purpose of this study is to find the maximum tolerated dose of the drug Marqibo® (vincristine

sulfate liposome injection) that can be given in combination with rituximab and bendamustine for patients with certain types of lymphoma. This will be determined by looking at the side effects that occur during the treatment with the combination. In this study, your doctors hope to show that rituximab and bendamustine can be safely combined with Marqibo® in your type of lymphoma, called non-Hodgkin lymphoma (NHL). Two previous studies indicated that Marqibo® can be safely combined with rituximab and full-dose alkylating agents (similar to Bendamustine, which belongs to this same class of drugs) for the treatment of NHL without unexpected side effects.

Marqibo® is already approved by Food and Drug Administration (FDA) for the treatment of acute lymphoblastic leukemia that has relapsed after at least two other lines of therapy. Acute lymphoblastic leukemia is a very aggressive kind of lymphoma that involves blood and bone marrow. Marqibo® has been combined with rituximab and other chemotherapy drugs for treatment of other kinds of lymphoma in some studies. The active ingredient of Marqibo® (vincristine) is commonly used in chemotherapy combinations for many kinds of lymphoma, but Marqibo® is not at present FDA-approved for the treatment of your type of non-Hodgkin lymphoma.

The use of Marqibo® in combination with rituximab/bendamustine in this study is experimental. The doses and schedules of rituximab and bendamustine in this study are the same as those used for patients in routine clinical practice. The dose of Marqibo® will be decided on for each patient participating in the study, depending on side effects seen in all previous patients enrolled in this study. Because in this study Marqibo® is used in combination with rituximab/bendamustine, the doses of Marqibo® used in this study are lower than the FDA-approved dose for acute lymphoblastic leukemia.

Approximately 10 patients will be treated on this study.

Explanation of Procedures

<u>What will happen if I take part in this research study?</u>

If the following exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests, while on the study. They are part of regular cancer care.

- Medical history
- A physical examination with performance status, toxicity assessment, weight, vitals, and an assessment of the medications you are taking
- Blood and urine tests, including blood counts, kidney and liver function, a pregnancy test (if you are a woman who can become pregnant) and tests for the HIV and hepatitis viruses; many of these tests will be repeated during the study; approximately three tablespoons of blood will be taken;
- An electrocardiogram—a simple test that involves putting electrode stickers on your chest to record the heart's electrical activity;
- A scan to obtain measurements of any lymphoma tumors inside your body. This may be a CT (Computed Tomography) scan or a PET-CT (Positron Emission Tomography and Computed Tomography) scan.

- If your doctor feels it is necessary, a bone marrow aspirate and biopsy will be performed. This is a procedure performed by a physician that involves collecting a sample of the marrow from the hip bone to find out if it contains lymphoma cells.

While on study:

Different doses of Marqibo® are being tested in this study and each patient will be registered to their own dose based on how well previous patients did in the study (ranging from the smallest dose of 1.8 mg of drug per square meter of body surface area to the highest dose of 2.4 mg of drug per square meter of body surface area).. Patients will be treated to determine the highest safe dose of Marqibo® in combination with bendamustine and rituximab.

The Brown University Oncology Research Group, the group coordinating this trial, will calculate the dose of Marqibo® to be used for your treatment. This calculation will take into consideration information about any side effects that happened to any patients previously treated in the study, in order to lower the risk of side effects. Neither you nor your doctor can choose which dose you will receive and your dose will not be increased.

Once your dose has been calculated, you will start the study treatment. The treatment will be given in "cycles" of four weeks (28 days) for a maximum of 6 cycles (about 6 months). It will involve chemotherapy with rituximab, bendamustine and Marqibo®, given intravenously (through a vein) according to the schedule below.

On **Day 1** of each treatment cycle (your visit is expected to last about 6 hours):

- You will undergo a physical examination including vital signs, ECOG performance status, height, weight, and recording of all medications you take.
- Laboratory tests before the treatment to confirm normal blood counts, kidney and liver function (approximately 2 tablespoons of blood).
- Urinalysis
- If you are a woman of childbearing potential you will also have a pregnancy test

You will then receive:

- Medications to prevent allergic reactions and nausea (by mouth or intravenously). These are routinely given (they are standard) to patients receiving rituximab or bendamustine.

