CITY OF HOPE MEDICAL CENTER
1500 E. DUARTE ROAD
DUARTE, CA 91010

DEPARTMENT OF HEMATOLOGY AND HEMATOPOIETIC CELL TRANSPLANTATION

TITLE: A Phase 2 Study of Venetoclax and Romidepsin with Safety Lead-in for Treatment of Relapsed/Refractory Mature T-cell Lymphomas

CITY OF HOPE PROTOCOL NUMBER/VERSION: IRB # 18119 **PROTOCOL DATE: 11/03/2020**

Initial Review Submission	(Protocol dated 05/10/2018)	Version: 00
COH Amendment 01	(Protocol dated 07/12/2018)	Version: 01
COH Amendment 02	(Protocol dated 03/08/2019)	Version: 02
COH Amendment 03	(Protocol dated 11/21/2019)	Version: 03
COH Amendment 04	(Protocol dated 11/03/2020)	Packet: 04
COH Amendment 05 at Cont.	(Protocol dated 11/03/2020)(TP)	Packet: 05

DATE(S)/ OF AMENDMENT(S)/REVISION(S):

DISEASE SITE: T-cell Lymphoma

STAGE: Relapsed/Refractory

MODALITY:

TYPE: Phase II

PRINCIPAL INVESTIGATOR: Jasmine Zain, M.D.

CO INVESTIGATOR: Steven Rosen, M.D.

PARTICIPATING CLINICIANS: Elizabeth Budde, M.D., Ph.D.
Alex Herrera, M.D.
Larry Kwak, M.D., Ph.D.
Matthew Mei, M.D.
Liana Nikolaenko, M.D.
Leslie Popplewell, M.D.
Christiane Querfeld, M.D., Ph.D
Tanya Siddiqi, M.D.

BIOSTATISTICIAN Lu Chen, Ph.D.

PARTICIPATING SITES: City of Hope Duarte
University of Nebraska

City of Hope National Medical Center
1500 E. Duarte Road
Duarte, CA 91010

Clinical Trial Protocol

A Phase 2 Study of Venetoclax and Romidepsin with Safety Lead-in for Treatment of Relapsed/Refractory Mature T-cell Lymphomas

Version Date:	11/03/20
Protocol Version:	04
City of Hope #:	18119
Agents:	Venetoclax
IND Number:	140127
Sponsor/ IND Holder:	City of Hope
Funding Support/Industry Partner:	AbbVie
NCT Number:	NCT03534180
Participating Sites:	City of Hope, University of Nebraska

Principal Investigator
Jasmine Zain, MD
City of Hope National Medical Center
Dept. of Hematology
T: (626)-256-4673 ext 82405
Email: jazain@coh.org

Coordinating Center
Data Coordinating Center
City of Hope National Medical Center
T: (626)-218-7904
Email: DCC@coh.org

PROTOCOL TEAM

Biostatistician

Lu Chen, PhD
City of Hope National Medical Center
Dept. Computational and Quantitative Medicine
T: 626-218-6266
Email: lchen@coh.org

Protocol Development Scientist

D. Lynne Smith, PhD
City of Hope National Medical Center
Toni Stephenson Lymphoma Center
T: 626-218-1134
Email: lysmith@coh.org

Co-Investigator

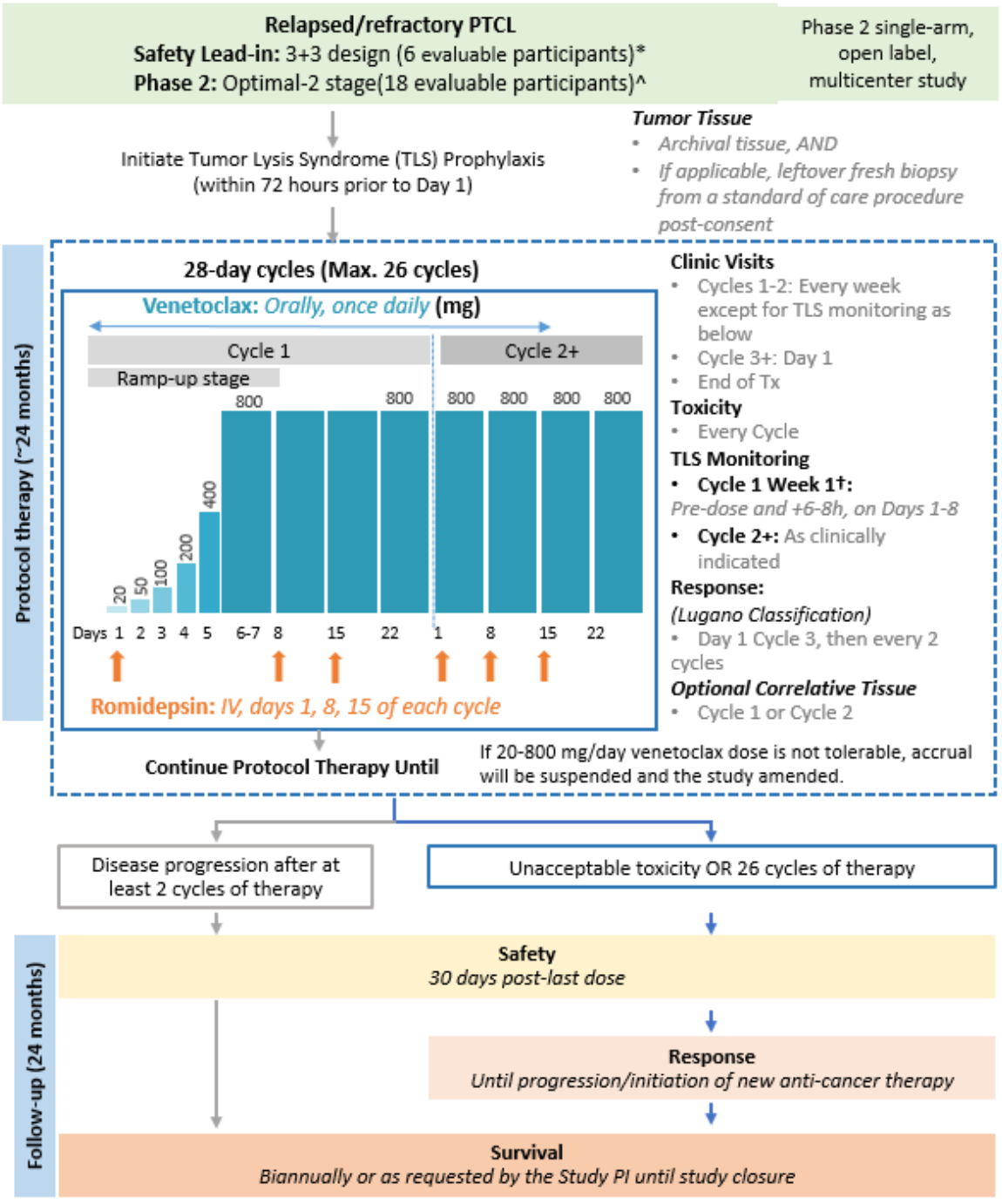
Steven Rosen, M.D.
Director, Comprehensive Cancer Center and Beckman Research Institute
City of Hope National Medical Center
Dept. of Pathology
T: (626)-218-9150
Email: srosen@coh.org

Participating non-COH sites

Site PI

Matthew Lunning
University of Nebraska Medical Center
986840 Nebraska Medical Center
Omaha, NE 68198-6840
T: 402-559-8500
Email: mlunning@unmc.edu

EXPERIMENTAL DESIGN SCHEMA



*Participants treated at the tolerable dose from Safety Lead-in will be included in the Phase 2 portion if they are evaluable for response.
^An early stopping rule for futility is based on the response rate in the first 7 patients treated at the tolerable dose.
†Day 2 dose should not be administered until the 24 hours post-dose lab results are reviewed by the investigator.

PROTOCOL SYNOPSIS

Protocol Title

A Phase 2 Study of Venetoclax and Romidepsin with Safety Lead-in for Treatment of Relapsed/Refractory Mature T-cell Lymphomas

Study Detail

Population/Indication(s):	Peripheral T-cell Lymphoma (PTCL)
Phase:	Safety Lead-in/ Phase 2
Sample Size:	Safety Lead-in: 6 evaluable Phase 2: 18 evaluable (Safety Lead-in patients included)
Estimated Accrual Duration:	24 months
Estimated Study Duration	6 years
Participant Duration:	48 months
Participating Sites:	• City of Hope Duarte, CA • University of Nebraska
Study Agents:	Venetoclax, Romidepsin
Sponsor:	City of Hope
Industry Partner:	AbbVie, Celgene
Industry Partner Protocol #:	11354

Rationale for this Study

Peripheral T cell lymphomas (PTCL) arise from post thymic lymphocytes, representing non-Hodgkin lymphoma (NHL) in the western populations. Based on immunophenotyping, molecular, clinical and pathologic features, there are about 22 different subtypes of PTCL that are broadly classified into nodal, extranodal, leukemic variant and cutaneous T cell lymphomas (CTCL) based on the site of origin of the disease. Approximately 5,000 new cases of PTCL are diagnosed annually in the US. Most PTCL cases have a dismal prognosis with a 5 year survival of less than 30% with the exception of ALK+ ALCL.

The Bcl-2 family proteins are important regulators of the intrinsic apoptosis pathway. Bcl-2 over-expression is a major contributor to the pathogenesis of some types of lymphoid malignancies and has been extensively studied in B cell lymphomas, including CLL and DLBCL. In studies of T-cell lymphoma at City of Hope , Bcl-2 has been found to be expressed in 52-76% of cases of PTCL and 25% of CTCL. So far there is no published data regarding the use of Bcl-2 inhibitors in the treatment of peripheral T cell lymphomas and cutaneous T cell lymphomas.

Venetoclax (also known as ABT-199) is a novel, orally available, small molecule Bcl-2 family protein inhibitor that binds with high affinity to Bcl-2 and with lower affinity to other Bcl-2 family proteins such as Bcl-xL and Bcl-w. There is currently clinical experience with venetoclax in CLL/small lymphocytic leukemia and B-cell NHL. In the Phase 1 study of venetoclax in diffuse large B-cell lymphoma and follicular lymphoma the overall response rate was 15% and 34% with a median duration of response of 3.3 months and 10 months, respectively. In diffuse large B-cell lymphoma, there is an ongoing trial evaluating the combination of venetoclax with rituximab or obinutuzumab plus CHOP (NCT02055820). We hypothesize that interference of BCL2 will lead to antitumor activity in mature T-cell lymphomas.

Experience with the first 6 patients on the venetoclax monotherapy was that only 2 patients were able to complete the unacceptable toxicity evaluation period (2 cycles). PTCL are aggressive lymphomas, and during the first version of the protocol with a weekly ramp up it became evident that most patients progressed before the completion of C1. Three patients were enrolled on the weekly ramp up, two of them had clinical PD/PD after 1 cycle of therapy and terminated treatment without unacceptable toxicities; they had to be replaced. The 3rd patient completed 2 cycles with no unacceptable toxicities. The protoocl was then modified to accelerate the ramp up to 1 week. This is similar to studies of Venetoclax that have been conducted in aggressive heamtological malignancies including AML[1] where a more rapid ramp up was studied and felt to be safe. Once the protocol was modified, 3 additional patients have been accured. Two patients are off-treatment before completing the 1st cycle without unacceptble toxicities and had to be replaced, due to disease progression (n=1) or due to neutropenia (n=1, several grade 2 and 3 neutropenia events but grade 3 only lasted for a day). The 3rd patient completed 2 cycles without unacceptable toxicities. Since it remains a promising strategy to be studied in PTCL, we propose to evaluate venetoclax in

combination with another active agent, the histone deacetylase inhibitor (HDACi) romidepsin. Romidepsin has regulatory approval for use as a single agent in relapsed CTCL and PTCL, and has been shown in vitro and in primary patient samples to act synergistically with venetoclax via effects on Bcl-2 family proteins to increase antineoplastic efficacy. Therefore it is hoped that addition of romidepsin will slow disease progression, allow patients to complete the unacceptable toxicity period in the Safety Lead-in portion of the trial and then enable accrual and evaluation on the phase 2 portion.

Objectives

Primary Objectives

Safety Lead-in:

- To assess the safety and tolerability of the combination of venetoclax with romidepsin, including the dose ramp-up, in adults with relapsed or refractory mature T-cell lymphoma.

Phase 2:

- To estimate the efficacy as measured by the overall response rate [ORR]) of venetoclax with romidepsin in patients with relapsed or refractory mature T-cell lymphoma.

Phase 2 Secondary Objectives

- To evaluate the complete response rate, duration of response, time to response, overall survival and progression free survival associated with venetoclax and romidepsin in relapsed/refractory mature T-cell lymphoma.
- To further characterize the safety and toxicities of venetoclax and romidepsin combination in relapsed/refractory mature T-cell lymphoma.

Exploratory Objective

- BCL2 protein expression in baseline treatment tumor samples and correlation with response
- To determine changes in Bcl-2 gene expression in pre- and post-treatment tumor samples of mature T- cell lymphoma

Study Design

This is an open-label multi-site Phase 2 study with a Safety Lead-in to test the safety and efficacy of venetoclax with romidepsin for the treatment mature T-cell lymphoma.

During the safety-lead in, 6 evaluable participants will be enrolled using a 3+3 design. A Simon 2-stage optimal design will be utilized for the Phase 2 portion of the trial. Participants enrolled during the Safety Lead-in will be included in the Phase 2 portion of the study if they are evaluable for response. In the absence of study holds to accrual for toxicity or for futility, accrual will continue until 18 evaluable participants are treated.

PTCL patients will be treated with up to 26 cycles with venetoclax and romidepsin. Treatment cycles will be 28-days.

Participants will continue with treatment until disease progression, unacceptable toxicity or completion of 26 cycles of protocol therapy, whichever comes first.

Evaluation Criteria and Endpoints

Safety

Toxicity will be recorded using the NCI CTCAE v 5.0. During the first 2 cycles, all grades of toxicity will be collected. After cycle 2, only the highest grade of any toxicity will be collected for each cycle during protocol treatment and for the period of safety follow-up after end of treatment.

Unacceptable toxicity for Safety Lead-in

Unacceptable toxicity will be defined as one of the following AEs that is at least possibly related to either study drug within the **first 2 cycles** of protocol therapy:

- *Hematologic*

- Grade 3 or 4 neutropenia lasting > 7 days (despite the use of growth factor support)
- Grade 4 thrombocytopenia associated with bleeding requiring transfusion
- Grade 4 anemia not associated with lymphoma

- *Non-hematologic*

- Clinical TLS (per Howard criteria)
- Grade 4 metabolic laboratory abnormalities that do not resolve within 3 days to ≤ Grade 2 with supportive measures
- Any other ≥ Grade 3 toxicity that does not resolve to ≤ Grade 1 or baseline within 7 days with the exception of:
- Grade 3 asymptomatic laboratory abnormalities, including lipase or amylase, that are not clinically relevant, not requiring hospitalization or delay of treatment
- Grade 3 nausea, vomiting, or fatigue controlled with supportive measures
- Vitiligo

Response

Lugano Criteria 2014

Clinical Outcome Endpoints

Endpoint	Definition
Overall response rate (ORR)	Proportion of patients achieving CR or PR
Complete response (CR) rate	Proportion of patients achieving CR
Time to response	Date of initiation of protocol treatment to date when criteria for response (PR or CR) is first met
Duration of response (DOR)	Date when criteria for response (CR or PR) is first met until date criteria for PD or relapse is first met
Progression free survival (PFS)	Date of initiation of protocol treatment to date criteria for PD is first met or death as a result of any cause
Overall survival (OS)	Date of initiation of protocol treatment to date of death from any cause

Statistical Considerations

Safety Lead-in

Up to 6 patients may be enrolled under a "3+3" design at the proposed dose (maximum dose of 800 mg/day with a 1-week dose ramp up schedule). Unacceptable toxicities will be evaluated during the first 2 cycles of therapy. This will ensure monitoring of participants during the ramp-up period (Cycle 1, Days 1-8) and while participants are on steady-state dose (Cycle 1 Days 8-28, Cycle 2). Initially up to 3 patients can be enrolled and treated. After 3 patients are treated and evaluated for unacceptable toxicities, if 0/1 out of 3 patients experience unacceptable toxicities during the first 2 cycles, up to 3 additional patients will be enrolled and treated to bring the total number of patients treated to 6. If ≤1/6 patients experience unacceptable toxicities during the first 2 cycles, the proposed treatment dose/schedule will be considered tolerable and be used for the subsequent Phase 2 response evaluation. If ≥2/3 (after the initial 3) or ≥2/6 (after the total 6 in 2 cohorts) patients experience unacceptable toxicities during the first 2 cycles, the accrual will be suspended and the study will be amended.

Phase 2

The primary endpoint for Phase 2 is ORR after 2 cycles of treatment. The response evaluation will be based on a Simon's Two-Stage Optimal design to distinguish a promising 30% response rate (alternative hypothesis) from a disappointing rate (null hypothesis) of 10%, at a one-sided type I error of 10% and a power of 80%. In the first stage, 7 evaluable subjects will be accrued. If there is 0 response among the 7, the study accrual will be suspended. If there are 1 or more responses among the 7, the study will remain open to accrue a total of 18 evaluable patients. Observing 4 or more responses among 18 evaluable patients will

reject the null hypothesis and indicate the response rate being promising in this study setting. Observing 3 or fewer responses among 18 evaluable patients will fail to reject the null hypothesis and will not establish efficacy of the treatment.

Stopping rules for Tumor Lysis Syndrome (TLS)

The study will implement accrual stopping rules for both clinical TLS and laboratory TLS. When a stopping rule is triggered, the study PMT will review and assess the safety of the trial and submit a report to the COH DSMC. The COH DSMC will review for approval any decision to continue or permanently suspend accrual to the trial.

- Clinical TLS Stopping Rule
  - Study accrual will be suspended when the first incidence of clinical TLS is reported.
- Laboratory TLS Stopping Rule

The incidence of laboratory TLS will be monitored with 12% being the benchmark based on IB. Operationally, the study accrual will be suspended if:

- 1 patient experiences laboratory TLS when there have been ≤5 patients treated
- 2 patients experience laboratory TLS when there have been ≤14 patients treated
- 3 patients experience laboratory TLS regardless of the number of patients treated

The rule is derived based on a <50% probability of the rule being triggered when the true laboratory TLS incidence is ≤12%.

Abbreviated Eligibility Criteria

Main Inclusion Criteria

- Adult relapsed/refractory PTCL (WHO criteria 2016) excluding CTCL. Transformed mycosis fungoides is allowed.
- ECOG ≤ 2
- Failed at least 2 prior systemic therapie
- Measurable disease (CT/MRI/PET-CT). At least one measurable lesion (Lugano 2014)
- ANC ≥ 1,000/mm^3 * (unless documented bone marrow involvement by lymphoma)
- Platelets ≥ 30,000/mm^3 * (unless documented bone marrow involvement by lymphoma)
- Total bilirubin ≤ 1.5 x ULN (except Gilbert's Syndrome or documented hepatic involvement by lymphoma)
- ALT and AST ≤ 3 x ULN (≤ 5 x ULN if hepatic involvement by lymphoma)
- Creatinine clearance of ≥ 50 mL/min

* Platelet transfusions/ growth factor not permitted within 7 days of assessment unless cytopenia is secondary to disease involvement

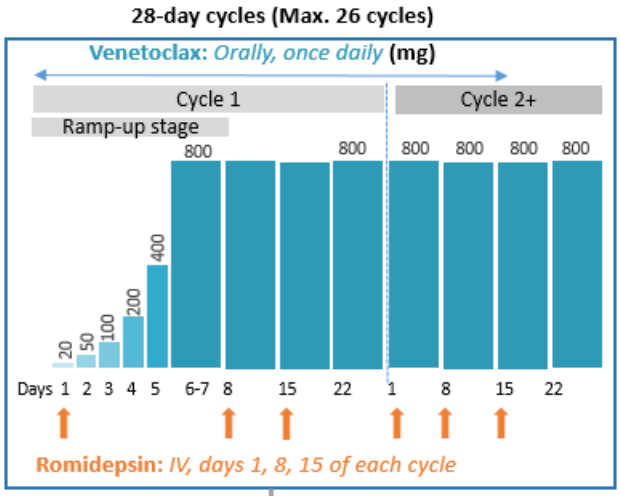
Main Exclusion Criteria

- Bcl2 inhibitors
- Any systemic therapy, including monoclonal antibody within 28 days or 5 half-lives (whichever is shorter) of initiating protocol therapy
- Radiation and/or surgery (except lymph node or other diagnostic biopsies) within 14 days prior to Day 1 of protocol therapy
- Strong or moderate CYP3A inhibitors within 7 days prior to Day 1 of protocol therapy
- Strong or moderate CYP3A inducers within 7 days prior to Day 1 of protocol therapy
- P-gp inhibitors within 7 days prior to Day 1 of protocol therapy.
- Narrow therapeutic index P-gp substrates within 7 days prior to Day 1 of protocol therapy.
- Short course systemic corticosteroids for disease control, improvement of performance status or non-cancer indication within 7 days prior to Day 1 of protocol therapy. Stable ongoing corticosteroid use (i.e. at least 30 days) up to an equivalent dose of 20 mg of prednisone is permissible.

