STUDY PROTOCOL
IPI-145-07

Protocol Title:	A Phase 3 Study of IPI-145 versus Ofatumumab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
Protocol Number:	IPI-145-07
Phase:	Phase 3
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Sponsor:	Verastem, Inc 117 Kendrick Street, Suite 500 Needham, MA 02494

INVESTIGATOR PROTOCOL APPROVAL

A Phase 3 Study of IPI-145 versus Ofatumumab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to principles of Good Clinical Practice and local regulations and requirements.

Institution/Clinic: _____

Principal Investigator

Print Name: _____

Signature: _____

Date (mm/dd/yyyy): _____

SPONSOR PROTOCOL APPROVAL

A Phase 3 Study of IPI-145 versus Ofatumumab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

I have read this protocol and I approve the design of this study:

H Youssoufian 08 FEB 2017

Signature *Date*

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For urgent study-related questions please call the Medical Monitor at the following number:

1-877-462-0134

PROTOCOL SYNOPSIS

Study Title:	A Phase 3 Study of IPI-145 versus Ofatumumab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
Protocol Number:	IPI-145-07
Study Phase:	3
Investigational Agent:	Duvelisib (IPI-145)
Study Objectives:	Primary Objective: • To examine the efficacy of duvelisib monotherapy versus ofatumumab monotherapy in subjects with relapsed or refractory Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) Secondary Objectives: • To determine the safety of duvelisib in subjects with CLL or SLL • To evaluate the pharmacokinetics (PK) of duvelisib and, if applicable, its metabolite(s) Exploratory Objectives: • To evaluate the health-related quality of life (QoL) of subjects • To evaluate pharmacodynamic biomarkers of duvelisib • To evaluate biomarkers that may predict duvelisib clinical activity and/or safety • To evaluate mechanisms of resistance in subjects who exhibit disease progression while being treated with duvelisib or ofatumumab • To evaluate genomic features of tumors predictive of response in subjects treated with duvelisib or ofatumumab

Study Treatment:	**Treatment Arm A**: **Duvelisib** Duvelisib is administered orally and supplied as 5 mg and 25 mg formulated capsules. **Treatment Arm B: Ofatumumab** Ofatumumab is administered as an intravenous (IV) infusion and is supplied in single-use vials at two strengths, 100 mg/5 mL and 1000 mg/50 mL
Study Design:	Study IPI-145-07 is a two-arm, randomized (1:1 ratio), open-label, phase 3, superiority trial designed to evaluate the efficacy and safety of duvelisib compared to ofatumumab. Subjects will be stratified by: 1. High-risk cytogenetics (presence vs absence of del[17p]) 2. Refractory/early relapse to purine analog-based therapy (defined as progression <12 months after fludarabine/pentostatin: yes vs no) 3. Grade 4 cytopenia(s) (presence vs absence of neutropenia or thrombocytopenia at baseline) Schedule of Administration Duvelisib (Arm 1) Subjects randomized to duvelisib will be given a starting dose of duvelisib 25 mg administered orally twice daily (BID) initially in a 21-day treatment cycle followed by 28-day treatment cycles for up to 18 cycles or until disease progression or unacceptable toxicity (whichever comes first). After 18 complete cycles of treatment, subjects may receive additional cycles of duvelisib until disease progression or unacceptable toxicity if they, in the judgment of the investigator, may derive benefit from continued treatment (see Section 4.2.1.2). Schedule of Administration Ofatumumab (Arm 2) Subjects randomized to ofatumumab will receive treatment consistent with the approved product labeling: 8 weekly infusions, starting with an initial dose of ofatumumab 300 mg IV on Day 1 followed by seven weekly doses of 2000 mg. Thereafter, subjects will receive ofatumumab 2000 mg once every month for four months or until disease progression or unacceptable toxicity (whichever comes first), as outlined in the schedule of assessments. Administration of ofatumumab will not exceed the 12 doses (within 7 cycles) as described in the prescribing information. Disease Response Assessments (All Subjects) Disease response assessments will include computed tomography (CT) scans, bone marrow biopsy (when indicated), complete blood count (CBC) and differential counts, focused physical exams (PE), and assessment of disease-related constitutional symptoms. Disease Response Assessments will occur at Screening, and Day 1 of Cycles 3, 5, 7, 11, 15, and 19 for subjects on both treatment arms. After Cycle

	19 Day 1, ongoing assessments will be every 6 months for the duration of the study or until disease progression, subject withdrawal, or initiation of additional anticancer therapy.
Study Population:	Approximately 300 subjects with a diagnosis of relapsed and/or refractory CLL or SLL will enroll in the study and be randomized equally to one of two treatment groups: 1. Duvelisib 25 mg BID (N=150) 2. Ofatumumab (N=150)
Study Duration:	Study subjects will be followed for survival for up to 6 years from randomization. It is anticipated that the entire study will accrue subjects over approximately 16 months from the randomization of the first subject.
Study Centers:	Enrollment is anticipated at approximately 100 sites, with approximately 25 sites in the US and 75 sites outside the US.
Inclusion Criteria:	Subjects are eligible for inclusion in the study if they meet the following criteria: 1. ≥ 18 years of age 2. Diagnosis of active CLL or SLL that meets at least one of the IWCLL 2008 criteria for requiring treatment (Binet Stage ≥ B and/or Rai Stage ≥ I) 3. Disease that has progressed during or relapsed after at least one previous CLL/SLL therapy 4. Not appropriate for treatment with a purine-based analogue regimen (per National Comprehensive Cancer Network [NCCN] or European Society for Medical Oncology [ESMO] guidelines), including relapse ≤ 36 months from a purine-based chemoimmunotherapy regimen or relapse ≤ 24 months from a purine-based monotherapy regimen 5. A cytogenetics or fluorescence in situ hybridization (FISH) analysis of the leukemic cells within 24 months of randomization is required to document the presence or absence of del(17p). Note: if a sample from within 24 months is not available, it should be evaluated as part of the screening laboratory evaluation to inform stratification 6. Measurable disease with a lymph node or tumor mass > 1.5 cm in at least one dimension as assessed by computed tomography (CT) 7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (corresponds to Karnofsky Performance Status [KPS] ≥ 60%)

	8. Willingness by subject to be randomized to receive either ofatumumab or duvelisib at the dose and schedule defined in the protocol 9. Must meet the following laboratory parameters: a. Serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) ≤ 3 x upper limit of normal (ULN) b. Total bilirubin ≤ 1.5 x ULN c. Serum creatinine ≤ 2.0 x ULN d. Hemoglobin ≥ 8.0 g/dL with or without transfusion support e. Platelet count ≥ 10,000 µL with or without transfusion support 10. For women of childbearing potential (WCBP): negative serum β-human chorionic gonadotropin (βhCG) pregnancy test within 1 week before randomization (WCBP defined as a sexually mature woman who has not undergone surgical sterilization or who has not been naturally post-menopausal for at least 24 consecutive months [women ≤ 55 years] or 12 consecutive months [women > 55 years]) 11. Willingness of male and female subjects who are not surgically sterile or postmenopausal to use medically acceptable methods of birth control from the first dose of study drug to 30 days after the last dose of duvelisib and for 12 months after last dose of ofatumumab. Sexually active men, and women using oral contraceptive pills, should also use barrier contraception 12. Ability to voluntarily sign consent for and adhere to the entire study visit schedule and all protocol requirements 13. Signed and dated institutional review board (IRB)/independent ethics committee (IEC)-approved informed consent form (ICF) before any study specific screening procedures are performed
Exclusion Criteria:	Subjects are to be excluded from the study if they meet any of the following criteria: 1. History of Richter's transformation or prolymphocytic leukemia 2. Autoimmune hemolytic anemia (AIHA) or idiopathic thrombocytopenic purpura (ITP) that is uncontrolled or requiring > 20 mg once daily (QD) of prednisone (or equivalent) to maintain hemoglobin > 8.0 g/dL or platelets > 10,000 µL without transfusion support

	3. Refractory to ofatumumab (defined as progression or relapse <12 months of receiving ofatumumab monotherapy or < 24 months of receiving an ofatumumab-containing regimen) 4. Prior allogeneic transplant (prior autologous stem cell transplant >6 months prior to study entry is permitted) 5. Known central nervous system (CNS) lymphoma or leukemia; subjects with symptoms of CNS disease must have a negative CT scan or negative diagnostic lumbar puncture prior to randomization 6. Prior exposure to a phosphoinositide-3-kinase (PI3K) inhibitor (eg, GS-1101, duvelisib) or a Bruton's tyrosine kinase (BTK) inhibitor 7. Use of any of the following medications or procedures within the specified timeframe: – Use of live or live attenuated vaccines within 30 days prior to randomization – Chemotherapy, radiation therapy, or ablative therapy within 3 weeks of randomization – Tyrosine kinase inhibitor within 7 days of randomization – Other investigational therapy (not included above) within 3 weeks of randomization 8. Ongoing treatment with chronic immunosuppressants (eg, cyclosporine) or systemic steroids > 20 mg prednisone (or equivalent) QD 9. History of tuberculosis treatment within the preceding two years 10. Ongoing systemic bacterial, fungal, or viral infections at the time of initiation of study treatment (defined as requiring IV antimicrobial, antifungal or antiviral agents) – Subjects on antimicrobial, antifungal or antiviral prophylaxis are not specifically excluded if all other inclusion/exclusion criteria are met and there is no evidence of active infection at randomization 11. Human immunodeficiency virus (HIV) infection 12. Prior, current, or chronic hepatitis B or hepatitis C infection 13. History of alcohol abuse or chronic liver disease (other than metastatic disease to the liver) 14. Unable to receive prophylactic treatment for pneumocystis or herpes simplex virus (HSV) 15. Baseline QT interval corrected with Fridericia's method (QTcF) > 480 ms (average of triplicate readings) Note: This

	criterion does not apply to subjects with a right or left bundle branch block (BBB) 16. Unstable or severe uncontrolled medical condition (eg, unstable cardiac function, unstable pulmonary condition), or any important medical illness or abnormal laboratory finding that would, in the investigator's judgment, increase the subject's risk while participating in this study 17. Concurrent active malignancy other than nonmelanoma skin cancer or carcinoma in situ of the cervix, bladder, or prostate not requiring treatment. Subjects with previous malignancies are eligible provided that they have been disease free for ≥2 years 18. History of stroke, unstable angina, myocardial infarction, or ventricular arrhythmia requiring medication or mechanical control within the last 6 months 19. Administration of medications or foods that are strong inhibitors or inducers of CYP3A within 2 weeks of randomization 20. Prior surgery or gastrointestinal dysfunction that may affect drug absorption (eg, gastric bypass surgery, gastrectomy) 21. Major surgery or invasive intervention within 4 weeks prior to randomization 22. Pregnant or breastfeeding women 23. Hypersensitivity to ofatumumab or its excipients
Study Endpoints:	Primary Endpoint: • Progression-free survival (PFS), defined as time from randomization to the first documentation of progressive disease (PD) as determined by independent review or death due to any cause Secondary Endpoints: • Overall Response Rate (ORR), with overall response (based on independent review) defined as best response of complete response/remission (CR), CR with incomplete marrow recovery (CRi), partial response/remission (PR), or PR with lymphocytosis (PRwL), according to the IWCLL or revised IWG Response Criteria, with modification for treatment-related lymphocytosis • Lymph node response rate, with lymph node response defined as ≥ 50% decrease in the sum of the products (SPD) of target lymph nodes • Overall Survival (OS), defined as time from randomization to death

	• Hematologic improvement rate, with hematologic improvement defined as any of following, for at least 60 days without transfusion or exogenous growth factors:
	  o Neutrophil count > 1,500/μL or an increase ≥ 50% from Baseline; or
	  o Hemoglobin > 11 g/dL or an increase ≥ 50% from Baseline; or
	  o Platelet count >100,000/μL or an increase ≥ 50% from Baseline
	• Duration of Response (DOR), defined as time from the first documentation of response to first documentation of PD or death due to any cause
	• Treatment-emergent adverse events (TEAEs) and changes in safety laboratory values
	• PK parameters derived from plasma duvelisib concentrations and, if applicable, its metabolite(s)
	Exploratory Endpoints:
	• Improvement in disease-related symptoms of fatigue, weight loss, unexplained fevers and night sweats from Baseline
	• Minimal Residual Disease (MRD) in subjects with documented CR or CRi
	• Health-related QoL of subjects as assessed by the following subject-reported questionnaires:
	  o EuroQol-5D (EQ-5D)
	  o Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)
	• Serum and tissue biomarkers and blood immunophenotype
	• Tumor genomic features (eg, DNA sequence variation, DNA copy number variation, and/or RNA expression)
	• Germline DNA sequence variations

Statistical Methodology:	Sample Size Determination The sample size was determined to provide sufficient power to test the primary endpoint of PFS in a group sequential design with one planned interim analysis. Assuming an exponential distribution for PFS, a total number of 185 PFS events (deaths or progressions) will provide approximately 93% power to detect a hazard ratio of 0.6 (median PFS of 9 months in the ofatumumab group vs 15 months in the duvelisib group) using a one-sided log-rank test at a 2.5% overall significance level (ie, alpha of 0.025). A total of 300 subjects will be randomized in a 1:1 ratio to receive either ofatumumab or duvelisib. Assuming a peak accrual rate of 30 subjects per month with 11 months for accrual ramp-up and a 4% cumulative dropout rate per year, then enrollment would complete in 16 months, with the final analysis for PFS estimated to occur approximately 27.5 months from the randomization of the first subject. Analysis Sets The Intent-to-Treat (ITT) analysis set will include all subjects who were randomized, with treatment group designated according to initial randomization. The ITT analysis set will serve as the primary analysis set for all efficacy endpoints and demographics. The All-Treated (AT) analysis set will include all subjects who received any amount of study drug (duvelisib or ofatumumab), with treatment group designated according to actual study treatment received. The AT analysis set will be the primary analysis set for safety endpoints. Primary Efficacy Analyses: A stratified log-rank test (1-sided) will be used to compare PFS of the duvelisib arm against PFS of the ofatumumab arm at the interim and final analyses with the overall one-sided significance level controlled at 0.025. The nominal p-value required for statistical significance at an analysis will be calculated based on the numbers of PFS events at all preceding and current analyses. The hazard ratio and the corresponding 2-sided 95% confidence interval will be estimated using a stratified Cox proportional hazards model. For both the stratified log-rank test and the stratified Cox model, the strata will be those used for stratified randomization, with potential pooling of strata specified in the Statistical Analysis Plan (SAP). PFS will be plotted for each treatment group using the Kaplan-Meier method.

Table 1: Screening Assessments Checklist for All Subjects [a]

○ Informed consent	○ Electrocardiogram (ECG, 12-lead) [c]
○ Inclusion/exclusion criteria	○ Blood chemistry [c]
○ Medical history & demographics	○ Hematology [c, d]
○ Cancer history	○ Coagulation tests [c]
○ Prior Cytogenetics / FISH results [b]	○ Hepatitis, cytomegalovirus (CMV), and Epstein-Barr virus (EBV)
○ Prior/Concomitant Medications & Procedures	○ HIV [e]
○ Vital signs	○ Serum βhCG pregnancy test [f]
○ Physical examination [c]	○ CT scans of the chest, abdomen and pelvis [g]
○ ECOG Performance status	○ Bone marrow biopsy and/or bone marrow aspiration [h]
○ Disease-related symptoms assessment	○ Adverse Event (AE)/Serious Adverse Event (SAE) assessment [i]
○ Quality of life (QoL) EQ-5D & FACT-F	○ Randomization [j]

a. Screening performed ≤ 30 days from dosing (Cycle 1 Day 1). See Section 6 for details on each study assessment.
b. Documentation of prior results within 24 months required for randomization. Can be performed locally during screening.
c. New clinically significant findings after signing informed consent form (ICF) should be captured as an AE.
d. Includes coombs testing (both a direct and indirect). Documentation of hematology labs within 7 days prior to randomization is required to confirm presence or absence of Grade 4 cytopenia for stratification at randomization.
e. Subjects without documentation of a prior negative HIV test result (eg, antibody, antigen or PCR-based test) are required to undergo an HIV test during screening. Only subjects with a negative HIV result will be randomized.
f. For all women of child bearing potential (WCBP), the screening pregnancy test will be serum and must be performed within 7 days prior to first dose to confirm eligibility.
g. Additional scans may be performed (eg, head/neck CT) if clinically indicated or if the area is a site of known disease. Magnetic resonance imaging (MRI) may be substituted if clinically indicated, but the modality chosen to evaluate each individual subject should be the same throughout the duration of the study.
h. Bone marrow biopsy and/or aspirate are required at Screening as a baseline for response assessment (unless clinically contraindicated). Sample and corresponding pathology report should be sent for biomarker analysis if available.
i. For all subjects AEs should be monitored from time of the signing of the ICF. Any new medical or worsening preexisting conditions arising after signing the ICF will be captured as an AE for randomized subjects. SAEs for all subjects will be reported from the signing of the ICF as defined in Section 8.1.3.
j. Dosing should occur within 1 week of randomization after all screening assessments have been obtained and eligibility confirmed.

Table 2: Schedule of Assessments for Subjects Receiving Duvelisib [a]

	Cycle 1 (21±2 days) [o]		**Cycle 2** (28±4 days) [o]		**Cycles 3 – 7** (28±4 days) [o]	**Cycle 9-19 every odd cycle** (28±4 days) [o]	**> Cycle 19 every odd cycle** (28±4 days)[p]	**Early Treatment Termination (ETT) from Duvelisib** [q]	**Safety Follow-up**
	D1	D8±2	D1±2	D15± 2	D1±4	D1±4	D1±4	≤7 d from last dose	30+7 d from last dose
Concomitant medications & Procedures	X	X	X	X	X	X	X	X	X
AE/SAE assessment [b]	X	X	X	X	X	X	X	X	X
Focused physical examination	X		X		X	X	X	X	
Blood chemistry [c]	X [d]	X	X	X	X	X	X	X	
Hematology [c]	X [d]	X	X	X	X	X	X	X	
Coagulation tests [c]	X [d]								
Serum Immunoglobulins	X				X [e]	X [e]		X [e]	
βhCG pregnancy test [c, f]					X	X	X	X	
Blood for Cytogenetics/FISH analysis [g]	X [h, i]								
Blood for IGHV mutation analysis [g]	X [h]								
Blood for Immunophenotyping [g, j]	X [k]				X [e]	X [e]		X [e]	
Serum for biomarkers [g, j]	X [k]		X		X [e]	X [e]		X [e]	
Blood for biomarkers [g]	X [k]		X		X [e]	X [e]		X [e]	
Pharmacogenomics [g]	X [l]								
EQ-5D & FACIT-F	X [d]				X [m]	X [m]	X [m]	X [m]	
ECOG Performance status	X [d]	**See Table 5: Disease Response Assessments**							

Response assessments		**See Table 5: Disease Response Assessments**	
Archival tumor tissue	**X** [n]		
Study drug administration	**X**	**Continuous Dosing**	

a. See Section 6.2 and 6.3 for additional information on each assessment.
b. AEs are collected (and SAEs reported) through 30 days post last dose of duvelisib.
c. Additional (unscheduled) assessments should be done as clinically indicated. Blood samples should be drawn and results reviewed within 72 hours of the designated clinic visit.
d. Screening evaluations performed within 7 days of Cycle 1 Day 1 can be used and assessments do not need to be repeated at Cycle 1 Day 1 (predose)
e. Drawn only on Day 1 of Cycles 3, 5, 7, 11, 15, 19, and ETT. Blood for immunophenotyping, serum for biomarkers, and blood for biomarkers do not need to be collected beyond the ETT visit or treatment discontinuation.
f. May be either urine or serum, and performed every odd cycle while on treatment.
g. To be sent to the central laboratory.
h. Sample may be drawn at screening or Cycle 1 Day 1 (predose). Collection at Cycle 1 Day 1 is preferred. If drawn at screening, a sample is not needed at Cycle 1 Day 1.
i. This sample will be analyzed centrally and is separate from the documentation of prior del(17p) analysis required for eligibility and stratification.
j. Additional blood for immunophenotyping/biomarker serum samples may be requested from any subject receiving duvelisib at qualified sites (when feasible) at the time of a drug interruption/hold due to an AE, or for any usual safety event or efficacy event.
k. Samples on Cycle 1 Day 1 should be drawn predose.
l. Pharmacogenomics sample (buccal swab) is optional.
m. QoL assessments to be captured at on Day 1 of Cycles 3, 5, 7, 11, 15, and 19 until disease progression, subject withdrawal, or initiation of additional anticancer therapy, and when possible, at the ETT (if >1 month from last administered questionnaire).
n. Requests for archival tissue (pretreatment sample) should be initiated at Cycle 1 Day 1. In the event a request is placed but no archival tissue can be located, this sample type is not required.
o. Subjects who discontinue treatment from duvelisib prior to Cycle 19 Day 1 for reasons other than PD, will maintain the clinical visit schedule through Cycle 19 Day 1 until disease progression, subject withdrawal, or initiation of additional anticancer therapy.
p. Subjects who, in the judgment of the investigator, may derive benefit from continued treatment, may receive additional cycles of duvelisib beyond Cycle 19 Day 1 until disease progression or unacceptable toxicity. .
q. The Early Treatment Termination (ETT) Visit should occur for any subject who discontinues duvelisib treatment prior to Cycle 19 Day 1. The ETT assessments need not be performed if the subject has had a previous assessment within the previous 2 weeks or previous 30 days for Disease Response Assessments [see Table 5] and the QoL assessment.

