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

DEPARTMENT OF HEMATOLOGY AND HEMATOPOIETIC CELL TRANSPLANTATION

TITLE: A Phase II study of intermittent duvelisib dosing in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) (19402)

CITY OF HOPE PROTOCOL NUMBER/VERSION: IRB # 19563 Protocol Date: 10/14/20

Initial Submission	Protocol dated 03/02/2020	Version: 00
COH Amendment 01	Protocol dated 10/14/20	Packet: 01
COH Amendment 02	Protocol dated 10/14/20(TP)	Packet: 02

SITE: Chronic Lymphocytic Leukemia (CLL)/ Small Lymphocytic Lymphoma (SLL)

STAGE (If applicable):

MODALITY:

TYPE: Phase II

PRINCIPAL INVESTIGATOR: Alexey Danilov, M.D.

PARTICIPATING CLINICIANS:
Elizabeth Budde, M.D., Ph.D.
Matthew Mei, M.D.
Liana Nikolaenko, M.D.
Leslie Popplewell, M.D.
Steven Rosen, M.D.
Geoffrey Shouse, D.O.
Jasmine Zain, M.D.
Tanya Siddiqi, M.D.
Swetha Kambhampati, M.D.
John Baird, M.D.

BIOSTATISCIAN: Lu Chen, Ph.D.

Study Title:	A Phase II study of intermittent duvelisib dosing in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)
Protocol Number:	**19563**
Investigational product:	Duvelisib
Version Number:	4.0
Version Date:	14 Oct 2020
Replaces:	3.0 dated 02 Mar 2020
Principal Investigator:	**Alexey Danilov, MD PhD** City of Hope National Medical Center Dept. of Hematology 1500 E Duarte Rd, Duarte, CA 91010 Phone: 626-218-2405 Email: adanilov@coh.org
Sub-Investigators at COH:	Elizabeth Budde, MD PhD, Matthew Mei, MD, Liana Nikolaenko, MD, Leslie Popplewell, MD Steven Rosen, MD, Geoffrey Shouse, DO Jasmine Zain, MD.
Co-Investigator at OHSU	**Stephen Spurgeon, MD PhD** Center for Hematologic Malignancies Oregon Health & Science University 3181 SW Sam Jackson Park Road, L592 Portland, OR 97239 Phone: 503-494-8969 Email: spurgeos@ohsu.edu
Co-Investigator at DFCI	**Jennifer R. Brown, MD PhD** CLL Center Dana-Farber Cancer Institute 450 Brookline Ave Boston, MA 02215 Phone: 617-632-6246 E-mail: Jennifer_Brown@dfci.harvard.edu
Statistician:	Lu Chen, PhD. Dept Computational and Quantitative Medicine City of Hope National Medical Center Phone: 626-218-6626 Email: lchen@coh.org

SYNOPSIS

Study Title	A Phase II study of intermittent duvelisib dosing in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)
Protocol #	19563
Study Center	multicenter [U.S. only]
Sites	City of Hope (COH) and Dana Farber Cancer Institute (DFCI)
Clinical Phase	Phase II - Single Agent
Investigational Component	Investigational Drug
Interventional Study Type	*Single-arm*
Précis	B-cell receptor (BCR)-targeting agents (e.g. ibrutinib, idelalisib) are an approved therapy for several B-cell malignancies. However, treatment with BCR inhibitors does not result in disease eradication, and the remaining cells may be a reservoir of treatment resistance. Targeting phosphatidylinositol 3-kinase (PI3K) has emerged as a promising pathway for the treatment of CLL and NHL; however, toxicities of the PI3K inhibitors are anticipated to be an important concern limiting their use. Duvelisib is a potent oral inhibitor of both the PI3K-δ and PI3K-γ isoforms that is now approved for treatment of relapsed/refractory CLL/SLL after at least two prior therapies. It is also approved for treatment of relapsed/refractory follicular lymphoma. This study will assess if intermittent administration of duvelisib can result in optimal efficacy, but not be associated with severe adverse events. Specifically, participants will undergo a duvelisib treatment regimen consisting of an induction phase and a maintenance phase. Whereas the induction phase is comprised of continuous dosing of duvelisib (25 mg *b.i.d* PO), the maintenance phase will have participants receive intermittent dosing of duvelisib consisting of 2 days on-treatment at 75 mg b.i.d. PO and 5 days off-treatment. The rationale for this 2-day (i.e., 4-dose) alternative treatment regimen is thought to facilitate a 'steady-state' concentration of study drug for a significant period of time, which effectively mimics the concentrations achieved during continuous treatment. Meanwhile, weekly treatment holidays is thought to mitigate the adverse events.
Primary Objectives	To evaluate the efficacy of duvelisib (induction followed by maintenance [intermittent dosing]) in patients with relapsed or refractory CLL, as measured by the progression-free survival (PFS).
Secondary Objectives	1. To evaluate safety of duvelisib induction and maintenance (by intermittent dosing) in relapsed/refractory CLL 2. To evaluate clinical benefits to duvelisib treatment
Exploratory Objectives	To evaluate T-cell populations in patients with CLL treated with duvelisib
Primary Endpoints	Proportion of PFS at 12 months
Secondary Endpoints	1. Objective Response Rate (including CR and PR rate) 2. Median PFS 3. Duration of response 4. Incidence of toxicity [per CTCAE v5.0 and IWCLL 2018 guidelines] 5. Duration of therapy

Exploratory Endpoints	% of T-cell subsets in duvelisib-treated CLL patients
Number of Participants	A total of 30 participants are planned for enrollment to this study.
Duration of Therapy	Participants will continue on-study treatment with duvelisib until disease progression, or upon occurrence of predefined adverse events
Duration of Follow Up	Until death, next therapy or a minimum of 12 months end of treatment
Key Inclusion Criteria	1. Histologically or flow cytometry confirmed diagnosis of B-CLL/SLL 2. Participant underwent ≥ 1 prior chemotherapy-based or immunotherapy-based regimen or targeted therapy (e.g., inhibitors of BTK, BCL2 etc.) administered for ≥2 cycles (i.e., ≥8 weeks for oral therapies), and have had either documented disease progression or no response (stable disease) to the most recent treatment regimen. i) Participants intolerant of ibrutinib therapy and those who progress on ibrutinib are eligible as long as they satisfy the above criteria. 3. Patients must demonstrate active disease meeting at least 1 of the IWCLL 2008 criteria for requiring treatment: i) A minimum of any one of the following constitutional symptoms: • Unintentional weight loss >10% within the previous 6 months prior to screening. • Extreme fatigue (unable to work or perform usual activities). • Fevers of greater than 100.5 F for ≥2 weeks without evidence of infection. • Night sweats without evidence of infection. ii) Evidence of progressive marrow failure as manifested by the development of, or worsening of anemia or thrombocytopenia. iii) Massive (i.e., >6 cm below the left costal margin), progressive or symptomatic splenomegaly. iv) Massive nodes or clusters (i.e., > 10 cm in longest diameter) or progressive lymphadenopathy. v) Progressive lymphocytosis with an increase of >50% over a 2-month period, or an anticipated doubling time of less than 6 months. vi) Autoimmune anemia or thrombocytopenia that is poorly responsive to corticosteroids. 4. Patients must have ECOG performance status ≤2 5. Patients must have organ function as defined below: i) total bilirubin ≤2 X institutional ULN (unless due to known Gilbert's syndrome or compensated hemolysis directly attributable to CLL) ii) AST or ALT less than 2.5 X institutional ULN iii) estimated CrCL using the Cockroft-Gault equation ≥30 mL/min. iv) platelets ≥30,000/mm^3 independent of transfusion support, with no active bleeding, and absolute neutrophil count (ANC) ≥500/mm^3, unless due to disease involvement in the bone marrow.

Key Exclusion Criteria	1. Prior therapeutic intervention with any of the following: i) therapeutic anticancer antibodies within 4 weeks; ii) radio- or toxin-immunoconjugates within 10 weeks; iii) inhibitors of BTK (ibrutinib), BH3-mimetic venetoclax, lenalidomide and other "targeted" therapy – within 6 half-lives (i.e., 36 hours for ibrutinib) iv) all other chemotherapy, radiation therapy within 3 weeks prior to initiation of therapy. v) PI3K inhibitors (idelalisib, copanlisib or any investigational PI3K inhibitor including duvelisib and umbralisib) at any time 2. Inadequate recovery from adverse events related to prior therapy to grade ≤1 (excluding Grade 2 alopecia and neuropathy). 3. Chronic use of corticosteroids in excess of prednisone 30 mg/day or its equivalent. 4. Allogeneic stem cell transplant within the past 12 months, or ongoing immunosuppressive therapy other than prednisone ≤ 10 mg/day (or equivalent) 5. Use of strong CYP3A4 inhibitors or inducers, in the one week prior to initiating study treatment or concomitant 6. History of prior malignancy except: i) malignancy treated with curative intent and no known active disease present for ≥ 2 years prior to initiation of therapy on current study; ii) adequately treated non-melanoma skin cancer or lentigo maligna (melanoma in situ) without evidence of disease; iii) adequately treated in situ carcinomas (e.g., breast, cervical, esophageal, etc.) without evidence of disease; iv) asymptomatic prostate cancer managed with "watch and wait" strategy; 7. Uncontrolled immune hemolysis or thrombocytopenia (positive direct antiglobulin test in absence of hemolysis or history of immune-mediated cytopenias are not exclusions). 8. History of Human Immunodeficiency Virus (HIV) infection or active hepatitis B or C. 9. Major surgery (requiring general anesthesia) within 2 weeks prior to initiation of therapy. 10. Active uncontrolled infection
Investigational Product	Duvelisib
Statistical Considerations	A sample size of 27 patients produces a two-sided exact Clopper-Pearson 95% confidence interval with a width equal to 0.39 (0.30-0.69) when the target proportion is 0.5. Anticipating a dropout rate of 10%, a total of 30 patients will need to be enrolled.

SCHEMATIC OF STUDY DESIGN

Contents

LIST OF TABLES

LIST OF ABBREVIATIONS

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (Classification System)
AUC	Area under the curve
BCR	B-cell antigen receptor
BUN	Blood urea nitrogen
CBC	Complete blood cell (count)
CFR	United States Code of Federal Regulations
CoC	National Institutes of Health (NIH) Certificate of Confidentiality
CLL	Chronic lymphocytic leukemia
CR	Complete remission
CRC	Clinical Research Coordinator
CRMS	Clinical research management system
CRQA	Clinical Research Quality & Administration
CRRC	Clinical Research Review Committee (OHSU)
CRF	Case report form
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECG, EKG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eCRIS	Electronic Clinical Research Information System
EDC	Electronic data capture
FDA	United States Food and Drug Administration
FL	Follicular lymphoma
GCP	Good Clinical Practice
HBeAg	Hepatitis B “e” antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIPPA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational new drug application
IGHV	Immunoglobulin heavy chain variable region
IRB	Institutional Review Board
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
LDH	Lactate dehydrogenase
LFT	Liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NHL	Non-Hodgkin’s lymphoma
OHRP	Office for Human Research Protections
OHSU	Oregon Health & Science University

ORR	Objective response rate
PD	Progressive Disease
PET	Positron emission tomography
PFS	Progression free survival
PI	Principle Investigator
PI3K	Phosphatidyl-inositol 3 kinase
PK	Pharmacokinetics
PO	*Per os* (by mouth, orally)
PR	Partial remission
RBC	Red blood cell (count)
RNI	Reportable new information
SAE	Serious adverse event
SLL	Small lymphocytic leukemia
TCL	T-cell lymphoma
T-reg	T regulatory
ULN	Upper limit of normal
UP	Unanticipated problem
WBC	White blood cell (count)

1. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 OVERVIEW OF CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

Chronic lymphocytic leukemia (CLL) accounts for nearly 34% of all new leukemia cases and 1.2% of all new cancer cases in the United States.[1] The majority (>70%) of patients with CLL are aged >65 years, with males affected nearly 2-times more often than females. In the United States, approximately 20,940 new cases of CLL and 4,510 deaths are expected in 2018. The disease is characterized by the clonal proliferation and accumulation of mature and typically $CD5^+$ B-cells within the blood, bone marrow, lymph nodes, and spleen. In the absence of peripheral clonal lymphocytes, the presence of clonal B-cell populations within enlarged lymph nodes is termed small lymphocytic lymphoma (SLL), and is considered a clinical variant of the same histopathologic disease.

1.2 B-CELL ANTIGEN RECEPTOR (BCR) SIGNALING

Constitutive activation of the B-cell antigen receptor (BCR) appears to be a key driver of CLL, whereby BCR activation elicits activation of Src family kinases SYK and LYN that in turn activates Bruton's tyrosine kinase (BTK) and phospholipase C (PLC)-γ2 molecules.[2] Likewise, BCR signaling also elicits activation of the phosphatidylinositol 3 kinase (PI3K) δ subunit, which further elicits AKT-mediated activation of multiple downstream effectors that promote proliferation and survival.[3,4] Both BTK and PI3K-δ activation are intrinsically higher in CLL, and their identification as important mediators of BCR signaling has resulted in the development of several targeted therapies that have entered the clinic (e.g., ibrutinib and idelalisib, respectively).[5]

Ibrutinib is an oral selective and irreversible inhibitor of BTK that prevents kinase activity and blocks downstream signaling pathways. Approved for the therapy of any CLL patient in any line of therapy, ibrutinib is associated with durable clinical responses in relapsed/refractory (R/R) CLL patients, as well as those that have high-risk (17p deletion) cytogenetic abnormalities. Treatment with ibrutinib in patients with relapsed/refractory CLL yields an overall response rate (ORR) of 70–90%, but complete remission is only achieved in a relative minority of patients.[6-8] A pooled analysis of the PCYC-1102 and PCYC-1112 studies, in which CLL patients received single agent ibrutinib, revealed that 32 of 327 patients (9.8%) achieved a complete response (CR), where the median time to CR was 14.7 months.[9] Although the precise incidence is unknown, resistance to ibrutinib emerges early in up to 13% of patients with all R/R CLL, and in up to 43% of high-risk patients.[10] Regardless, for those patients that develop resistance to ibrutinib, the outcome is extremely poor, with ~3 months of median survival following discontinuation.[11] For such patients treatment options are limited and commonly include a PI3K inhibitor (e.g., idelalisib in combination with rituximab), a BH3-mimetic venetoclax, chemotherapy, or investigational agents.[5]

1.2.1 PI3K THERAPEUTIC TARGETING AND TOXICITY

The PI3K heterodimer is comprised of a catalytic and regulatory subunit, with the p110 catalytic subunit of PI3K existing as four possible isotypes: alpha, beta, gamma, and delta. Whereas p110-α and p110-β subunits are ubiquitously expressed in mammalian tissue, the expression of p110-δ and p110-γ subunits is predominantly found in leukocytes and are shown to contribute to a variety of hematological malignancies.[12,13] In CLL patients with leukemic clones having minimal (< 2% difference from germline) or no mutation in the immunoglobulin heavy chain variable region (IGHV) gene (unmutated CLL [U-CLL]) the prognosis is worse than those with IGHV-mutated CLL (M-CLL).[14,15] Notably, PI3K-mediated signaling is constitutively activated in

CLL, where U-CLL patients have significantly greater PI3K expression compared to those with M-CLL.[16,17] Likewise, the elevated activation of PI3K-AKT signaling in ibrutinib-resistant lymphomas has provided further rationale for subsequent targeting of the PI3K-AKT pathway as means to overcome ibrutinib resistance.[18]

There are several PI3K inhibitors in different stages of clinical development (Table 1); however, notable toxicities such as increased incidences of colitis, hepatitis, pneumonitis, and infectious complications, have limited their use in widespread clinical practice. It has been proposed that these treatment-emergent adverse events (TEAEs) are immune-mediated, and, in general, may be attributed to an overall PI3K inhibitor class effect. Moreover, these TEAEs appear more frequently in patients with an intact immune system not previously treated; a phenomenon that is possibly associated with multiple rounds of prior therapy having further compromised their immune system.[19]

