A PHASE I/II STUDY OF GEMCITABINE AND BENDAMUSTINE IN PATIENTS WITH RELAPSED OR REFRACTORY HODGKIN'S LYMPHOMA

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Patient Eligibility

Histologically confirmed classic Hodgkin's lymphoma that is recurrent or refractory after at least one prior therapy.
Patients who are eligible for curative treatment with a stem cell transplant may receive 2-3 cycles of protocol therapy as salvage therapy prior to stem cell transplantation(see Section 5.1).
Measurable disease (see Section 5.5).
Prior stem cell transplant is permitted.
No prior treatment with bendamustine.
Non-pregnant and non-nursing.

Initial Required Laboratory Values

ANC ≥ 1000/μL
Platelets ≥ 75,000/μL
Creatinine ≤ 2.0 mg/dL
Bilirubin ≤ 2.0mg/dL
AST/ALT ≤ 2.0 x ULN

Staging and Entry Parameters

History and physical examination.
CBC with differential
Creatinine, bilirubin, AST, ALT, ESR
PET/CT scan

TREATMENT SCHEMA

Table 1. Phase I Dose Escalation Schema

Dose level	Gemcitabine IV over 30 minutes day 1	Bendamustine IV over 30 minutes days 1 and 2	Cycle Length
-1	800 mg/m²	60 mg/m²	28 days
1	1000 mg/m²	60 mg/m²	28 days
2	1000 mg/m²	90 mg/m²	28 days
3	1000 mg/m²	120 mg/m²	28 days
4	1000 mg/m²	90 mg/m²	21 days
5	1000 mg/m²	120 mg/m²	21 days

- Gemcitabine administered first followed by Bendamustine on Day 1 and Bendamustine alone on Day 2. Pegfilgrastim 6mg SQ will be administered to all patients on Day 3.
- Na, K, Cr, Ca, bilirubin, alkaline phosphatase, AST, ALT, and LDH day 1 of each cycle.
- Response should be assessed every 2 cycles. Patients who have stable disease or continued response may continue treatment up to a maximum of 6 cycles or until evidence of progression or unacceptable toxicity. Responding patients eligible to undergo stem cell transplantation may be removed from study therapy after 2 or more cycles for transplantation.
- A Phase II study will commence once the recommended Phase II doses of bendamustine and gemcitabine have been determined. Patients will be treated on the same schedule

as the Phase I Study with Gemcitabine followed by Bendamustine on Day 1 and Bendamustine alone on Day 2. All patients will receive Pegfilgrastim 6mg SQ on Day 3.

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1.0 INTRODUCTION

Advances in Hodgkin's lymphoma (HL) therapy have resulted to 5-year failure free survival rates of 61-89%,[1,2] even in the setting of advanced stage or bulky disease. However, there remains a 15-40% rate of relapse after front-line therapy, with increased risk of relapse in those patients with advanced disease or multiple risk factors by the International Prognostic Index Score[1]. This includes those patients with lab abnormalities including anemia, hypoalbuminemia, and leukocytosis, as well as extensive spread of disease. Patients who relapse typically receive 2-3 cycles of salvage chemotherapy followed by autologous stem cell transplantation as standard of care[2]. Current options for salvage therapy include GVD, ICE, IGEV, ESHAP, DHAP, and GDP, with response rates ranging from 70-88%[3-6]. Unfortunately, these regimens often require inpatient hospitalization and are associated with significant toxicities including myelosuppression. In addition, roughly 50% of patients undergoing autologous stem cell transplant will eventually relapse. Further salvage regimens for those who relapse after transplant often yield short-lived, if any response. Therefore, additional combination salvage regimens are required for patients who relapse after transplant. Agents without serious late toxicities are particularly attractive in this disease, given the young median age and high percentage of long-term survivors.

Bendamustine was originally described over 30 years ago but has recently been re-evaluated as an effective agent in many malignancies including indolent non-Hodgkin's lymphoma, CLL, as well as solid tumor malignancies. The molecule is thought to combine an alkylating agent with an anti-metabolite. A phase II trial evaluating single agent Bendamustine for treatment of relapsed indolent NHL or Mantle Cell Lymphoma found an overall response rate of 90% with a complete response rate of 66%. Many of these patients had received multiple prior therapies.[7] A recently presented Phase II study by Moskowitz et al demonstrated significant activity with single agent Bendamustine in patients with relapsed or refractory Hodgkin's lymphoma[8]. Responses were observed in 75% of patients with toxicities consisting of nausea, thrombocytopenia, neutropenia, and infections. Overall, toxicity was limited compared to other salvage regimens for Hodgkin's Lymphoma and Bendamustine can be administered in the outpatient setting. In addition, D'Elia et al recently published a case report of a heavily pretreated patient with relapsed Hodgkin's lymphoma who obtained a complete response after failing to do so on multiple prior regimens including autologous stem cell transplant.[9]

Gemcitabine has also been shown to be effective in the treatment of relapsed and refractory Hodgkin's Lymphoma, both as a single agent and as part of a multi-agent regimen[3,8]. This study aims to determine the maximum tolerated dose for gemcitabine and bendamustine when administered together for the treatment of relapsed and refractory Hodgkin's Lymphoma. Once this dose is determined, a Phase II trial will commence to determine whether this regimen should be evaluated in further trials.

In addition, many of the patients requiring salvage therapy for relapsed or refractory HL will ultimately be evaluated for and undergo autologous stem cell transplant. At this time, there is little data regarding stem cell toxicity and feasibility of stem cell mobilization after bendamustine therapy in patients with lymphoma. This is particularly problematic as autologous stem cell transplant is generally the only chance for cure for patients with relapsed HL. A prior study of R-Bendamustine compared to R-CHOP for indolent lymphoma followed 549 patients, with 23 in each arm ultimately underoing autologous transplant[9]. In this population, there was no difference in the median CD34+ cell count between R-CHOP and R-Bendamustine with a median CD34+ cell count of 4.55 $x10^6$ (range 1.68-12.34). Only 1 patient was unable to mobilize more than 2.0 x 10^6 CD 34+ cells. As part of the phase I/II trial of combined gemcitabine and bendamustine, we will plan to collect data regarding stem cell collection, mobilization regimen, number of days of

apheresis, and time to engraftment in order to evaluate the feasibility of stem cell collection in heavily pre-treated patients with Hodgkin's Lymphoma receiving bendamustine salvage therapy.

1.1 Phase I Results

The phase I portion of this study has been nearly completed with 15 patients enrolled to date. No dose limiting toxicities were encountered throughout all 5 dose levels. One patient failed to return for cycle 1, day 2 bendamustine dose and has subsequently been replaced for the purposes of dose limiting toxicity assessment. All other patients completed cycle 1. Additional encountered toxicities included two episodes of pulmonary toxicity. In one case, the patient experienced gemcitabine-related pulmonary toxicity that was biopsy-proven. This patient was treated with steroids and removed from study therapy, resulting in complete resolution of symptoms. The other patient experienced pulmonary toxicity on treatment that was initially felt to be related to an infection. This patient completed a full evaluation and the cause of the pulmonary toxicity was never elucidated.

