Copy produced by PhlexEview

NCT #: NCT02049515

STUDY PROTOCOL
IPI-145-12

Protocol Title:	A Study of IPI-145 and Ofatumumab in Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Previously Enrolled in Study IPI-145-07
Protocol Number:	IPI-145-12
Phase:	3 (extension)
IND Number:	112,486
EudraCT:	2013-003639-31
Date of Protocol:	30 October 2017 (Amendment 4.1 - Global)
Amendment 4:	27 September 2016
Amendment 3:	24 March 2016
Amendment 2:	02 March 2015
Amendment 1:	02 April 2014
Original	22 August 2013
Sponsor:	Verastem, Inc. 117 Kendrick Street, Suite 500 Needham, MA 02494 USA

Not for Distribution – Do Not Copy

This study protocol contains confidential information and is the proprietary property of Verastem, Inc. The protocol is for use by the Principal Investigator and his/her designated representatives participating in this investigational trial. This protocol may not be copied or made available for review by an unauthorized person or firm without the prior written authorization of Verastem, Inc.

Copy produced by PhlexEview

INVESTIGATOR PROTOCOL APPROVAL

A Study of IPI-145 and Ofatumumab in Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Previously Enrolled in Study IPI-145-07

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): _____

Copy produced by PhlexEview

SPONSOR PROTOCOL APPROVAL

A Study of IPI-145 and Ofatumumab in Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Previously Enrolled in Study IPI-145-07

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

Signature [redacted] *Date* 30 Oct 2017

[redacted]

Verastem, Inc
117 Kendrick Street, Suite 500
Needham, MA 02494

Copy produced by PhlexEview

CONTACT INFORMATION

Sponsor:	Verastem, Inc. 117 Kendrick Street, Suite 500 Needham, MA 02494

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

[redacted]

Copy produced by PhlexEview

PROTOCOL SYNOPSIS

Study Title:	A Study of IPI-145 and Ofatumumab in Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Previously Enrolled in Study IPI-145-07
Protocol Number:	IPI-145-12
Study Phase:	3 (extension study)
Investigational Agent:	Duvelisib (IPI-145)
Study Objectives:	Primary Objectives: • To examine the efficacy of duvelisib monotherapy in subjects with Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) who experienced disease progression after treatment with ofatumumab in Study IPI-145-07 • To examine the efficacy of ofatumumab monotherapy in subjects with CLL or SLL who experienced disease progression after treatment with duvelisib in Study IPI-145-07 Secondary Objectives: • To evaluate the safety of duvelisib in subjects with CLL or SLL who experienced disease progression after treatment with ofatumumab in Study IPI-145-07 • To evaluate the safety of ofatumumab in subjects with CLL or SLL who experienced disease progression after treatment with duvelisib in Study IPI-145-07
Study Treatment:	**Duvelisib** Duvelisib is administered orally and supplied as 5 mg and 25 mg formulated capsules. **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:	This protocol will enroll subjects previously enrolled in Study IPI-145-07 who have experienced disease progression after being treated with either duvelisib or ofatumumab which correlates with independent radiologic assessment. Subjects who consent to participate in this study will receive the opposite treatment from what they received in Study IPI-145-07:

Copy produced by PhlexEview

	Treatment Study IPI-145-07 → **Treatment Study IPI-145-12** Duvelisib (25 mg BID) → Ofatumumab Ofatumumab → Duvelisib (25 mg BID) Schedule of Administration Duvelisib Subjects who receive duvelisib will be given a starting dose of 25 mg duvelisib administered orally twice daily (BID) initially in a 21-day treatment cycle followed by 28-day treatment cycles for up to 11 cycles. After 11 complete cycles of treatment, subjects may receive additional cycles of duvelisib if they have documented evidence of response and disease requiring continued treatment according to the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) or the revised International Working Group (IWG) criteria until disease progression or unacceptable toxicity. Schedule of Administration Ofatumumab Subjects assigned to ofatumumab will receive treatment consistent with the approved product labeling: 8 weekly infusions, starting with an initial dose of 300 mg ofatumumab IV on Day 1 followed by 7 weekly doses of 2000 mg. Thereafter, subjects will receive 2000 mg ofatumumab 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.
Study Population:	All subjects previously enrolled in Study IPI-145-07 (approximately 300 subjects) who experience radiologically-confirmed disease progression while participating in that study may be eligible for this study; it is anticipated that approximately 150 subjects may enroll.
Study Duration:	Following treatment with duvelisib, study subjects will be followed until disease progression, discontinuation from study participation, or start of subsequent therapy, whichever comes first. Following treatment with ofatumumab, study subjects will be followed until disease progression, discontinuation from study participation, start of subsequent therapy, or 2 years (24 cycles) from their first dose, whichever comes first.
Study Centers:	All study sites initiated for Study IPI-145-07 will be eligible to participate in this extension study; for Study IPI-145-07 enrollment is anticipated at 74 sites, with 15 sites in the US and 59 sites outside the US.
Inclusion Criteria:	Subjects are eligible for inclusion in this extension study if they meet the following criteria: 1. Received either duvelisib or ofatumumab while participating in Study IPI-145-07 and experienced radiologically-confirmed disease progression

Copy produced by PhlexEview

	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. Measurable disease with a lymph node or tumor mass >1.5 cm in at least one dimension as assessed by computed tomography (CT) 4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (corresponds to Karnofsky Performance Status [KPS] ≥60%) 5. 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 6. For women of childbearing potential (WCBP): negative serum β-human chorionic gonadotropin (βhCG) pregnancy test within 1 week before first dose (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]) 7. 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 8. Ability to voluntarily sign consent for and adhere to the entire study visit schedule and all protocol requirements 9. 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. Discontinued study participation in Verastem-sponsored IPI-145-07 2. >3 months from confirmed progressive disease (PD) on Study IPI-145-07 3. Richter's transformation or prolymphocytic leukemia 4. Autoimmune hemolytic anemia (AIHA) or idiopathic thrombocytopenia purpura (ITP) that is uncontrolled or requires >20 mg daily (QD) of prednisone (or equivalent) to maintain hemoglobin >8.0 g/dL or platelets >10,000 µL without transfusion support.

Copy produced by PhlexEview

	5. Known central nervous system (CNS) lymphoma or leukemia; subjects with symptoms of CNS disease must have a negative computed tomography (CT) scan or negative diagnostic lumbar puncture prior to first dose 6. Use of any anticancer medication from documented PD on Study IPI-145-07 to enrollment – Note: corticosteroids to manage CLL/SLL-related symptoms are allowed 7. Ongoing systemic bacterial, fungal, or viral infections at the time of initiation of study treatment (defined as requiring IV antimicrobial, antifungal, or antiviral agents) o 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 Screening and/or Cycle 1 Day 1 (predose) 8. Human immunodeficiency virus (HIV) infection 9. Prior, current, or chronic hepatitis B or hepatitis C infection 10. History of alcohol abuse or chronic liver disease (other than metastatic disease to the liver) 11. Unable to receive prophylactic treatment for pneumocystis and herpes simplex virus (HSV) 12. Baseline QT interval corrected with Fridericia's method (QTcF) >480 ms NOTE: this criterion does not apply to subjects with a right or left bundle branch block (BBB) 13. 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 14. History of stroke, unstable angina, myocardial infarction, or ventricular arrhythmia requiring medication or mechanical control within the last 6 months 15. 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 16. Prior surgery or gastrointestinal dysfunction that may affect drug absorption (eg, gastric bypass surgery, gastrectomy) 17. Subjects to receive duvelisib: Administration of medications or foods that are strong inhibitors or inducers of cytochrome P450 (CYP) 3A within 2 weeks of starting duvelisib 18. Major surgery or invasive intervention within 4 weeks prior to first dose