Table 1. PI3K Inhibitors in clinical development

Drug	PI3K Specificity	Cancers	Clinical Trial Phase	Clinical Trial Status
Idelalisib	Δ	R/R CLL, lymphoma	I-III	FDA-approved
Duvelisib	γ/δ	R/R CLL, lymphoma	I-III	FDA-approved
TGR-1202	Δ	CLL, lymphoma	I-III	Ongoing
AMG319	Δ	B-cell malignancies, HNSCC	I	Discontinued
Acalisib	β/δ	Lymphoid malignancies	I	Ongoing
Copanlisib	Pan	MCL, iNHL, breast cancer, HNSCC	I-III	FDA-approved
Pilaralisib	Pan	CLL, lymphoma, solid malignancies	I and II	Completed
Buparlisib	Pan	CLL, glioblastoma, breast cancer, lung cancer	I	Ongoing
SAR260301	B	Various	I	Ongoing
GSK2636771	B	Lymphoma, prostate cancer, gastric cancer	I	Ongoing
PX-866	Pan	NSCLC, prostate cancer, glioblastoma	I and II	Ongoing
Alpelisib	A	Metastatic breast cancer	I-III	Ongoing
Pictilisib	α/δ	Breast cancer, NSCLC	I	Ongoing
AZD8186	β/δ	NSCLC, prostate cancer, TNBC	I	Ongoing
ZSTK474	Pan	Solid malignancies	I	Ongoing

Table adapted from Vangapandu et al[20]

Idelalisib is a potent and selective inhibitor of p110-δ, which is FDA-approved for use in relapsed/refractory CLL, follicular lymphoma (FL), and small lymphocytic lymphoma (SLL).[21] Preferential inhibition of p110-δ by idelalisib inhibits pro-survival pathways, and the combination of idelalisib and rituximab is associated with producing an overall response rate (ORR) of 77% and a 12-month PFS of 66% in R/R CLL.[22] Although efficacious, idelalisib administration is also associated with several toxicities; particularly, the occurrence of autoimmune and infectious toxicities, including grade ≥ 3 transaminitis, hypotension, rash, sepsis, and pulmonary infiltrates.[23-26] Additionally, idelalisib is also associated with late-onset induced diarrhea, where many patients who are treated with idelalisib for ≥3 months and develop colitis exhibit findings intestinal inflammation with intra-epithelial lymphocytosis, crypt cell apoptosis, and neutrophilic

infiltration of crypt epithelium.[27,28] The delayed onset of idelalisib-induced diarrhea is thought to be a symptom of autoimmune-mediated colitis.[27]

Duvelisib is a potent oral inhibitor of both the p110-δ and p110-γ isoforms. The FDA granted approval for use of duvelisib in adult patients with relapsed or refractory CLL/SLL or follicular lymphoma (FL) who have received at least two prior therapies. Clinical investigators who participated in a phase I study reported on the safety and efficacy of duvelisib given to 210 patients with advanced hematological malignancies.[29] Patients were administered duvelisib twice daily in continuous 28 day cycles (dose range = 8-100 mg) for a median treatment duration of 16 weeks across all doses. The authors observed clinical responses across several disease subtypes with the ORR in patients with iNHL (n=31), R/R CLL (n = 55), peripheral T-cell lymphoma (TCL; n = 16), and cutaneous TCL (n=19) reported as 58%, 56%, 50%, 32%, respectively. The median time to response was approximately 1.8 months. Specifically, among the 55 patients with R/R CLL, the authors reported 1 complete response (CR), 30 partial response (PR), and a median PFS of 15.7 months. Similar to results from patients treated with idelalisib, severe (grade ≥3) adverse events occurred in 84% of patients administered duvelisib, including: neutropenia (32%), alanine transaminase (ALT) increase (20%), aspartate transaminase (AST) increase (15%), anemia and thrombocytopenia (each 14%), diarrhea (11%), and pneumonia (10%). Severe diarrhea had a late onset of 5 to 6 months from start of treatment.[29]

Copanlisib is a pan-class I PI3K inhibitor, with predominant activity against the p110-α and p110-δ isoforms. U.S. Food and Drug Administration granted accelerated approval to copanlisib (ALIQOPA, Bayer HealthCare Pharmaceuticals Inc.) for the treatment of adult patients with relapsed FL who have received at least two prior systemic therapies. Dreyling et al[30] carried out a phase 2 study to evaluate the clinical efficacy of administering copanlisib to 84 patients with either indolent lymphoma (n = 33) or aggressive lymphoma (n = 51). Patients in this study were given copanlisib intravenously (0.8 mg/kg) on days 1, 8, and 15 of a 28 day cycle. The authors reported an objective response rate of 44% and 27% in the indolent and aggressive disease cohorts, respectively. The median PFS across the indolent and aggressive disease cohorts was 294 days and 70 days, respectively. Serious grade ≥ 3 treatment emergent adverse events (TEAEs) occurring in two or more patients included: grade 3 lung infection (10.7%), grade 3 diarrhea (3.6%), and grade 3 febrile neutropenia (3.6%). Additional severe toxicities observed included grade 4 decreased neutrophil count, grade 3 hyperglycemia, grade 3 pneumonitis, grade 3 pancreatitis, grade 3 cardiac disorders—other, and grade 3 infection/infestations (2.4% each).[30]

In contrast to reports of adverse effects of idelalisib and duvelisib, onset of copanlisib-induced diarrhea was reported in 40.5% of patients, of which only 4.8% had diarrhea grade ≥3, and there were no reports of colitis.[30] Moreover, results of several idelalisib studies have reported a 48% to 60% incidence of all-grade elevations in aminotransferases, with an 8% to 13% incidence of grade ≥3 elevations.[23,25,26] Likewise, duvelisib was associated with 38% incidence of all-grade elevations in aminotransferases, with a 15% to 19.5% incidence of grade ≥ 3 elevations.[29] In contrast, Dreyling et al[30] reported that the incidence of ALT and AST elevations associated with intermittent copanlisib treatment were grade 1 events (23.2% and 24.4%, respectively), with only a small proportion of patients experiencing grade 3 ALT and AST elevations (3.7% and 2.4%, respectively).

1.2.1.1 *PI3K inhibition in T-cells and autoimmune toxicity*

The p110-δ and p110-γ isoforms appear to be important in the functioning of regulatory T-cells.[31] Though the exact mechanism is unknown, in vivo mouse modeling of single point mutation in p110-δ resulted in its inactivation, and was associated with the mice developing

inflammatory bowel disease in the large intestine.[32] Similar to B-cell targeting of p110-δ and p110-γ isoforms, emerging evidence suggests that PI3K inhibitors also inactivate these isoforms in T-cells, and this may be associated with autoimmune toxicity.

O'Brien et al[33] observed the presence of T-cell infiltrates in the colonoscopic biopsies of patients with diarrhea after receiving idelalisib. In another study, Matos et al[34] observed that patients who received idelalisib had decreased number of T regulatory (Treg) cells that resulted in a comparatively higher ratio of conventional CD4 and CD8 T-cells to Tregs, respectively. Though there was no difference observed in these ratios between patients who did or did not experience autoimmune toxicities, the authors noted that in patients who developed autoimmunity, baseline Tregs had higher expression of PD-1 and lower expression of certain other markers, such as GITR, Tbet, CXCR3, PDL-1, granzyme-β and TIM-3.

1.3 **OVERVIEW OF DUVELISIB**

Duvelisib's affinity for targeted inhibition of both p110-δ and p110-γ isoforms is being exploited as a potential therapeutic for a variety of hematologic malignancies. In addition to perturbing BCR and cytokine-dependent survival signaling, the combined inhibition of p110-δ and p110-γ also impacts the functional microenvironment supporting CLL tumor cells. For example, duvelisib inhibition of p110-γ can prevent the migration of T-cells, which in turn play a role in supporting CLL tumor cell survival by way of producing cytokines and cell-to-cell contact.[35]

Over 20 completed or ongoing clinical studies have been implemented to assess the safety and efficacy of duvelisib in the treatment of hematological malignancies, asthma, and rheumatoid arthritis. Oral administration of duvelisib is characterized by rapid absorption, with peak concentrations occurring approximately 0.5 to 2 hours after dosing. The mean half-life of duvelisib ranges from 2.6 to 7.5 hours, with steady state concentrations reached within 48 to 72 hours.[36] Results of study IPI-145-02, a phase 1, open-label, dose escalation study established the maximum tolerated dose (MTD) of duvelisib as being 75 mg *b.i.d*.. In this study, 124 patients were treated with 75 mg p.o. bid, with a median time on therapy of 4 months. The adverse event profile and efficacy were similar between the two doses (25 mg po, b.i.d and 75 mg po b.i.d). Administration of duvelisib at 25 mg b.i.d provided clinically meaningful activity (i.e., rapid and sustained reductions in p-AKT and Ki67 expression) and was selected as the recommended dose in CLL and B-cell lymphoma.[29] Meanwhile, duvelisib is used at 75 mg po b.i.d in combination studies in T-cell lymphoma, as it is anticipated that additional PI3K-γ isoform inhibition will be achieved at this dose level. Refer to investigator brochure for additional details regarding pharmacokinetics, pharmacodynamics, as wells safety and efficacy results.[36]

Flinn et al[37] reported on IPI-145-07 (DUO, NCT02004522), a 2-arm, randomized, open label, phase III trial designed to compare the efficacy and safety of duvelisib to ofatumumab in patients with R/R CLL/SLL. Three-hundred and nineteen (319) patients with R/R CLL/SLL were randomized 1:1 to receive either duvelisib (25 mg *b.i.d)* or ofatumumab. The authors observed a median progression free survival (mPFS) of 13.3 months among those treated with duvelisib compared to 9.9 months for those receiving ofatumumab; representing a 48% reduction in the risk of progression or death. The ORR was significantly greater among those receiving duvelisib over ofatumumab (73.8% vs 45.3%, respectively; $p<0.0001$), with reduced lymph node burden >50% among duvelisib-treated patients versus those in the ofatumumab treatment arm (85% vs 16%). Overall Survival (OS) was similar for those randomized to either duvelisib or ofatumumab. In an extension to this study, Kuss et al[38] further showed that among 89 patients that had disease progression with ofatumumab that were allowed to crossover to the duvelisib treatment arm, achieved an ORR of 73%, with a mPFS of 15 months. Moreover, 83% of evaluable patients had >50% reduction in target nodal lesions.

1.4 **RATIONALE**

Therapy with both idelalisib and duvelisib has been associated with delayed severe adverse events, including diarrhea/colitis and pneumonitis. Increased levels of liver transaminases are also commonly observed among patients receiving either idelalisib or duvelisib. Moreover, the risk of those adverse events is highest in patients who have not received prior therapy and younger patients.[19] As CLL therapy moves toward targeted agents such as ibrutinib, and many patients are never exposed to chemotherapy, toxicities of the PI3K inhibitors are anticipated to be an important concern limiting their widespread use.

In contrast to both idelalisib and duvelisib, copanlisib, is associated with very low frequency of autoimmune events.[19,29,30] While p110-δ inhibition is known to down-modulate suppressive T-regs[39], targeted inhibition of p110-α has limited effect on T-cell function.[40] Rather, one explanation for reduced autoimmune toxicity observed with copanlisib may be related to interrupted dosing. Specifically, Dreyling et al[30] reported that copanlisib was administered intravenously on days 1, 8, and 15 of a 28 day cycle. Given the half-life of copanlisib ($t_{1/2}$ = 39.1 hours [range: range: 14.6 to 82.4 hours]), weekly IV administration results in strong fluctuations in plasma drug concentration, it is possible that intermittent saturation of the target is sufficient to induce durable anti-tumor responses. *This study is founded on the hypothesis that similar, intermittent administration of duvelisib will result in optimal efficacy, but will not be associated with severe adverse events.*

This study is intended to assess whether intermittent dosing of duvelisib can achieve clinical efficacy while reducing unwanted treatment-related toxicities. Specifically, participants will receive a duvelisib treatment regimen consisting of an induction phase and a maintenance phase. Whereas the induction phase is comprised of continuous dosing of duvelisib (25 mg *b.i.d* PO), the maintenance phase will have participants receive intermittent dosing of duvelisib 75 mg *b.i.d* PO consisting of 2 days on-treatment and 5-days off-treatment. The rationale for this 2-day (i.e., 4-dose) intermittent treatment regimen is thought to facilitate a 'steady-state' concentration of study drug, which effectively mimics the concentrations achieved during continuous treatment, for a short period of time. In general, the approximate maximal concentration (C_{max}) of duvelisib following 25 mg *b.i.d* administration is 3 μM. Given that the mean $t_{1/2}$ of duvelisib ranges from 2.6 to 7.5 hours following multiple dose administrations, steady state concentrations are expected to be reached within 48-72 hours.

During the maintenance phase of the study, we will use duvelisib 75 mg PO *b.i.d*., rather than 25 mg po b.i.d. for 2 out of 7 days. While duvelisib 25 mg po *b.i.d* achieves nearly complete inhibition of PI3K-δ isoform, this dose only reaches ~50% of PI3K-γ isoform. It is hoped that higher dose of duvelisib will help reach improved coverage of the PI3K-γ isoform and thus modulation of the microenvironment. In the Phase I study (IPI-145-02), 124 patients were treated with 75 mg PO *b.i.d*, with a median time on therapy of 4 months. Of those patients, 22 patients had relapsed/refractory CLL. While not directly compared, the adverse event profile and efficacy were similar between the two doses. The respective frequency of AEs in patients treated with 75 mg PO *b.i.d* or 25 mg PO *b.i.d*., corresponded as follows: febrile neutropenia - 11.3% and 6%, gastrointestinal AEs – 17.7% and 18.2%, colitis 4% and 6.1%, and infections – 29.8% and 24.2% Currently, duvelisib is used at 75 mg po *b.i.d* in combination studies in T-cell lymphoma.

This study is focused on examining intermittent therapy in R/R CLL/SLL patients. As such, it is anticipated that patients who progress on ibrutinib or venetoclax will likely be enrolled on to this

study. Results of a prior study show that patients that progress on ibrutinib and receive subsequent treatment with idelalisib have a PFS of approximately 9 months; however, nearly half of these patients discontinue idelalisib due to toxicity.[41] Thus, with the goal of reducing TEAEs via intermittent duvelisib dosing, this study anticipates a lower discontinuation rate and expects the PFS to be similar to that reported with continuous therapy. As such, the primary endpoint of this study is to evaluate a target PFS of 50% at 12 months.

1.5 **POTENTIAL RISKS AND BENEFITS**

1.5.1 **KNOWN POTENTIAL RISKS**

Frequent treatment-emergent severe adverse events (TESAE); i.e., occurring in ≥ 5% of patients) across hematologic oncology studies include febrile neutropenia, pneumonia, diarrhea, disease progression, and pyrexia.[36] Refer to investigator's brochure and Section 9.4 for additional information.

1.5.2 **KNOWN POTENTIAL BENEFITS**

Intermittent dosing may alleviate TEAEs associated with PI3K inhibitors and may provide access to a new treatment approach not previously available. It cannot, however, be guaranteed that participants in this study will directly benefit from treatment during participation, as the clinical trial is designed to provide information about the safety and effectiveness of the investigational approach.

1.6 **EXPLORATORY STUDIES**

Limited data exist regarding the functional outcomes of *in vivo* targeting of different PI-3K isoforms in T-cells. In preclinical studies, selective targeting PI3Kδ with a tumor-specific vaccine down-modulated suppressive Treg cells and increased numbers of vaccine-induced CD8 T-cells within the tumor microenvironment, eliciting potent antitumor efficacy [39]. Therefore, targeting PI3Kγ/δ is expected to result in enhanced expression of T-cell activation markers, and down-modulation of Treg cells, an increase in Th17 cells with increased T-cell mediated cytotoxicity. However, we anticipate that intermittent dosing of duvelisib may result in attenuated effects on the immune system. In this setting, it is possible that we will observe recovery of Treg cells following completion of duvelisib induction. We will use this hypothesis as a rationale for detailed evaluation of T-cell repertoire and the T-cell activation markers following induction and maintenance therapy with duvelisib.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVES

To evaluate the efficacy of duvelisib (induction followed by maintenance [intermittent dosing]) in patients with relapsed or refractory CLL, as measured by the PFS.