- Patients with known cardiac abnormalities such as:
  - Congenital long QT syndrome
  - QTc (Corrected QT interval on ECG) interval >480 milliseconds
  - Any cardiac arrhythmia requiring anti-arrhythmic medication.
- Patients with a history of sustained ventricular tachycardia (VT), ventricular fibrillation (VF), Torsade de Pointes, or cardiac arrest, unless currently addressed with an automatic implantable cardioverter defibrillator (AICD).

Investigational Product Dosage and Administration

- All participants (safety lead-in and Phase 2) will ramp-up daily over the first week of Cycle 1 to the maximum venetoclax dose. From Cycle 1 Days 8-28 and Cycle 2+ Days 1-28, participants will continue at the maximum dose.
- Patients will be monitored for TLS on an outpatient basis for the first 8 days of treatment.



Clinical Observations and Tests to be Performed

- Medical history and physical exam
- Safety assessments (CBCs with differential, comprehensive chemistry panel, EKG and coagulation)
- Post-dose TLS monitoring during Cycle 1
- CT/ MRI/ PET-CT scans
- Correlative tumor tissue

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

ABBREVIATIONS

Abbreviation	Meaning
AE	Adverse Event
AESI	Adverse Event of Special Interest
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CFR	Code of Federal Regulations
COH	City of Hope
CR	Complete Response
CRC	Clinical Research Coordinator
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	Cutaneous T-Cell Lymphoma
CTEP	Cancer Therapy Evaluation Program
Diff	Differential
DSMC	Data & Safety Monitoring Committee
ECP	Extracorporeal Photopheresis
FDA	Food and Drug Administration
FDG	[^{18}F]fluorodeoxyglucose
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HDAC	Histone deacetylase
IB	Investigator's Brochure
IDS	Investigational Drug Services
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
OIDRA	Office of IND Development and Regulatory Affairs
ORR	Overall Response Rate
PD	Progressive Disease
PET	Positron Emission Tomography
PI	Principal Investigator
PLT	Platelets
PMT	Protocol Management Team
PR	Partial Response
PT	Prothrombin
PTCL	Peripheral T-cell Lymphoma
SAE	Serious Adverse Event
SD	Stable disease
SOC	Standard of Care
SOP	Standard Operating Procedure
TNMB	Tumor, Node, Metastasis, Blood
Tx	Protocol Therapy
TBSA	Total Body Surface Area
TLS	Tumor Lysis Syndrome
ULN	Upper Limit of Normal

1.0 OBJECTIVES

1.1 Primary Objectives

Safety Lead-in:

- To assess the safety and tolerability of the combination of venetoclax with romidepsin, including the dose ramp-up, in adults with relapsed or refractory mature T-cell lymphoma.

Phase 2:

- To estimate efficacy (as measured by the overall response rate [ORR]) of venetoclax with romidepsin in patients with relapsed or refractory mature T-cell lymphoma.

1.2 Phase 2 Secondary Objectives

- To evaluate the complete response rate, duration of response, time to response, overall survival and progression free survival associated with venetoclax and romidepsin in relapsed/refractory mature T-cell lymphoma.
- To further characterize the safety and toxicities of venetoclax and romidepsin combination in relapsed/refractory mature T-cell lymphoma.

1.3 Exploratory Objectives

- To determine BCL2 protein expression in baseline treatment tumor samples and correlate with response
- To determine changes in Bcl-2 gene expression in pre- and post-treatment tumor samples of mature T- cell lymphoma

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

2.1.1 Burden of disease

Peripheral T cell lymphomas (PTCL) arise from post thymic lymphocytes, representing non-Hodgkin lymphoma (NHL) in the western populations. Approximately 5,000 new cases of PTCL are diagnosed annually in the US [2]. Based on immunophenotyping, molecular, clinical and pathologic features, there are about 22 different subtypes of PTCL that are broadly classified into nodal, extranodal, leukemic variant and cutaneous T cell lymphomas (CTCL) based on the site of origin of the disease [3, 4]. In North America, the most common subtypes are PTCL-not otherwise specified, anaplastic large cell lymphoma (ALCL) and angioimmunoblastic T cell lymphoma (AITL) [5] .

Most PTCL cases have a dismal prognosis with a 5 year survival of less than 30% with the exception of ALK+ ALCL. Anthracycline based combination therapies are the most common initial treatment used for PTCL but primary response rate is less than 60% and most patients relapse after initial therapy [5]. There are now 4 FDA approved agents (Table 2.1.1) for the treatment of PTCL in the relapsed setting in the US but none of them are curative. Other than ALCL most patients with PTCL are in dire need for new and improved therapeutic options. Currently there are many agents that are being evaluated for relapsed and refractory PTCL.

Table 2.1.1. Current Therapies for PTCL

Agent	% Overall Response Rate/ Complete Response	Duration of Response	FDA approved in the US	Comments
Pralatrexate [6]	29/11	10.1 months	Yes	
Romidepsin [7]	25/15	13.4 months	Yes	Also approved for relapsed CTCL
Belinostat [8]	25.8/10.8	13.6 months	Yes	
Brentuximab vedotin in ALCL[9]	86/57	12.6 months	Yes for ALCL	
Chidamide[10]	28/14	PFS 2.1 months	No	Approved in China

2.2 BCL2 and Mature T-Cell Lymphomas

The Bcl-2 family proteins are important regulators of the intrinsic apoptosis pathway. The Bcl-2 oncogene was first identified in follicular lymphoma where the t(14;18) chromosomal translocation results in significant over-expression of the protein in B-cells. The Bcl-2 family of genes encodes a family of closely related proteins that possess either pro-apoptotic or anti-apoptotic activity and share up to four Bcl-2 Homology (BH) domains [11-14]. Bcl-2 over-expression is a major contributor to the pathogenesis of some types of lymphoid malignancies and has been extensively studied in B cell lymphomas, including CLL and DLBCL. Bcl-2 is also over-expressed in acute and chronic leukemias. Chronic lymphocytic leukemia (CLL) is a genetic disease where the microRNAs miR15a and miR16-1 that negatively regulate the transcription of Bcl-2 are deleted or down-regulated, resulting in uncontrolled expression of Bcl-2 [14].

Bcl-2 over-expression has been found to be associated with progression of various B cell lymphoid malignancies and is targetable with selective anti- BCL2 therapy including Venetoclax resulting in meaningful clinical responses in CLL and other B cell malignancies [15]. Similar studies have demonstrated over-expression of Bcl-2 in cases of CTCL [16]. Using immunohistochemical methods on tissue samples

and a 10% cut off, Bcl-2 was detected in 46% of cases in PTCL along with other members of the Bcl-2 family [17]. The expression pattern of the BCL family of proteins was variable, with a distinct pattern seen in only Alk +ALCL and EATCL that were Bcl-2 negative and MCL-1 positive. Further studies conducted using a TUNEL assay and proliferation index revealed that the Bcl-2 family protein levels correlated with apoptotic rates and proliferation index. It was hypothesized that over-expression of these proteins may explain the poor response of the many types of PTCL to chemotherapy. A later study attempted to correlate the expression of Bcl-2, Bax and p53 with progression of PTCL using paraffin-embedded specimens from patients [18]. These included CTCL. In this study, Bcl-2 over-expression was strongly associated with advanced stage and a high IPI index. Within the groups that over-expressed BcL2, p53 over-expression was associated with poor survival. The 3 year OS was 82% for Bcl-2+/p53- cases and only 32% for Bcl-2+/p53+ cases, indicating that Bcl-2 over expression seemed to correlate with progression of PTCL through a p53-dependent pathway3. In studies of T-cell lymphoma at City of Hope , Bcl-2 has been found to be expressed in 52-76% of cases of PTCL and 25% of CTCL [19, 20] (unpublished data from Joo Song, City of Hope). Hence, there is strong rationale to consider that interference of the Bcl-2 pathway in PTCL and CTCL may be a favorable anti lymphoma target. So far there is no published data regarding the use of Bcl-2 inhibitors in the treatment of peripheral T cell lymphomas and cutaneous T cell lymphomas. We hypothesize that interference of BCL2 will lead to antitumor activity in mature T-cell lymphomas.

2.3 Venetoclax

Venetoclax (also known as ABT-199) is a novel, orally available, small molecule Bcl-2 family protein inhibitor that binds with high affinity (Ki < 0.010 nM) to Bcl-2 and with lower affinity to other Bcl-2 family proteins such as Bcl-xL and Bcl-w (> 4,000-fold and > 2,000- to > 20,000-fold lower affinity than to Bcl-2, respectively) [21]. Selective inhibition by venetoclax disrupts Bcl-2 signaling and rapidly induces multiple hallmarks of apoptotic cell death in Bcl-2-dependent human tumor cell lines [22]. Importantly, venetoclax inhibition of Bcl-2 is independent of p53 activity.

Venetoclax has been FDA approved for patients with chronic lymphocytic leukemia (CLL) with 17p deletion, as detected by an FDA approved test, who have received at least one prior therapy.

2.3.1 Pre-clinical experience

Previous agents targeting Bcl-2 were non-specific and had inhibitory effects on BCL-X_L as well as BCL-w that resulted in significant clinical thrombocytopenia due to the role of BCL-X_L in platelet survival [23]. This led to the development of Venetoclax or ABT-199 which has specific inhibition of Bcl-2 with platelet sparing effects with sub-nanomolar affinity to Bcl-2 (K*i* < 0.010nM) and anti- tumor activity a gains NHL, CLL and acute leukemia in vitro [21, 24, 25]. Multiple experiments demonstrate that venetoclax acts to induce apoptosis. As expected, venetoclax was ineffective against murine embryonic fibroblasts (MEFs) lacking Bax and Bak, essential mediators of the intrinsic apoptosis program. However, in the Bcl-2-dependent ALL cell line RS 4;11, venetoclax rapidly induced key hallmarks of apoptosis, including cytochrome *c* release, caspase activation, and the externalization of phosphatidylserine.

Venetoclax exhibited potent activity against patient-derived tumor cells treated ex vivo killing CLL cells with an average EC50 of 6.0 nM (N = 35) and AML cells with a median IC50 of 10 to 20 nM (N = 57). Venetoclax was equally potent against the subset of CLL samples bearing the high-risk 17p del, with an average EC50 of 0.008 μM (N = 5), indicating that venetoclax may have a significant utility in treating patients with this high-risk lesion. Venetoclax also demonstrated cell killing activity against lymphoma and leukemia cell lines including B-cell FLs, MCLs, DLBCLs, AMLs, ALLs, and MMs. Venetoclax was especially potent against cell lines expressing high levels of Bcl-2. The majority of sensitive FL and DLBCL cell lines

were positive for the t(14;18) chromosome translocation that drives high level expression of Bcl-2 from the immunoglobulin heavy chain enhancer. Bcl-2 levels and the t(14;18) chromosome translocation thus represent potential predictive biomarkers for sensitivity to venetoclax. Venetoclax also demonstrated potent killing of MM cell lines and primary tumor samples bearing the t(11;14) translocation[26]. These cells tended to express high levels of Bcl-2 relative to Mcl-1. Mouse xenograft studies showed activity against aggressive Myc positive lymphoma as well as acute leukemia [27, 28].

2.3.2 Clinical experience

As of version 11 of the venetoclax Investigator's Brochure [29] a total of 2939 subjects received at least 1 dose of venetoclax in AbbVie studies and had data available as of 28 November 2018. Among these 2939 subjects, 1313 subjects had CLL/small lymphocytic leukemia (SLL), 570 subjects had non-Hodgkin's lymphoma (NHL), 218 subjects had multiple myeloma (MM), 361 had acute myeloid leukemia (AML), 59 subjects had myelodysplastic syndrome (MDS), 20 subjects had acute lymphocytic leukemia (ALL) and 219 were healthy volunteers. A total of 1137 received the drug as monotherapy, and 1406 received the drug in combination with other therapies. Doses administered in venetoclax clinical studies have ranged from 20 mg to 1200 mg.

The most common adverse events (incidence > 20%) reported for all subjects in monotherapy studies were nausea, diarrhea, neutropenia, anemia, thrombocytopenia and lymphopenia. Infections, including serious infections, although also common with the underlying malignancies, have been reported with venetoclax treatment and their incidence is higher with combination treatments. The most common adverse events that were grade 3 and above were neutropenia (31.0%) and anemia (13.8%). The most common serious adverse events were febrile neutropenia and malignant neoplasm progression (5.7% each). The most common treatment emergent adverse event that led to death was malignant neoplasm progression (2.1%).

Tumor lysis syndrome (TLS) is an important risk of Bcl-2 inhibitors, and is highest in CLL and MCL. As a result of on-target effects, the potential for TLS with venetoclax was identified early in the program when the initial 3 subjects with CLL/SLL received starting doses of 100 mg or 200 mg and experienced TLS, which was reported as an adverse event for each. Subsequently, 2 fatal events in the setting of TLS and another event of clinical TLS in subjects with CLL/SLL occurred in December 2012. After comprehensive review of all safety data available from studies with venetoclax, starting from May 2013, a revised dosing regimen with a dose-titration phase of 4 to 5 weeks and enhanced TLS prophylaxis and monitoring measures were implemented in all CLL studies. In May 2014, a subsequent analysis of data from subjects with CLL/SLL following the implementation of prophylaxis measures, who completed monotherapy, indicated a marked reduction in severity and frequency of TLS when compared to the previous analysis. None of the subjects experienced any serious (including fatal) or non-serious events of clinical TLS or laboratory TLS or had study treatment discontinued because of TLS. Overall, the clinical data strongly support that the risk of TLS with venetoclax in CLL/SLL subjects is highest when initiating venetoclax dosing (5 week dose titration phase), as well as being greater in subjects with a large tumor burden. Currently, since May 2014, a more personalized approach for prophylaxis and monitoring measures, where subjects with low tumor burden could receive venetoclax on an out-patient basis, has been implemented with no clinical TLS [30].

More specifically, in the Phase 1 study of venetoclax in CLL, the recommended Phase 2 dose (R2PD) of venetoclax was 400 mg per day. Given the risk of tumor lysis, dosing was ramped up weekly for 5 weeks (20 mg, 50 mg, 100 mg, 200 mg, 400 mg). Among the 116 patients who received venetoclax on this study, the overall response rate was 79%, and complete remissions occurred in 20% of patients. The 15 month estimate for progression-free survival for those dosed at 400 mg was 69% [31]. Clinical tumor lysis

syndrome did not occur in any of the 60 patients treated in the expansion cohort of this study but did occur in 3 of the 56 patients treated in the Phase 1 portion of the study. There was one death due to tumor lysis in the dose escalation portion of the study.

In the Phase 1 study of venetoclax in diffuse large B-cell lymphoma and follicular lymphoma, the RP2D dose was 1200 mg. In this study, there were two events of laboratory tumor lysis syndrome, but no patients had clinical tumor lysis. Therefore, in the expansion cohort portion for this study, dosing was ramped up weekly over 3 weeks (400 mg, 800 mg, 1200 mg). Of the 41 patients with diffuse large B-cell lymphoma, the overall response rate was 15% with a median duration of response of 3.3 months. Among the 29 patients with follicular lymphoma, the overall response rate was 34%, and the median duration of response was 10 months. The most common adverse events were diarrhea (44%), fatigue (44%), nausea (33%), and vomiting (23%). Serious adverse events included hyponatremia (4%), dehydration (3%), diarrhea (3%), and febrile neutropenia (3%) [15, 32]. In diffuse large B-cell lymphoma, there is an ongoing trial evaluating the combination of venetoclax with rituximab or obinutuzumab plus CHOP (NCT02055820).

2.4 HDAC inhibition in mature T cell lymphomas

Histone deacetylases (HDAC) are enzymes that catalyze the removal or acetyl groups from the lysine residues of various proteins, including histones and transcription factors. The transcription of genes is partially regulated by acetylation of nucleosomal histones. The core nucleosomal histones are the most widely studied of the proteins that become acetylated following inhibition of HDAC activity.[33] In some cancer cells there is an overexpression of HDACs, or an aberrant recruitment of HDACs to oncogenic transcription factors causing hypoacetylation of core nucleosomal histones. Hypoacetylation of histone is associated with a condensed chromatin structure and repression of gene transcription.

Inhibition of HDAC activity allows for the accumulation of acetyl groups on the histone lysine residues resulting in an open chromatin structure and transcription activation. HDAC inhibitors can induce tumor cell growth arrest, differentiation, or apoptosis in vitro and inhibit tumor growth in animals.[34, 35] HDAC inhibitors as a class appear to have significant activity in T-cell lymphomas for reasons that are not clearly understood. HDAC inhibitors work through several different mechanisms including alteration in the expression of genes that regulate cell cycle, acetylation of non-histone proteins that may impair their function to influence cell growth and survival, and by direct activation of apoptotic pathways.[36] Attempts at understanding the mechanisms of HDAC inhibitors have involved gene expression profiling on paired tissue samples both pre- and post-treatment that have shown only 5-10% of the genome can be affected. As many genes are unregulated as are down regulated following treatment with most HDAC inhibitors. The genes that were consistently affected included genes that alter cell cycle (CCND1, IGF1), apoptosis (septin10, TEF, SORBBS2), angiogenesis (GUCY1A1, ANGPT1), and immune modulation (LAIR1). [37] QT-PCR was used to confirm that the findings on the gene array analysis were indeed biologically accurate, with a strong correlation between gene array and the PCR data. Tumor tissue specimens treated with various HDAC inhibitors have shown an increase in histone acetylation, decreased vascularity, and translocation of nuclear proteins like STAT-s which is associated with inactivation. [38]

2.5 Romidepsin

Romidepsin (also known as Istodax®, FK228) is a HDAC inhibitor commercially available from Celgene. It is a unique HDAC inhibitor as it is a prodrug. Upon entering cells romidepsin is reduced to an active compound, capable of preferentially interacting with zinc in the active site of HDAC1, HDAC2 and HDAC3 (Class I). [39] Romidepsin currently has FDA approval for patients with cutaneous T-cell lymphomas (CTCL)

that have received at least one prior therapy (as well as for relapsed/refractory PTCL). It is currently being assessed for the treatment of a variety of malignant and inflammatory diseases.

2.5.1 Clinical Experience

The clinical experience with romidepsin from multiple clinical trials has shown a well-tolerated toxicity profile. Phase 1 trials have provided the safety profile and dosing schedule. [40, 41] Romidepsin doses ranging from 1.0 to 24.9 mg/m^2 administered intravenously over 4 hours have been investigated in treatment of advanced cancers.[42] A more standardized regimen has been defined as 14 mg/m^2 intravenously over a 4 hour period on days 1, 8, and 15 of a 28-day cycle. [7] The major hematologic toxicity includes anemia, leukopenia, lymphopenia, and thrombocytopenia. Other common adverse events include gastrointestinal symptoms, constitutional symptoms, and dysgeusia. In addition, it was found that romidepsin may cause QTc prolongation/ECG changes, however, this may be the result of a drug:drug interaction with select antiemetics. Based on on-clinical findings, male and female fertility may be compromised by treatment with romidepsin.

The use of romidepsin is best established in CTCL. A phase 2 trial with romidepsin in relapsed CTCL showed single agent activity in patients that previously had been heavily pretreated with a median of 4 prior therapies. [43] A total of 71 patients were treated with an overall response rate (ORR) of 34% including 4 patients with complete response. The median duration of response (DOR) was 13.7 months. This trial and a registration directed trial by Gloucester Pharmaceuticals, previous owners of romidepsin, led to full regulatory approval by the FDA for the treatment of relapsed CTCL. A phase 2 trial of romidepsin in patients with heavily treated relapsed/refractory PTCL demonstrated an ORR of 25% with median DOR lasting a somewhat remarkable 17 months. [7] The treatment regimen was romidepsin administered as a 4-hour infusion on days 1, 8, and 15 of a 28-day cycle with a dose of 14 mg/m^2. Based on this trial, romidepsin gained FDA approval in 2011 for used in relapsed/refractory PTCL.

2.6 Combination of Bcl-2 inhibitors and HDACi

There is a growing body of work suggesting that Bcl-2 inhibition and HDAC inhibition are synergistic and therefore hold promise as combination therapy in lymphoma, where Bcl-2 prosurvival proteins are commonly overexpressed. In the Eμ-myc lymphoma cell model the HDACi vorinostat and romidepsin both mediated apoptosis via the intrinsic apoptotic pathway, mediated by the BH3-only proteins Bim and Bid.[44] These proteins show tumor-suppressor function in certain contexts and inactivating mutations or loss of expression in human cancer samples have been reported. Transcriptional activation of the proapoptotic Bcl-2 family BH3-only genes *BIM*, *BMF*, and *NOXA* is the apparent mechanism of HDACi-induced apoptosis. Selective knockdown of the three corresponding proteins rescued cells from vorinostat-induced apoptosis. Combined inhibition of BcL2 members and HDACis has shown synergistic effects in CTCL and other malignancies, including mantle cell lymphoma and glioblastoma: vorinostat enhanced the activity of the BH3-mimetic ABT-263 (navitoclax) in MCL cells, leading to synergistic apoptosis induction.[45] Notably, overexpression of the prosurvival protein Bcl-2, which inhibits activation of the intrinsic apoptotic pathway, completely suppressed the apoptotic and therapeutic activities of vorinostat. [46, 47] Another mechanism of pan HDACis panobinostat and vorinostat to rapidly inhibit HDAC7 and induce the expression and translocation of the proapoptotic nuclear orphan receptor Nur 77 to the mitochondria where it binds to Bcl-2 and promotes apoptosis. Cotreatment with the Bcl-2/ Bcl xL antagonist ABT-737 decreased resistance and was synergistic with panobinostat in inducing apoptosis.[47] Higher sensitivity to venetoclax that correlates with higher levels of BcL-2 expression and mRNA has been seen in CTCL patient samples in vitro,[48] similar to observations in CLL. In addition, when these patient

samples were exposed to a combination of venetoclax with either vorinostat or romidepsin a synergistic cell death was seen that involved caspase 3/7 activation.