Copy produced by PhlexEview

	19. Pregnant or breastfeeding women 20. Subjects to receive ofatumumab: hypersensitivity to ofatumumab or its excipients
Study Endpoints:	Primary Endpoint: • Overall Response Rate (ORR), with overall response 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 Secondary Endpoints: • Treatment-Emergent adverse events (TEAEs) and changes in laboratory values • Duration of Response (DOR), defined as the time from the first documentation of response to the first documentation of PD or death due to any cause • Progression-free survival (PFS), defined as the time from the first dose of study treatment to the first documentation of PD or death from any cause
Statistical Methodology:	This protocol enables subjects to have access to duvelisib or ofatumumab following treatment with the alternative therapy in Verastem-sponsored study IPI-145-07. Therefore, no formal statistical sample size calculation was performed for this study. It is anticipated that approximately 150 subjects may be treated on this protocol. All subjects who received at least one dose of study drug in this extension study will be included in the All-Treated (AT) analysis set. This analysis set will be the primary analysis set for all efficacy and safety endpoints. ORR will be summarized for each treatment arm using a point estimate along with a 95% confidence interval employing the exact binomial method. The proportion of subjects in each response category will also be presented.

Copy produced by PhlexEview

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

- Informed consent
- Inclusion/exclusion criteria
- Medical history & demographics
- Prior/concomitant medications & procedures
- Vital signs
- Physical examination [b]
- ECOG Performance status
- Disease-related symptoms assessment
- Electrocardiogram (ECG, 12-lead) [b]
- Blood chemistry [b]
- Hematology [b]
- Coagulation tests [b]
- Serum βhCG pregnancy test [c]
- CT scans of the chest, abdomen, and pelvis [d]
- Bone marrow biopsy and/or bone marrow aspiration
- Hepatitis, cytomegalovirus (CMV) and Epstein-Barr Virus (EBV) [e]
- Human immunodeficiency virus (HIV) [e]
- Adverse Event (AE)/Serious Adverse Event (SAE) assessment [f]

a. Screening performed ≤ 6 weeks from Cycle 1 Day 1. Screening procedures captured at the last visit of Study IPI-145-07 do not need to be repeated if the Screening visit for IPI-145-12 is within 30±7 days (possible exclusion of CT scans: see footnote e. below). If feasible, the Screening Visit and Cycle 1 Day 1 can occur on the same day. See Section 6 for details on each study assessment.

b. New clinically significant findings after signing informed consent form (ICF) should be captured as an AE.

c. 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.

d. CT scan demonstrating PD on Study IPI-145-07 may be used as baseline if < 6 weeks from Cycle 1 Day 1. Additional scans may be performed (eg, head/neck 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.

e. Documented results obtained from Study IPI-145-07 for these assessments may be used as baseline in this study, and need not be repeated at Screening.

f. 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 all treated subjects. SAEs for all subjects will be reported from the signing of the ICF as defined in Section 8.1.3.

Copy produced by PhlexEview

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

	Cycle 1 (21±2 days)		Cycle 2 (28±4 days)		Cycles 3–7 (28±4 days)	Cycle 8 through Cycle 18 every other cycle (28±4 days)[f]	Cycle 21 and beyond every third cycle (28±4 days)[f]	Early Treatment Termination from Duvelisib (ETT) [g]	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]								
βhCG pregnancy test [c, e]			X		X	X	X	X	
ECOG performance status	X [d]	See Table 4: Disease Response Assessments							
Response assessments		See Table 4: Disease Response Assessments							
Study drug administration	X	Continuous dosing through Cycle 12 Day 1 →							

a. See Section 6 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 don't need to be repeated at Cycle 1 Day 1.
e. May be either urine or serum, and performed every even cycle while on treatment.
f. Subjects will maintain clinical visits every even cycle, starting at Cycle 8 with the same assessments as Cycle 8. Subjects who receive additional duvelisib beyond Cycle 12 Day 1 (based on documented evidence of response and disease requiring continued treatment according to the IWCLL/ IWG) will maintain clinical visits every even cycle through Cycle 18 and then every third cycle thereafter (eg, Cycle 21, 24, 27) through the end of their treatment.
g. The Early Treatment Termination (ETT) Visit should occur for any subject who discontinues duvelisib treatment prior to Cycle 12 Day 1. The ETT assessments need not be performed if the subject has had a previous assessment within the previous 2 weeks (30 days for Disease Response Assessments).