Table 3: Pharmacokinetic Assessments for Subjects Receiving Duvelisib Only [a]

	Cycle 2 [d]			Cycle 3	Cycle 7
	Day 1±2			Day 1±2	Day 1±2
Time (h) relative to duvelisib administration	Predose	0.5-2h	3-5h	Anytime	Anytime
Pharmacokinetic blood sample collection [b, c]	X	X	X	X	X

a. See Section 6.3.7 for additional information on pharmacokinetic (PK) assessments.
b. The date and time of the PK samples will be recorded, along with the date and time of the previous two doses of duvelisib.
c. Additional PK samples may be requested from any subject receiving duvelisib at qualified sites (when feasible) at the time of a drug interruption/hold due to an AE, or for any usual safety event or efficacy event.
d. The morning dose of duvelisib will be administered in the clinic on Cycle 2 Day 1.

Table 4: Schedule of Assessments for Subjects Receiving Ofatumumab [a]

	Cycle 1 (21±2 days) [o]			**Cycle 2** (28±4 days) [o]				**Cycle 3-7** (28±4 days) [o]	**Early Treatment Termination (ETT) [n] from Ofa** ≤ 7 d from last dose	**Safety Follow-up Visit** 30+7d from last dose	**Clinical Assessment Period [o]** C9-C19 (28±4 days) Day 1±4
	Ofa 300 mg D1	Ofa 2000 mg D8±2	Ofa 2000 mg D15±2	Ofa 2000 mg D1±2	Ofa 2000 mg D8±2	Ofa 2000 mg D15±2	Ofa 2000 mg D22±2	Ofa 2000 mg D1±4			
Concomitant Meds & Procedures	X	X	X	X	X	X	X	X	X	X	X
AE/SAE assessment [b]	X	X	X	X	X	X	X	X	X	X	
Focused physical exam	X			X				X	X		X
Blood chemistry [c]	X [d]	X		X		X		X	X		X
Hematology [c]	X [d]	X		X		X		X	X		X
Coagulation tests [c]	X [d]										
Serum Immunoglobulins	X							X [e]	X [e]		X [e]
βhCG pregnancy test [c, f]								X	X		
Blood for Cytogenetics /FISH analysis [g]	X [h, i]										
Blood for IGHV mutation analysis [g]	X [h]										
Blood for Immunophenotyping [g]	X [j]							X [e]	X [e]		X [e]
Serum for biomarkers [g]	X [j]			X				X [e]	X [e]		X [e]
Blood for biomarkers [g]	X [j]			X				X [e]	X [e]		X [e]
Pharmacogenomics [g]	X [k]										
EQ-5D & FACIT-F	X [d]							X [l]	X [l]		X [l]
ECOG performance status	X [d]	**See Table 5: Disease Response Assessments**									
Response assessments		**See Table 5: Disease Response Assessments**									
Archival tumor tissue	X [m]										

	Cycle 1 (21±2 days) [o]			**Cycle 2** (28±4 days) [o]				**Cycle 3-7** (28±4 days) [o]	**Early Treatment Termination (ETT) [n]**	**Safety Follow-up Visit**	**Clinical Assessment Period [o]**
	Ofa 300 mg D1	Ofa 2000 mg D8±2	Ofa 2000 mg D15±2	Ofa 2000 mg D1±2	Ofa 2000 mg D8±2	Ofa 2000 mg D15±2	Ofa 2000 mg D22±2	Ofa 2000 mg D1±4	**from Ofa** ≤ 7 d from last dose	30+7d from last dose	C9-C19 (28±4 days) Day 1±4
Study drug administration	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			

a. See Section 6.2 and 6.3 for additional information on each assessment.
b. AEs are collected (and SAEs reported) through 30 days post last dose of ofatumumab.
c. Additional (unscheduled) assessments should be done as clinically indicated. Blood samples should be drawn and results reviewed within 72 hours of the designated clinic visit.
d. Screening evaluations performed within 7 days of Cycle 1 Day 1 can be used and assessments don't need to be repeated at Cycle 1 Day 1 (predose)
e. Drawn at Day 1 of Cycles 3, 5, 7, 11, 15, 19, and ETT. Blood for immunophenotyping, serum for biomarkers, and blood for biomarkers does not need to be collected beyond the ETT visit or treatment discontinuation
f. May be either urine or serum, and will be performed every odd cycle while on treatment.
g. To be sent to the central laboratory.
h. This sample may be drawn at screening or Cycle 1 Day 1 (predose). Collection at Cycle 1 Day 1 is preferred. If drawn at screening, a sample is not needed at Cycle 1 Day 1.
i. This sample will be analyzed centrally and is separate from the documentation of prior del(17p) analysis required for eligibility and stratification.
j. Samples on Cycle 1 Day 1 should be drawn predose.
k. Pharmacogenomics sample (buccal swab) is optional.
l. QoL assessments to be captured at on Day 1 of Cycles 3, 5, 7, 11, 15, and 19, until disease progression, subject withdrawal, or initiation of additional anticancer therapy and when possible, at the ETT (if >1 month from last administered questionnaire).
m. Requests for archival tissue (pretreatment sample) should be initiated at Cycle 1 Day 1. In the event a request is placed but no archival tissue can be located, this sample type is not required.
n. The Early Treatment Termination (ETT) Visit should occur for any subject who discontinues ofatumumab treatment prior to Cycle 7 Day 1. ETT assessments need not be performed for those assessments performed within the previous 2 weeks (previous 30 days for Disease Response Assessments [see Table 5] and the QoL assessment).
o. The clinical visit schedule should be maintained until Cycle 9 for subjects who discontinue study treatment prior to Cycle 9 for reasons other than PD. The clinical assessment period then begins at Cycle 9, with visits occurring every other month until disease progression, subject withdrawal, or initiation of additional anticancer therapy; no additional study drug (ofatumumab) will be administered.

Table 5: Disease Response & Follow-up Assessments for All Subjects

Assessments [d]	**Screening** (baseline)	**Cycle 3** Day 1	**Cycles 5, 7, 11, 15, & 19** Day 1	**Early Termination from Study Treatment (ETT)** [a] ≤7 days of last dose	**Disease Follow-up** [b] Every 6 months (±4 weeks)	**Survival Follow-up** [c] Every 6 months (± 4 weeks)
CT scans of chest, abdomen and pelvis [e]	X	X	X	X	X	
Bone marrow biopsy and/or bone marrow aspiration [f]	X	X	X	X	X	
Complete blood count (CBC) and differential count [g]	X	X	X	X	X [i]	
Blood sample for assessment for minimum residual disease (MRD) [h]		X	X	X	X	
Focused physical examination [g], disease related constitutional symptoms assessment, and ECOG performance status	X	X	X	X	X	
Survival						X

a. ETT Disease Response Assessment is not necessary if a Disease Response Assessment was performed within the previous 30 days. In the absence of disease progression or initiation of subsequent anticancer therapy, all subjects with ETT prior to Cycle 19 Day 1 will maintain the disease response assessment schedule (Cycles 5, 7, 11, 15, & 19)

b. All subjects with no disease progression by Cycle 19 Day 1 will continue Disease Response Assessments (Section 6.5.3.1) every 6 months until disease progression, subject withdrawal, or initiation of additional anticancer therapy. The first disease follow-up assessment after Cycle 19 Day 1 should occur approximately 6 months after last disease assessment.

c. All subjects will have Survival Follow-up for up to 6 years after randomization or until death. This assessment can be conducted by telephone interview. Information on initiation of other anticancer therapy (including start date, therapy type, and response on treatment) will also be collected.

d. On-treatment Disease Response Assessments should be delayed if a subject's dose (duvelisib or ofatumumab) is held for >1 week at the time of the scheduled assessment; subjects should be on treatment for a minimum of 1 week prior to having a response assessment.

e. CT scans of the chest, abdomen and pelvis are required for all subjects in both treatment arms. These assessments may be performed within 7 days (Day -7 to Day 1) of initiating the next cycle of therapy. The frequency provided is the minimum required for study participation. Other scans may be performed (eg, head/neck CT) if clinically indicated or if the area is a site of known disease. Copies of all scans must be sent for independent review of response assessment. MRI may be substituted if clinically indicated, but the modality chosen to evaluate each individual subject should be the same throughout the duration of the study.

f. Bone marrow biopsy and/or bone marrow aspirate are required for all subjects at Screening and in subjects for whom a bone marrow biopsy and/or bone marrow aspirate result is required to meet the criteria for a CR or CRi. If bone marrow aspirate and/or bone marrow biopsy is performed, samples and corresponding pathology report should be sent for biomarker analysis if available. The bone marrow biopsy/aspirate may be performed within 7 days (Day -7 to Day 1) of initiating the next cycle of therapy.

g. Please see Table 1, Table 2, and Table 4 for the full schedule of assessments.

h. The MRD assessment for subjects with CR and CRi only will include collection of a blood sample to be evaluated via flow cytometry at a central laboratory. This blood sample is to be collected as soon as CR is identified and sent to the central laboratory for assessment.

i. CBC to be performed every 3 months during Disease Follow-up.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADL	Activities of daily living
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse Event
AIHA	Autoimmune hemolytic anemia
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AKT (PKB)	A serine/threonine protein kinase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AT	All Treated
AUC	Area under the curve
BBB	Bundle branch block
βhCG	β human chorionic gonadotropin
BID	Twice a day
BTK	Bruton's tyrosine kinase
BUN	Blood urea nitrogen
CAL-101	Idelalisib (GS-1101): a PI3K-δ inhibitor in clinical development for patients with hematologic malignancies
CBC	Complete blood count
CD20	B-lymphocyte antigen CD20
CEC	Central Ethics Committee
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
cm	Centimeters
C_{max}	Maximum concentration
CNS	Central nervous system
CMV	Cytomegalovirus
CO_2	Chloride bicarbonate

Abbreviation	Definition
CR	Complete response
CRi	Complete response with incomplete marrow recovery
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
d	Day
DDI	Drug-drug interaction
Del(17p)	Deletion of the 17p13 chromosomal region
dL	Deciliter(s)
DLT	Dose limiting toxicity
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
DOR	Duration of response
Duvelisib (IPI-145)	(*S*)-3-(1-(9H-purin-6-ylamino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one
EBV	Epstein-Barr virus
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
EQ-5D	EuroQol – 5D (health-related QoL assessment)
ETT	Early treatment termination
EU	European Union
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FACT	Functional Assessment of Cancer Therapy
FcεRI	High-affinity IgE receptor
FCγRII	Fc fragment of IgG, low affinity IIa, receptor (CD32)
FDA	Food and Drug Administration

Abbreviation	Definition
FISH	Fluorescence in situ hybridization
FMLP	*N*-formyl-leucine-methionine-phenylalanine
g	Gram(s)
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GM-CSF	Granulocyte macrophage-colony stimulating factor
GPCR	G-protein coupled receptor
GRAS	Generally regarded as safe
GS-1101	Idelalisib (see CAL-101)
h	Hour(s)
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HCV Ab	Hepatitis C virus antibodies
HIV	Human immunodeficiency virus
HSV	Herpes simplex virus
IC_{50}	Half maximal inhibitory concentration
IC_{90}	90% inhibitory concentration
ICF	Informed consent form
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IGHV	Immunoglobulin heavy chain variable
in	inches
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITP	Idiopathic thrombocytopenic purpura
ITT	Intent-to-treat
IV	Intravenous(ly)
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
IWG	International Working Group

Abbreviation	Definition
K_d	Dissociation constant
kg	Kilogram(s)
KPS	Karnofsky Performance Status
L	Liter(s)
LDH	Lactate dehydrogenase
LEC	Local Ethics Committee
LLC	Lewis lung carcinoma
MedDRA	Medical Dictionary for Regulatory Activities
MEOI	Medical Events of interest
mg	Milligram(s)
µg	Microgram(s)
µL	Microliter(s)
mL	Milliliter(s)
µM	Micromolar
MRD	Minimum residual disease
MRI	Magnetic resonance imaging
ms	Millisecond(s)
MTD	Maximum tolerated dose
N	Number
NCCN	National Comprehensive Cancer Network
ng	Nanogram(s)
nM	Nanomolar
Ofa	Ofatumumab
ORR	Overall response rate
OS	Overall survival
pAKT	Phosphorylated AKT
PCR	Polymerase chain reaction
PD	Progressive disease
PE	Physical exam
PET	Positron emission tomography
PDK-1	3-phosphoinositide dependent protein kinase-1

Abbreviation	Definition
PE	Physical examination
PFS	Progression-free survival
P-gp	P-glycoprotein
PH	Pleckstrin homology
PI3K	Phosphoinositide-3-kinase
PIP3	Phosphatidylinositol (3,4,5)-trisphosphate
PK	Pharmacokinetics
pM	Picomolar
PML	Progressive multifocal leukoencephalopathy
PR	Partial response
PRwL	Partial response with lymphocytosis
PT	Prothrombin time
PTEN	Phosphatase and tensin homolog
QD	Once a day
QoL	Quality of life
QTcF	QT interval corrected with Fridericia's method
RAS	Protein subfamily of small GTPases involved in cellular signal transduction
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable disease
SH2	Src homology 2
SLL	Small lymphocytic lymphoma
SmPC	Summary of Product Characteristics
SPD	Sum of the products
$T_{1/2}$	Terminal elimination half-life
TAMs	Tumor-associated macrophages
TEAE	Treatment-emergent adverse events
TRAP-6	Thrombin receptor activating peptide-6
ULN	Upper limit of normal

Abbreviation	Definition
US/USA	United States of America
USPI	United States Package Insert
UV	Ultraviolet
VZV	Varicella zoster virus
WCBP	Women of child-bearing potential

1 BACKGROUND AND RATIONALE

1.1 INTRODUCTION

Duvelisb is a potent phosphoinositide-3-kinase (PI3K)-δ,γ inhibitor being developed by Verastem , Inc. (Verastem). PI3K-δ and PI3K-γ isoforms are necessary for adaptive and innate immunity, and are important mediators in inflammatory disorders and hematologic malignancies. Therefore, duvelisib is being developed as an orally administered potential therapeutic in hematologic malignancy and inflammatory disease indications.

In a Phase 1 study of duvelisib in patients with relapsed or refractory hematologic malignancies, clinical activity was observed early in dose-escalation in subjects with relapsed or refractory Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL). In addition, duvelisib was dosed below the maximum tolerated dose (MTD) in a cohort of relapsed or refractory CLL/SLL subjects. The preliminary safety and efficacy profile of duvelisib observed to date in this patient population suggests duvelisib has clinical activity in patients with CLL/SLL and may have a superior progression-free survival (PFS) and/or overall response rate (ORR) compared to ofatumumab, a CD20-directed cytolytic therapy recommended for use in treating relapsed or refractory CLL/SLL. The purpose of this study is to evaluate duvelisib compared to ofatumumab in the treatment of subjects with relapsed or refractory CLL or SLL.

1.2 BACKGROUND

1.2.1 Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

CLL is the most common adult leukemia in Western countries with an incidence of 4.2 per 100,000 per year. In the elderly (> 80 years of age), the incidence increases to > 30 per 100,000 per year.[3] The median age at diagnosis is 72 years, with approximately 10% younger than 55 years. [4] CLL and SLL are different manifestations of the same disease and are managed in much the same way. The major difference is that in SLL, the abnormal lymphocytes are found predominantly in the lymph nodes, while in CLL the abnormal lymphocytes are also found in the bone marrow and peripheral blood (≥ 5,000 clonal cells/μL).[5]

Treatment of CLL/SLL is indicated in the presence of active, symptomatic disease. The intensity of the therapy is dependent on patient age, relative comorbidities, and the presence or absence of high-risk cytogenetic features (eg, deletion of 17p [del(17p)]).

In the first-line setting, chemotherapy with alkylating agents has been the treatment of choice for patients with advanced and progressive CLL. Since the introduction of chemoimmunotherapy regimens using purine nucleoside-analogs (such as fludarabine and cladribine) and pentostatin alkylating agents (such as chlorambucil and bendamustine) in combination with rituximab, a CD20-directed cytolytic antibody, these have become the preferred therapies for patients with low comorbid burden with or without high-risk cytogenetic features. In frail or elderly patients, single agent therapies are routinely used and include: chlorambucil; bendamustine; or alemtuzumab, a CD52-directed cytolytic antibody. Similarly, patients with specific molecular features like del(17p) do not derive as much

benefit from chemoimmunotherapy. Therefore, first-line treatment of CLL patients includes selection of single agent therapies based on patient age, relative comorbidities, and the presence or absence of high-risk cytogenetic features [ie, del(17p)]. Despite available treatment options, the majority of patients with CLL will relapse following first-line therapy and can acquire high-risk genetic abnormalities.

In relapsed or refractory CLL/SLL, treatment options are again dependent of the patient age, relative comorbidities, and the presence or absence of high risk cytogenetics. Patients are often re-treated with previously administered regimens if the relapse occurs ≥12 or 24 months after chemotherapy or chemoimmunotherapy, respectively. However, the majority of patients are not cured of their CLL/SLL and will eventually develop high-risk disease for which retreatment with prior therapies has no perceived benefit or alternative therapies have little clinical benefit (ie, bendamustine in relapsed high risk cytogenetics) or no longer routinely available (ie, alemtuzumab). In this setting, ofatumumab, a humanized CD20-directed cytolytic antibody, has demonstrated significant benefit.

1.2.2 Choice of Comparator

Ofatumumab was selected for use in this study based on the evolving treatment patterns across the regions intended for participation in this study. Use of ofatumumab in the patient population defined in this study is supported by information obtained from a review of the literature, [6, 7] established treatment guidelines [4, 8] and consultation with multiple expert advisors. It is expected that ofatumumab will be an acceptable choice for use at treatment centers where subjects with relapsed/refractory CLL who, unless otherwise contraindicated per treatment guidelines, would have routinely already received purine-analog based therapy (ie, fludarabine or pentostatin).

1.2.3 Ofatumumab Background

Ofatumumab is the first human anti-CD20 monoclonal antibody to be approved for CLL patients in the US and European Union (EU). On October 26, 2009 and April 19, 2010, the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) granted approval of ofatumumab (ARZERRA®, GlaxoSmithKline) for the treatment of CLL in patients who are refractory to fludarabine and alemtuzumab. Approval was based on the unmet medical need and provisions allowing early access to promising agents (US approval granted under 21 CFR 601, Subpart E; EU approval granted under conditional circumstances). Approvals were based on a clinically meaningful and durable ORR observed in a single-arm trial.[9]

Following an efficacy supplement filed in April 2014, ofatumumab was converted to full approval by both the FDA and the EMA on April 17, 2014 and May 22, 2014, respectively. Per the FDA, ofatumumab is now also indicated in combination with chlorambucil for the treatment of previously untreated patients with CLL for whom fludarabine-based therapy is considered inappropriate (the EMA indication statement also includes ofatumumab in combination with bendamustine). The full approval was based on data from the Phase III study of ofatumumab in combination with chlorambucil vs. chlorambucil, which demonstrated statistically significant improvement in median PFS in patients who received the

combination of ofatumumab and chlorambucil, compared to patients who received chlorambucil alone.

The National Comprehensive Cancer Network's (NCCN's) Drugs & Biologics Compendium recommends the use of ofatumumab as a single-agent or combination salvage therapy in rituximab-intolerant patients for disease that does not respond to primary therapy or for progressive or relapsed disease. For additional information on ofatumumab, please refer to the latest product label.[10, 11]

1.2.4 Functions of PI3K-δ and PI3K-γ

There are four mammalian isoforms of class 1 PI3Ks: PI3K-α, β,δ (class 1a PI3Ks) and PI3K-γ (class 1b PI3K). These PI3Ks catalyze the production of phosphatidylinositol (3,4,5)-trisphosphate (PIP3), leading to activation of the downstream effector pathways important for cellular survival, differentiation, and function. PI3K-α and PI3K-β are widely expressed, and are important mediators of signaling from cell surface receptors. PI3K-α is the isoform most often found mutated in cancers, and has a role in insulin signaling and glucose homeostasis.[12, 13] PI3K-β is activated in cancers where phosphatase and tensin homolog (PTEN) is deleted. Both isoforms are targets of small molecule therapeutics in development for cancer. PI3K-δ and P13K-γ are preferentially expressed in leukocytes, and are important in leukocyte function.

PI3K-δ is activated by cellular receptors (eg, receptor tyrosine kinases) through interaction with the SH2 domains of the PI3K regulatory subunit (p85), or through direct interaction with RAS.

PI3K-γ is associated with G-protein coupled receptors (GPCRs), is responsible for the very rapid induction of PIP3 in response to GPCRs, and can be also activated by RAS downstream of other receptors. PIP3 produced by PI3K activates effector pathways downstream through interaction with pleckstrin homology (PH) domain containing enzymes (eg, PDK-1 and AKT [PKB]).[14]

1.2.5 Functions of PI3K-δ and PI3K-γ in Hematologic Cancers

PI3K-δ and PI3K-γ are expressed in hematopoietic cells, and are critical for the ability of normal immune cells to respond to survival and differentiation signals in their environment. In cancer patients, where the pathways mediated by PI3K-δ,γ contribute to survival, proliferation, and differentiation of cancer cells, treatment with duvelisib may be beneficial. The tumor microenvironment plays an important role in the development and maintenance of cancer cells.[15] Cancer cells through the expression of various cytokines, growth factors, and chemokines recruit multiple cell types including myeloid cells capable of differentiating into tumor-associated macrophages (TAMs) which promote angiogenesis and augment tumor growth.[16] Therefore, agents that target TAMs as well as other types of infiltrating leukocytes are of potential therapeutic interest in oncology. Recently, it has been demonstrated that tumor growth, invasion of CD11b+ myeloid cells, angiogenesis and metastasis of tumors implanted into PI3K-γ deficient mice, were substantially suppressed compared to wild-type controls.[17] Treatment of mice bearing Lewis Lung Carcinoma (LLC) allografts with the selective PI3K-γ inhibitor TG100-115, suppressed tumor inflammation, growth and

angiogenesis despite having no effect on LLC proliferation in vitro. Because the expression of PI3K-γ is restricted to the hematological lineage, data suggests that PI3K-γ inhibition acts in a cancer cell-extrinsic manner to suppress tumor associated inflammation, angiogenesis and tumor progression.[17]

1.3 DUVELISIB

PI3K-δ and PI3K-γ contribute to the development and maintenance of inflammatory and autoimmune diseases, and hematologic malignancies.[13, 14, 18, 19] Duvelisib is a potent PI3K-δ,γ inhibitor being developed as a potential therapeutic in hematologic malignancy and inflammatory disease indications.