2.7 Overview and Rationale of Study Design

This is an open-label multi-site Phase 2 study with a Safety Lead-in to test the safety and efficacy of venetoclax with romidepsin for the treatment of relapsed/refractory mature T-cell lymphoma.

Eligibility

Eligible patients will be adults with histologically confirmed peripheral T-cell lymphoma as defined per the WHO criteria 2016 [49]. Eligible patients must be naïve to prior Bcl-2 therapies and must have failed at least one prior systemic therapy.

Treatment program

Participants will receive venetoclax once daily orally, and romidepsin once a week for the first three weeks of each 28-days treatment cycle. Prior data suggest that B-cell NHL patients can tolerate up to 1200 mg/day venetoclax [15, 32]. However, due to biologic differences in T cell and B cell lymphomas and aggressive nature of T-cell disease, a maximum dose of 800 mg/day will be tested in this study. Romidepsin dosing will be according to the label.

On-target effect of either romidepsin or venetoclax could lead to rapid cell death and pose a risk of TLS. Based on prior clinical experience with the agent, a ramp up dosing schedule will be implemented during Cycle 1. The venetoclax dose will be ramped up over 7 days, in line with current practice for AML [30].

Once the safety and tolerability of the proposed dose combination and schedule is established after the safety lead-in, additional patients will be enrolled and treated for the Phase 2 response evaluation using the same dose combination and schedule (which includes the ramp-up in Cycle 1).

Participants will continue with treatment until disease progression, unacceptable toxicity or completion of 26 cycles (~24 months) of therapy, whichever comes first. If a patient is still benefiting from treatment at the completion of 26 cycles of therapy, we will consider amending the study to extend the duration of therapy for that particular patient.

Dose and Schedule:

During Cycle 1, participants will take venetoclax 20 mg/day on Day 1, 50 mg/day on Day 2, 100 mg/day on Day 3, 200 mg/day on Day 4, 400 mg/day on Day 5, and 800 mg/day on Days 6-7 in the ramp-up phase and 800 mg/day on Days 8-28. Romidepsin 14 mg/m^2 will be administered on Days 1, 8, and 15 of the 28-day cycle.

During Cycle 2+, participants will take 800 mg/day venetoclax. Romidepsin 14 mg/m^2 will be administered on Days 1, 8, and 15 of each 28-day cycle.

Safety Lead-in

During the safety-lead in, up to 6 evaluable participants will be enrolled using a 3+3 design.

In the event the proposed combination of venetoclax (20-800 mg/day) with romidepsin is not tolerable (2+ patients with unacceptable toxicity in ≤ 6 evaluable participants), the accrual will be suspended and the study will be amended.

Unacceptable toxicities will be evaluated during the first 2 cycles of therapy. This will ensure monitoring of participants during the ramp-up period (Cycle 1) and while participants are on steady-state dose (Cycle

2). Unacceptable toxicities will focus on commonly observed toxicities for venetoclax such as neutropenia, thrombocytopenia, blood chemistries and tumor lysis syndrome.

Phase 2

Once the Safety Lead-in is completed and the proposed dose combination and schedule (including ramp-up) is confirmed safe and tolerable, additional patients will be enrolled and treated for the Phase 2 response evaluation. The Phase 2 portion will utilize a Simon's two-stage optimal design. Patients enrolled during the Safety Lead-in will be included in the Phase 2 portion of the study if they are evaluable for response. In the absence of study holds to accrual for toxicity or for futility, accrual will continue until 18 evaluable participants are treated at the tolerated dose and schedule.

An early stopping rule for futility will be based on the response rate in the first 7 patients. Accrual may need to be temporarily held at 7 patients pending response evaluation.

TLS Prophylaxis and Monitoring

To mitigate the risk for TLS, all participants will initiate TLS prophylaxis and undergo pre-dose and real-time post-dose monitoring during the ramp-up stage (see Section 5.10.2). Patients will be monitored for TLS on an outpatient basis for the first 8 days of treatment.

Response

PTCL specific response assessment criteria per Lugano Classification will be used for this study [50]; these criteria incorporate PET for response assessment. PTCL is considered [^{18}F] fluorodeoxyglucose (FDG) avid [51, 52] and PET-CT is recommended for staging of routinely FDG-avid histologies [50]. CT is preferred for low or variable FDG avidity.

Radiographic imaging will occur every 2 cycles. Ending treatment due to disease progression will occur after completing at least two cycles of treatment. This is to ensure that participants have had enough time to be exposed to the steady-state venetoclax dose.

Correlative studies

Baseline and optional tumor tissue samples during Cycle 1 or 2 treatment will be collected. Correlative studies will characterize the gene expression profile in patient samples and explore relevance to the Bcl-2 pathway. Additionally, these studies will explore response to therapy and toxicity based on the patient's BCL-2 status.

3.0 ELIGIBILITY CRITERIA

Patient MRN	Patient Initials (F, M, L):

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

3.1 Inclusion Criteria

Informed Consent and Willingness to Participate

__1. Documented informed consent of the participant and/or the legally authorized representative

__2. Be willing to provide tissue (See Section 9.1)

Age and Performance Criteria

__3. Age ≥ 18 years

__4. ECOG ≤ 2

Nature of Illness and Treatment History

__5. Resolution of all acute toxic effects of prior therapy or surgical procedures to CTCAE Grade ≤ 1 (except alopecia).

__6. Failed at least 2 prior systemic therapies. For ALCL histologies this must include failure or intolerable side effects of brentuximab vedotin

__7. Histologically confirmed PTCL as defined by the WHO criteria 2016, excluding CTCL. Transformed mycosis fungoides is allowed.

__8. Measurable disease defined as:

- CT/MRI/ or PET scan, with at least one nodal site of disease which is 1.5 cm in longest dimension, and/or spleen > 13 cm in vertical length, and/or diffuse enlargement of liver with or without focal nodules (Lugano 2014). Extra nodal sites with biopsy proven abnormal lesions are allowed including skin.
- Patients with only bone marrow involvement will be acceptable.

__9. Prior stem cell transplant allowed

- If allogeneic HCT must have recovered from acute toxicity
- Cannot have active acute or chronic GvHD and must be off immunosuppressive therapies

Clinical Laboratory Criteria (To be performed within 14 days prior to Day 1 of protocol therapy)

__10. ANC ≥ 1,000/mm^3 **NOTE:** Growth factor is not permitted within 7 days of ANC assessment unless cytopenia is secondary to disease involvement. **Exception:** Unless documented bone marrow involvement by lymphoma	ANC:	Date:
__11. Platelets ≥ 30,000/mm^3 **NOTE:** Platelet transfusions are not permitted within 7 days of platelet assessment unless cytopenia is secondary to disease involvement. **Exception:** Unless documented bone marrow involvement by lymphoma	Plts:	Date:

__12. Total bilirubin ≤ 1.5 x ULN (≤ 3 x ULN for Gilbert's Syndrome or documented hepatic involvement by lymphoma)	ULN: Bil:	Date:
__13. AST ≤ 3 x ULN If hepatic involvement by lymphoma: AST ≤ 5 x ULN	ULN: AST:	Date:
__14. ALT ≤ 3 x ULN If hepatic involvement by lymphoma: ALT ≤ 5 x ULN	ULN: ALT:	Date:
__15. Creatinine clearance of ≥ 50 mL/min per 24 hour urine or the Cockcroft-Gault formula $\text{CrCl (mL/min)} = \frac{(140\text{-age}) \times \text{actual body weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$ (x 0.85 for females) **Or** $\text{CrCl (mL/min)} = \frac{(140\text{-age}) \times \text{actual body weight (kg)}}{0.8136 \times \text{serum creatinine (umol/L)}}$ (x 0.85 for females)	Serum Cr: Cr Clearance:	Date:
__16. Women of childbearing potential (WOCBP): negative urine or serum pregnancy test If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required	Urine: Serum:	Date:

Contraception

__17. Agreement by WOCBP **and** males of childbearing potential* to use an adequate method of birth control (hormonal contraception is inadequate) or abstain from heterosexual activity for the course of the study through 90 days after the last dose of protocol therapy.

*Childbearing potential defined as not being surgically sterilized (men and women) or have not been free from menses for > 1 year (women only).

3.2 Exclusion Criteria

Previous therapies

__1. Bcl2 inhibitors

__2. Any systemic anti-lymphoma therapy, including monoclonal antibody within 28 days or 5 half-lives (whichever is shorter) of initiating protocol therapy

__3. Radiation and/or surgery (except lymph node or other diagnostic biopsies) within 14 days prior to Day 1 of protocol therapy.

__4. Short course systemic corticosteroids for disease control, improvement of performance status or non-cancer indication within 7 days prior to Day 1 of protocol therapy. Stable ongoing corticosteroid use (i.e. at least 30 days) up to an equivalent dose of 20 mg of prednisone is permissible.

__5. Strong or moderate CYP3A inhibitors within 7 days prior to Day 1 of protocol therapy.

__6. Strong or moderate CYP3A inducers within 7 days prior to Day 1 of protocol therapy.

__7. P-gp inhibitors within 7 days prior to Day 1 of protocol therapy.

__8. Narrow therapeutic index P-gp substrates within 7 days prior to Day 1 of protocol therapy.

__9. Any other investigational agent or used an investigational device within 21 days prior to Day 1 of protocol therapy.

Other illnesses or conditions

__10. Prior surgery or gastrointestinal dysfunction that may affect drug absorption (e.g., gastric bypass surgery, gastrectomy)

__11. Active human immunodeficiency virus (HIV) or hepatitis C virus (HCV) or hepatitis B virus (HBV). Subjects who have an undetectable HIV viral load with CD4 > 200 and are on HAART medication are allowed. Subjects who are positive for hepatitis B core antibody or hepatitis B surface antigen must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded. Patients who have had Hepatitis C but have finished treatment and are PCR negative will be allowed. (Testing to be done only in patients suspected of having infections or exposures).

__12. Concurrent malignancy requiring active therapy.

__13. Known central nervous system or meningeal involvement (in the absence of symptoms, investigation into central nervous system involvement is not required).

__14. Congestive heart failure (CHF) that meets New York Heart Association (NYHA) Class II to IV definitions (See Appendix E).

__15. Patients with known cardiac abnormalities such as:

- Congenital long QT syndrome
- QTc (Corrected QT interval on ECG) interval >480 milliseconds
- Any cardiac arrhythmia requiring anti-arrhythmic medication.

__16. Patients with a history of sustained ventricular tachycardia (VT), ventricular fibrillation (VF), Torsade de Pointes, or cardiac arrest, unless currently addressed with an automatic implantable cardioverter defibrillator (AICD).

__17. Active infection requiring systemic therapy.

__18. Unable to swallow capsules, has a partial or small bowel obstruction, or has a gastrointestinal condition resulting in a malabsorptive syndrome (e.g. small bowel resection with malabsorption).

__19. WOCBP: Pregnant or breastfeeding.

__20. Any other condition that would, in the Investigator's judgment, contraindicate the patient's participation in the clinical study due to safety concerns with clinical study procedures.

Noncompliance

__21. Prospective participants who, in the opinion of the investigator, may not be able to comply with all study procedures (including compliance issues related to feasibility/logistics).

Eligibility Confirmed* by (Choose as applicable):	Print Name	Signature	Date
☐ Site PI			
☐ Authorized study MD			
☐ Study Nurse			
☐ Study CRA/ CRC			
☐ Other:_____			
*Eligibility should be confirmed per institutional policies.			

4.0 PARTICIPANT ENROLLMENT

NOTE: Sites must meet activation requirements prior to enrolling participants.

4.1 Pre-Enrollment Informed Consent and Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility will be done only after obtaining written informed consent. Studies or procedures that are performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values and/or to determine pre-eligibility, even if the studies were done before informed consent was obtained. The informed consent process is to be fully documented (see Section 16.4), and the prospective participant must receive a copy of the signed informed consent document. Screening procedures are listed in Section 10.0.

4.2 Participant Enrollment

Eligible participants will be registered on the study centrally by the DCC at City of Hope. DCC staff are **available between the hours of 8:00 a.m. and 5:00 p.m. PST, Monday through Friday (except holidays).** DCC contact information is as follows:

- Phone: (626) 218-7904
- E-mail: DCC@coh.org

4.3 Slot verification and reservation

Once the Safety Lead-in is completed and the proposed dose and schedule is shown to be tolerable, participants will enroll at the tolerable dose and schedule (which includes the ramp-up stage) (Section 5.3).

Issues that would cause treatment delays should be discussed with the Principal Investigator.

Designated study staff should call the DCC to verify current slot availability, and to reserve a slot for a specific prospective subject. Slots can only be held for a limited time.

The DCC should be notified of cancellations of prospective participants holding slots as soon as possible.

4.4 Registration Process

To register a participant, the subsequent procedure is to be followed.

1. The participating site's data manager/coordinator/research nurse should contact the DCC via telephone or email to provide notification regarding the pending registration and communicate desired timeline of the registration, especially if it must be completed promptly to meet the registration window.
2. The data manager/coordinator/research nurse should then e-mail copies to DCC@coh.org of the following documents to the DCC:
    - Registration Cover Sheet (Appendix H-1)
    - Completed Eligibility Criteria List (printed from Section 3.0 of the protocol)
    - Source documentation to support eligibility criteria**
    - Signed informed consent document
    - Signed HIPAA authorization form (if separate from the informed consent document)
    - Signed subject's Bill of Rights (COH only)

**For COH participants, provide copies of source documentation only if not readily available as a finalized record in a COH Electronic Medical Record (EMR).

3. After having received all transferred documentation, the DCC will complete the review the documents to verify eligibility, working with the participating site as needed to resolve any missing required source elements. A participant failing to meet all protocol eligibility requirements will not be registered.
4. Once eligibility has been confirmed, DCC staff will register the participant by: assigning a subject accession number, register the subject on study centrally into COH clinical trials management system for non-COH participants, and enter the participant into the eCRF system, Medidata RAVE.
5. Once registration has been completed, DCC staff will send a Confirmation of Registration Form within 24 hours, including the participant study number to:
    - The study team: Site Lead Investigator, treating physician, protocol nurse, CRC and pharmacy
    - The COH sponsor team designees

4.5 Screen Failures and Registered Participants Who Do Not begin Study Treatment

The DCC is to be notified of all participants who sign consent but do not meet eligibility criteria or do not initiate protocol therapy. For non-COH sites, the reason for screen failure will be documented in registration coversheet (see Appendix H-1) and submitted to the DCC.

5.0 TREATMENT PROGRAM

5.1 Treatment Program Overview

This is a multi-center, open-label, single-arm Phase 2 trial of venetoclax with romidepsin for patients with relapsed/refractory mature T-cell lymphoma.

The study consists of a Safety Lead-in stage to evaluate safety/tolerability and a Phase 2 stage to evaluate anti-tumor activity in the study population (Section 5.3). Participants will receive up to 26 cycles of therapy and each cycle will be 28 days.

Protocol treatment will continue until disease progression, unacceptable toxicities, completing 26 cycles of therapy, or meeting other Section 5.7 criteria, whichever comes first. If a patient is still benefiting from treatment at the completion of 26 cycles of therapy, we will consider amending the study to extend the duration of therapy for that particular patient.

During Cycle 1, all participants will be monitored closely for tumor lysis syndrome (TLS, Section 5.9.2).

Participants who discontinue protocol therapy will undergo follow-up (see Section 5.8). Windows for all assessments and treatments are detailed in Section 10.0.

5.2 Treatment Cycle Definition

The treatment cycle will be a fixed 28 days (**Note:** exceptions due to unusual operational considerations may be permitted as described in Section 6.2).

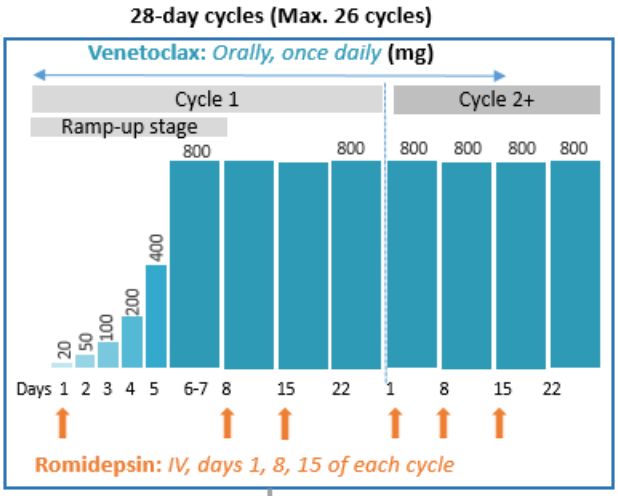
The cycle day count and cycle count will continue despite a hold in venetoclax or romidepsin administration due to toxicities (See Section 6.2) - i.e. a cycle may initiate even if either drug is being held.

Cycle 1 Day 1 is defined as the first day of venetoclax and romidepsin administration.

5.3 Treatment Plan

Participants will ramp-up daily over the first week of Cycle 1 to the maximum venetoclax dose. From Cycle 1 Days 8-28 and Cycle 2+ Days 1-28, participants will continue at the maximum dose (Figure 5.3) of venetoclax. Romidepsin 14 mg/m^2 will be administered on days 1, 8, and 15 of each cycle.

Figure 5.3. Dosing Schedule



5.3.1 Safety Lead-in

During the safety-lead in, 6 evaluable participants will be enrolled using a 3+3 design. Unacceptable toxicities are defined in Section 11.2 and will be evaluated during the first 2 cycles of therapy.

In the event the proposed dose (20-800 mg/day) of venetoclax plus romidepsin is not tolerable (2+ participants with unacceptable toxicity in ≤ 6 evaluable participants), the accrual will be suspended and the study will be amended.

5.3.2 Phase 2

Once the Safety Lead-in is completed and the proposed dose is shown to be tolerable, additional patients will be enrolled and treated for the Phase 2 response evaluation. A Simon 2-stage optimal design will be utilized. Patients enrolled during the Safety Lead-in will be included in the Phase 2 portion of the study if they are evaluable for response. In the absence of study holds to accrual for toxicity or for futility, accrual will continue until 18 evaluable participants are treated.

See Section 12.0 for details.

5.4 Agent Administration

5.4.1 Venetoclax

Participants must initiate TLS prophylaxis prior to initiating venetoclax (refer to Table 5.9.1). Delay initiating Cycle 1 Day 1 dose if the participant is experiencing laboratory TLS (see Appendix B).

Venetoclax tablets should be taken orally once daily with a meal with water. The tablets should be swallowed whole.

If a participant misses a dose and > 8 hours have passed since the scheduled dose time, the missed dose will be skipped and will not be made up.

Doses that are vomited will not be made up. Doses that are withheld due to toxicity will not be made up.

Participants will be given a Pill Diary to document each dose of venetoclax that is taken or missed (Appendix G).

Management and dose reductions/delays associated with protocol-therapy related AEs, including TLS are outlined in Section 6.2.

5.4.2 Romidepsin

Romidepsin should be handled in a manner consistent with recommended safe procedures for handling cytotoxic drugs.

Romidepsin must be reconstituted with the supplied diluent and further diluted with 0.9% Sodium Chloride Injection, USP before intravenous infusion.

Each 10 mg single-use vial of romidepsin must be reconstituted with 2mL of the supplied diluent. With a suitable syringe, aseptically withdraw 2 mL from the supplied Diluent vial, and slowly inject it into the romidepsin for injection vial. Swirl the contents of the vial until there are no visible particles in the resulting solution. The reconstituted solution will contain romidepsin 5 mg/mL. The reconstituted romidepsin solution is chemically stable for at least 8 hours at room temperature. However, whenever possible, drug should be prepared within 4 hours of dose administration.

Extract the appropriate amount of romidepsin from the vials to deliver the desired dose, using proper aseptic technique. Before intravenous infusion, further dilute the romidepsin in 500mL 0.9% Sodium Chloride Injection, USP.

Infuse over 4 hours. Patients will receive romidepsin (at a dose of either 14 or 12 mg/m^2 – see Section 7.2 for details) IV on days 1, 8, and 15 of each cycle. On these days it does not matter whether venetoclax is given before or after the romidepsin infusion.

The diluted solution is compatible with polyvinyl chloride (PVC), ethylene vinyl acetate (EVA), polyethylene (PE) infusion bags as well as glass bottles. Romidepsin is stable for 24 hours at room temperature after reconstitution per package insert.

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit.

5.5 Assessments and Special Monitoring

Section 10.0 summarizes the trial procedures to be performed. It may be necessary to perform study procedures at unscheduled time points if deemed clinically necessary by the investigator.