On **Day 1** of each treatment cycle you will receive**:**

- **Rituximab** as an intravenous infusion, which may take up to 4-5 hours to complete.
- **Bendamustine** as an intravenous infusion, over approximately 10 to 30 minutes.

On **Day 2** of each treatment cycle (your visit is expected to last about 2 hours) you will receive:

- **Bendamustine** as an intravenous infusion, over approximately 10 to 30 minutes.
- **Marqibo®** as an intravenous infusion, at a dose calculated for you at the time of enrollment, over approximately 60 minutes.

If your doctor recommends it, you may also receive an additional medication (pegfilgrastim) on Day 3 or 4 of each cycle. Pegfilgrastim is given as an injection under the skin for patients who are at higher risk of serious infections during chemotherapy. It lowers the risk of infections by increasing the number of a type of white blood cells called neutrophils, which may drop during chemotherapy.

During cycle 1:

During the first cycle of treatment, you will come in for three weekly checkup visits after treatment on; **day 8**, **day 15** and **day 22**. Each of these visits is expected to last about 1 hour. You will have the following done:

- Vital signs, ECOG performance status, and weight
- Toxicity assessment
- Laboratory tests, approximately 2 tablespoons of blood

During Cycles 2-6:

You will be assessed prior to day 1 of cycles 2-6 as explained above. You will then receive treatment on Day 1 and 2 as explained above.

Day 15: You will also be seen on day 15 of cycles 2-6 (each or these visits are expected to last about 1 hour) for the following:

- Vital signs, ECOG performance status, weight
- Toxicity assessment
- A scan to obtain measurements of any lymphoma tumors inside your body using a CT (Computed Tomography) scan or a PET-CT (Positron Emission Tomography and Computed Tomography) scan will be done after cycle 3 and after cycle 6 or when you come off study.
- If your doctor feels it is necessary, a bone marrow aspirate and biopsy may be performed if your doctor feels your cancer is responding. This is a procedure performed by a physician that involves collecting a sample of the marrow from the hip bone to find out if it contains lymphoma cells.

For all patients, treatment on study will be given in cycles of every 4 weeks (28 days) for a maximum of 6 cycles.

End of study treatment

Between 30- 42 days after your last treatment you will undergo the following:

- History and physical examination, including vital signs, ECOG performance status, weight, and recording of all medications you take.
- Toxicity assessment. If there are any important side effects, your doctor will continue to follow your condition until they stabilize or resolve.
- A scan to obtain measurements of any lymphoma tumors inside your body may also be done (as noted above) if you come off prior to completing all your treatment.

How long will I be in this study?

You will receive the study treatment for 6 months.

Can I stop being in this study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the discontinuation of treatment can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

Costs of participating in this study

Acrotech Biopharma, LLC, the maker of Marqibo®, will provide Marqibo® at no charge while you take part in this study. All other services you will receive during this research study are considered to be "routine clinical services" that you would have received even if you were not participating in the research study. These include all study doctor visits, blood tests, urine tests, bendamustine and rituximab, drugs and administration costs, drugs used to reduce side effects, CT scans, PET scans, EKGs and bone marrow biopsies. Therefore, all of the services listed in this paragraph will be billed to your health insurance company, but you will be responsible for paying any deductibles, co-payments, or co-insurance that are a normal part of your health insurance plan. If you do not have health insurance or your insurance does not cover these services, you will be responsible for those costs.