1.3.1 Nonclinical Summary of Duvelisib

Table 6 below summarizes the expression, role, isoform, and biochemical activity of duvelisib. See the duvelisib Investigator's Brochure for detailed summaries on pharmacology, toxicology, and absorption, distribution, metabolism, and excretion (ADME) of duvelisib.

Table 6: The Expression, Role, and Isoform Biochemical Activity of Duvelisib

PI3K Isoform	PI3K-δ	PI3K-γ	PI3K-β	PI3K-α
Expression	Primarily Leukocytes	Primarily Leukocytes	Ubiquitous	Ubiquitous
Role	B-cell & T-cell activation, proliferation, and differentiation Innate immune function	T-cell development and survival Innate immune function and cell trafficking	Platelet activation Metabolic control	Metabolic control Vascular homeostasis
Biochemical Activity (K_d)	23 pM	243 pM	1564 pM	25900 pM
Whole Blood Assay (IC_{50}) (Healthy Donors)	96±76 nM Basophils-Anti-FcεR1	1028±803 nM Basophils-fMLP	4700±1800 nM Platelet-TRAP-6	Not determined

FcεRI = high-affinity IgE receptor; fMLP = N-formyl-leucine-methionine-phenylalanine; IC_{50} = half maximal inhibitory concentration; TRAP-6 = thrombin receptor activating peptide-6

1.3.2 Clinical Studies in Humans

1.3.2.1 Study IPI-145-01 (Phase 1, first-in-human study)

Study IPI-145-01 was a randomized, double-blind, placebo-controlled, Phase 1 study in healthy adult subjects designed to evaluate the safety, tolerability, PK and pharmacodynamics of single and multiple ascending doses of duvelisib and to assess the effect of food and ketoconazole on the PK of duvelisib. One-hundred and six (106) subjects were enrolled. In

this setting duvelisib was well tolerated at the doses evaluated. There were no deaths and no serious adverse events (SAEs).

Pharmacokinetic assessments demonstrated that duvelisib is rapidly absorbed following single and multiple oral dose administration, with the maximum plasma concentration observed typically 1 hour after dosing. Across the dose ranges evaluated, duvelisib exposure increased proportionally to dose. The mean elimination half-life ranged from 6.5 to 11.7 hours after repeat dosing and did not depend on the dose level administered. Duvelisib accumulation was less than 2-fold following 14 days of Q12 h oral administration.

Data from the drug-drug interaction (DDI) portion indicated that concomitant administration of 200 mg ketoconazole every 12 hours (Q12 h) increased exposure to duvelisib. On average, $C_{max,}$ $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ increased by approximately 66%, 285% and 295%, respectively, in the presence of ketoconazole compared to duvelisib administered alone.

See the duvelisib Investigator's Brochure for further information.

1.3.2.2 Study IPI-145-02 (Phase 1, Hematologic Malignancies)

Study IPI-145-02 is a Phase 1, open-label, dose-escalation study of duvelisib administered orally twice daily during each 28-day cycles at doses ranging from 8 mg BID to 100 mg BID in adult subjects with advanced hematologic malignancies. Enrollment in all phases of the study is complete, with follow-up ongoing. As of 08 October 2014, 210 subjects received at least one dose of duvelisib including 55 subjects with relapsed/refractory CLL/SLL (8 mg [n=1]; 15 mg [n=2]; 25 mg [n=28]; 75 mg [n=24]). The median time on treatment for all relapsed/refractory subject doses was 5.9 months (range 0.9 to 34.1 months), and 7.6 months (range 0.9 to 34.1 months) for doses ≤ 25 mg.[20]

The maximum tolerated dose (MTD) was determined to be 75 mg BID based upon two dose limiting toxicities (DLTs) experienced by two subjects receiving 100 mg BID (Grade 3 rash and Grade 3 alanine aminotransferase [ALT]/aspartate aminotransferase [AST] elevations). Six expansion cohorts were enrolled at 25 mg BID or 75 mg BID to further define the safety and efficacy of duvelisib in select diseases. The 25 mg dose was selected for phase 3 development based on clinical activity.[21]

Clinical Safety in Relapsed/Refractory CLL/SLL

Frequently occurring (≥ 20% subjects) AEs observed in all relapsed/refractory CLL/SLL subjects (n=55) included neutropenia (53%), rash (combined terms) (46%), diarrhea (44%), cough (38%), fatigue (38%), pneumonia (combined terms) (36%), ALT/AST increased (29%), anemia (29%), pyrexia (27%), nausea (26%), decreased appetite (24%), and thrombocytopenia (22%). Serious adverse events occurring in more than 1 relapsed/refractory CLL/SLL subject included pneumonia (combined terms) (15 [27%])), febrile neutropenia (8 [15%]), diarrhea (3 [5%]), constipation (2 [4%]), hypercalcemia (2 [4%]), pyrexia (2 [4%]), and stomatitis (2 [4%]).[20]

These events are not unexpected based on the patient population and the mechanism of action of duvelisib. Infection prophylaxis and dose modifications included in the IPI-145-07 protocol are intended to reduce the risk of the frequently occurring events.

Clinical Efficacy in Relapsed/Refractory CLL/SLL

As of 08 October 2014, 52 subjects overall with relapsed/refractory CLL/SLL and 30 subjects who received duvelisib ≤ 25 mg BID with relapsed/refractory CLL/SLL had available efficacy data.

The investigator-reported ORR (CR + PR), as defined by the IWCLL/IWG was 58% among all relapsed/refractory CLL/SLL subjects with a response assessment, which included 1 CR, and 29 PR. The ORR for relapsed/refractory CLL/SLL subjects who received duvelisib ≤ 25 mg BID was 57%, which included 1 CR and 16 PR (Table 7). The median time to IWCLL/IWG response was 1.9 months.[20]

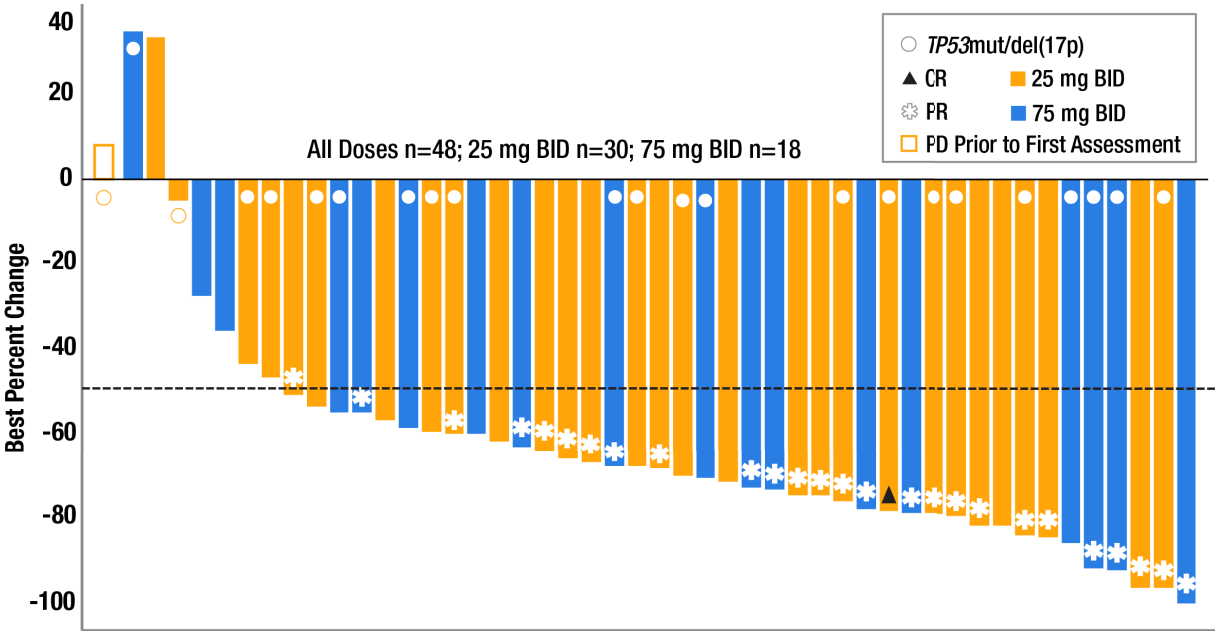
Table 7: Clinical Responses in Subjects with Relapsed/Refractory CLL/SLL (as of 08 October 2014) from Study IPI-145-02

Population	Patients (n)	Best Response (n)				ORR by IWCLL/IWG (CR + PR)
	Evaluable	CR	PR	SD*	PD	
Overall R/R CLL	52	1	29	21	1	58%
≤ 25 mg BID	30	1	16	12	1	57%

Includes efficacy evaluable patients only = at least one response assessment or PD without a response assessment
* Stable disease includes patients with PR + lymphocytosis

Figure 1 below shows the proportion of CLL/SLL subjects with a nodal response in Study IPI-145-02. A nodal response (reduction ≥ 50%) was observed in 83% (25/30) of CLL patients at 25 mg BID with a baseline CT scan.[20]

Figure 1: Maximum Change in Adenopathy by CT Scan Assessment in Subjects with Relapsed/Refractory CLL (as of 08 October 2014) from Study IPI-145-02



Pharmacokinetics

Preliminary PK data from Study IPI-145-02 demonstrate duvelisib is rapidly absorbed following oral dosing in subjects with advanced hematologic malignancies, with the maximum plasma concentration (C_{max}) generally achieved at approximately 1 hour post-dose. Steady state exposure over the dosing interval (AUC_{0-12}) is proportional to dose. Following repeat dose administration of 25 mg BID, mean C_{max} and AUC_{0-12} values are 1460 ng/mL and 8129 ng*h/mL, respectively. Duvelisib elimination half-life ($t_{1/2}$) does not appear to vary with dose and the mean $t_{1/2}$ was 4.5 hours following 25 mg BID administration.

1.4 RATIONALE FOR DUVELISIB AS A POTENTIAL THERAPY FOR SUBJECTS WITH CLL AND SLL

PI3K-δ and PI3K-γ are expressed in hematopoietic cells, and are critical for the ability of normal immune cells to respond to survival and differentiation signals in their environment. In cancer patients, where the pathways mediated by PI3K-δ,γ contribute to survival, proliferation, and differentiation of cancer cells, treatment with duvelisib may be beneficial. The tumor microenvironment plays an important role in the development and maintenance of cancer cells.[15] Cancer cells through the expression of various cytokines, growth factors, and chemokines recruit multiple cell types including myeloid cells capable of differentiating into TAMs which promote angiogenesis and augment tumor growth.[16] Therefore, agents that target TAMs as well as other types of infiltrating leukocytes are of potential therapeutic interest in oncology.

PI3Ks play pivotal roles in cell signaling and regulate a variety of cellular functions relevant to oncogenesis. Impaired development and function of B and T lymphocytes has been

demonstrated in PI3K-δ and PI3K-γ isoform knockout mice, supporting the development of PI3K-δ,γ specific inhibitors for B- and T-cell lymphoid malignancies.

1.5 DETERMINATION OF STARTING DOSE AND REGIMEN

Dose levels of duvelisib ranging from 8 mg BID to 100 mg BID were evaluated in Study IPI-145-02, a Phase 1, open-label, dose-escalation study in subjects with advanced hematologic malignancies where duvelisib was administered BID continuously in 28-day cycles as a single agent. At the time this protocol was developed, the dose-escalation phase of Study IPI-145-02 was complete and the MTD was determined to be 75 mg BID. A total of 193 subjects had been dosed in the study as of 28 October 2013.

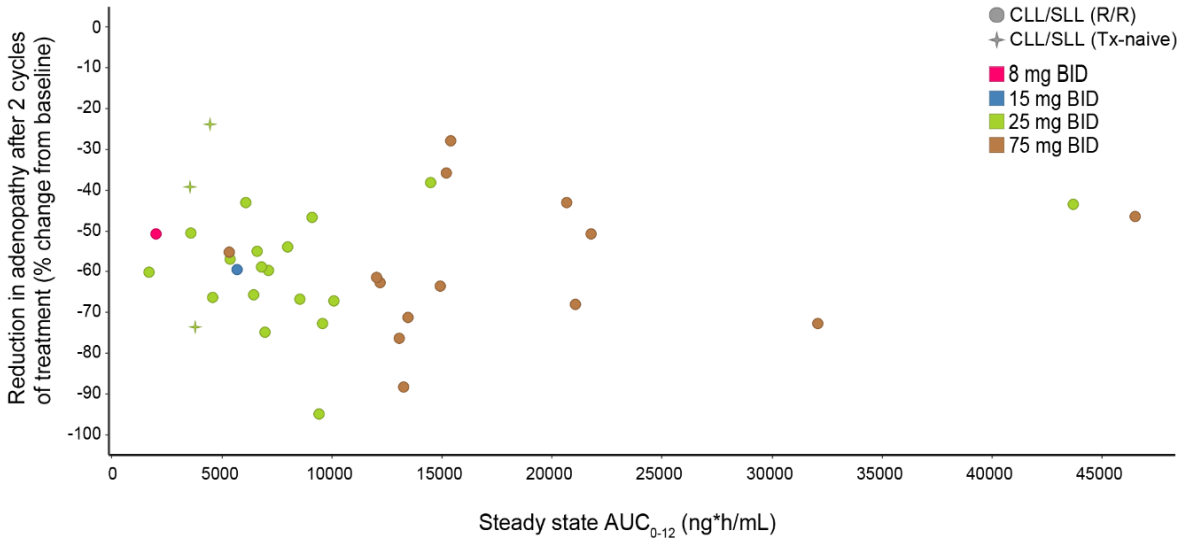
Based on the available data, the following findings were considered in determining the dose and schedule (25 mg BID) for this study:

- Of the 27 relapsed/refractory CLL/SLL subjects with evaluable efficacy data who received ≤ 25 mg BID of duvelisib, 1 subject achieved a CR and 12 subjects achieved a PR based on IWCLL 2008 response criteria (best response);
- The median time to response was rapid (1.9 months) with a PR observed in 6 subjects after 2 cycles, in 4 subjects after 4 cycles, and in 2 subjects after 6 cycles of duvelisib treatment;
- 85% (11/13) of the relapsed/refractory CLL/SLL subjects with evaluable efficacy data who received ≤ 25 mg BID of duvelisib with stable disease have demonstrated a nodal response, defined as > 50% reduction in adenopathy based on CT scans. Eight of 11 subjects experienced a nodal response after 2 cycles of duvelisib treatment; and
- After 2 cycles of duvelisib treatment, a nodal response was reported in 4 out of the 6 subjects who went on to achieve a PR after 4-6 cycles of duvelisib treatment. These data introduce the possibility that nodal responses (> 50% reduction in adenopathy) may be a precursor of response as defined by the IWCLL criteria. In clinical studies of other therapies in development in CLL, it has been reported that nodal responses have preceded PRs or CRs. [22]

Pharmacodynamics

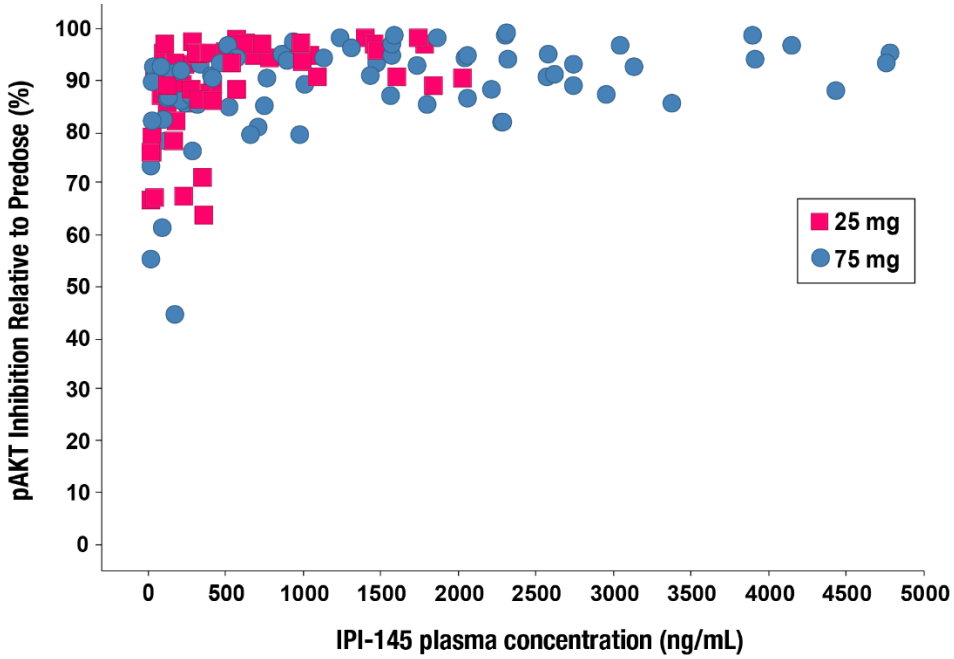
Preliminary exposure-response analyses observed in Study IPI-145-02 supported the rationale that duvelisib dosed at 25 mg BID is expected to be efficacious. The relationship between steady state exposure (collected at the beginning of Cycle 2) and reduction in lymph node size (assessed at the beginning of Cycle 3) in patients with CLL is provided in Figure 2. Increased exposure did not result in greater reductions in adenopathy; based on these preliminary data, a dose of 25 mg BID provides exposure anticipated to be efficacious.

Figure 2: Steady State Exposure (AUC_{0-12}) Versus Response (Reduction in Adenopathy) in CLL/SLL Subjects (Study IPI-145-02; preliminary data)



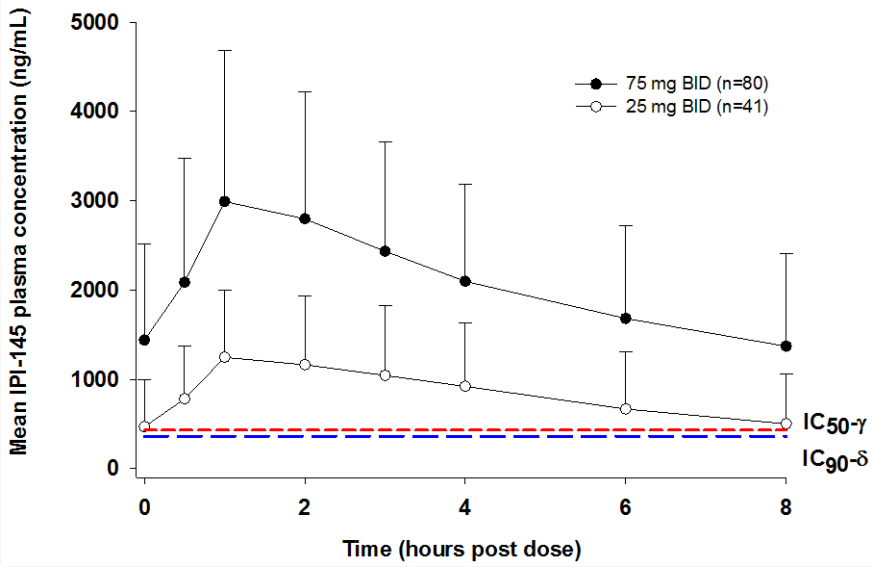
The serine/threonine kinase AKT is directly phosphorylated by PI3Ks, therefore the reduction in phosphorylated AKT (pAKT) was used as a pharmacodynamic marker for tumor cell PI3K inhibition in subjects with CLL in Study IPI-145-02. Percent pAKT inhibition versus duvelisib plasma concentration following a single dose is depicted in Figure 3. Duvelisib inhibits phosphorylation of AKT in a concentration-dependent manner, with maximal effects observed at concentrations observed following a 25 mg dose of duvelisib. Further elevations in duvelisib plasma concentration did not provide additional inhibition of pAKT.

Figure 3: Duvelisib (IPI-145) Plasma Concentration Versus Tumor Cell pAKT Inhibition Following a Single Dose in CLL/SLL Subjects (Study IPI-145-02; preliminary)



The potential of duvelisib to inhibit PI3K-δ and PI3K-γ was evaluated in vitro through quantitation of the reduction in CD63 cell surface expression on CCR3+ basophils in donor whole blood following stimulation with FcεR1 (PI3K-δ dependent) and fMLP (PI3K-γ dependent). Mean plasma concentrations following 25 mg BID remained at or above the IC_{90} for PI3K-δ inhibition and near or above the IC_{50} for PI3K-γ inhibition throughout the dosing interval (Figure 4).

Figure 4: Mean Duvelisib (IPI-145) Plasma Concentration-Time Profiles on Cycle 2, Day 1 (Study IPI-145-02; preliminary data)



2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of this trial is to examine the efficacy of duvelisib monotherapy versus ofatumumab monotherapy in subjects with relapsed or refractory CLL or SLL.

2.2 SECONDARY OBJECTIVES

- To determine the safety of duvelisib in subjects with CLL or SLL
- To evaluate the PK of duvelisib and, if applicable, its metabolite(s)

2.3 EXPLORATORY OBJECTIVES

- To evaluate the health-related quality of life (QoL) of subjects
- To evaluate pharmacodynamic biomarkers of duvelisib
- To evaluate biomarkers that may predict duvelisib clinical activity and/or safety
- To evaluate mechanisms of resistance in subjects who exhibit disease progression while being treated with duvelisib or ofatumumab
- To evaluate genomic features of tumors predictive of response in subjects treated with duvelisib or ofatumumab

3 STUDY ENDPOINTS

3.1 PRIMARY ENDPOINT

The primary endpoint is progression-free survival (PFS), defined as time from randomization to first documentation of progressive disease (PD) as determined by independent review or death due to any cause.

