CLINICAL STUDY PROTOCOL

Study Title: A phase I, open-label, dose-escalation study of Venetoclax and BEAM conditioning followed by autologous stem cell transplantation for patients with relapsed, refractory, or high-risk non-Hodgkin lymphoma

IRB Protocol Number: 2018C0087

Protocol Version: Version 5.0
Protocol Date: December 2, 2020

Study Phase: Phase I

Agents:

Venetoclax	Supplier:	Commercial
Carmustine	Supplier:	Commercial
Etoposide	Supplier:	Commercial
Cytarabine	Supplier:	Commercial
Melphalan	Supplier:	Commercial

ClinicalTrials.gov Identifier: NCT03583424

Corresponding Organization: The Ohio State University

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TEST PRODUCTS:

Venetoclax (ABT-199, GDC-0199, RO5537382)

Contents

LIST OF ABBREVIATIONS

AE	Adverse event
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
ASCT	Autologous stem cell transplant
Bcl-2	B-cell lymphoma 2
BEAM	BCNU, Etoposide, Cytarabine, Melphalan
BMP	Basic metabolic profile
CBC	Complete blood count
CLL	Chronic lymphocytic leukemia
CMP	Complete metabolic profile
CT	Computed tomography
DDI	Drug-drug interactions
DLBCL	Diffuse Large B-Cell Lymphoma
DLT	Dose-limiting toxicity
EFS	Event-free survival
FL	Follicular lymphoma
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HDC	High-dose chemotherapy
LMW	Low molecular weight
MCL	Mantle cell lymphoma
MM	Multiple myeloma
NHL	Non-Hodgkin's lymphoma
OS	Overall Survival
PET	Positron emission tomography
PFS	Progression Free Survival
R/R	Relapsed or refractory
TLS	Tumor lysis syndrome
T-PLL	T-cell Prolymphocytic Leukemia

1 PROTOCOL SYNOPSIS:

1.1 Summary

This is a single-center, open-label, phase I study of escalating doses of venetoclax (in 3 dosing cohorts) followed by high dose chemotherapy with BEAM (carmustine, etoposide, cytarabine, melphalan) and autologous stem cell transplantation (ASCT) in patients with relapsed/refractory non-Hodgkin lymphoma (NHL) or high-risk NHL in first complete remission. The primary objective of this study will be to determine the maximal dose of venetoclax that can be safely combined with BEAM and ASCT. The secondary objective will be to determine the efficacy of this regimen as measured by ORR at day 100, in addition to progression free survival and overall survival at one year. Traditional 3+3 design will be used to find the maximum tolerated dose (MTD). After the MTD is established, 10 more patients will be accrued to that dose level as an expansion cohort to obtain a preliminary estimate of overall response rate (ORR). The maximum number of patients enrolled will be 28 patients.

1.2 Hypotheses:

Venetoclax is safe in combination with BEAM in patients with relapsed or refractory non-Hodgkin lymphoma (NHL)

1.3 Objectives:

1.3.1 Primary Objectives:

1. Determine the maximum tolerated dose (MTD) of venetoclax that can be safely combined with BEAM prior to autologous stem cell transplant

1.3.2 Secondary Objectives:

1. To evaluate the safety and tolerability of venetoclax combined with BEAM prior to autologous stem cell transplant
2. To obtain a preliminary estimate of the efficacy of venetoclax in combination with BEAM as measured by overall response rate (ORR) at day 100
3. To estimate the progression free survival (PFS) and overall survival (OS) of venetoclax and BEAM followed by ASCT

1.3.3 Optional Exploratory objectives

1. Determine any correlation of response and survival endpoints with the expression of BCL-2, BCL-XL, and MCL-1 as measured by immunohistochemistry (IHC)

1.4 Trial Design

Phase IB, open-label, dose-escalation using 3+3 design with an expansion cohort

2 INTRODUCTION

2.1 High-dose chemotherapy and ASCT for relapsed/refractory NHL

High-dose chemotherapy (HDC) with autologous stem cell transplantation (ASCT), using regimens such as carmustine, etoposide, cytarabine, and melphalan (BEAM) is standard treatment of patients with chemosensitive relapsed diffuse large B-cell lymphoma (DLBCL); the most common type of NHL. However, relapse post-HDC/ASCT remains a major problem, particularly in patients who received transplant for primary refractory disease or had high-risk features at relapse. Patients relapsing within one year of initial therapy, patients without chemosensitive disease, or patients not in complete remission at time of HDC have a 2-year event-free survival (EFS) of less than 30% and are in clear need for more active therapies [1, 2].

The CORAL trial demonstrated that, in the post-rituximab era, patients with DLBCL who relapse in the first year after treatment, or sustain only partial response to induction therapy have a poor prognosis. For those patients, salvage chemotherapy followed by ASCT results in a dismal 20% PFS at 3 years. This clearly highlights the need for better therapies for these patients [3].

In follicular lymphoma, ASCT is indicated at first relapse in the absence of a suitable donor for allogeneic transplantation. However, ASCT is non-curative and most patients progress afterwards [4].

Indeed, ASCT does improve long term survival in many patients with relapsed or high-risk NHL. Patients with NHL relapsing after ASCT have poor outcomes [1, 5]. and prior interventions aimed at augmenting the HDC regimen to improve chemosensitivity or maintenance strategies post ASCT have not been successful. Prevention of relapse after ASCT for NHL represents an unmet medical need.

BEAM has gained popularity as the HDC regimen of choice for ASCT for patients with lymphoma. Although there has been no prospective trials, large retrospective trials have shown superior outcomes compared to older regimens like cyclophosphamide, BCNU, and etoposide (CBV) or busulfan and cyclophosphamide [6]. Prior attempts to add novel drugs to the BEAM backbone has not revealed any extra toxicity beyond what to be expected of BEAM regimen itself. Agents that has been safely combined with BEAM before included rituximab [7], bortezomib [8], bendamustine to substitute BCNU [9], yttrium-90, ibritumomab tiuxetan [10], and iodine-131 tositumomab [11]. None of such novel regimens have proven superior to standard BEAM either in a direct prospective comparison or as compared to historic controls. No attempt to directly target bcl family of proteins, or other targets within mitochondria/apoptosis pathways, has been attempted to date.

2.2 Venetoclax (ABT-199, GDC-0199)

2.2.1 Pharmacology

Venetoclax (also referred to as ABT-199 and GDC-0199) is a novel, orally bioavailable, small-molecule, B-cell lymphoma-2 (Bcl-2) family inhibitor in the biarylacylsulfonamide

chemical class. Venetoclax binds with high affinity (inhibition constant [Ki] < 0.010 nM) to the antiapoptotic protein Bcl-2 and with lower affinity to other antiapoptotic Bcl-2 family proteins, like Bcl-xl and BCL-w (> 4,000-fold and > 2,000- to > 20,000-fold lower affinity than to Bcl-2, respectively).
Antiapoptotic Bcl-2 family members are associated with tumor initiation, disease progression, and chemotherapy resistance, as well as autoimmunity. Overexpression of Bcl-2 is a major contributor to the pathogenesis of some lymphoid malignancies; antagonism of the action of these proteins may enhance response to therapy andovercome resistance, and thus, these proteins are compelling targets for anti-tumor therapy.

In vitro, venetoclax demonstrated cell killing activity against patient-derived chronic lymphocytic leukemia (CLL) and acute myeloid leukemia (AML) cells and a variety of lymphoma and leukemia cell lines, including B-cell follicular lymphomas (FLs), mantle cell lymphomas (MCLs), DLBCLs, AMLs, and multiple myeloma (MM) cell lines. Venetoclax was especially potent against NHL cell lines expressing high levels of Bcl-2. Venetoclax inhibits subcutaneous xenograft growth of human tumor cell lines derived from acute lymphoblastic leukemia (ALL), NHL, and AML, and is highly efficacious using various doses and combined with other regimens. The drug is also active in a model of disseminated ALL and AML. Venetoclax enhanced the activity of a broad variety of chemotherapeutic agents in other human hematological models.

Multiple pre-clinical observation supports the hypothesis that combination of ABT-199 with cytotoxic chemotherapeutic agents potentiates their cytotoxicity. The combination of chemotherapy with ABT-199 and doxorubicin or cytarabine synergistic cell kill against double-hit lymphoma (DHL) cell lines; DHL is an aggressive subtype of DLBCL usually characterized by refractoriness to cytotoxic chemotherapy [12]. The combination of ABT-199 with doxorubicin or etoposide led to a significant decrease in cell viability at 48 hours compared to each single agent alone in 4 different DLBCL cell lines [13]. ABT-199 was also shown to restore sensitivity to cyclophosphamide in murine xenograft models for neuroblastoma [14]. ABT-199 synergizes with etoposide in cytochrome C release and induction of apoptosis in leukemia cell lines [15].

Bcl-2 is also expressed in T-cell lymphomas and correlates with apoptotic rate and proliferation index [16]. Boidol et al. reported on venetoclax activity in single-cell suspension of T-cell prolymphocytic leukemia (T-PLL) [17]. Most of peripheral blood malignant T-cells isolated from 25 patients with cutaneous T-cell lymphomas (CTCL) were also shown to be sensitive to venetoclax; with mean IC_{50} as low as 79 nM [18].

2.2.2 Pharmacokinetics and pre-clinical toxicology

Venetoclax exhibited moderate permeability in the Caco-2 assay. In rats, venetoclax was widely distributed into liver, kidneys, spleen, heart, lungs, small intestine, and white fat, but was poorly distributed in testes, brain, muscle, bone, and pigmented tissues. In rat, 14.3% of the dose was recovered as parent drug after 48 hours post dose, while 76.9% of the dose was excreted as metabolites in bile. Profiles in bile indicated that metabolism was the major clearance mechanism, while biliary excretion of parent drug played a secondary role in drug elimination. Biotransformation of [^{3}H]venetoclax proceeded via a combination of oxidation and conjugation.

Venetoclax and its major human metabolite, M27, are predominately metabolized by CYP3A4 in vitro, thus CYP3A4 inhibitors or inducers are expected to cause changes in venetoclax and M27 exposures. Clinical studies have supported the in vitro observations for venetoclax as a sensitive substrate of CYP3A4: > 5-fold increase in AUC when co-dosed with ketoconazole (Study M13-364), and > 50% decrease in AUC when co-dosed with rifampin (Study M14-497). At the 400 mg QD dose venetoclax and M27 are not predicted to be perpetrators of the major CYP enzymes, but venetoclax may weakly inhibit UGT1A1. Both venetoclax and M27 are substrates for the efflux transporters P-gp and BCRP, and inhibitors or inducers of these transporters are expected to cause change in the exposure of venetoclax and M27. Venetoclax and M27 are P-gp and BCRP inhibitors and may interact with substrates for these transporters. Venetoclax may inhibit OATP1B1 and cause weak interaction with drugs that are substrates of this transporter.

Venetoclax was tested in a battery of safety pharmacology assays and produced no effects in central nervous system (CNS)/neurobehavioral, or respiratory studies in mice at oral doses up to 600 mg/kg. In dogs, mild reductions in cardiac contractility and cardiac output were observed at plasma concentrations of ≥ 16 µg/mL; concentrations greater than the concentration of venetoclax in humans (average maximum observed plasma concentration [Cmax] = 6.09 µg/mL at 1200 mg dose). However, no effects on blood pressure, heart rate, or electrocardiogram (ECG) parameters were observed in dogs at a maximum drug concentration of 46 µg/mL.

The primary toxicities associated with repeat-dose administration of venetoclax were effects on the hematologic system (decreased lymphocytes and red blood cell [RBC] mass) in mice, rats and dogs, the male reproductive system (testicular germ cell depletion in dogs) and embryo fetal toxicity in mice. Other noteworthy findings were epithelial single cell necrosis in multiple tissues and hair coat color change, both in dogs.