Copy produced by PhlexEview

Table 3: Schedule of Assessments for Subjects Receiving Ofatumumab [a]

	Cycle 1 (21±2 days)			**Cycle 2** (28±4 days)				**Cycle 3-7** [g] (28±4 days)	**Early Treatment Termination (ETT) from Ofa** [f]	**Safety Follow-up Visit**
	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	≤7 d from last dose	30+7d from last dose
Concomitant Meds & Procedures	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	
Blood chemistry [c]	X [d]	X		X		X		X	X	
Hematology [c]	X [d]	X		X		X		X	X	
Coagulation tests [c]	X [d]									
βhCG pregnancy test [c, e]				X				X	X	
ECOG performance status	X [d]	**See Table 4: Disease Response Assessments**								
Response assessments		**See Table 4: Disease Response Assessments**								
Study drug administration	X	X	X	X	X	X	X	X		

Note: Ofa = ofatumumab

a. See Section 6 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.
e. May be either urine or serum, and will be performed every even cycle while on treatment.
f. Early Treatment Termination (ETT) should occur for any subject who discontinues from the 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).
g. Subjects who receive ofatumumab will not receive additional treatment with ofatumumab beyond Cycle 7.

Copy produced by PhlexEview

Table 4: Disease Response Assessments for All Subjects

Assessments [a, b]	**Screening/ Baseline**	**Cycles 4, 8, 12, and 18** [b] Day 1	**Cycle 24 and Every 6 Cycles Thereafter** [b, c] Day 1	**Early Treatment Termination (ETT)** [d] ≤7 days of last dose
CT scans of chest, abdomen, and pelvis [e]	**X** [f]	**X**	**X**	**X**
Bone marrow biopsy and/or bone marrow aspiration [g]	**X**	**X**	**X**	**X**
Complete Blood Count (CBC) and differential count [h]	**X**	**Every 2 cycles**	**Every 3 cycles**	**X**
Focused physical examination, [i] disease related constitutional symptoms assessment, and ECOG performance status	**X**	**X**	**X**	**X**

a. 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.
b. All disease assessments (except CBC and differential count) should occur approximately 6 months after the last on-treatment Disease Response Assessment and every 6 months thereafter until PD, subject withdrawal, or start of subsequent therapy.
c. For subjects in the ofatumumab treatment arm, their final assessment will be at Cycle 24.
d. ETT Disease Response Assessment is not necessary if a previous Disease Response Assessment was within the previous 30 days.
e. CT scans of the chest, abdomen and pelvis are required for all subjects in both treatment arms. These assessment may be performed within 7 days (Day -7 to Day 1) of initiating the next cycle. 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. 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. CT Scans collected at final Disease Response Assessment for Study IPI-145-07 can be used as baseline scans for this trial as long as they were collected within 6 weeks of Cycle 1 Day 1.
g. Bone marrow biopsy and/or bone marrow aspirate 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. The bone marrow biopsy/aspirate may be performed within 7 days (Day -7 to Day 1) of initiating the next cycle of therapy.
h. CBC and differential count will be performed approximately 2 months after the last on-treatment Disease Response Assessment, and every 2 months thereafter through 18 cycles and every 3 cycles thereafter (eg Cycle 21, 24, 27) or until PD, subject withdrawal, or start of subsequent therapy.
i. Please see Table 1, Table 2, and Table 3 for the full schedule of assessments.