2.2 SECONDARY OBJECTIVES

1. To evaluate safety of duvelisib induction and maintenance (by intermittent dosing) in relapsed/refractory CLL
2. To evaluate clinical benefits to duvelisib treatment

2.3 EXPLORATORY OBJECTIVES

To evaluate T-cell populations in patients with CLL treated with duvelisib.

3. STUDY DESIGN AND ENDPOINTS

3.1 DESCRIPTION OF THE STUDY DESIGN

Refer to Section 10*, Statistical Considerations, for additional information regarding statistical methods used in this study.*

This is a phase II, single-arm, open label study to assess the efficacy and safety of intermittent maintenance dosing of duvelisib in patients with R/R CLL/SLL. Participants must meet the inclusion criteria, have none of the exclusion criteria, and have provided written informed consent before the conduct of any screening tests not performed routinely in their treatment.

In this study, eligible participants with R/R CLL/SLL will receive duvelisib treatment in two phases: **induction and maintenance**. In the induction phase, duvelisib (25 mg *b.i.d,* PO*)* will be administered to participants in a continuous fashion for 12 weeks (i.e., three 4-week cycles). Participants that experience predefined adverse toxicities during the 12 week induction period (see Section 6.1.1) may switch early to the maintenance phase of treatment regimen (i.e., before the end of 12 week induction period). Participants entering the maintenance phase of the treatment regimen will receive duvelisib (75 mg *b.i.d*, PO) for 2 consecutive days (i.e., 4 doses) followed by a 5-day break in treatment. This intermittent dosing schedule will continue until participants experience prohibitive adverse events, or undergo disease progression.

Primary and secondary endpoints in this study will evaluate the clinical efficacy and safety associated with duvelisib induction and intermittent maintenance dosing. This study plans on enrolling 30 participants with R/R CLL/SLL.

3.2 STUDY ENDPOINTS

3.2.1 PRIMARY ENDPOINT

Endpoint	Start	End
Proportion of PFS at 12 months	First dose of duvelisib	Death, time of progression, start of new therapy, or 12 months from start of therapy, whichever occurs first

3.2.2 SECONDARY ENDPOINTS

Endpoint	Start	End
1. Objective Response Rate (ORR)	First dose of duvelisib	At designated time points
2. Median PFS		Death, time of progression, or start of new therapy, whichever occurs first
3. Duration of response	Time of ORR	Death, time of progression, start of new therapy, or end of follow-up, whichever occurs first
4. Incidence of toxicity	First dose of duvelisib	3 months post-discontinuation of duvelisib
5. Duration of therapy		Time of duvelisib discontinuation

3.2.3 **EXPLORATORY ENDPOINTS**

Endpoint	**Start**	**End**
Percent distribution of circulating T-cells within duvelisib-treated CLL patients	First dose of duvelisib	After 3 (end of induction), 6 and 12 cycles of therapy

4. STUDY ENROLLMENT AND WITHDRAWAL

Patient MRN (COH Only)	Patient Initials (F, M, L):
Institution:	

4.1 PARTICIPANT INCLUSION CRITERIA

To be eligible to participate in this study, an individual must meet all of the following criteria:

1. Ability to understand and the willingness to sign a written informed consent document.
2. Participants are ≥ 18 years old at time of informed consent.
3. Histologically or flow cytometry confirmed diagnosis of B-CLL/SLL according to NCI-WG 1996 guidelines. Patients who lack CD23 expression on their leukemia cells should be examined for (and found NOT to have) either t(11;14) or cyclin D1 overexpression, to rule out mantle cell lymphoma.
4. Participants have undergone ≥ 1 prior chemotherapy-based or immunotherapy-based regimen or targeted therapy (e.g., inhibitors of BTK [e.g., ibrutinib], or BCL2 [e.g., venetoclax]) administered for ≥2 cycles (≥8 weeks for oral therapies), and have had either documented disease progression or no response (i.e., stable disease [SD]) to the most recent treatment regimen.

   Note: Individuals intolerant to ibrutinib therapy and those who progress on ibrutinib are eligible as long as they satisfy the above criteria.
5. Patients with CLL/SLL must demonstrate active disease meeting at least 1 of the IWCLL 2018 criteria for requiring treatment:
   i) A minimum of any one of the following constitutional symptoms:
      - Unintentional weight loss >10% within the previous 6 months prior to screening.
      - Extreme fatigue (unable to work or perform usual activities).
      - Fevers of greater than 100.5°F for ≥2 weeks without evidence of infection.
      - Night sweats without evidence of infection.

   ii) Evidence of progressive marrow failure as manifested by the development of, or worsening of anemia or thrombocytopenia.

   iii) Massive (i.e., >6 cm below the left costal margin), progressive or symptomatic splenomegaly.

   iv) Massive nodes or clusters (i.e., > 10 cm in longest diameter) or progressive lymphadenopathy.

   v) Progressive lymphocytosis with an increase of >50% over a 2-month period, or an anticipated doubling time of less than 6 months.

   vi) Autoimmune anemia or thrombocytopenia that is poorly responsive to corticosteroids.

   vii) Symptomatic or functional extranodal involvement (eg, skin, kidney, lung, spine)
6. Patients must have ECOG performance status ≤ 2 (**Appendix** A).
7. Prior to starting study agent, participant must have organ function as defined below:

i) Total bilirubin ≤2 X institutional upper limit of normal (ULN); unless due to known Gilbert's syndrome or compensated hemolysis directly attributable to CLL

ii) AST or ALT less than 2.5 X institutional ULN

iii) Estimated CrCL using the Cockroft-Gault equation (or an alternative equation, per institutional standard) ≥30 mL/min.

iv) Platelets ≥30,000/mm^3 independent of transfusion support, with no active bleeding, and absolute neutrophil count (ANC) ≥500/mm^3, unless due to disease involvement in the bone marrow.

8. Participant must be able to swallow tablets or capsules. A participant with any gastrointestinal disease that would impair ability to swallow, retain, or absorb drug is not eligible.
9. Female participants of childbearing potential (defined as a sexually mature woman who has not undergone surgical sterilization or who has not been naturally postmenopausal for at least 12 consecutive months for women >55 years of age) must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
10. Female participants of childbearing potential must agree to use adequate methods of contraception (**Appendix B**) starting with the first dose of study therapy through 60 days after the last dose of study therapy.

    Participants of childbearing potential are those who have not been surgically sterilized or have not been free from menses for >1 year without an alternative medical cause.

11. Male participants must agree to use an adequate method of contraception (**Appendix B**) starting with the first dose of study therapy through 60 days after the last dose of study therapy.

4.2 PARTICIPANT EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Prior therapeutic intervention with any of the following:
    i) Therapeutic anticancer antibodies within 4 weeks;

    ii) Radio- or toxin-immunoconjugates within 10 weeks;

    iii) Inhibitors of BTK (e.g., ibrutinib), BH3-mimetic venetoclax, lenalidomide and other *"targeted"* therapy – within 6 half-lives (i.e., 36 hours for ibrutinib)

    iv) All other chemotherapy, radiation therapy within 3 weeks prior to initiation of therapy.

    v) PI3K inhibitors (idelalisib, copanlisib or any investigational PI3K inhibitor including duvelisib and umbralisib) at any time
2. Any adverse event related to prior therapy that has not recovered to grade ≤ 1
3. Chronic use of corticosteroids in excess of prednisone 30 mg/day or its equivalent.
4. Allogeneic stem cell transplant within the past 12 months, or ongoing immunosuppressive therapy other than prednisone ≤ 10 mg/day (or equivalent)

5. Use of strong CYP3A4 inhibitors or inducers, in the one week prior to initiating study treatment or concomitant.
6. Unable to receive prophylactic treatment for pneumocystis, herpes simplex virus (HSV), or herpes zoster (VZV) at screening
7. History of prior malignancy except:
    i) Malignancy treated with curative intent and no known active disease present for ≥ 2 years prior to initiation of therapy on current study;
    ii) Adequately treated non-melanoma skin cancer or lentigo maligna (melanoma in situ) without evidence of disease;
    iii) Adequately treated in situ carcinomas (e.g., breast, cervical, esophageal, etc.) without evidence of disease;
    iv) Asymptomatic prostate cancer managed with "watch and wait" strategy
8. Uncontrolled immune hemolysis or thrombocytopenia (positive direct antiglobulin test in absence of hemolysis or history of immune-mediated cytopenias are not exclusions).
9. History of Human Immunodeficiency Virus (HIV) infection or active hepatitis B or C.
10. History of chronic liver disease
11. Major surgery (requiring general anesthesia) within 2 weeks prior to initiation of therapy.
12. Patients with clinically significant medical condition of malabsorption, inflammatory bowel disease, chronic conditions which manifest with diarrhea, refractory nausea, vomiting or any other condition that will interfere significantly with drug absorption.
13. History of stroke, unstable angina, myocardial infarction, or ventricular arrhythmia requiring medication or a pacemaker within the last 6 months prior to screening
14. Baseline QT interval corrected with Fridericia's method (QTcF) >500 ms
    [NOTE: criterion does not apply to subjects with a right or left bundle branch block BBB]
15. Active uncontrolled infection
16. Psychiatric illness/social situations that would limit compliance with study requirements
17. Participant is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.

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.			

4.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Participants for this study will primarily be recruited from hematology and oncology practices

within City of Hope (PI: Alexey V. Danilov) and the subsites: Dana-Farber Cancer Institute (DFCI) CLL center (co-PI: Jennifer R. Brown) and Oregon Health and Science University (PI: Stephen Spurgeon). Participants may be identified and referred to this study by their primary treating physician from within COH or the subsite, or from the outside community. Participants may be identified by a member of the patient's treatment team, the PI, research team, or medical and surgical oncology clinics part of COH or the subsite. As a member of the treatment team, the investigator(s) will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Referral of potential participants to investigator(s) of this study is made as part of standard of care, with the referring physician seeking advice on the diagnosis, evaluation, and/or treatment of the patient's malignancy.

The investigators(s) may also screen the medical records of potential participants with whom the investigator does not have a treatment relationship. This will be done for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these potential individuals regarding the possibility of participating in the study. Participants may also initiate contact with the investigator through information of this study posted on the clinicaltrials.gov website.

4.3.1 ACCRUAL ESTIMATES

An estimated 30 participants (12 at COH, 12 at DFCI and 6 at OHSU) will be recruited over a 24 month period.

4.3.2 INCLUSION OF CHILDREN

This protocol does not include children as the number of children with this type of cancer is limited.

4.4 REGISTRATION PROCEDURES

4.4.1 REGISTRATION

Participants will be required to give written informed consent to participate in the study before any screening tests or evaluations are conducted that are not part of standard care.

4.4.2 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, and the prospective participant must receive a copy of the signed informed consent document. Screening procedures are listed in Section 7.9 (Study Calendar).

4.4.3 PARTICIPANT ENROLLMENT

4.4.3.1 *COH DCC Availability and Contact Information*

Eligible participants will be registered on the study centrally by the Data Coordinating Center (DCC) at City of Hope.

DCC staff are available **between the hours of 8.00 am and 5.00 pm PST, Monday through Friday (except holidays)**.

- E-mail: DCC@coh.org

4.4.3.2 *Slot verification and reservation*

A designated study team member should email the DCC to verify current slot availability, and to reserve a slot for a specific prospective subject (provide DCC with subject initials), including a tentative treatment date. Slots can only be held for a limited time, at the discretion of the study PI.

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

4.4.3.3 *Registration Process*

Allow up to 24 hours for the DCC to review eligibility. To register a participant the subsequent procedure is to be followed:

1. The study team should contact the DCC via 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 study team will email a **Complete Eligibility Packet** to the DCC, which consists of a copy of the following documents:
    - Registration Cover Sheet (Appendix E)
    - Completed eligibility checklist (printed from Section 4.0 of the protocol) with required signature(s)
    - Source documents that support all eligibility criteria listed in the eligibility checklist
    - Signed Informed Consent
    - Signed HIPAA authorization form (if separate from informed consent)
    - Signed subject's bill of Rights (California only)

3. When all source documents are received, the DCC will review to verify eligibility, working with the study team to resolve any missing required source elements. Any missing documents may delay review and registration. A participant failing to meet all protocol eligibility requirements will not be registered and the study team will be immediately notified.

4. Once eligibility is confirmed, the DCC will send a Confirmation of Registration Form and signed Eligibility Checklist, including the Subject Study Number and cohort assignment to:
    - The study team: Site Lead Investigator, treating physician/ sub-investigator, protocol nurse, CRC and pharmacy (as needed).

- The COH Study PI and COH study team designees (including but not limited to study monitor(s) and statistician(s)).

5. Upon receipt of the Confirmation of Registration Form, COH study team will register the patient in OnCore. The DCC will register non-COH patients in OnCore.

4.4.4 SCREEN FAILURES AND REGISTERED PARTICIPANTS WHO DO NOT BEGIN STUDY TREATMENT

Notify the DCC immediately if the participant screen fails after registration or if the participant does not start treatment.

For non-COH sites, the reason for screen failure will be documented in the registration coversheet (Appendix E) and submitted to the DCC.

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

5. INVESTIGATIONAL PRODUCT

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 9.4, Adverse Events List.

5.1 DUVELISIB

Duvelisib (VS-0145 [IPI-145]) is an orally active, dual inhibitor of p110-δ and p110-γ. The following information is derived from the IB, please refer to the IB for additional details.[36]

5.1.1 ACQUISITION

Duvelisib will be supplied by the manufacturer, Verastem Inc., and prepared by the research pharmacy at each institution per manufacturer instructions.

Both COH and study subsites will request drug directly from Verastem by completing and emailing the drug request form provided in Appendix E.

5.1.2 FORMULATION, APPEARANCE, PACKAGING AND LABELING

Duvelisib is characterized as a freebase, hydrate (hydration can vary with humidity), white-to-off-white solid, and is made available in 2 different capsule strengths (15 mg and 25 mg) for oral delivery. Duvelisib capsules are packaged in opaque high-density polyethylene bottles with induction sealed child resistant caps, or thermoform blister strips with push-through lidding packaged into wallets (dose pack).

5.1.3 PRODUCT STORAGE AND STABILITY

Duvelisib is chemically stable under the recommended storage condition of 20°C to 25°C (excursions permitted between 15°C to 30°C).

5.1.4 HANDLING

National Institute for Occupational Safety and Health (NIOSH) recommends the use of single gloves by anyone handling intact tablets or capsules or administering from a unit-dose package.

Manufacturer urges caution when handling duvelisib, including avoidance of eye or skin contact with the drug product. If there is exposure to the drug product, the individual should be treated for physical exposure (skin washing) or inhalation (move to fresh air, as necessary), and, if needed, seek medical advice.

5.1.5 ADMINISTRATION

Duvelisib (25 mg or 75 mg during the maintenance phase) is to be administered orally, with or without a meal.

5.1.6 ACCOUNTABILITY

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of the study agent. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage).

Responsibility for drug accountability at the study site rests with the Investigator; however, the Investigator may assign some of the drug accountability duties to an appropriate pharmacist or designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities or other oversight bodies.

The Investigator or designee will collect and retain all used, unused, and partially used containers of study medication until full accounting has been completed. The Investigator or designee must maintain records that document:

- Investigational product delivery to the study site.
- The inventory at the study site.
- Use by each participant including pill/unit counts from each supply dispensed.
- Return of investigational product to the Investigator or designee.
- Destruction or return of investigational product for final disposal.

These records should include dates, quantities, batch/serial numbers (if available), and the unique code numbers (if available) assigned to the investigational product and study participants.

The investigational product must be used only in accordance with the protocol. The Investigator will also maintain records adequately documenting that the participants were provided the correct study medication specified.