In mice, rats, and dogs, venetoclax produced robust decreases in lymphocytes in the peripheral blood (up to 75% in mice, 64% in rats, and 81% in dogs) and in lymphoid tissues. These findings are consistent with the expected pharmacologic effects of venetoclax (a selective Bcl-2 inhibitor). In mice, total lymphocyte counts at 600 mg/kg/day after 4 weeks of dosing were minimally decreased 21% to 6% relative to concurrent controls at the end of the 4-week recovery period. In dogs, the recovery of peripheral blood decreases in total lymphocytes and lymphocyte subsets (CD4+ T-cells and CD8+ T-cells and [CD21+] mature B cells) was prolonged, requiring up to 18 weeks after a single dose or after completion of 2 weeks of dosing. B-cells were the most sensitive lymphocyte subtype based on the magnitude of decrease (> 90%) and/or the length of time required for recovery. Lymphocyte decreases in lymphoid tissues were reversible in mice and dogs. Venetoclax produced dose-related decreases in RBC mass due to decreased cellular hemoglobin in mice and dogs; these effects were adverse at the highest dosages in the 4- week mouse and dog studies and were reversible. In studies to select carcinogenicity dose levels, RBC mass decreases were also observed in rats and were generally more severe than in mice or dogs. Venetoclax produced adverse, non-dose related microscopic findings of testicular germ cell depletion in dogs at all doses tested; reversibility was not observed following a 4-week recovery period. There were no testicular effects in mice. Venetoclax resulted in increased

post-implantation loss and decreased fetal body weights in the mouse embryo fetal development study at the highest dosage administered (150 mg/kg/day); the no-observed-adverse-effect-level (NOAEL) was defined at the mid dose of 50 mg/kg/day. In mice and rabbits, venetoclax was not teratogenic, and there were no other effects on development or fertility.

Additional noteworthy effects of venetoclax included white hair coat discoloration in dogs (occurring after approximately three months of dosing in the 9-month study) and minimal to mild single cell necrosis in multiple epithelial tissues (e.g., gallbladder and exocrine pancreas) in dogs. None of these effects were considered to be adverse.

M27 is a major human metabolite of venetoclax. Although observed in mice and dogs, M27 is present at much lower levels (0.05- to 0.09-fold), as compared with steady-state levels in humans, and therefore is a disproportionate metabolite. By in silico analysis, M27 does not generate new alerts for mutagenicity, as compared with the venetoclax parent compound. Additionally, M27 shows low in vitro potency (at least 58-fold less than parent) and produced no evidence of in vitro genotoxicity in Ames and chromosome aberration assays. In a secondary pharmacology receptor panel screening study, M27 produced significant displacement of control-specific binding at the delta-opioid receptor (DOP Ki = 0.65 μM); however, when evaluated in a functional assay, agonist or antagonist activity was not observed at the DOP receptor up to a maximum concentration of 10 μM. No CNS or respiratory adverse events that could be attributed to off-target receptor-mediated pharmacologic effects of M27 have been observed in clinical trial subjects.

2.2.3 Clinical Safety and Pharmacology

As of 28 November 2016, based on data available in the AbbVie and Genentech/Roche clinical databases, a total of 2759 subjects have been exposed to at least 1 dose of venetoclax in the oncology and immunology development programs. A total of 2534 oncology subjects had data available in AbbVie and Genentech/Roche studies as of 28 November 2016. Of these 2534, 1435 subjects had CLL/small lymphocytic leukemia (SLL), 626 subjects had NHL, 178 subjects had MM, and 295 had AML. An additional 127 subjects were healthy volunteers. A total of 663 oncology subjects received the drug as monotherapy and 1871 received the drug in combination with other therapies. Additionally, 98 subjects were exposed to at least 1 dose of venetoclax in the AbbVie immunology study, Study M13-093, as of 28 November 2016.

Pharmacokinetic data for venetoclax are available from studies in subjects with cancer (CLL/SLL, AML, NHL, and MM), healthy subjects, and a single study in subjects with SLE. Following multiple-dose administration, the maximum plasma concentration of venetoclax was attained 5 to 8 hours after dosing. The harmonic mean terminal half-life ($t_{1/2}$) ranged from 17 to 41 hours following a single oral dose of venetoclax. In subjects with CLL, venetoclax showed minimal accumulation, and steady-state AUC increased proportionally over the dose range of 150 to 800 mg. Venetoclax has been administered with food in all clinical studies, as food increased the bioavailability of venetoclax by approximately 3- to 5-fold. Venetoclax is highly bound to plasma proteins with unbound fraction (f_u) < 0.01, and it is primarily eliminated as metabolites in feces with negligible renal elimination (< 0.1%).

Drug-drug interaction studies of venetoclax with ketoconazole, rifampin, warfarin, ritonavir, and digoxin were conducted to provide dosing recommendations for patients concomitantly taking CYP3A and/or P-gp inhibitors, inducers, and/or warfarin. Pharmacokinetic studies were conducted in healthy Chinese subjects and in Japanese subjects to provide dosing recommendations for those specific populations. Additionally, a dedicated study to evaluate the pharmacokinetics of venetoclax in subjects with hepatic impairment is ongoing. Based on the population pharmacokinetic analysis, age, sex, race, weight, mild and moderate renal or hepatic impairment do not have an effect on venetoclax clearance.

2.2.4 Clinical Experience with Venetoclax

Multiple ongoing Phase 1/2 AbbVie and Phase 1/2/3 Genentech/Roche clinical studies are evaluating safety, tolerability, pharmacokinetics, and efficacy of venetoclax as monotherapy or in combination with other therapies (rituximab [R], obinutuzumab (GA101) [G], rituximab or obinutuzumab plus CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP or G-CHOP, respectively], BR, bendamustine plus obinutuzumab [BG], bortezomib plus dexamethasone, azacitidine or decitabine, and cytarabine) in subjects with hematologic malignancies. Data are available from drug-drug interaction (DDI) studies of venetoclax interaction with ketoconazole, rifampin, warfarin, digoxin, and ritonavir. Additionally, two Phase 3 studies are ongoing: one study in relapsed/refractory (R/R) CLL exploring the combination of venetoclax and rituximab against BR and one Phase 3 study in first-line CLL exploring the combination of venetoclax and obinutuzumab against obinutuzumab plus chlorambucil. All oncology clinical studies which enrolled subjects as of 28 November 2016 are summarized in Table 7 in the investigator brochure submitted with this protocol.

Based on nonclinical and clinical data available with venetoclax administration, important identified risks are tumor lysis syndrome (TLS) and neutropenia. The risk of TLS is highest in CLL and MCL. Infection is a potential risk. Other adverse events commonly observed with venetoclax include nausea, diarrhea, and other hematological effects (including anemia, thrombocytopenia, and lymphopenia). Decreased spermatogenesis has been observed in nonclinical studies with dogs and could present a risk to male infertility. In addition, as venetoclax is being evaluated in subjects with R/R disease who had previously been treated with various cytotoxic agents, second primary malignancies are closely monitored.

Preliminary efficacy results are available for subjects with CLL/SLL, NHL, MM, and AML as listed below. Preliminary data indicate that venetoclax continues to show promising efficacy in various hematological malignancies.

2.2.5 Clinical Experience with Venetoclax in Lymphomas

Arm B of M12-175 was a phase I first-in-human study of venetoclax in patients with R/R NHL that included 106 patients. They received venetoclax once daily until progressive disease or unacceptable toxicity at target doses from 200 to 1200 mg in dose-escalation and safety expansion cohorts. Treatment commenced with a 3-week dose ramp-up period for most patients in dose-escalation cohorts and for all patients in safety expansion. It included

patients with lymphoproliferative disorders excluding Burkitt or Burkitt-like lymphomas, lymphoblastic lymphoma/leukemia and post-transplant lymphoproliferative diseases. Venetoclax was generally well tolerated. Clinical tumor lysis syndrome was not observed. Three patients had evidence of laboratory TLS. Treatment emergent adverse events were reported in 103 patients (97%), a majority of which were grade 1 to 2 in severity. Grade 3 to 4 events were reported in 59 patients (56%), and the most common were hematologic, including anemia (15%), neutropenia (11%), and thrombocytopenia (9%). Overall response rate was 44% (MCL, 75%; FL, 38%; DLBCL, 18%). Estimated median progression-free survival was 6 months (MCL, 14 months; FL, 11 months; DLBCL, 1 month) [16].

Venetoclax was also studied in combination with other chemotherapies. In the ongoing study M12-630 (NCT01594229), venetoclax was given for short courses of 3, 7, or 28 days in 28-day cycles in combination with Rituximab and Bendamustine. The ORR as of 10/20/2016 was 65.0%. Most common grade 3/4 AEs (≥10%) during combination therapy were neutropenia (32%), lymphocyte count decrease (26%), thrombocytopenia (21%), anemia (15%), and leukopenia (13%). The most frequent serious AE was febrile neutropenia (9%). Three deaths occurred; none were drug-related AEs [17].

Venetoclax is also being studied in the front-line setting and minimally-treated patients (≤ 1 line of therapy) in a phase IB, dose-escalation manner in combination with either R-CHOP or G-CHOP. As of 6/10/2016, 56 patients were enrolled. The most common DLTs were hematologic including cytopenias and gastrointestinal toxicities. They are summarized in Table 1. The most common Grade 3/4 AEs were neutropenia (46%), febrile neutropenia (29%), and thrombocytopenia (21%). Three pts had laboratory TLS after the first venetoclax dose without any clinical sequelae, which resolved by no intervention (1) or medical intervention including holding dose (2). No cases of clinical TLS were observed. Of the 42 pts in the intent-to-treat analysis that were evaluable for efficacy response (≥1 cycles with available end of treatment response assessment or discontinued prior to assessment), 18/21 (85.7%) in Arm A and 17/21 (81%) in Arm B had a response (Table 2) [21].

Table 1. Safety Results – Safety-Evaluable Population

	Cohort 1: 200mg continuous		Cohort 2: 400mg C1 D4–10, C2–8 D1–10		Cohort 3: 600mg C1 D4–10, C2–8 D1–10		Cohort 4: 800mg C1 D4–10, C2–8 D1–10; C1 D4–8, C2–10 D1–5	
Arm (N pts)	A (7)	B (7)	A (3)	B (7)	A (8)	B (6)	A (6)	B (12)
DLT*	1	2	-	1	1	1	-	-
Laboratory TLS	-	-	-	-	1	1	-	1
Laboratory Gr 4 TCP	3	2	-	-	2	3	-	5

*Cohort 1A: Gr 3 neutropenia with dose delay; 1B: Gr 3 pneumonia, Gr 3 infection/acute coronary syndrome; 2B: Gr 4 febrile neutropenia; 3A: Gr 4 TLS; 3B: Gr 4 sepsis

Table 2. Disease Response by PET/CT scan – Response-Evaluable Population

	Arm A (n=21)				Arm B (n=21)			
	Cohort 1 (n=7)	Cohort 2 (n=2)	Cohort 3 (n=6)	Cohort 4 (n=6)	Cohort 1 (n=7)	Cohort 2 (n=3)	Cohort 3 (n=5)	Cohort 4 (n=6)
Responders	6	2	5	5	5	2	4	6
CR	5	2	3	4	3	2	3	5
PR*	1		1	1	2		1	1
SD								
PD			1	1				
Discontinued early	1				2	1	1	

BM=bone marrow; CR=complete response; PR=partial response, SD=Stable Disease; PD=progressive disease

*6 Pts (3 pts in Arm A and 3 pts in Arm B [2 in Cohort 1, 1 in Cohort 4]) with BM involvement at baseline who achieved radiologic CR were classified as having PR due to missing BM data at EOT

In T-cell malignancies, Bose and Konopleva treated two patients with relapsed/refractory T-PLL with venetoclax and both achieved a partial response for several months [22]. This was based on the preclinical data mentioned previously about the activity of venetoclax in single-cell suspensions of T-PLL [17]. There is an ongoing phase II trial of venetoclax in patients with relapsed or refractory T-cell lymphomas (NCT03534180) based on promising pre-clinical activity of venetoclax in T-cell malignancies.