Copy produced by PhlexEview

TABLE OF CONTENTS

Section **Page**

Copy produced by PhlexEview

Copy produced by PhlexEview

Copy produced by PhlexEview

Copy produced by PhlexEview

LIST OF TABLES

Copy produced by PhlexEview

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
°C	Degrees Celsius
°F	Degrees Fahrenheit
ADL	Activities of daily living
AE	Adverse Event
AIHA	Autoimmune hemolytic anemia
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
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
CBC	Complete blood count
CEC	Central Ethics Committee
CLL	Chronic lymphocytic leukemia
cm	Centimeters
CNS	Central nervous system
CMV	Cytomegalovirus
CO_2	Chloride bicarbonate
CR	Complete response
Cri	Complete response with incomplete marrow recovery
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events

Copy produced by PhlexEview

Abbreviation	Definition
CYP	Cytochrome P450
DDI	Drug-drug interactions
dL	Deciliter
DMC	Data Monitoring Committee
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
ETT	Early treatment termination
FDA	Food and Drug Administration
g	Grams
G-CSF	Granulocyte-colony stimulating factor
GCP	Good Clinical Practice
GM-CSF	Granulocyte macrophage-colony stimulating factor
GRAS	Generally regarded as safe
HIV	Human immunodeficiency virus
HSV	Herpes simplex virus
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
in	inches
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITP	Idiopathic thrombocytopenic purpura
IV	Intravenous(ly)
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
IWG	International Working Group

Copy produced by PhlexEview

Abbreviation	Definition
KPS	Karnofsky Performance Status
L	Liter(s)
LDH	Lactate dehydrogenase
LEC	Local Ethics Committee
MedDRA	Medical Dictionary for Regulatory Activities
MEOI	Medical Events of interest
mg	Milligram(s)
mL	Milliliter(s)
MRI	Magnetic resonance imaging
µg	Microgram(s)
µL	Microliter(s)
µM	Micromolar
MRI	Magnetic resonance imaging
ms	Millisecond(s)
MTD	Maximum tolerated dose
N, n	Number
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ng	Nanogram(s)
nM	Nanomolar
Ofa	Ofatumumab
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PE	Physical examination
PFS	Progression-free survival
P-gp	P-glycoprotein
PI3K	Phosphoinositide-3-kinase
PML	Progressive multifocal leukoencephalopathy
PR	Partial response
PRwL	PR with lymphocytosis

Copy produced by PhlexEview

Abbreviation	Definition
PT	Prothrombin time
QD	Once a day
QTcF	QT interval corrected with Fridericia's method
RBC	Red blood cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable disease
SE	Standard error
SLL	Small lymphocytic lymphoma
SmPC	Summary of Product Characteristics
SPD	Sum of the product of the diameters
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse events
ULN	Upper limit of normal
US or USA	United States of America
USPI	United States Package Insert
UV	Ultraviolet
VZV	Varicella zoster virus
WCBP	Women of child-bearing potential

Copy produced by PhlexEview

1 BACKGROUND AND RATIONALE

Duvelisib 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 purpose of this study is to allow subjects randomized to either duvelisib or ofatumumab on Study IPI-145-07 to receive additional (opposite) therapy as part of this extension study.

For detailed information on the clinical safety and efficacy, pharmacokinetics, and the nonclinical summary of duvelisib, please refer to the duvelisib Investigator's Brochure.

Copy produced by PhlexEview

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVES

- To examine the efficacy of duvelisib monotherapy in subjects with CLL or SLL who experienced disease progression after treatment with ofatumumab in Study IPI-145-07
- To examine the efficacy of ofatumumab monotherapy in subjects with CLL or SLL who experienced disease progression after treatment with duvelisib in Study IPI-145-07

2.2 SECONDARY OBJECTIVES

- To evaluate the safety of duvelisib in subjects with CLL or SLL who experienced disease progression after treatment with ofatumumab in Study IPI-145-07
- To evaluate the safety of ofatumumab in subjects with CLL or SLL who experienced disease progression after treatment with duvelisib in Study IPI-145-07

3 STUDY ENDPOINTS

3.1 PRIMARY ENDPOINT

The primary endpoint of this extension study is:

- Overall Response Rate (ORR), with overall response 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 International Workshop on Chronic Lymphocytic Leukemia (IWCLL) or revised International Working Group (IWG) Response Criteria, with modification for treatment-related lymphocytosis

3.2 SECONDARY ENDPOINTS

The secondary endpoints of this extension study are:

- Treatment-emergent adverse events (TEAEs) and changes in laboratory values
- Duration of Response (DOR), defined as the time from the first documentation of response to first documentation of progressive disease (PD) or death due to any cause
- Progression-free survival (PFS), defined as the time from first dose of study treatment to first documentation of PD or death from any cause

4 STUDY DESIGN

Study IPI-145-12 is a two-arm, open-label, extension study of duvelisib and ofatumumab in patients with CLL/SLL designed to enable subjects who experience radiologically-confirmed disease progression in Study IPI-145-07 to receive the alternative treatment (either duvelisib or ofatumumab) than what they received during study IPI-145-07.

Copy produced by PhlexEview

Subjects who meet eligibility criteria will have the option to enroll in this extension study and receive the opposite treatment from what they received in Study IPI-145-07. Both study drugs will be administered in the same manner as defined in Study IPI-145-07.

4.1 SCHEDULE OF ADMINISTRATION

Subjects who are randomized, receive treatment, and experience disease progression at any time on Study IPI-145-07, will have the option to enroll in this extension study. Following disease progression, subjects will return to the clinic to provide informed consent, assess eligibility, and on Day 1 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).

Duvelisib: Subjects who received ofatumumab in study IPI-145-07 will receive duvelisib during this study. Subjects will receive their first dose of duvelisib 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, 8, 10, and 12) will have only one clinic visit on Day 1. After completing approximately 11 cycles of treatment with duvelisib, subjects who, in the judgment of the Investigator, may derive benefit from continued treatment may continue to receive additional cycles of duvelisib until disease progression or unacceptable toxicity. However, to receive additional cycles of duvelisib beyond 11 cycles, subjects must have evidence of response and CLL/SLL requiring treatment according to the IWCLL/IWG by Cycle 12 Day 1.

Ofatumumab: Subjects assigned to ofatumumab will receive intravenous (IV) treatment according to the approved prescribing information.[1, 2] The initial dose of ofatumumab is 300 mg followed by seven weekly doses of 2000 mg. Thereafter, subjects will receive 2000 mg ofatumumab once every cycle for 4 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.

4.2 DOSE INTERRUPTION/HOLD/MODIFICATION GUIDELINES

4.2.1 Duvelisib Guidelines

Duvelisib treatment will consist of 25 mg administered orally twice a day (BID) continuously for up to 11 cycles. Duvelisib may be continued beyond 11 cycles (Cycle 12 Day 1), if the subject has a documented response and meets the criteria for additional treatment (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 5 may be implemented. Deviations from these guidelines may occur based on the clinical judgment of the

Copy produced by PhlexEview

Investigator with notification to the Medical Monitor/Sponsor. There should be no attempt to make up for missed doses of duvelisib.

Table 5: 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 6 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/antivirals should have duvelisib held until infection resolves (subject may be 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-

Copy produced by PhlexEview

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) QTcF prolongation. A ≥ Grade 3 QTcF prolongation requires an electrocardiogram (ECG) and the use of Fridericia's correction method (QTcF). For subjects with a right or left bundle branch block (BBB), a Grade 3 QTc prolongation is defined as an increase in QTcF of >100 ms from the predose 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 levels are described in Table 6.

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 hemorrhage

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 6.

Copy produced by PhlexEview

Table 6: 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 <11 complete cycles of duvelisib therapy:

Prior to completion of 11 cycles of duvelisib therapy (Cycle 12 Day 1), 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 6.3.6 for definitions) of >6 months duration.

Treatment discontinuation after 11 or more complete cycles of duvelisib therapy:

After completion of 11 cycles of duvelisib therapy (beginning on Day 1 Cycle 12), 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 6.3.6]) of >3 months duration:

- CR or CRi
- Partial response (that includes all target lesions ≤1.5 cm in diameter) but with a peripheral blood 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).

Treatment continuation after 11 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 6.3.6]) at the end of 11 complete cycles (Day 1 Cycle 12) of duvelisib therapy:

Copy produced by PhlexEview

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

Disease Response Assessments by CT scan will continue every 6 cycles until disease progression (see Table 4).