The response rate for the first 15 evaluable patients was 80%, with 5 patients achieving CR and 7 patients achieving PR. The median PFS was estimated at 10.1 months while the 1-year PFS is 41.9%. Six patients have discontinued study therapy to pursue stem cell transplantation, including 3 patients who attempted stem cell collection (with 2 patients successfully collecting).

2.0 OBJECTIVES

2.1 Primary Objectives

2.1.1 To evaluate the toxicity and determine the maximum tolerated dose (MTD) of combined bendamustine and gemcitabine in patients with relapsed or refractory Hodgkin's lymphoma.

2.1.2 To determine the overall response rate of bendamustine and gemcitabine in patients with relapsed and refractory Hodgkin's lymphoma.

2.2 Secondary Objective

2.2.1 To determine whether therapy with bendamustine in the setting of relapsed or refractory Hodgkin's lymphoma will impact future stem cell collection.

3.0 ON-STUDY GUIDELINES

The following guidelines are to assist physicians in selecting patients for whom protocol therapy is safe and appropriate. Physicians should recognize that the following may seriously increase the risk to the patient entering this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent
- Medical condition such as uncontrolled infection, uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers. Patients are not considered to have a "currently active" malignancy if they have completed therapy and considered by their physician to be at less than 30% risk of relapse.
- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic

potential of the chemotherapy and radiation therapy utilized in this trial. Appropriate methods of birth control include oral contraceptives, implantable hormonal contraceptives (Norplant), or double barrier method (diaphragm plus condom).

- Life expectancy less than three months.

4.0 ELIGIBILITY CRITERIA

4.1 Histologically documented Classical or nodular lymphocyte predominant Hodgkin's lymphoma that is recurrent or refractory after standard chemotherapy. Core biopsies are acceptable if they contain adequate tissue for primary diagnosis and immunophenotyping. Bone marrow biopsies as the sole means of diagnosis are not acceptable.

4.1.1 Patients with Hodgkin's lymphoma may have one of the following World Health Organization subtypes:

- **Nodular sclerosis Hodgkin's lymphoma**
- **Lymphocyte-rich Hodgkin's lymphoma**
- **Mixed cellularity Hodgkin's lymphoma**
- **Lymphocyte depletion Hodgkin's lymphoma**
- **Nodular lymphocyte predominant Hodgkin's lymphoma**

4.2 Prior Treatment: Patients must have relapsed or progressed after at least one prior therapy.

4.2.1 Patients with relapsed or refractory disease following stem cell transplantation are permitted.

4.2.2 No prior treatment with bendamustine. Prior therapy with gemcitabine is permitted.

4.3 Age $\geq$ 18 years of age.

4.4 ECOG Performance Status 0-2.

4.5 Measurable disease must be present either on physical examination or imaging studies. Non-measurable disease alone is not acceptable.

4.5.1 Measurable Disease

Lesions that can be accurately measured in at least two dimensions as ≥ 1.0 x 1.0 cm by physical exam, computerize d tomography (CT), PET/CT (positron emission tomography/CT), or magnetic resonance imaging (MRI).

4.5.2 Non-measurable Disease

All other lesions, including small lesions (less than 1.0 x 1.0 cm) and truly non-measurable lesions.

Lesions that are considered non-measurable include the following:

- Bone lesions (lesions if present should be noted)
- Ascites
- Pleural/pericardial effusion
- Lymphangitis cutis/pulmonis
- Bone marrow (involvement by Hodgkin's lymphoma should be noted)

4.6 Non-pregnant and non-nursing. Due to the teratogenic potential of these agents, pregnant or nursing patients may not be enrolled. Women and men of reproductive potential should agree to use an effective means of birth control.

4.7 Patients with HIV infection are eligible. Patients with HIV infection must meet the following: No evidence of co-infection with hepatitis B or C; CD4+ count ≥ 400/mm; no evidence of resistant strains of HIV; on anti-HIV therapy with an HIV viral load < 50 copies HIV RNA/mL; no history of AIDS defining conditions.

4.8 Required Initial Laboratory Data:

Granulocytes	≥ 1000/µl
Platelet count	≥ 75,000/µl
Creatinine	≤ 2.0 mg/dL
Bilirubin	≤ 2.0 mg/dL
AST/ALT	≤ 2.0 x upper limits of normal

5.0 REGISTRATION PROCEDURES

5.1 GENERAL GUIDELINES

OSU patients will be registered by the OSU research coordinator.

Subsite patients will be entered on study centrally at The Ohio State University by the Subsite Coordinator. All subsites should call the Subsite Coordinator to verify enrollment availabilities.

Following registration, patients should begin protocol treatment within 10 calendar days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Subsite Coordinator should be notified of cancellations as soon as possible.

For patients who sign consent, but are deemed ineligible by the subsite, please submit the signed consent form and a completed Screen Failure Form (refer to the Supplemental Forms Document) to the OSU Subsite Coordinator.

5.2 REGISTRATION PROCESS

To register a subsite patient, the following documents should be completed by the research nurse or data manager and faxed or securely e-mailed to the Subsite Coordinator:

- Registration Form
- Eligibility Checklist
- ALL SOURCE DOCUMENTS verifying each eligibility criteria
- All screening tests required per the protocol calendar
- Signed patient consent form
- HIPAA authorization form

The Subsite Coordinator will email the research nurse or data manager to confirm receipt of the registration request and supporting documents. The research nurse or data manager at the participating site should call the Subsite Coordinator if the email confirmation is not received within 1-2 hours. To complete the registration process, the Subsite Coordinator will:

- verify all eligibility criteria are met and supporting documents are provided
- assign a patient study number

- register the patient on the study
- assign the patient a dose
- fax and securely e-mail the patient study number and dose to the participating site

6.0 REQUIRED DATA

Guidelines For Pre-Study Testing

To be completed within 16 DAYS before registration:
- All bloodwork, history and physical exam.

To be completed within 28 DAYS before registration:
Scan of any type that is utilized for tumor measurement per protocol.

Tests & Observations	Prior to Registration	Day 1 of each cycle	Time of Restaging (Q 2 cycles)	Post Treatment Follow up*
History and Progress Notes	X	X		X
Physical Examination	X	X		X
Height/Weight/Body Surface Area	X			
Performance Status	X	X		
Tumor Measurements	X	A	A	X**
Drug Toxicity Assessment	X	X		X
Laboratory Studies				
CBC, Diff, Plts	X	B		X
Serum Creatinine, BUN	X	C		
Serum Electrolytes	X	C		
Ca^{++}	X	C		
AST, ALT, Bilirubin, Alk.Phos, ESR	X	C		
Serum or urine pregnancy test	X#			
Restaging				
PET/CT, CT, or MRI scan (chest, abdomen, pelvis)	D		D	X**
	E		E	E
Histologic Review	X			

* At least every 3 months for 2 years, then every 6 months for a maximum of 5 years from study entry.

** Every 6 months for 2 years, then annually for a maximum of 5 years from study entry.

Women of childbearing potential.

A If accessible to physical examination.