2.3 Rationale

Based on the above preclinical and clinical data, we believe that venetoclax is sufficiently active in NHL, both as monotherapy and in combination. Given that patients with primary refractory NHL have little treatment options, and that the available treatment options (HDC/ASCT) are not ideal, we postulate that adding venetoclax to the BEAM conditioning regimen prior to ASCT will be safe and will improve response rates.

The toxicities observed with venetoclax in the above studies include grade 1-2 gastrointestinal (GI) toxicities and grade 3-4 cytopenias. These toxicities overlap with those of the conditioning regimen. However, we expect the GI toxicities of the conditioning regimen to occur later throughout the treatment course, well after venetoclax would have been discontinued. Thus, they would not be additive because of temporal spacing.

The purpose of the venetoclax lead-in is to down-regulate the anti-apoptotic pathways before BEAM administration. Having a lead-in will also allow for more accurate assessment of acute toxicities of venetoclax. The MTD of venetoclax in combination with BEAM is unknown, we propose a dose escalation in three dosing cohorts. After the MTD is determined in phase I of the study, we plan on enrolling 10 additional patients using the MTD as a dose expansion cohort. Although venetoclax has modest activity in DLBCL on its own, we postulate that combining it with BEAM HDC would augment cytotoxicity of HDC and that would translated into better patient outcomes. Although prior attempts of incorporating novel agents into the BEAM backbone has not been successful in improving outcomes; albeit proven safe, no prior attempts have been made to incorporate drugs that directly target bcl family of proteins, or other targets within mitochondria/apoptosis pathways. Another clinical trial that is currently open to accrual (NCT03064867) incorporates venetoclax with the standard regimen rituximab, ifosfamide, carboplatin, and etoposide (RICE) regimen in relapsed/refractory DLBCL building on the same hypothesis

we are proposing; improving chemosensitivity to standard cytotoxic agents by directly inhibiting pathways involved in resistance to apoptosis.

As detailed in section 2.2.5 above; total of 209 patients were reported from 3 separate trials in patients with non-Hodgkin lymphomas (NHL); 2 trials in relapsed/refractory patients (as a single agent and in combination with chemotherapy) and 1 trial upfront in combination with chemotherapy. In only one trial, laboratory evidence of TLS syndrome was seen in three patients with no evidence of clinical TLS observed. One of the two patients with T-PLL treated experienced evidence of TLS. Hence, we believe that the risk of clinically significant TLS is low to warrant exclusion of patients with high tumor burden or to warrant inpatient monitoring of such patients.

We will also investigate markers of response and resistance. Venetoclax is more active in malignancies that overexpress Bcl-2. We will correlate response with levels of expression of Bcl-2 by IHC.

2.4 Background and rationale of secondary and exploratory objectives

Venetoclax is a Bcl-2 inhibitor and is most active in malignancies that are known to overexpress that pathway. However, it maintains activity in malignancies that do not overexpress it. Furthermore, not all tumors with high Bcl-2 expression are sensitive to venetoclax. Given the targeted nature of the drug, mechanisms of action and resistance have been examined. A proposed mechanism of resistance is upregulation of other anti-apoptotic proteins, namely BCL-X_L and MCL-1. Changes in the BH3 drug-binding domain have also been observed [19]. We will attempt to examine the levels of expression of these proteins by IHC on our clinical samples and correlate that to ORR and survival outcomes.

3 OBJECTIVES

3.1 Primary Objectives:

1. Determine the maximum tolerated dose (MTD) of venetoclax that can be safely combined with BEAM prior to autologous stem cell transplant

3.2 Secondary Objectives:

1. To evaluate the safety and tolerability of venetoclax combined with BEAM prior to autologous stem cell transplant
2. To obtain a preliminary estimate of the efficacy of venetoclax in combination with BEAM as measured by overall response rate (ORR) at day 100
3. To estimate the progression free survival (PFS) and overall survival (OS) of Venetoclax and BEAM followed by ASCT

3.3 Optional Exploratory objectives

1. Determine any correlation of response and survival endpoints with the expression of BCL-2, BCL-XL, and MCL-1 as measured by immunohistochemistry (IHC)

4 INCLUSION AND EXCLUSION CRITERIA

4.1 Inclusion Criteria

- Subjects must have histologically confirmed diagnosis of non-Hodgkin's lymphoma that is refractory after upfront induction therapy, in partial remission or worse after salvage, or relapsed. Refractory and partial remission are defined by the Lugano criteria listed in Appendix III [24]. Excluded histologies are post-transplant lymphoproliferative disorder, and chronic lymphocytic leukemia/small lymphocytic lymphoma. All other histologies are eligible. These include but are not limited to: diffuse-large B-cell lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma (PTCL), hairy cell leukemia (classic or variant), lymphoblastic lymphoma, prolymphocytic leukemia (T or B-cell), follicular lymphoma (grades I, II, and III), marginal zone lymphoma, transformed indolent lymphoma, grey zone lymphoma, and undifferentiated B-cell lymphoma. Patients with NHL who are at high risk of relapse can be regardless of response.
    - High risk is defined as 1) requiring 3 or more lines of therapy, 2) transformed lymphoma, 3) relapse within 12 months of D1 of last cycle of induction chemotherapy, 4) MCL or PTCL undergoing consolidation with ASCT in CR1/PR1
- Expected survival of more than six months
- Age >18 years
- Karnofsky Performance status ≥ 80% (appendix-I)
- Subjects must have normal organ and marrow function, within 1 week prior to initiation of treatment, as defined below:
    - AST/ALT < 3x upper limits of normal (ULN) unless due to disease
    - Total bilirubin <2x ULN unless due to disease
    - Calculated GFR of 30 ml/min or greater
    - ANC > 500 cells/mm3
    - Platelet Count > 50 mm3.
- Left ventricular ejection fraction ≥ 40% (within 6 weeks of start of treatment)
- Diffusion capacity of carbon monoxide (DLCO) ≥ 50% predicted (within 6 weeks of start of treatment)
- Ability to collect 2 x 10^6/kg CD34+ cells for transplantation
- Patient must be otherwise eligible for ASCT per local institutional guidelines
- No serious disease, or condition, that, in the opinion of the investigator, would compromise the patient's ability to participate in the study
- Subjects must have the ability to understand and the willingness to sign a written informed consent document.

4.2 Exclusion Criteria

- Subjects who sustained a complete metabolic response (CMR) by PET-CT (5-point scale of < 3) unless lymphoma relapsed within 12 months from the first day of last cycle of induction chemotherapy or patients have "high risk disease" as defined in section 4.1 above.
- Subjects receiving any other investigational agents.
- Patients with central nervous system (CNS) involved by lymphoma can be

included if CNS disease is deemed controlled prior to enrollment as determined by the investigator. Patients with uncontrolled CNS disease will be excluded.

- History of allergic reactions attributed to compounds of similar chemical or biologic composition to venetoclax or other agents used in this study.
- Subjects with uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- Patients who are HIV positive and receiving combination antiretroviral therapy will be excluded; because of the potential for pharmacokinetic interactions with venetoclax.
- Patients receiving strong inhibitors or inducers of CYP3A4 (see Appendix IV). All such medications would have to be discontinued for 72 hours prior to start of venetoclax.
- Female patients who are pregnant or breast-feeding. Confirmation that the subject is not pregnant must be established by a negative serum -human chorionic gonadotropin (β-hCG) pregnancy test result obtained during screening. Pregnancy testing is not required for post-menopausal or surgically sterilized women. Male or female patients, who are sexually active and of the child bearing age, must be willing to practice accepted birth control measures

5 STUDY DESIGN

5.1 Summary

This is an open-label, single-center, phase I trial with a dose expansion cohort in which up to 28 patients with relapsed/refractory or high-risk NHL will receive venetoclax in combination with BEAM and autologous hematopoietic stem cell transplantation. In addition to the BEAM and ASCT, venetoclax will be administered in three doses, 400 mg, 800 mg, and 1200 mg in a ramp-up schedule. Patients will be accrued in a 3+3 study design, described in the statistical analysis part below. These subjects will be evaluated for toxicities to establish the maximum tolerated dose (MTD) of venetoclax that can be tolerated in combination with BEAM/ASCT. Once established, the maximum tolerated dose will be utilized in treating an additional 10 subjects. Data collected will be utilized to obtain a preliminary estimate of the response rate, cumulative incidence of progression, PFS and OS using this regimen.

5.2 Treatment Regimen Overview

5.2.1 Screening Evaluation

Prior to initiating the process of mobilization and collection

- History and physical examination
- Disease status assessments with CT scans or PET scans (results within 6 weeks of screening are acceptable). PET-CTs are preferred.
- Bone marrow biopsy if clinically indicated (results within 6 weeks of screening are acceptable)
- CBC/Differential and complete metabolic panel

- MUGA or Echocardiogram
- Pulmonary function testing including DLCO
- Pregnancy test (serum beta-HCG) for females of childbearing age
- HIV testing

5.2.2 Before starting venetoclax and BEAM

- History and physical examination
- CBC/Differential and complete metabolic panel
- Repeat pregnancy test (serum beta-HCG) for females of childbearing age if the prior test has been more than 14 days ago
- Tumor lysis labs for baseline
- Start on prophylactic allopurinol

5.2.3 During transplant (T-6 through hospital discharge)

- Standard of practice care with daily history and physical examinations, complete blood count and metabolic profile
- Management of complications per standard of practice

5.2.4 Day +30, +60, and +100 visit (+/- 7 days)

- History and physical examination
- CBC/Differential and complete metabolic panel
- Disease assessment by PET or CT scans; PET-CT scan is preferred (to be done between days 91 and 100 post-ASCT)

5.2.5 Follow-up during first year post-ASCT (q3 months +/- 7 days)

- History and physical examination
- CBC/Differential and complete metabolic panel
- Disease assessment by imaging (ONLY if clinically indicated)

5.2.6 First Annual visit post-ASCT (+/- 7 days)

- History and physical examination
- CBC/Differential and complete metabolic panel
- Disease assessment by imaging (ONLY if clinically indicated)
- Would be considered “study closure” visit

5.2.7 Study Schema / Calendar

Day[1]	S*	-17	-16	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	+1	+21	+30	+60	+100
H and P	X	X						X	X	X	X	X	X	X	X	X	X	X	X
CBC-D	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CMP	X	X															X	X	X
TLS Labs[2]	X	X		X	X	X	X	X	X	X	X	X	X	X					
Allopurinol[3]		X	X	X	X	X	X	X	X	X	X	X	X						
HIV Test	X																		
MUGA/ECHO	X																		
Beta-hCG	X																		
PET/CT[4]	X																		X
Collection			X[7]																
Venetoclax[5]				100	200	400	X	X	X	X	X	X	X						
Admission							X												
Discharge[6]																X			
BEAM								X											
Transplant														X					

*S = Screening visit. Can coincide with day -17. If less than 5 days apart from day -17, blood work and scans need not be repeated. Evaluation includes pulmonary function testing with DLCO and bone marrow biopsy if clinically indicated (results within 6 weeks of screening are acceptable).