3.2 SECONDARY ENDPOINTS

The secondary endpoints of the study are:

- Overall Response Rate (ORR), with overall response (based on independent review) defined as the best response of complete response/remission (CR), CR with incomplete marrow recovery (CRi), partial response/remission (PR), or PR with lymphocytosis (PRwL), according to the IWCLL or revised IWG Response Criteria, with modification for treatment-related lymphocytosis
- Lymph node response rate, with lymph node response defined as ≥ 50% decrease in the SPD of target lymph nodes
- Overall Survival (OS), defined as time from randomization to death

- Hematologic improvement rate, with hematologic improvement defined as any of following, for at least 60 days without transfusion or exogenous growth factors:
  - Neutrophil count > 1,500/μL or an increase ≥ 50% from Baseline; or
  - Hemoglobin > 11 g/dL or an increase ≥ 50% from Baseline; or
  - Platelet count >100 000/μL or an increase ≥ 50% from Baseline
- Duration of Response (DOR), defined as time from the first documentation of response to first documentation of PD or death due to any cause
- TEAEs and changes in safety laboratory values
- PK parameters derived from plasma duvelisib concentrations and, if applicable, its metabolite(s)

3.3 EXPLORATORY ENDPOINTS

The exploratory endpoints of the study are:

- Improvement in disease-related symptoms of fatigue, weight loss, unexplained fevers and night sweats from Baseline
- Minimal Residual Disease (MRD) in subjects with documented CR or CRi
- Health-related QoL of subjects as assessed by the following subject-reported questionnaires:
  - EuroQol-5D (EQ-5D)
  - Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)
- Serum and tissue biomarkers and blood immunophenotype
- Tumor genomic features (eg, DNA sequence variation, DNA copy number variation, and/or RNA expression)
- Germline DNA sequence variations

4 STUDY DESIGN

Study IPI-145-07 is a two-arm, randomized (1:1 ratio), open label, phase 3, superiority trial designed to evaluate the efficacy and safety of duvelisib compared to ofatumumab. Subjects will be stratified by:

1. High-risk cytogenetics (presence vs absence of del[17p])
2. Refractory/early relapse to purine analog based therapy (defined as progression < 12 months after fludarabine/pentostatin: yes vs no)
3. Grade 4 cytopenia(s) (presence vs absence of neutropenia or thrombocytopenia at baseline)

Eligible subjects will be randomized in a 1:1 ratio to one of two treatment arms:

- Arm 1: Duvelisib, 25 mg BID
- Arm 2: Ofatumumab

First dose is to occur within 7 days of randomization after all screening assessments have been completed.

4.1 SCHEDULE OF ADMINISTRATION

Subjects who meet all the eligibility criteria at Screening will return to the clinic on Day 1 to receive their first dose of study drug (either duvelisib or ofatumumab). The first treatment cycle for each treatment arm will be 3 weeks (21±2 days). Subsequent treatment cycles will be 4 weeks (28±4 days).

Arm 1 (Duvelisib): Subjects randomized to duvelisib will receive their first dose of study drug in clinic on Day 1, initiating Cycle 1 of treatment. These subjects will return for a second clinical visit on Day 8±2. Cycle 1 will be 21 days, with all subsequent cycles 28 days in length. Cycle 2 will have clinic visits on Day 1 and on Day 15±2. Each subsequent cycle (Cycle 3-7) and then every odd cycle (Cycle 9 to 19) will have only one clinic visit on Day 1. Subjects will receive duvelisib continuously for 18 cycles or until disease progression or unacceptable toxicity, whichever comes first. After completing approximately 18 cycles of treatment with duvelisib, subjects who, in the judgment of the investigator, may derive benefit from continued treatment may receive additional cycles of duvelisib until disease progression or unacceptable toxicity. However, to receive additional cycles of duvelisib beyond 18 cycles, subjects must have CLL/SLL requiring treatment by Cycle 19 Day 1 (Reference 4.2.1.2). Subjects who receive duvelisib beyond 18 cycles (Cycle 19 Day 1) will maintain clinical visits every odd cycle (Cycle 21, 23, etc) until disease progression, subject withdrawal, or initiation of additional anticancer treatment. After Cycle 18, disease response assessments will continue every 6 cycles for those subjects who have not had disease progression, withdrawn consent, or initiated additional anticancer treatment.

Arm 2 (Ofatumumab): Subjects randomized to ofatumumab will receive IV treatment according to the approved prescribing information.[10, 11] Subjects will receive 8 weekly IV infusions, starting with an initial dose of ofatumumab of 300 mg followed by seven weekly doses of 2000 mg. Thereafter, subjects will receive 2000 mg ofatumumab once every cycle for four cycles or until disease progression or unacceptable toxicity, whichever comes first.

Administration of ofatumumab will not exceed the 12 doses (within 7 cycles) as described in the prescribing information. After dosing with ofatumumab is complete (ie, through Cycle 7 or ETT), subjects will continue to have clinical assessments every odd cycle (Clinical Assessment Period) through Cycle 19 Day 1 or until disease progression, subject withdrawal, or initiation of additional anticancer treatment. After Cycle 19 Day 1, disease response assessments will continue every 6 cycles until disease progression, subject withdrawal, or initiation of additional anticancer treatment.

If a subject initiates another anticancer therapy following treatment with ofatumumab, then the subject will be discontinued from the Clinical Assessment Period and will be followed for survival as described in Table 5.

Subjects who have documentation of PD confirmed centrally at any time during the study may be eligible to receive the opposite study medication as part of a separate Verastem-sponsored extension protocol (Study IPI-145-12). Additional extension protocol eligibility criteria must also be met.

4.2 DOSE INTERRUPTION/HOLD/MODIFICATION GUIDELINES

4.2.1 Duvelisib Guidelines

Duvelisib treatment will consist of 25 mg administered orally BID continuously for up to 18 cycles. Duvelisib may be continued beyond 18 complete cycles, if the subject meets the criteria for additional treatment at Cycle 19 Day 1 (see Section 4.2.1.2). Duvelisib dosing may be modified due to benefit or toxicity as described below.

4.2.1.1 Duvelisib treatment modification guidelines due to duvelisib-related toxicities

Subjects will be monitored continuously for toxicity while on study treatment. Toxicity will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03. If a subject has an AE at least possibly related to duvelisib, then dose interruptions/holds with possible modifications as described below in Table 8 may be implemented. Deviations from these guidelines may occur based on the clinical judgment of the Investigator with notification to the Medical Monitor/Sponsor. There should be no attempt to make up for missed doses of duvelisib.

Table 8: Dose Interruption/Hold/Modifications for Duvelisib-Related Toxicities

Duvelisib-related Toxicities [a, b]	Dose Interruption/Hold/Modification/Recommendation for Duvelisib [c]
Nonhematologic: Grade 2 or higher Pneumonitis/Pneumonia Or Grade 3 or higher other Nonhematologic	**First occurrence:** Withhold until return to ≤Grade 1 or baseline level; re-challenge therapy at original dose level. **Second occurrence of the same AE:** Withhold until return to ≤Grade 1 or baseline level; re-initiate therapy at one dose level lower from current dose. **Third occurrence of the same AE:** Withhold until return to ≤Grade 1 or baseline level; re-initiate therapy at one dose level lower from current dose. **Fourth occurrence of the same AE:** Discontinue subject from study drug
Hematologic: Grade 3 or higher febrile neutropenia Or Grade 3 or higher thrombocytopenia with Grade ≥2 hemorrhage.	
Recommendations for implementing duvelisib dose interruptions Immediate hold for Grade 4 or higher nonhematologic toxicity and Grade 3 or higher febrile neutropenia. For all other events, reduce from BID dosing to QD for two days, then hold.	

a. Duvelisib-related toxicity = possible, probable, or definite relationship to duvelisib as defined in Section 8.2.1.
b. Toxicity grades are defined per CTCAE Version 4.03. Note if parameter is not defined by CTCAE, then AE grading criteria (Section 8.2.1) should be utilized.
c. Refer to Table 9 for duvelisib dose levels.

Treatment Interruption for Nonhematologic Toxicity

Treatment with duvelisib should be interrupted for the following nonhematologic toxicities:

- Grade 2 or higher pneumonitis/pneumonia, defined as symptomatic and requiring medical intervention, including oral antimicrobials and/or steroids
  - Subjects who develop new pulmonary symptoms (eg, cough, shortness of breath, dyspnea on exertion) or new radiographic findings should have duvelisib held and receive empiric antimicrobial coverage while undergoing evaluation. Corticosteroids for symptomatic treatment of pneumonitis is recommended (and allowed per protocol). Restarting treatment with duvelisib is allowed after complete resolution of symptoms.
- Grade 3 or higher other nonhematologic toxicity including the following:
  - Infections: Subjects who develop infections requiring IV antibiotics/antifungals/anti-virals should have duvelisib held until infection resolves (subject may restart duvelisib when completing a course of oral therapy). Prophylaxis to prevent recurrence/opportunistic infections will not preclude the subject from restarting treatment.
  - Hepatic events: Subjects who develop Grade 3 or higher transaminase (ALT/AST) elevations with or without clinical symptoms should have duvelisib held until return to baseline. Additional work-up to evaluate viral infection/re-activation, exposure to environmental toxins (eg, alcohol/con-meds), or other causes is recommended before restarting treatment with duvelisib.

- Gastrointestinal: Subjects who develop Grade 3 or higher nausea, vomiting or diarrhea despite optimal treatment should have duvelisib held until resolution of symptoms. Evaluation of concomitant medications, gastrointestinal infections or inflammatory bowel (via endoscopy and biopsy) should be considered with persistent diarrhea or recurrence with restarting duvelisib. Corticosteroids (budesonide) with taper are allowed if colitis is suspected/cannot be ruled out.
- Skin rash: Subjects who develop Grade 3 or higher skin rashes should have duvelisib held until resolution of symptoms. In the setting of new Grade 1-2 skin rash early intervention is recommended to ameliorate risk of worsening symptoms. Evaluation of concomitant medications, environmental exposure, infections or other contributing factors is recommended.
- Cardiac: Subjects who develop Grade 3 or higher cardiac events should have duvelisib held until resolution of symptoms. This includes ≥ Grade 3 (≥ 500 ms) QT interval corrected with Fridericia's method (QTcF) prolongation. A ≥ Grade 3 QTcF prolongation requires triplicate ECGs with the average measurement used and the use of Fridericia's correction method (QTcF). For subjects with a right or left BBB, a Grade 3 QTc prolongation is defined as an increase in QTcF of >100 ms from the pre-dose ECG to any post dose ECG as the QRS interval is prolonged at Baseline (by approximately 40 ms) in subjects with a BBB

Subjects requiring treatment interruption should be re-evaluated at least weekly until the toxicity improves to ≤ Grade 1 or returns to Baseline level. Duvelisib dose will be restarted at doses described in Table 9.

Treatment Interruption for Hematologic Toxicity

Worsening or transient Grade 3 or higher neutropenia, anemia, and/or thrombocytopenia caused by the subject's existing disease (CLL or SLL) or by duvelisib are to be expected. Blood counts should be monitored as prescribed in the protocol with the frequency increased as clinically indicated in the setting of new or worsening Grade 3 or higher cytopenias. Duvelisib dosing may be interrupted at any time, at the discretion of the treating physician.

Treatment with duvelisib should be interrupted for the following symptomatic hematologic toxicities:

- Grade 3 or higher febrile neutropenia
- Grade 3 or higher thrombocytopenia associated with Grade 2 or higher haemorrhage

The subject should be re-evaluated at least weekly until the toxicity improves to ≤Grade 1 or returns to Baseline.

Duvelisib may be withheld up to 42 days for toxicity. Doses withheld for > 42 days due to treatment-related toxicity will result in permanent discontinuation from treatment. Any subject who requires a dose < 5 mg BID due to treatment-related toxicities will be permanently discontinued from treatment. Dose levels are shown in Table 9.

Table 9: Dosing Levels Duvelisib

Dose Level	**Dose (mg)**
1	25 BID
-1	15 BID
-2	10 BID
-3	5 BID

Subjects who have a dose reduction due to a toxicity may be eligible for a dose increase back to the dose level prior to the reduction (ie, the starting dose or dose of previous reduction if subject was dose reduced more than one level) if the following criteria are met:

1. Subject has tolerated the lower treatment dose for >1 treatment cycle
2. Subject has recovered to baseline levels from the toxicity which caused the dose reduction

4.2.1.2 Duvelisib treatment modification guidelines due to benefit/maximal benefit.

Treatment discontinuation due to benefit after < 18 complete cycles of duvelisib therapy:

Prior to completion of 18 cycles of duvelisib therapy, discontinuation of duvelisib may be considered, after discussion with the medical monitor, should a CLL subject demonstrate a CR/CRi per IWCLL 2008 criteria or an SLL subject demonstrate a CR per IWG 2007 criteria (see Section 6.3.9 for definitions). The timing of duvelisib treatment discontinuation relative to the duration of a CR should be considered as follows:

- < 12 months of duvelisib therapy: duration of CR/CRi > 6 months before discontinuation
- ≥ 12 months of duvelisib therapy: duration of CR/CRi > 3 months before discontinuation

Disease response assessments by CT scan will continue every 6 cycles until disease progression (see Table 5).

Treatment discontinuation after 18 or more complete cycles of duvelisib therapy:

After completion of 18 cycles (beginning on Day 1 Cycle 19) of duvelisib therapy, discontinuation of duvelisib may be considered if a subject demonstrates the following responses (per modified IWCLL criteria/IWG criteria or as otherwise indicated [see Section 6.3.9]) of > 3 months duration:

- CR or CRi
- Partial response (that includes all target lesions ≤ 1.5 cm in diameter) but with a peripheral blood absolute lymphocyte count (ALC) ≥ 4,000/µL (Rai Stage 0)

- Persistent lymphadenopathy > 50% of baseline (with at least 1 target lesion ≥ 1.5 cm in diameter) and persistent lymphocytosis ≥ 4,000/µL (and > 50% of baseline)

Disease response assessments by CT scan will continue every 6 cycles until disease progression (see Table 5).

Treatment continuation after 18 or more complete cycles of duvelisib therapy:

Duvelisib therapy may continue if there is potential benefit to the subject based on the following disease response assessments (per IWCLL criteria /IWG criteria or as otherwise indicated [see Section 6.3.9]) at the end of 18 cycles (Day 1 Cycle 19) of duvelisib therapy:

- CR or CRi < 3 months duration
- PR with or without lymphocytosis
- SD

Disease response assessments by CT scan will continue every 6 cycles while the subject remains on duvelisib treatment (see Table 5).

4.2.2 Ofatumumab Guidelines

Ofatumumab treatment guidelines follow the manufacturer recommendations for 12 ofatumumab infusions administered over 6-7 months: 8 weekly ofatumumab infusions followed by an ofatumumab infusion every month for 4 months. During the 6-7 months of ofatumumab infusions, therapy may be modified due to toxicity as described below. Ofatumumab dosing will not be extended beyond the 12 ofatumumab infusions, as described in Table 4 and the latest ARZERRA® prescribing information.[10, 11]

4.2.2.1 Ofatumumab treatment modification guidelines due to ofatumumab related toxicities

Subjects will be monitored continuously for toxicity while on study treatment. Toxicity will be assessed using the NCI CTCAE Version 4.03. If a subject has an AE at least possibly related to ofatumumab, then dose interruptions/holds with possible modifications are described below. If the dose of ofatumumab is reduced, all reductions should be made per Prescribing Information.[10, 11] Additional details on study drug dosage and administration are described in Section 7.2.1 and 7.2.2, respectively. Deviations from these guidelines may occur based on the clinical judgment of the Investigator with notification to the Medical Monitor/Sponsor. There should be no attempt to make up for a missed weekly dose of ofatumumab or a monthly dose of ofatumumab if delayed by >3 weeks.

Table 10: Dose Interruption/Hold/Modifications for Ofatumumab-Related Toxicities

Ofatumumab-related Toxicities [a, b]	Dose Interruption/Hold/Modification/Recommendation for Ofatumumab

Infusion Reactions	Infusion interruptions
	• For Grade 1, 2, or 3 infusion reaction, if the infusion reaction resolves or remains less than or equal to Grade 2, resume infusion with the following modifications according to the initial Grade of the infusion reaction.
	  ○ Grade 1 or 2: Infuse at one-half of the previous infusion rate.
	  ○ Grade 3: Infuse at a rate of 12 mL/hour.
	• After resuming the infusion, the infusion rate may be increased according to the Principal Investigator, based on subject tolerance.
	• For Grade 4 infusion reactions, do not resume the infusion.
	
	Modifications:
	• Grade 3 or 4 infusion reaction with previous infusion:
	  ○ Reduce next ofatumumab dose to 300 mg
	• Increase subsequent dose(s) to 2000 mg if no Grade 3 or 4 infusion reaction occurs

Nonhematologic: Grade 3 or higher	Withhold until return to ≤ Grade 1 or baseline level; re-challenge therapy at original dose level.
Hematologic: Grade 3 or higher febrile neutropenia	Withhold until return to ≤ Grade 1 or baseline level; re-challenge therapy at original dose level.
Grade 3 or higher thrombocytopenia associated with Grade 2 or higher hemorrhage	Withhold until return to ≤ Grade 1 or baseline level; re-challenge therapy at original dose level.

a. Related = possible, probable, or definite relationship to ofatumumab as defined in Section 8.2.1.
b. Toxicity grades are defined per CTCAE Version 4.03. Note if parameter is not defined by CTCAE, then AE grading criteria (Section 8.2.1) should be utilized.

Treatment Interruption for Infusion-related Toxicity

The initial dose of ofatumumab will be 300 mg IV to reduce the possibility of infusion reactions. If the subject tolerates this infusion without occurrence of any infusion-associated AEs of ≥ Grade 3, subsequent doses of ofatumumab will be at a dose of 2000 mg for the duration of study treatment. If the subject experiences Grade 4 infusion reaction, the infusion should be stopped. If the subject experiences a Grade 1-3 infusion reaction during the first infusion, ofatumumab should be interrupted and appropriate supportive care given. If the infusion reaction improves to ≤ Grade 2, then administer at a slower rate (as described in Table 10 and the ARZERRA® package insert).

Appropriate supportive care should also be given, until the infusion reaction improves to ≤ Grade 1. Following a Grade 3/4 infusion reaction, the next ofatumumab dose should be given at the starting dose of 300 mg. The ofatumumab dose may be escalated to 2000 mg following a dose in which no Grade 3/4 infusion reactions are experienced.

Treatment Interruption for Nonhematologic Toxicity

Treatment with ofatumumab may be interrupted at any time, at the discretion of the treating physician. Treatment with ofatumumab should be interrupted for the following nonhematologic toxicities:

- Any Grade 3 or higher nonhematologic toxicity (with the following modifications)
  - Grade 3 or higher diarrhea despite optimal antidiarrheal treatment
  - Grade 3 nausea, or vomiting despite optimal anti-emetic treatment
  - Grade 3 or higher cardiac events including ≥ Grade 3 QTcF prolongation (≥ 500 ms). A ≥ Grade 3 QTcF prolongation requires triplicate ECGs with the average measurement used and the use of Fridericia's correction method (QTcF). For subjects with a right or left BBB, a Grade 3 QTc prolongation is defined as an increase in QTcF of >100 ms from the pre-dose ECG to any post dose ECG as the QRS interval is prolonged at Baseline (by approximately 40 ms) in subjects with a BBB
  - Subjects who develop infections requiring IV antibiotics will have treatment held until the infection resolves (subject may restart ofatumumab while completing a course of oral therapy). Requirement of prophylaxis for further infection will not prevent the subject from continuing treatment

Subjects requiring dose interruption should be re-evaluated at least weekly until the toxicity improves to ≤ Grade 1 or returns to Baseline level.

Treatment Interruption for Hematologic Toxicity

Worsening or transient Grade 3 or higher neutropenia, anemia, and/or thrombocytopenia caused by the subject's existing disease (CLL/SLL) or by ofatumumab are to be expected. Blood counts should be monitored as prescribed in the protocol with the frequency increased as clinically indicated in the setting of new or worsening Grade 3 or higher cytopenias.

Ofatumumab dosing may be interrupted at any time, at the discretion of the treating physician. Treatment with ofatumumab should be held for the following symptomatic hematologic toxicity:

- Grade 3 or higher febrile neutropenia
- Grade 3 or higher thrombocytopenia associated with Grade 2 or higher hemorrhage

The subject should be re-evaluated at least weekly until the toxicity improves to ≤ Grade 1 or returns to Baseline.

Ofatumumab will be discontinued in subjects who develop viral hepatitis or have a diagnosis or symptoms suspicious of progressive multifocal leukoencephalopathy (PML).

4.3 TREATMENT DISCONTINUATION

A subject should be withdrawn from the study treatment if, in the opinion of the investigator, it is medically necessary, or if it is the wish of the subject.

Subjects will be withdrawn from treatment in case of any of the following reasons:

- An adverse event that requires permanent discontinuation of duvelisib or ofatumumab
- Protocol-specified disease progression
- Subject death
- Subject lost to follow-up
- Noncompliance to protocol
- Investigator decision (including for benefit as described in Section 4.2.1.2)
- Subject becomes pregnant
- Termination of the study by sponsor
- Voluntary withdrawal by subject
- Subject requires additional anticancer therapy

Adverse events leading to the discontinuation of a subject will be followed until resolution, resolution to baseline or until the event is considered stable or chronic.

If a subject does not complete dosing through Cycle 19 Day 1 (duvelisib) or through Cycle 7 (ofatumumab), then he/she should attend an Early Treatment Termination (ETT) Visit within 7 days of last dose or the decision leading to treatment discontinuation (see Section 6.4). Assessments collected within 14 days of the ETT (within 30 days for Disease Response Assessment and QoLs) Visit do not need to be repeated at the ETT Visit. Following last dose, either due to ETT or completion of dosing, all subjects will complete a 30-day safety follow-up visit (see Section 6.5.1). Scans will be performed at the ETT if a previous scan has not been performed within 30 days of the ETT visit. All subjects who discontinue treatment will be followed for survival (see Section 6.5.3.2).