Note the following:

- Review of safety assessments must be performed **within 72 hours prior to the first venetoclax** administration **(Cycle 1 Day 1)**.
- **Cycle 1 Day 1-6 (venetoclax ramp-up stage):** The **24 hours** post-dose laboratory values must be reviewed prior to the next venetoclax administration.

Tumor Lysis Syndrome (TLS)

- There is a potential risk with both venetoclax and romidepsin for TLS in participants with PTCL, especially in those with renal dysfunction and dehydration. In addition, on-target effect of venetoclax could lead to rapid cell death and pose a risk of TLS.
- Patients will be closely monitored for the first 8 days of treatment (Cycle 1, Days 1-8) for signs and symptoms of TLS, laboratory evaluation, and appropriate intervention.
  - Examples of TLS symptoms: fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion and seizures.
- If any clinical features are observed (see Appendix B), recheck potassium, phosphorus, uric acid, calcium and creatinine within 1 hour.
- A rapidly rising serum potassium is a medical emergency.
- TLS monitoring during Cycle 1 and prophylaxis are described in Table 5.9.1.

5.6 Duration of Therapy and Criteria for Removal from Protocol Therapy

Participants will receive protocol therapy until one of the below criteria are met:

- Disease progression
- Completed 26 cycles (~24 months) of protocol therapy
- Participant is deemed intolerant to protocol therapy because of toxicity, despite dose modification/ delay
- General or specific changes in the patient's condition which render the patient unacceptable for further treatment in the judgment of the investigator
- Withdrawal of consent for further protocol therapy (see Section 16.5)

Once participants meet criteria for removal from protocol therapy, the participant should then proceed to End of Treatment assessments. If a patient is still benefiting from treatment at the completion of 26 cycles of therapy, we will consider amending the study to extend the duration of therapy for that particular patient.

Documentation of the reason for discontinuing protocol therapy and the date effective should be made in the source documentation and appropriate eCRF. The COH DCC should be promptly notified of the change in participant status.

5.7 Follow-Up

Following completion of protocol therapy, all participants will enter follow-up for up to 24 months after ending protocol treatment. This is comprised of:

- **Follow-up for safety-** All participants will be followed until resolution or stabilization of reportable AEs occurring during protocol therapy or starting within 30-days post last dose of protocol therapy. Refer to Section 7.7 for reporting details.
- **Follow-up for response** for those who have yet to have disease progression.
- **Follow-up for survival** - for those who initiated an anti-cancer therapy or have disease progression.

Assessment time points and windows are detailed in Section 10.0.

5.8 Duration of Study Participation

Study participation may conclude when any of the following occur:

- Completion of study activities (treatment and follow-up)
- Participant withdrawal (see Section 16.5).
- Participant is lost to follow-up. All attempts to contact the participant must be documented.
- At the discretion of the investigator for safety, behavioral or administrative reasons

Documentation of the reason for discontinuing study participation and the date effective should be made in the medical record and appropriate eCRF. The COH DCC should be promptly notified of the change in participant status.

5.9 Supportive Care, Prohibited Medications and Concomitant Therapy

Participants must be instructed not to take any additional medications (including over-the-counter products) during the trial without prior consultation with the investigator.

Participants should not consume grapefruit, grapefruit products, Seville oranges (including marmalades containing Seville oranges), or star fruits while receiving protocol therapy.

With the exception of prohibited therapies listed in Section 5.9.1, participants should receive appropriate supportive care measures as deemed necessary by the treating investigator per institutional standards. TLS prophylaxis guidelines are detailed in Section 5.9.3. Examples of prohibited and cautionary medications are listed in Appendix D.

5.9.1 Prohibited and Cautionary Agents

Prohibited Agents

The following are prohibited until from Day 1 of protocol therapy to 30 days post last dose.

- Live virus vaccines
- Other anticancer agents
- Other investigational therapy/agent
- Herbal medications

Prohibited Agents During Cycle 1 and Cautionary Thereafter with Venetoclax Dose Reductions

- Strong CYP3A inhibitors

• Prohibited during Cycle 1 and consider alternative medications. If subject requires use of these medications after Cycle 1, use with caution and reduce the venetoclax dose by at least 4-fold during co-administration.

- Moderate CYP3A inhibitors or P-gp inhibitors

• Prohibited during Cycle 1 and consider alternative medications. If subject requires use of these medications after Cycle 1, use with caution and reduce the venetoclax dose by 2-fold during co-administration.

After discontinuation of CYP3A inhibitor, wait for 2 to 3 days before venetoclax dose is increased back to the initial maintenance/target dose. Examples of moderate and strong CYP3A inhibitors are found in Appendix D

- Strong and moderate CYP3A inducers
- Prohibited during Cycle 1. Consider alternative medications. If subject requires use of these medications after Cycle 1, use with caution as they may reduce venetoclax exposure and efficacy.

Cautionary Agents

- Warfarin and coumarin derivatives
  P-gp substrates
  BCRP substrates
  OATP1B1/1B3 substrates
  BCRP inhibitors

5.9.2 Supportive Therapy for Romidepsin Infusions

- 30 min prior: 5-HT3 receptor antagonist
  - The recommended agent/dose is Zofran 16 mg IVPB or equivalent
- Dexamethasone 10 mg IVPB

5.9.3 Tumor Lysis Syndrome (TLS) Prophylaxis Guidelines

To mitigate the risk for TLS all participants will initiate TLS prophylaxis and undergo monitoring (see Table 5.9.1). Consider all participant co-morbidities before final determination of prophylaxis.

Table 5.9.1. Recommended TLS Prophylaxis Pre-Cycle 1 and Blood Chemistry Monitoring During Cycle 1

Recommended TLS Prophylaxis		**Blood Chemistry Monitoring[c] and Frequency**
Hydration[a]	**Anti-hyperuricemics[b]**	
Oral (1.5-2 L) and intravenous (150-200 mL/hr as tolerated)	Allopurinol; consider rasburicase if baseline uric acid is elevated	• *Cycle 1-Day 1-8*: Pre venetoclax dose[d], and post-dose at 6-8, 24 (±2) hours for each dose level increase. Next dose should not be administered until 24 h blood chemistry values are evaluated. ******NOTE: Cycle 1 post-dose Day 1-8 blood chemistry must be reviewed in real-time unless stated otherwise.******
a Administer intravenous hydration for any patient who cannot tolerate oral hydration. IV hydration must be initiated the night before dosing and continued for 24 hours after dose. b Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of venetoclax. c Evaluate blood chemistries (potassium, uric acid, inorganic phosphorus, calcium, and creatinine) d Pre-dose blood collection is to be performed within 4 hours from venetoclax administration.		

The management recommendations below focus on the minimum initial responses required. Any abnormal chemistry tests should be corrected promptly.

If a diagnosis of TLS is established, ongoing intensive monitoring and multi-disciplinary management will be per institutional practice. Refer to Table 7.2.1.

5.9.3.1 Hyperkalemia (including rapidly rising potassium)

- For potassium increase ≥0.5 mmol/L from baseline, or any value >5.0 mmol/L, recheck potassium, phosphorus, uric acid, calcium and creatinine and follow first guideline.

If Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])

- Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour.
  - If further ≥ 0.2 mmol/L increase in potassium, but still < upper limit of normal (ULN), manage as per potassium ≥ ULN (see below).
  - Otherwise recheck in 1 hour.
- Resume per protocol testing if change in potassium is < 0.2 mmol/L, and potassium < ULN, and no other evidence of tumor lysis.
- Per investigator discretion recheck prior to hospitalization.
  - If stable or decreased, and still WNL, hospitalization is at the discretion of the investigator.
  - Potassium, phosphorus, uric acid, calcium and creatinine must be rechecked within 24 hours.

If Potassium ≥ ULN

- Perform EKG and commence telemetry.
- Consult Nephrology (or other acute dialysis service).
- Administer Kayexalate 60 g (or Resonium A 60 g).
- Administer furosemide 20 mg IV × 1.
- Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is EKG/telemetry evidence of life threatening arrhythmias.
- Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour.
  - If potassium < ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 1, 2 and 4 hours, if no other evidence of tumor lysis.

If Potassium > 6.0 mmol/L(6.0 mEq/L) and/or symptomatic (e.g. muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)

- Perform EKG and commence telemetry.
- Nephrology (or other acute dialysis service) assessment with consideration of initiating dialysis.
- Administer Kayexalate 60 g (or Resonium A 60 g).
- Administer furosemide 20 mg IV × 1.
- Administer sodium bicarbonate 1 to 2 mEq/kg IV push.
  - If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation.
- Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is
- EKG/telemetry evidence of life threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate.
- Recheck potassium, phosphorus, uric acid, calcium and creatinine.

5.9.3.2 Hyperuricemia

If Uric acid ≥ 8.0 mg/dL (476 µmol/L)

- Consider rasburicase (dose based on institutional guidelines).

  - If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation.
- Recheck potassium, phosphorus, uric acid, calcium and creatinine.

If Uric acid ≥ 10 mg/dL (595 µmol/L)

OR

Uric acid ≥ 8.0 mg/dL(476 µmol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027 mmol/L) from pre dose level

- Administer rasburicase (dose based on local guidelines and/or institutional standards).
  - When rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation.
- Notify nephrology (or other acute dialysis service).
- Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour.
- If uric acid < 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.

5.9.3.3 Hypocalcemia

If Calcium ≤ 7.0 mg/dL (1.75 mmol/L) AND Patient symptomatic (e.g. muscle cramps, hypotension, tetany, cardiac arrhythmias)

- Administer calcium gluconate 50 to 100 mg/kg IV slowly with EKG monitoring.
- Telemetry.
- Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour.
- If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
- Calculate corrected calcium and check ionized calcium if albumin low.

5.9.3.4 Hyperphosphatemia

If Phosphorus increase of >0.5 mg/dL AND >4.5 mg/dL

- Administer phosphate binder and recheck potassium, phosphorus, uric acid, calcium and creatinine.

If Phosphorus ≥ 5.0 mg/dL (1.615 mmol/L) with≥ 0.5 mg/dL (0.16 mmol/L) increase

- Administer a phosphate binder (eg, aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate).
- Nephrology (or other acute dialysis service) notification (dialysis required for phosphorus ≥ 10 mg/dL).
- Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour.
- If phosphorus < 5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.

5.9.3.5 Creatinine

Increase ≥ 25% from baseline

- Start or increase rate of IV fluids.
- Recheck potassium, phosphorus, uric acid, calcium and creatinine.

6.0 ANTICIPATED TOXICITIES & DOSE MODIFICATION/ DELAY GUIDELINES

6.1 Anticipated Toxicities

6.1.1 Venetoclax

Per the IB version 11 dated Jun 2019 the expected toxicities for venetoclax are as follows:

System Organ Class	Adverse Reactions
Blood and lymphatic (including hematological labs)	
Very Common Common	Anemia, neutropenia, febrile neutropenia, thrombocytopenia lymphopenia
Gastrointestinal	
Very Common	Constipation, diarrhea, nausea, vomiting, abdominal pain, mucositis
General disorders and administration site conditions	
Very Common	Fatigue, edema
Infections and infestations	
Very Common Common	Pneumonia, upper respiratory tract infection Sepsis, urinary tract infection
Investigations	
Common Uncommon	Blood creatinine increased, blood phosphorus increased, lymphocyte count decreased, neutrophil count decreased, serum albumin decreased Blood calcium decreased, blood potassium increased, hemoglobin decreased
Metabolism and Nutrition Disorders	
Common	Hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia, hyponatremia, tumor lysis syndrome
Musculoskeletal and connective tissue disorders	
Very Common	Musculoskeletal pain, arthralgia
Nervous system disorders	
Common	Headache, dizziness
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnea, cough
Skin and subcutaneous tissue disorders	
Very Common	rash
Vascular disorders	
Common	Hypertension
Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000); not known (cannot be estimated from the available data).	

6.1.2 Romidepsin

Per the package insert dated March 2020 the expected toxicities for romidepsin are as follows:

System Organ Class	Adverse Reactions
Blood and lymphatic (including hematological labs)	
Very Common Common	thrombocytopenia, neutropenia, anemia, leukopenia febrile neutropenia
Gastrointestinal	

System Organ Class	Adverse Reactions
Very Common	nausea, vomiting, diarrhea, constipation, abdominal pain, stomatitis
General disorders and administration site conditions	
Very Common	Fatigue, edema, pyrexia, chills, peripheral edema
Infections and infestations	
Very Common Common	infections pneumonia, sepsis, cellulitis, HBV reactivation
Investigations	
Very Common Common	weight decreased, aspartate aminotransferase increased, alanine aminotransferase increased ECG T-wave changes, blood bilirubin increased
Metabolism and Nutrition Disorders	
Very Common Common	anorexia, hypokalemia dehydration, hypocalcemia, tumor lysis syndrome
Musculoskeletal and connective tissue disorders	
Very Common	Musculoskeletal pain, arthralgia
Nervous system disorders	
Very Common	disguesia, headache
Respiratory, thoracic and mediastinal disorders	
Very Common Common	dyspnea, cough hypoxia
Cardiac disorders	
Very Common Common	tachycardia ventricular arrhythmia
Vascular Disorders	
Very Common Common	hypotension deep vein thrombosis
Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000); not known (cannot be estimated from the available data).	

7.0 DOSE DELAY/ MODIFICATION GUIDELINES

7.1 General Information

- Baseline values are from screening evaluations.
- For supportive care guidelines see Section 5.9.
- Venetoclax doses missed for toxicity will not be made up.
- Romidepsin doses missed for toxicity will not be made up.
- Permanently **discontinue protocol therapy** if:
  - Participant requires a dose reduction and is already on 100 mg/day of venetoclax
  - Participant requires a dose reduction and is already on 10 mg/m^2 romidepsin
  - Unable to resume treatment within 14 days after last dose of venetoclax
- If the venetoclax dose was reduced during Cycle 1, intra-patient daily re-escalation to steady-state venetoclax dose may be permitted in the absence of a recurrence of the toxicity that led to the reduction following consultation with the Study PI.
- The initiation of a new cycle may be delayed for up to 7 days with written approval from the Study PI in circumstances where the participant is unable to come to the clinic as planned to initiate the new cycle (e.g. planned vacation by participant, lack of transportation etc.).*

  *If prior approval from the Study PI is obtained, then these modifications will not be considered a protocol deviation. The Study PI will document assessment of the impact of these determinations on the study design, objectives and endpoints or risk to participants. If any modifications to the treatment plan might affect the study design, objectives, and endpoints, or impact the risk of participants, a single subject exception will be sought by the IRB. If the treating investigator is the Study PI, the determination and the rationale for the determination will clearly be documented in the source document(s).

7.2 Treatment Modification Guidelines

Toxicity	**Treatment Modification**	
Metabolic and nutrition	*Romidepsin*	*Venetoclax*
Hyperuricemia, hyperphosphatemia, hyperkalemia, hypocalcemia and creatinine changes with no evidence of clinical TLS (See Appendix B). *Potassium > 6.0 mmol/L* *Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])* *Potassium > upper limit of normal* *Phosphorus > 4.5 mg/dL (1.5 mmol/L)* *Uric acid > 8.0 mg/dL (475.8 µmol/L)*		• Hold the dose until resolution • Refer to Section 5.10.3 for recommended supportive care. • *1st occurrence* – If resolved within 3 days to resume at the same dose – If toxicity resolves > 3 days resume at a 50% dose reduction • *2nd occurrence* – If resolves within 3 days to ≤ Grade 1 or baseline,

Toxicity	**Treatment Modification**	
Metabolic and nutrition	*Romidepsin*	*Venetoclax*
Corrected calcium <7.0 mg/dL *Creatinine increase ≥ 25% from baseline*		resume at a 50% dose reduction – If toxicity lasts > 3 days permanently discontinue protocol therapy
Symptoms suggestive of clinical TLS (e.g. acute renal failure, cardiac arrythmia, seizures) See Appendix B.		• Hold venetoclax dose until TLS is resolved • If toxicity resolves within 24-48 hours resume venetoclax at current dose • If toxicity takes longer than 48 hours to resolve, resume at the previous dose in the ramp sequence.*2nd occurrence*, consider permanently discontinuing protocol therapy
Other Grade 4 metabolic laboratory abnormalities		• Hold the dose until resolution to ≤ Grade 2 or baseline • *1st occurrence* – If resolved within 3 days to resume at the same dose • If toxicity resolves > 3 days resume at a 50% dose reduction • *2nd occurrence* – If resolves within 3 days to ≤ Grade 2 or baseline, resume at a 50% dose reduction – If toxicity lasts > 3 days permanently discontinue protocol therapy
Hematologic	*Romidepsin*	*Venetoclax*
Grade 3 neutropenia *<1000 - 500/mm^3*	• *1st occurrence* – Hold until ANC ≥1.5 x 10^9/L – Restart at prior dose • *2nd occurrence* – Hold until ANC ≥1.5 x 10^9/L – Dose reduce to 12 mg/m^2	• Hold the dose until ANC ≤ Grade 2 or baseline • Consider using G-CSF • Resume at pre-hold dose

Toxicity	**Treatment Modification**	
Metabolic and nutrition	*Romidepsin*	*Venetoclax*
	• *3rd occurrence* • *Remove from trial*	
Grade 4 neutropenia *<500/mm³*	• *1st occurrence* – Hold until ANC ≥1.5 x 10^9/L – Restart at prior dose • *2nd occurrence* – Hold until ANC ≥1.5 x 10^9/L – Dose reduce to 12 mg/m² • *3rd occurrence* – Remove from trial	• Hold the dose until ANC ≤ Grade 2 or baseline • Consider using G-CSF • Consider a 50% dose reduction per investigator discretion
Grade 3 febrile neutropena *G3: < ANC <1000/mm³ with a single temperature of > 38.3 degrees C (101 degrees F) or a sustained temperature of ≥ 38 degrees C (100.4 degrees F) for more than one hour.*		• Hold the dose until ANC ≤ Grade 2 or baseline • Consider using G-CSF • Consider a 50% dose reduction per investigator discretion
Grade 4 febrile neutropena *G4: life threatening consequences*	• *1st occurrence* – Hold until cytopenia returns to Grade 1 or baseline – Restart at prior dose • *2nd occurrence* – Hold until ANC ≥1.5 x 10^9/L – Dose reduce to 12 mg/m² • *3rd occurrence* – Remove from trial	• Hold the dose until ANC ≤ Grade 2 or baseline • Consider using G-CSF • Consider a 50% dose reduction per investigator discretion
Grade 3-4 thrombocytopenia, and/or anemia, and/or thrombocytopenia requiring transfusion	• *1st occurrence* – Hold until platelet count ≥75 x 10^9/L or baseline – Restart at prior dose • *2nd occurrence* – Hold until platelet count ≥75 x 10^9/L or baseline – Dose reduce to 12 mg/m² • *3rd occurrence* • Remove from trial	• *Grade 4 other unspecified hematologic toxicities (except lymphopenia)* • *For Grade 4 thrombocytopenia* – Hold the dose until platelets ≤ Grade 2 or baseline • *1st occurrence*, – resume at same dose if toxicity resolves within 7 days • consider a 50% dose reduction if toxicity lasts > 7 days *2nd*

Toxicity	**Treatment Modification**	
Metabolic and nutrition	*Romidepsin*	*Venetoclax*
		occurrence and subsequent occurrence, – consider a 50% dose reduction if toxicity resolves within 7 days if toxicity lasts > 7 days, consider permanently discontinuing protocol therapy
Other unspecified Non-hematologic- **RELATED**	*Romidepsin*	*Venetoclax*
≥ Grade 3	• 1st occurrence – Hold until resolved to ≤ Grade 1 – then reduce to 12 mg/m^2 • *2nd or 3rd occurrence Grade 3* – Hold until resolved to ≤ Grade 1 – Dose reduce to 10 mg/m^2 • *Any recurrence of Grade 4* • Remove from trial therapy	• Hold the dose until ≤ Grade 1 or baseline • *1st occurrence*, – resume at same dose if toxicity resolves within 7 days • consider a 50% dose reduction if toxicity lasts > 7 days *2nd occurrence and subsequent occurrence*, – consider a 50% dose reduction if toxicity resolves within 7 days – if toxicity lasts > 7 days, consider permanently discontinuing protocol therapy
Other unspecified Non-hematologic- **UNRELATED**	*Romidepsin*	*Venetoclax*
Any Grade	• *1st occurrence* – Maintain protocol therapy for Grades 0-2 – Hold until resolved from Grade 3-4 to ≤ Grade 1 – Dose reduce to 12 mg/m^2 • *2nd or 3rd occurrence Grade 3* – Hold until resolved to ≤ Grade 1 – Dose reduce to 10 mg/m^2 • *Any recurrence of Grade 4* – Remove from trial therapy	• Maintain protocol therapy • Interruption of protocol therapy is permitted if the investigator consults the Study PI to determine that this is in the best interest of the participant.

8.0 AGENT INFORMATION

8.1 Venetoclax

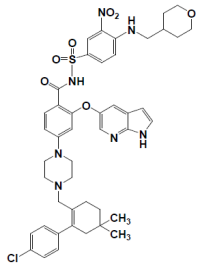
Venetoclax has been FDA approved for patients with chronic lymphocytic leukemia (CLL) with 17p deletion, as detected by an FDA approved test, who have received at least one prior therapy.