[1]Study preferred to begin on a Monday so that stem cell infusion will occur on Thursday

[2]Tumor lysis labs include (in addition to the metabolic profile), uric acid, phosphate, lactate dehydrogenase. Tumor lysis labs will occur 8 (+/-2) hours after every dose of venetoclax during the escalation phase with the venetoclax. If deemed stable, frequency can be decreased later

[3]Allopurinol can be held when uric acid is less than 4 mg/dL

[4]PET-CT will occur per clinical guidelines for documentation of disease and assessment. Screening CT or PET scan can be done up to 6 weeks prior to the screening visit. Re-staging PET-CT is typically performed at day +91-100 post-ASCT or sooner as clinically indicated (if there is high clinical suspicion for progression).

[5]Venetoclax dosing will occur in a ramp-up fashion. All patients on all dosing cohorts will begin with 100 mg. If no toxicity or tumor lysis is observed, they will go on to receive 200 mg the following day, then 400 mg. The dose the following day will depend on their dosing cohort (400, 800, or 800-1200).

[6]Discharge is per the discretion of the treating physician but usually occurs around this range

[7]Patients will not start venetoclax until peripheral blood stem collection is completed and confirmed to be adequate for ASCT.

5.2.8 Drug administration and schedule

- Patients will be started on allopurinol per institutional guidelines for tumor lysis prophylaxis preferably on the Monday preceding their mobilization and collection date. They will remain on allopurinol until they are no longer at risk for tumor lysis, which usually coincides with a consistent downtrending of their uric acid levels after administration of their treatment
- They will undergo stem cell mobilization and apheresis for collection of CD34+ cells per standard institutional guidelines. They will be assigned an admission date that preferably falls on a Thursday (day -7).
- They will start venetoclax four days prior to that, which would coincide with day -10. They will continue venetoclax per the assigned schedule till day -1.
- They will start BEAM following their admission. They will receive standard doses of BEAM in parallel with venetoclax till day -1, followed by ASCT as per standard of care. Dose adjustment for renal impairment is allowed per institutional guidelines.
    - BCNU is given on day -6 at 300 mg/m^2
    - Etoposide is given at 100 mg/m^2 IV bid days -5 through -2
    - Cytarabine is given at 100 mg/m^2 IVbid days -5 through -2
    - Melphalan is given at 140 mg/m^2 on day -1
- Venetoclax is an oral medication and can be taken as an outpatient or inpatient. It is best bioavailable when given with food. Tumor lysis labs will be checked 8 hours after every dose of venetoclax during the escalation phase in all cohorts. A grade 3 or 4 adverse event will prompt holding the medication
    - Cohort 1 will receive 100 mg on day -10, 200 mg on day -9, then 400 mg on d-8 till d -1 if there are no grade 3/4, non-hematological, adverse effects related to venetoclax occur (please see DLT definition in section 5.3 below)
    - Cohort 2 will receive 100 mg on day -10, 200 on d -9, 400 on d-8, then 800 mg starting d-7 till d -1 if no grade 3/4, non-hematological, adverse effects related to venetoclax occur (please see DLT definition in section 5.3 below)
    - Cohort 3 will receive 100 mg on d-10, 200 on d-9, 400 on d-8, 800 on d-7, 1200 on d-6 till d-1 if no grade 3/4, non-hematological, adverse effects related to venetoclax occur (please see DLT definition in section 5.3 below)
- Please see below table for a summary

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
D -17	D -16	D -15	D -14	D -13	D -12	D -11
Allopurinol	Mobilization and collection					
D -10	D -9	D -8	D -7	D -6	D -5	D -4
Venetoclax* 100 mg PO	Venetoclax 200 mg PO	Venetoclax 400 mg PO	Venetoclax+ per dosing cohort Coh 1 = 400 Coh 2 = 800 Coh 3 = 1200	Venetoclax per dosing cohort BCNU 300 mg/m2	Venetoclax Etoposide 100 mg/m2 IV bid Cytarabine 100 mg/m2 IV bid	Venetoclax Etoposide 100 mg/m2 IV bid Cytarabine 100 mg/m2 IV bid
D -3	D -2	D -1	D 0			
Venetoclax Etoposide 100 mg/m2 IV bid Cytarabine 100 mg/m2 IV bid	Venetoclax Etoposide 100 mg/m2 IV bid Cytarabine 100 mg/m2 IV bid	Venetoclax Melphalan 140 mg/m2	SC Infusion			

5.2.9 Dosing cohorts

Venetoclax will be administered in three dose cohorts, 400 mg, 800 mg, and 1200 mg in a ramp-up scheduled detailed in the below table. Three patients will be accrued to dose level 1. BEAM will be given at the same standard dose for all cohorts.

Cohort	D -10	D -9	D -8	D -7	D -6	D -5 till D -1
1	100	200	400	400	400	400
2	100	200	400	800	800	800
3	100	200	400	800	1200	1200

Venetoclax dosing

5.2.10 Phase I Dose Escalation

Dose escalation will proceed within each cohort using the 3+3 design according to the following scheme. DLT is defined in the following section.

Number of Subjects with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 subjects at the next dose level.
1 out of 3	Enter 3 more subjects at this dose level. • If 0 of these 3 subjects experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional subjects will be entered at the next lowest dose level if only 3 subjects were treated previously at that dose.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional subjects will be entered at the next lowest dose level if only 3 subjects were treated previously at that dose. If ≥2 DLTs are encountered in first cohort, the study will terminate.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended maximally tolerated dose. At least 6 subjects should be entered. This will be the dose used for the expansion cohort.

5.3 Definition of Dose-Limiting Toxicity (DLTs)

Transplant related toxicities will be followed for determination of DLTs. The CTCAE v4.03 which is available online (http://ctep.info.nih.gov) will be used to define DLTs from days -10 to -7. During this period, DLT is defined as any non-disease-related, **non-hematological** adverse event of CTCAE grade 3 or higher with the exceptions of alopecia, grade 3 or 4 electrolyte disturbances that resolve within 24 hours with electrolyte correction and not

clinically significant, grade 3 nausea or vomiting that does not require hospitalization or support with total parenteral nutrition and resolves to < grade 2 within 72 hours, grade 3 or 4 infection/bleeding, and grade 3 or 4 cytopenias.

If the patient experiences a DLT between days -10 to -7 (prior to start of BEAM and defined above), and is deemed unsafe to continue on trial, patient may proceed to standard BEAM followed by ASCT or receive another therapy at the discretion of the treating physician.

The Bearman scale [21] for Transplant-related toxicities (Appendix-II) will be used for defining DLTs from days -6 through hospital discharge after engraftment (usually occurs between day +14 to day +21 after ASCT). Per the Bearman scale, a DLT is defined as a grade 3 or higher toxicity. No dose modifications are planned as all patients will be receiving a single course of venetoclax. Each cohort will be reviewed after being fully accrued for time to neutrophil engraftment (defined as ANC $\geqslant 0.5 \times 10^9$), time to platelet engraftment (defined as platelet levels of $\geqslant 20 \times 10^9$ unsupported by transfusions). In a recent study, reflecting contemporary practice, median time to neutrophil was 9 (range 8-11 days) and median time to platelet engraftment was 10.5 days (7-19 days) [22]. Each cohort will also be reviewed for average number of red blood cell (RBC) transfusions received. In a contemporary study, the average number of RBC transfusions received after ASCT was 4-6 units [23]. **Time to neutrophil engraftment 21 days, time to platelet engraftment 30 days, or more than 10 RBC units transfused before discharge from the hospital will also constitute a DLT.**

The DLT observation period will end at the time of discharge from the hospital. Per institutional policy, patients are not discharged until engraftment has occurred and all acute toxicities have resolved. This usually falls around day +21 after transplant. Patients who experience early progression prior to start of BEAM regimen, die, or withdraw for other reasons prior to start BEAM will be considered unevaluable for dose-escalation decisions and will be replaced. After each dosing cohort has finished accrual, the PI will review all patients treated on such cohort for unusual infections or other toxicities. **Each cohort needs to fully accrue and all patients treated on that cohort will be observed until hospital discharge before the subsequent cohort is opened for accrual; PI will review data on each cohort after all patients treated on that dose level has been discharged from the hospital before opening subsequent cohort to accrual. Deaths will be reviewed if they are related to venetoclax or not with stopping rules followed as detailed in section 6.4 below**.

5.4 Hematopoietic Stem Cell Collection

Peripheral blood stem cells will be mobilized and collected as per the discretion of the treating physician. Once an adequate number of CD34+ cells/kg have been collected (as per existing institutional guidelines) the patient will begin the preparative regimen for transplant. The minimum number of CD34+ cells required for enrollment is 2 x 10^6/kg. A clinical trial consent is not required prior to stem cell mobilization and collection being a standard of care procedure for ASCT.

5.5 Venetoclax Administration

Venetoclax is currently FDA-approved for chronic lymphocytic leukemia (CLL) with 17p deletion after one line of therapy. The approved dose is 400 mg with a ramp up from 20 mg given the high incidence of TLS in the CLL population. In the NHL studies, there was no observed clinical TLS. We are planning on starting with 100 mg on day -10, 200 mg on day -9, 400 mg on day -8. For cohort 1, this will be the target dose. For cohort 2, the dose on day -7 will be 800 mg. Cohort 3 will receive 1200 mg on day -6. Tumor lysis labs will be checked 8 hours after each dose during the escalation phase. A TLS mitigation strategy will be implemented.

In the pharmacokinetic studies, venetoclax was administered orally, in the morning, after a low-fat breakfast. Patients would need to avoid grapefruit or St John's Wort, and Seville oranges as well as other strong CYP3A4 inhibitors and inducers (outlined in Appendix IV).

5.6 Body surface area calculation

Dosage calculations for all cycles of treatment will be based on the patient's body surface area, as determined during the screening evaluations. Actual height and weight should be used in determining body surface area. However, ideal body weight or corrected ideal body weight can be used per local institutional practice.

5.7 Administration of BEAM high-dose regimen

Administration of BEAM (BCNU, etoposide, cytarabine, and melphalan) is as per standard institutional practice and is as follows:

Day –6:	Carmustine 300 mg/m^2 IV once
Day –5 to Day –2:	Etoposide 100 mg/m^2 and cytarabine 100 mg/m^2 IV twice daily
Day –1:	Melphalan 140 mg/m^2 IV once

Volumes of reconstitution of chemotherapeutic agents, duration of infusion, and premedications/supportive care is per standard institutional practice.

5.8 Hematopoietic Stem Cell Infusion

On day 0 of treatment, the previously stored hematopoietic stem cells will be re-infused. The cells will be removed from the storage freezer, brought to the patient area, thawed in a water bath, and administered intravenously through a central catheter to the patient. Patients will then be cared for as standard transplant patients. Criteria for release of stem cells, parameters for infusion, and monitoring throughout infusion is per standard institutional practice.

5.9 Concomitant Medications and Supportive Care Guidelines

The patients will be cared for as standard bone marrow transplant patients. All patients during the period of neutropenia will be cultured for temperatures >100.4 F and will receive appropriate other examinations, cultures and antibiotic therapy which will be adjusted clinically according to the patients' status. Patients are monitored with physical examinations, CBC, liver and renal function routinely throughout the treatment. Transfusional support will occur per institution guidelines. Patients will be discharged from the hospital and followed on an outpatient basis as clinically indicated.

The use of hematopoietic growth factors (G-CSF or GM-CSF) to stimulate blood cell production will be initiated post stem-cell transplant as per existing institutional policy on day +5. Antibiotics, medications to help with nausea, vomiting, diarrhea, and pain medication will be administered as required. Patients will be followed by a transplant dietician and will receive hyperalimentation through central venous access if oral intake is not adequate.

Appropriate anti-coagulation is allowed during the study (i.e. LMW heparin, direct factor Xa inhibitors, etc.) for patients who have an indication for anticoagulation and have a sustained platelet count above 50,000. Warfarin is allowed during the study provided that patients are monitored for INR twice a week. In general, oral Factor Xa inhibitors are preferred.