Risks or Discomforts:

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop the chemotherapy. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death. You should talk to your study doctor about any side effects that you have while taking part in the study. The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

VINCRISTINE SULFATE LIPOSOME INJECTION (MARQIBO®)
COMMON, SOME MAY BE SERIOUS In 100 people receiving Marqibo®, more than 20 and up to 100 may have (>20%):
• Constipation, diarrhea, nausea, vomiting, belly pain • Loss of appetite and weight loss • Anemia which may require blood transfusions • Infection, especially when white blood cell count is low • Difficulty sleeping • Chills, Fever, tiredness • Numbness and tingling of the arms and legs, weakness and difficulty walking • Hair loss

VINCRISTINE SULFATE LIPOSOME INJECTION (MARQIBO®)
COMMON, SOME MAY BE SERIOUS In 100 people receiving Marqibo®, more than 20 and up to 100 may have (>20%):
• Headache, jaw pain/and or muscle pain • Low platelets, which may increase risk of bleeding • Pain and redness at the site of injection • Swelling of lower legs • Dehydration
OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Marqibo®, from 4 to 20 may have (4-20%):
• Heart stops beating • Low blood pressure, which may cause feeling faint • High blood pressure • Bruising, bleeding • Severe blood infection • Muscle weakness • Difficulty emptying bladder or urinating • Sores in stomach or bowel • Damage to the lungs, which may cause shortness of breath • Hoarseness
RARE, AND SERIOUS In 100 people receiving Marqibo®, 3 or fewer may have (<3%):
• Liver damage • Kidney damage which may require dialysis • Allergic reaction which may cause rash, wheezing, swelling of the face or throat • Seizure or changes in consciousness

RITUXIMAB
COMMON, SOME MAY BE SERIOUS In 100 people receiving Rituximab, more than 20 and up to 100 may have (>20%):
• Nausea • Chills, fever • Allergic reaction during or following infusion of the drug • Infection, especially when white blood cell count is low • Anemia (low blood count) which may require blood transfusions • Numbness and tingling • Tiredness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Rituximab, from 4 to 20 may have (4-20%):
• Bruising, bleeding • Abnormal heartbeat • Heart attack or heart failure which may cause shortness of breath, swelling of ankles, and tiredness • Sores in eye • A tear or a hole in the stomach that may require surgery • Diarrhea, vomiting • Pain • Swelling of the body • Hepatitis which may cause yellow eyes and skin • Dizziness, headache • Kidney damage which may require dialysis • Cough, scarring of the lungs • Stuffy nose • Blockage of internal organs which may cause shortness of breath, wheezing, vomiting • Increased sweating • Itching, rash, blisters on the skin • Severe skin rash with blisters and peeling which can involve mouth and other parts of the body • Low blood pressure which may cause feeling faint

RARE, AND SERIOUS In 100 people receiving Rituximab, 3 or fewer may have (<3%):
• Damage to the brain caused by a virus which may result in tiredness, weakness, changes in thinking, and disability. This is called progressive multifocal leukoencephalopathy (PML). • Heart stops beating, death

BENDAMUSTINE
COMMON, SOME MAY BE SERIOUS In 100 people receiving Bendamustine, more than 20 and up to 100 may have (>20%):
• Anemia which may cause tiredness, or may require blood transfusions • Constipation, diarrhea, nausea, vomiting • Fever, tiredness • Bruising, bleeding • Infection, especially when white blood cell count is low • Loss of appetite • Headache • Cough

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Bendamustine, from 4 to 20 may have (4-20%):
• Sores in mouth which may cause difficulty swallowing • Pain at the site of injection • Swelling and redness at the site of the medication injection • Weight loss • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Severe blood infection • Dehydration • A new cancer resulting from treatment of earlier cancer • Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions • Kidney damage which may cause swelling, may require dialysis • Blisters on the skin • Itching, rash • Severe skin rash with blisters and peeling which can involve mouth and other parts of the body • High blood pressure which may cause dizziness, blurred vision • Shortness of breath

RARE, AND SERIOUS In 100 people receiving Bendamustine, 3 or fewer may have (<3%):
• None

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that if you are a man or woman of childbearing potential you must use birth control while on this study and for up to 4 months post the last dose of study treatment. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives (Norplant), or double barrier method (diaphragm plus condom). Check with your study doctor about what kind of birth control methods to use and how long to use them. Women will be asked to have a pregnancy test before starting this study. In case of a pregnancy, you must report it to your study doctor immediately. The drugs used in the study may also make you unable to have children in the future. If you wish to re-start breastfeeding after treatment, you should discuss the appropriate timing with your physician.