For additional information refer to the IB.

8.1.1 Other Names

VENCLEXTA™, ABT-199, A-1195425.0, GDC-0199, RO5537382

8.1.2 Description

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

8.1.3 Mechanism of Action

Venetoclax is a novel, orally available small molecule Bcl-2 family protein inhibitor that binds with > 500-fold higher affinity to Bcl-2 and with lower affinity to other Bcl-2 family proteins Bcl-XL and Bcl-w. Overexpression of anti-apoptotic Bcl-2 family proteins is associated with increased resistance to chemotherapy, and antagonism of the action of these proteins might enhance response to such therapy and overcome resistance. Anti-apoptotic Bcl-2 family members are associated with tumor initiation, disease progression, and drug resistance, making them compelling targets for antitumor therapy.

8.1.4 Pharmacokinetics

Half-life:	~26 hrs
Distribution:	Highly bound to plasma protein
Metabolism:	Predominantly by CYP3A4/5; M27 is a major metabolite
Excretion:	>99.9% feces, < 0.1% urine

8.1.5 Human Toxicity

See Section 6.1.

8.1.6 Formulation

Venetoclax tablets will be used for this study.

8.1.7 Storage

Store at 15° to 25 °C.

8.1.8 Handling and Dispensing

The investigator should ensure that investigational agent venetoclax is stored in accordance with the environmental conditions (temperature, light, and humidity) as per product information and the Investigator Brochure and per local regulations.

The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact AbbVie immediately.

8.1.9 Administration

See Section 5.4.1

8.1.10 Supplier

The investigational venetoclax will be supplied free of charge by AbbVie.

8.1.11 Ordering

Sites will place orders for venetoclax via the AbbVie drug portal. The timing for initial and resupply will be the same.

Sites should place orders a week in advance of the shipment.

8.1.12 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using a drug accountability log.

It is the responsibility of the investigator to ensure that investigational product is only dispensed to study participants.

8.1.13 Destruction and Return

The investigator is responsible for keeping accurate records of the clinical supplies received from AbbVie or designee, the amount dispensed to participants, and the amount remaining at the conclusion of the trial.

Any unused agent at the end of the study, expired agent, and damaged agent will be destroyed according to applicable federal, state, local and institutional guidelines and procedures. **Prior to the destruction of venetoclax, the DCC should be notified and an acknowledgement to proceed from the DCC should be received**.

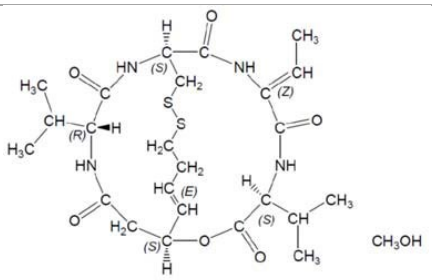
Destruction will be documented in a drug accountability log.

8.2 Romidepsin

8.2.1 Other names

Istodax®, Romidepsin for injection, FK228, depsipeptide

8.2.2 Description

Structural Formula:	
Molecular Formula:	$C_{24}H_{36}N_4O_6S_2 \bullet CH_4O$
Molecular Weight:	572.74 kDa

8.2.3 Mechanism of Action

Romidepsin is a unique bicyclic depsipeptide originally isolated from *Chromobacterium violaceum* strain 968. Romidepsin is an antineoplastic agent that has been identified as a novel HDAC inhibitor. Romidepsin has been shown to induce hyperacetylation of histones and other nonhistone protein species resulting in a variety of phenotypic changes, induction of the upregulation of gene transcription, G1 and G2/M arrest of the cell cycle, morphological reversion of transformed cells, cell growth inhibition, apoptotic cell death, and inhibition of angiogenesis. In vitro, romidepsin causes the accumulation of acetylated histones, and induces cell cycle arrest and apoptosis of some cancer cell lines with IC_{50} values in the nanomolar range. The mechanism of the antineoplastic effect of romidepsin observed in nonclinical and clinical studies has not been fully characterized.

8.2.4 Pharmacokinetics

Half-life:	~3 hrs
Distribution:	Highly bound to plasma protein
Metabolism:	Predominantly by CYP3A4/5
Excretion:	accumulates in bile and excreted in feces

8.2.5 Human Toxicity

See Section 6.2

8.2.6 Formulation

Romidepsin Injection is a sterile, clear colorless to pale yellow solution and is supplied in single-dose vials. Each mL contains romidepsin 5 mg, povidone 10 mg, DL-apha-tocopherol 0.05 mg, dehydrated alcohol 157.8 mg (20.1% v/v) and propylene glycol 828.8 mg.

8.2.7 Storage

20° to 25° C, excursions permitted between 15° to 30° C. (See USP Controlled Room Temperature.)

8.2.8 Handling and dispensing

Romidepsin should be handled in a manner consistent with recommended safe procedures for handling cytotoxic drugs.

Romidepsin must be reconstituted with the supplied diluent and further diluted with 0.9% Sodium Chloride Injection, USP before intravenous infusion.

8.2.9 Administration

See Section 5.4.2.

8.2.10 Supplier

Romidepsin will be available through commercial supply.

9.0 CORRELATIVE/ SPECIAL STUDIES

9.1 Tumor Tissue Studies

An overview of collection, processing, and analysis details are shown in Table 9.1.

Table 9.1. Overview of Tumor Tissue Studies

Tissue Type	Timepoint of collection	Planned Future Analaysis
Formalin fixed archived biopsy	Baseline	• BCL2 expression status and correlation with response • Changes in gene expression
Fresh tissue	• Baseline • *Optional*: During Cycle 1 or Cycle 2	

9.1.1 Timepoints of Collection

- *Baseline tissue*:
  - *Fresh tissue (after informed consent)*: If a standard of care fresh core or excisional biopsy of the tumor lesion is to be performed, attempts should be made to take extra tissue for research.
  - *Formalin-fixed tissue*: Archived biopsy tumor tissue should be submitted.
- *During Cycle 1 or Cycle 2 (optional)*: Submit fresh core or excisional biopsy of the tumor lesion for research if the participant is willing.

9.1.2 Guidelines for archival specimens

Using the formalin-fixed paraffin embedded (FFPE) tissue block, the following samples will be processed for correlative studies:

- If tissue block is available submit:
  - 6 paraffin scrolls measuring 10 μm thick placed into a Nunc tube and frozen at -80° C AND
  - 10 x 5 μm unstained slides
- If tissue block is unavailable submit 20 x 5 μm unstained slides

9.1.3 Guidelines for fresh tumor tissue processing

9.1.3.1 Non-COH sites

Tumor lesion core or excisional biopsies should be flash frozen and kept at -80°C until batch shipment.

9.1.3.2 COH only

Tumor lesion core or excisional biopsies will be collected in saline.

9.1.4 Labeling of samples

Samples will labeled with the study number, institution (for non-COH sites), subject ID, date, timepoint of collection (i.e. baseline or progression) and if applicable patient initials.

9.1.5 Sample shipment and receiving lab

Tissue specimens collected at the above indicated timepoints will either be taken to (COH only) or batch-shipped (non-COH sites) to COH Pathology Core. For all sites, please include the **Correlative Tissue form (Appendix F-2)** with your shipment.

Please note that samples should only be **batch shipped from non-COH sites on Monday-Wednesday** for receipt Tuesday-Friday. Refer to Appendix F-1 for shipment details.

10.0 STUDY CALENDAR

All procedures may increase in frequency if clinically indicated.

Table 10.0 Study Activity Calendar

Protocol Activity [dd]	Screening [a]	Protocol Therapy [b,c]							EOT [g]	Post-last Dose Follow-up (24 months)		
		Cycle 1					Cycle 2 D1 & then weekly	Cycle 3+ D1		Safety 30-days post [h]	Response [i]	Survival [j]
		D 1 [d,e]	D 2-7 [f]	D 8	D 15	D 22						
Informed Consent [k]	X											
Medical History [l]	X											
Eligibility [m]	X											
Registration [n]	X											
Physical Exam [o] & Vital signs [p]	X	X	X	X	X	X	X	X	X	X		
Height	X											
ECOG Status (Appx. A)	X	X	X	X	X	X	X	X	X	X		
Con-med review [q]	X	X	X	X	X	X	X	X	X	X		
AE Assessment [r]	X [r]	----------X[s]----------										
12-lead EKG	X [u]											
Pregnancy [t]	X [u]											
CBC w/diff, plt & Serum chemistry [v]	X [u]	X	X [f]	X	X	X	X	X	X			
TLS serum chemistry monitoring [w]		X [w]	X [w]	X [w]								
CT/MRI imaging [x]	X							X [y]	X [g]		X	
FDG-PET scan [z]	X								X			
Bone marrow biopsy/ aspirate	X [aa]											
Response [bb]								X [y]	X		X	
TLS prophylaxis	X [cc]											
Venetoclax		Orally, daily [e,f]										
Romidepsin [ee]		X		X	X		X [ee]	X [ee]				
Pill diary [ff]		X	X	X	X	X	X	X	X			
Tumor tissue	X [gg]	*Optional*: During Cycle 1 or 2 [hh]										
Survival status [j]												X

a. Screening activities to occur within 28 days prior to start of protocol therapy except for laboratory assessments, bone marrow biopsy/aspirate and TLS prophylaxis.
b. Protocol therapy may last up to 26 cycles (~ 24 months), until unacceptable toxicity or disease progression (see Section 5.7 for more comprehensive list). If a patient is still benefiting from treatment at the completion of 26 cycles of therapy, we will consider amending the study to extend the duration of therapy for that particular patient.
c. Each treatment cycle lasts 28 days. The cycle duration does not change, even if venetoclax is held (Note: exceptions due to unusual operational considerations may be permitted; see Section 6.2).
d. Cycle 1 Day 1 is defined as the day of venetoclax and romidepsin initiation. Delay the Cycle 1 Day 1 dose if the participant is experiencing laboratory TLS as defined in Appendix B.
e. Assessments must be **performed and reviewed within 72 hours prior** to the C1D1 venetoclax dose (except tumor imaging).
f. Cycle 1 Day 2-7 (± 2 hours) laboratory assessments must be performed and reviewed prior to administration of the Cycle 1 Day 2-7 venetoclax doses.
g. *End of protocol therapy (EOT) assessments* to be performed no later than 7 days after decision to end treatment (except tumor imaging); assessments performed after last dose of study agent and within 7 days of the decision to end treatment may serve as EOT assessments. **NOTE:** Tumor imaging performed after last dose of study agent and within 28 days of the decision to end treatment may serve as EOT imaging assessment.
h. *Safety visit* to occur 30 (-2/+7) days post-last dose of protocol therapy. Expedited reporting will occur during this period (See Section 7.7.2). Safety follow-up may be extended until resolution/ stabilization of reportable AEs.
i. For participants yet to progress, Response Follow-up will occur every 2 months (+/- 7 days) from the day of last response evaluation until progression or the initiation of a new therapy.
j. Participants who end Response Follow-up will enter Survival Follow-up. Survival assessment to occur bi-annually or as requested by the Study PI via medical record review, review of social security registry, or telephone call.
k. *Informed consent* process to be fully documented (see Section 16.4). Informed consent must occur prior to any research only (non-SOC) screening procedures.
l. *Medical history* to include a review of treatment history, any ongoing medical conditions and medical history pertaining to eligibility on study and involvement during study
m. *Eligibility criteria* are detailed in Section 3.0.
n. *Registration* into a COH clinical trial management system (CTMS).
o. *Standard physical exam* includes weight and skin analysis.
p. *Vital signs*: heart rate, blood pressure, respiration rate, and temperature.
q. *Concurrent medications* and reason for administration to be documented from within 10 days prior to protocol therapy up to 30-days-post last dose visit. See Section 5.9 for concomitant medication restrictions and guidelines.
r. *Adverse event (AE)* will be assessed using CTCAE v.5.0. SAEs related to study procedures will be recorded and reported from time of informed consent until Day 1 of protocol therapy.
s. Toxicities AE recording and reporting will continue until the completion of Safety Follow-up period or until resolution or stabilization of any reportable AE occurring during Safety Follow-up.
t. *Women of child bearing potential*: Pregnancy serum or urine test.
u. *Screening laboratory assessments* to be performed within 14 days prior to start of protocol therapy.
v. *Serum chemistry* panel to include: glucose, Blood Urea Nitrogen (BUN), creatinine, uric acid, total protein, albumin, magnesium, bicarbonate, calcium, inorganic phosphorous, sodium, potassium, chloride, total CO_2, total bilirubin, alkaline phosphatase, ALT, AST, and LDH.
w. *TLS serum chemistry monitoring post-Day 1, Day 2, Day 3, Day 4, Day 5, Day 6, Day 7 and Day 8 dose* to include potassium, uric acid, phosphorus, calcium, and creatinine. **Monitoring times are:** predose, and post dose 6-8 hours

and 24 (+/- 2) hours. Next dose should not be administered until 24 h blood chemistry values are evaluated. See **Table 5.9.1.**

x. CT/MRI imaging for PTCL at baseline.

y. *Disease and response assessment*: Cycle 3 Day 1 (-7 days), then every 2 cycles (-7 days). CT scan may take place within 7 days prior to D1 but not *after* D1 of the cycle in question.

z. FDG-PET scan will be performed at screening. Subsequent PET scans will not be needed until the EOT visit or disease progression, whichever comes first.

aa. *Bone marrow biopsy/aspirate* that was performed within 120 days prior to Day 1 may serve as Screening assessment.

bb. PTCL response (Lugano criteria). Refer to Section 11.3 for details.

cc. *TLS prophylaxis* to be initiated prior to protocol therapy within 72 hours as stated in Table 5.9.1. Participants should receive continued TLS prophylaxis as clinically indicated.

dd. Refer to Section 5.3 for the treatment plan. Refer to Section 6.2 for dose modification/ delay guidelines and Section 5.9 for supportive care guidelines.

ee. Romidepsin will be administered intravenously on Days 1, 8, and 15 of each cycle. A window is allowed for romidepsin infusion visits (within ±3 days of day 1 and within +3 days of days 8 and 15)

ff. *Pill Diary* will be given to the participant and will be reviewed for adherence. See Appendix G.

gg. *Baseline tissue*: Archival tissue of a biopsy and if applicable, fresh core or excisional biopsy of a tumor lesion at time of standard of care biopsy.

hh. *Optional*: Research fresh core or excisional biopsy of the tumor lesion only if the participant is willing.

11.0 ENDPOINT EVALUATION CRITERIA/MEASUREMENT OF EFFECT

11.1 Safety

Toxicity will be graded according to the NCI-Common Terminology Criteria for Adverse Events version 5.0. During the first 2 cycles, all grades of toxicity will be collected. After cycle 2, only the highest grade of any toxicity will be collected for each cycle during protocol treatment and for the period of safety follow-up after end of treatment.

11.2 Unacceptable Toxicity During Safety Lead-In

Unacceptable toxicity will be defined as one of the following AEs that is **at least possibly related** to either venetoclax or romidepsin treatment within the first 2 cycles of protocol therapy:

Hematologic

- Grade 3 or 4 neutropenia lasting > 7 days (despite the use of growth factor support)
- Grade 3 or 4 thrombocytopenia associated with bleeding requiring transfusion
- Grade 4 anemia not associated with lymphoma

Non-hematologic

- Clinical TLS (per Howard criteria)
- Grade 4 metabolic laboratory abnormalities that do not resolve within 3 days to ≤ Grade 2 with supportive measures
- Any other ≥ Grade 3 toxicity that does not resolve to ≤ Grade 1 or baseline within 7 days with the **exception** of:

- Grade 3 asymptomatic laboratory abnormalities, including lipase or amylase, that are not clinically relevant, not requiring hospitalization or delay of treatment
- Grade 3 nausea, vomiting, or fatigue controlled with supportive measures
- Vitiligo

11.3 Efficacy Endpoints

11.3.1 PTCL Efficacy Endpoints

Disease parameters and methods for assessing the disease are in Appendix C-1. PTCL response will be assessed using Lugano Classification (see Appendix C-2) [50]. Endpoints are describes in Table 11.3.

Table 11.3. Clinical Endpoints

Endpoint	Patients	Definition
Overall response rate (ORR)	Evaluable patients	Proportion of patients achieving CR or PR
Complete response (CR) rate	Evaluable patients	Proportion of patients achieving CR
Time to response	Evaluable patients	Date of initiation of protocol treatment to date when criteria for response (PR or CR) is first met
Duration of response (DOR)	CR and PR only	Date when criteria for response (CR or PR) is first met until date criteria for PD or relapse is first met
Progression free survival (PFS)	Evaluable patients	Date of initiation of protocol treatment to date criteria for PD is first met or death as a result of any cause
Overall survival (OS)	Evaluable patients	Date of initiation of protocol treatment to date of death from any cause
Note: Evaluable patients are patients evaluable for response, as defined in Section 12.3.		

12.0 STATISTICAL CONSIDERATIONS

12.1 Statistical Design

This is a multi-institution, single arm Phase 2 trial to evaluate the anti-tumor activity and safety/tolerability of venetoclax with romidepsin in patients with relapsed/refractory mature T-cell lymphoma. Patients will take oral venetoclax daily and romidepsin on days 1, 8, and 15 of each cycle for up to 26 cycles (28-day cycle) Response will be assessed after every 2 cycles until disease relapse/progression. Patients will be followed for 24 months after the end of protocol treatment. The primary endpoint is overall response rate. Secondary endpoints include toxicities, CR rate, duration of response, time to response, PFS, and OS. The study will accrue up to 18 evaluable patients for the primary response endpoint evaluation. The first 6 patients enrolled on the study will be part of a Safety Lead-in to evaluate the safety and tolerability of the proposed dose of venetoclax with romidepsin as described below in Section 12.1.1.

12.1.1 Safety Lead-In

Prior to formally initiating the Phase 2 response evaluation, a patient Safety Lead-in will be conducted to ensure the proposed treatment is tolerable. Up to 6 evaluable patients may be enrolled in two cohorts of 3 patients each at the proposed venetoclax dose (maximum dose of 800 mg/day with a 1-week dose ramp up schedule) plus romidepsin as outlined below. Initially up to 3 evaluable patients can be enrolled and treated. After 3 patients are treated and evaluated for unacceptable toxicities, if 0/1 out of 3 evaluable patients experience unacceptable toxicities during the first 2 cycles, up to 3 additional patients will be enrolled and treated to bring the total number of patients treated to 6. If ≤1/6 evaluable patients experience unacceptable toxicities during the first 2 cycles, the proposed treatment dose/schedule (including ramp-up) will be considered tolerable and be used for the subsequent Phase 2 response evaluation. At any time during the Safety Lead-in, if ≥2 patients experience unacceptable toxicities during the first 2 cycles, the accrual will be suspended and the study will be amended. The unacceptable toxicities are defined in Section 11.2. Unacceptable toxicities will be evaluated during the first 2 cycles of therapy to ensure monitoring of participants during the venetoclax ramp-up period (Cycle 1) and while participants are on steady-state venetoclax dose (Cycle 2). Patients inevaluable for unacceptable toxicities during the Safety Lead-in will be replaced (see below in Section 12.3).

12.1.2 Phase 2

The Phase 2 response evaluation will accrue a minimum of 7 evaluable patients and a maximum of 18 evaluable patients. Patients enrolled during the Safety Lead-in period of the study (n=6) will be included in the Phase 2 response evaluation provided that they are evaluable for response (defined in Section 12.3). The response evaluation will be based on a Simon's Two-Stage Optimal design [53], to distinguish a promising 30% response rate (alternative hypothesis) from a disappointing rate (null hypothesis) of 10%, at a one-sided type I error of 10% and a power of 80%. In the first stage, 7 evaluable subjects will be accrued. If there is 0 response among the 7, the study accrual will be suspended. If there are 1 or more responses among the 7, the study will remain open to accrue a total of 18 evaluable patients. Observing 4 or more responses among 18 evaluable patients will reject the null hypothesis and indicate the response rate being promising in this study setting. Observing 3 or fewer responses among 18 evaluable patients will fail to reject the null hypothesis and will not establish efficacy of the treatment.

For the purpose of the 1st stage response evaluation, study accrual may be temporarily suspended until all Stage 1 enrollments are assessed for response after at least 4 cycles of treatment or are otherwise off-treatment. If by that time no responders have been observed, the study accrual will be terminated. On

the other hand, if at least one responder has been observed prior to enrolling the 7th patient for Phase II, then Phase II accrual will continue directly to Stage 2 without interruption.

If no toxicity is noted at the proposed dose/schedule and there is no efficacy either, the protocol may be amended after discussion with the industry partner to increase the maximum dose of venetoclax up to 1200 mg/day.

12.2 Accrual and Expected Duration of Trial

The expected sample size for the Phase 2 response evaluation is 18 patients evaluable for response (assuming the response evaluation passes the first stage). Patients enrolled during the Safety Lead-in of the romidepsin/venetoclax combination will be included in the Phase 2 response evaluation if they are evaluable for response which requires a response evaluation after 2 cycles. We expect that all patient enrolled during safety lead-in will have a response evaluation after 2 cycles. Therefore, the total sample size for the study including the Safety Lead-in is expected to be 18 evaluable patients. Assuming approximately 10% of the patients need to be replaced for safety lead-in or Phase 2 evaluation, the maximum sample size for evaluating the combination of venetoclax and romidepsin is 20 patients.