External beam radiation therapy will not be administered during the transplant course. External beam radiation may, however be given following the transplant as felt to be clinically indicated for areas of bulky tumor prior to transplant. Treatment with corticosteroids is permitted per standard of care as need for control or prevention of nausea or vomiting or for infusion reactions to medications or blood products including hematopoietic stem cells or any other indication at the discretion of treating physician. Non-steroidal hormones administered for non-lymphoma-related conditions, e.g., insulin for diabetes, are acceptable.

No other cancer therapy or investigational agents will be permitted while patients are on this study.

5.10 Criteria for Removal from Study

- Withdrawal of consent
- Unacceptable toxicity deemed to be related to venetoclax. For example, tumor lysis syndrome that cannot be controlled occurring prior to BEAM administration.
- The investigator considers it, for safety reasons, to be in the best interest of the subject.
- Pregnancy during the course of the study for a child-bearing participant
- Death
- Sponsor reserves the right to temporarily suspend or prematurely discontinue this study. The date and reason for discontinuation must be documented. Every effort should be made to complete the appropriate assessments.

5.11 Duration of Follow Up

Patients will be followed for adverse events (AEs) starting at day -10 through day +100 after transplantation. Patients will be followed for one year after transplantation for PFS and OS.

Serious adverse events that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

5.12 Dose Delays/Dose Modifications

Should unanticipated circumstances arise that might require minor variances from the prescribed dosing and schedule of protocol therapy in order to ensure safety and allow patients to continue to receive treatment on study, the PI should be contacted in advance for discussion and approval.

The dose of BEAM will remain constant for each subject throughout the study. The assigned dose of venetoclax will remain constant for each subject throughout the study.

Venetoclax may be held or discontinued completely for uncontrolled grade 3 or 4 toxicities during the course of treatment that are not manageable with supportive care. This excludes hematological toxicities.

5.13 Dose Adjustments for Changes in BSA

No adjustments in doses for post-screening changes in body surface area will be made.

5.14 Missed or Vomited Doses

Missed doses maybe replaced within 2 hours. If a dose is vomited within one hour of ingestion, it will be considered a missed dose. The dose will not be repeated that same day but the patient will follow regular schedule starting the next study dosing day. If vomiting occurs more than 1 hour after dosing, it will still be considered a complete dose.

5.15 Number of Subjects

The number of patients accrued to this study is variable and will depend on the toxicities seen. The maximum number of patients accrued to phase I will be 18 with the maximum number of patients accrued to the entire study as 28.

5.16 Expected Duration of Treatment and Subject Participation

The duration of treatment will be 10 days. For standard BEAM, it is 6 days. Four days of lead-in venetoclax will be added. Venetoclax administration will continue with BEAM. Patients will be followed till day 100 after transplant. The long-term outcomes will also be recorded.

5.17 Subject Selection

Each of the criteria in the sections that follow must be met in order for a subject to be considered eligible for this study. Use the eligibility criteria to confirm a subject's eligibility.

5.18 Inclusion of Women and Minorities

Men, women and members of all races and ethnic groups are eligible for this trial.

6 STATISTICAL ANALYSIS

6.1 Primary End Points

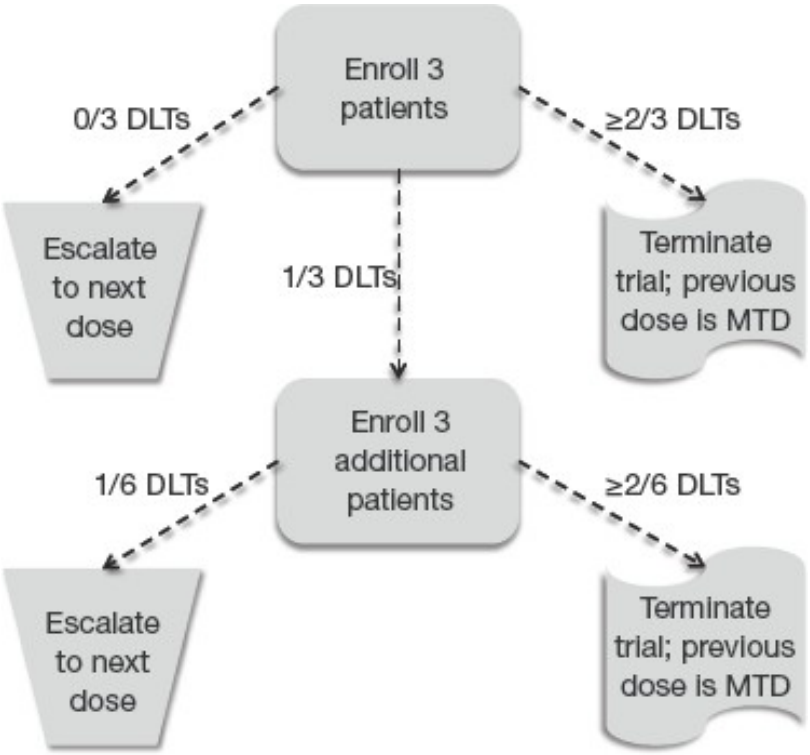
1. To establish the maximum tolerated dose (MTD) of venetoclax that can be safely given with BEAM in patients with relapsed or refractory NHL.

6.2 Secondary End Points

1. To evaluate the safety and tolerability of venetoclax combined with BEAM prior to autologous stem cell transplant
2. To obtain a preliminary estimate of the efficacy of venetoclax in combination with BEAM as measured by overall response rate (ORR) at day 100
3. To estimate the progression free survival (PFS) and overall survival (OS) of Venetoclax and BEAM followed by ASCT

6.3 Sample Size

This is a dose-escalation, phase I study with an expansion cohort. The number of patients enrolled will vary depending on the dose escalation portion of the trial. We will use the 3+3 design for accruing patients. Please refer to study section 5.2.10 for details regarding the 3+3 design. A schematic is provided for reference below. Thus, the minimum number of patients will be 3 and the maximum number will be 28 (maximum number accrued to dose escalation portion is 18 in addition to 10 patients accrued to expansion cohort at MTD). Patients who experience early progression prior to start of BEAM regimen, die, or withdraw for other reasons prior to start BEAM will be considered unevaluable for dose-escalation decisions and will be replaced. The study is not powered for efficacy however if the ORR and OS compares favorably against the recently reported dismal outcomes in the SCHOLAR-1 analysis of 636 patients of with primary refractory DLBCL; ORR 26% (CR 7%) and median OS of 6.3 months [24], along with demonstrated safety, a well-powered phase II (or randomized phase II trial) may be entertained in the future.



3+3 Design. [25]

6.4 Stopping Rules

During the dose-escalation portion, the safety stopping rules are defined by the dose escalation plan. Analysis of day +100 treatment-related mortality (TRM) will be performed after each dosing cohort has accrued. If 1, or more, of the first 10 patients treated on trial experience TRM due to the addition of the venetoclax, the protocol will be suspended for further accrual until reviewed by DSMB. The study will not be terminated unless the TRM is deemed to be directly related to the addition of venetoclax and not due to the usual toxicities of ASCT (sepsis and/or multi-organ failure is the leading cause of mortality after ASCT). Examples of TRM related to venetoclax after start of BEAM conditioning would be massive tumor lysis or unexplained grade 3 toxicity on the Bearman scale (appendix II). If 2 or more out of 10 experience any TRM (90% confidence interval 5.5%-100%), the trial will be suspended for further accrual until reviewed by DSMB. given that the expected TRM of a standard BEAM and ASCT is expected to be 5%.

6.5 Evaluable Patients

All patients who receive at least one dose of venetoclax will be included in the analysis for toxicity, efficacy and survival outcomes.

6.6 Analysis of Primary Endpoint

The MTD will be determined by 3+3 design. The rate and severity of toxicities encountered will be reported. Toxicities will be tabulated by type and grade using NCI-CTCAE Version 4.03 and Bearman criteria, and displayed in summary form.

6.7 Analysis of Secondary Endpoints

The overall response rate (ORR) will be estimated as the proportion of patients who achieve a CR or PR divided by the number of evaluable patients.

Response to therapy will be classified as complete response (CR), partial response (PR), no response (NR), progressive disease (PD), early death, or not evaluable. Response to therapy will be determined at Day 100. The use of PET-CT imaging is preferred at day +100 for measurement of response (unless not indicated). These will

be defined according to the Lugano criteria, referenced in Appendix III. Any patient who receives at least one dose of venetoclax and have day +100 assessment will be evaluable for the response. Patients who fail to have the response assessment due to early progression, death or toxicity will be considered evaluable for response and categorized as no-response. Patients who fail to have the response assessment for other reasons (withdraw consent, travel constraints) will be considered unevaluable and will not be included in the denominator when calculating response rate. The overall response rate will be reported with their associated 95% confidence interval.

Progression-free survival will be defined from the first treatment date until the date of progression or death, whichever occurs first, and patients will be censored at the last date of clinical assessment if no progression. Any patient who begins a non-protocol therapy will be censored at the last assessment date prior to the subsequent therapy. Overall survival (OS) will be defined from the first treatment date until the date of death or date last known alive. PFS and OS will be summarized by the Kaplan-Meier method. The cumulative incidence of progression will be estimated from the cumulative incidence curves treating death without relapse as competing risk.

6.8 Optional Correlative Outcomes

We will evaluate the association between response/survival endpoints and patient genetic characteristics such as the expression of BCL-2, BCL-XL, and MCL-1 as measured by immunohistochemistry (IHC), using various graphical displays to identify patterns and trends. Given the small numbers, this analysis is exploratory in nature however we will attempt quantitative analysis using univariable logistic regression model for response outcome, or Cox proportional hazard regression model for survival outcomes. The association between outcome and various subtypes of NHL will be analyzed using a similar approach. Based on prior investigations, BCL-2 expression of 40% is considered “positive” [26]. Plan to analyze BCL-2 positivity as a binary variable (positive/negative) against ORR but also will analyze BCL-2 positivity as a continuous variable against ORR. As part of research, we plan to obtain slides and blocks from department of pathology and outside hospitals. Patients will sign a consent addendum to obtain slides from outside hospitals.

6.9 Expected Accrual

We are expected to accrue 1 patient/month for this trial. Given the DLT observation period is approximately 38 days, it will take about 4.5 months for a 3 patient cohort. The minimum of 9 months and maximum of 27 months will be needed for the MTD stage of the study. The maximum accrual will take about 37 months including 10 patients for the expansion cohort.

7 POTENTIAL RISKS

7.1 Potential Risks of venetoclax

As of 11/28/2016, 7 phase I/II studies were ongoing with venetoclax in NHL. Preliminary safety data came from Arm B of M12-175. This was a phase I study of venetoclax monotherapy in patients with relapsed or refractory NHL. Most subjects (97.2%) experienced at least 1 treatment-emergent adverse event. An overview of adverse events, grade ≥ 3 adverse events, and serious adverse events reported are summarized below which is duplicated from the Investigator’s Brochure.

	Number of Subjects (%)			
	M12-175 Arm B (N = 106)	M13-834 (N = 26)[a]	M13-835 (N = 11)	Total (N = 135)[b]
Any treatment-emergent adverse event	103 (97.2)	26 (100)	9 (81.8)	130 (96.3)
Any treatment-emergent grade 3 or above adverse event	59 (55.7)	20 (76.9)	7 (63.6)	80 (59.3)
Any treatment-emergent serious adverse event	37 (34.9)	2 (7.7)	5 (45.5)	44 (32.6)
Any treatment-emergent adverse event leading to discontinuation of study drug	18 (17.0)	1 (3.8)	3 (27.3)	22 (16.3)
Any treatment-emergent fatal adverse event[c]	10 (9.4)	0	3 (27.3)	13 (9.6)

a. Includes 2 subjects with MM and 6 subjects with CLL/SLL.

b. Total number of subjects for the NHL monotherapy studies excludes the 2 MM subjects and 6 CLL/SLL subjects with safety data in Study M13-834.

c. Includes events of disease progression.