Subjects who discontinue study treatment for reasons other than PD, and have not withdrawn consent from overall study participation should enter the Clinical Assessment Period (Section 6.5.2) and continue Disease Response Assessments (Section 6.5.3.1) as applicable.

4.4 STUDY DISCONTINUATION

Subjects may voluntarily withdraw from the study at any time for any reason without prejudice.

Subjects will be withdrawn from the study in case of any of the following reasons:

- Subject death
- Subject lost to follow-up
- Completion of the follow-up period
- Termination of the study by sponsor
- Voluntary withdrawal by subject

If the subject withdraws consent from the study overall participation (and not just study treatment), no further evaluations should be performed and no attempts should be made to collect additional data.

5 STUDY POPULATION

Approximately 300 subjects with a diagnosis of relapsed and/or refractory CLL or SLL will enroll in the study and be randomized equally (150 subjects per arm) to one of two treatment groups (25 mg duvelisib BID or ofatumumab).

Approximately 100 sites will be initiated worldwide. It is anticipated that the entire study will accrue subjects over approximately16 months from the randomization of the first subject.

5.1 ENTRY CRITERIA

5.1.1 Inclusion Criteria

Subjects must meet all of the following criteria:

1. ≥ 18 years of age
2. Diagnosis of active CLL or SLL that meets at least one of the IWCLL 2008 criteria for requiring treatment (Binet Stage ≥ B and/or Rai Stage ≥ I)
3. Disease that has progressed during or relapsed after at least one previous CLL/SLL therapy
4. Not appropriate for treatment with a purine-based analogue regimen (per NCCN or European Society for Medical Oncology [ESMO] guidelines), including relapse ≤ 36 months from a purine-based chemoimmunotherapy regimen or relapse ≤ 24 months from a purine-based monotherapy regimen
5. A cytogenetics or FISH analysis of the leukemic cells within 24 months of randomization is required to document the presence or absence of del(17p). Note: if a sample from within 24 months is not available, it should be evaluated as part of the screening laboratory evaluation to inform stratification
6. Measurable disease with a lymph node or tumor mass > 1.5 cm in at least one dimension as assessed by computed tomography (CT)
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (corresponds to Karnofsky Performance Status [KPS] ≥ 60%)
8. Willingness by subject to be randomized to receive either ofatumumab or duvelisib at the dose and schedule defined in the protocol
9. Must meet the following laboratory parameters:
   - Serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) ≤ 3 x upper limit of normal (ULN)
   - Total bilirubin ≤ 1.5 x ULN
   - Serum creatinine ≤ 2.0 x ULN
   - Hemoglobin ≥ 8.0 g/dL with or without transfusion support
   - Platelet count ≥ 10,000 μL with or without transfusion support

10. For women of childbearing potential (WCBP)**:** negative serum β-human chorionic gonadotropin (βhCG) pregnancy test within 1 week before randomization (WCBP defined as a sexually mature woman who has not undergone surgical sterilization or who has not been naturally post-menopausal for at least 24 consecutive months [women ≤ 55 years] or 12 consecutive months [women > 55 years])
11. Willingness of male and female subjects who are not surgically sterile or postmenopausal to use medically acceptable methods of birth control from the first dose of study drug to 30 days after the last dose of duvelisib and for 12 months after last dose of ofatumumab. Sexually active men, and women using oral contraceptive pills, should also use barrier contraception
12. Ability to voluntarily sign consent for and adhere to the entire study visit schedule and all protocol requirements
13. Signed and dated institutional review board (IRB)/independent ethics committee (IEC)-approved informed consent form (ICF) before any study specific screening procedures are performed

5.1.2 Exclusion Criteria

Subjects are to be excluded from the study if they meet any of the following criteria:

1. History of Richter's transformation or prolymphocytic leukemia
2. Autoimmune hemolytic anemia (AIHA) or idiopathic thrombocytopenic purpura (ITP) that is uncontrolled or requiring > 20 mg once daily (QD) of prednisone (or equivalent) to maintain hemoglobin > 8.0 g/dL or platelets > 10,000 μL without transfusion support
3. Refractory to ofatumumab (defined as progression or relapse < 12 months of receiving ofatumumab monotherapy or < 24 months of receiving an ofatumumab-containing regimen)
4. Prior allogeneic transplant (prior autologous stem cell transplant > 6 months prior to study entry is permitted)
5. Known central nervous system (CNS) lymphoma or leukemia; subjects with symptoms of CNS disease must have a negative CT scan or negative diagnostic lumbar puncture prior to randomization
6. Prior exposure to a PI3K inhibitor (eg, GS-1101, duvelisib) or a Bruton’s tyrosine kinase (BTK) inhibitor
7. Use of any of the following medications or procedures within the specified timeframe:
   - Use of live or live attenuated vaccines within 30 days prior to randomization
   - Chemotherapy, radiation therapy, or ablative therapy within 3 weeks of randomization
   - Tyrosine kinase inhibitor within 7 days of randomization

- Other investigational therapy (not included above) within 3 weeks of randomization

8. Ongoing treatment with chronic immunosuppressants (eg, cyclosporine) or systemic steroids > 20 mg prednisone (or equivalent) QD.
9. History of tuberculosis treatment within the preceding two years
10. Ongoing systemic bacterial, fungal, or viral infections at the time of initiation of study treatment (defined as requiring intravenous [IV] antimicrobial, antifungal or antiviral agents)
    - Subjects on antimicrobial, antifungal or antiviral prophylaxis are not specifically excluded if all other inclusion/exclusion criteria are met and there is no evidence of active infection at randomization
11. Human immunodeficiency virus (HIV) infection
12. Prior, current or chronic hepatitis B or hepatitis C infection
13. History of alcohol abuse or chronic liver disease (other than metastatic disease to the liver)
14. Unable to receive prophylactic treatment for pneumocystis or herpes simplex virus (HSV)
15. Baseline QTcF > 480 ms (average of triplicate readings) Note: This criterion does not apply to subjects with a right or left bundle branch block (BBB)
16. Unstable or severe uncontrolled medical condition (eg, unstable cardiac function, unstable pulmonary condition), or any important medical illness or abnormal laboratory finding that would, in the investigator's judgment, increase the subject's risk while participating in this study
17. Concurrent active malignancy other than nonmelanoma skin cancer or carcinoma in situ of the cervix, bladder, or prostate not requiring treatment. Subjects with previous malignancies are eligible provided that they have been disease free for ≥ 2 years
18. History of stroke, unstable angina, myocardial infarction, or ventricular arrhythmia requiring medication or mechanical control within the last 6 months
19. Administration of medications or foods that are strong inhibitors or inducers of CYP3A within 2 weeks of randomization
20. Prior surgery or gastrointestinal dysfunction that may affect drug absorption (eg, gastric bypass surgery, gastrectomy)
21. Major surgery or invasive intervention within 4 weeks prior to randomization
22. Pregnant or breastfeeding women
23. Hypersensitivity to ofatumumab or its excipients

6 STUDY PROCEDURES AND ASSESSMENTS

The Schedules of Assessments are summarized in Table 1, Table 2, Table 3, Table 4, and Table 5. Details related to the assessments are described below.

6.1 INFORMED CONSENT

Subjects potentially eligible for participation must sign an informed consent form (ICF) prior to initiating any study specific procedures. Standard of care assessments that fulfill study eligibility requirements may be performed prior to subject signing the ICF.

6.2 SCREENING PERIOD

6.2.1 Medical History, Physical Examination, and Screening Assessments

The Investigator at the site is responsible for maintaining a record of all subjects screened and those who are enrolled into the study.

During the screening visit, the following assessments will be performed:

- Obtain signed ICF
- Review inclusion/exclusion criteria
  - Prior histologic confirmation of CLL or SLL
- Complete medical history: includes demographics, cancer history and documentation of all previous treatments and treatment results (ie, best response to previous disease specific treatments) prior procedures, current medications, and all medications used within 30 days prior to Screening
- Obtain/confirm documentation of cytogenetics/FISH results with analysis for del(17p). In order to be valid, these previous results must be within 24 months (2 years) of randomization. Additional results for other cytogenetic abnormalities will be collected (if available)
- Full physical examination, which includes vital signs (temperature, blood pressure [sitting for 5 minutes], pulse rate, and respiratory rate), height, and weight
- ECOG* performance status (see Appendix 4)
- Disease-related constitutional symptoms, (fatigue [as measured by ECOG Performance Status], fever [ie, temperature >38°C/100.5°F] without evidence of infection, weight loss, and drenching night sweats without evidence of infection
- Subject-reported health-related QoL* questionnaires (EQ-5D and FACIT-F) will be administered at Screening. If these instruments are not captured at Screening (< 7 days prior to Day 1 Cycle 1), then these assessments must be assessed at Cycle 1 Day 1 predose; English language examples of these instruments are shown in Appendix 5 and Appendix 6
- 12-lead ECG which should be conducted following an approximate 10-minute rest period in a semi-recumbent or supine position and obtained in triplicate within approximately a 5

minute time period. QTc measurements will use the Fridericia's correction method (QTcF).

- Blood chemistry laboratory parameters* (including liver function tests): sodium, potassium, chloride, bicarbonate (or CO_2), albumin, total protein, creatinine, blood urea nitrogen (BUN) or urea, lipase, amylase, uric acid, calcium, phosphorus, magnesium, glucose, LDH, serum ALT, serum AST, total and direct bilirubin, and alkaline phosphatase.
- Hematology laboratory parameters*: red blood cell (RBC) count, hemoglobin, hematocrit, platelets, white blood cell count with 5-part differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils) such that an absolute neutrophil count (ANC) and an ALC can be derived if it is not already provided as part of the laboratory analysis, and coombs testing (direct and indirect). Documentation of hematology labs within 7 days prior to randomization is required to confirm presence or absence of Grade 4 cytopenia for stratification at randomization.
- Coagulation laboratory parameters* including prothrombin time (PT), and activated partial thromboplastin time (aPTT). For subjects receiving anticoagulation therapy affecting the PT, an International normalized ratio (INR) must be obtained.
- Anti-hepatitis C antibody (HCV Ab), hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb).
- Laboratory studies to assess the status of prior or current Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) infection. These may include any or all of the following: CMV Ab (via a serology) and antigen [viral load detection via polymerase chain reaction (PCR)] or immunohistochemistry (pp65 CMV) and Epstein-Barr virus serology.
- Serum pregnancy test for WCBP (must be performed within 7 days of randomization)
- HIV test for all subjects without documentation of a prior negative HIV test
- Baseline disease assessments, which include:
  - CT scans of chest, abdomen and pelvis are required for all subjects. Other scans may be performed (eg, head/neck CT) if clinically indicated or if the area is a site of known disease. Copies of all imaging/radiology films will be sent to a central laboratory for independent review.
    - **Note:** Magnetic resonance imaging (MRI) may be substituted if clinically indicated, but the modality chosen to evaluate each individual subject should be the same throughout the duration of the study.
  - Bone marrow aspirate and/or bone marrow biopsy (unless clinically contraindicated).

** ECOG, QoL, hematology, liver function tests, blood chemistry, or coagulation evaluations may be performed within 7 days prior to study treatment (predose Cycle 1 Day 1). If these Screening evaluations are performed within 7 days of Cycle 1 Day 1, these Screening results can be used in place of the Cycle 1 Day 1 assessments.*

6.2.2 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria (Section 5.1.1, Section 5.1.2, respectively) will be reviewed for each potential subject and documented in the source and electronic Case Report Form (eCRF). During the screening period a subject number will be assigned by the Interactive Response Technology (IRT). At randomization, the dose and schedule of study drug (duvelisib or ofatumumab) will be assigned by the IRT (see Section 7.6 for treatment assignment).

6.3 TREATMENT PERIOD

6.3.1 Assessments

6.3.1.1 Physical Examinations

A focused physical exam should be performed at all clinic visits indicated in Table 2 and Table 4 and is to include assessment of liver/spleen size, clinical assessment of tumor masses (if accessible) and other clinically significant findings (new or previously noted at Screening). Results from the focused physical exams as outlined above will be utilized for disease status assessments at time points specific in Table 5. Any new clinically significant abnormality from baseline should be recorded as an AE.

6.3.1.2 Vital Signs

Vital signs should be performed throughout the study only if clinically indicated. Clinically significant changes should be recorded on the AE eCRF.

6.3.1.3 ECOG Performance Status

For Cycle 1 Day 1 (predose), the ECOG performance evaluation may be performed within 7 days prior to study treatment (Cycle 1, Day 1). If the ECOG performance evaluation is performed within 7 days of Cycle 1 Day 1, this Screening result can be used in place of the Cycle 1 Day 1 ECOG performance.

6.3.1.4 Additional Assessments

- Adverse events collection (Section 6.3.4)
- Concomitant medication collection (Section 6.3.6)
- Pharmacokinetic sample collection (Section 6.3.7)
- Biomarker sample collection (Section 6.3.8)
- CLL/SLL Disease Response Status Assessment (Section 6.3.9)

6.3.2 Clinical Laboratory Tests

The following laboratory parameters will be conducted according to Table 1, Table 2, and Table 4:

- A serum pregnancy test at screening and urine or serum pregnancy tests while on treatment will be collected from all women of childbearing potential (WCBP).
- Hematology laboratory parameters include RBC, hemoglobin, hematocrit, platelets, and white blood cell count with 5-part differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils) such that an ANC and an ALC can be derived if it is not already provided as part of the laboratory analysis. Blood samples should be drawn and results reviewed within 72 hours of the designated clinic visit.
- Coagulation laboratory parameters include prothrombin time (PT) and activated partial thromboplastin time (aPTT). The INR must be obtained for subjects receiving anticoagulation therapy. Blood samples should be drawn and results reviewed within 72 hours of the designated clinic visit.
- Blood chemistry laboratory parameters include: albumin, total protein, uric acid, sodium, potassium, calcium, phosphorous, chloride, bicarbonate (or CO_2), BUN or urea, creatinine, lipase, amylase, magnesium, and glucose. Liver function tests include lactate dehydrogenase (LDH), serum ALT, serum AST, total and direct bilirubin, and alkaline phosphatase. Blood samples should be drawn and results reviewed within 72 hours of the designated clinic visit.
- Serum quantitative Immunoglobulins (includes IgA, IgM, and IgG).

For Cycle 1 Day 1 (predose), hematology, liver function tests, blood chemistry, or coagulation evaluations may be performed within 7 days prior to study treatment (Cycle 1, Day 1). If these Screening evaluations are performed within 7 days of Cycle 1, Day 1, these Screening results can be used in place of the Cycle 1, Day 1 results.

Clinically significant laboratory findings, including but not limited to those findings resulting in a drug interruption/reduction/discontinuation or medical intervention should be reported as an AE (see protocol Section 8.1.1 for definition of an AE). In the presence of Grade 3 or higher cytopenias, more frequent monitoring per institutional guidelines is recommended.

6.3.3 Study Drug Administration, Criteria for Treatment

6.3.3.1 Duvelisib

Beginning on Cycle 1 Day 1, duvelisib 25 mg BID will be administered daily in an initial 21-day cycle BID, followed by 28-day cycles. Subjects are required to receive pneumocystis prophylaxis concomitant with treatment with study drug per institutional guidelines. Subjects who are found to be intolerant of pneumocystis prophylaxis may continue with study treatment at the discretion of the Investigator. Herpes (HSV/VSV) or CMV prophylaxis concomitant with study drug is also recommended (Section 6.3.5).

For a twice daily schedule, doses should be taken every 12 hours within ±2 hours of the scheduled dose. If reduced to a once daily dosing, doses must be taken once every 24 hours within ±4 hours of the scheduled dose. Missed doses outside this window or vomited doses should not be taken or repeated. Duvelisib doses will be dispensed to the subject so that the subject has enough duvelisib doses until at least the next dispensation visit, taking into

account the dispensation visit window. Additional details on study drug dosage and administration are described in Section 7.2.1 and 7.2.2, respectively.

An attempt should be made to enable each dose to be taken at approximately the same time of day.

For dose modifications due to adverse events and laboratory abnormalities, see Section 4.2.1.

6.3.3.2 Ofatumumab

Ofatumumab will be administered in accordance with the ARZERRA® Prescribing Information. Each subject randomized to ofatumumab will receive no more than 12 doses as described in Table 4. Refer to Section 6.3.5 for recommended prophylactic treatment.

If the dose of ofatumumab is reduced, all reductions should be made per Table 10 (based on Prescribing Information). Additional details on study drug dosage and administration are described in Section 7.2.1 and 7.2.2, respectively.

The date, time, and quantity of each infusion will be recorded in the source documents.

For dose modifications due to adverse events and laboratory abnormalities, see Section 4.2.2 and the ARZERRA® package insert.

6.3.4 Adverse Events

For all subjects (including screen-failures), monitoring of AEs will be performed from the signing of the ICF. For randomized subjects, AEs will be collected on the AE eCRF from the signing of the ICF through 30 days after the final dose of either duvelisib or ofatumumab.

See Section 8.2 for a full description of the collection and reporting of AEs during this study.

6.3.5 Subject-reported Outcomes Assessment

The health outcomes assessment surveys are for the purpose of exploring the subject's own perceptions about his or her QoL. Every effort should be made to maintain an unbiased assessment. If the subject cannot complete the health outcomes assessments because of illiteracy or other documented reason, a proxy (such as a caregiver) cannot complete the questionnaires, as these questionnaires are intended to be subject-reported measures only.

The Functional Assessment of Cancer Therapy (FACT) is a modular approach to assess patient health status using a 'core' set of questions (FACT-G), as well as a cancer site specific module. The FACIT-Fatigue is a 13-item questionnaire derived from the FACT-G designed to assess patient concerns relating to the symptoms of fatigue.

The EuroQol-5D is a standardized instrument that provides a simple descriptive profile and a single index value for health status, and patient preference or utility for a health state. It comprises 5 items, covering the domains of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each of these domains is rated on 3 levels, higher levels indicating greater difficulty.

6.3.6 Concomitant Medication and Therapies

At every clinic visit, assessment of concomitant medications and procedures will occur. At screening, concomitant / previous medications will be assessed and includes all medications/procedures that have occurred within the previous 30 days.

For all subjects during treatment

- *Antimicrobial prophylaxis:*

Infection is a recognized complication in patients with relapsed/refractory CLL leading to many treatment centers to employ antimicrobial prophylaxis. Based on the duvelisib clinical experience to date and the ofatumumab product label (ARZERRA®) the following are required or recommended:

  - Pneumocystis infections have been reported in clinical studies with duvelisib and ofatumumab, therefore subjects are required to receive pneumocystis prophylaxis concomitant with treatment with study drug. Please follow institutional guidelines. Subjects who are found to be intolerant of pneumocystis prophylaxis may continue with study treatment at the discretion of the Investigator.
  - Herpes simplex (HSV) and herpes zoster (VZV) infections have been observed with duvelisib and ofatumumab; therefore, subjects are recommended to receive herpes (HSV/VZV) prophylaxis concomitant treatment per investigator discretion. Please follow institutional guidelines.
  - For subjects with history of CMV infection that required treatment, prophylactic treatment per institutional guidelines is recommended.
    - Subjects with history of CMV or EBV infection and/or who enter the study while receiving antiviral prophylaxis should be monitored for reactivation via serology or viral load detection per institutional guidelines while on study treatment
  - Other antimicrobial prophylaxis based on the individual subject's medical history may be considered if no contraindications based on drug-drug interactions (DDI). See below.

- *Transfusion support (prophylaxis or supportive care):*

At study entry or during any time on treatment, blood cell transfusions (packed red blood cells or platelets) to maintain a subject's hemoglobin ≥8.0 mg/dL or platelets ≥10,000 per μL is recommended. Transfusions may be used at any time as clinically indicated.

For subjects treated with ofatumumab

- *Premedication:*

Premedicate 30 minutes to 2 hours prior to each dose with oral acetaminophen 1,000 mg (or equivalent), oral or intravenous antihistamine (diphenhydramine 50 mg or equivalent), and intravenous corticosteroid (prednisolone 100 mg or equivalent). Do not reduce corticosteroid dose for Doses 1, 2, and 9. Corticosteroid dose may be reduced as follows for Doses 3 through 8 and 10 through 12:

- Doses 3 through 8: Gradually reduce corticosteroid dose with successive infusions if a Grade 3 or greater infusion reaction did not occur with the preceding dose.
- Doses 10 through 12: Administer prednisolone 50 mg to 100 mg or equivalent if a Grade 3 or greater infusion reaction did not occur with Dose 9.

6.3.6.1 Prohibited: Use of Vaccines

For all subjects, the use of live or live attenuated vaccines is prohibited during the treatment with either study drug.

The use of inactivated (or killed) vaccines is allowed during the study, however subjects and their physicians should be aware that the effectiveness of any vaccine administered concomitantly with duvelisib and ofatumumab may be diminished. The ability to generate an immune response to any vaccine following the administration of either duvelisib or ofatumumab has not been studied.

6.3.6.2 Prohibited: Immunosuppressants

Subjects are not to receive ongoing treatment with chronic immunosuppressants (eg, cyclosporine) or systemic steroids for >1 week at doses > the equivalent of 20 mg prednisone QD.

6.3.6.3 Prohibited: PI3K Inhibitors or BTK Inhibitors

Subjects are not to have received any prior exposure to any PI3K or BTK inhibitor prior to study entry.

6.3.6.4 Prohibited: Other Anticancer Therapy or Investigational Agents

During the Clinical Assessment Period (through Cycle 19 Day 1 for both treatment arms), subjects are not to receive any additional anticancer therapy or other investigational agents (including BTK inhibitors and other PI3K inhibitors) not outlined in the protocol during the study.