The 6 patients enrolled on the previous versions of protocols with single agent venetoclax will be analyzed separately and excluded from the main analyses which evaluate the combination of venetoclax and romidepsin. Therefore, the maximum sample size of the study will be 26 accounting for these 6 prior enrollments.

City of Hope saw ~160 PTCL patients per year, with ~30 new patients per year (mix of newly diagnosed and relapsed or refractory). This will be a multicenter study with 3 total sites. We expect a total accrual of 1-2 patients per month across all sites. Therefore, accrual is expected to be completed in 24 months.

Participant duration is planned for 4 years which includes maximum time for treatment (24 months) and expected post-treatment follow-up (24 months). The estimated total study duration will be 6 years, with 2 years of accrual and approximately 4 years of treatment and follow-up for the last patient.

12.3 Evaluable Participants and Participant Replacement

- ***Evaluable for unacceptable toxicity during Safety Lead-in***: Patients evaluable for unacceptable toxicity (defined in Section 11.2) are:
  1) Those who received at least 75% of the total dose of each drug for the first 2 cycles of therapy combined OR
  2) Those who experience any unacceptable toxicity during the first 2 cycles regardless of actual dose received.

During safety lead-in, patients who are not evaluable for unacceptable toxicities will be replaced.

- ***Evaluable for response:*** Patients evaluable for response are those who received at least 2 cycles of protocol treatment and have a response evaluation after 2 cycles. Subjects who terminate treatment prior to 2 cycles due to disease relapse/progression or unacceptable toxicity will be considered evaluable for response and be considered non-responders. Patients who terminate prior to 2 cycles for other reasons will be inevaluable for response. Patients not evaluable for response will be replaced.

12.4 Stopping Rules for Tumor Lysis Syndrome (TLS)

Besides prophylaxis and dose modification for TLS per Section 5.9.3 and Section 7.2, the study will implement accrual stopping rules for both clinical TLS and laboratory TLS. When a stopping rule is triggered, the study PMT will review and assess the safety of the trial and submit a report to the COH DSMC. The COH DSMC will review for approval any decision to continue or permanently suspend accrual to the trial.

12.4.1 Clinical TLS Stopping Rule

Study accrual will be suspended when the first incidence of clinical TLS is reported.

12.4.2 Laboratory TLS Stopping Rule

The incidence of laboratory TLS will be monitored with 12% being the benchmark based on IB. Operationally, the study accrual will be suspended if:

- 1 patient experiences laboratory TLS when there have been ≤5 patients treated
- 2 patients experience laboratory TLS when there have been ≤14 patients treated
- 3 patients experience laboratory TLS regardless of the number of patients treated

The rule is derived based on a <50% probability of the rule being triggered when the true laboratory TLS incidence is ≤12%.

12.5 Statistical Analysis Methods

Patient demographics and baseline disease characteristics, including age, gender, medical history, and prior therapy, will be summarized using descriptive statistics. For continuous variables, descriptive statistics such as number, mean, standard deviation, standard error, median (range) etc. will be provided. For categorical variables, patient counts and percentages will be provided.

Rates and 95% Clopper-Pearson binomial confidence interval (CI) will be calculated for overall response rate (patients that have confirmed CR or PR), as well as for CR rate. Time to response, duration of response (only among subjects achieving CR/PR), overall survival, and progression-free survival will be estimated using the product-limit method of Kaplan- Meier with the Greenwood estimator of standard error. Median progression-free survival and overall survival and their corresponding 95% CIs will be estimated. Observed toxicities will be summarized as summary statistics in terms of type (organ affected or laboratory determination), severity, attribution, time of onset, duration, probable association with the study treatment, and reversibility of outcome.

For the exploratory objective on determining the changes in Bcl-2 gene expression in pre- and post-treatment tumor samples, summary statistics and plots will be used to describe the pre- and post-treatment gene expression levels and the associated change between the timepoints. Paired t-test or Wilcoxon signed rank test will be used to explore the difference in gene expression levels before and after treatment. Data transformation such as log transformation will be considered if appropriate. Exploratory analyses will be performed to investigate the association of the pre-/post-treatment Bcl-2 gene expressions and the change in gene expression with the clinical outcomes. For the exploratory correlation of these gene expression level/change with response, analyses comparing groups of participants defined by response may be conducted by two-sample t-test or Wilcoxon rank sum test. For the exploratory correlation of these endpoints with survival outcomes, survival analysis techniques such as Log rank test will be used. Appropriate regression models will also be considered, such as logistic regression model for

analyses on response and Cox proportional hazards models for analyses on survival outcomes. All these analyses are exploratory in nature and are intended to generate hypotheses that may be validated in larger studies; no multiple comparison adjustments will be made in these exploratory analyses.

13.0 DATA HANDLING, DATA MANAGEMENT, RECORD KEEPING

13.1 Source Documents

Source documents are original documents, data, and records (e.g., medical records, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. The investigator or their designee 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 documents must be adequate to reconstruct all data transcribed onto the case report forms.

13.2 Data Capture Methods and Management

Data for this trial will be collected using Medidata Rave.

13.3 Case Report Forms/Data Submission Schedule

Study personnel will enter data from source documents corresponding to a participant's visit into the protocol-specific electronic Case Report Form (eCRF) when the information corresponding to that visit is available.

The investigator is responsible for all information collected on participants enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the investigator. All case report forms must be completed by designated study personnel. The completed case report forms must be reviewed, signed and dated by the Investigator or designee in a timely fashion.

All data will be collected using electronic data collection, stored as indicated in Section 13.2, and will be submitted according to the timelines indicated in Table 13.3.

Table 13.3 Data Submission Schedule

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration
On Study Forms	Within 14 calendar days of registration
Baseline Assessment Forms	Within 14 calendar days of registration
Treatment Forms	Within 14 calendar days of treatment administration
Adverse Event Report Forms	**Safety Lead-in Cycle 1 and 2**: Within 7 calendar days of the assessment/notification **Safety Lead-in Cycle 3+ and Phase 2**: Within 10 calendar days of the assessment/notification
Response Assessment Forms	Within 10 calendar days of the response assessment
Other Assessment Forms	Within 10 calendar days of the assessment
Off Treatment/Off Study Forms	Within 10 calendar days of completing treatment or being taken off study for any reason
Follow up/ Survival Forms	Within 14 calendar days of the protocol defined follow up visit date or call

13.4 Regulatory Records

The investigator will maintain regulatory records, including updating records in accordance with Good Clinical Practice guidelines and FDA regulations

14.0 ADVERSE EVENTS AND UNANTICIPATED PROBLEMS

14.1 Definitions

14.1.1 Adverse Event (AE)

An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

14.1.2 Serious Adverse Event (SAE)

A serious adverse event is any expected or unexpected adverse events that result in any of the following outcomes:

- Death
- Is life-threatening experience (places the subject at immediate risk of death from the event as it occurred)
- Unplanned hospitalization (equal to or greater than 24 hours) or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Secondary malignancy*
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

*Modified from 21 CFR 312.32

14.1.3 Unanticipated Problems Involving Risks to Subjects or Others

An unanticipated problem is any incident, experience, or outcome that **meets all three** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; **AND**
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); **AND**
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

14.1.4 Adverse Events of Special Interest (AESI)

Specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities. These events, regardless of seriousness, will be reported.

14.1.4.1 Study Specific AESIs

- Tumor lysis syndrome (see Section 7.5)
- Overdose (see Section 7.6)

14.2 Assessment of Adverse Events

The site Investigator will be responsible for determining the event name, assessing the severity (i.e. grade), expectedness, and attribution of all adverse events.

14.2.1 Assessment of Adverse Event Name and Grade

Adverse events will be characterized using the descriptions and grading scales found in the most recent version of CTCAE v. 5.0. A copy of the scale can be found at NCI/ CTEP web site. The determination of severity for all other events not listed in the CTCAE v. 5.0 should be made by the investigator based on medical judgment and the severity categories of Grade 1 to 5 as defined below:

- Grade 1 (mild) – An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Grade 2 (moderate) – An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
- Grade 3 (severe) – An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
- Grade 4 (life threatening) – An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc).
- Grade 5 (fatal) – Death (loss of life) as a result of an event.

14.2.2 Assessment of Attribution

The following definitions will be used to determine the causality (attribution) of the event to the study agent or study procedure.

- **Unrelated –** The event is clearly related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant medications administered to the participant.
- **Unlikely –** The event is doubtfully related to the investigational agent(s). The event was most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Possible –** The event follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.

- **Probable –** The event follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the study drug. The event cannot be reasonably explained by other factors such as the participant's clinical state, therapeutic interventions, or concomitant drugs.
- **Definite –** The event follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern to the study drug, cannot be reasonably explained by other factors such as the participant's condition, therapeutic interventions, or concomitant drugs, AND occurs immediately following study drug administration, improves upon stopping the drug, or reappears on re-exposure.

14.2.3 Assessment of Expectedness

The following definitions will be used to determine the expectedness of the event:

- **Unexpected**– An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event. *Modified from 21 CFR 312.32 (a)
- **Expected –** An adverse event is expected if it does not meet the criteria for an unexpected event, OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

14.3 Reporting of Adverse Events

14.3.1 Routine Reporting of Non-Serious Adverse Events by Site Investigators

Routine AE recording will occur via data entry into the study eCRF. Recording of adverse events will begin once the patient is consented and will continue until 30 days after the last dose of protocol therapy. Adverse events will be monitored by the Protocol Management Team (PMT). Adverse events that do not meet the criteria of serious OR are not unanticipated problems do not require expedited reporting. AEs reported through expedited processes (i.e. reported to the IRB, DSMC, FDA, etc.) must also be reported in routine study data submissions.

14.3.2 Expedited Reporting Requirements of SAEs and UPs by Site Investigators

14.3.2.1 Criteria for Reporting SAEs/UPs to the Coordinating Center

Serious Adverse Events meeting the criteria specified below will be reported to the Coordinating Center within **24 hours** of notification that the event occurred.

Adverse events that require expedited reporting include:

- AEs or SAEs that meet the definition of an unanticipated problem
- AEs associated with
  - TLS (Section 14.5)
  - overdose (Section 14.6), suspected abuse/ misuse,

- pregnancies (Section 14.7)

- All deaths that occur within 30 days of active treatment
- All deaths that occur after 30 days of active treatment that are unexpected and possibly, probably, or definitely related to the study agent or procedure
- All serious adverse events, regardless of relationship to study agent or study procedure, that occur within 30 days of the last day of treatment
- All serious adverse events that occurred after 30 days of active treatment/therapy that are considered possibly, probably, or definitely related to the study agent or procedure

Note: Follow-up reports must be submitted for all events that require expedited reporting when the status of the event changes and until the resolution or stabilization of the event.

Reportable serious adverse events must be followed until the event is resolved, stabilized, or determined to be irreversible by the participating investigator; for ongoing reportable adverse events that are unrelated to study agent, the follow-up period may end at the 30-days post study-drug assessment. The Coordinating Center should be consulted prior to ending the follow-up of events that have stabilized.

14.3.2.2 Non-COH Sites: Procedure for Reporting SAEs/UPs to the COH Data Coordinating Center

1. Sites are to report to their local IRB per their site's specific institutional and IRB guidelines. As soon as possible, non-COH sites will provide to the COH Data Coordinating Center copies of the IRB submission and corresponding IRB response.
2. Document/describe the SAE/UP on each of the following:
    a. MedWatch 3500A

        i. Downloadable form at http://www.fda.gov/medwatch/getforms.htm

    b. UP/SAE Coversheet

        i. SAE Coversheet is found in Appendix H-2. A modifiable Microsoft Word document is also available from the Data Coordinating Center. An electronic signature on the document will be accepted.
3. Scan and email above documents to DCC@coh.org with the subject title as "IRB # SAE".
    a. All SAE reports received at this account are forwarded immediately to study Principal Investigator, and to Coordinating Center personnel.
    b. While not required, if available and applicable, please also include the local IRB submission for this event in the submission.
4. If an email receipt from Coordinating Center personnel is not received within one working day, please call 626-218-7904 and/or email DCC@COH.org.

14.3.2.3 COH Investigative Sites: Procedure for Reporting SAEs/UPs to the Coordinating Center

1. Email the following information to DCC@coh.org and jazain@coh.org:
    a. Participant ID, date the event met criteria for reporting, whether the event meets the definition of serious, whether the event is an unanticipated problem, grade of event, attribution of event, whether the event is a known expected toxicity to study agent.
2. Complete the iRIS AE/UP reporting form per COH reporting timeline.

14.3.3 Additional Reporting Requirements of the Study Principal Investigator

14.3.3.1 Reporting to COH IRB and DSMC

The study PI (or designee) will report to COH IRB and DSMC via iRIS all reportable serious adverse events that occur at COH and non-COH sites and meet COH IRB and DSMC expedited reporting criteria according to City of Hope's Institutional policy. The study PI will also submit a Protocol Management Team (PMT) report to the COH DSMC at the frequency outlined in Section 3.6. This report will include a review of aggregate adverse event data.

14.3.3.2 Reporting to the FDA

The study PI (or designee) will be responsible for contacting the Office of IND Development and Regulatory Affairs (OIDRA) at COH to ensure prompt reporting of safety reports to the FDA. OIDRA will assist the PI with the preparation of the report and submit the report to the FDA in accordance with the approved City of Hope's Institutional policy.

Serious Adverse Events meeting the requirements for expedited reporting to the Food and Drug Administration (FDA), as defined in 21 CFR 312.32, will be reported as an IND safety report using the MedWatch Form FDA 3500A for Mandatory Reporting.

The criteria that require reporting using the Medwatch 3500A are:

- Any unexpected fatal or life threatening adverse experience associated with use of the drug must be reported to the FDA no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]
- Any adverse experience associated with use of the drug that is both serious and unexpected must be submitted no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]
- Any follow-up information to a study report shall be reported as soon as the relevant information becomes available. [21 CFR 312.32(d)(3)]

In addition, the study PI will submit annually within 60 days (via COH OIDRA) of the anniversary date of when the IND went into effect, an annual report to the FDA which is to include a narrative summary and analysis of the information of all FDA reports within the reporting interval, a summary report of adverse drug experiences, and history of actions taken since the last report because of adverse drug experiences.

14.3.3.3 Reporting to Participating Investigators

The study PI (or designee) will report all reportable serious adverse events to participating investigators as an IND Safety Report occurring within 30 calendar days of receipt of sponsor (lead site) notification, and indicate whether or not a protocol and/or consent form change is required. A cover letter will indicate the protocol title, the IND#, whether the FDA was informed, and, for non-COH sites, a statement that the report should be submitted to their local IRB for review as an IND safety report if applicable per local IRB policy.

The study PI will also forward to participating sites all IND safety reports received from AbbVie, indicating whether a consent form or protocol change is required within 30 days of notification to study PI.

14.3.3.4 Reporting to AbbVie

All serious adverse events and AESIs (initial and follow-up information) will be reported by the study PI to AbbVie within 24 hours per the following guidelines: The initial report will be as complete as possible and include an assessment of the causal relationship between the event and the study agent(s). Information not available at the time of the initial report will be documented on a follow-up report and submitted to AbbVie. The principal Investigator shall make available to AbbVie promptly such records as may be necessary and pertinent to investigate any such event, if specifically requested by AbbVie. In addition, report to AbbVie all non-serious adverse events of tumor lysis syndrome (TLS).

- Copy AbbVie on the submission to the FDA of events meeting the definition of IND safety reports at the time of submission to the Agency.
- Notify AbbVie upon any subjects receiving venetoclax whose pregnancy has resulted in a negative outcome or untoward event during the course of pregnancy or upon delivery.

The AbbVie tracking number (**Study # 11354**) will be included on expedited reports (or on the fax cover letter). A copy of the fax transmission confirmation of the expedited report to AbbVie will be retained with the patient records.

AbbVie's contact for reporting serious adverse drug experiences, pregnancy experiences, non-serious adverse events of tumor lysis syndrome, and communication of FDA submissions of IND safety reports is:

E-mail: PPDINDPharmacovigilance@abbvie.com

- Submit annually within 60 days (via COH OIDRA) of the anniversary date of when the IND went into effect, an annual report to the FDA which is to include a narrative summary and analysis of the information of all FDA reports within the reporting interval, a summary report adverse drug experiences, history of actions taken since the last report because of adverse drug experiences.
- Report every 3 months to the COH DSMC a Protocol Management Team (PMT) report, to include aggregate analysis of safety information and accrual and participant status.
- Circulate to all participating sites for submission to their IRBs the COH DSMC report and DSMC recommendation, in accordance with NIH guidance.
- Report to AbbVie aggregate safety information every 3 months at time of COH PMT report.
- Forward to participating sites all reportable AE/UPs as an IND Safety Report occurring within 30 calendar days of receipt of lead site notification, and indicate whether or not a protocol and/or consent form change is required. A cover letter will indicate the protocol title, the IND#, whether

the FDA was informed, and, for non-COH sites, a statement that the report should be submitted to their local IRB for review as an IND safety report if applicable per local IRB policy.

- Forward to participating sites all safety reports received from AbbVie for venetoclax that have not occurred directly on this protocol, indicating whether a consent form or protocol change is required within 30 days of notification to Study PI.

Product Complaints: In addition to compliance with all FDA requirements pursuant to 21 CFR 211 and 21 CFR 820, Principal Investigator will report to AbbVie within 24 hours any suspected quality defect in an AbbVie Product or its AbbVie-provided packaging, labeling, or medical device component (collectively, "Product Complaint"). Principal Investigator will report Product Complaints that involve an AbbVie Product, whether AbbVie has supplied the AbbVie Product used in the Study or not. AbbVie's contact for reporting Product Complaints is:

RD_PQC_QS@abbvie.com

14.4 Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

The investigator must immediately notify the Study PI/ DCC via an expedited report (see Section 7.3.2).

14.5 Tumor Lysis Syndrome

The investigator must immediately notify the Study PI/ DCC via an expedited report any serious or non-serious adverse events of TLS (see Section 7.3.2).

14.6 Overdose

The maximum allowed daily dose of venetoclax in this study is 800 mg, with the intention that participants move incrementally to this dose as described in the protocol.

Any dose of study drug in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any Serious Adverse Event criterion must be reported as a Serious Adverse Event in the appropriate time frame and documented as clinical sequelae to an overdose.

There is no specific antidote for venetoclax. In the event of an overdose, subjects should be closely monitored and given appropriate supportive treatment.

14.7 Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female participant occurring after the participant receives the first dose of protocol therapy through up to 90 days post-last dose of venetoclax are considered immediately reportable events. Protocol therapy is to be discontinued immediately. **The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Study PI/ DCC immediately within 24 hours of awareness** (see Section 7.3.2). The female subject may be referred to an obstetrician-gynecologist (preferably one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

The Investigator should make every effort to follow the female participant until completion of the pregnancy per institutional policies, and should notify the Study PI/ DCC.

Abnormal pregnancy outcomes and neonatal deaths that occur within 28 days of birth should be reported as an SAE per expedited reporting guidelines (see Section 7.3.2).

Any infant death after 28 days that the Investigator suspects is related to the in utero exposure to protocol therapy should also be reported as an SAE per expedited reporting guidelines (see Section 7.3.2)

14.7.1 Male participants

If a female partner of a male participant becomes pregnant within 90 days post-last dose, the male participant should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

The Investigator should make every effort to follow the outcome of the pregnancy per institutional policies, and should notify the Study PI/ DCC.

15.0 PROTOCOL DEVIATIONS AND SINGLE SUBJECT EXCEPTIONS

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. Brief interruptions and delays may occasionally be required because of travel delays, airport closures, inclement weather, family responsibilities, security alerts, government holidays, and so forth. Delays can also extend to complications of disease or unrelated medical illnesses not related to disease progression. The PI has the discretion to deviate from the protocol when necessary so long as such a deviation does not threaten patient safety or protocol scientific integrity. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

15.1 Definitions

15.1.1 Deviation

A deviation is a divergence from a specific element of a protocol. Deviations from the protocol should be avoided, except when necessary to eliminate immediate hazard(s) for the protection, safety, and well-being of a research participant. All protocol deviations and planned protocol deviations will be reported in accordance with the Clinical Research Protocol Deviation Policy. Protocol deviations may be on the part of the subject, the investigator, or the study staff.

15.1.2 Planned Deviations (Single Subject Exceptions)

A **planned deviation** involves circumstances that could increase patient risk or alter protocol integrity, and require prior IRB approval of a single subject exception (SSE) request. In addition, if contractually obligated, the sponsor must also approve the deviation. An IRB pre-approved SSE protocol modification is considered an amendment to the protocol and not a deviation.

15.2 Reporting of Deviations and SSEs

15.2.1 Reporting Deviations

For any deviation, the Investigator will notify the COH DSMC and IRB within 5 calendar days of its occurrence via iRIS in accordance with the Clinical Research Protocol Deviation policy.
A list of deviations from all participating sites will be submitted along with the Protocol Management Team (PMT) progress report to the COH DSMC.

For non-COH sites:

- The local IRB and/or DSMC must be notified according to local institutional policies.