B During cycle 1 only, repeat CBC on days 1, 8, 15, and 22. For all other cycles only day 1 is required.

C. During cycle 1 only, repeat electrolytes, creatinine, BUN, calcium, AST, ALT, bilirubin, alkaline phosphatase, and ESR on days 1 and 15. For all other cycles, only day is required.

D PET/CT preferred at the time of study registration and at re-staging after cycles 2, 4, and 6. PET/CT, CT, or MRI may be utilized according to physician preference during follow-up.

E Bone marrow biopsy and aspirate is only required for patients with suspected involvement at the discretion of the treating physician and should only be performed if felt to be necessary as part of the patient's routine care. Patients who do undergo bone marrow biopsy and aspirate

and who are found to have involvement with Hodgkin lymphoma should repeat the procedure at time patient achieves a CR.

7.0 CORRELATIVE STUDIES

7.1 Planned laboratory correlates to clinical trial

For patients who undergo autologous stem cell transplantation following protocol therapy, the following data will be collected prospectively in order to evaluate the effects of bendamustine and gemcitabine on stem cell mobilization:

a. Mobilization regimen (chemotherapy, AMD3100/plerixafor, or GCSF)

b. Number of mobilization attempts

c. Number of CD34+ cells collected

d. Number of days of apheresis with each mobilization attempt

e. Days to neutrophil recovery $\geq$ 1000 and platelet recovery $\geq$ 50,000 after stem cell transplantation

8.0 TREATMENT PLAN

8.1 Phase 1 Study

8.1.1 Dose Escalation Schema

Table 1. Phase I Dose Escalation Schema.

Cohort	Gemcitabine IV over 30 minutes day 1	Bendamustine IV over 30 minutes days 1 and 2	Cycle Length
-1	800 mg/m2	60 mg/m2	28 days
1	1000 mg/m2	60 mg/m2	28 days
2	1000 mg/m2	90 mg/m2	28 days
3	1000 mg/m2	120 mg/m2	28 days
4	1000 mg/m2	90 mg/m2	21 days
5	1000 mg/m2	120 mg/m2	21 days

In the phase I trial, three patients will be enrolled at each dose level starting at dose level 1(See above dose escalation schema) using a standard 3+3 dose escalation phase I design. If one patient experiences a dose limiting toxicity

(DLT), this dose level will be expanded to 6 patients. The dose where 2 or more DLT's are observed will be declared the maximum administered dose and will have exceeded the maximum tolerated dose (MTD). If 2 or more DLT's are observed at a given dose level, the previous dose level will be expanded to a total of 6 patients and if 1 or fewer DLT's is observed at this level, this will be the maximum tolerated or recommended phase 2 dose (RP2D). If 2 or more DLTs are observed at dose level 1, the doses of bendamustine and gemcitabine will be de-escalated to dose level -1. If dose escalation reaches dose level 5, this dose level will expand to 6 patients to ensure patient safety. If 1 or fewer patients experience DLT at dose level 5, this will be used as the RP2D, and the trial will proceed to phase II. All patients treated within a dose level must complete one cycle of therapy prior to dose escalation to the next level. Patients who do not complete one cycle of therapy for reasons other than toxicity will be replaced on that dose level.

A cycle will be defined as one 28-day (dose levels 1-3) or 21-day (dose levels 4-5) treatment period for patients at dose disease may continue to receive bendamustine and gemcitabine for a maximum of 6 cycles. Response will be assessed after every 2 cycles by PET/CT scan (preferred), CT of the chest, abdomen, and pelvis, or MRI scan. BM biopsy will be repeated in those patients with evidence of a complete response and pre-treatment bone marrow involvement.

8.1.2 Definition of Dose limiting toxicity during the Phase 1 Trial

Dose limiting toxicity will be defined during cycle 1 only of the phase I trial. Patients with a dose limiting toxicity during cycle 1 will be removed from the study. Toxicities during cycles 2-6 or that do not meet criteria for dose limiting toxicity will be managed according to section 8.0 Dose modifications.

Table 2. Definition of Dose Limiting Toxicity
Hematologic and Infectious Dose Limiting Toxicities
Grade 3 febrile neutropenia persisting >7 days.
Grade 4 infection or febrile neutropenia.
Treatment delay >14 days due to grade 3-4 neutropenia or thrombocytopenia.
Non-Hematologic Dose Limiting Toxicities
Any grade 3 or 4 non-hematologic toxicity related to study treatment with the exception of nausea or vomiting, alopecia, or electrolyte/glucose abnormalities that are correctable within 72 hours.

8.2 Phase II Study

Based on the determined recommended phase 2 dose (i.e., dose level 5) , patients shall receive gemcitabine 1000mg/m² on day 1 and bendamustine 120mg/m² on days 1 and 2 of each 21 day cycle. Gemcitabine shall be administered prior to bendamustine on day 1 of each cycle. Patients enrolled on the phase 2 trial will receive pegfilgrastim 6mg SQ on day 3 of all cycles. Response will be assessed by PET/CT (preferred), CT of the chest, abdomen, and pelvis, or MRI after every 2 cycles (i.e. cycles 2, 4, and 6), and patients without evidence of disease progression may continue for a maximum of 6 cycles of therapy. Responding patients may stop protocol therapy after 2 or more cycles to undergo stem cell transplantation.

8.3 Order of Drug Administration

Gemcitabine shall be administered first on day 1, followed by bendamustine in all patients, at all dose levels. Bendamustine will be administered alone on day 2.

8.4 Criteria for Retreatment

On the phase I and phase II trials, patients without evidence of disease progression may continue protocol therapy for up to 6 cycles. To start a cycle, the absolute neutrophil count must be $\geq$ 1000/μL and the platelet count must be $\geq$ 75,000/mm³, with recovery of all other treatment-related toxicities (excluding anemia) $\leq$ grade 2. Treatment delays for grade 3-4 non-hematologic toxicity or for hematologic recovery exceeding 14 days will lead to protocol removal.

8.5 Treatment Duration and Staging

Re-staging should be performed after every 2 cycles of Gemcitabine and Bendamustine (see section 5.0) for patients on the Phase I and Phase II trials. Patients will receive a minimum of two cycles of therapy, unless rapid disease progression or dose-limiting toxicity is noted. Patients without evidence of progressive disease may continue to receive Gemcitabine and Bendamustine for a total of 6 cycles. Responding patients may stop after 2 or more cycles to undergo stem cell transplantation.

9.0 DOSE MODIFICATIONS AND MANAGEMENT OF TOXICITY

The following dose modifications will apply to all patients in the phase 1 trial during cycle 1 who do not meet the criteria for dose limiting toxicity (see Section 7.1.2), to all patients receiving cycles 2-6 in the phase I trial, and to all patients receiving therapy on the phase 2 trial.

9.1 Hematologic Toxicity: The following dose modifications should be made for febrile neutropenia, nadir blood counts, and blood counts obtained within 2 days prior to each subsequent cycle. If more than one of these applies, use the most stringent (i.e., the greatest dose reduction.)