6.3.6.5 Prohibited: (Duvelisib Subjects Only)

- *Medications or Food that Inhibit or Induce CYP3A4:*

In vitro data indicate that oxidative metabolism may play an important role in the elimination of duvelisib, with CYP3A4 identified as a primary contributor to drug metabolism. Data from a drug-drug interaction study with ketoconazole (a potent CYP3A inhibitor) indicate exposure to duvelisib increased approximately 4-fold in the presence of ketoconazole. Similarly, exposure to duvelisib was reduced approximately 80% when coadministered with rifampin, a recognized CYP3A inducer. Based on these data, **the concomitant use of drugs or foods that are strong inhibitors or inducers of CYP3A are not allowed during study treatment with duvelisib.**

Appendix 1 provides a list of medications known to be strong inhibitors or inducers of CYP3A. Please note that Appendix 1 is not a comprehensive list of all medications which may modulate CYP3A activity.

Subjects should avoid eating grapefruits or grapefruit-containing products. In addition, subjects should avoid herbal supplements including, but not limited to, St. John's wort throughout the study as this is known to be a strong inducer of CYP3A.

The Sponsor should be contacted with any questions regarding concomitant use of medications that are thought to modulate CYP3A activity. The concomitant use of moderate or weak inhibitors may be allowed in selected circumstances after consultation with the medical monitor.

6.3.6.6 Use with Caution (Duvelisib Subjects Only):

- *Medications that are Substrates of CYP3A or CYP2C8*

In vitro studies in human liver microsomes have demonstrated duvelisib is an inhibitor of cytochrome P450 (CYP) enzymes CYP2C8 and CYP3A4. Coadministration of duvelisib with midazolam, a probe CYP3A substrate, resulted in an approximate 4-fold increase in midazolam systemic exposure (AUC). Systemic exposure to other medications that are substrates for CYP3A4 may be increased in subjects receiving duvelisib. The in vivo effect of duvelisib on the exposure of CYP2C8 substrates is not known. **Caution should be used if duvelisib is used concomitantly with drugs or foods that are substrates of CYP2C8 and CYP3A4, particularly those with a narrow therapeutic index**.

Appendix 2 provides a list of medications known to be substrates of CYP3A or CYP2C8. Please note that Appendix 2 is not a comprehensive list of all medications which may be substrates of CYP3A or CYP2C8. The Sponsor should be contacted with any questions regarding concomitant use of medications that are CYP3A or CYP2C8 substrates.

- *Medications that are Substrates or Inhibitors of P-glycoprotein*

In vitro data indicate that duvelisib is a substrate for P-glycoprotein (P-gp). Concomitant medications that inhibit P-gp may cause the steady state concentration of duvelisib to be reached more quickly than usual. Additionally, in vitro studies demonstrated that duvelisib has the potential to inhibit the active transport of other P-gp substrates. **These medications may be used as medically indicated but with caution.**

Appendix 3 provides a list of medications that are substrates or inhibitors of P-gp. Please note that Appendix 3 is not a comprehensive list of all medications which may be substrates of P-gp or may modulate P-gp activity. The Sponsor should be contacted with any questions regarding concomitant use of medications that are thought to modulate P-gp activity.

6.3.6.7 Antiemetics and Antidiarrheals

Antiemetic and antidiarrheal treatments may be used at the discretion of the Investigator and in accordance with the American Society of Clinical Oncology (ASCO) guidelines. The choice of antiemetic or antidiarrheal treatment, if required, will be made at the discretion of the Investigator. Subjects on stable doses of antiemetics and/or antidiarrheals to treat baseline conditions may continue on these therapies at the baseline dose.

6.3.6.8 Hematopoietic Growth Factors

Hematopoietic growth factors may be used at the discretion of the Investigator and in accordance with the ASCO guidelines. Prophylactic use of growth factors such as granulocyte-colony stimulating factor (G-CSF) and granulocyte macrophage-colony stimulating factor (GM-CSF) may be implemented if clinically indicated, in accordance with local guidelines and medical practice (eg, if a subject has Grade 4 neutropenia for ≥7 days, Grade 4 febrile neutropenia, or according to the NCCN practice guidelines for myeloid factors). Subjects on a stable dose of erythropoietin to treat baseline anemia may continue on this therapy at this dose.

6.3.6.9 Other Concomitant Therapies

Any other medication which is considered necessary for the subject's welfare, and which is not expected to interfere with the evaluation of duvelisib or ofatumumab, may be given at the discretion of the Investigator.

6.3.6.10 Photosafety

The effect of this medication on the skin, especially when in direct sunlight or with artificial ultraviolet (UV) light (eg, tanning booths) is not known. As a general precaution, subjects should be advised to use appropriate protective measures to minimize exposure to direct sunlight or UV light sources during the treatment period and for at least 30 days after the last dose of duvelisib.

6.3.7 Pharmacokinetic Sampling

Peripheral blood will be collected from all subjects at qualified sites who are randomized to the duvelisib study treatment arm to characterize the PK profile of duvelisib and, if applicable, its metabolites. Samples will be collected at the following time points, as describe in Table 3.

- Cycle 2 Day 1: ≤ 2 hours predose, 0.5 to 2 hours postdose, and 3 to 5 hours postdose. The morning dose of study medication will be administered in the clinic
- Cycle 3 Day 1: anytime during the visit
- Cycle 7 Day 1: anytime during the visit

The exact date and time of the PK blood draws will be recorded, along with the date and time of the previous 2 doses of study medication. Additionally, collection of a PK sample is requested when feasible at the time of drug interruption/hold for an AE. If a subject permanently discontinues study treatment prior to Cycle 7, Day 1, PK blood samples no longer need to be collected.

Subjects who have an unusual safety or efficacy event (ie, an AE different in type and severity from that which is expected in the setting of duvelisib use or an exceptional response to treatment) may be asked to have additional PK samples collected. These blood draws for pharmacokinetic analysis will only be performed after discussion between the Medical Monitor and the Principal Investigator.

6.3.8 Biomarker Assessments

The following biomarker samples will be collected throughout the study (time points described in Table 2 and Table 4) from subjects randomized to duvelisib or ofatumumab:

- Serum
- Blood
- Buccal swab (if optional ICF is signed)
- Archival tumor tissue (if available at any time during the study – not required for enrollment)
- Bone marrow biopsies and/or aspirates (if obtained as part of clinical disease response assessments and tissue is remaining after clinical analysis, including pathology reports)

The biomarker samples may be analyzed at a central laboratory, the Sponsor, or a specialized laboratory vendor for the various markers outlined below:

- Serum for pharmacodynamic and predictive biomarkers such as chemokines, cytokines, and matrix metalloproteinases; serum may also be utilized to examine levels of known serum drug binding proteins.
- Blood, archival tissue, and/or bone marrow biopsies for DNA and RNA pharmacodynamic and predictive biomarkers (includes genome-wide assessment of somatic mutations, DNA copy number changes, and gene expression changes to study CLL signaling pathways, disease pathogenesis, and response/resistance to duvelisib treatment)
- Blood for assessment of del(17p), del(11q), del(13q), trisomy 12, and possibly other common leukemic cytogenetic abnormalities
- Blood for tumor immunoglobulin heavy chain variable (IGHV) somatic hypermutation status
- Blood for Immunophenotyping evaluations (eg, B/T-lymphocyte panel and CLL markers such as CD38 and ZAP70)
- Tissue (archival, bone marrow biopsies and aspirates) for immunohistochemistry of PI3K pathway components such as PTEN and pS6
- Buccal swab for germline DNA for pharmacogenomics and confirmation of mutations as somatic. (Optional with ICF)

See the IPI 145-07 Laboratory Manual for biomarker sample handling procedures.

6.3.9 Disease Response Assessments

Response and progression will be measured by the following assessments as indicated in Table 5:

– Bone marrow aspirate and/or bone marrow biopsy

- CT scans of chest, abdomen and pelvis (See Section 6.3.9.1)
- CBC and differential count
- Blood sample for assessment of MRD in subjects with documented CR or CRi
- Disease-Related symptoms
    - Focused Physical exam
    - ECOG performance status as a measure of fatigue
    - Disease-related constitutional symptoms (fever [ie, temperature >38°C/100.5°F] without evidence of infection, weight loss, and drenching night sweats without evidence of infection)

These evaluations will be done until PD is documented or other anticancer therapy is initiated (at which point the subject will enter the Survival Follow-up Period), or death occurs.

6.3.9.1 CT Scans

CT scans (contrast-enhanced preferred) of the chest, abdomen, and pelvis are required for all subjects to document measureable disease at baseline and will be performed as outlined in Table 5. Other scans may be performed (eg, head CT) if clinically indicated or if the area is a site of known disease. MRI may be substituted if clinically indicated, but the modality chosen to evaluate each individual subject should be the same throughout the duration of the study.

If the subject is discontinued early from study treatment (eg, before Day 1 Cycle 7 of ofatumumab study treatment or before Day 1 Cycle 19 of duvelisib study treatment) and a previous assessment has not been performed within 30 days, CT scans will be also performed at the ETT and the subject will continue to undergo assessments as outlined in Disease Follow-up in Table 5.

6.3.9.2 Investigator assessment of response and progression status

Assessment of response and progression status will be evaluated by the investigator for clinical decision-making using criteria derived from the IWCLL response criteria for subjects with CLL (Table 11) and IWG response criteria for subjects with SLL (Table 12).

The CLL/SLL response definitions for this protocol (provided below) include modifications to the IWCLL/IWG response criteria related to PD based on the understanding that agents like duvelisib, which target the B-cell receptor signaling pathway, can mobilize CLL/SLL cells from tissues into the peripheral blood [23] interfering with their homing.[24, 25] Specifically, two modifications have been made: (1) an additional category has been added to allow for PR with lymphocytosis (PRwL); and (2) the criteria for PD do not include PD based only on worsening lymphocytosis or isolated increase in target lesion(s) in the absence of other objective evidence of disease progression.

Table 11: CLL Response Criteria (modified from IWCLL) [1, 22]

Variable	Complete Response (CR)	Partial Response (PR)	Progressive Disease (PD)
GROUP A			
Lymphadenopathy (CT scan)	None > 1.5 cm	Decrease ≥ 50%	New lesions (> 1.5 cm) or increase ≥ 50% in diameter of any single lesion or the SPD [a]
Hepatomegaly (CT scan) [b]	None	Decrease ≥ 50% or normal	Increase ≥ 50% of previously noted or *de novo* appearance [a]
Splenomegaly (CT scan) [b]	None	Decrease ≥ 50% or normal	Increase ≥ 50% of previously noted or *de novo* appearance [a]
Blood lymphocytes	< 4000/µL	Decrease ≥ 50% from baseline or < 4,000/µL	Increase ≥ 50% over baseline or nadir (whichever is lowest) and ≥ 5,000 per µL
Marrow [c]	Normocellular, < 30% lymphocytes, no B-lymphoid nodules. Hypocellular defines CRi in CLL subjects only	*If performed:* 50% reduction in marrow infiltrate, or presence of B-lymphoid nodules	
GROUP B			
Platelet count without transfusions or growth factors	> 100,000/µL	> 100,000/µL or increase ≥ 50% over baseline	Decrease of ≥ 50% from baseline secondary to CLL
Hemoglobin without transfusions or growth factors	> 11.0 g/dL	> 11.0 g/dL or increase ≥ 50% over baseline	Decrease of > 2 g/dL from baseline secondary to CLL
Neutrophils without growth factors	> 1500/µL	> 1500/µL or ≥ 50% improvement over baseline	

Note: **Group A** criteria define tumor load; **Group B** criteria define the function of the hematopoietic system (or marrow)
SPD = Sum of the products of multiple lymph nodes (as evaluated by CT scans). Use of Positron Emission Tomography (PET) imaging is not indicated in CLL/SLL.

a. Disease progression confirmed by CT scan is required in the setting of PE findings without other Group A criteria or worsening disease-related constitutional symptoms/cytopenia(s).
b. PE is the minimum requirement to meet criteria for PR or SD; CT scan is required for determination of response to confirm CR/CRi (CLL subjects only) or if PE is inconclusive.
c. Bone marrow parameters may be irrelevant in the setting of some response categories.

Complete Response/Remission (CR): all of the criteria have been met, and subjects have no disease-related constitutional symptoms

Partial Response/Remission (PR): at least two of Group A criteria plus one Group B criteria have to be met. For subjects with lymphadenopathy at baseline as the only abnormal Group A criteria (eg. no organomegaly, blood lymphocyte count < 4,000/µL, and negative bone marrow), all Group A criteria plus one Group B criteria have to be met.

PR with Lymphocytosis (PRwL): For subjects with lymphadenopathy at baseline as the only abnormal **Group A** criteria (eg. no organomegaly, blood lymphocyte count < 4,000/µL, and negative bone marrow) who have a ≥ 50% reduction in lymphadenopathy plus one **Group B** criteria but with isolated progressive lymphocytosis (blood lymphocyte count ≥ 4,000/µL).

Stable Disease (SD): absence of PD and failure to achieve at least a PR/PRwL

Progressive Disease (PD): appearance of any new lesions or at least one of the **Group A** or **Group B** criteria met with the following exceptions:

- Due to the pharmacologic property of duvelisib to mobilize CLL cells from tissues into the peripheral blood, isolated lymphocytosis should not be considered progressive disease in the setting of other indications of response such as reduced lymph node size or organomegaly or improvement in hemoglobin/platelets[22]
- If a new lesion or isolated increase in target lesion(s) may be attributed to another cause (eg, infection), these findings alone should not be considered to determine progressive disease, especially when observed in the setting of reduced lymph node size or organomegaly, or improvement in hemoglobin/platelets. Radiological persistence of these findings for >4 weeks is likely to indicate disease progression (CT scan confirmation required)

Table 12: SLL Response Criteria (modified from IWG) [2, 22]

Response	Lymph Nodes [a]	Spleen/Liver	Blood Lymphocytes	Bone Marrow [b]
Complete Response (CR)	Regression to normal size	Normal size; nodules not present	< 4000/µL	If infiltrate present at screening, infiltrate cleared on repeat biopsy
Partial Response (PR) [c]	Decrease ≥ 50% in SPD of up to 6 largest masses; no increase in size of other nodes	Decrease ≥ 50% in SPD of nodules (or greatest transverse diameter for single lesion); no increase in size of liver or spleen	Decrease ≥ 50% from baseline or < 4,000/µL	Irrelevant if positive prior to therapy; cell type should be specified
Stable Disease (SD)	Failure to achieve CR/PR criteria or progressive disease			
Progressive Disease (PD) [d,e,f]	New lesions (> 1.5 cm) or increase ≥ 50% in the SPD from nadir of more than 1 node, or ≥ 50% increase in the longest diameter of a node > 1 cm in short axis	> 50% increase from nadir in the SPD of any previous nodules; unequivocal increase in liver/spleen size or de novo appearance of nodules	Increase ≥ 50% over baseline or nadir (whichever is lowest) and ≥ 5,000/µL	

a. Evaluated by CT (or MRI) with sum of the products (SPD) of multiple (up to 6) lymph nodes determined. Use of Positron Emission Tomography (PET) imaging is not indicated in CLL/SLL.
b. Subjects with CR by CT (or MRI) assessment of lymph nodes, liver/spleen, and peripheral blood without a negative bone marrow result (at baseline or at time of response assessment) will be considered a PR.
c. PRwL: subjects who have a ≥ 50% reduction in lymphadenopathy, no organomegaly and a negative bone marrow (at baseline or at time of response assessment) with isolated progressive lymphocytosis (blood lymphocytes ≥ 4,000/µL).
d. PD must be confirmed by CT (or MRI) scan
e. Due to the pharmacologic property of duvelisib to mobilize SLL cells from tissues into the peripheral blood, isolated lymphocytosis should not be considered progressive disease in the setting of other indications of response such as reduced lymph node size or organomegaly or improvement in hemoglobin/platelets[22]
f. If a new lesion or isolated increase in target lesion(s) may be attributed to another cause (eg, infection), these findings alone should not be considered to determine progressive disease, especially when observed in the setting of reduced lymph node size or organomegaly, or improvement in hemoglobin/platelets. Radiological persistence of these findings for >4 weeks is likely to indicate disease progression (CT scan confirmation is required)

At each scheduled disease response assessment, the investigator will be asked to provide a clinical response based on the parameters provided in Table 11 and Table 12 and assessment of disease-related constitutional symptoms.

6.3.9.3 Independent assessment of response and progression status

Disease progression and response for the primary and secondary endpoints will be evaluated by an independent panel of radiologists and oncologists using criteria derived from the IWCLL criteria (Table 11) for CLL subjects and the revised IWG criteria (Table 12) for SLL subjects. All disease response assessment data, including peripheral blood, physical exam, disease-related constitutional symptoms, and CT scans will be utilized in determining response and disease progression. Central review of imaging will be utilized to confirm investigator-assessed PD at the time of PD determination up to the time of the final analysis.

6.4 EARLY TREATMENT TERMINATION OF DUVELISIB OR OFATUMUMAB

If at any time during treatment with study drug (duvelisib or ofatumumab) a subject has an AE resulting in permanent discontinuation of study treatment, PD, initiates new anticancer therapy, or withdraws consent, then the assessments outlined below will be performed within 7 days of study treatment discontinuation or the decision to discontinue study treatment. ETT assessments include:

<u>If performed within previous 14 days, do not need to be repeated:</u>

- Urine or serum pregnancy tests will be collected from all women of childbearing potential (WCBP)
- Concomitant Medications and Procedures collection
- AE and SAE assessment
- Blood chemistry
- Liver function tests
- Biomarker assessments

<u>If performed within previous 30 days, do not need to be repeated:</u>

- Disease response assessments:
    - Focused physical exam /constitutional symptoms
    - Bone marrow biopsy/aspirate (if indicated)
    - Hematology
    - Blood sample for MRD
    - ECOG
    - CT scan
    - Quality of life (QoL) EQ-5D and FACIT-F

6.5 POST-TREATMENT PERIOD

6.5.1 Safety Follow-up Visit (30 Days Post-Treatment)

6.5.1.1 Duvelisib

For subjects randomized to duvelisib, a visit should occur 30+7 days after discontinuation or last dose of duvelisib as outlined in Table 2. If possible, this visit should be conducted prior to initiation of any subsequent therapy. This visit may be a conducted as a phone screen as long as the study subject does not require laboratory and/or other assessments related to any new or ongoing AEs, in which case a clinical visit will be required. Assessments should include:

- AEs/SAEs collection
- Concomitant medications and procedures collection

Following the last dose of duvelisib, subjects will continue follow-up as described in Table 2 and Table 5.

6.5.1.2 Ofatumumab

For subjects randomized to ofatumumab, a visit should occur 30+7 days after discontinuation or last administration of ofatumumab. If possible, this visit should be conducted prior to initiation of any subsequent therapy. This visit may be a conducted as a phone screen as long as the study subject does not require laboratory and/or other assessments related to any new or ongoing AEs, in which case a clinical visit will be required. Assessments include:

- AEs/SAEs collection
- Concomitant medications

Following the last dose of ofatumumab, subjects will continue follow-up as described in Table 4 and Table 5.

6.5.2 Clinical Assessment Period

6.5.2.1 Duvelisib

Subjects who come off treatment with duvelisib prior to Cycle 19 Day 1 for reasons other than PD will continue clinic visits every other month through Cycle 19 Day 1. During this period, subjects will not receive any additional anticancer therapy (including duvelisib).

Assessments are outlined in Table 2 and Table 5.

Note: If a subject experiences PD within this period, then that subject may be offered ofatumumab treatment as part of another study (Study IPI-145-12) to evaluate the safety and efficacy of ofatumumab therapy after duvelisib therapy.

All subjects will be followed every 6 months for survival for up to 6 years from randomization.

6.5.2.2 Ofatumumab

Subjects who complete treatment with ofatumumab (Cycle 7) or come off for reasons other than PD will enter a Clinical Assessment Period through Cycle 19 Day 1. During this period, clinical visits will occur every other (odd) month and subjects will not receive any additional anticancer therapy (including ofatumumab).

Assessments in the Clinical Assessment Period are outlined in Table 4 and Table 5.

Note: If a subject experiences PD within this period, then that subject may be offered duvelisib treatment as part of another study to evaluate the safety and efficacy of duvelisib therapy after ofatumumab therapy.

All subjects will be followed every 6 months for survival for up to 6 years from randomization.

6.5.3 Follow-up

6.5.3.1 Disease Follow-up

Subjects who discontinue treatment with duvelisib or ofatumumab early (ie, ETT) due to reasons other than PD will continue to undergo disease response assessments up until Cycle 19 Day 1 (ie, Cycles 5, 7, 11, 15 and 19) or until disease progression, subject withdrawal, or initiation of additional anticancer therapy. After Cycle 19 Day 1, all subjects without progressive disease will enter Disease Follow-up. CBC and differential count will be performed approximately 3 months after the last assessment, and every 3 months thereafter until disease progression, subject withdrawal, or initiation of additional anticancer therapy. All other disease assessments should occur approximately 6 months after the Cycle 19 Day 1 Disease Response Assessment, and every 6 months thereafter until disease progression, subject withdrawal, or initiation of additional anticancer therapy. The following assessments should be performed as outlined in Table 5.

Every 3 months

- CBC and differential count

Every 6 months

- CT scans of chest, abdomen and pelvis
- Bone marrow biopsy and/or bone marrow aspiration (when clinically indicated)
- Blood sample for assessment for minimum residual disease (MRD) in subjects with documented CR or CRi
- Focused physical examination, ECOG performance status, and disease-related constitutional symptoms

6.5.3.2 Survival Follow-up

For all subjects, survival follow-up will occur every 6 months for up to 6 years after randomization or until death. The first follow-up should occur 6 months (±4 weeks) from documentation of PD or treatment discontinuation. For both duvelisib and ofatumumab-treated subjects, information on initiation of other anticancer therapy will also be collected at

each survival follow-up; these assessments may be collected through a telephone interview. Please see Table 5 for more details on the follow-up assessments.