- The study Principal Investigator must be notified as soon as practical (within 24 hours of notification of the event) via email to jazain@coh.org and dcc@coh.org. This email should provide input on the following:
    - Description of the event
    - Impact on participant safety or the safety to others
    - Impact on the study design
    - A corrective and preventative action plan

15.2.2 Reporting Single Subject Exceptions

The SSE must be submitted as a "Single Subject Exception Amendment Request" via iRIS in accordance with IRB guidelines and the Clinical Research Protocol Deviation policy. An IRB approved SSE does not need to be submitted as a deviation to the DSMC.

All non-emergency planned deviations from the protocol must have **prior** approval by the Study Principal Investigator, the Site Principal Investigator, COH IRB, and when applicable, the local IRB. In addition, if contractually obligated, the sponsor must also approve the deviation.

16.0 STUDY OVERSIGHT, QUALITY ASSURANCE, AND DATA & SAFETY MONITORING

16.1 All Investigator Responsibilities

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.

All Investigators agree to:

- Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when necessary to protect the safety, rights or welfare of subjects.
- Personally conduct or supervise the study (or investigation).
- Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
- Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
- Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
- Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
- Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
- Promptly report to the IRB and the Sponsor all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
- Seek IRB and Sponsor approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
- Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

16.2 Study Principal Investigator Responsibilities

The Study Principal Investigator is responsible for the conduct of the clinical trial, including overseeing that sponsor responsibilities as defined in § 21 CFR 312. Subpart D are executed in accordance with federal regulations.

16.3 Protocol Management Team (PMT)

The Protocol Management Team (PMT), minimally consisting of the study PI, site investigators, collaborating investigators, research nurse, clinical research associate/coordinator, and the study

biostatistician, is responsible for ongoing monitoring of the data and safety of this study, including implementation of the stopping rules for safety/toxicity.

The PMT is recommended to meet (in person or via teleconference) at least monthly to review study status. This review will include, but not be limited to, reportable AEs and UPs, and an update of the ongoing study summary that describes study progress in terms of the study schema. The meeting will be a forum to discuss study related issues including accrual, SAE/AEs experienced, study response, deviations/violations and study management issues. The appropriateness of further subject enrollment and the specific intervention for subsequent subject enrollment are addressed. It is recommended that minutes of these discussions be taken to document the date of these meetings, attendees and the issues that were discussed (in a general format).

16.4 Monitoring

Clinical site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and regulatory requirements, and that the quality and integrity of study data and data collection methods are maintained. Monitoring for this study will be performed by the City of Hope Office of Clinical Trials Auditing and Monitoring (OCTAM).

The site Investigator/Institution will permit the study monitors and appropriate regulatory authorities direct access to the study data and to the corresponding source data and documents to verify the accuracy of this data. The Investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

Details of clinical site monitoring are documented in the OCTAM SOP that is provided as a supplement to this document. This document specifies the frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of subject data to be reviewed), and the distribution of monitoring reports. Staff from OCTAM will conduct monitoring activities and provide reports of the findings and associated action items in accordance with the details described in the CMP. Documentation of monitoring activities and findings will be provided to the site study team, the site PI, study PI, and the COH DSMC.

16.5 Quality Assurance

The City of Hope Clinical Research Information Support will provide support for this multi-center trial as detailed in the COH DCC Operations Plan provided as a supplement to this document.

16.6 City of Hope Data and Safety Monitoring Committee

This is a risk level 4 study as defined in the City of Hope Institutional Data and Safety Monitoring Plan. This determination was made because the study involves a COH held IND.

The DSMC is a multidisciplinary committee charged with overseeing the monitoring of safety of participants in clinical trials, and the conduct, progress, validity, and integrity of the data for all clinical

trials that are sponsored by City of Hope. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. The committee reviews the progress and safety of all active research protocols that are not monitored by another safety and data monitoring committee or board.

The Study Principal Investigator is required to submit periodic status reports (the PMT report) according to the guidelines outlined in the City of Hope Institutional Data and Safety Monitoring Plan. The PMT report will be submitted to the COH DSMC every 3 months from the date of activation.

The COH Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The DSMC will review up-to-date participant accrual; summary of all adverse events captured via routine and expedited reporting; a summary of deviations; any response information; monitoring reports, and summary comments provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request. For Phase I studies, a Phase I Tracking Log will be utilized and reviewed by the DSMC to monitor data and safety for dose escalation. A review of outcome results (response, toxicity and adverse events) and factors external to the study (such as scientific or therapeutic developments) is discussed, and the Committee votes on the status of each study. Information that raises any questions about participant safety will be addressed with the Principal Investigator, statistician and study team. The PMT report and DSMC recommendations will be circulated to all participating sites for submission to their IRBs, in accordance with NIH guidance.

17.0 ETHICAL AND REGULATORY CONSIDERATIONS

17.1 Ethical Standard

This study will be conducted in conformance with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979) and the Declaration of Helsinki.

17.2 Regulatory Compliance

This study is to be conducted in compliance with the IRB approved protocol and according to the following considerations:

- US Code of Federal Regulations (CFR) governing clinical study conduct
  - Title 21 Part 11 – Electronic Records; Electronic Signatures
  - Title 21 Part 50 – Protection of Human Subjects
  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
  - Title 21 Part 56 – Institutional Review Boards
  - Title 21 Part 58 – Good Laboratory Practice for Nonclinical Laboratory Studies
  - Title 21 Part 312 – Investigational New Drug Application
  - Title 45 Part 46 – Protection of Human Subjects
- US Federal legislation, including but not limited to
  - Health Insurance Portability and Accountability Act of 1996
  - Section 801 of the Food and Drug Administration Amendments Act
- Applicable state and local laws. For research occurring in California, this includes but is not limited to State of California Health and Safety Code, Title 17

- Applicable institutional research policies and procedures

17.3 Institutional Review Board

Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents by an appropriate IRB holding a current US Federal wide Assurance issued by and registered with the Office for Human Research Protections (OHRP).

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB's written unconditional approval of the study protocol and the informed consent document will be in the possession of the Investigator, and, for sites external to COH, the possession of the coordinating center, before the study is initiated. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

The IRB will be informed of revisions to other documents originally submitted for review; serious unexpected or unanticipated adverse experiences occurring during the study, and any additional adverse experiences in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

Any amendment to the protocol document and accompanying informed consent document/template, as developed and provided by the Study PI, will require review and approval by the IRB before the changes are implemented in the study. The protocol and consent will be reviewed and approved by the COH IRB before submission to a participating site IRB.

17.4 Informed Consent

For a multi-site study, each participating institution will be provided with a model informed consent form. Each institution may revise or add information to comply with local and/or institutional requirements, but may not remove procedural or risk content from the model consent form. Furthermore, prior to submission to the IRB (initial submission and amendments), the consent and accompanying HIPAA form, if separate to the consent, must be reviewed and approved by the DCC.

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

Before implementing any study procedure, informed consent shall be documented by the use of a written consent form approved by the IRB/IEC and signed and dated by the patient or the patient's legally authorized representative at the time of consent. A copy of the signed informed consent will be given to the patient or patient's legally authorized representative. The original signed consent must be maintained by the Site Investigator and available for inspection sponsor designated representatives, or regulatory authority at any time.

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation.

17.5 Participant Withdrawal

Participants may withdraw from the study at any time and for any reason without prejudice. The withdrawal must be documented per institutional policies. The COH DCC should be promptly notified of the change in participant status.

Participant withdrawal may consist of any of the following with regard to study procedures and data collection:

- Withdrawal from study treatment, but agreement to continue with active study procedures and chart review and survival follow-up.
- Withdrawal from study treatment and all active procedures, but agreement for chart review and survival follow-up.
- Withdrawal from study treatment, all active procedures, and any future data collection.

Participants who agreed to the collection of research blood samples may withdraw consent to use their specimens, if they are not yet processed as detailed in the consent form. Once the PI and site PI is notified of this withdrawal of informed consent, the research specimens will not be used in any research. At that time, any of the existing specimens will be destroyed.

17.6 Special and Vulnerable Populations

17.6.1 Inclusion of Women and Minorities

The study is open anyone regardless of gender, race or ethnicity. Efforts will be made to extend the accrual to a representative population. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

Pregnant women are excluded because the effect of Bcl-2 inhibition on pregnancy has not been fully characterized.

17.6.2 Exclusion of Pediatric Population

Pediatric participants (< 18 years old of age) are excluded from this study since safety and effectiveness of protocol therapy has not been defined for PTCL. Additional studies may be performed in the pediatric population once safety and effectiveness of protocol therapy is defined in the adult PTCL population.

The incidence of PTCL is rare in the pediatric population.

17.6.3 Inclusion of HIV Positive Individuals

Patients with active human immunodeficiency virus (HIV) are excluded. Subjects who have an undetectable HIV viral load with CD4 > 200 and are on HAART medication are allowed.

17.6.4 Vulnerable Populations

45 CFR §46.111 (a)(3) and 45 CFR §46, Subparts B-D identifies children, prisoners, pregnant women, mentally incapacitated persons, or economically or educationally disadvantaged persons as vulnerable populations.

Adults lacking capacity to consent are not excluded from participation. This study does not pose additional risks for adults lacking capacity than for the general population. In such instances, informed consent will be sought and documented from the prospective participant's legally authorized representative in agreement with institutional policies and local IRB approval.

17.7 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to any study information relating to participants.

This research will be conducted in compliance with federal and state requirements relating to protected health information (PHI), including the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require a signed subject authorization informing the subject of the nature of the PHI to be collected, who will have access to that information and why, who will use or disclose that information, ant the rights of a research participant to revoke their authorization for use of their PHI. In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508. When results of this study are reported in medical journals or at meetings, identification of those taking part will not be disclosed and no identifiers will be used.

Medical records of subjects will be securely maintained in the strictest confidence, according to current legal requirements. Data will be entered, analyzed and stored in encrypted, password protected, secure computers that meet all HIPAA requirements. All data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. Source documents provided to coordinating center for the purpose of auditing or monitoring will be de-identified and labeled with the study number, subject ID, and if applicable patient initials.

The investigator/institution will permit direct access to source data and documents by sponsor representatives, the FDA, and other applicable regulatory authorities. The access may consist of trial-related monitoring, including remote monitoring, audits, IRB/IEC reviews, and FDA/regulatory authority inspections. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Participant specimens will be de-identified (coded) prior to submission to research laboratories. The specimens will be labeled with the study number, subject ID, date and timepoint of collection. The key to the code will be maintained in the COH clinical trials management system which is a secure environment.

17.8 Use of Unused (Leftover) Specimens Collected for this Trial

Unused samples in existence at study completion (i.e. completion of all research activities under this study) will either be: (a) placed in a COH IRB approved biorepository with some clinical information and potentially PHI attached or (b) discarded.

With regard to which option will apply, each site IRB may choose to either: (a) leave the determination to the participant via a question in the informed consent document, which would be communicated to the study registrar (DCC) at the time of participant registration, OR b) may choose to make a single determination on behalf of their respective participants, and communicate that determination to their respective participants via the informed consent.

17.9 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study Sponsor (City of Hope) prior to participation in this study. All City of Hope investigators will follow the City of Hope conflict of interest policy.

17.10 Financial Obligations, Compensation, and Reimbursement of Participants

Venetoclax will be provided free of charge to participants.

Neither the research participant nor the insurance carrier will be responsible for the research procedures related to this study.

Standard of care drugs or procedures provided during the course of study participation will be the responsibility of the research participant and/or the insurance carrier. The participant will be responsible for all copayments, deductibles, and other costs of treatment and diagnostic procedures as set forth by the insurance carrier. The participant and/or the insurance carrier will be billed for the costs of treatment and diagnostic procedures in the same way as if the participant were not in a research study.

In the event of physical injury to a participant resulting from research procedures, appropriate medical treatment will be available at City of Hope or at the non-COH site to the injured participant. There are no plans for City of Hope to provide financial compensation in the event of physical injury to a participant.

The research participant will not receive reimbursement or payment for taking part in this study.

17.11 Publication/ Data Sharing

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by City of Hope for the purposes of performing the study, will be published or passed on to any third party without the written approval of the Study PI. Any investigator involved with this study is obligated to provide City of Hope with complete test results and all data derived from the study.

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement between City of Hope and AbbVie. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

In accordance with the U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801, this trial will be registered onto ClinicalTrials.gov and results will be reported on ClinicalTrials.gov within 12 months of the estimated or actual completion date of the trial, whichever date is earlier.

18.0 REFERENCES

1. DiNardo, C.D., et al., *Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia.* Blood, 2019. **133**(1): p. 7-17.
2. Abouyabis, A.N., et al., *Incidence and outcomes of the peripheral T-cell lymphoma subtypes in the United States.* Leuk Lymphoma, 2008. **49**(11): p. 2099-107.
3. Jaffe, E.S., et al., *Classification of lymphoid neoplasms: the microscope as a tool for disease discovery.* Blood, 2008. **112**(12): p. 4384-99.
4. Savage, K.J., *Peripheral T-cell lymphomas.* Blood Rev, 2007. **21**(4): p. 201-16.
5. Weisenburger, D.D., et al., *Peripheral T-cell lymphoma, not otherwise specified: a report of 340 cases from the International Peripheral T-cell Lymphoma Project.* Blood, 2011. **117**(12): p. 3402-8.
6. O'Connor, O.A., et al., *Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study.* J Clin Oncol, 2011. **29**(9): p. 1182-9.
7. Coiffier, B., et al., *Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy.* J Clin Oncol, 2012. **30**(6): p. 631-6.
8. O'Connor, O.A., et al., *Belinostat in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma: Results of the Pivotal Phase II BELIEF (CLN-19) Study.* J Clin Oncol, 2015. **33**(23): p. 2492-9.
9. Pro, B., et al., *Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study.* J Clin Oncol, 2012. **30**(18): p. 2190-6.
10. Shi, Y., et al., *Results from a multicenter, open-label, pivotal phase II study of chidamide in relapsed or refractory peripheral T-cell lymphoma.* Ann Oncol, 2015. **26**(8): p. 1766-71.
11. Willis, S., et al., *The Bcl-2-regulated apoptotic pathway.* J Cell Sci, 2003. **116**(Pt 20): p. 4053-6.
12. Cory, S., D.C. Huang, and J.M. Adams, *The Bcl-2 family: roles in cell survival and oncogenesis.* Oncogene, 2003. **22**(53): p. 8590-607.
13. Borner, C., *The Bcl-2 protein family: sensors and checkpoints for life-or-death decisions.* Mol Immunol, 2003. **39**(11): p. 615-47.
14. Cimmino, A., et al., *miR-15 and miR-16 induce apoptosis by targeting BCL2.* Proc Natl Acad Sci U S A, 2005. **102**(39): p. 13944-9.
15. Gerecitano, J.F., et al., *A Phase 1 Study of Venetoclax (ABT-199 / GDC-0199) Monotherapy in Patients with Relapsed/Refractory Non-Hodgkin Lymphoma.* Blood, 2015. **126**(23).
16. Reed, J.C., et al., *BCL-2 family proteins: regulators of cell death involved in the pathogenesis of cancer and resistance to therapy.* J Cell Biochem, 1996. **60**(1): p. 23-32.
17. Rassidakis, G.Z., et al., *BCL-2 family proteins in peripheral T-cell lymphomas: correlation with tumour apoptosis and proliferation.* J Pathol, 2003. **200**(2): p. 240-8.
18. Jung, J.T., et al., *Clinical role of Bcl-2, Bax, or p53 overexpression in peripheral T-cell lymphomas.* Ann Hematol, 2006. **85**(9): p. 575-81.
19. Mao, X., et al., *BCL2 and JUNB abnormalities in primary cutaneous lymphomas.* Br J Dermatol, 2004. **151**(3): p. 546-56.
20. O'Malley, D.P., et al., *Utility of BCL2, PD1, and CD25 immunohistochemical expression in the diagnosis of T-cell lymphomas.* Appl Immunohistochem Mol Morphol, 2014. **22**(2): p. 99-104.
21. Souers, A.J., et al., *ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets.* Nat Med, 2013. **19**(2): p. 202-8.

22. Del Gaizo Moore, V., et al., *BCL-2 dependence and ABT-737 sensitivity in acute lymphoblastic leukemia.* Blood, 2008. **111**(4): p. 2300-9.

23. Mason, K.D., et al., *Programmed anuclear cell death delimits platelet life span.* Cell, 2007. **128**(6): p. 1173-86.

24. Vogler, M., et al., *ABT-199 selectively inhibits BCL2 but not BCL2L1 and efficiently induces apoptosis of chronic lymphocytic leukaemic cells but not platelets.* Br J Haematol, 2013. **163**(1): p. 139-42.

25. Pan, R., et al., *Selective BCL-2 inhibition by ABT-199 causes on-target cell death in acute myeloid leukemia.* Cancer Discov, 2014. **4**(3): p. 362-75.

26. Touzeau, C., et al., *The Bcl-2 specific BH3 mimetic ABT-199: a promising targeted therapy for t(11;14) multiple myeloma.* Leukemia, 2014. **28**(1): p. 210-2.

27. Vandenberg, C.J. and S. Cory, *ABT-199, a new Bcl-2-specific BH3 mimetic, has in vivo efficacy against aggressive Myc-driven mouse lymphomas without provoking thrombocytopenia.* Blood, 2013. **121**(12): p. 2285-8.

28. Peirs, S., et al., *ABT-199 mediated inhibition of BCL-2 as a novel therapeutic strategy in T-cell acute lymphoblastic leukemia.* Blood, 2014. **124**(25): p. 3738-47.

29. AbbVie, *Venetoclax Investigator's Brochure*. 2019.

30. AbbVie, *ABT-199 Investigator's Brochure*. 2015.

31. Roberts, A.W., et al., *Targeting BCL2 with Venetoclax in Relapsed Chronic Lymphocytic Leukemia.* N Engl J Med, 2016. **374**(4): p. 311-22.

32. Davids, M.S., et al., *Phase I First-in-Human Study of Venetoclax in Patients With Relapsed or Refractory Non-Hodgkin Lymphoma.* Journal of Clinical Oncology, 2017: p. JCO.2016.70.4320.

33. Grunstein, M., *Histone acetylation in chromatin structure and transcription.* Nature, 1997. **389**(6649): p. 349-52.

34. Johnstone, R.W., *Histone-deacetylase inhibitors: novel drugs for the treatment of cancer.* Nat Rev Drug Discov, 2002. **1**(4): p. 287-99.

35. Marks, P., et al., *Histone deacetylases and cancer: causes and therapies.* Nat Rev Cancer, 2001. **1**(3): p. 194-202.

36. Bates, S.E., et al., *Laboratory correlates for a phase II trial of romidepsin in cutaneous and peripheral T-cell lymphoma.* Br J Haematol, 2010. **148**(2): p. 256-67.

37. Imesch, P., D. Fink, and A. Fedier, *Romidepsin reduces histone deacetylase activity, induces acetylation of histones, inhibits proliferation, and activates apoptosis in immortalized epithelial endometriotic cells.* Fertil Steril, 2010. **94**(7): p. 2838-42.

38. Woo, S., et al., *Population pharmacokinetics of romidepsin in patients with cutaneous T-cell lymphoma and relapsed peripheral T-cell lymphoma.* Clin Cancer Res, 2009. **15**(4): p. 1496-503.

39. Furumai, R., et al., *FK228 (depsipeptide) as a natural prodrug that inhibits class I histone deacetylases.* Cancer Res, 2002. **62**(17): p. 4916-21.

40. Byrd, J.C., et al., *A phase 1 and pharmacodynamic study of depsipeptide (FK228) in chronic lymphocytic leukemia and acute myeloid leukemia.* Blood, 2005. **105**(3): p. 959-67.

41. Marshall, J.L., et al., *A phase I trial of depsipeptide (FR901228) in patients with advanced cancer.* J Exp Ther Oncol, 2002. **2**(6): p. 325-32.

42. Sandor, V., et al., *Phase I trial of the histone deacetylase inhibitor, depsipeptide (FR901228, NSC 630176), in patients with refractory neoplasms.* Clin Cancer Res, 2002. **8**(3): p. 718-28.

43. Piekarz, R.L., et al., *Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma.* J Clin Oncol, 2009. **27**(32): p. 5410-7.

44. Newbold, A., et al., *Characterisation of the novel apoptotic and therapeutic activities of the histone deacetylase inhibitor romidepsin.* Mol Cancer Ther, 2008. **7**(5): p. 1066-79.

45. Xargay-Torrent, S., et al., *Vorinostat-induced apoptosis in mantle cell lymphoma is mediated by acetylation of proapoptotic BH3-only gene promoters.* Clin Cancer Res, 2011. **17**(12): p. 3956-68.

46. Fiskus, W., et al., *Cotreatment with vorinostat enhances activity of MK-0457 (VX-680) against acute and chronic myelogenous leukemia cells.* Clin Cancer Res, 2008. **14**(19): p. 6106-15.

47. Chen, J., et al., *Cotreatment with BCL-2 antagonist sensitizes cutaneous T-cell lymphoma to lethal action of HDAC7-Nur77-based mechanism.* Blood, 2009. **113**(17): p. 4038-48.

48. Cyrenne, B.M., et al., *Synergy of BCL2 and histone deacetylase inhibition against leukemic cells from cutaneous T-cell lymphoma patients.* Blood, 2017. **130**(19): p. 2073-2083.

49. Swerdlow, S.H., et al., *The 2016 revision of the World Health Organization classification of lymphoid neoplasms.* Blood, 2016. **127**(20): p. 2375-90.