Completed accountability records will be archived by the site. At the completion of the study, the Investigator or designee will oversee shipment of any remaining study drug back to Verastem Inc. for destruction according to institutional standard operating procedures. If local procedures mandate site destruction of investigational supply, prior written approval must be obtained from Verastem Inc.

5.1.7 **DESTRUCTION AND RETURN**

At the end of the study, or earlier upon approval from study management, unused supplies of duvelisib should be destroyed according to institutional policies. Drug supplies will be counted and reconciled in full at the site with all monitoring procedures complete before destruction. Destruction will be documented in the Drug Accountability Record Form.

6. TREATMENT PLAN

6.1 DOSAGE AND ADMINISTRATION

Treatment will be administered on an *out-patient* basis (in-patient administration is allowed if deemed necessary by the Investigator), with 28 consecutive days (4 weeks) defined as a treatment cycle. Reported adverse events and potential risks are described in Section 9.4, Adverse Event List. Appropriate dose modifications or delays are described in Section 6.2. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Duvelisib Regimen Description				
Agent	**Dose**	**Route**	**Schedule**	**Cycle Length**
Duvelisib –induction	25 mg *b.i.d*	PO	Continuous dosing for 12 weeks (3 cycles)	28 days
Duvelisib -maintenance	75 mg b.i.d		Repeated intermittent dosing: 2 days on-treatment, 5 days off-treatment	

6.1.1 DUVELISIB INDUCTION PHASE

Duvelisib will be dosed continuously at 25 mg PO *b.i.d*, with induction lasting for 12 weeks. Participants may, however, enter into maintenance phase of treatment regimen earlier than 12 weeks if they experience any one of the following toxicities:

- All Grade ≥ 4 hematological toxicities persisting for > 14 days,
- Febrile neutropenia
- Clinical CMV infection or viremia
- All Grade ≥ 3 non-hematological toxicities (except for tumor lysis or alopecia, or Grade 3 nausea, vomiting, or uncomplicated electrolyte abnormalities that resolve within 48 hours with medical intervention),
- Any toxicity requiring a second dose reduction
- Any of the following hepatic toxicities:
  - ALT/AST > 8 X ULN, ***or***
  - ALT/AST > 5 X and ≤ 8 X ULN, that fails to return to Grade 0-1 within 2 weeks despite medical intervention, ***or***
  - Total bilirubin > 5 ULN, ***or***
  - ALT/AST > 3 X ULN and concurrent total bilirubin > 2 X ULN, ***or***
  - Recurrence of ALT/AST > 3 X ULN after re-challenge following initial hepatotoxicity

Maintenance will be initiated at a planned dose of 75 mg PO *b.i.d* as described in Section 6.1.2.

6.1.2 DUVELISIB MAINTENANCE PHASE

The maintenance portion of this study will include intermittent duvelisib dosing administered at 75 mg PO *b.i.d* for 2 days (preferably to occur on Saturday and Sunday), followed by 5-days of being off-treatment (e.g., Monday through Friday). Maintenance therapy using this intermittent dosing schedule should continue until disease progression, treatment intolerance, participant withdrawal, or death.

6.2 DOSING DELAYS AND MANAGEMENT OF TOXICITIES

Any toxicity observed during the course of the study could be managed by an interruption of the study drug treatment. Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion.

In general, dosing interruptions are permitted in the case of medical / surgical events or logistical reasons (i.e., elective surgery, unrelated medical events) not related to study therapy. Participants should be placed back on study therapy within 2 weeks of the scheduled interruption, unless otherwise discussed with the investigator. The reason for interruption should be documented in the participant's study record.

If vomiting occurs shortly after the duvelisib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should a participant miss a scheduled dose for whatever reason (e.g., forgot to take the tablets, or vomiting), the participant will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the participant should take their allotted dose at the next scheduled time.

Please see Duvelisib Prescribing Information for details. General guidelines are in **Table 2** and **Table 3**.

Table 2. Recommended Duvelisib Dose Modifications for Non-hematologic Adverse Reactions

Toxicity	Adverse Reaction Grade	Recommended Management
Non-infectious Diarrhea / Colitis	Grade 1-2 (defined as an increase of up to 6 stools/day over baseline); • Responsive to anti-diarrheal agents	• No dose interruption • Use supportive care with antidiarrheal agents as appropriate • Monitor weekly until resolved
	Grade 1-2 (defined as an increase of up to 6 stools/day over baseline); • Unresponsive to anti-diarrheal agents	• Interrupt duvelisib • Monitor weekly until resolved • Resume at reduced dose (see **Table 4**)
	Grade 3 (defined as ≥ 7 stools/day over baseline or hospitalization due to diarrhea) OR • radiologically or histologically confirmed **colitis**	• Interrupt duvelisib • Monitor weekly until resolved • If occurs during induction phase: start maintenance dosing • If occurs during maintenance phase: Resume at reduced dose (see **Table 4**)
	• Grade 4 (defined as life threatening diarrhea)	• Permanently withhold duvelisib

Table 2. Recommended Duvelisib Dose Modifications for Non-hematologic Adverse Reactions		
Toxicity	**Adverse Reaction Grade**	**Recommended Management**
Recommended management using antidiarrheal agents: • ≤ Grade 1: Treat with loperamide • Grade 2: Consider treatment with loperamide. If the diarrhea does not resolve within 24 hours, consider treatment budesonide or prednisolone at 1mg/kg with a taper. • Grade 3: Treat with budesonide, and consider prednisolone at 1 mg/kg with a quick taper. • Grade 4: Treat with budesonide or prednisolone at 1 mg/kg with a taper.		
Transaminitis	• Grade 2 (defined as ALT/AST >3x ULN – 5x ULN)	• Continue at current dose. Monitor LFT levels weekly until return to < 3 X ULN
	• Grade 3 (defined as ALT/AST > 5-20 x ULN)	• Interrupt duvelisib • Monitor LFT levels weekly until return to < 3 X ULN • If occurs during induction phase: see Section 6.1.1 for guidelines to switch to maintenance phase • If occurs during maintenance phase or induction phase and a switch to maintenance phase is not indicated: Resume duvelisib at same dose (first occurrence) or reduced dose for subsequent occurrences (see **Table 4**)
	• Grade 4 (defined as > 20 x ULN)	• Interrupt duvelisib • Monitor weekly until return to < 3 X ULN • Induction phase: switch to maintenance phase • Maintenance Phase: Permanently discontinue duvelisib
Pneumonitis	• Moderate (Grade 2) symptomatic pneumonitis	• Interrupt duvelisib until resolved • Induction phase: switch to maintenance phase • Maintenance phase: resume duvelisib at reduced dose • Discontinue duvelisib if pneumonitis recurs
	• Severe (Grade 3) pneumonitis that is radiologically or histologically confirmed	Discontinue duvelisib
Infections	• Clinical CMV infection or viremia (positive PCR or antigen test)	• Interrupt duvelisib until infection or viremia has resolved • Induction phase: switch to maintenance

Table 2. Recommended Duvelisib Dose Modifications for Non-hematologic Adverse Reactions		
Toxicity	**Adverse Reaction Grade**	**Recommended Management**
		• Maintenance phase: discontinue duvelisib
	• Confirmed Pneumocystis jiroveci pneumonia (PJP)	Discontinue duvelisib
	• Grade 3 infections	• Interrupt duvelisib until resolved • Induction phase: see Section 6.1.1 • Maintenance phase: resume at same (first occurrence) or reduced dose for subsequent occurrences (see **Table 4**)

Table 3. Recommended Duvelisib Dose Modifications for Hematologic Adverse Reactions*		
Toxicity	**Adverse Reaction Grade**	**Management**
Neutropenia	ANC < 1,000 /μL (Grade 3-4) without fever	Monitor ANC at least weekly
	Febrile neutropenia	• Interrupt duvelisib • Monitor ANC until > 500 /μL and resolution of febrile neutropenia • Induction phase: switch to maintenance phase • Maintenance phase: Resume duvelisib at same dose (first occurrence) or reduce dose for subsequent occurrences (see **Table 4**)
Thrombocytopenia	Platelet count decreased by 50-74% from baseline value (Grade 3) without clinically significant bleeding	Monitor platelet counts at least weekly
	Platelet count decreased by 50-74% from baseline value (Grade 3) with clinically significant bleeding or Platelet count decreased by ≥75% from baseline (Grade 4)	• Interrupt duvelisib • Monitor platelet counts until > 25% of baseline value and resolution of bleeding (if applicable) • Resume duvelisib at same dose (first occurrence) or reduce dose for subsequent occurrences (**Table 4**)
*Growth factors allowed per investigator discretion		

Table 4. Duvelisib Dose Modifications	
Dose Level	**Dose**
Induction Phase	
Initial Dose (Induction Phase)	25 mg twice daily
First Dose Reduction	15 mg twice daily
Second Dose Reduction	Switch to maintenance phase
Maintenance Phase	
Initial Dose (Maintenance Phase)	75 mg twice daily
First Dose Reduction	25 mg twice daily
Second Dose Reduction	15 mg twice daily
Subsequent Dose Modification	Discontinue duvelisib

6.3 TREATMENT PERIOD AND MAINTENANCE

Following a maximum of 12 weeks of continuous duvelisib therapy during the induction phase, participants will initiate intermittent maintenance dosing of duvelisib. This intermittent maintenance dosing will continue until disease progression, treatment intolerance, participant withdrawal, or death.

6.4 CONCOMITANT MEDICATION AND SUPPORTIVE CARE GUIDELINES

Medications required to treat AEs, manage cancer symptoms, concurrent diseases and supportive care agents, such as pain medications, anti-emetics and anti-diarrheals are allowed in general. The participant must be told to notify the investigational site about any new medications begun after the start of the study treatment. All medications or nutritional/herbal supplements known to interact with study agent should be excluded. If the medication or supplement cannot be discontinued or replaced, the subject should be excluded from this study. Each participant's medication and supplement profile should be reviewed by investigator and/or an oncology trained pharmacist to ensure compliance with this aspect of care. All medications (other than investigational products) and significant non-drug therapies (including vitamins, herbal medications, physical therapy and blood transfusions) administered during the study must be listed on the CRF.

6.4.1 INFECTION PROPHYLAXIS AND TREATMENT

Patients receiving duvelisib are at risk for infection, including pneumocystis, herpes, aspergillus, cytomegalovirus (CMV), and respiratory syncytial virus (RSV), as well as various bacterial infections. Please consult Duvelisib Prescribing Information for guidance. Some suggestions also follow below.

Pneumocystis (PJP): Participants receiving duvelisib should receive pneumocystis prophylaxis in accordance with institutional standards. Examples include Bactrim DS 1 pills by mouth three times per week; pentamidine 300 mg IV every 4 weeks etc. For participants who are intolerant of pneumocystis prophylaxis, an alternative regimen should be considered. If patients are unable or unwilling to receive PJP prophylaxis, their care should be discussed with the Principal Investigator (Alexey V. Danilov, MD), to determine if they are able to continue on study therapy.

Herpes and CMV infections: Peripheral blood analysis for CMV DNA is recommended at least every 4 weeks during induction phase, and at least every 8 weeks during maintenance phase of therapy. Additional prophylaxis for herpes and CMV viral infections may be used per institutional standards for the duration that they receive duvelisib.

In general, participants with documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the Investigator for a given infectious condition, according to standard institutional practice.

Pneumonia: Participants that develop new pulmonary symptoms (e.g., cough, shortness of breath, dyspnea on exertion) or new radiographic findings suggestive of pulmonary infection should have duvelisib held as specified in the protocols, and receive antibiotics or other anti-infective agents as considered appropriate by the Investigator. Duvelisib should be held and subsequently restarted after complete resolution of symptoms. Non-infectious pneumonitis should be considered on the differential diagnosis.

6.4.2 **NAUSEA/VOMITING**

No routine prophylactic anti-emetic treatment is required at the start of treatment; however, participants should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter per institutional guidelines.

6.4.3 **DIET**

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

6.4.4 **TRANSFUSION OF PLATELETS AND RED BLOOD CELLS (RBC)**

Platelet transfusion are permitted as medically necessary per institutional guidelines (e.g., for platelets <10,000/μL in the absence of clinical bleeding). Red blood cell transfusion should be considered for all patients with anemia, especially those with hemoglobin values ≤7 g/dL, or per institutional guidelines.

6.4.5 **ANTI-PLATELET AGENTS AND ANTICOAGULANTS**

May be used in patients who have controlled coagulopathy at baseline, as well as those who develop a coagulopathy on study. Patients who develop a requirement for therapeutic anticoagulation while on study (e.g., new atrial fibrillation, or venous thrombosis) may stay on study, and will be carefully monitored for bleeding risks.

6.4.6 **GROWTH FACTORS**

Allowed at the discretion of the Investigator

6.4.7 **SKIN RASHES**

Suggests regarding management of rashes are noted in **Table 5**.

Table 5. Recommended Management by Toxicity Grade – Skin rash

Grade	Management of Duvelisib
Grade 1	Continue duvelisib. • Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream) per institutional guidelines

Table 5. Recommended Management by Toxicity Grade – Skin rash	
Grade	**Management of Duvelisib**
Grade 2	For persistent (>1 to 2 weeks) Grade 2 events, hold scheduled study drug until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.
Grade 3	Hold duvelisib until resolution to Grade ≤1 or baseline. If temporarily holding duvelisib does not provide improvement of the Grade 3 skin rash to Grade ≤1 or baseline within 28 days, then permanently discontinue study drug/study regimen. • Consult dermatology as needed. • Promptly initiate empiric IV methylprednisolone (1 to 2 mg/kg/day) or equivalent per institutional guidelines o Gradually taper steroids over ≥28 days once improvement in symptoms is observed. Consider prophylactic antibiotics, antifungals, and anti-PCP treatment per institutional guidelines.
Grade 4	Permanently discontinue duvelisib

6.4.8 **TUMOR LYSIS SYNDROME**

Tumor lysis syndrome should be monitored (e.g., uric acid) and appropriate hydration measure and therapy with anti-hyperuricemic (e.g., allopurinol) should be performed as clinically indicated per institutional guidelines. There were no cases of tumor lysis syndrome observed in patients with CLL treated with duvelisib in prior clinical trials.

6.4.9 **CONTRACEPTION**

The study agent described within this protocol may have adverse effects on a fetus in utero. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use adequate methods of birth control (Refer to Appendix B) or are considered highly unlikely to conceive.

Highly unlikely to conceive women are defined as:

1. Surgically sterilized, or
2. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:
   a. Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
   b. Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).
3. Not heterosexually active for the duration of the study.

Participants should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study individuals must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in Section 9.7. If there is any question that a participant will not reliably comply with the requirements for contraception, they should not be entered into the study.

6.4.10 **USE IN PREGNANCY**

If a participant inadvertently becomes pregnant while on treatment with study agent, the participant will immediately be removed from the study. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The pregnancy will be recorded on the CRF and reported by the Investigator to the IRB (refer to Section 9.10.1).

6.4.11 **USE IN NURSING WOMEN**

It is unknown whether duvelisib is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breast-feeding are not eligible for enrollment.

6.5 **PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES**

Duvelisib and its major metabolite, IPI-656, have the potential to inhibit CYP3A4. When midazolam, a sensitive CYP3A4 substrate, was co-administered with duvelisib, a moderate increase in AUC_{∞} (4.3-fold) was observed. Use caution when co-administering duvelisib with CYP3A4 substrates. Refer to Appendix C for examples.

6.6 **PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES**

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Duvelisib is primarily metabolized by CYP3A4, and inhibition of this enzyme results in increased duvelisib levels. Likewise, use of CYP3A inducers greatly decrease duvelisib levels.[36] As such, concomitant use of drugs or foods that are strong inhibitors or inducers of CYP3A are not allowed during treatment with duvelisib. Refer to Appendix C for examples. Minimal changes in exposure are expected in the presence of mild or moderate CYP3A4 inhibitors and therefore, no dose adjustment is recommended.
- Any anti-cancer systemic chemotherapy, biological therapy, or radiation therapy while receiving duvelisib
- Use of herbal and dietary supplements is discouraged. Their use should be approved by the Investigator and clearly documented. Use of supplements which may interfere with CYP3A4 is strongly discouraged.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management may be removed from the trial. Participants may receive other medications that the investigator deems to be medically necessary. Participant exclusion criteria (Section 4.2) describes other medications prohibited in this trial.