The most common adverse events in these NHL subjects were nausea (48.1%), diarrhea (45.3%), fatigue (42.5%), and vomiting and decreased appetite (21.7% each). Adverse events grade 3 and above were reported for 55.7% subjects. The most common events grade 3 or above were anemia (17.0%) and neutropenia (11.3%). Serious adverse events were reported in 34.9% subjects. The most common serious adverse events were malignant neoplasm progression (9.4%), and influenza, lower respiratory tract infection, pneumonia, and hyponatremia (2.8% each). A total of 18 (17.0%) subjects experienced adverse events that led to discontinuation of venetoclax. The most common adverse events leading to discontinuation were malignant neoplasm progress (6 [5.7%] subjects), and thrombocytopenia and nausea (2 [1.9%] subjects each). All other events leading to discontinuation were reported in 1 subject each. A total of 10 (9.4%) subjects experienced adverse events that led to death, including 9 events of malignant neoplasm progression and 1 event each of disease progression and respiratory failure. All fatal events were considered to have no reasonable possibility of being related to venetoclax.

Study M13-834, titled "Phase 1 Study Evaluating the Safety and pharmacokinetics of Venetoclax in Japanese Subjects with Hematological Malignancies," is an ongoing, open-label, dose-escalation study. The primary objectives of this study are to assess the safety profile and characterize the pharmacokinetics of venetoclax when administered in Japanese subjects with hematological malignancies. The secondary objectives are to evaluate preliminary efficacy data regarding the effect of venetoclax on overall response rate, time to tumor progression and duration of response. All (100%) subjects in Study M13-834 experienced at least 1 treatment-emergent adverse event. The most common adverse events were lymphopenia (73.1%), neutropenia (61.5%), nausea (46.2%), and leukopenia (38.5%). Of the 26 subjects, 20 (76.9%) experienced adverse events grade 3 or above, including events of lymphopenia and neutropenia (13 subjects each), and leukopenia (6 subjects). One subject experienced an adverse event of drug eruption that led to discontinuation of study drug. None of the adverse events resulted in death.

Study M13-835, titled "An Extension Study of ABT-199 in Subjects with Advanced Non-Hodgkin Lymphoma," is an ongoing, open label, extension study of subjects with advanced NHL who completed a prior venetoclax study or were active and assigned to venetoclax when the study completed. The primary objective is to evaluate the safety of venetoclax monotherapy in adults with advanced NHL. As of 28 November 2016, 11 subjects have been rolled over from Study M13-364 (drug-drug interaction study of ketoconazole), and had safety data available in Study M13-835. An overview of adverse events, grade 3 adverse events, and serious adverse events reported in Study M13-835 is presented in the above table. Of the 11 subjects, 9 (81.8%) subjects experienced at least 1

treatment adverse event; the most common events were diarrhea (4 subjects), thrombocytopenia, nausea, malignant neoplasm progression, and cough (3 subjects each). Seven subjects experienced events grade 3 or above, including serious malignant neoplasm progression in 3 subjects, serious syncope in 2 subjects, and thrombocytopenia in 2 subjects; other events occurred in 1 subject each. Three subjects experienced events that led to study drug discontinuation. Fatal events occurred in 3 subjects: malignant neoplasm progression in 2 subjects and ischemic stroke in 1 subject. Below is a table duplicated from the Investigator's Brochure summarizing adverse events that occurred at a rate of ≥ 10%.

System Organ Class Preferred Term[a]	M12-175 Arm B N = 106	M13-834 N = 26[b]	M13-835 N = 11	Total N = 135[c]
	n (%)	n (%)	n (%)	n (%)
Any adverse event	103 (97.2)	26 (100)	9 (81.8)	130 (96.3)
Blood and lymphatic system disorders	36 (34.0)	23 (88.5)	4 (36.4)	57 (42.2)
Anaemia	20 (18.9)	6 (23.1)	1 (9.1)	25 (18.5)
Lymphopenia	3 (2.8)	19 (73.1)	0	17 (12.6)
Neutropenia	18 (17.0)	16 (61.5)	1 (9.1)	29 (21.5)
Thrombocytopenia	13 (12.3)	3 (11.5)	3 (27.3)	18 (13.3)
Gastrointestinal disorders	82 (77.4)	18 (69.2)	6 (54.5)	101 (74.8)
Constipation	22 (20.8)	3 (11.5)	1 (9.1)	25 (18.5)
Diarrhoea	48 (45.3)	6 (23.1)	4 (36.4)	57 (42.2)
Nausea	51 (48.1)	12 (46.2)	3 (27.3)	64 (47.4)
Vomiting	23 (21.7)	7 (26.9)	1 (9.1)	29 (21.5)
General disorders and administration site conditions	64 (60.4)	5 (19.2)	6 (54.5)	73 (54.1)
Fatigue	45 (42.5)	1 (3.8)	2 (18.2)	47 (34.8)
Pyrexia	12 (11.3)	3 (11.5)	1 (9.1)	15 (11.1)
Infections and infestations	45 (42.5)	13 (50.0)	3 (27.3)	59 (43.7)
Upper respiratory tract infection	18 (17.0)	2 (7.7)	1 (9.1)	20 (14.8)
Metabolism and nutrition disorders	56 (52.8)	12 (46.2)	4 (36.4)	69 (51.1)
Decreased appetite	23 (21.7)	4 (15.4)	0	26 (19.3)
Musculoskeletal and connective tissue disorders	43 (40.6)	3 (11.5)	2 (18.2)	47 (34.8)
Back pain	17 (16.0)	2 (7.7)	0	19 (14.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	21 (19.8)	4 (15.4)	4 (36.4)	29 (21.5)
Malignant neoplasm progression	12 (11.3)	0	3 (27.3)	15 (11.1)
Nervous system disorders	44 (41.5)	4 (15.4)	3 (27.3)	50 (37.0)
Dizziness	13 (12.3)	0	2 (18.2)	15 (11.1)
Headache	19 (17.9)	2 (7.7)	0	21 (15.6)

7.2 Potential Risks of stem cell mobilization with filgrastim

Filgrastim (G-CSF) is the agent most commonly used in stem cell mobilization. G-CSF stimulates the production, maturation and activation of neutrophils and activates neutrophils to increase their migration and cytotoxicity. Toxicities that are likely to occur include myalgias and medullary bone pain. The bone pain can be generally controlled with non-narcotic analgesia. Less likely side effects include fluid retention, pericardial effusion, local inflammation at the injection site and transient laboratory abnormalities including mild elevations in uric acid, lactic dehydrogenase (LDH), alkaline phosphatase, and leukocytosis. Rare but serious side effects include reported cases of spleen swelling resulting in splenic rupture, adult respiratory distress syndrome (ARDS) and allergic reactions.

7.3 Potential Risks of stem cell collection

A central venous catheter is usually required for stem cell collection, but can also be done peripherally. Central catheter placement is associated with a small risk of infection, bleeding, or pneumothorax. The apheresis

procedure, used to collect mobilized stem cells, is associated with a small risk of hypersensitivity reaction due to cytokine release and hypocalcemia.

7.4 Potential Risks of autologous stem cell transplantation (ASCT)

ASCT recipients incur risks from high-dose conditioning and post-ASCT therapy, which must be weighed against the risk of the disease for which the ASCT is prescribed. Major risks following transplantation include: 1) Infection which can be bacterial, viral, parasitic, or fungal. Often, these infections are life-threatening, particularly when caused by viral or fungal agents, and are associated with high mortality in the transplant population; 2) Damage of all or any of the major organs may occur as a result of reactions to drugs (e.g., chemotherapy, antibiotics, anti-fungal medications), and as a result of destructive processes (e.g., infection), and may have a fatal outcome; brain damage can result in severe loss of cognitive or neurologic function; 3) Relapse or progression of lymphoma may occur, especially in patients with advanced disease status at time of treatment; 4) Unknown toxicities may occur in any individual patient due to multiple events and cumulative effects which may involve any and all organs, including the brain; and 5) Death (there is standard mortality risk with ASCT of about 5%).

7.5 Potential Risks of Carmustine (BCNU)

Carmustine is an alkylating agent. Common side effects include myelosuppression, nausea, vomiting, headache, and jaw pain. Less common side effects include transient hypotension, dizziness, hyperpigmentation of the skin, hepatoxicity and a delayed inflammatory lung response (pneumonitis).

7.6 Potential Risks of Etoposide (VP-16)

VP-16 is a semi-synthetic podophyllotoxin derivative. Side effects that are likely to occur include nausea, vomiting and diarrhea, myelosuppression, mucositis, alopecia, and fatigue. Less likely side effects include a skin rash, peripheral neuropathy, and hepatotoxicity. Hypotension may occur if the drug is infused quickly. A rare but serious side effect is a small risk of developing a second cancer.

7.7 Potential Risks of Cytarabine (Ara-C)

Cytarabine, commonly known as Ara-C, is a synthetic nucleoside. Likely side effects include myelosuppression, nausea, vomiting and diarrhea, oral and anal inflammation or ulceration, hepatic dysfunction, fever, rash, and thrombophlebitis. Less likely side effects include conjunctivitis (when Ara-C is given at high doses, and preventable by the prophylactic use of corticosteroid eye drops), abdominal pain, alopecia, pruritis, headache, and the occurrence of a cytarabine syndrome characterized by fever, myalgias, arthralgias, chest pain, maculopapular rash, conjunctivitis and malaise - this syndrome occurs 6-12 hours following drug administration. Corticosteroids are beneficial in treating this syndrome. A rare but serious side effect is cerebral/cerebellar dysfunction (more common at very high doses and in older patients).

7.8 Potential Risks of Melphalan

Melphalan, an alkylating agent, is a phenylalanine derivative of nitrogen mustard. At high doses, the likely toxicities include myelosuppression, gastrointestinal toxicity and alopecia. The duration of profound myelosuppression decreases with the use of stem cell transplantation and colony stimulating factors. Gastrointestinal toxicity, which includes potentially severe stomatitis, esophagitis and diarrhea, may require intravenous narcotics for mucositis related pain, intravenous hydration and alimentation, and antibiotics. Less likely is hepatotoxicity. Rare but serious toxicities reported include pulmonary fibrosis and interstitial pneumonitis, venoocclusive disease of the liver, skin hypersensitivity, vasculitis, hemolytic anemia, allergic reactions, and a small risk of developing second cancers.

8 SAFETY AND REPORTING REQUIREMENTS

8.1 Assessment of safety

Safety assessments will consist of monitoring and recording adverse events (and serious adverse events; measurements of protocol-specified hematology, clinical chemistry, and other laboratory variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s) and should be consistent with institutional standards and Good Clinical Practice.

8.2 Definitions

8.2.1 Adverse event

An adverse event (AE) is any unfavorable or unintended event, physical or psychological, associated with a research study, which causes harm or injury to a research participant as a result of the participant's involvement in a research study. The event can include abnormal laboratory findings, symptoms, or disease associated with the research study. The event does not necessarily have to have a causal relationship with the research, any risk associated with the research, the research intervention, or the research assessments.

Adverse events may be the result of the interventions and interactions used in the research; the collection of identifiable private information in the research; an underlying disease, disorder, or condition of the subject; and/or other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.