9.1.1 Febrile Neutropenia

If febrile neutropenia (defined as temperature ≥ 38.5°C [101 F] concomitant with an ANC < 500/ µl) develops in a given cycle, dose reduce bendamustine and gemcitabine one level below the current dose according to Table 3. These dose reductions will be applied to the next and all subsequent cycles:

9.1.2 Nadir Blood Counts

In patients with a platelet count < 25,000/µl or a ANC < 500/µl at any time during the cycle, dose reduce bendamustine and gemcitabine one dose level below the current dose according to Table 3. These modifications will apply to the next and all subsequent cycles.

- Treatment should be held until the patient has an ANC ≥ 1000/µl and a platelet count ≥ 75,000/µl.
- Treatment delays > 2 weeks will lead to study removal.
- Once the ANC or platelet count has improved, therapy can be re-instituted at the next lowest dose level.

9.1.3 Blood Counts on Day 1 of Cycle

In patients with a platelet count < 75,000/µl or a ANC < 1000/µl obtained within 2 days prior to the start of each cycle of therapy, dose reduce bendamustine and gemcitabine one dose level below the current dose according to Table 3. These dose reductions will apply to the next and all subsequent cycles.

- Treatment should be held until the patient has an ANC ≥ 1000/µl and a platelet count ≥ 75,000/µl.
- Treatment delays > 2 weeks will lead to study removal.
- Once the ANC or platelet count has improved, therapy can be re-instituted at the next lowest dose level.

Table 3. Gemcitabine and Bendamustine Dose Reductions

Gemcitabine dosing (reduce one level below current dose)	Bendamustine dosing (reduce one level below current dose)
1000 mg/m²	120 mg/m²
800 mg/m²	90 mg/m²
600 mg/m²	60 mg/m²
Discontinue Gemcitabine	Discontinue Bendamustine

9.2 Non-Hematologic Toxicity

9.2.1 Gastrointestinal Toxicity

For nausea, vomiting, diarrhea, or constipation please follow these guidelines:

- **For grade 1-2 gastrointestinal toxicity**: Please provide appropriate supportive measures including anti-emetics (dexamethasone and steroidal anti-emetics are permitted), laxatives, IV fluids, or anti-diarrheals.
- **For grade 3 or 4 gastrointestinal toxicity despite maximal use of anti-emetics, anti-diarrheals, and other supportive measures:**
  - Hold therapy until the toxicity improves to grade 2 or better.
  - Treatment delays > 2 weeks will lead to study removal.
  - Once the toxicity is improved, therapy can be reinstituted at one lower dose level according to Table 3.
  - These modifications will apply to the next and all subsequent cycles.

9.2.2 Hepatic Toxicity

- **For grade 3 or 4 hepatic toxicity**
  - Hold therapy until the toxicity improves to grade 2 or better.
  - Treatment delays > 2 weeks will lead to study removal.
  - Once the toxicity is improved, therapy can be reinstituted at one lower dose level according to Table 3.
  - These modifications will apply to the next and all subsequent cycles.

9.2.3 Other Non-Hematologic Toxicity

- **For grade 3 or 4 non-hematologic toxicity related to protocol therapy with the exception of alopecia or electrolyte/glucose abnormalities that correct with in 72 hours:**
  - Hold therapy until the toxicity improves to grade 2 or better.
  - Treatment delays > 2 weeks will lead to study removal.
  - Once the toxicity is improved, therapy can be reinstituted at one lower dose level according to Table 3.
  - These modifications will apply to the next and all subsequent cycles.

9.3 Dose Modification for Obese Patients

There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, **all dosing is to be determined solely by (1) the patient's BSA as calculated from actual weight or (2) actual weight without any modification**. This will eliminate the risk of calculation error and the possible introduction of variability in dose administration.

10.0 Drug Formulation, Availability, And Preparation

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

10.2 Discard unused portions of injectable chemotherapeutic agents that do not contain a bacteriostatic agent or are prepared with unpreserved diluents (i.e., Sterile Water for Injection USP or 0.9% Sodium Chloride for Injection USP) within eight hours of vial entry to minimize the risk of bacterial contamination.

10.3 The total administered dose of chemotherapy may be rounded up or down within a range of 5% of the actual calculated dose.

10.4 Gemcitabine (Gemzar ®)

Availability

Gemzar® is commercially available.

Preparation

To reconstitute, add 5mL of 0.9%NaCl injection to the 200mg vial or 25mL to the 1 Gram vial. These dilutions each yield a concentration of 38 mg/mL. The appropriate dose may be administered as prepared by further diluting in NS to concentrations as low as 0.1 mg/mL.

Storage and Stability

Gemzar® solutions are stable for 24 hours at controlled room temperature. Unopened vials are stable until the expiration date indicated on the package when stored at controlled room temperature.

Administration

Administer IVPB over 30 minutes

Toxicities

Myelosuppression, nausea, vomiting, diarrhea, stomatitis, transient elevation in transaminases, mild proteinuria and hematuria, fever, rash, dyspnea, edema, flu-like symptoms, irritation at site of injection.

10.5 Bendamustine (Treanda)

Please refer to the FDA-approved package insert for bendamustine for product information and a complete list of adverse events.

AVAILABILITY

Bendamustine will be provided by Teva Pharmaceutical Industries Ltd./Cephalon. Each bendamustine for injection single-use vial contains 100 mg of bendamustine HCl formulated as a lyophilized powder. It is supplied as a sterile non-pyrogenic

white to off-white lyophilized powder in a single-use vial with no antimicrobial preservative.

STORAGE &STABILITY
Once diluted with 0.9% Sodium Chloride, the final admixture, is stable for 24 hours when stored refrigerated (2-8°C or 36 – 47°F) or for 3 hours when stored at room temperature (15 – 30°C or 59 – 86°F) and room light.

PREPARATION

Each 100 mg bendamustine vials is to be aseptically reconstituted with 20 mL of Sterile Water for Injection, USP, yielding a clear, colorless to pale yellow solution with a bendamustine HCL concentration of 5 mg/mL. The lyophilized powder should be completely dissolved within 5 minutes and the reconstituted product should not be used if particulate matter is observed.

The volume needed for the required dose (based on 5 mg/mL concentration) should be aseptically withdrawn and immediately transferred to a 500 mL infusion bag of 0.9% Sodium Chloride Injection, USP (normal saline) within 30 minutes of reconstitution. The admixture should be a clear and colorless to slightly yellow solution. Compatibility with dilutents other than Sterile Water for Injection, USP and 0.9% Sodium Chloride Injection has not been determined. The admixture should be prepared as close as possible to the time of patient administration.

ADMINISTRATION

Bendamustine will be administered intravenously over 30 minutes on days 1 and 2.

TOXICITY

Myelosuppression: In the randomized study of bendamustine in CLL, myelosuppression was observed, including grade 3/4 neutropenia (24%), febrile neutropenia (3%), red blood cell transfusions (20%), and platelet transfusions (<1%). Hematologic nadirs are expected in the third week of treatment.

Infection: Infections, including pneumonia and sepsis have occurred in patients receiving bendamustine. Cases of infection-associated hospitalization, septic shock, and death have been reported. Patients who develop myelosuppression are at higher risk of infection.