7. STUDY PROCEDURES/EVALUATIONS AND SCHEDULE

7.1 STUDY SPECIFIC PROCEDURES

7.1.1 MEDICAL HISTORY

A medical history will be obtained by the investigator or qualified designee. In addition to collecting information on demographics, the medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the participant's CLL/SLL will be recorded separately and not listed as medical history.

7.1.2 DISEASE ASSESSMENT

The Investigator or qualified designee will obtain prior and current details regarding the participant's CLL/SLL.

7.1.3 MEDICATION HISTORY

A complete medication history will be acquired concurrent with medical history.

7.1.4 PHYSICAL EXAMINATION

Physical exams must be performed by a medically qualified individual such as a licensed physician, Physician's Assistant or advanced Registered Nurse Practitioner as local law permits. The physical exam at baseline should include a complete physical exam per institutional standards. All other physical exams after baseline will include an evaluation of any AEs, or any previously reported symptoms, or prior physical examination findings.

A physical examination may include evaluating: weight, general appearance, head, ears, eyes, nose, throat, neck, skin, cardiovascular system, respiratory system, gastrointestinal system, and nervous system. Physical examination will also include assessment of number of sites and sizes of lymphadenopathies, hepatomegaly and splenomegaly. More extensive physical exams will be performed if guided by the development of new symptoms.

As part of screening visit, physical examination is to be conducted within 30 days prior to start of treatment. All physical examinations will also include:

7.1.4.1 *Vital signs*

Vitals to be collected include BP, HR, temperature, and oxygen saturation by pulse oximetry. Vitals will be obtained during each study visit.

Significant findings that were present prior to the signature of the informed consent must be included in the Medical History CRF page. Significant new findings that begin or worsen after beginning study treatment must be recorded on the Adverse Event CRF page.

7.1.4.2 *Height and weight*

Weight is collected as part of physical examination. Height is only required as part of screening.

7.1.4.3 *Performance status*

Refer to **Appendix A** for performance criteria.

7.1.5 ELECTROCARDIOGRAM (ECG)

Resting 12-lead ECGs will be recorded at screening, and as clinically indicated throughout the study (refer to schedule in Section 7.9).

7.1.6 RADIOGRAPHIC OR OTHER IMAGING ASSESSMENTS

Computed tomography (CT) scan of neck, chest, abdomen and pelvis per institutional guidelines (with intravenous contrast, wherever possible), should be performed at screening, then at the end of 3 (induction phase), 6 and 12 cycles of therapy. Positron emission topography with CT (PET-CT) and/or magnetic resonance imaging studies will be performed as clinically indicated, per institutional guidelines, and is acceptable in place of CTs, if performed. For example, PET-CT may be performed if disease transformation is suspected.

7.1.7 ADVERSE EVENT EVALUATION

Toxicities and adverse experiences will be assessed at each visit using the CTCAE v5.0. Hematologic toxicities will be assessed per IWCLL 2018 guidelines [42]. Safety will be monitored by assessing physical examination, vital signs, body height and weight, performance status, hematology, chemistry, coagulation, urinalysis, thyroid function, pregnancy, ECG, cytokine testing, as well as collecting of the AEs at every visit after initiation of therapy.

The AE reporting period begins from the time the patient starts treatment through and including 30 calendar days after the last study drug dose. All treatment-related AEs/SAEs should be followed until resolution or stabilization. Any SAE occurring after the reporting period must be promptly reported if a causal relationship to the investigational drug is suspected. If the patient begins a new anticancer therapy, the safety reporting period ends at the time the new treatment is started, however, death must always be reported if it occurs during the AE reporting period irrespective of intervening treatment.

Participants will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs throughout the study. All AEs (serious and non-serious) must be recorded on the source documents and CRFs regardless of the assumption of a causal relationship with the study drug, except for the following: (specify any AEs and/or grades that are excluded from this requirement). Refer to Section 9 for details on AE collection and reporting.

7.1.8 ASSESSMENT OF STUDY AGENT ADHERENCE

Participants will self-administer oral study agent, duvelisib, and are required to maintain a medication diary to assess compliance (refer to Appendix D). Participants will receive instruction on how to administer study drug from a physician, clinical research nurse, or other designated, qualified research team member such as study coordinators.. Participants will be provided with a medical diary and are required to record the date, dose, and the time of the ingestion.

7.2 LABORATORY PROCEDURES AND EVALUATIONS

Refer to Section 7.9 for a schedule of all laboratory test and procedures. Additional laboratory tests and procedures may be performed as clinically indicated.

7.2.1 **HEMATOLOGY**

Complete Blood Count (CBC) with differential, including: RBC, hematocrit, hemoglobin, platelet, WBC, and WBC Differential.

Reticulocyte count is required at screening, and may be performed thereafter as clinically indicated.

7.2.2 **BIOCHEMISTRY**

Comprehensive metabolic panel (CMP), including: Na, K, Cl, CO_2, BUN, Creatinine, Ca, Glu, Albumin, Alkaline Phosphatase, total bilirubin, AST, ALT, total protein, lactate dehydrogenase (LDH), uric acid.

Beta-2-microglobulin will be evaluated at screening only.

HIV test is not required. History of HIV is sufficient. Hepatitis B (e.g., HBsAg) and Hepatitis C (e.g., HCV Ab) status are required at screening only. Prior results from within 12 months from time to first dose of study treatment are acceptable.

Direct Coomb's test is required at screening, and may be performed thereafter as clinically indicated.

Serum immunoglobulins, IgG, IgM, and IgA are required at screening and at end of treatment.

7.2.3 **URINALYSIS**

Urinalysis will be collected at screening.

7.2.4 **COAGULATION PANEL**

Activated Partial Thromboplastin Time (aPTT) and pro-thrombin time (INR) are only required at screening

7.2.5 **PREGNANCY TEST**

A serum pregnancy test will be done at screening. A serum or urine pregnancy test will be done on Day 1 of each cycle for women of childbearing potential. If the urine pregnancy test is positive, a serum pregnancy test must be performed per institutional standards.

7.2.6 **LYMPH NODE BIOPSY**

A lymph node biopsy not required for this study, but may be requested at the discretion of the investigator or treating physician to establish the diagnosis of a transformation into an aggressive lymphoma (e.g., Richter syndrome), if suspected.

7.2.7 **BONE MARROW BIOPSY**

Bone marrow biopsy procedure will be performed according to institutional standards. It is not

required for the study at screening and is performed at the discretion of the Investigator. Results of molecular and genetic assays (listed below) derived from a bone marrow biopsy performed within 6 months prior to the first dose of study treatment are acceptable.

An additional on-study bone marrow biopsy should be performed in participants who are suspected of achieving CR within 4 weeks.

7.2.7.1 *Molecular and genetic assays*

Testing results are not required to proceed with study enrollment. Cellular and molecular assays will be performed according to institutional standards, at screening.
The following assays will be planned as per standard of care:

- CLL FISH Panel (as per institutional standards)
- immunoglobulin heavy chain (IGVH) mutational status
- prognostic gene panel (e.g., HopeSeq panel performed at COH).

7.3 EXPLORATORY STUDIES

The exploratory objectives of this study are to evaluate the T-cell repertoire in participants with CLL that receive duvelisib. The effects of duvelisib treatment on T-cell repertoire will be evaluated by flow cytometry.

i) Collection of Specimen(s)

Peripheral blood for research purposes will be collected at specified time points as outlined under “Research blood draw” in the Schedule of Events Section 7.9.. Four green-top sodium heparin tubes (15-20 mL of peripheral blood in total) will be collected prior to first dose of study drug (at C1D1 visit), after three cycles (at C4D1 visit – except if maintenance starts early – see below), after six cycles (at C7D1) and after twelve (at C13D1) cycles of therapy.

If a study participant switches to maintenance therapy prior to C4D1, a research blood draw will occur at that time (i.e., at the beginning of the corresponding first Maintenance cycle), rather than on C4D1.

ii) Handling of Specimens at Investigators’ Laboratories (COH and DFCI)

Peripheral blood samples will be diluted 1:1 with phosphate buffered saline (PBS) before separation of peripheral blood mononuclear cells (PBMCs) by density gradient centrifugation. Cells will be washed in RPMI1640 supplemented with 10% fetal calf serum and 25 mg of gentamicin, and either used immediately or frozen and stored in liquid nitrogen. Flow cytometry will be used to evaluate leukocyte subpopulations (e.g., CD3, CD4, CD45, TCRγδ, CD14, CD16, CD56). Additional surface markers will be used to discriminate different maturation stages of effector cells (CD28, CD27, CD45RA, CD3, CD8, CCR7, CD4, CD45): naive T cells, central memory, effector memory and CD45RA expressing effector memory cells; Tregs (CD4+CD25+FoxP3+CD127low); Th17 (IL-17positive).

iii) Shipping of Specimens

Freshly isolated samples will be transported in a closed container from clinic to City of Hope (Danilov) or DFCI (Brown) research laboratories, respectively, for processing as described

above.

For shipping from OHSU to City of Hope Danilov lab, please see Appendix H and Appendix I for forms and instructions.

For COH- & OHSU-derived specimens:

Samples will be transported to Dr. Danilov's laboratory:

Alexey Danilov MD, PhD
Kaplan Clinical Research Building 1st floor, 158-1022
City of Hope National Medical Center
1500 E Duarte Rd, Duarte, CA

For DFCI-derived specimens:

Samples will be transported to Dr. Jennifer Brown's laboratory:

Stacey Fernandes
CLL Center, J. Brown Lab
1 Jimmy Fund Way
JF426
Boston MA 02115
617-632-5828

iv) Site Performing Correlative Study

Flow cytometry for research purposes will be performed in investigators' laboratories.

7.4 SCREENING ASSESSMENTS

A screening (consultation) visit may occur as part of standard of care. If a participant is eligible for the study after review of key inclusion/exclusion criteria, additional screening visits will be scheduled while staff members are requesting insurance authorization to participate in a clinical trial.

The following will be reviewed at screening visit:

- Clinical history and physical exam (per standard of care)
- Informed consent obtained and documented

Toxicities which occur prior to the start of treatment will not be subject to analysis. Consent must be obtained before initiation of any clinical screening procedure that are performed solely for the purpose of determining eligibility for this research study. Evaluations performed as part of routine care before informed consent can be utilized as screening evaluations if done within the defined time period.

7.5 ASSESSMENTS DURING TREATMENT

Specific on-study assessments are listed in the Section 7.9, Schedule of Events. Visits should occur on Day 1 of every cycle. Under certain circumstances (e.g., clinic holiday, inclement weather) scheduled visits may be delayed by no more than 3 days, or may occur earlier than

scheduled by no more than 3 days during each treatment cycle cycles (induction phase). For maintenance phase, 7-day window is permitted.

During induction phase, clinical visits, including laboratory testing, should occur every 2 weeks for the first 12 weeks (i.e., during induction phase). During maintenance phase, visits will occur every 4 weeks until cycle 13, and then every 8 weeks thereafter. When physical exam is not required, laboratory studies may be performed locally.

7.6 END OF TREATMENT OR EARLY TERMINATION VISIT

Any participant that discontinues treatment must be evaluated within 30 days after termination or prior to the initiation of any other off-study interventional therapy, if not performed within the last 30 days. End of treatment assessments are listed in the Section 7.9, Schedule of Events.

If participants do not reach the end of treatment due to transition to hospice or death, an end of treatment visit will not be conducted. At the discretion of the investigator, participants may have the option to continue on study drug; particularly if there is a documented clinical benefit.

7.7 FOLLOW-UP

Participants removed from protocol therapy for unacceptable AE(s) will be followed until resolution or stabilization of the AE. Participants will be followed every 3 months after removal from protocol therapy until 12 months after end of treatment, introduction of next treatment, or death, whichever occurs first (see Section 7.9, Schedule of Events).

7.8 UNSCHEDULED VISITS

Unscheduled study visits may occur at any time if medically warranted.

7.9 SCHEDULE OF EVENTS

	Screen (30-day window)	INDUCTION (cycle 1-3)		MAINTENANCE (cycle 4-12)	MAINTENANCE (cycles 13 -)	End of treatment	Follow-up †
		Day 1 (±3 days)	Day 14 (±3 days)	Day 1 (±7 days)	Day 1 (±7 days) EVERY 8 weeks		Every 3 months (±2 weeks)
Informed consent	X						
Inclusion/exclusion criteria	X						
Medical history	X	X		X	X	X	X
Medication history[A]	X	X		X	X	X	X
Physical Examination[B]	X	X		X	X	X	X
CT Imaging[C]	X			X (C4D1, C7D1)	X (C13D1)		
12-lead ECG[D]	X						
Hematology[E]	X	X	X	X	X	X	X
Reticulocyte Count[E]	X						
CMP[F]	X	X	X	X	X	X	X
Hepatitis B & C Status[G]	X						
Serum IgG, IgA, IgM	X					X	
Beta-2-Microglobulin	X						
Direct Coomb's test[H]	X						
Urinalysis	X						
Coagulation	X						
Pregnancy test[I]	X	X		X	X		
Molecular+genetic tests[J]	X						
Bone Marrow Exam[K]	X						
Research blood draw		X(C1D1)		X (C4D1[M], C7D1)	X (C13D1)		
AE assessment[L]		X		X	X	X	X

Treatment cycles are 28 days. During induction, duvelisib is administered as continuous dosing (25 mg *b.i.d*) for 12 weeks (3 cycles). During maintenance, duvelisib is administered as repeated intermittent dosing consisting of 2 days on-treatment, followed by 5 days off-treatment.

† Follow-up should occur every 3 months after removal from protocol therapy until 12 months after end of treatment, introduction of next treatment, or death, whichever occurs first.

[A] For concomitant medications – enter new medications started during the trial through the end of treatment visit. Record all medications taken for grade 3 and 4 SAEs (see Section 9.7).

[B] All physical exams will include assessing weight, vital signs, and ECOG performance status.

[C] Imaging should be performed at the end of induction (C4D1), and after 6 and 12 cycles. ORR assessment will co-occur with CTs

[D] 12-lead ECG will be checked at screening and may be performed thereafter as clinically indicated.

[E]Complete Blood Count (CBC) with differential, including: RBC, hematocrit, hemoglobin, platelet, WBC, and WBC Differential. Reticulocyte count is required at screening, and may be performed thereafter as clinically indicated.

[F] CMP (Na, K, Cl, CO2, BUN, Creatinine, Ca, Glu, Albumin, Alkaline Phosphatase, total bilirubin, AST, ALT, total protein, lactate dehydrogenase (LDH), uric acid. Beta-2-microglobulin at screening only. History of HIV is sufficient. Hepatitis B (e.g., HBsAg) and Hepatitis C (e.g., HCV Ab) status are required at screening only. Prior results from within 12 months from time to first dose of study treatment are acceptable.

[G] Hepatitis B and C status are required at screening. Prior results from within 12 months from time to first dose of study treatment are acceptable.

[H] Direct Coomb's required only at screening and may be performed thereafter as clinically indicated

[I] For women of reproductive potential: Serum pregnancy test at screening, and urine pregnancy test should be performed on Day 1 of every cycle beginning with C2 during first 12 cycles, and then every 8 weeks. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test is required.

[J] CLL FISH (as per institutional standards), immunoglobulin heavy chain (IGVH) mutational status, prognostic gene panel.

[K] Bone marrow biopsy to be performed as per Investigator discretion at screening, and in patient who are suspected having achieved CR

[L] AEs and laboratory safety measurements will be graded per NCI CTCAE version 5.0. Hematologic toxicities will be assessed per IWCLL 2018 guidelines. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness.. Report grade 3 and 4 hematological and non-hematological SAEs (related and unrelated to trial treatment) occurring up until 30 days after the last dose of trial treatment, or the start of new anti-cancer treatment, whichever comes first. Afterwards, report only SAEs that are related to trial treatment

[M]If maintenance starts earlier than cycle 4, research blood draw should occur at the time point corresponding to the first Maintenance cycle visit.