50. Cheson, B.D., et al., *Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification.* Journal of Clinical Oncology, 2014.

51. Feeney, J., et al., *Characterization of T-cell lymphomas by FDG PET/CT.* AJR Am J Roentgenol, 2010. **195**(2): p. 333-40.

52. Weiler-Sagie, M., et al., *(18)F-FDG avidity in lymphoma readdressed: a study of 766 patients.* J Nucl Med, 2010. **51**(1): p. 25-30.

53. Simon, R., *Optimal two-stage designs for phase II clinical trials.* Control Clin Trials, 1989. **10**(1): p. 1-10.

54. Oken, M.M., et al., *Toxicity and response criteria of the Eastern Cooperative Oncology Group.* Am J Clin Oncol, 1982. **5**(6): p. 649-55.

55. Howard, S.C., D.P. Jones, and C.H. Pui, *The tumor lysis syndrome.* N Engl J Med, 2011. **364**(19): p. 1844-54.

56. Dolgin, M., et al., *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels.* 9 edn (Boston, Little, Brown and Company). 1994.

APPENDIX A: PERFORMANCE STATUS

ECOG Performance Scale [54]	
Grade	**Descriptions**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: TUMOR LYSIS SYNDROME CLASSIFICATION

Based on Howard et al., 2011 [55].

Metabolic Abnormality	Criteria for Classification of Laboratory Tumor Lysis Syndrome*	Criteria for Classification of Clinical Tumor Lysis Syndrome**
Hyperuricemia	Uric acid > 8.0 mg/dl (475.8 µmol/L)	
Hyperphosphatemia	Phosphorus > 4.5 mg/dl (1.5 mmol/L)	
Hyperkalemia	Potassium > 6.0 mmol/L	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hypocalcemia	Corrected calcium < 7.0 mg/dL (1.75 mmol/L(or ionized calcium < 1.12 (0.3 mmol/L)†	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia
Acute kidney injury‡ *If no institutional ULN is specified, age/sex ULN creatinine may be defined as follows: > 1 to < 12 years of age, both male and female, 61.6 µmol/L; ≥ 12 to < 16 years, both male and female, 88 µmol/L; ≥ 16 years, female 105.6 µmol/L, male 114.4 µmol/L.*	N/A	Increase in the serum creatinine level of 0.3 mg/dL (26.5 µmol/liter) or the presence of oliguria (average urine output of < 0.5 mL/kg/hr over a 6-hour period)

* In laboratory tumor lysis syndrome ≥ 2 metabolic abnormalities must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 afterwards.
** Clinical TLS requires the presence of laboratory TLS plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.
† Corrected calcium = measured calcium level in mg/dL + 0.8 x (4-albumin in g/dL).
‡ Acute kidney injury, unless attributable to another cause, represents clinical TLS even if criteria for laboratory TLS are not satisfied.

APPENDIX C-1: PTCL-DISEASE PARAMETERS & METHODS OF EVALUATION AND RESPONSE

Response will be assessed per Lugano Classification [50]

Disease Parameters

- Measurable disease

  Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥15 mm (≥ 1.5 cm) by chest x-ray, CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

  Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable

- Malignant lymph nodes

  To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

- Non-measurable disease

  Pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

  - Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
  - 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

- Target lesions

  All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

- Non-target lesions
  All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- Clinical lesions
  Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

- Conventional CT and MRI
  This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

  Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the Lugano Classification [5] to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. For this trial, MRI will not be used as standard imaging study for disease assessment.

- **PET-CT** at present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with Lugano Classification [5]. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

- **FDG-PET:** While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
  - FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

APPENDIX C-2: PTCL RESPONSE CRITERIA

Response	Site	CT-Based Response	PET-CT Based Response
Complete Response		Complete radiologic response (all of the following)	Complete metabolic response (even with a persistent mass)
	Lymph nodes and extralymphatic sites	Target nodes/nodal masses must regress to ≤1.5 cm in longest diameter. No extralymphatic sites of disease.	Score ≤ 3* with or without a residual mass on 5-point scale†. It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., 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.
	Nonmeasured lesion	Absent	Not applicable
	Organ enlargement	Regress to normal	Not applicable
	New lesions	None	None
	Bone marrow	Normal by morphology; if determinate, IHC negative	No evidence of FDG-avid disease in marrow
Partial Response		Partial remission (all of the following)	Partial metabolic response
	Lymph nodes and extralymphatic sites	≥ 50% decrease in SPD of up to 6 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	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*

Response	Site	CT-Based Response	PET-CT Based Response
	Nonmeasured lesion	Absent/normal, regressed, but no increase	Not applicable
	Organ enlargement	Spleen must have regressed by > 50% in length beyond normal	Not applicable
	New lesions	None	None
	Bone marrow	Not applicable	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
No response or stable disease		Stable disease	No metabolic response
	Target nodes/nodal masses, extranodal lesions	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met	Score 4 or 5† with no significant change in FDG uptake from baseline at interim or end of treatment
	Nonmeasured lesion	No increase consistent with progression	Not applicable
	Organ enlargement	No increase consistent with progression	Not applicable
	New lesions	None	None
	Bone marrow	Not applicable	No change from baseline
Progressive disease		Progressive disease requires at least 1 of the following	Progressive metabolic disease
	Individual target nodes/nodal masses	PPD progression:	Score 4 or 5 with an increase in intensity of uptake from baseline and/or
	Extranodal lesions	An individual node/lesion must be abnormal with: Longest diameter (LDi) > 1.5 cm and Increase by ≥ 50% from PPD nadir and	New FDG-avid foci consistent with lymphoma at interim OR • End-of-treatment assessment

Response	Site	CT-Based Response	PET-CT Based Response
		An increase in LDi or smallest diameter (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% of the extent of its prior increase beyond baseline (e.g., 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 lesion	New or clear progression of preexisting nonmeasured lesions	None
	New lesions	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	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.
	Bone marrow	New or recurrent involvement	New or recurrent FDG-avid foci

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 (e.g., 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 (e.g., 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).

*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).

†PET 5-point score:

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.

Abbreviations:

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.

APPENDIX D: SAMPLE LIST OF PROHIBITED AND CAUTIONARY AGENTS

Prohibited during Cycle 1 and Cautionary Thereafter:

Strong CYP3A inducers - avasimibe, carbamazepine, enzalutamine, mitotane, phenytoin, rifampin, St. John's wort

Moderate CYP3A inducers - bosentan, efavirenz, etravirine, modafinil, nafcillin,

Strong CYP3A inhibitors† - boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, elvitegravir/ritonavir, idelalisib,* indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir, nefazodone, nelfinavir, ritonavir, paritaprevir/ritonavir combinations, posaconazole, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir, voriconazole

Moderate CYP3A inhibitors‡ - amprenavir, aprepitant, atazanavir, cimetidine, ciprofloxacin, clotrimazole, crizotinib*, cyclosporine*, darunavir/ritonavir, diltiazem[1], erythromycin, fluconazole, fosamprenavir, imatinib*, isavuconazole, tofisopam, verapamil

P-gp inhibitors

Amiodarone, azithromycin, captopril, carvedilol, dronedarone, felodipine, quercetin, quinidine, ronalzine, ticagrelor

Cautionary

Warfarin and coumarin derivatives**

P-gp substrates

Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus*, fexofenadine, lapatinib*, loperamide, maraviroc, nilotinib*, ranolazine, saxagliptin, sirolimus*, sitagliptin, talinolol, tolvaptan, topotecan*

BCRP substrates

Methotrexate*, mitoxantrone*, irrinotecan*, lapatinib*, rosuvastatin, sulfasalazine, topotecan*

OATP1B1/1B3 substrates

Atrasentan, atorvastatin, ezetimibe, fluvastatin, glyburide, rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, telmisartan, valsartan, olmesartan

BCRP inhibitors

Geftinib*

Note that this is not an exhaustive list. For an updated list, see the following link:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

In addition to the medications listed in this table, subjects receiving venetoclax should not consume grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or starfruit.

* These are anticancer agents; consult contact AbbVie medical monitor before use.

** Closely monitor the international normalized ratio (INR).

[1] Moderate CYP3A inhibitor per venetoclax FDA USPI.

†Reduce the venetoclax dose by at least 4-fold during co-administration

‡Reduce the venetoclax dose by 2-fold during co-administration

APPENDIX E: NYHA CARDIAC GRADING CRITERIA

Modified from Dolgin et al., 1994 [56]

New York Heart Association Classification of Heart Failure	
Class I	No symptoms. Ordinary physical activity such as walking and climbing stairs does not cause fatigue or dyspnea.
Class II	Symptoms with ordinary physical activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold weather, in wind or when under emotional stress causes undue fatigue or dyspnea.
Class III	Symptoms with less than ordinary physical activity. Walking one to two blocks on the level and climbing more than one flight of stairs in normal conditions causes undue fatigue or dyspnea.
Class IV	Symptoms at rest. Inability to carry on any physical activity without fatigue or dyspnea.

APPENDIX F-1: TISSUE SHIPPING GUIDELINES FOR EXTERNAL NON-COH SITES

These guidelines apply to non-COH sites only.

All biological material must be shipped according to applicable government and International Air Transport Association (IATA) regulations.

Shipping guidelines can also be found on the FedEx website.

1. Aim to ship samples on a **Monday through Wednesday**. If this is not feasible, advance arrangements should be made with City of Hope Pathology Core (DL-PATHCORE-BiospecimenSupport@COH.org).
2. Notify City of Hope Pathology Core (DL-PATHCORE-BiospecimenSupport@COH.org) of impending shipment. To request a FedEx shipping label, email DCC@coh.org and indicate the planned shipment date.
3. **Slides/Blocks:** Batch ship at room temperature via FedEx. During extreme heat, include refrigerated (not frozen) gel packs or gel insulators.

   It is recommended to ship samples via FedEx overnight (for a delivery by 3 pm or earlier the next day) or FedEx 2-day (with a morning delivery). During extreme heat, ship via FedEx overnight (for a delivery ideally by 10.30 am, or 3 pm the next day).
4. **Frozen samples** should be batch shipped on dry ice via FedEx following collection. The shipment should contain enough dry ice to last at least 72 hours.
5. On the day of shipment, email the sample shipment information to City of Hope Pathology Core (DL-PATHCORE-BiospecimenSupport@COH.org).
6. Ship samples with a **copy of the correlative tissue form (Appendix X)** and a **copy of the pathology report** to:

   Karen Miller
   COH Pathology Core
   City of Hope National Medical Center
   1500 E. Duarte Road
   Familian Science (Building 084), Room 1207
   Duarte, CA 91010
   T: 626-218-8408
   Email: DL-PATHCORE-BiospecimenSupport@COH.org

APPENDIX F-2: CORRELATIVE TISSUE FORM (FOR ALL SITES)

A copy of this form should <u>accompany the sample shipments</u> to COH Pathology Core.

Non-COH sites: refer to Appendix F-1 for shipping instructions to COH Pathology Core.

COH IRB number: 18119	Shipping date (MM-DD-YYYY): _____/_____/_____
Subject ID (issued by DCC):	Participant Initials (F, M, L) (if applicable):
Institution:	
Date of collection/ biopsy (MM-DD-YYYY): _____/_____/_____	
Time point: ☐ Baseline ☐ Progression	
Diagnosis:	
Tissue type (FFPE scrolls, slides, biopsies):	
Number of scrolls:	Number of slides:

CRA/Study Coordinator/Nurse Printed Name:
CRA/Study Coordinator/Nurse Signature:
Contact Number:

APPENDIX G-1: VENETOCLAX PILL DIARY INSTRUCTIONS

Remember to bring this diary, all pill bottles, and any unused pills to each clinic visit.

Call your study doctor or nurse immediately if you are having any new or worsening side effects.

Study drug Instructions – When and How:

- Take venetoclax **once a day** by mouth
- Take the pills with a meal and water at approximately the same time each day
- Swallow pills; do not chew them or crush them
- Do not skip any doses unless your doctor tells you to.
- Do not drink grapefruit juice, eat grapefruit, Seville oranges or marmalades, or starfruit while you are taking venetoclax.

When to stop taking venetoclax

- Do not stop taking venetoclax unless your doctor tells you to.

What if I miss a scheduled dose?

- If **less than 8 hours** have passed from the scheduled time, then **take the missed dose** as soon as you remember.
- If more than 8 hours have passed from the scheduled time, then skip the missed dose. Wait for your next scheduled dose. Do not take extra medicine to make up the missed dose.

What if I vomit after taking venetoclax?

- If you vomit your pills, write this down in your pill diary.
- Wait until the next scheduled dose; do not take extra medicine to make up the vomited dose.

Additional Instructions:

- Bring this diary, all pill bottles, and any unused pills to each clinic visit.
- Keep your study drug in the original container until you take it.
- Do NOT throw away empty pill bottles or unused pills.
- **Your dose may be adjusted based on your side effects**

Contact Information		
Study Doctor **Phone:** **Name:**	**Study Nurse** **Phone:** **Name:**	**Backup Study Nurse** **Phone:** **Name:**

APPENDIX G-2: VENETOCLAX PILL DIARY (CYCLE 1)

Subject ID#:	Patient Initials (F, M, L):	
Institution:	Cycle #:	Cycle start date:
	☐ Safety Lead-in ☐ Phase 2	

Call your study doctor or nurse <u>immediately</u> if you are having any new or worsening side effects.

Your study doctor or nurse will tell you what to do.

Your dose may be adjusted based on your side effects.

Day	Week Day	Date	Time	# Pills Taken	Comments
1			___:___AM/PM		Planned # pills___
2			___:___AM/PM		**Planned clinic day. DO NOT take your pill(s) until the study team tells you to do so.** Planned # pills___
3			___:___AM/PM		Planned # pills___
4			___:___AM/PM		Planned # pills___
5			___:___AM/PM		Planned # pills___
6			___:___AM/PM		Planned # pills___
7			___:___AM/PM		Planned # pills___

Day	Week Day	Date	Time	# Pills Taken	Comments
8			___:___AM/PM		**Planned clinic day. DO NOT take your pill(s) until the study team tells you to do so.** Planned # pills___
9			___:___AM/PM		Planned # pills___
10			___:___AM/PM		Planned # pills___
11			___:___AM/PM		Planned # pills___
12			___:___AM/PM		Planned # pills___
13			___:___AM/PM		Planned # pills___
14			___:___AM/PM		Planned # pills___

Day	Week Day	Date	Time	# Pills Taken	Comments
15			___:___AM/PM		**Planned clinic day. DO NOT take your pill(s) until the study team tells you to do so.** Planned # pills___
16			___:___AM/PM		Planned # pills___
17			___:___AM/PM		Planned # pills___
18			___:___AM/PM		Planned # pills___
19			___:___AM/PM		Planned # pills___
20			___:___AM/PM		Planned # pills___
21			___:___AM/PM		Planned # pills___

Participant/Caregiver Signature (please sign when submitting your diary):	**Date:** ____/_____/_____

Subject ID#:	Patient Initials (F, M, L):	
Institution:	Cycle #:	Cycle start date:
	☐ Safety Lead-in ☐ Phase 2	

Day	Week Day	Date	Time	# Pills Taken	Comments
22			___:___AM/PM		**Planned clinic day. DO NOT take your pill(s) until the study team tells you to do so.** Planned # pills___
23			___:___AM/PM		Planned # pills___
24			___:___AM/PM		Planned # pills___
25			___:___AM/PM		Planned # pills___
26			___:___AM/PM		Planned # pills___
27			___:___AM/PM		Planned # pills___
28			___:___AM/PM		Planned # pills___

Participant/Caregiver Signature (please sign when submitting your diary):	**Date:** ____/_____/_____

Study Team ONLY: # of Pill Bottles Returned: _____ # of Pills Returned: _____

Compare with drug diary entries made by participant/guardian. If there is a discrepancy (in the # of bottles or the # of pills returned), please reconcile (initials & date):_____

APPENDIX G-3: VENETOCLAX PILL DIARY (CYCLE 2+)

Subject ID#:	Patient Initials (F, M, L):	
Institution:	Cycle #:	Cycle start date:
	☐ Safety Lead-in ☐ Phase 2	

Call your study doctor or nurse <u>immediately</u> if you are having any new or worsening side effects.

Your study doctor or nurse will tell you what to do.

Your dose may be adjusted based on your side effects.

Day	Week Day	Date	Time	# Pills Taken	Comments
1			___:___AM/PM		Planned # pills___
2			___:___AM/PM		Planned # pills___
3			___:___AM/PM		Planned # pills___
4			___:___AM/PM		Planned # pills___
5			___:___AM/PM		Planned # pills___
6			___:___AM/PM		Planned # pills___
7			___:___AM/PM		Planned # pills___

Day	Week Day	Date	Time	# Pills Taken	Comments
8			___:___AM/PM		Planned # pills___
9			___:___AM/PM		Planned # pills___
10			___:___AM/PM		Planned # pills___
11			___:___AM/PM		Planned # pills___
12			___:___AM/PM		Planned # pills___
13			___:___AM/PM		Planned # pills___
14			___:___AM/PM		Planned # pills___

Day	Week Day	Date	Time	# Pills Taken	Comments
15			___:___AM/PM		Planned # pills___
16			___:___AM/PM		Planned # pills___
17			___:___AM/PM		Planned # pills___
18			___:___AM/PM		Planned # pills___
19			___:___AM/PM		Planned # pills___
20			___:___AM/PM		Planned # pills___
21			___:___AM/PM		Planned # pills___

Participant/Caregiver Signature (please sign when submitting your diary):	**Date:** ____/_____/_____

Subject ID#:	Patient Initials (F, M, L):	
Institution:	Cycle #:	Cycle start date:
	☐ Safety Lead-in ☐ Phase 2	

Day	Week Day	Date	Time	# Pills Taken	Comments
22			___:___AM/PM		Planned # pills___
23			___:___AM/PM		Planned # pills___
24			___:___AM/PM		Planned # pills___
25			___:___AM/PM		Planned # pills___
26			___:___AM/PM		Planned # pills___
27			___:___AM/PM		Planned # pills___
28			___:___AM/PM		Planned # pills___

Participant/Caregiver Signature (please sign when submitting your diary):	**Date:** ____/_____/_____

Study Team ONLY: # of Pill Bottles Returned: _____ # of Pills Returned: _____

Compare with drug diary entries made by participant/guardian. If there is a discrepancy (in the # of bottles or the # of pills returned), please reconcile (initials & date):_____

APPENDIX H-1: DCC REGISTRATION COVERSHEET

COH Protocol #18119: **A Phase 2 Study of Venetoclax with Safety Lead-in for Treatment of Relapsed/Refractory Mature T-cell Lymphomas**

Data Coordinating Center
City of Hope
1500 Duarte Road
Duarte, CA 91010
Tel: 626-218-7904
Email: DCC@coh.org (use #secure# in subject line)

Site Principal Investigator
Name:
Address:

Phone:
Fax:
e-mail:

CRA/Study Coordinator:	Contact Number:
Patient's Initials: (F M L):	Institution:
Medical Record No:	Investigator/Treating Physician:
Patient's DOB:	IRB approval valid until (date):
Sex: _____Male _____Female	Date Informed Consent Signed:
	Projected start date of treatment:

Race		Ethnicity		Method of Payment:_____	
☐	Black	☐	Hispanic	Codes:	
☐	Caucasian	☐	Non-Hispanic	01 Private	06 Military or Veterans Adm. sponsored
☐	Asian	☐	Other_____	02 Medicare	07 Self-pay (no insurance)
☐	American Indian			03 Medicare & private ins.	08 No means of payment (no insurance)
☐	Native Hawaiian/Pacific Islander			04 Medicaid	09 Unknown
☐	Other_____ _____			05 Medicaid & Medicare	

APPENDIX H-2: SAE/UP REPORTING COVERSHEET

NOTIFICATION OF UNANTICIPATED PROBLEM/SERIOUS ADVERSE EVENT

For Use by Participating Institutions Only

THIS FORM ALONG WITH A COPY OF THE MEDWATCH 3500 OR IRB REPORTING FORM MUST BE EMAILED TO DCC@COH.ORG WITHIN 24 HOURS OF KNOWLEDGE OF ONSET OF SERIOUS ADVERSE EVENT OR UNANCTICIPATED PROBLEM

COH Protocol #18119- Participating Site IRB # _____

From:	Date:
Phone No.:	Email:
Reporting Investigator:	
Event:	
Participant ID:	Institution:
Date Event Met Reporting Criteria (as defined in protocol):	

Type of Report:	☐ Initial ☐ Follow-up
CTCAE Grade:	☐ G1/mild ☐ G2/moderate ☐ G3/severe ☐ G4/life threatening ☐ G5
Attribution to **Venetoclax:**	☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite
Attribution to **Romidepsin:**	☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite
Historical/Known Correlation to **Agent Venetoclax**:	☐ Expected ☐ Unexpected
Historical/Known Correlation to **Agent Romidepsin:**	☐ Expected ☐ Unexpected
Meets Definition of Serious AE:	☐ Serious ☐ Non-serious
Meets Definition of Unanticipated Problem:	☐ UP ☐ Not a UP
Has the event been reported to the following institution's IRB?	☐ No ☐ Yes; Date:_____/____/_____

Authorized Investigator Signature:	Date:____/____/____