Infusion Reactions and Anaphylaxis: Common infusion reactions include fever, chills, pruritus, and rash, but rare cases of anaphylactic and anaphylactoid reactions have been reported. Infusion reactions seem to be more common in the second and subsequent cycles of therapy. Patients should be monitored for signs and symptoms suggestive of infusion reactions.

Tumor Lysis Syndrome: Tumor lysis syndrome associated with bendamustine treatment has been reported in patients in clinical trials and in spontaneous reports. The onset tends to be within the first treatment cycle of bendamustine and, without intervention, may lead to acute renal failure and death.

Dermatologic Toxicity: Skin reactions, including rash, toxic skin reactions, and bullous exanthema has been reported. Reports of Stevens-Johnson syndrome and Toxic Epidermal Necrolysis, some fatal, have been reported when bendamustine was administered concomitantly with allopurinol and other medications known to cause

these syndromes. When skin reactions occur, they may be progressive and increase in severity with further treatment.

Other Adverse Reactions: Other frequent adverse reactions include fever, nausea, vomiting, asthenia, fatigue, malaise, weakness, dry mouth somnolence, cough, constipation, headache, mucositis, and stomatitis. Worsening hypertension, including hypertensive crisis has been reported rarely.

11.0 Ancillary Therapy

11.1 Patients should receive *full supportive care*, including transfusions of blood and blood products, erythropoietin, antibiotics, antiemetics, etc., when appropriate. The reason(s) for treatment, dosage, and the dates of treatment should be recorded on the flow sheets

11.2 Treatment with *hormones or other chemotherapeutic agents* may not be administered except for steroids given for nausea, adrenal failure, or hormones administered for non-disease-related conditions (e.g., insulin for diabetes). Use of dexamethasone and other steroidal antiemetics is permitted.

11.3 *Palliative radiation therapy* may not be administered. Irradiate a symptomatic lesion, or one that may produce disability (e.g., unstable femur) prior to study initiation, provided other measurable disease is present.

11.4 Use of Growth Factors

The following guidelines are applicable unless otherwise specified in the protocol:

11.4.1 Erythropoietin (EPO)

Use of erythropoietin (EPO) is **permitted** at the discretion of the treating physician.

11.4.2 Filgrastim (G-CSF) and sargramostim (GM-CSF)

1. As all patients will receive Pegfilgrastim injections on Day 3 of each cycle, filgrastim (G-CSF) and sargramostim (GM-CSF) treatment is prohibited **unless a patient did not receive pegilgrastim on day 3 of a cycle.**
2. The use of filgrastim or sargramostim may be indicated in patients **who did not receive pegfilgrastim on day 3 of a cycle,** who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome) or fungal infection, as per the ASCO guidelines. Investigators should therefore use their own discretion in using the CSF's in this setting. The use of CSF (filgrastim or sargramostim) must be documented and reported on flow sheets.
3. If filgrastim or sargramostim are used, they must be obtained from commercial sources.

12.0 Criteria For Response, Progression, And Relapse

For the purposes of this study, patients will be restaged using PET,CT, CT, or MRI scan and PET/CT according to Section 5.0 after cycles 2, 4, and 6 of induction therapy, every 3 months for 2 years during follow-up, and then every year during years 3-5 for a maximum of 5 years from study entry.

12.1 Definitions of Response [11]

12.1.1 Complete Response (CR):

- Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.
- In patients with no pre-treatment PET scan, or if the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET-negative.
- The spleen and/or liver, if considered enlarged prior to 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.
- 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 until data become available demonstrating a clear difference in patient outcome.

12.1.2 Partial Response (PR):

- At least a 50% decrease in the 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 prior to initiation of therapy according to all of the following: a) they should be clearly measurable in at least two perpendicular dimensions; b) if possible, they should be from disparate regions of the body; and c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
- No increase should be observed in the size of other nodes, liver, or spleen.
- Splenic and hepatic nodules must regress by ≥ 50% in their SPD, or, for single nodules, in the greatest transverse diameter.
- With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.
- 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 (e.g., 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. 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.
- No new sites of disease should be observed.
- For patients with no pre-treatment 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.

12.1.3 Stable Disease (SD): Patient fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see below). The PET should be positive at prior sites of disease, with no new areas of involvement on the post-treatment CT or PET.

12.1.4 Progression (PD) or Relapse:

- Lymph nodes should be considered abnormal if the long axis is > 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 > 1.0. Lymph nodes ≤ 1.0 cm by ≤ 1.0 cm will not be considered as abnormal for relapse or progressive disease.
- Appearance of any new lesion > 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.
- 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 (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of < 1.0 cm must increase by ≥ 50% and to a size of 1.5 x 1.5 cm, or > 1.5 cm in the long axis.
- At least a 50% increase in the longest diameter of any single previously identified node > 1.0 cm in its short axis.
- Lesions should be PET-positive if a typical FDG-avid lymphoma or the lesion was PET-positive prior to therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

12.2 Guidelines for Evaluation of Measurable Disease

12.2.1 Clinical Lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes).

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

12.2.3 Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen, and pelvis. Head & neck and extremities usually require specific protocols.

12.2.4 Ultrasound (US) should not be used to measure tumor lesions that are clinically not easily accessible when the primary endpoint of the study is objective response evaluation. It is a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

13.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

13.1 Duration of Treatment

13.1.1 CR, PR, or SD

Continue treatment until the appearance of disease progression or unacceptable toxicity or for a maximum of 6 cycles. Responding patients eligible for stem cell transplantation may come off study after 2 or more cycles to undergo transplant.

13.1.2 Disease Progression

Give a minimum of two cycles of therapy unless there is evidence of rapid disease progression after one cycle, either by physical examination or radiographs. All patients with documented disease progression should stop protocol therapy.

13.2 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy shall be discontinued.

14.0 Statistical Considerations

14.1 Phase 1 Trial

The primary endpoint for the phase I dose escalation study of this study will be adverse events using CTCAE v4 criteria. We will use the standard 3 + 3 phase I dose escalation design with 3-6 patients being treated at each dose level. Dose limiting toxicity [DLT] will be defined during cycle 1 as 1) grade 3-4 neutropenia or thrombocytopenia that leads to treatment delays > 14 days; 2) grade 4 febrile neutropenia or infection; 3) grade 3 febrile neutropenia or infection that fails to resolve within 7days, or 4) other grade 3-4 non-hematologic toxicity excluding infection. The DLT observation period will be the first cycle; i.e. the first cycle will be used to determine DLT and inform does escalation decision. Patients who do not complete 1 cycle of therapy for reasons other than toxicity will be replaced on that dose level.