8. EFFICACY MEASURES

8.1 DISEASE EVALUATION

Physical examination – physical exams will focus on documenting a change in the number of sites and sizes of lymphadenopathies, hepatomegaly and splenomegaly at schedule time points defined in Section 7.9. More extensive physical exams will be performed if guided by the development of new symptoms.

CBC – white blood cell count, hemoglobin and hematocrit, platelet count, and differential count, including both percent and absolute number of lymphocytes. CBC with differential should be assessed at schedule time points defined in Section 7.9.

CT scan of neck, chest, abdomen and pelvis with contrast, will be performed at schedule time points defined in Section 7.9.

8.2 EFFICACY CRITERIA FOR TUMOR RESPONSE

Treatment response will be determined per the investigators' assessment, according to IWCLL 2018 guidelines as in Hallek et al[42]. All participants who receive at least one dose of study medication will be evaluable for efficacy.

Table 8. Response Definition for CLL/SLL

Group	Parameter	CR	PR	PD	SD
A	**Lymph Nodes**	None ≥ 1.5 cm	Decrease ≥ 50% (from baseline)*	Increase ≥ 50% from baseline or from response	Change of - 49% to + 49%
	Liver and/or spleen size	Spleen size <13 cm; liver size normal	Decrease ≥ 50% (from baseline)	Increase ≥ 50% from baseline or from response	Change of - 49% to + 49%
	Constitutional symptoms	None	Any	Any	Any
	Circulating lymphocyte count	Normal	Decrease ≥ 50% (from baseline)**	Increase ≥ 50% over baseline	Change of - 49% to + 49%
B	**Platelet count**	≥ 100 x 10^9/L	≥ 100 x 10^9/L or increase ≥ 50% over baseline	Decrease of ≥50% from baseline secondary to CLL	Change of - 49% to + 49%
	Hemoglobin	≥ 11.0 g/dL (untransfused and without erythropoietin)	≥11 g/dL or increase ≥50% over baseline	Decrease of ≥ 2 g/dL from baseline secondary to CLL	Increase <11.0 g/dL or <50% over baseline, or decrease <2 gl/dL
	Marrow	Normocellular, no CLL cells, no B-lymphoid nodules	Presence of CLL cells, or of B-lymphoid nodules, or not done	Increase of CLL cells by ≥ 50% on successive biopsies	No change in marrow infiltrate

*Sum of the products of 6 or fewer lymph nodes (as evaluated by CT scans and physical examination)
**Patients not meeting the PR criterion for circulating lymphocyte count, but meeting all PR criteria otherwise, should be regarded as having PR-L. Presence of lymphocytosis for these patients will be documented.
CR, complete remission (all of the criteria have to be met); PD, progressive disease (at least 1 of the criteria of group A or group B has to be met); PR, partial remission (for a PR, at least 2 of the parameters of group A *and* 1 parameter of group B need to improve if previously abnormal; if only 1 parameter of both groups A and B is abnormal before therapy, only 1 needs to improve); SD, stable disease (all of the criteria have to be met; constitutional symptoms alone do not define PD).
NOTE: PD based on circulating lymphocyte count is determined as increase ≥50% over nadir. However, duvelisib may initially cause redistribution lymphocytosis. Please refer to Section 5.3 of Hallek et al, 2018 (ref 42) and contact the Sponsor-Investigator if clarification is required.

8.2.1 **PROGRESSION-FREE SURVIVAL**

PFS will be estimated from start of duvelisib treatment until death, time of progression, start of new therapy, or end of follow-up, whichever occurs first. PFS will be censored at the start of new therapy or end of follow-up, whichever occurs first.
Proportion of PFS at 12 months is the primary endpoint in this study. In addition, median PFS will be estimated.

8.2.2 **OBJECTIVE RESPONSE RATE**

The rate of response will be measured as the proportion of participants who have a CR or PR (including PR-L) at the pre-specified time-points, to coincide with CT measurements at the end of Cycles 3, 6 and 12 of study intervention (refer to Section 7.9, Schedule of Events).

8.2.3 **DURATION OF RESPONSE**

Duration of response (DOR), for participants who responded to the study intervention, should be measured from the time of first documented objective response (i.e., CR or PR/PR-L) until evidence of progressive disease, start of new therapy, death, or end of follow-up. DOR will be censored at the start of new therapy or end of follow-up, whichever occurs first.

8.3 **RESPONSE REVIEW**

Response assessment will be determined by the investigator.

9. SAFETY

9.1 SPECIFICATION OF SAFETY PARAMETERS

The Investigator is responsible for monitoring the safety of participants who have enrolled in the study. Safety assessments will be based on medical review of adverse events and the results of safety evaluations at specified time points as described in Section 7.9, Schedule of Events. Any clinically significant adverse events persisting at the end of treatment visit will be followed by the Investigator until resolution/stabilization or death, whichever comes first.

9.2 DEFINITIONS

9.2.1 ADVERSE EVENT (AE)

An adverse event is defined as any undesirable physical, psychological or behavioral effect experienced by a participant during their participation in an investigational study, in conjunction with the use of the investigational product, whether or not considered intervention-related (21 CFR 312.32 (a)). In general, this includes signs or symptoms experienced by the participant from the time of the first dose of study drug to completion of the study.

AEs may include, but are not limited to:
- Subjective or objective symptoms spontaneously offered by the participant and/or observed by the Investigator or medical staff.
- Clinically significant laboratory abnormalities.
- A significant worsening of the participant's condition from study entry.
- Disease signs and symptoms and/or laboratory abnormalities existing prior to the use of the study treatment that resolve but then recur after treatment.
- Disease signs and symptoms and/or laboratory abnormalities existing prior to the use of the study treatment which increase in frequency, intensity, or a change in quality after treatment.

For laboratory abnormalities, the criteria for determining whether an abnormal test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing outside of protocol-stipulated dose adjustments or discontinuation from the study, significant additional concomitant drug treatment, or therapy, and/or
- Test result is considered to be an adverse event by the Investigator

9.2.2 SERIOUS ADVERSE EVENT (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator, it results in any of the following outcomes:

- Death,
- A life-threatening adverse event,
- In-patient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- 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 or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

*Modified from 21 CFR 312.32

9.3 ASSESSMENT OF ADVERSE EVENTS

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

9.3.1 ASSESSMENT OF ADVERSE EVENT NAME AND GRADE:

Adverse events will be characterized, when applicable, using the descriptions and grading scales found in the current version of the CTCAE v5.0. Hematologic toxicities will be graded per IWCLL 2018 guidelines. In the event of an AE for which no grading scale exists, the Investigator will classify the AE as defined below:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activity of daily living (ADL)
Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
Grade 4: Life-threatening consequences; urgent intervention indicated.
Grade 5: Death related to AE.

Note: a semi-colon indicates 'or' within the description of the grade.

iwCLL Guidelines[42]

Grading scale for hematological toxicity in CLL studies

Grade*	Decrease in platelets† or Hb‡ (nadir) from baseline value, %	Absolute neutrophil count (nadir)§ x 10^9/L
0	No change to 10	≥2
1	11-24	≥1 and <2
2	25-49	≥1 and <1
3	50-74	≥0.5 and <1
4	≥75	<0.5

*Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from baseline will be recorded as grade 5.

†Platelet counts must be below normal levels for grades 1-4. If, at any level of decrease the platelet count is $<20 \times 10^9$/L, this will be considered grade 4 toxicity unless a severe or life-threatening decrease in the initial platelet count (eg, 20×10^9/L) was present at baseline, in which case the patient is not evaluable for toxicity referable to platelet counts.

‡Hb levels must be below normal levels for grades 1-4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity, but should be documented.

§If the absolute neutrophil count (ANC) reaches $<1 \times 10^9$/L, it should be judged to be grade 3 toxicity. Other decreases in the white blood cell count or in circulating granulocytes are not to be considered because a decrease in the white blood cell count is a desired therapeutic end point. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was $<1 \times 10^9$/L before therapy, the patient is not evaluable for toxicity referable to the ANC. The use of G-CSF is irrelevant for the grading of toxicity, but should be documented

9.3.2 ASSESSMENT OF ATTRIBUTION

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **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.

9.3.3 ASSESSMENT OF EXPECTEDNESS

The following definitions will be used to determine the expectedness of the event:
Unexpected Adverse Event - [Modified from 21 CFR 312.32 (a)] 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.

Expected Adverse Event - 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.

9.4 ADVERSE EVENT LIST

9.4.1 ADVERSE EVENT LIST FOR DUVELISIB

In studies to treat hematological malignancies, use of duvelisib has been related to 19 deaths, of which 14 participant deaths were associated with a serious infection. Across all hematologic oncology studies (n= 443), the most common SAE associated with duvelisib includes:, pneumonia (10.84%), diarrhea (10.16%), pyrexia (3.61%), febrile neutropenia (5.87%), pneumonitis (3.39%), and rash (1.35%). The most frequent (≥ 10%) TEAEs among all participants with any hematological malignancy studied and those specifically with CLL/SLL are summarized in **Table 6** and **Table 7**.[36] Refer to investigator's brochure for additional details.[36]

Table 6. Summary of most frequent TEAEs – All Disease Groups	
	Frequency (n = 588)
Diarrhea	49.0%
Neutropenia	34.7%
Rash	34.7%
Fatigue	33.2%
Cough	26.7%
Upper respiratory tract infection	22.3%
Transaminase Elevation	22.8%
Musculoskeletal Pain	22.6%
Edema peripheral	16.7%
Headache	13.8%
Renal insufficiency	11.7%

Table 7. Summary of most frequent TEAEs – R/R CLL/SLL	
	Frequency (n = 331)
Diarrhea	52.9%
Neutropenia	36.6%
Rash	32.9%
Fatigue	27.8%
Pneumonia	26.9%
Upper respiratory tract infection	25.7%
Cough	23.6%
Musculoskeletal Pain	17.2%
Transaminase Elevation	14.5%

9.5 UNANTICIPATED PROBLEMS (UP)

Unanticipated Problem (UP) - 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 (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document, or Investigator Brochure (IB); and (b) the characteristics of the participant 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 outcome may have been caused by the procedures involved in the research); **AND**
3. Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

9.6 ADVERSE EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an UP, AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, seriousness, expectedness, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and date of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution (until grade 1, or until per Investigator's opinion, AEs stabilized and further resolution is unlikely).

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed.

At each study visit, the Investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution (to at least grade 1) or stabilization.

Any SAE that occurs after 30 days of last active treatment will be reported only if the Investigator or current treating physician has assessed the SAE as related to the study treatment. Adverse events will be evaluated using the current version of the CTCAE v5.0. Hematologic toxicities will be evaluated per IWCLL 2018 guidelines.

9.7 ROUTINE AE COLLECTION AND REPORTING GUIDELINES

9.6.1 REPORTING OF ADVERSE EVENTS

Routine Reporting of Non-Serious Adverse Events by Site Investigators
Routine AE recording will occur via data entry into the study eCRF. 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.

9.6.2 EXPEDITED REPORTING REQUIREMENTS OF SAES AND UPS

Criteria for Reporting SAEs/UPs

Adverse events that require expedited reporting include:

- AEs or SAEs that meet the definition of an unanticipated problem
- All serious adverse events (Grades 1-5) that occur within 30 days of active treatment
- All serious adverse events occurring 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.

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

All events that meet the criteria will be reported to the DCC and Study PI within 24 hours of notification that the event met the expedited reporting criteria.

1. Document/describe the AE/UP on each of the following:
    a. MedWatch 3500A or local IRB submission document*
    MedWatch 3500A is downloadable form at
    http://www.fda.gov/medwatch/getforms.htm
        *The local IRB submission document may be used if the document template is approved by the DCC
    b. Expedited Reporting Coversheet. The Expedited Reporting Coversheet is found in Appendix F. A modifiable Microsoft Word document is also available from the DCC. An electronic signature on the document will be accepted.
2. Scan and email above documents to DCC@coh.org with the subject title as "[Verastem] SAE COH IRB #19563".
    a. All expedited reports received at this account are immediately forwarded to the Study PI, and to DCC personnel.
    b. While not required, if available and applicable, please also include the local IRB submission for this event in the submission.
3. If an email receipt from DCC personnel is not received within one working day, please call (626)-218-7904 and/or email DCC@coh.org.

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 11.6. This report will include a review of aggregate adverse event data.

Email the following information to DCC@coh.org and the Study PI: 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.

9.8 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.

9.9 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.

9.10 MANUFACTURER REPORTING REQUIREMENTS

All initial and follow-up SAEs and Safety Information will be reported to Verastem, Inc. Safety and Pharmacovigilance within 24 hours of knowledge of the event. Reports should be submitted

in English via the Sponsor-Investigator internal AE form, MedWatch or CIOMS forms. SAE and Safety Information reports must contain the following minimum information:

- At least one identifiable reporter
- One single identifiable patient
- At least one suspect adverse reaction or Safety Information
- At least one suspect medicinal product
- The Sponsor-investigator's assessment of causality for the event

Copies of any correspondence or telephone conversation logs with the applicable Regulatory Authorities regarding all SAE(s), irrespective of association with the Study Drug(s), within a reasonable time frame must be provided to Verastem, Inc. Safety and Pharmacovigilance using the following contact information:

Via email: PVSafety@Verastem.com

Vial mail: COH shall send via a certified overnight service with a signature required and all fees prepaid to:

Verastem, Inc. Safety and Pharmacovigilance
117 Kendrick Street, Suite 500
Needham, MA 02494 USA

9.10.1 REPORTING OF PREGNANCY

To ensure participant safety, each pregnancy in a participant on study treatment must be reported within 24 hours of learning of its occurrence. The pregnancy should be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or any pregnancy- or childbirth-related and/or newborn complications.

The pregnancy should be recorded on a CRF and reported by the Investigator to the Verastem Inc. Pregnancy follow-up should be reported using the same form. Any SAE experienced during pregnancy must be reported.

If while on study treatment a participant's sexual partner becomes pregnant, the pregnancy and pregnancy outcomes must also be reported as described above. Consent to report information regarding the pregnancy should be obtained from the pregnant individual.

9.11 STUDY STOPPING RULES

The accrual to this study will be temporarily suspended until a full review performed by the study PI's (COH PI: Dr. Alexey Danilov, DFCI PI Dr. Jennifer Brown; OHSU PI Dr. Stephen Spurgeon) and the DSMC if the following events occur:

- Life-threatening grade 4 toxicity attributable to protocol therapy that is unexpected.
- Death suspected to be related to duvelisib

In addition, the following toxicities will result in temporary suspension of study accrual and a full review by study PI's and the DSMC if one of them occurs in ≥2 patients and is attributable to protocol therapy:

- Grade 4 suspected or biopsy-proved colitis which persists for > 7 days despite adequate therapy (including IV steroids) and results in prolonged hospital stay
- Grade 4 hepatic failure
- Grade 4 pneumonitis

Since duvelisib is FDA approved in treatment of relapsed/refractory CLL/SLL, it is not anticipated that the study will need to be stopped. However, this decision will remain at the discretion of study PI's and DSMC. Furthermore, dose de-escalation during maintenance phase (to 25 mg po bid 2 days out of 7) will be considered if the above toxicities occur during maintenance phase of the study.

With 30 patients, the probabilities of having at least one incidence of the specific events (as defined above) that will trigger the stopping rule at the first occurrence, as well as the probabilities of having at least two incidences of the specific events (as defined above) that will trigger the stopping rule at the second occurrence, are shown in the table below.

True toxicity incidence	Probability of having at least 1 incidence of the toxicity in 30 patients	Probability of having at least 2 incidences of the toxicity in 30 patients
1%	26%	4%
2%	45%	12%
3%	60%	23%
4%	71%	34%
5%	79%	45%
6%	84%	54%
7%	89%	63%
8%	92%	70%
9%	94%	77%
10%	96%	82%

10. STATISTICAL CONSIDERATIONS

Refer to Section 3.1, Description of the Study Design for a detailed description of the study design and endpoints.