6.6 MISSED VISITS

If a subject misses a scheduled visit, the subject will continue on the protocol and attend the next scheduled visit. If a subject misses 2 scheduled visits, then the subject's continued participation in the study must be re-evaluated (see Section 4.3 and Section 4.4).

7 INVESTIGATIONAL MEDICINAL PRODUCT

7.1 DESCRIPTION OF INVESTIGATIONAL MEDICINAL PRODUCT

Duvelisib drug substance is a white to off-white crystalline powder. The duvelisib drug product is formulated with excipients (Diluent, glidant, disintegrant, and lubricant) that are listed in Food and Drug Administration's (FDA) Inactive Ingredients Database for approved drug products and/or Generally Regarded as Safe (GRAS) in two different capsule strengths (5 mg and 25 mg) for oral delivery.

7.2 DOSAGE AND ADMINISTRATION

7.2.1 Dosage

7.2.1.1 Duvelisib

Duvelisib will be administered daily in 28-day cycles (with the exception of Cycle 1 which is 21 days). Duvelisib is administered orally as a capsule formulation and will be supplied by the Sponsor. Duvelisib will be administered as a fixed dose in mg/day and should be administered using the minimal number of capsules necessary.

For an individual subject, dose reductions and discontinuations may be based on the clinical judgment of the Investigator with notification to the Medical Monitor/Sponsor (see Section 4.2.1.1).

7.2.1.2 Ofatumumab

Subjects randomized to ofatumumab will receive treatment consistent with the approved product labeling: an initial IV dose of 300 mg ofatumumab on Day 1 followed by seven weekly doses of 2000 mg. Thereafter, subjects will receive 2000 mg ofatumumab once every month for four months through Cycle 7 or until disease progression or unacceptable toxicity (whichever comes first), as outlined in the schedule of assessments. Administration of ofatumumab will not exceed the 12 doses (within 7 cycles) as described in the prescribing information. For an individual subject, dose reductions (see Table 10) and discontinuations may be based on the clinical judgment of the Investigator with notification to the Medical Monitor/Sponsor.

7.2.2 Administration

7.2.2.1 Duvelisib

Duvelisib should be taken daily BID (every 12 ±2 hours) in 28-day cycles. Cycle 1 is a 21-day cycle.

On Cycle 2 Day 1, the morning dose of study medication will be administered in the clinic to accommodate PK sample collection. An attempt should be made to enable each dose to be

taken at approximately the same time of day. Missed doses outside the windows defined above or vomited doses should not be taken or repeated.

Duvelisib doses will be dispensed to the subject so that the subject has enough duvelisib doses until at least the next dispensation visit, taking into account the dispensation visit window.

Duvelisib capsules should be swallowed whole with a glass of water (approximately 8 ounces or 240 mL) at approximately the same time(s) each day. Subjects must avoid grapefruit and grapefruit juice.

Duvelisib may be administered without regard to meals.

7.2.2.2 Ofatumumab

Ofatumumab will be administered via infusion, as described in the ofatumumab (ARZERRA®) package insert.[10, 11] Please refer to the country-specific package insert for more details.

7.3 PACKAGING AND LABELING

Duvelisib will be supplied to the clinical trial site as open-label medication. Please refer to the IPI-145-07 Pharmacy Manual for details regarding packaging and labeling of Investigational Product.

7.4 STORAGE AND HANDLING

7.4.1 Duvelisib

Duvelisib must be stored at room temperature (15 to 30°C).

Caution is required when handling duvelisib. Pharmacists should follow standard procedures for the handling of investigational drugs, including avoidance of eye or skin contact with the drug product. If there is exposure to the drug product, provide treatment as necessary for physical exposure (skin washing) or inhalation (move to fresh air) and seek medical advice as necessary.

When duvelisib capsules are distributed for self-administration, they should only be handled by the study subject. After handling capsules, the subject should wash their hands thoroughly. If someone who is not enrolled in a clinical trial involving duvelisib swallows a capsule or inhales drug powder from a broken capsule of duvelisib, they should contact the relevant Principal Investigator to determine whether safety monitoring is necessary. Capsules should always be stored in the container provided to the study subject. Refer to Section 8.2.3.2 for details on reporting any exposure.

7.4.2 Ofatumumab

Ofatumumab (ARZERRA®) is supplied as a sterile, clear to opalescent, colorless, preservative-free liquid concentrate (20 mg/mL) for dilution and intravenous administration provided in single-use glass vials with a latex-free rubber stopper and an aluminum over seal.

Each vial contains either 100 mg ofatumumab in 5 mL of solution or 1,000 mg ofatumumab in 50 mL of solution.

Store ARZERRA® refrigerated between 2° to 8°C (36° to 46°F). Do not freeze. Vials should be protected from light.

See ARZERRA® package insert for more details.[10, 11]

7.5 INVESTIGATIONAL MEDICINAL PRODUCT ACCOUNTABILITY

7.5.1 Duvelisib

The Investigator or designee is responsible for taking an inventory of each shipment of duvelisib investigational supplies received, and comparing it with the accompanying drug accountability form.

All unused duvelisib will be retained at the site. After full drug accountability and reconciliation, the Investigator will dispose of the study drug at the clinical trial site according to site procedures, or at the Sponsor's request will return all duvelisib to the Sponsor, or its designee. If any study drug is lost or damaged, the disposition of the study drug should be documented.

Subjects should be instructed to bring all unused duvelisib to each study visit. The study site should count all capsules that the subject returns, and should take account for taken doses, missed doses, doses reduced due to missing or lost capsules, etc., before dispensing new study drug to the subject. Any subject who does not take the prescribed dose should be requested to return the remaining drug to the clinical trial site for accountability.

7.5.2 Ofatumumab

For Sponsor supplied Ofatumumab, the Investigator or designee is responsible for taking an inventory of each shipment received, and comparing it with the accompanying drug order form.

All unused Ofatumumab will be retained at the site. After full drug accountability and reconciliation, the Investigator will dispose of the study drug at the clinical trial site according to site procedures, or at the Sponsor's request will return all ofatumumab to the Sponsor, or its designee. If any study drug is lost or damaged, the disposition of the study drug should be documented.

7.6 ASSIGNMENT TO TREATMENT

Once a subject has met all entry criteria, the IRT will be used to generate a distinct subject identifier. Eligible subjects will be randomized within 7 days prior to receipt of first dose of study drug. If a subject discontinues from the study, the subject identifier will not be reused and the subject will not be allowed to re-enter the study.

Eligible subjects will be randomized via IRT in a 1:1 ratio to one of two treatment arms:

- Arm 1: Duvelisib 25 mg BID

- Arm 2: Ofatumumab

In order to ensure subject balance between treatment groups, study subjects will be stratified by the following:

- High risk cytogenetics (presence vs absence of del[17p])
- Refractory/early relapse to purine analog based treatment (progression <12 months after fludarabine/pentostatin: yes vs no)
- Grade 4 cytopenia(s) (presence vs absence of neutropenia or thrombocytopenia at baseline)

Randomization is to occur within 7 days of first dose after all screening assessments have been completed.

7.7 ASSESSMENT OF COMPLIANCE

7.7.1 Duvelisib

At each applicable visit, doses will be dispensed to the subject so that the subject will have enough doses until the next applicable visit, taking into account the window for that subsequent visit. Compliance for doses taken outside of the clinic will be assessed by a count of the capsules returned to the study trial site by the subject and review with the subject.

7.7.2 Ofatumumab

Ofatumumab will be administered via infusion as described in the package insert by the test article administrator.

7.8 TREATMENT OF OVERDOSE

In the case of overdose, clinic staff should be notified immediately and supportive care is to be given as indicated. Subjects should be informed to contact their doctor immediately if they have taken an overdose and should stop taking duvelisib.

No data is available regarding overdosage with ofatumumab. Supportive care is to be given as indicated in the event of an ofatumumab overdosage.

8 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.1 DEFINITIONS

The definitions of AEs and SAEs are provided below.

8.1.1 Adverse Event

An AE is any untoward medical occurrence associated with the use of a drug or with study participation, regardless of the relationship of the occurrence to study drug or protocol. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the drug, whether or not considered related to the drug. An AE can arise from any use of the drug, and from any route of administration, formulation or dose, including an overdose.

Medical conditions present prior to the initiation of the study, as well as ongoing changes in laboratory values/conditions that are being treated at baseline, will be captured as an AE if the condition worsens.

8.1.2 Adverse Reactions and Suspected Adverse Reactions

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. Suspected adverse reactions are any adverse events for which there is a reasonable possibility that the drug caused the adverse event. Adverse reactions also include medication errors and uses outside of what is foreseen in the protocol, which may include misuse, abuse, and overdose (intentional or unintentional) of the product.

8.1.3 Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF (as documented as medical history on the eCRF), or
  - Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience
- Results in persistent or significant disability / incapacity
- Results in congenital anomaly / birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered a serious adverse drug experience when, based upon

appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.2 PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

8.2.1 Eliciting and Recording Adverse Events

Subjects will be instructed to report all AEs and will be asked a general health status question at each study visit. All AEs occurring in randomized subjects will be recorded in the eCRF from the time of ICF until 30 days after the last dose of study treatment. An AE will be followed until it is either resolved, has returned to baseline, or is determined to be a stable or chronic condition. All SAEs occurring from the signing of ICF through 30 days post last study drug will be processed as outlined in Section 8.2.3.

At each required visit during the trial, all AEs that have occurred since the previous visit must be reviewed. The Investigator or appropriate designee must determine if the adverse event is serious or non-serious.

8.2.1.1 Relationship to Study Drug

The Investigator is required to provide an assessment of relationship of AEs and SAEs to study drug. A number of factors should be considered in making this assessment including: 1) the temporal relationship of the event to the administration of study drug; 2) whether an alternative etiology has been identified; and/or 3) biological plausibility. The following guidelines should be used by Investigators to assess the relationship of an AE to the administration of the study drug.

Relationship assessments that indicate the event is "Not Drug Related":

- None: The event is related to an etiology other than the study product administration (the alternative etiology must be documented in the study subject's medical record).
- Remote: The event is unlikely to be related to the study product and likely to be related to factors other than study product.

Relationship assessments that indicate the event is "Drug Related":

- Possible: There is an association between the event and the administration of study drug, and there is a plausible mechanism for the event to be related to the study product; but there may also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease.
- Probable: There is an association between the event and the administration of study drug, there is a plausible mechanism for the event to be related to the study product, and the event could not be reasonably explained by known characteristics of the subject's clinical status or an alternative etiology is not apparent.

- Definite: There is an association between the event and the administration of study drug, there is a plausible mechanism for the event to be related to the study product, and causes other than study drug have been ruled out and/or the event re-appeared on re-exposure to study drug.

8.2.1.2 Adverse event severity

The Grade of the AE will be assessed according to the NCI-CTCAE Version 4.03. Toxicities that are not specified in NCI-CTCAE Version 4.03 will be defined as follows:

- 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 activities 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: it is important to distinguish between SAEs and severe AEs. Severity is a measure of intensity, whereas seriousness is classified by the criteria based on the regulatory definitions as described in Section 8.2.1.2 above.

8.2.2 Specific Instructions for Recording Adverse Events on the eCRF

8.2.2.1 Diagnosis versus Signs and Symptoms

If a diagnosis is known at the time of reporting, this should be recorded in the eCRF and/or SAE Report Form, as applicable, rather than the individual signs and symptoms (eg, record only hepatitis rather than elevated transaminases, bilirubin, jaundice). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an SAE or AE on the eCRF (and SAE Report Form, if applicable). If a diagnosis is subsequently established, it should be reported as follow-up on the eCRF (and follow up SAE report, as applicable) and should replace the individual signs and/or symptoms as the event term on the eCRF (and SAE report form, if applicable), unless the signs/symptoms are clinically significant.

8.2.2.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (eg, clinical sequelae or a cascade of events) should be identified by their primary cause. For example, if severe vomiting is known to result in dehydration, it is sufficient to record only vomiting as the SAE or AE on the eCRF (and SAE Report Form, if applicable). However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent

events on the eCRF (and SAE Report Form, if applicable). For example, if severe vomiting leads to acute renal failure, both events should be recorded on the eCRF (SAE Report Form)

8.2.2.3 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between subject evaluation time points. Such events should only be recorded once on the AE eCRF (and SAE Report Form, if applicable). If a persistent AE changes in grade, it should be recorded as a new AE on the eCRF.

A recurrent AE is one that occurs and resolves between subject evaluation time points, and subsequently recurs. All recurrent AEs should be recorded on the eCRF (and SAE Report Form if applicable).

8.2.2.4 Abnormal Laboratory Values

If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE or SAE, and the associated laboratory value or vital sign should be considered additional information and collected on the relevant eCRF. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the eCRF (and SAE Report Form, if applicable). Abnormal laboratory values will be reported as an AE if the laboratory result:

- requires an adjustment in the trial drug(s) or discontinuation of treatment
- require additional testing or surgical intervention
- is associated with accompanying symptoms
- is considered to be an AE by the investigator

8.2.2.5 New Cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the serious criteria (see Section 8.1). New primary cancers are those that are not the primary reason for the administration of the trial treatment and have developed after the inclusion of the subject into the trial. They do not include metastases of the original cancer.

Progression of the disease under study (disease progression) is not an AE/SAE, unless fatal.

8.2.2.6 Medication Errors, Misuse and Abuse of Study Drug

Overdose, medication error, misuse and abuse are defined as follows:

- *Overdose*: refers to the administration of a quantity of study drug given per administration or cumulative, which is above the maximum dose according to the protocol. Clinical judgment should always be applied.
- *Medication error:* refers to an unintentional error in dispensing or administration of study drug not in accordance with the protocol.

- *Off-label use*: relates to situations where the study drug is intentionally used for medical purpose not in accordance with the protocol.
- *Misuse*: refers to situations where the study drug is intentionally and inappropriately used not in accordance with the protocol.
- *Abuse*: corresponds to the persistent or sporadic, intentional excessive use of the study drug, which is accompanied by harmful physical or psychological effects.
- *Occupational exposure*: refers to the exposure to the study drug as a result of one's professional or non-professional occupation.

Overdoses, medication errors, abuse or misuse will be collected as part of investigational medicinal product dosing information and/or as a protocol violation, as required.

Any AE associated with an overdose, medication error, misuse or abuse of study drug should be recorded on the AE eCRF with the diagnosis of the AE.

8.2.3 Reporting of Serious Adverse Events

8.2.3.1 Immediate Reporting of Serious Adverse Events by Investigator to Sponsor

All SAEs (including SAEs occurring in screen failure and randomized subjects) will be reported to the Sponsor or designee within 24 hours of the Investigator's first knowledge of the event, even if the experience does not appear to be related to duvelisib or ofatumumab, from the time of signing ICF through 30 days after the last dose of study drug.

Serious adverse events should be communicated on an SAE report form as follows:

- Email: rtpsafety@ppdi.com
- Hotline (Phone): 888-483-7729 (USA)
- Fax: 888-529-3580 (USA)
- For international numbers, please refer to the SAE Report Form and supporting documentation.

The initial SAE report must be as complete as possible, including details of the current illness and (serious) AE, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (eg, final diagnosis, an end date for the AE, or relevant laboratory values received after the report) must be documented on a follow-up SAE Report Form. All SAE follow-up information must be reported in the same timelines as initial information (ie, within 24 hours of the investigator's first knowledge of information).

At any time after completion of the AE reporting period (ie, 30 days post-treatment), if an Investigator becomes aware of an SAE that is suspected by the Investigator to be related to study drug, the event must be reported as described above.

8.2.3.2 Immediate Reporting of Medical Events of Interest

Reports or laboratory results of **AST or ALT > 3x ULN in combination with total bilirubin > 2x ULN are medical events of interest,** and therefore immediately reportable events, even if the events do not meet serious adverse event criteria.

Clinical findings of **Grade 3 or higher rash are medical events of interest**, and therefore immediately reportable events, even if the events do not meet serious adverse event criteria. Pre-existing skin conditions that recur would not meet this definition unless the recurrence is of a greater severity/frequency than previously experienced.

All medical events of interest will be reported to the Sponsor or designee within 24 hours of the Investigator's first knowledge of the event, even if the experience does not appear to be related to study drug. Medical Events of Interest should be communicated on the SAE / Medical Events of Interest (MEOI) report form, as described above for SAEs.

Any occupational exposure or exposure of an individual not enrolled in the study to the investigational medicinal product must be reported to the Sponsor or designee within 24 hours of the Investigator's first knowledge of the event, even if the exposure does not result in an adverse event. Unintentional exposures should be communicated on the SAE/MEOI report form, as described above for SAEs.

8.2.3.3 Reporting of Serious Adverse Events to the Institutional Review Board (IRBs)/ Ethics Committee

Verastem or designee shall notify the Investigator and/or the IRBs/ECs per institutional guidelines of potential serious risks from clinical trials or any other sources, including the following:

- Suspected adverse reaction that is both serious and unexpected.
- Any findings from other studies that suggest a significant risk in humans exposed to the drug.
- Any finding from animal or in vitro testing that suggest a significant risk to humans exposed to the drug, such as mutagenicity, teratogenicity, or carcinogenicity; or report of significant organ toxicity at or near the expected human exposure.

Verastem or designee shall notify Central Ethics Committees (CEC) of new serious, related, and unexpected AE(s) or significant risks to subjects, per country requirements.

The Investigator will notify Local Ethics Committees (LECs) of serious, related and unexpected AE(s) or significant risks to subjects, per local country requirements.

The Investigator must keep copies of all AE information on file, including correspondence with Verastem or Local Ethics Committees.

8.2.3.4 Reporting of Serious Adverse Events to Regulatory Authorities

Verastem or designee shall notify Regulatory Authorities of serious, unexpected adverse reactions or other adverse events, per local requirements. Expectedness will be determined

using the current duvelisib Investigator Brochure and the ofatumumab United States Package Insert (USPI; 2009) or the Summary of Product Characteristics (SmPC).

8.2.4 Pregnancy and *In Utero* Drug Exposure

Since duvelisib has not been evaluated in pregnant or nursing women, the treatment of pregnant women or women of childbearing potential who are not using effective contraception is contraindicated (see Section 5.1.1 and Section 6.2.1 for instructions on pregnancy testing and birth control).

Pregnancies occurring in subjects or partners of male subjects during the study treatment period until 30 days after the subject's last dose of study treatment are considered immediately reportable events. If a pregnancy occurs in a subject, study treatment must be discontinued immediately. The pregnant woman should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

The pregnancy must be reported to Verastem or designee within 24 hours of the Investigator's knowledge of the pregnancy using the Pregnancy Notification Form as follows:

- Hotline (Phone): 888-483-7729 (USA)
- Fax: 888-529-3580 (USA)
- For International numbers, please refer to the Pregnancy Notification Form and supporting documentation.

The Investigator will follow the pregnant woman until completion of the pregnancy, and must notify Verastem of the outcome within 24 hours of the Investigator's knowledge of the pregnancy outcome. The Investigator will provide this information on the Pregnancy Outcome Report Form. This notification includes pregnancies resulting in live, "normal" births.

If the pregnant subject experiences an SAE during pregnancy, or the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting SAEs (ie, report the event to Verastem within 24 hours of the Investigator's knowledge of the event).

All neonatal deaths and congenital anomalies that occur within 30 days of birth (regardless of causality) should be reported as SAEs to Verastem. In addition, any infant death or congenital anomaly occurring after 30 days that the Investigator suspects is related to the *in utero* exposure to the study drug should also be reported to Verastem.

9 STATISTICAL METHODS

Details of the statistical methods for this study will be documented in a Statistical Analysis Plan (SAP). The SAP may modify the statistical methods outlined in the protocol; however, any major modification will also be reflected in a protocol amendment.

9.1 SAMPLE SIZE

This study employs a randomized, open-label, parallel design to assess the potential superiority of duvelisib treatment over ofatumumab treatment on PFS in CLL or SLL subjects.

The sample size was determined to provide sufficient power to test the primary endpoint of PFS in a group sequential design with one planned interim analysis.

Assuming an exponential distribution for PFS, a total number of 185 PFS events (deaths or progressions) will provide approximately 93% power to detect a hazard ratio of 0.6 (median PFS of 9 months in the ofatumumab group versus 15 months in the duvelisib group) using a one-sided log-rank test at a 2.5% overall significance level (ie, alpha of 0.025). The study design employs the Lan-DeMets spending function for O'Brien-Fleming boundary as the alpha spending function and the Hwang-Shih-DeCani gamma (-4) spending function as the beta spending function. A total of 300 subjects will be randomized in a 1:1 ratio to receive either ofatumumab or duvelisib. Assuming a peak accrual rate of 30 subjects per month with 11 months for accrual ramp-up and a 4% cumulative dropout rate per year, then enrollment would complete in 16 months, with the final analysis for PFS estimated to occur approximately 27.5 months from the randomization of the first subject.

9.2 ANALYSIS SETS

The two most important analysis sets are defined in this section, with additional analysis sets to be defined in the SAP.

9.2.1 Intent-to-Treat Analysis Set

The Intent-to-Treat (ITT) analysis set will include all subjects who were randomized, with treatment group designated according to initial randomization. The ITT analysis set will serve as the primary analysis set for all efficacy endpoints and demographics.

9.2.2 All-treated Analysis Set

The All-Treated (AT) analysis set will include all subjects who received any amount of study drug (duvelisib or ofatumumab), with treatment group designated according to actual study treatment received. The AT analysis set will be the primary analysis set for safety endpoints.

9.3 DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

A tabulation of subject disposition will be presented, which will include the number of subjects randomized to each treatment, and the number of subjects dosed for each treatment.