The maximum tolerable dose [MTD] is defined as the highest dose level where at most one of 6 patients experience DLT. Three patients will be enrolled at each dose level, starting at dose level 1. If one patient experiences a DLT, this dose level will be expanded to 6 patients. The dose where 2 or more DLTs are observed will be declared the maximum administered dose and will have exceeded the MTD. The previous dose level will be expanded to a total of 6 patients and if 1 or fewer DLTs are observed at this level, this will be the maximum tolerated or recommended phase 2 dose (RP2D). There will be no intra-patient dose escalation. If 2 or more DLTs are observed at dose level 1, the doses of bendamustine and gemcitabine will be de-escalated to dose level -1. If dose escalation reaches dose level 5, this dose level will expand to 6 patients to ensure patient safety. If 1 or fewer patients experiences DLT at dose level 5, this will be used as the recommended phase 2 dose and the trial will proceed to phase 2. A phase 2 study will be conducted in patients with relapsed or refractory Hodgkin's lymphoma at the phase 1 determined MTD. Those 6 patients at RP2D in the phase 1 study will be included in the responses evaluated as part of the phase 2 study of this trial.

Descriptive statistics (i.e. means, standard deviations, 95% confidence intervals for continuous variables, and frequencies for discrete data) and graphical analyses will be used for all correlative laboratory parameters. The associations between correlative laboratory parameters and clinical response will be evaluated using two sample t test or Fisher's exact test, whichever is appropriate.

14.2 Phase 2 Trial

Based on this phase I preliminary data of efficacy (see section 1.1), an overall response rate of75%, with acceptable toxicity, would warrant further investigation of this regimen. Simon's two-stage Minimax design will be employed to test the null hypothesis (H0), that the response rate is ≤ 40% versus the alternative (HA), that the response rate is ≥ 75%. These constraints require a minimum of 6 and a maximum of 13 patients, and an alpha of 0.10 and beta of 0.10. Those 6 patients at the RP2D in the phase 1 portion of this study will be considered as the first stage of the phase 2 portion of the study, thus 7 additional patients will be accrued during the second stage. If 2 or fewer responders are seen in the first 6 patients, (the 6 patients at MTD) accrual will be terminated early and this regimen will be deemed ineffective for this patient population. If 3 or more patients respond in the first 6 patients, 7 additional patients will be treated for a total of 13 patients. If 8 or more patients respond of the13, we will recommend that the regimen be studied further. If 13 patients are treated and the true percentage of complete response generation is 75%, we will be able to estimate the frequency of response with a 95% confidence interval of +/- 23.5%. Patients who have any treatment will be evaluable for the response. Patients who withdraw for toxicity, disease progression, or refusal will be considered treatment failures and will be included in the denominator when calculating the response rate. Patients will be followed for progression or death from any cause for 5 years after study entry.

Descriptive statistics (i.e. means, standard deviations, 95% confidence intervals for continuous variables, and frequencies for discrete data) and graphical analyses will be used for all correlative laboratory parameters. The associations between correlative laboratory parameters and clinical response will be evaluated using two sample t test or Fisher's exact test, whichever is appropriate.

15.0 ADVERSE EVENT (AER) REPORTING

Investigators are required by Federal Regulations to report serious adverse events. Investigators are required to notify the OSU PI, Teva Pharmaceutical Industries Ltd./Cephalon, the FDA and the Institutional Review Board if a patient has a reportable serious adverse event (follow guidelines in the sections below). This study will utilize the CTCAE version 4.0 to determine the severity of the reaction for adverse event reporting.

NOTE: Subsites are NOT permitted to report directly to the FDA. Subsite SAEs must be submitted to the OSU PI and Subsite Coordinator for FDA reporting.

Reporting requirements and procedures depend upon: (1) whether agents are suspected of causing the adverse event, (2) whether the possibility of such an adverse event was reported in the protocol, consent form, or manufacturer's literature (expected or unexpected adverse event), (3) the severity or grade of the adverse event, (4) the phase of the study and attribution (the determination of whether an adverse event is related to a medical treatment or procedure). All reactions in a "reportable" category must be reported. Reactions attributable to a regimen including only commercial agents must be reported to the FDA on Medwatch FDA Form #3500A.

15.1 Reporting Requirements for Regimens Containing Investigational Agents

Definitions of adverse event and expedited reporting for adverse events (including hospitalization defined below) attributable to investigational agent(s) are described below.

The reporting of serious adverse reactions is in addition to and does not supplant the reporting of adverse events as part of the report of the results of the clinical trial, e.g., study summary forms or data reporting forms. All reportable serious adverse reactions should also be forwarded to entities as explained throughout this section.

All deaths within 30 days of the last dose of treatment, regardless of attribution, must be reported to the OSU PI and Subsite Coordinator within 24 hours of knowledge of the event and should be reported to local IRBs as per institutional policy.

Serious Adverse Event or Adverse Drug Reaction (AE/ADR)" means any AE/ADR occurring at any dose that results in any of the following outcomes:

(a) Death;

(b) A life-threatening AE/ADR (i.e, the patient/subject was, in the view of the initial reporter/investigator, at immediate risk of death from the AE/ADR as it occurred. It does not refer to an AE/ADR that hypothetically might have caused death if more severe);

(c) Inpatient hospitalization or prolongation of existing hospitalization (i.e, hospitalization was required to treat or diagnose the AE/ADR; excludes hospitalization for unrelated reasons);

(d) A persistent or significant disability or incapacity (disability here means that there is a substantial disruption of a person's ability to conduct normal life functions;

(e) A congenital anomaly/birth defect.

(f) An important medical event (i.e., AEs/ADRs that might not be immediately life-threatening, or result in death or hospitalization might be considered serious when, based upon appropriate medical and scientific judgment, they might jeopardize the patient/subject or might require medical or surgical intervention to prevent one of the other serious outcomes listed above);

Sponsor-Investigator shall use his/her judgment to determine the relationship between the Serious Adverse Drug Experience and the Study Drug.

Institutions shall notify their local IRB as per local policy and shall notify Teva Pharmaceutical Industries Ltd./Cephalon and The Ohio State University PI and Subsite Coordinator within one (1) business day, by facsimile, upon learning of the occurrence during the Study of:

(a) All Serious AE/ADR as defined in Section 15.1, regardless of causality;

(b) All Expedited AE/ADR;

(c) Any exposure of a pregnant Study participant to the Study Drug within thirty (30) days of exposure;

(d) A female partner of a male Study participant becoming pregnant within thirty (30) days of exposure;

(e) Any medical event which may reasonably be believed to impair the integrity, validity or ongoing viability of the Study.

15.2 Investigator Reporting Responsibilities.

The conduct of the study will comply with all FDA *safety reporting requirements.* All adverse experience reports must include the patient number, age, sex, weight, severity

of reaction (mild, moderate, severe), relationship to drug (probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for "serious" and as defined above are present. The investigator is responsible for reporting adverse events as described below.

15.3 Procedures for AE and SAE Reporting

15.3.1 Report of Adverse Events to the Institutional Review Board

The principal Investigator is required to notify his/her Institutional Review Board (IRB) of a serious adverse event according to institutional policy. For OSU reporting, the OSU IRB form is available below.
NOTE: Subsites are NOT permitted to report directly to the FDA or the OSU IRB. All subsite SAE reports must be sent to the OSU Subsite Coordinator for OSU IRB reporting.

In the event the IRB requests additional safety information from Sponsor-Investigator, Sponsor-Investigator shall notify Teva Pharmaceutical Industries Ltd./Cephalon of such request within one (1) business day.