8.2.2 Serious Adverse Events

A **serious adverse event** (SAE) is any adverse experience occurring at any dose that results in any of the following outcomes:

- Results in **death.**
- Is a **life-threatening** adverse experience. The term life-threatening in the definition of serious refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.
- Requires **inpatient hospitalization or prolongation of existing hospitalization**. Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following expectations is met:
    - The admission results in a hospital stay of less than 24 hours OR
    - The admission is pre-planned (e.g., planned admission to the hospital for BEAM and ASCT) OR
    - The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care.

However, it should be noted that invasive treatment during any hospitalization may fulfill the criteria of "medically important" and as such may be reportable as a serious adverse event dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

- Results in **persistent or significant disability/incapacity**. The definition of disability is a substantial disruption of a person's ability to conduct normal life's functions.
- Is a congenital anomaly/birth defect.
- Is an **important medical event**. Important medical events that may not result death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood disease or disorders, or convulsions that do not result in inpatient hospitalization, or the

development of drug dependency or drug abuse. The development of a new cancer is always considered an important medical event.

- For the purpose of this study, a toxicity of grade 4 or greater on CTCAE version 4.03 during venetoclax treatment, or 3 or greater on the Bearman scale from days -10 through hospital discharge after transplant (usually occurs between day +14 to day +21 after ASCT), would constitute an SAE. Hematological toxicities and alopecia will be excluded from AE assessment.

8.2.3 Suspected Adverse Reaction

A Suspected Adverse Reaction is any adverse event for which there is a "reasonable possibility" that the drug caused the adverse event. "Reasonable Possibility", for the purposes of safety reporting, means there is evidence to suggest a causal relationship between the drug and the adverse event. Examples of evidence that would suggest a causal relationship between the drug and the adverse event are:

• A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, blood dyscrasias, rhabdomyolysis, hepatic injury, anaphylaxis, and Stevens-Johnson Syndrome).

• One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., include tendon rupture or heart valve lesions in young adults, or intussusception in healthy infants). If the event occurs in association with other factors strongly suggesting causation (e.g., strong temporal association, event recurs on rechallenge), a single case may be sufficiently persuasive; but often, more than one occurrence (from one or multiple studies) would be needed before the sponsor could make a determination of whether the drug caused the event.

• An aggregate analysis of specific events that can be anticipated to occur in the study population independent of drug exposure. Such events include known consequences of the underlying disease or condition under investigation (e.g., symptoms or disease progression), or events unlikely to be related to the underlying disease or condition under investigation, but commonly occur in the study population independent of drug therapy (e.g., cardiovascular events in an elderly population). An aggregate analysis (across studies) will identify those events that occur more frequently in the drug treatment group than in a concurrent or historical control group.

8.2.4 Unexpected

An "unexpected" AE is an AE that is not listed in the Investigator Brochure or is not listed at the specificity or severity that has been observed. For example, hepatic necrosis would be "unexpected" (by virtue of greater severity) if the Investigator Brochure referred only to elevated hepatic enzymes or hepatitis. "Unexpected" also refers to AEs that are mentioned in the Investigator Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the study drug under investigation.

8.3 Adverse Event Evaluation

The investigator or designee is responsible for ensuring that all adverse events (both serious and non-serious) observed by the clinical team or reported by the subject which occur after the subject has signed the informed consent are fully recorded in the subject's medical records. Source documentation must be available to support all adverse events.

A laboratory test abnormality considered clinically relevant should be reported as an adverse event. As all patients will be undergoing ASCT, hematological toxicities and alopecia will not be considered AEs.

The investigator or sub-investigator (treating physician if applicable) will provide the following for all adverse events (both serious and non-serious):

- Event term (as per CTCAE days -10 to -7, then utilizing the Bearman scale)
- Description of the event
- Date of onset and resolution

- Expectedness of the toxicity
- Grade of toxicity
- Attribution of relatedness to the investigational agent- (this must be assigned by an investigator, sub-investigator, or treating physician)
- Action taken as a result of the event, including but not limited to; no changes, dose interrupted, reduced, discontinued, etc. or action taken with regard to the event, i.e. no action, received concurrent medication or other intervention, etc.
- Outcome of event

Descriptions and **grading scales** found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting.

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

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

8.4 SAE Report Form

SAEs will be recorded on the FDA Form 3500A (MedWatch) but should only be reported as instructed. The electronic FDA SAE reporting forms should not be used.

8.5 Reporting Procedures for Serious Adverse Events

For the purposes of safety reporting, all adverse events will be reported that occur from days -10 through hospital discharge after transplant (usually occurs between day +14 to day +21 after ASCT). Adverse events, both serious and non-serious, and deaths that occur during this period 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 subject's stable or chronic condition or intercurrent illness(es). Related AEs will be followed until resolution to baseline or grade 1 or stabilization.

8.6 SAE Reporting Requirements

Participating investigators must report all serious adverse events to the Principal Investigator within **24 hours** of discovery or notification of the event. The participating investigator must also provide follow-up information on the SAE until final resolution.

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The Principal Investigator will review the SAE and report the event to the FDA, external collaborator(s), and IRB as applicable. It is the Investigator's responsibility to ensure that ALL serious adverse events that occur on the study are reported to all participating sites.

All SAEs (initial and follow-up information) will be reported on an Event Reporting form and submitted to the OSU IRB within 24 hours of the discovery of the event or information. All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself. The

primary cause of death on the autopsy report should be the term reported. If study drug is discontinued because of an SAE, this information must be included in the SAE report.

8.7 SAE of Special Interest

Venetoclax events of special interest are

- Grade ≥ 3 TLS
- Grade ≥ 3 infection
- Grade ≥ 3 elevations in AST, ALT, or serum bilirubin or cases of elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice

8.8 Data Safety and Toxicity Committee

The PI will ensure that ALL SAEs occurring on this trial (internal or external) are reported to the FDA, appropriate IRBs, sponsoring company and other applicable parties.

8.9 Data and Safety Monitoring Plan (DSMP)

The Phase 1 clinical trial proposed in this application will be conducted using a DSMP that is in compliance with the Institutional (OSU-CCC) DSMP guidelines approved by the NCI in 2008. The data and safety monitoring plan for this phase 1 trial will involve the continuous evaluation of safety, data quality and data timeliness. Investigators will conduct continuous review of data and patient safety at the program meetings (twice monthly) and at the Phase 1/2 weekly meeting which is led by Dr. Michael Grever. This review of the trials includes discussion of 'milestone' events such as dose escalation or encounters of DLT or SAEs. All discussions 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 OSU-CCC Data and Safety Monitoring Committee (DSMC).

8.10 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. Investigators and study staff will undergo training on Good Clinical Practice (GCP) through the Collaborative Institutional Training Initiative (CITI). GCP training sets the standard for the design, conduct, recording, and reporting of studies involving human subjects, ensuring that study subjects rights, safety, and well-being are protected. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and wellbeing of the patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, Investigator's Brochures, informed consent form, written information given to the patients (including pill diaries), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator, as allowable by local regulations. The principal investigator will ensure that the study will be conducted according to the protocol and all applicable regulations. The protection of each subject's rights and welfare will be maintained.

8.11 Retention of records

FDA regulations (21 CFR § 312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of clinical trials and the distribution of investigational drug, patient records, consent forms, laboratory test results, and medication inventory records, must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since

formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

For studies conducted outside the United States under a U.S. IND, the Principal Investigator must comply with the record retention requirements set forth in the FDA IND regulations and the relevant national and local health authorities, whichever is longer.

8.12 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 9.

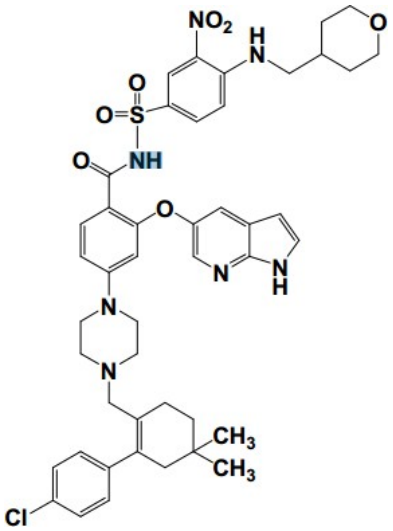
9 INVESTIGATIONAL AGENTS

9.1 Venetoclax

9.1.1 Nomenclature

Associated Name(s): ABT-199, A-1195425.0, GDC-0199, RO5537382
Generic Name: venetoclax
INN (International Nonproprietary Name): venetoclax
USAN (United States Adopted Name): venetoclax Chemical Abstracts Service (CAS) Registry Number 1257044-40-8
Japanese Accepted Name (JAN): venetoclax

9.1.2 Structural formula



9.1.3 Molecular Formula and Molecular Weight

Molecular Formula: $C_{45}H_{50}ClN_7O_7S$
Molecular Weight: 868.44

9.1.4 Physical and Chemical Properties of the Drug Substance

Description: Light yellow to yellow to dark yellow powder.
Solubility: The solubility of venetoclax in various media is detailed in the table below.

Optical Isomerism: There are no optical isomers.

Solvent	Solubility (mg/mL)	Descriptive Term (Per USP)
1% Sodium dodecyl sulfate (w/v aq)	2.79	Slightly soluble
1% polysorbate 80 (w/v aq)	0.30	Very slightly soluble
1% polysorbate 20 (w/v aq)	0.08[a]	Practically insoluble
1% Poloxamer 124 (w/v aq)	< 0.0006	Practically insoluble
Vinylpyrrolidone dimer	> 200	Very soluble
Methanol	0.44	Very slightly soluble
Methylene chloride	20 to 25	Very soluble
Ethyl acetate	< 8.8	Sparingly soluble

USP = United States Pharmacopeia; w/v aq = weight/volume aqueous solution

a. A different residual x-ray powder diffraction pattern was observed for polysorbate 20 only.

9.1.5 Pharmaceutical properties (Formulation)

Dosage form: Tablets
Strength: 10, 50, 100 mg
Excipients: Copovidone, colloidal silicon dioxide, polysorbate 80, sodium stearyl fumarate, calcium phosphate dibasic 10 mg and 100 mg: coating contains iron oxide yellow, polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc. 50 mg: coating contains iron oxide yellow, iron oxide red, iron oxide black, polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc.

9.1.6 Storage and Handling

The clinical supply should be stored at 15 – 25 ℃ (59 – 77 ℉)

9.2 Commercial Agents

9.2.1 Filgrastim

Other Names: Neupogen, G-CSF
Product description: Filgrastim is commercially available from Amgen, Inc. (Thousand Oaks, CA) in single-dose vials containing either 1 ml or 1.6 ml, in boxes of 10 vials each. Each vial of filgrastim contains 300 µg/ml. The product is formulated in a 10nM sodium acetate buffer at pH 4.0, containing sorbitol and 0.004% Tween 80.

Solution preparation: N/A

Storage requirements: Filgrastim should be stored at 2 C to 8 C (36 F to 46 F) and should not be frozen.

Stability: Filgrastim vials and prefilled syringes are stable for 7 days at 9°C to 30°C (47°F to 86°F), however, the manufacturer recommends discarding after 24 hours because of microbiological concerns. The product is packaged without a preservative.
Undiluted filgrastim is stable for 24 hours at 15°C to 30°C and for 2 weeks at 2°C to 8°C (36°F to 46°F) in tuberculin syringes. However, the manufacturer recommends using immediately because of concern for bacterial contamination.

Route of administration: Filgrastim is administered subcutaneously in single per institutional standard of care practices. Filgrastim should not be administered earlier than 24-48 hours after chemotherapy, nor should it be administered in the 24-hour period prior to chemotherapy.

Drug Procurement: From commercial supply

9.2.2 BCNU (bis-chloronitrosourea or carmustine)

Other Names: Carmustine

Product description: BCNU is supplied as a lyophilized powder containing no preservatives.