For more detailed information about risks and side effects, ask your study doctor.

By signing this document you are acknowledging that you understand and agree to the information presented in this Reproductive Risk section.

Medications to prevent nausea and infusion reactions: As part of the treatment you will receive medications to prevent nausea and allergic infusion reactions, which are routinely given to patients who receive bendamustine and rituximab. These medications have few side effects, although

medications used to prevent nausea and vomiting may cause drowsiness, dry mouth, diarrhea, constipation, headache, restlessness, agitation, anxiety, dizziness, involuntary tremors, skin rash, and possible allergic reaction.

Venipuncture (inserting a needle into a vein to obtain blood or give medication): May cause inflammation, pain, bruising, bleeding, or infection.

When you receive chemotherapy by vein, there is a slight risk that some of the drug may leak out around the needle at the injection site. A skin burn may result. Most skin burns are treatable and heal well.

In order to monitor the side effects, your physician will examine you frequently and obtain laboratory tests (blood tests, chest x-rays, or CT scans as needed) to determine the effects of your treatment and alter the drug dosages if necessary.

Risk of CT imaging: CT imaging uses x-rays. The radiation dose associated with this procedure is estimated to be a small fraction of the annual permissible dose to an x-ray technologist. There is no significant risk from this amount of radiation.

There may be other side effects that have not been reported. If you have any unusual symptoms, you should report them immediately to your doctor or nurse.

Benefits:

You may receive no direct benefit from your participation in this study. Your lymphoma might respond to the treatment better or for longer if the study treatment is more effective than standard chemotherapy, but this is not known at this time. We do know that the information from this study will help doctors learn more about the way that combined chemotherapy drugs work together as a treatment for cancer. This information could help future cancer patients.

Alternatives:

If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the usual treatment approach described above
- you may choose to take part in a different study, if one is available
- or you may choose not to be treated for the lymphoma, but receive comfort care to relieve symptoms.

Talk to your doctor about your choices before you decide if you will take part in this study.

Refusal/Withdrawal

It is up to you whether you want to be in the study. You are not required to enroll or participate. If you decide to participate, you can always change your mind and quit at any time. If you decide not to be in the study, or if you quit later, you will still be able to get the health care services you normally get. If you join, but later on the researcher or your doctor feels being in the study is no longer good for you, they may choose to take you out of the study before it is over. If new information becomes available that might change your mind about whether you want to stay in the study the researcher will share this information with you as soon as possible.

If you make the decision to withdraw from this study (stop taking study medication) for any reason, tell your doctor immediately. You will be asked to sign a form indicating whether you give your permission for your doctor and the research staff to continue to collect and submit follow-up information on your health status from your physicians and medical record. After signing the form, you still have the right to change your mind, at any time, regarding follow-up after withdrawal.

Compensation in Case of Injury:

A research injury is any physical or mental injury or illness caused by being in the study. If you are injured by a medical treatment or procedure you would have received even if you were not in the study that is not a research injury. To help avoid research injury and added medical expenses, it is very important to follow all study directions carefully. If you do experience a research injury, <INSERT HOSPITAL NAME> or the study doctor can arrange medical treatment for you. Such treatment will be paid for as described below.

Medical treatment will be available if you suffer a research related injury; however, you and/or your health insurance company will be charged for this treatment. The study will not pay for this medical treatment. Neither Dr. Adam Olszewski nor BrUOG, the coordinating center, have money set aside to reimburse you for medical bills from treatment of a research related injury or otherwise compensate you in the event of a study-related injury.

If you have insurance and have a research injury that is not covered by the study, it is possible that some or all of the cost of treating you could be billed to your insurer. If your health insurance will not cover such costs, it is possible you would have to pay out of pocket. In some cases, <INSERT HOSPITAL NAME> might be able to help you pay if you qualify for free care under <INSERT HOSPITAL NAME> policy. However, <INSERT HOSPITAL NAME> has no policy to cover payment for such things as lost wages, expenses other than medical care, or pain and suffering.