15.3.2 Investigator Reporting to the FDA

Serious adverse events (SAEs) that are unlisted/unexpected, and at least possibly associated to the drug, and that have not previously been reported in the Investigators brochure, or reference safety information document should be reported promptly to the Food and Drug Administration (FDA) by telephone or by fax. Fatal or life threatening SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 7 calendar days after awareness of the event. All other SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 15 calendar days after awareness of the event. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related. Reports to the FDA will be submitted using a MedWatch FDA 3500A form. Refer to FDA CFR 312.32 for detailed information.

NOTE: Subsite institutions are NOT permitted to report directly to the FDA or the OSU IRB. All reports must be sent to the OSU PI and Subsite Coordinator for submission to the FDA and the OSU IRB.

A list of agent specific expected adverse events can be found in Section 10.0 (Drug Formulation, Availability and Preparation).

The 3500A form is available at:

http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

The 3500A form will be mailed to the FDA at:

Food and Drug Administration

Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

15.3.3 Procedure for SAE Reporting to Teva

Toxicity will be scored using CTCAE Version 4.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP homepage at http://ctep.info.nih.gov.

SAE reporting will conform to company guidelines as stipulated by Teva Pharmaceutical Industries Ltd./ Cephalon as below.

Serious adverse events (SAE) are defined above. The investigator must inform Teva Pharmaceutical Industries Ltd./Cephalon in writing using a Teva Pharmaceutical Industries Ltd./Cephalon SAE Report form (or a MedWatch 3500A form) of any SAE within 24 hours/ one (1) business day of being aware of the event. The written report must be completed and submitted to Teva Pharmaceutical Industries Ltd./Cephalon by facsimile (215-795-4243) or e-mail (us.clinops.sae@tevapharm.com) within 24 hours/one (1) business day. The initial report must be as complete as possible, including an assessment of causal relationship between the event and the investigational product(s) if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. A copy will be sent to the FDA (if applicable) by the investigative site.

Teva Pharmaceutical Industries Ltd. Drug Safety Contact Information:

Teva Pharmaceutical Industries Ltd.
1090 Horsham Road
North Wales, PA 19454

USA Pharmacovigilance – US Drug Information Inquiries/Reporting
E-mail: us.clinops.sae@tevapharm.com
Fax: 215-795-4243
Medical Information: 888-838-2872
Report Product Related Emergency: 800-545-8800
Report a Problem with a Medication: 215-591-8659

15.3.4 Procedure for Subsite SAE Reporting

NOTE: Subsite institutions are NOT permitted to report directly to the FDA or the OSU IRB. All reports must be sent to the OSU Principal Investigator and Subsite Coordinator for submission to the FDA and OSU IRB.

Subsites must report SAEs to their IRB of record as per their institutional and IRB policies.

Subsites must report all SAEs to the lead Principal Investigator and the OSU Subsite Coordinator within 24 hours of knowledge of the event. SAEs are to be reported on

MedWatch 3500A form and submitted with the SAE Submission Form (refer to the Supplemental Forms Document). All SAEs and unanticipated problems involving risk to subjects or others will be reported by the OSU Subsite Coordinator following institutional, protocol, and FDA guidelines. In addition, all serious adverse events (SAEs) are reported by the OSU Subsite Coordinator to The Ohio State University Office of Responsible Research Practices, Teva Pharmaceutical Industries Ltd./Cephalon and to the Food and Drug Administration (FDA) if applicable and within the timeframes outlined in the below table. Subsite institutions are NOT permitted to directly report to The Ohio State University Office of Responsible Research Practices or FDA, but should report to Teva Pharmaceutical Industries Ltd./Cephalon as per 15.3.3 above. All AE/SAEs will be reported to the OSU DSMC at the quarterly DSMC review meetings; however, the investigator determines corrective action is necessary, and "ad hoc" DSMC meeting will be called.

Fatal adverse events related to treatment which are unexpected must be reported within 24 hours of the Investigators first awareness of the event to the OSU Principal Investigator, OSU Subsite Coordinator, and Teva Pharmaceutical Industries Ltd./Cephalon. The OSU Subsite Coordinator will immediately report to The Ohio State University Office of Responsible Research Practices and the DSMC. Fatalities not related to the study drug/device must be reported within 5 days.

15.3.5 Monitoring of Adverse Events and Period of Observation

Adverse events, both serious and non-serious, and deaths that occur during the patient's study participation will be recorded in the source documents. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

15.3.6 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects she is pregnant while participating in this study, she must inform her treating physician immediately and permanently discontinue drug therapy. Teva Pharmaceutical Industries Ltd./Cephalon must also be contacted immediately by faxing a completed Serious Adverse Event Report Form to Teva Pharmaceutical Industries Ltd./Cephalon. The pregnancy must be followed through outcome (i.e. delivery, still birth, miscarriage).

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to Teva Pharmaceutical Industries Ltd./Cephalon immediately. Every effort should be made to follow the pregnancy for the final pregnancy outcome.
Pregnancy of a female subject or the female partner of a male subject occurring while the subject is on Bendamustine or within 4 weeks after the subject's last dose of Bendamustine are considered expedited reportable events. If the subject is on Bendamustine, it is to be discontinued immediately. The pregnancy must be reported to Teva Pharmaceutical Industries Ltd./Cephalon Drug Safety and Pharmacovigilance within 24 hours of the Investigator's knowledge of the pregnancy by e-mail or facsimile using the SAE Form. The Investigator will follow the pregnant female until completion of the pregnancy, and must notify Teva Pharmaceutical Industries Ltd./Cephalon Drug Safety of the outcome as specified below. The Investigator will provide this information as a follow-up to the initial SAE. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or

congenital anomaly), the Investigator should follow the procedures for Expedited Reporting of SAEs to Teva Pharmaceutical Industries Ltd./Cephalon (i.e., report the event to Teva Pharmaceutical Industries Ltd./Cephalon Drug Safety and Pharmacovigilance by facsimile within 24 hours of the Investigator's knowledge of the event). Any suspected fetal exposure to Bendamustine must be reported to Teva Pharmaceutical Industries Ltd./Cephalon within 24 hours of being made aware of the event. The pregnant female should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigators suspect is related to the in utero exposure to Bendamustine should also be reported. In the case of a live "normal" birth, Teva Pharmaceutical Industries Ltd./Cephalon Drug Safety and Pharmacovigilance should be advised as soon as the information is available.

15.4 Adverse Event Updates & IND Safety Report Procedures

15.4.1 Adverse event updates/IND safety reports

Teva Pharmaceutical Industries Ltd./Cephalon shall notify the Investigator via an IND Safety Report of the following information:

- Any AE associated with the use of drug in this study or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects. The Investigator must keep copies of all AE information, including correspondence with Teva Pharmaceutical Industries Ltd./Cephalon and the IRB/EC, on file.

NOTE: The OSU Subsite Team will distribute IND Safety Reports to the subsite institution(s).

15.4.2 IND Annual Reports - (If Applicable)

If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed in the study's Regulatory Binder, and a copy provided to Teva Pharmaceutical Industries Ltd./Cephalon as a supporter of this study as follows.