Solution preparation: Due to its water insolubility, it is to be reconstituted with the diluent provided (3 ml of absolute ethanol) and then with either 27 ml or 17 ml of sterile water for injection to provide a resulting concentration of 3.3 mg/ml or 5 mg/ml, respectively.

Storage requirements: Unopened vials are stable under refrigeration for two years. BCNU has a low melting point requiring refrigeration at all times prior to reconstitution. Do not use if an oil film is present at the bottom of vial.

Stability: Stability upon reconstitution (less than 8% potency lost) is eight hours at room temperature or 24 hours if refrigerated and protected from light. BCNU solution may be further diluted with 500 ml of 5% Dextrose OR sodium chloride injection, USP, and will be stable for 8 hours. Diluted solution should be protected from light.

Route of administration: BCNU should be administered by IV drip over three hours. Absorption of BCNU to plastics has been documented. Thus, PVC free bags and polyethylene tubing should be used during the administration of BCNU.

Drug Procurement: From commercial supply

9.2.3 Etoposide

Other Names: VP-16, Toposar®

Product description: Etoposide Injection USP is available for intravenous use as 20 mg/mL solution in 100 mg (5 mL), 500 mg (25 mL), and 1 g (50 mL) sterile, multiple-dose vials. The pH of the clear, nearly colorless to yellow liquid is 3 to 4. Each mL contains 20 mg etoposide USP, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg modified polysorbate 80/tween 80, 650 mg polyethylene glycol 300, and 30.5 percent (v/v) alcohol.

Solution preparation: Etoposide Injection must be diluted prior to use with either 5% Dextrose Injection, or 0.9% Sodium Chloride Injection, to give a final concentration of 0.2 to 0.4 mg/mL. If solutions are prepared at concentrations above 0.4 mg/mL, precipitation may occur.

Storage requirements: Unopened vials of Etoposide Injection are stable for 24 months at room temperature (25°C).

Stability: Vials diluted as recommended to a concentration of 0.2 or 0.4 mg/mL are stable for 96 and 24 hours, respectively, at room temperature (25°C) under normal room fluorescent light in both glass and plastic containers. The use of non-PVC containers and tubing is recommended due to the potential for polysorbate 80 leaching of diethylhexyl phthalate (DEHP), from polyvinyl chloride (PVC) containers and tubing into etoposide IV solution.

Route of administration: Etoposide should be given by intravenous infusion over 2 hours.

Drug Procurement: From commercial supply

9.2.4 Cytarabine

Other Names: Ara-C, Cytosar®

Product description: Cytarabine is provided as a sterile lyophilized material for reconstitution and intravenous, intrathecal or subcutaneous administration. It is available in multi-dose vials containing 100 mg, 500 mg, 1 g or 2 g sterile cytarabine.

Solution preparation: For IV use, reconstitute the 100-mg vial with 5 mL bacteriostatic water for injection to achieve a concentration of 20 mg/mL. Add 10 mL of bacteriostatic water to the 500-mg vial to achieve a final concentration of 50 mg/mL. Add 10 and 20 mL of bacteriostatic water to the 1 and 2 gm vials respectively to achieve a final concentration of 100 mg/mL. For subcutaneous use, reconstitute the powder with sterile water or saline to a concentration of 50-100 mg/mL.

Storage requirements: The drug is stored unreconstituted at controlled room temperature, 15° to 30°C (59° to 86°F).

Stability: Solutions reconstituted with sterile water without preservative should be used immediately; solutions reconstituted with Bacteriostatic of Water are stable up to 48 hours at controlled room temperature (15o to 30oC). Solutions with a slight haze should be discarded.

Route of administration: Cytarabine is administered by IV infusion over 1-2 hours.

Drug Procurement: From commercial supply

9.2.5 Melphalan

Other Names: L-phenylalanine mustard, phenylalanine mustard, L-PAM, L-sarcolysin, Alkeran®

Product description: Melphalan is supplied as a sterile, nonpyrogenic, freeze-dried powder. Each single-use vial contains melphalan hydrochloride equivalent to 50 mg melphalan and povidone. ALKERAN for Injection is reconstituted using the sterile diluent provided. Each vial of sterile diluent contains sodium citrate, propylene glycol, ethanol (96%), and water for injection to a total of 10 mL.

Solution preparation: Melphalan must be reconstituted at room temperature by rapidly injecting 10 mL of the supplied diluent directly into the vial of lyophilised powder using a sterile needle (20-gauge or larger needle diameter) and syringe. Immediately shake vial vigorously until a clear solution is obtained. Rapid addition of the diluent, as a single quantity, followed by immediate vigorous shaking is important for proper dissolution.
Immediately dilute the dose to be administered in 0.9% Sodium Chloride Injection to a concentration not greater than 0.45 mg/mL.

Storage requirements: Melphalan vials should be stored below 30°C and protected from light.

Stability: Following reconstitution with sterile diluent, melphalan hydrochloride solution containing 5 mg/ml is stable for up to 90 minutes at room temperature; this reconstituted solution should not be refrigerated since a precipitate may form at 5oC. The reconstituted solution should be diluted further with 0.9% sodium chloride injection to provide a solution with a concentration not exceeding 0.45 mg/ml. This diluted solution is stable for 60 minutes at room temperature.

Route of administration: Melphalan should be administered as IV push or rapid infusion over 10 minutes.

Drug Procurement: From commercial supply

10 DOCUMENTATION, RECORD ACCESS AND MAINTENANCE OF STUDY RECORDS

10.1 Written Informed consent

Provision of written informed consent must be obtained prior to any study-related procedures. The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the subject's financial responsibility. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and be allowed time to consider the information provided.

The original, signed written Informed Consent Form must be kept with the Research Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form must be given to the subject. Additionally, documentation of the consenting process should be located in the research chart.

10.2 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), a subject must sign an authorization to release medical information to the sponsor and/or allow the sponsor, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

10.3 Retention of records

The Principal Investigator of supervises the retention of all documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for as long as needed to comply with local, national and international regulations. No records will be destroyed until the Principal Investigator confirms destruction is permitted.

10.4 Audits and inspections

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements.

10.5 Adverse Events

Adverse events will be reported as outlined in section 8.

10.6 Data Reporting

The Investigator will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each patient enrolled in this clinical trial. Source records must be adequate to reconstruct all data transcribed onto the Case Report Forms (CRFs).

10.7 Regulatory Considerations

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

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APPENDIX I

PERFORMANCE STATUS CRITERIA

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

APPENDIX II - BEARMAN SCALE

Seattle criteria (Bearman) assess post-transplant regimen-related toxicity in eight organs: the heart, bladder, kidneys, lungs, liver, mucosa, central nervous system (CNS), and gut. As the criteria exclusively assess RRT, they exclude adverse events attributable to GVHD and infection. Similarly, renal failure is excluded when it coincides with the administration of known nephrotoxic agents.

Toxicity	Grade 1	Grade 2	Grade 3
Heart	Mild electrocardiogram abnormality, not requiring medical intervention; or noted heart enlargement on CXR with no clinical symptoms	Moderate electrocardiogram abnormalities requiring and responding to medical intervention; or requiring continuous monitoring without treatment; or congestive heart failure responsive to digitalis or diuretics	Severe electrocardiogram abnormalities with no or only partial response to medical intervention; or heart failure with no or only minor response to medical intervention: or decrease in voltage by more than 50%
Bladder	Macroscopic hematuria after 2 days from last chemotherapy dose with no subjective symptoms of cystitis and not caused by infection	Macroscopic hematuria after 7 days from last chemotherapy dose not caused by infection; or hematuria after 2 days with subjective symptoms of cystitis not caused by infection	Hemorrhagic cystitis with frank blood, necessitating invasive local intervention with installation of sclerosing agents, nephrostomy or other surgical procedures
Kidney	Increase in creatinine up to twice the baseline value	Increase in creatinine above twice baseline but not requiring dialysis	Requirement of dialysis
Lung	Dyspnea without CXR changes not caused by infection or congestive heart failure; or CXR showing isolated infiltrate or mild interstitial changes without symptoms not caused by infection or congestive heart failure	CXR with extensive localized infiltrate or moderate interstitial changes combined with dyspnea and not caused by infection or CHF; or decrease of PO_2 (>10% from baseline) but not requiring mechanical ventilation or >50% O_2 on mask and not caused by infection	Interstitial changes requiring mechanical ventilatory support or >50% oxygen on mask and not caused by infection or CHF
Liver	Mild hepatic dysfunction with 2.0 mg/dl <bilirubin <6.0 mg/dl or weight gain >2.5% and <5% from baseline, of noncardiac origin; or serum AST increase more than two-fold but less than five-fold from lowest preconditioning	Moderate hepatic dysfunction with bilirubin >6 mg/dl <20 mg/dl; or serum AST increase >five-fold from preconditioning; or clinical ascites or image-documented ascites >100 ml; or weight gain >5% from baseline of noncardiac origin	Severe hepatic dysfunction with bilirubin >20 mg/dl; or hepatic encephalopathy; or ascites compromising respiratory function
CNS	Somnolence but the patient is easily arousable and oriented after arousal	Somnolence with confusion after arousal; or other new objective CNS symptoms with no loss of consciousness not more easily explained by other	Seizures or coma not explained (documented) by other medication, CNS infection, or bleeding

Toxicity	Grade 1	Grade 2	Grade 3
		medication, bleeding, or CNS infection	
Stomatitis	Pain and/or ulceration not requiring a continuous i.v. narcotic drug	Pain and/or ulceration requiring a continuous i.v. narcotic drug (morphine drip)	Severe ulceration and/or mucositis requiring preventive intubation; or resulting in documented aspiration pneumonia with or without intubation
GI toxicity	Watery stools >500 ml but <2000 ml every day not related to infection	Watery stools >2000 ml every day not related to infection; or macroscopic hemorrhagic stools with no effect on cardiovascular status not caused by infection; or subileus not related to infection	Ileus requiring nasogastric suction and/or surgery and not related to infection; or hemorrhagic enterocolitis affecting cardiovascular status and requiring transfusion

Grade IV regimen-related toxicity is defined as fatal toxicity.
CXR=chest X ray; i.v.=intravenous; CNS=central nervous system; GI=gastrointestinal; CHF=congestive heart failure.

APPENDIX III – LUGANO RESPONSE CRITERIA [20]

Response and site	PET/CT-based response	CT-based response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS¶ It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.	Target nodes/nodal masses must regress to ≤1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesions	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None

Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5¶ with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥50 percent decrease in SPD of up to six target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value When no longer visible, 0 x 0 mm For a node >5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by >50 percent in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	<50 percent decrease from baseline in SPD of up to six dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least one of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi >1.5 cm and

		Increase by ≥50 percent from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤2 cm 1.0 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase by >50 percent of the extent of its prior increase beyond baseline (eg, a 15 cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

5PS: 5-point scale; CT: computed tomography; FDG: fluorodeoxyglucose; IHC: immunohistochemistry; LDi: longest transverse diameter of a lesion; MRI: magnetic resonance imaging; PET: positron emission tomography; PPD: cross product of the LDi and perpendicular diameter; SDi: shortest axis perpendicular to the LDi; SPD: sum of the product of the perpendicular diameters for multiple lesions.
* A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow),

FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

¶ PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Appendix IV – CYP3A4 INHIBITORS OR INDUCERS

Strong CYP3A4 Inhibitors	Moderate CYP3A4 Inhibitors	CYP3A4 Inducers
Boceprevir	Aprepitant	Avasimibe
Clarithromycin	Ciprofloxacin	Carbamazepine
Conivaptan	Diltiazem	Modafinil
Itraconazole	Erythromycin	Phenytoin
Ketoconazole	Fluconazole	Rifabutin
Nefazodone	Imatinib	Rifampin
Posaconazole	Verapamil	St. John's Wort
Telithromycin		
Voriconazole		
HIV medications		