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 3. If the investigator wishes to treat the subject beyond 12 infusions after the initial protocol dosing, per the latest ARZERRA® prescribing information;[1, 2] the subject can withdraw from the study to receive additional ofatumumab infusions off-study.

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.[1, 2] Additional details on study drug dosage and administration are described in Section 7.2. 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.

Copy produced by PhlexEview

Table 7: 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 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 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 7 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 a 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.

Copy produced by PhlexEview

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 (≥ 500 ms) QTcF prolongation. A ≥ Grade 3 QTcF prolongation requires an ECG 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 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:

Copy produced by PhlexEview

- 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 12 Day 1 for duvelisib or through Cycle 7 for ofatumumab), then he/she must attend an Early Treatment Termination (ETT) Visit within 7 days of last dose or the decision leading to treatment discontinuation. Assessments collected within 14 days of the ETT Visit do not need to be repeated at the ETT Visit (Table 2 and Table 3). ETT Disease Response Assessments (Table 4) are not necessary if a previous Disease Response Assessment was within the previous 30 days. Following last dose, either due to ETT or completion of dosing, all subjects will complete a 30-day safety follow-up visit.

Subjects who discontinue study treatment for reasons other than PD, and have not withdrawn consent from overall study participation will enter Follow-up (Section 6.5.1.3).

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
- Protocol-specific disease progression
- 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.

Copy produced by PhlexEview

5 STUDY POPULATION

All subjects previously enrolled in Study IPI-145-07 (n=300) with radiographic evidence of disease progression while participating in that study may be eligible for this extension protocol. In this extension study, subjects who choose to participate and meet all entry criteria will receive the opposite treatment from what they received in Study IPI-145-07.

5.1 NUMBER OF SUBJECTS

It is anticipated that approximately 150 subjects may be enrolled in this extension protocol.

5.2 ENTRY CRITERIA

5.2.1 Inclusion Criteria

Subjects are eligible for inclusion in the extension study if they meet the following criteria:

1. Received either duvelisib or ofatumumab while participating in Study IPI-145-07 and experienced radiologically-confirmed disease progression
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. Measurable disease with a lymph node or tumor mass >1.5 cm in at least one dimension as assessed by computed tomography (CT)
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (corresponds to Karnofsky Performance Status [KPS] ≥60%)
5. 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
6. For women of childbearing potential (WCBP): negative serum β-human chorionic gonadotropin (βhCG) pregnancy test within 1 week before first dose (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])
7. 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

Copy produced by PhlexEview

8. Ability to voluntarily sign consent for and adhere to the entire study visit schedule and all protocol requirements
9. Signed and dated institutional review board (IRB)/independent ethics committee (IEC)-approved informed consent form (ICF) before any study specific screening procedures are performed

5.2.2 Exclusion Criteria

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

1. Discontinued study participation in Verastem-sponsored IPI-145-07
2. >3 months from confirmed PD on Study IPI-145-07
3. Richter's transformation or prolymphocytic leukemia
4. Autoimmune hemolytic anemia (AIHA) or idiopathic thrombocytopenia purpura (ITP) that is uncontrolled or requires >20 mg QD of prednisone (or equivalent) to maintain hemoglobin >8.0 g/dL or platelets >10,000 µL without transfusion support
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 first dose
6. Use of any anticancer medication post documented PD on Study IPI-145-07 and prior to enrollment
   - Corticosteroids to manage CLL/SLL-related symptoms are allowed
7. 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 Screening and/or Cycle 1 Day 1 predose
8. Human immunodeficiency virus (HIV) infection
9. Prior, current or chronic hepatitis B or hepatitis C infection
10. History of alcohol abuse or chronic liver disease (other than metastatic disease to the liver)
11. Unable to receive prophylactic treatment for pneumocystis and herpes simplex virus (HSV)
12. Baseline QTcF >480 ms NOTE: this criterion does not apply to subjects with a right or left bundle branch block (BBB)
13. 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
14. History of stroke, unstable angina, myocardial infarction, or ventricular arrhythmia requiring medication or mechanical control within the last 6 months