10.1 ANALYSIS POPULATIONS

The safety analysis set includes all enrolled participants that receive at least one dose of study medications.

The efficacy analysis set includes all participants who receive at least one dose of duvelisib.

10.2 DESCRIPTION OF STATISTICAL METHODS

10.2.1 GENERAL APPROACH

This is a phase II, single arm, open label study to assess the efficacy and safety of duvelisib in patients with R/R CLL/SLL. For continuous variables, descriptive statistics will include the mean, standard deviation (or standard error), median, range, and interquartile range. For categorical variables, descriptive statistics will include the number and percent.

10.2.2 ANALYSIS OF PRIMARY ENDPOINT

Using efficacy analysis set, the proportion of subjects achieving 12 month PFS will be estimated along with a two-sided exact Clopper-Pearson 95% confidence interval.

10.2.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Using efficacy analysis set, the probability of having ORR will be measured and reported (if available) with 95% exact confidence interval. The descriptive statistics of DOR including mean, median, minimum, maximum, standard deviation, and 95% confidence interval will be reported.

The incidence of having Grade 3+ acute toxicity will be determined for participants with CLL/SLL that received at least one dose of duvelisib. The 95% confidence interval will be reported with the point estimate of toxicity rate.

Using efficacy analysis set, the estimated distribution of the PFS will be plotted using Kaplan Meier curves and reported with median PFS and 95% confidence intervals if available.

Using the safety analysis set, estimate the duration of therapy from the first dose of study drug until therapy is discontinued for any reason. The proportion of subjects completing the induction phase will be reported including 95% confidence interval. Proportion who move prematurely to maintenance phase will be reported.

10.2.4 ANALYSIS OF THE EXPLORATORY ENDPOINT(S)

Flow cytometry will be used to assess T-cell repertoire and evaluate changes associated with duvelisib. The distribution of T-cell subtypes distribution will be described by mean, standard deviation (SD), minimal, and maximal values. .

10.3 SAMPLE SIZE, POWER, ACCRUAL RATE AND STUDY DURATION

10.3.1 SAMPLE SIZE AND POWER

A sample size of 27 patients produces a two-sided exact Clopper-Pearson 95% confidence interval with a width equal to 0.394 (0.303-0.697) when the target 12 month PFS rate is 0.5 (see Table 8). Anticipating a dropout rate of 10%, a total of 30 patients will need to be enrolled.

Table 8. Sample size estimate

Confidence Level	Size (N)	Proportion (P)	Lower Limit	Upper Limit	Width if Target P = 0.5
0.95	17	0.5	0.254	0.746	0.493
0.95	18	0.5	0.260	0.740	0.480
0.95	19	0.5	0.266	0.734	0.467
0.95	20	0.5	0.272	0.728	0.456
0.95	27	0.5	0.303	0.697	0.394
0.95	28	0.5	0.306	0.694	0.387
0.95	29	0.5	0.310	0.690	0.380
0.95	30	0.5	0.313	0.687	0.374

10.4 HANDLING OF MISSING DATA

Every attempt will be made to obtain data at the defined time points as described in the primary and secondary endpoints. For time points that have no data, we will evaluate whether or not the other time points can be used to fulfill the primary and secondary data. If the data are not sufficient to analyze specific endpoints, the participant's data may be excluded entirely or partially, depending on the specific endpoints in question and in consultation with the biostatistician. No missing data will be imputed. Whenever possible, all available data will be included in the analysis. A sample size for each analysis will be clearly stated along with the reason for exclusion, if any participant is excluded from the analysis due to missing data.

10.5 DURATION OF STUDY

The duration of study will be 4 to 6 years (e.g., accrual 2 years + treatment 1-3 years + follow-up 1 year).

11. DATA AND SAFETY MONITORING

11.1 PROTOCOL DEVIATIONS

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly. 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.

Deviation
Any change, divergence, or departure from the study design or procedures of a research protocol.

Planned Protocol Deviation (PPD)
Any anticipated change, divergence, or departure from the study design or procedures of a research protocol that receives prospective IRB approval prior to implementation.

11.2 REPORTING OF DEVIATIONS AND PPDS

Reporting Deviations
Deviations from the protocol will be reported to the COH DSMC and IRB within 5 calendar days of notification 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).

Reporting Planned Protocol Deviations
The PPD must be submitted via iRIS in accordance with IRB guidelines and the Clinical Research Protocol Deviation policy. An IRB approved PPD does not need to be submitted as a deviation to the DSMC.

For non-COH sites:
The local IRB and/or DSMC must be notified according to local institutional policies. 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.

11.3 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.

11.4 **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).

11.5 **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. Documentation of monitoring activities and findings will be provided to the site study team, the site PI, study PI, and the COH DSMC.

11.6 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 and frequency outlined in the City of Hope Institutional Data and Safety Monitoring Plan.

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. The DSMC will 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.

12. DATA HANDLING AND MANAGEMENT RESPONSIBILITIES

12.1 SOURCE DATA/DOCUMENTS

The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The Investigator will maintain adequate case histories of study participants, including accurate case report forms (CRFs), and source documentation.

12.2 PARTICIPANT & DATA CONFIDENTIALITY

The information obtained during the conduct of this clinical study is confidential, and unless otherwise noted, disclosure to third parties is prohibited. Information contained within this study will be maintained in accordance with applicable laws protecting participant privacy, including the provisions of the Health Insurance Portability and Accountability Act (HIPAA).

Participant confidentiality is strictly held in trust by the participating Investigator(s) and study team. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or manufacturer supplying study product may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

Upon enrollment, participants will be assigned a code that will be used instead of their name, medical record number or other personally identifying information. Electronic files or data analysis will contain only the participant code. Codes will not contain any part of the 18 HIPAA identifiers (e.g., initials, DOB, MRN). The key associating the codes and the participants' personally identifying information will be restricted to the Investigator and study staff. Electronic case report forms, participant, and study information will be kept in an electronic password protected database indefinitely. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and institutional guidelines. No records will be destroyed without the written consent of the sponsor-investigator. It is the responsibility of the sponsor to inform the Investigator when these documents no longer need to be retained.

12.3 DATA COLLECTION & STORAGE: PRIVACY, CONFIDENTIALITY & SECURITY

Data for this trial will be collected using Medidata RAVE, City of Hope's electronic capture system. Medidata RAVE is a web-based, password-protected system that is fully compliant with global regulatory requirements, including 21CRF Part 11 compliant.

Study personnel will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF).

The investigator is responsible for all information collected on subjects 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.

This research will be conducted in compliance with federal and state of California requirements relating to protected health information (PHI). When results of this study are reported in medical journals or at meetings, identification of those taking part will not be disclosed. Medical records of subjects will be securely maintained in the strictest confidence, according to current legal requirements. They will be made available for review, as required by the FDA, HHS, or other authorized users such as the NCI, under the guidelines established by the Federal Privacy Act and rules for the protection of human subjects.

12.3.1 **FUTURE USE OF STORED SPECIMENS**

Each participant who signs consent will be assigned a unique coded identifier consisting of numbers. This identifier will be associated with the participant throughout the duration of their participation in the trial. The coded identifier will be used to identify any participant specific samples. Biological samples collected for the purposes of this protocol will be stored in Dr. Danilov's laboratory at City of Hope in the event that additional analysis is required. Tissue and blood samples derived from participants enrolled at DFCI will be stored in Dr. Brown's laboratory, and samples derived from participants enrolled at OHSU will be transferred to Dr. Danilov's laboratory at City of Hope in the event that additional analysis is required. All participants will be made aware of the sample storage conditions during the consent and enrollment process.

12.4 **MAINTENANCE OF RECORDS**

Records and documents pertaining to the conduct of this study, source documents, consent forms, laboratory test results and medication inventory records, must be retained by the Investigator for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indicate, until 2 years after the investigation is discontinued and FDA is notified.

If the Investigator relocates or for any reason withdraws from the study, the study records must be transferred to an agreed upon designee, such as another institution or another investigator at COH. Records must be maintained according to institutional or FDA requirements.

12.5 **MULTICENTER GUIDELINES**

COH Coordinating Center will manage trial data in the following ways:

a. Confirm that all sites have received and are using the most recent version of the protocol. Documentation of the version that was sent to the site must be kept in the regulatory binders.
b. Confirm that the protocol and informed consent form have local IRB approval at each site

prior to registration of the first participant. Documentation of IRB approval from other sites for continuing review must be submitted and kept in the binder.

c. Provide centralized participant registration in the clinical research management system.
d. .
e. Maintain documentation for all SAE reports and submit regular summaries of all AEs, SAEs and UPs from all sites to the DSMC per DSMC requirements.
f. Ensure that relevant IRB correspondence and study status changes are communicated to all participating sites. Any changes that affect participant safety of study enrollments will be communicated immediately.
g. Participating sites must submit regulatory documents including, but not limited to the following:
    - Current CV (signed and dated) for each Investigator.
    - Current medical license number for physician investigators.
    - Current signed FDA Form 1572.
    - Certificate of completion of institution-required human participant training course, the NIH online training in the protection of human research participants or other appropriate training.
    - Documentation of institutional Conflict of Interest.
h. IRB approved site-specific ICF (must be reviewed and approved by the subsite's Investigator and study team prior to submission to the local IRB.
i. All IRB approved documents and approval memos.
j. Delegation log.
k. .
l. Completed CRFs (data entry) within 10 business days of study visit.

12.6 PUBLICATION AND DATA SHARING POLICY

This study will adhere to the requirements set forth by the ICMJE and FDAAA that requires all clinical trials to be registered in a public trials registry (e.g., ClinicalTrials.gov) prior to participant enrollment.

12.7 DELIVERY OF PROGRESS REPORTS TO STUDY FUNDER

Upon the request of Verastem Inc., the Institution will submit oral or written reports on the progress of the Study as provided by this protocol. Within one hundred twenty (120) days following the completion or termination of the study, Institution will furnish Verastem Inc. with a final report detailing the results of the Study.

13. ETHICS/PROTECTION OF HUMAN PARTICIPANTS

13.1 ETHICAL STANDARD

The Investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312 (if applicable), and/or the ICH E6.

13.2 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 NIH policies and procedures
- Applicable institutional research policies and procedures

13.3 INSTITUTIONAL REVIEW BOARD

An Institutional Review Board (IRB) that complies with the federal regulations at 45 CFR 46 and 21 CFR 50, 56 and State of California Health and Safety code, Title 17, must review and approve this protocol, informed consent form and any additional documents that the IRB may need to fulfill its responsibilities (Investigator's Brochure, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) prior to initiation of the study. Revisions to approved documents will require review and approval by the IRB before the changes are implemented in the study. All institutional, NCI, Federal, and State of California regulations must be fulfilled.

Each participating non-COH 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). The protocol and consent will be reviewed and approved by the COH IRB before submission to a participating site IRB.

The IRB's written unconditional approval of the study protocol and the informed consent document must be in the possession of the investigator, and, for external sites, the possession of the DCC, before the study is initiated.

The IRB will be informed of serious unexpected, unanticipated adverse experiences, and unanticipated problems 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.

13.4 **INFORMED CONSENT**

Each participating non-COH 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 site's IRB (initial submission and amendments), the consent and accompanying HIPAA form, if separate to the consent, must be reviewed and approved by the DCC.

The Principal Investigator or IRB approved named designee will explain the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other information contained in the informed consent document. In addition, they will review the experimental subject's bill of rights if applicable, and the HIPAA research authorization form. Prospective participants will be informed that they may withdraw from the study at any time and for any reason without prejudice, including as applicable, their current or future care or employment at City of Hope or participating institution or any relationship they have with City of Hope. Prospective participants will be afforded sufficient time to consider whether or not to participate in the research.

After the study has been fully explained, written informed consent will be obtained from either the prospective participant 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.

A copy of the signed informed consent will be given to the participant or his/her legally authorized representative. The original signed consent must be maintained by the investigator and available for inspection by 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.

13.5 **PROTOCOL REVIEW**

The protocol and informed consent form for this study must be reviewed and approved in writing by the COH Cancer Protocol Review and Monitoring Committee (CPRMC) and the appropriate IRB prior to any participant being consented on this study.

13.6 **CHANGES TO PROTOCOL**

Any modification of this protocol must be documented in the form of a protocol revision or amendment submitted by the Investigator and approved by the CPRMC (if applicable) and IRB, before the revision or amendment may be implemented. The only circumstance in which the amendment may be initiated without regulatory approval is for a change necessary to eliminate an apparent and immediate hazard to the participant. In that event, the Investigator must notify the local IRB (and other regulatory authorities, if applicable) within 5 business days after the implementation. An Investigator who holds an IND application must also notify the FDA of changes to the protocol per 21 CFR 312.

14. REFERENCES

1. Noone AM, Howlader N, Krapcho M, et al. SEER Cancer Stat Facts: Chronic Lymphocytic Leukemia. *SEER Cancer Statistics Review.* 2018;https://seer.cancer.gov/statfacts/html/clyl.html.
2. Avalos AM, Meyer-Wentrup F, Ploegh HL. Chapter One - B-Cell Receptor Signaling in Lymphoid Malignancies and Autoimmunity. In: Ploegh HL, ed. *Advances in Immunology.* Vol 123: Academic Press; 2014:1-49.
3. Herzog S, Reth M, Jumaa H. Regulation of B-cell proliferation and differentiation by pre-B-cell receptor signalling. *Nature Reviews Immunology.* 2009;9:195.
4. Manning BD, Cantley LC. AKT/PKB Signaling: Navigating Downstream. *Cell.* 2007;129(7):1261-1274.
5. Woyach JA. How I manage ibrutinib-refractory chronic lymphocytic leukemia. *Blood.* 2017;129(10):1270-1274.
6. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with Ibrutinib in Relapsed Chronic Lymphocytic Leukemia. *The New England journal of medicine.* 2013;369(1):32-42.
7. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus Ofatumumab in Previously Treated Chronic Lymphoid Leukemia. *The New England journal of medicine.* 2014;371(3):213-223.
8. Byrd JC, Furman RR, Coutre SE, et al. Three-year follow-up of treatment-naïve and previously treated patients with CLL and SLL receiving single-agent ibrutinib. *Blood.* 2015;125(16):2497-2506.
9. O'Brien SM, Jaglowski S, Byrd JC, et al. Prognostic Factors for Complete Response to Ibrutinib in Patients With Chronic Lymphocytic Leukemia: A Pooled Analysis of 2 Clinical Trials. *JAMA oncology.* 2018:e175604.
10. Zhang Shuang Q, Smith Sonali M, Zhang Shuang Y, Lynn Wang Y. Mechanisms of ibrutinib resistance in chronic lymphocytic leukaemia and non-Hodgkin lymphoma. *British Journal of Haematology.* 2015;170(4):445-456.
11. Jain P, Keating M, Wierda W, et al. Outcomes of patients with chronic lymphocytic leukemia after discontinuing ibrutinib. *Blood.* 2015;125(13):2062-2067.
12. Hawkins PT, Anderson KE, Davidson K, Stephens LR. Signalling through Class I PI3Ks in mammalian cells. *Biochemical Society Transactions.* 2006;34(5):647-662.
13. Castillo JJ, Iyengar M, Kuritzky B, Bishop KD. Isotype-specific inhibition of the phosphatidylinositol-3-kinase pathway in hematologic malignancies. *OncoTargets and therapy.* 2014;7:333-342.
14. Damle RN, Wasil T, Fais F, et al. Ig V Gene Mutation Status and CD38 Expression As Novel Prognostic Indicators in Chronic Lymphocytic Leukemia. *Presented in part at the 40th Annual Meeting of The American Society of Hematology, held in Miami Beach, FL, December 4-8, 1998.* 1999;94(6):1840-1847.
15. Hamblin TJ, Davis Z, Gardiner A, Oscier DG, Stevenson FK. Unmutated Ig V_H Genes Are Associated With a More Aggressive Form of Chronic Lymphocytic Leukemia. *Blood.* 1999;94(6):1848-1854.
16. Herman SEM, Gordon AL, Wagner AJ, et al. Phosphatidylinositol 3-kinase-δ inhibitor CAL-101 shows promising preclinical activity in chronic lymphocytic leukemia by antagonizing intrinsic and extrinsic cellular survival signals. *Blood.* 2010;116(12):2078-2088.
17. Kienle D, Benner A, Kröber A, et al. Distinct gene expression patterns in chronic lymphocytic leukemia defined by usage of specific VH genes. *Blood.*