Rights and Complaints

Signing this form does not take away any of your lawful rights. If you have any complaints about this study, or would like more facts about the rules for research studies, or the rights of people who take part in research studies you may contact <INSERT CONTACT NAME OF IRB>

Confidentiality

Your research records will be treated as private health care records and will be protected according to <INSERT HOSPITAL NAME> privacy practices and policies that are based on state and federal law. In particular, federal law requires us to get your permission to use or disclose (release your information to someone outside of <INSERT HOSPITAL NAME>) your health information for research purposes. If you sign this form you agree to be in this research study and you permit the use and disclosure of your health information for the purpose of conducting the research, providing treatment, collecting payment and running the business of the hospital. This permission has no expiration date. You may withdraw from the study at any time. However, if you do not want the researchers to use or disclose any further information in this study you must cancel permission in writing and may do so at any time. If you cancel your permission, you will stop taking part in the study and no new information will be collected about you. However, if you cancel your permission, it will not apply to actions already taken or information already collected about you by the hospital

or the researchers before you canceled your permission.

Generally, the entire research record and any medical records held by the hospital may be used and released for research purposes. The following people or businesses/companies might use, release, or receive such information:

- The researcher and their support staff;
- The study sponsor: Dr. Adam Olszewski and BrUOG, The Brown University Oncology Research Group and its representatives. Acrotech Biopharma, LLC, maker of the drug being used in this study and the financial supporter.
- Doctors, nurses, laboratories and others who provide services to you in connection with this study;
- The company or section of the U.S. government that is paying for the study and others they hire to oversee, administer, or conduct the research;
- The United States Food and Drug Administration, the Department of Health and Human Services, the Office of Inspector General, and the Office of Civil Rights;
- People who volunteer to be patient advocates or research volunteer protectors;
- Members of the hospital's administrative staff responsible for reviewing, approving and administering clinical trials and other healthcare or research activities.

There are times when the law might require or permit <INSERT HOSPITAL NAME> to release your health information without your permission. For example, <INSERT STATE> law requires researchers and health care workers to report abuse or neglect of children to the Department of Children, Youth and Families (DCYF) and to report abuse or neglect of people age 60 and older to the Department of Elderly Affairs.

All researchers and health care providers are required to protect the privacy of your health care information. Other people and businesses/organizations that are not health care providers are not required by law to do that so it is possible they might re-release your information.

You have the right to refuse to sign this form and not participate in the research. Your refusal would have no effect on your treatment, charges billed to you, or benefits at any Rhode Island Hospital health care site. If you do not sign, you will not be able to enroll in the research study and will not receive treatment as a study participant.

If you decide to quit the study after signing this form no new information will be collected about you unless you gave us permission to do so. However, the hospital or the researchers may continue to use information that was collected before you quit the study to complete analysis and reports of this research.

You will not be allowed to see or copy the information described in this form as long as the research study is open. You may see and copy the information when the study is completed.

Additionally, a description of this clinical trial will be available on the website http://www.ClinicalTrials.gov, as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

If after you have signed this form you have any questions relating to your rights, please contact

<INSERT IRB CONATACT INFORMATION>

For more detail about your privacy rights see the <INSERT HOSPITAL NAME> which has or will be given to you

Research authorization for use and disclosure of information.

The purpose of this section of the document is to provide you with some more information about how the information learned about you during the study will be used and shared.

We understand that your medical information is very personal and we will work hard to keep it private. If you sign this form you consent to participate in this research study and are giving us permission to use and share your personal health information in the ways described in this form.

Understandings and notifications

The main purpose of permitting the use and release of your information is to allow the research project to be conducted and to ensure that the information relating to that research is available to all parties who may need it for research purposes. Your information may also be used as necessary for your research-related treatment, to collect payment for your research-related treatment (when applicable), and to run the business operations of the hospital.