Teva/Cephalon, Inc.
41 Moores Road
Frazer, PA 19355
Tel: (610) 344-0200

15.5 Data Safety Monitoring Plan

The data and safety monitoring plan will involve the continuous evaluation of safety, data quality and data timeliness. Investigators will conduct continuous review of data and patient safety at their regular Disease Group meetings (at least monthly) and the discussion will be documented in the minutes. The PI of the trial will review toxicities

and responses of the trial where applicable at these disease center meetings and determine if the risk/benefit ratio of the trial changes. Frequency and severity of adverse events will be reviewed by the PI and compared to what is known about the agent/device from other sources; including published literature, scientific meetings and discussions with the sponsors, to determine if the trial should be terminated before completion. Serious adverse events and responses will also be reviewed by the OSUCCC Data and Safety Monitoring Committee (DSMC). The PI will also submit a progress report (biannually for Phase II and quarterly for Phase I) that will be reviewed by the committee per the DSMC plan. All reportable Serious Adverse Events (SAE) will also be reported to the IRB of record as per the policies of the IRB.

Subsite data must be submitted within 2 weeks of each patient visit using the Data Submission Form (refer to the Supplemental Forms Document) and the supplied Case Report Forms (CRFs) according to the submission guidelines provided with the CRFs.

16.0 References

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17.0 Model Consent Form:

A PHASE I/II STUDY OF GEMCITABINE AND BENDAMUSTINE IN PATIENTS WITH RELAPSED OR REFRACTORY HODGKIN'S LYMPHOMA

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family.

[Attach NCI booklet "Taking Part in Clinical Trials: What Cancer Patients Need To Know"*]*

You are being asked to take part in this study because you have Hodgkin's lymphoma that has come back after standard therapy.

[Reference and attach information about the type of cancer (and eligibility requirements, if desired).]

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to find out what effects (good and bad) the combinations of drugs Gemcitabine and Bendamustine has on you and your Hodgkin's lymphoma.

This research is being done to develop new treatments for patients with Hodgkin's lymphoma whose cancer has returned or resisted treatment with chemotherapy.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 30 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

Medical Tests

The following tests must be done to make sure that you are eligible for this study. None of these tests are experimental. They are routine. Depending on when you last had them, you may need to repeat some of these tests:

- Blood tests
- CT/MRI scan of your chest, abdomen, & pelvis
- Pregnancy test (if you are of childbearing potential)
-

Many of these tests will be repeated during the study. These are all standard tests that are usually a routine part of cancer care. If you participate in this study, some of these tests may be done more frequently than if you were not taking part in this research study.

Treatment

On this study you will receive Gemcitabine and Bendamustine through your vein every 4 weeks. On the first day, you will receive Gemcitabine and Bendamustine. On the following day you will receive only Bendamustine. You will receive an injection of Neulasta to stimulate your bone marrow to recover on the day following your second Bendamustine injection. Before each treatment, blood will be drawn to be sure that your blood counts are high enough to be safely treated. Each treatment will take about 30 -60 minutes. The treatment will be repeated 21- 28 days later. Every 21 - 28 days is called "a cycle".

CT scans will be repeated after every two cycles of treatment (that is, every eight weeks) to see if your Hodgkin's lymphoma is getting better. If your bone marrow biopsy contained Hodgkin's lymphoma before you began this treatment, you will need to have it repeated to see if the cancer cells are gone.

You may continue to receive Gemcitabine and Bendamustine as long as your Hodgkin's lymphoma is improving up to a total of 6 cycles. If your lymphoma no longer responds or appears to get worse, you will stop receiving this therapy and will need to speak with your oncologist about further options of therapy.

HOW LONG WILL I BE IN THE STUDY?

We think you will be in the study for up to six months of treatment. After you have completed treatment on this study you be asked to return to the clinic for follow-up tests every 3 months for two years, and then every 6 months thereafter for up to five years.

The researcher may decide to take you off this study if:

- You have significant side effects from the treatments.
- Your cancer begins to grow.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious

and uncomfortable. Many side effects go away shortly after the Gemcitabine and Bendamustine are stopped, but in some cases side effects can be serious or long lasting or permanent.

Very Likely:

- Low blood counts.
- Nausea.
- Fatigue.

Likely:

- Vomiting.
- Constipation.
- Diarrhea.
- Headache.
- Body aches.
- Fever.
- Decreased appetite.

Less Likely But Serious:

- Bleeding.
- Lowered white blood cell count that may lead to an infection for which you may be hospitalized.
- You may need a blood transfusion.
- Severe weakness or pain in arms or legs.
- Abnormalities in your liver tests.
- Lowering of the sodium level in your blood.
- Severe rash requiring you to be hospitalized.

Reproductive risks: Because the drugs in this study can affect an unborn baby, you should not become pregnant or father a baby while on this study. For this reason, both men and women will be asked to practice an effective method of birth control while you are participating in this study. Also because the risk to young children is unknown, you should not nurse your baby while on this study. Ask about counseling and more information about preventing pregnancy.

[Attach additional information about contraception, etc.]

For more information about risks and side effects, ask the researcher or contact _____.

[Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks.]

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with Hodgkin's lymphoma in the future.

WHAT OTHER OPTIONS ARE THERE?

You may obtain treatment for Hodgkin's lymphoma without being on this study. Instead of being in this study, you have these options:

- You may choose no therapy at this time but instead elect supportive care to help you feel more comfortable.
- You may choose to have treatment with other commonly used chemotherapy drugs for Hodgkin's lymphoma.
- You may choose treatment with other investigational agents.

Please talk to your regular doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as:
[List relevant agencies like the National Cancer Institute, Food and Drug Administration, study sponsor, etc.]

WHAT ARE THE COSTS?

Bendamustine will be provided by Cephalon for this study. Gemcitabine is commonly utilized in the treatment of relapsed Hodgkin's lymphoma and is commercially available.

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact the researcher *NAME(S)* at *TELEPHONE NUMBER*.

For questions about your rights as a research participant, contact the *NAME OF CENTER* Institutional Review Board (which is a group of people who review the research to protect your rights) at *TELEPHONE NUMBER*. *[And, if available, list patient representative (or other individual who is not on the research team or IRB).]*

It may be necessary to contact you at a future date regarding new information about the treatment you have received. For this reason, we ask that you notify the institution where you received treatment on this study of any changes in address. If you move, please provide your new address to the following person:
(name) _____ (title)_____
(address)_____ (phone number) _____.

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's **Cancer Information Service** at **1–800–4–CANCER (1–800–422–6237)** or **TTY: 1–800–332–8615**

Visit the NCI's Web sites…
cancerTrials: comprehensive clinical trials information **http://cancertrials.nci.nih.gov.**

CancerNet™: accurate cancer information including PDQ **http://cancernet.nci.nih.gov.**

You will get a copy of this form. You may also request a copy of the protocol (full study plan).
[Attach information materials and checklist of attachments. Signature page should be at the end of package.]

SIGNATURE

I agree to take part in this study.

Participant _____ Date _____