2006;107(5):2090-2093.
18. Chiron D, Di Liberto M, Martin P, et al. Cell Cycle Reprogramming for PI3K Inhibition Overrides Relapse-Specific C481S BTK Mutation Revealed by Longitudinal Functional Genomics in Mantle Cell Lymphoma. *Cancer discovery.* 2014;4(9):1022-1035.
19. Lampson BL, Kasar SN, Matos TR, et al. Idelalisib given front-line for treatment of chronic lymphocytic leukemia causes frequent immune-mediated hepatotoxicity. *Blood.* 2016;128(2):195-203.
20. Vangapandu HV, Jain N, Gandhi V. Duvelisib: A Phosphoinositide-3 Kinase δ/γ Inhibitor for Chronic Lymphocytic Leukemia. *Expert opinion on investigational drugs.* 2017;26(5):625-632.
21. Cheah CY, Fowler NH. Idelalisib in the management of lymphoma. *Blood.* 2016;128(3):331-336.
22. Sharman JP, Coutre SE, Furman RR, et al. Second Interim Analysis of a Phase 3 Study of Idelalisib (ZYDELIG®) Plus Rituximab (R) for Relapsed Chronic Lymphocytic Leukemia (CLL): Efficacy Analysis in Patient Subpopulations with Del(17p) and Other Adverse Prognostic Factors. *Blood.* 2014;124(21):330-330.
23. Flinn IW, Kahl BS, Leonard JP, et al. Idelalisib, a selective inhibitor of phosphatidylinositol 3-kinase-delta, as therapy for previously treated indolent non-Hodgkin lymphoma. *Blood.* 2014;123(22):3406-3413.
24. Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia. *New England Journal of Medicine.* 2014;370(11):997-1007.
25. Gopal AK, Kahl BS, de Vos S, et al. PI3Kdelta inhibition by idelalisib in patients with relapsed indolent lymphoma. *N Engl J Med.* 2014;370(11):1008-1018.
26. Kahl BS, Spurgeon SE, Furman RR, et al. A phase 1 study of the PI3Kdelta inhibitor idelalisib in patients with relapsed/refractory mantle cell lymphoma (MCL). *Blood.* 2014;123(22):3398-3405.
27. Coutré SE, Barrientos JC, Brown JR, et al. Management of adverse events associated with idelalisib treatment: expert panel opinion. *Leukemia & Lymphoma.* 2015;56(10):2779-2786.
28. Weidner A-S, Panarelli NC, Geyer JT, et al. Idelalisib-associated Colitis: Histologic Findings in 14 Patients. *The American Journal of Surgical Pathology.* 2015;39(12):1661-1667.
29. Flinn IW, O'Brien S, Kahl B, et al. Duvelisib, a novel oral dual inhibitor of PI3K-δ,γ, is clinically active in advanced hematologic malignancies. *Blood.* 2018;131(8):877-887.
30. Dreyling M, Morschhauser F, Bouabdallah K, et al. Phase II study of copanlisib, a PI3K inhibitor, in relapsed or refractory, indolent or aggressive lymphoma. *Annals of Oncology.* 2017;28(9):2169-2178.
31. Maharaj K, Sahakian E, Pinilla-Ibarz J. Emerging role of BCR signaling inhibitors in immunomodulation of chronic lymphocytic leukemia. *Blood Advances.* 2017;1(21):1867-1875.
32. Okkenhaug K, Bilancio A, Farjot G, et al. Impaired B and T Cell Antigen Receptor Signaling in p110δ PI 3-Kinase Mutant Mice. *Science.* 2002;297(5583):1031-1034.
33. O'Brien SM, Lamanna N, Kipps TJ, et al. A phase 2 study of idelalisib plus rituximab in treatment-naïve older patients with chronic lymphocytic leukemia. *Blood.* 2015;126(25):2686-2694.
34. Matos TR, Lampson BL, Hirakawa M, et al. Altered Expression of Functional Proteins in CD4 Regulatory T Cells during Therapy with Idelalisib. *Blood.* 2015;126(23):1735-1735.
35. Peluso M, Faia K, Winkler D, et al. Duvelisib (IPI-145) Inhibits Malignant B-Cell Proliferation and Disrupts Signaling from the Tumor Microenvironment through

Mechanisms That Are Dependent on PI3K-δ and PI3K-γ. *Blood.* 2014;124(21):328-328.
36. Verastem Inc. Duvelisib Investigator's Brochure version s8.0. 2019.
37. Flinn IW, Hillmen P, Montillo M, et al. Results from the Phase 3 DUO^{TM} Trial: A Randomized Comparison of Duvelisib Vs Ofatumumab in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma. *Blood.* 2017;130(Suppl 1):493-493.
38. Kuss B, Davids MS, Hillmen P, et al. The efficacy of duvelisib monotherapy following disease progression on ofatumumab monotherapy in patients with relapsed/refractory CLL or SLL in the DUO crossover extension study. American Society of Clinical Oncology; 2018.
39. Ahmad S, Abu-Eid R, Shrimali R, et al. Differential PI3Kdelta Signaling in CD4(+) T-cell Subsets Enables Selective Targeting of T Regulatory Cells to Enhance Cancer Immunotherapy. *Cancer Res.* 2017;77(8):1892-1904.
40. So L, Yea SS, Oak JS, et al. Selective inhibition of phosphoinositide 3-kinase p110alpha preserves lymphocyte function. *The Journal of biological chemistry.* 2013;288(8):5718-5731.
41. Mato AR, Hill BT, Lamanna N, et al. Optimal sequencing of ibrutinib, idelalisib, and venetoclax in chronic lymphocytic leukemia: results from a multicenter study of 683 patients. *Annals of oncology : official journal of the European Society for Medical Oncology.* 2017;28(5):1050-1056.
42. Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood.* 2018;131(25):2745-2760.
43. Cheson BD, Byrd JC, Rai KR, et al. Novel Targeted Agents and the Need to Refine Clinical End Points in Chronic Lymphocytic Leukemia. *Journal of Clinical Oncology.* 2012;30(23):2820-2822.

APPENDIX A: PERFORMANCE STATUS

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

APPENDIX B: CONTRACEPTION

Females of childbearing potential who are sexually active with a non-sterilized male partner or partners of male participant must use 2 highly effective method of contraception. These include: levonorgestrel-releasing intrauterine system (e.g., Mirena®), copper intrauterine device, and hormonal methods. Appropriate hormonal contraceptives include: Etonogestrel-releasing implants (e.g. Implanon® or Norplant®), ethinylestradiol/etonogestrel-releasing intravaginal devices (e.g. NuvaRing®), medroxyprogesterone injection (e.g., Depo-Provera®), normal and low dose combined oral contraceptive pill, norelgestromin/ethinylestradiol-releasing transdermal system (e.g. Ortho Evra®), progesterone based oral contraceptive pill using desogestrel (NB, Cerazette® is currently the only highly effective progesterone-based)

Non-sterilized male participants, or partners of female participant, must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Abstaining from sexual activity for the total duration of the drug treatment and the drug washout period is an acceptable practice for both female and male participants; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female participant should also refrain from breastfeeding throughout this period.

APPENDIX C: CYTOCHROME INHIBITORS, INDUCERS, AND SUBSTRATES

This is not an exhaustive list, investigators should review all concomitant medications for potential as CYP3A4 inhibitors or inducers, as well as those that are CYP3A4 or CYP2C8 substrates.

Strong CYP3A4 inhibitors
boceprevir, cobicistat, conivaptan, danoprevir, ritonavir, elvitegravir, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir, paritaprevir, posaconazole, telaprevir(h), troleandomycin, voriconazole
Strong CYP3A4 inducers
carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort
CYP3A4 Substrates
alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, everolimus, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, vardenafil, budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir, lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan, alprazolam, aprepitant, atorvastatin, colchicine, eliglustat, pimozide, rilpivirine, rivaroxaban, tadalafil

APPENDIX D: MEDICATION DIARY

Study Name: A Phase II study of intermittent duvelisib dosing in patients with CLL/SLL – **INDUCTION PHASE**

Participant Initials_____ Participant Study ID# _____

		Instructions: Take medication with a large glass of water (~250ml) at the same time each day. Swallow medication whole, not to chew, crush or open them.					
				Duvelisib 25 mg twice a day			
Day	Date	Time morning dose	Dose/ # caplets taken	Time evening dose	Dose/ # caplets taken		If dose missed, please provide reason:
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							
21							
22							

Instructions: Take medication with a large glass of water (~250ml) at the same time each day. Swallow medication whole, not to chew, crush or open them.

					Duvelisib 25 mg twice a day		
Day	Date	Time morning dose	Dose/ # caplets taken	Time evening dose	Dose/ # caplets taken		If dose missed, please provide reason:
23							
24							
25							
26							
27							
28							
Study personnel only:					Drug compliance:(# taken _____ / # expected _____) x 100 = _____ % Study personnel initials/date: _____		

Participant signature _____ Date _____

Should you miss a dose for whatever reason (e.g., forgot to take the tablets, or vomiting), you will be allowed to take the dose up to 2 hours late of your usual dose time. If greater than 2 hours after the usual dose time, the missed dose is not to be taken and you should take your dose at the next scheduled time.

Study Name: A Phase II study of intermittent duvelisib dosing in patients with CLL/SLL – **MAINTENANCE PHASE**

Participant Initials_____ Participant Study ID# _____

Instructions: Take medication with a large glass of water (~250ml) at the same time each day. Swallow medication whole, not to chew, crush or open them.

Duvelisib 75 mg twice a day– Dose only on Days 1, 2, 8, 9, 15, 16, 22 and 23

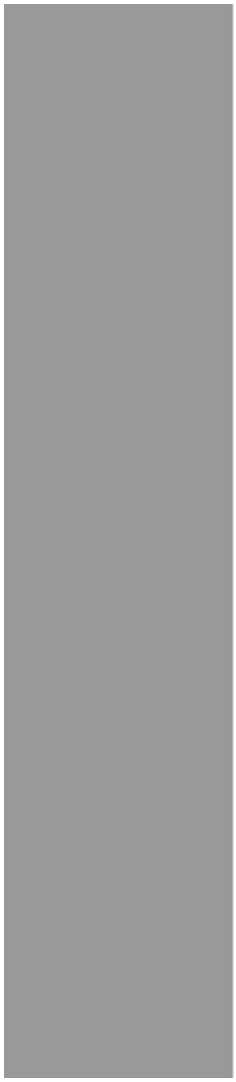
Day	Date	Time morning dose	Dose/ # caplets taken	Time evening dose	Dose/ # caplets taken		If dose missed, please provide reason:
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							
21							

		Instructions: Take medication with a large glass of water (~250ml) at the same time each day. Swallow medication whole, not to chew, crush or open them.					
					Duvelisib 75 mg twice a day– Dose only on Days 1, 2, 8, 9, 15, 16, 22 and 23		
Day	Date	Time morning dose	Dose/ # caplets taken	Time evening dose	Dose/ # caplets taken		If dose missed, please provide reason:
22							
23							
24							
25							
26							
27							
28							
Study personnel only:					Drug compliance:(# taken _____ / # expected _____) x 100 = _____ % Study personnel initials/date: _____		

Participant signature _____ Date _____

Should you miss a dose for whatever reason (e.g., forgot to take the tablets, or vomiting), you will be allowed to take the dose up to 2 hours late of your usual dose time. If greater than 2 hours after the usual dose time, the missed dose is not to be taken and you should take your dose at the next scheduled time.

APPENDIX E: DUVELISIB DRUG ORDER



Verastem

Protocol IST-DUV-004

Investigational Product Request and Shipment Authorization

Email to:Drugorders@verastem.com

Step 1: Investigational ProductRequest Information			
Protocol No. IST-DUV-004		**Site Prt. #:**	
Investigational Product Name: IPI-145 (duvelisib) Open Label 32-ct Blister Card			
Principal Investigator Name	**Site No.**		
Site Phone:	**Ship to:**		
Site Pharmacy Fax:			
Site Email:			
Step 2:Investigational Product Information			
Date Needed:		**Verastem Supply Operations Only**	
Description	**Quantity**	**Lot #**	**CMO Part #**
TOTAL	**blister cards**		
Requester Name:		**Phone:**	
Step 3: Email to drugorders@verastem.com			

Step 4: Verastem -Supply Operations- Authorization		
Processing Priority: ☒ Standard delivery ☐ RUSH (same day processing)		
Name:	Signature:	Date:

APPENDIX F: REGISTRATION COVERSHEET

COH IRB# 19563: A Phase II Study of Intermittent Duvelisib Dosing in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

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

Site Principal Investigator
Name:

CRA/Study Coordinator:	Contact Number:
Patient's Initials: (F M L):	Institution:
	PI/ Sub-Investigator:
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	

Reason for Screen Failure:

Reason for Failing to Initiate Protocol Therapy:

APPENDIX G: EXPEDITED 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 IRB #19563_- 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 **duvelisib:**	☐ Not Applicable* ☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite
Historical/Known Correlation to **duvelisib**:	☐ 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:_____/____/_____

*** Not Applicable should only be used if subject has not received this agent.**

Authorized Investigator Signature:	Date:____/____/____

APPENDIX H: CORRELATIVE BLOOD COLLECTION FORM FOR NON-COH SITES ONLY

Subject ID (issued by DCC):	Participant Initials (F, M, L) (if applicable):
Institution:	

To be used by **non-COH sites** for the following blood samples being sent to **COH Danilov Laboratory**:

Sample #	Time point of Collection *	Expected Volume	Tube Type Used	Collected Volume	Time of Collection	Date of Collection
1.	Cycle 1, Day 1 Pre-dose	20 mL	Green-top	_____ mL	____:____ AM/ PM	____/____/____
2.	Cycle 4, Day 1 Pre-dose	20 mL	Green-top	_____ mL	____:____ AM/ PM	____/____/____
3.	Cycle 7, Day 1 Pre-dose	20 mL	Green-top	_____ mL	____:____ AM/ PM	____/____/____
4.	Cycle 13, Day 1 Pre-dose	20 mL	Green-top	_____ mL	____:____ AM/ PM	____/____/____
5.	*Cycle ___, Day 1 Pre-dose	20 mL	Green-top	_____ mL	____:____ AM/ PM	____/____/____

** Use if a study participant switches to maintenance therapy prior to C4D1. Indicate Cycle in the space provided.*

A copy of this form should accompany the sample shipments to COH APCF. **Refer to the blood shipping guidelines for shipping instructions (Appendix I).**

CRA/Study Coordinator/ Nurse:	Contact Number:
CRA/Study Coordinator/ Nurse Signature:	Date:

APPENDIX I: BLOOD SHIPPING GUIDELINES TO CITY OF HOPE

*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 Thursday**. If this is not feasible, advance arrangements should be made with Danilov lab (DL-danilovlab@coh.org) or designee.

1. Blood samples in green-top tubes will be sent **overnight at around +4°C** with a refrigerated cool pack in an appropriate container via FedEx.
2. On the day of shipment, email Danilov lab (DL-danilovlab@coh.org) or designee the FedEx shipment tracking#.
3. Ship samples with a copy of the correlative blood collection form (Appendix H)and a copy of the latest CBC results (with differential) and the date of the test to:

The Danilov Laboratory
Kaplan Clinical Research Bldg [(KCRB) Building 158], Room #1022
City of Hope, 1500 East Duarte Rd, Duarte CA 91010
DL-danilovlab@coh.org
626-218-1959