All health care providers are required to protect the privacy of your information. However, most persons or entities (i.e., businesses, organizations) that are not health care providers are not bound by law to protect the privacy of your information. You understand that if the person or entity that receives your information is not a health care provider bound to protect your privacy, such person or entity might re-release your health information.

You have the right to refuse to sign this form. If you do not sign this form, none of your health care outside the study, or the payment for your health care, or your health care benefits will be affected. However, if you do not sign this form, you will not be able to enroll in the research study described in this form, and you will not receive treatment as a study participant.

If you sign this consent form, you may withdraw from the study at any time. However, if you do not want the researchers to use or disclose any further information in this study you must cancel permission in writing and may do so at any time. If you cancel your permission, you will stop taking part in the study and no new information will be collected about you. However, if you cancel your permission, it will not apply to actions already taken or information already collected about you by the hospital or the researchers before you canceled your permission. This information or action may be needed to complete analysis and reports of this research. This permission will never expire unless you cancel it. To cancel this permission, please write to Adam Olszewski, MD c/o the Medical Oncology Clinical Research Office at Rhode Island Hospital, 593 Eddy Street, APC Building Rm. 131, Providence, RI 02903.

If after you have signed this form you have any questions relating to your rights, please contact <INSERT IRB CONTACT>

Uses and releases covered by this authorization (permission)

Who will release, receive, and/or use your information?

This form will allow the following person(s), class(es) of persons, and/or organization(s)* to release, use, and receive the information listed below in connection with this Study, or as required

by law:

☒ Every research site for this study, including this hospital, and including each site's research staff and medical staff

☒ Health care providers who provide services to you in connection with this study

☒ Laboratories and other individuals and organizations that analyze your health information in connection with this study, in accordance with the study's protocol

☒ The following research sponsors and the people and companies that they use to oversee, administer, or conduct the research: The Principal Investigator Adam Olszewski, MD and BrUOG, the group coordinating the study, Acrotech Biopharma, LLC, the maker of the drug Marqibo being used in this study, and the financial supporter of this trial.

☒ The United States Food and Drug Administration, the Department of Health and Human Services, the Office of Inspector General, and the Office of Civil Rights

☒ The members and staff of the Institutional Review Board(s) or Ethics Committee(s) that approves this study

☒ Principal Investigator and other Investigators

☒ Study Coordinator

☒ Additional members of the Research Team

☐ The Patient Advocate or Research Volunteer Protector: _____

☒ Members of the hospital's administrative staff responsible for administering clinical trials and other research activities

☐ Contract Research Organization (A contract research organization is an independent organization that agrees to oversee and make possible, various aspects of the clinical research process for the research sponsor.)

☒ Data and Safety Monitoring Boards and others that monitor the conduct of the Study, for example a Clinical Events Committee

☐ The members and staff of the hospitals affiliated Privacy Board (if such a board is used)

☐ Others: _____

* If, during the course of the research, one of the companies or institutions listed above merges with or is purchased by another company or institution, this permission to use or release protected health information in the research will extend to the new company or institution.

☒ The entire research record and any medical records held by the hospital may be used and released.

☐ The following information: _____

SIGNATURE

I have read this informed consent and authorization form. ALL OF MY QUESTIONS HAVE BEEN ANSWERED, AND I WANT TO TAKE PART IN THIS RESEARCH STUDY.

By signing below, I give my permission to participate in this research study and for the described uses and releases of information. *I also confirm that I have been now or previously given a copy of the <INSERT HOSPITAL NAME> Privacy Notice*

This informed consent document expires on _____.
DO NOT sign this document after this expiration date

The Researcher is required to provide a copy of this consent to you.

_____ _____ _____

→ ***Signature of study volunteer****/authorized representative*Date and Time when signed*

I was present during the consent PROCESS AND signing of this agreement by the study volunteer or authorized representative

_____ _____

Signature of witness (required if consent is presented orally or at the request of the IRB) *Date*

_____ _____

Signature of Translator *Date*

_____ _____ _____

→ ***Signature of researcher*** *or designate Date and Time when signed*

** If signed by agent other than study volunteer, please explain below.*

_____