Discontinuation from study treatment will be summarized by reason for each treatment group. Discontinuation from study will also be summarized by reason for each treatment group.

Details for the summary of demographic and baseline characteristics will be provided in the SAP.

9.4 EFFICACY ANALYSES

9.4.1 Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is PFS based on disease status as determined by blinded, independent, central review and will be analyzed using the ITT analysis set.

Censoring of PFS will be performed as detailed in the table below. Additional clarifications will be provided in the SAP as needed.

Table 13: Primary PFS Censoring / Event Methodology

Situation	Date of Event or Censoring	Outcome
No adequate baseline disease status assessment	Date of randomization	Censored
No adequate post-baseline disease status assessment unless death occurs prior to first post-baseline assessment	Date of randomization + 1	Censored
No documented progression or death before data cutoff	Date of last adequate disease status assessment	Censored
Documented progression with ≤1 missing scheduled disease status assessment before progression	Date of the earliest assessment that results in a finding of unequivocal progression	Event
Death before progression being documented with ≤1 missing scheduled disease status assessment before death	Date of death	Event
Documented progression or death following a long gap between adequate disease status assessments (eg, 2 or more consecutive missed scheduled disease status assessments)	Date of last adequate disease status assessment before the gap	Censored
New anticancer treatment or procedure started before documented progression	Date of last adequate disease status assessment	Censored

Note: Disease status assessment includes CT scans (chest, abdomen and pelvis), bone marrow aspirate and/or biopsy (may not be required of all subjects at all scheduled disease status assessments), CBC and differential count, focused physical examination, disease related constitutional symptoms for disease assessment, and ECOG performance status. An adequate disease status assessment is any disease status assessment for which the blinded independent central review is able to arrive at a disease status (eg, CR, CRi, PR, PRwL, SD, and PD) per protocol-defined criteria.

A stratified log-rank test (1-sided) will be used to compare PFS of the duvelisib arm against PFS of the ofatumumab arm at the interim and final analyses with the overall one-sided significance level controlled at 0.025. The nominal p-value required for statistical significance at an analysis will be calculated based on the numbers of PFS events at all preceding and current analyses. The hazard ratio and the corresponding 2-sided 95% confidence interval (CI) will be estimated using a stratified Cox proportional hazards model. For both the stratified log-rank test and the stratified Cox model, the strata will be those used for stratified randomization, with potential pooling of strata specified in the SAP. PFS will be plotted for each treatment group using the Kaplan-Meier method. Median PFS and its associated 95% CI will be estimated for each treatment group.

Analyses of PFS using other censoring rules will be performed as sensitivity analyses. This will include a worst-comparison case sensitivity analysis in which surviving, non-progressing subjects who were lost to follow-up are treated as being censored at the last adequate disease assessment if they were on the ofatumumab arm, and treated as having an event at the time of the next scheduled disease assessment following the last adequate disease status assessment if they were on the duvelisib arm.

Analyses of PFS will be performed for subgroups of subjects based on selected baseline variables, including stratification factors used for randomization. The details of the subgroup analyses will be provided in the SAP.

9.4.2 Analysis of Key Secondary Efficacy Endpoints

Of the secondary endpoints, ORR, Lymph Node Response Rate, OS, and Hematologic Improvement Rate are designated as key secondary efficacy endpoints. If the primary endpoint is significant, the four key secondary endpoints will be sequentially tested at the 1-sided 0.025 significance level in the order listed above. If a null hypothesis is not rejected, formal sequential testing will be stopped. The detailed testing strategy will be specified in the SAP.

9.4.2.1 Overall Response Rate (ORR)

ORR will be analyzed using the Cochran-Mantel-Haenszel test (1-sided) to compare the two treatment groups. The strata for the test will be those used for stratified randomization, with potential pooling of strata specified in the SAP.

9.4.2.2 Lymph Node Response Rate

Lymph node response rate will be analyzed using the Cochran-Mantel-Haenszel test (1-sided) to compare the two treatment groups. The strata for the test will be those used for stratified randomization, with potential pooling of strata specified in the SAP.

9.4.2.3 Overall Survival (OS)

Subjects without documentation of death at the time of the data cutoff for analysis will be censored at the date the subject was last known to be alive, or the data cutoff date, whichever is earlier. A stratified one-sided log-rank test will be used to compare OS between the 2 treatment groups. The hazard ratios along with the 2-sided 95% CIs will be estimated using

a stratified Cox model. For both the stratified log-rank test and the stratified Cox model, the strata will be those used for stratified randomization, with potential pooling of strata specified in the SAP. The Kaplan-Meier survival curves and Kaplan-Meier medians (if estimable), along with the 2-sided 95% CIs, will be provided for each treatment group.

9.4.2.4 Hematologic Improvement Rate

A subject with a hematologic improvement is one who consistently met the criteria of an improvement in neutrophil count, hemoglobin or platelet count for a period of at least 60 days during which the subject did not have transfusion or exogenous cytokines. Missing data or missing scheduled assessments during a potential 60 day hematologic improvement episode will result in categorization of not having a hematologic improvement.

Hematologic improvement rate will be compared between treatment groups using one-sided Cochran–Mantel–Haenszel (CMH) test to adjust for the stratification factors. Details of this analysis will be specified in the SAP.

9.4.3 Analyses of Other Secondary Efficacy Endpoints

9.4.3.1 Duration of response (DOR)

Duration of response is defined only for subjects demonstrating a response (eg, CR, CRi, PR, PRwL), with the response and progression statuses both determined by the blinded, central independent review. The analysis will be descriptive for each treatment group only.

9.4.4 Analyses of Exploratory Efficacy Endpoints

Analyses of exploratory efficacy endpoints such as improvement in disease-related symptoms of fatigue, weight loss, unexplained fevers and night sweats from baseline, and minimal residual disease in subjects with documented CR or CRi will be specified in the SAP. Additional exploratory efficacy endpoints may also be defined in the SAP.

9.5 SAFETY ANALYSES

Safety endpoints will be summarized by treatment using the AT analysis set.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.1 or higher and will be graded according to the NCI-CTCAE, version 4.03 or as described in Section 8.2.1.

Tabulations of treatment emergent AEs (TEAEs) by System Organ Class and Preferred Terms will be produced. A TEAE is an AE that emerges or worsens in the period from the first dose of study treatment to 30 days after the last dose of study treatment.

Separate tabulations will also be produced for drug-related adverse events, serious adverse events, events that led to treatment discontinuation, and adverse events of at least Grade 3 severity.

For laboratory tests with NCI-CTCAE grades, a shift table from baseline grade to the maximum post-baseline grade will be provided. Listings will be provided for all laboratory test results and for laboratory test results grade 3 and higher.

9.6 PHARMACOKINETIC ANALYSES

Plasma samples will be analyzed for duvelisib and potential metabolite concentrations using a validated high performance liquid chromatography-tandem mass spectrometry (LC/MS/MS) method.

The PK data collected will be analyzed by standard population PK methods, using appropriate software. The intent of the analysis is to obtain exposure data in subjects with CLL/SLL, to characterize the parameters of PK disposition, and to identify relevant covariates affecting drug exposure. Analyses of exposure-response relationships for efficacy and safety endpoints may be conducted. The data may be pooled with the results of other studies to perform the population PK/pharmacodynamics analysis.

Additional details on the pharmacokinetic methods and analysis will be provided in the SAP.

9.7 ANALYSES OF OTHER ENDPOINTS

Analyses of other exploratory endpoints such as those for health-related QoL and biomarkers may be specified in the SAP or another document.

9.8 INTERIM ANALYSIS

After approximately 50% of the planned PFS events (ie, 93 PFS events) have been observed based on the blinded, independent, central review, an interim analysis of efficacy will be performed.

At the interim analysis, PFS will be tested at the alpha level based on the Lan-DeMets alpha spending function for O'Brien-Fleming boundary with the opportunity to stop the study (other than survival follow-up) for overwhelming evidence of efficacy. If the interim analysis occurs at exactly 50% of the planned events, the criterion of stopping for efficacy is one-sided p-value of 0.0015 (corresponding approximately to a HR of 0.540). In the meantime, PFS will also be tested at the alpha level for futility based on the alpha and beta spending functions specified for the study design. If the interim analysis occurs at exactly 50% of the planned events, the criterion of stopping for futility is one-sided p-value of 0.4791 (corresponding approximately to a HR of 0.990). The futility boundary of this study is non-binding, meaning that the Type I error is properly controlled even if the study is continued after the futility boundary for PFS is crossed at the interim analysis. Under the protocol design assumptions, the interim analysis is expected to occur approximately 17 months after the first subject is randomized.

If the study is not stopped at the interim analysis, the final analysis of PFS will be performed when approximately 185 PFS events have occurred in the study. The criterion of statistical significance (ie, boundary for efficacy) is one-sided p-value of 0.0245 (corresponding approximately to a HR of 0.748).

For the interim analysis, the actual p-value boundaries for efficacy and futility will be calculated based on the actual number of PFS events at the analysis. For the final analysis of PFS, the actual p-value boundary for efficacy will be calculated based on the actual number of PFS events at both the interim analysis and the final analysis.

The Independent Data Monitoring Committee (IDMC) will review PFS, OS and other efficacy data at the interim analysis.

The interim and final analysis for OS will be specified in the SAP.

10 STUDY ADMINISTRATION

10.1 GOOD CLINICAL PRACTICE STATEMENT

This study is to be performed in accordance with the protocol, the Declaration of Helsinki, the ICH Harmonised Tripartite Guideline for GCP, and all applicable local regulatory requirements.

10.2 INFORMED CONSENT

Verastem will provide a sample subject Informed Consent Form (ICF) for modification, as appropriate, by the Investigator. The ICF must include all elements required by ICH, GCP, and must adhere to the IRB/IEC requirements and the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator or his/her staff will explain the nature of the study, its purpose and associated procedures, the expected duration, and the potential risks involved to the subject prior to enrollment. The Investigator or designee will obtain written, informed consent. The subject will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Following the discussion regarding the study, a subject will be asked if they are willing to sign and personally date a statement of informed consent. Only if the subject voluntarily agrees to sign the informed consent statement and has done so, may he/she enter the study. A copy of the signed and dated ICF will be provided to the subject. The signed ICF is to remain in the Investigator's file, per local requirements.

The ICF and any other written information provided to the subjects will be revised whenever important new information becomes available that may be relevant to the subject's consent, or if there is an amendment to the protocol which necessitates a change to the content of the subject's informed consent. The Investigator will inform the subject of changes in a timely manner and will ask the subject to confirm continuation of their participation in the study by their signature on the revised informed consent form (if applicable). Any written ICF and written information must receive the approval/favorable opinion of the IRB/IEC in advance of use. Any additional approvals from the initial informed consent form should be forwarded to the Sponsor.

10.3 SUBJECT CONFIDENTIALITY

The written ICF will explain that study data will be stored in a database, maintaining confidentiality in accordance with national data legislation. All data processed by Verastem or its representative(s) will be identified by subject number and study code.

The written ICF will also explain that for data verification purposes, authorized representatives of Verastem, a regulatory authority, and IRB/IEC may require direct access to parts of the hospital or clinic records relevant to the study that include the subject's medical history.

The Investigator must ensure that the subjects' anonymity is maintained. On the eCRFs or other documents submitted to the Sponsor, subjects should not be identified by their names,

but by their assigned subject number and study code. Documents not for submission to the Sponsor, such as signed ICF, should be maintained in strict confidence by the Investigator.

10.4 INSTITUTIONAL REVIEW BOARD/ ETHICS COMMITTEE REQUIREMENTS

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB/IEC at each clinical trial site. The Principal Investigator must submit written approval to Verastem before he or she can enroll any subject into the study.

The Principal Investigator is responsible for informing the IRB/IEC of any amendment to the protocol. In addition, the IRB/IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB/IEC annually or as applicable.

Progress reports and notifications of SAEs will be provided to the IRB/IEC according to regulations and guidelines.

10.5 CASE REPORT FORMS AND SOURCE DOCUMENTATION

eCRF will be provided for the recording of all data. The Principal Investigator / Sub-Investigator or designee will record data from all observations, tests, and assessments specified in the protocol on the eCRFs provided by Verastem.

10.6 SPONSOR MONITORING

Before the first subject is enrolled into the study, a representative of Verastem will visit the study site to:

- Determine the adequacy of the facilities.
- Discuss with the Investigator(s) (and other personnel involved with the study) their responsibilities with regard to the protocol, and the responsibilities of Verastem.

During the conduct of the study, a representative of Verastem Pharmaceuticals, Inc. will have regular contact with the clinical trial site, and have regular visits to the clinical trial site to:

- Provide information and support the Principal Investigator.
- Confirm that the facilities remain acceptable.
- Confirm that the study team is adhering to the protocol, data are being accurately recorded in the eCRFs, and the investigational product is being properly maintained and accountability records are current.
- Perform source data verification with access to all original clinical records for each subject.

10.7 DATA MONITORING COMMITTEE

An Independent Data Monitoring Committee (IDMC) will be assembled to periodically review all available unblinded safety information and recommend whether or not the trial

should continue, or should continue with modifications, based on their review of the data. In addition, the IDMC will review PFS and other efficacy data at the time of the interim analysis and make a recommendation on overwhelming evidence of efficacy or futility of the study. All final decisions regarding study conduct will reside with the Sponsor. Membership and responsibilities of the IDMC will be documented in a separate IDMC Charter.

10.8 BLINDING

This study is open-label and Investigators, site staff, Sponsor and Sponsor designees will have access to treatment assignments for individual subjects. To reduce bias, a blinded independent central review of disease status will be conducted, which will be blinded to individual subject treatment assignments. Investigators, site staff, Sponsor and Sponsor designees will only have access to blinded (pooled) aggregate study data, except for a select number of Sponsor staff, who may review aggregate SAEs and MEOI data by treatment groups.

10.9 QUALITY ASSURANCE

In compliance with GCP and regulatory requirements, the Sponsor, a third party on behalf of the Sponsor, regulatory agencies or IRB/IECs may conduct quality assurance audits at any time during or following a study. The Investigator must agree to allow auditors direct access to all study-related documents including source documents, and must agree to allocate his or her time and the time of his or her study staff to the auditors in order to discuss findings and issues.

10.10 STUDY OR CLINICAL SITE TERMINATION

Sponsor or designee, reserves the right to terminate the study or a clinical trial site at any time. Conditions that may warrant termination of the study include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to subjects enrolled in the study.
- The decision on the part of Verastem to suspend or discontinue testing or the treatment of the study drug.
- Failure of the Investigator to comply with GCP.
- Submission of knowingly false information from the clinical trial site to Verastem or regulatory authorities.
- Insufficient adherence to protocol requirements.

If terminating the study, Verastem and the Investigator(s) will assure that adequate consideration is given to the protection of the subjects' interests.

10.11 DURATION OF THE STUDY, EXPECTED DURATION OF SUBJECT PARTICIPATION, AND END OF STUDY

The study is estimated to complete enrollment within 16 months from randomization of the first subject. Subjects will be followed for survival for up to 6 years after randomization. The maximum number of months to complete the study is expected to be 72 months.

10.12 RECORDS RETENTION

All correspondence related to this clinical study should be kept in appropriate study files. Records of subjects, source documents, eCRFs, drug inventory, IRB, and Sponsor correspondence pertaining to the study must be kept on file. All study documents must be kept secured for a period of 2 years after a marketing application is approved for duvelisib; or, until 2 years after shipment and delivery of the drug for investigational use is discontinued. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

10.13 PUBLICATIONS

Publication by the clinical trial site(s) of any data from this study must be carried out in accordance with the Clinical Trial Agreement.

11 REFERENCES

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11. ARZERRA (ofatumumab) Injection for intravenous infusion [Package Insert]. Greenford, Middlesex, United Kingdom: GlaxoSmithKline; 2014; Available from: http://us.gsk.com/products/assets/us_arzerra.pdf.

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12 APPENDICES

Appendix 1: Medications or Foods Known to Inhibit or Induce CYP3A

The following list provides medications known to induce or inhibit CYP3A activity. Note that this is not a comprehensive list of all medications which may modulate CYP3A activity. Additional information can be found at:

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

Note: Subjects receiving duvelisib are prohibited from concomitant use of medications or foods that are known to be strong inhibitors or inducers of CYP3A.

Classification of In Vivo Inhibitors of CYP3A

Strong Inhibitors(1)	Moderate inhibitors(2)	Weak inhibitors(3)
Boceprevir, clarithromycin, conivaptan, grapefruit juice,(5) indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, (6) nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, (5) imatinib, verapamil	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, (4) goldenseal,(4) isoniazid, nilotinib, oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, zileuton

1. A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a substrate for that CYP by equal or more than 5-fold or >80% decrease in CL.
2. A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold or 50-80% decrease in CL.
3. A weak inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 2-fold but equal to or more than 5-fold or 20-50% decrease in CL.
4. Herbal product.
5. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).
6. Withdrawn from the United States market because of safety reasons.

Appendix 1 (continued)

Classification of In Vivo Inducers of CYP3A

Strong Inducers ≥ 80% decrease in AUC	Moderate Inducers 50-80% decrease in AUC	Weak Inducers 20-50% decrease in AUC
Avasimibe,(1) carbamazepine, phenytoin, rifampin, St. John's wort(2)	Bosentan, efavirenz, etravirine, modafinil, nafcillin	Amprenavir, aprepitant, armodafinil, echinacea,(3) pioglitazone, prednisone, rufinamide

1. Not a marketed drug.
2. The effect of St. John's wort varies widely and is preparation-dependent.
3. Herbal product.

Appendix 2: Known CYP3A or CYP2C8 Substrates

The following lists provide known sensitive CYP3A substrates, CYP3A substrates with a narrow therapeutic range, and CYP2C8 substrates.

Additional information can be found at
http://www.medicine.iupui.edu/clinpharm/ddis/ClinicalTable.asp and
http://www.pharmacytimes.com/issue/pharmacy/2008/2008-09/2008-09-8687.

Sensitive CYP3A Substrates	
budesonide buspirone eplerenone eletriptan felodipine fluticasone lovastatin	midazolam saquinavir sildenafil simvastatin triazolam vardenafil
CYP3A Substrates with a Narrow Therapeutic Range	
alfentanil astemizole cisapride cyclosporine diergotamine ergotamine	fentanyl pimozide quinidine sirolimus tacrolimus terfenadine
CYP2C8 Substrates	
paclitaxel torsemide amodiaquine	cervistatin repaglinide rosiglitazone pioglitazone

Appendix 3: P-gp Substrates and Medications that are Inhibitors of P-gp

The following list provides medications that are substrates or inhibitors of P-gp. Note that this is not a comprehensive list of all medications which may be substrates of P-gp or may modulate P-gp activity.

P-gp Substrates	
Amitriptyline	Loperamide
Amiodarone	Losartan
Atorvastatin	Lovastatin
Cefoperazone	Methadone
Chlorpromazine	Methotrexate
Cimetidine	Methylprednisolone
Ciprofloxacin	Morphine
Clarithromycin	Nadolol
Colchicine	Norfloxacin
Cyclosporine	Nortriptyline
Dexamethasone	Ondansetron
Digoxin	Omeprazole
Diltiazem	Pantoprazole
Erythromycin	Phenytoin
Estradiol	Pravastatin
Fentanyl	Propranolol
Fexofenadine	Quinidine
Hydrocortisone	Ranitidine
Itraconazole	Sirolimus
Lansoprazole	Tacrolimus
Levofloxacin	Timolol
Lidocaine	Trimethoprim
	Verapamil

P-gp Inhibitors	
Amiodarone	Ketoconazole
Amitriptyline	Lovastatin
Carvedilol	Mefloquine
Chlorpromazine	Nicardipine
Clarithromycin	Nifedipine
Cortisol	Ofloxacin
Cyclosporine	Omeprazole
Desipramine	Pantoprazole
Diltiazem	Progesterone
Dipyridamole	Propafenone
Doxepin	Propranolol
Erythromycin	Quinidine
Felodipine	Rifampicin (Rifampin)
Fluphenazine	Saquinavir
Grapefruit juice	Simvastatin
Haloperidol	Sirolimus
Itraconazole	Tacrolimus
	Testosterone
	Verapamil

Source: Atkinson AJ et al. Principles of Clinical Pharmacology, 2nd ed. Academic Press, Massachusetts, 2007.

Appendix 4: ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source : Eastern Cooperative Oncology Group : http://www.ecog.org/general/perf_stat.html
As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982

Appendix 5: QoL Instrument - EQ-5D Questionnaire

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility
I have no problems in walking about ☐
I have some problems in walking about ☐
I am confined to bed ☐

Self-Care
I have no problems with self-care ☐
I have some problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

Usual Activities (*eg., work, study, housework, family or leisure activities)*
I have no problems with performing my usual activities ☐
I have some problems with performing my usual activities ☐
I am unable to perform my usual activities ☐

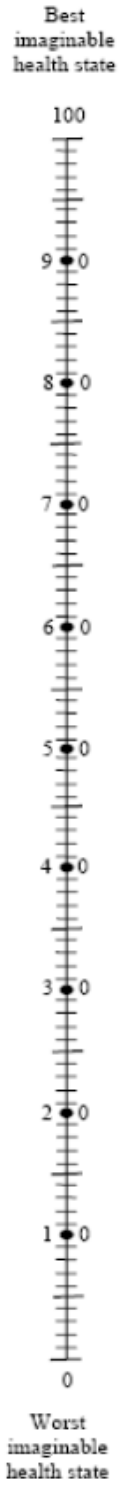
Pain/Discomfort
I have no pain or discomfort ☐
I have moderate pain or discomfort ☐
I have extreme pain or discomfort ☐

Anxiety/Depression
I am not anxious or depressed ☐
I am moderately anxious or depressed ☐
I am extremely anxious or depressed ☐

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today.



(English version for the US)

Appendix 6: Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	<u>PHYSICAL WELL-BEING</u>	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4