Copy produced by PhlexEview

15. 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
16. Prior surgery or gastrointestinal dysfunction that may affect drug absorption (eg, gastric bypass surgery, gastrectomy)
17. Subjects to receive duvelisib: Administration of medications or foods that are strong inhibitors or inducers of CYP3A within 2 weeks of starting duvelisib
18. Major surgery or invasive intervention within 4 weeks prior to first dose
19. Pregnant or breastfeeding women
20. Subjects to receive ofatumumab: Hypersensitivity to ofatumumab or its excipients

Copy produced by PhlexEview

6 STUDY PROCEDURES AND ASSESSMENTS

The Schedule of Assessments are summarized on Table 1, Table 2, Table 3, and Table 4.

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 PRE-FIRST DOSE

Subjects who experience disease progression on Study IPI-145-07 will have the opportunity to enroll in this extension study. The ETT or final study visit in Study IPI-145-07 may serve as the Screening Visit in this extension study if performed within the specified period of time outlined in Table 1.

The first day of treatment will be considered Day 1 of the first treatment cycle in this extension study.

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 (may coincide with the final visit of Study IPI-145-07), the following assessments will be performed:

- Obtain signed ICF
- Review inclusion/exclusion criteria
- HIV screening history: documented results obtained from IPI-145-07 may be used and need not be repeated at Screening
- Demographics
- Complete medical history: includes documentation of all previous treatments and treatment results (ie, best response to previous disease specific treatments), prior procedures, current medications, and all medications used since termination of Study IPI-145-07
- Full physical examination, which includes vital signs (temperature, blood pressure [sitting for 5 minutes], pulse rate, and respiratory rate, and weight
- ECOG performance status (see Appendix 4)
- Disease-related symptoms, [fatigue (as measure 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]
- 12-lead ECG should be conducted following an approximate 10-minute rest period in a semi-recumbent or supine position. QTc measurements will use the Fridericia's correction method (QTcF)

Copy produced by PhlexEview

- 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, lactate dehydrogenase (LDH), serum ALT, serum AST, total and direct bilirubin, and alkaline phosphatase
- Hematology laboratory parameters: hemoglobin, hematocrit, platelets, and white blood cell count with 5-part differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils) such that an absolute neutrophil count (ANC) and an absolute lymphocyte count (ALC) can be derived if it is not already provided as part of the laboratory analysis
- 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
- Serum pregnancy test for WCBP (must be performed within 7 days of Cycle 1 Day 1)
- 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
    - Note: 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)

6.2.2 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria (Section 5.2.1, Section 5.2.2, 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) (see Section 7.6 for treatment assignment).

Eligibility criteria will be verified before the first dose of duvelisib or ofatumumab in this extension study.

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, Table 3, 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 response

Copy produced by PhlexEview

assessments at time points specified in Table 4. 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 8.2)
- Concomitant medication collection (Section 6.3.5)
- CLL/SLL Response Assessment (Section 6.3.6)

6.3.2 Clinical Laboratory Tests

The following laboratory parameters will be conducted according to Table 1, Table 2, and Table 3:

- Urine or serum pregnancy tests will be collected from all women of childbearing potential (WCBP) throughout the study while they remain on treatment.
- Hematology laboratory parameters include, hemoglobin, hematocrit, platelets, and white blood cell count with 5-part differential neutrophils, lymphocytes, monocytes, eosinophils, basophils) such that an absolute neutrophil count (ANC) and an absolute lymphocyte count (ALC) can be derived if it is not already provided as part of the laboratory analysis.
- Coagulation laboratory parameters as clinically indicated include prothrombin time (PT), and activated partial thromboplastin time (aPTT). The international normalized ratio (INR) must be obtained for subjects receiving anticoagulation therapy. 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 LDH, serum ALT, serum AST, total and direct bilirubin, and alkaline phosphatase.
- Blood samples should be drawn and results should be reviewed within 72 hours of the designated clinic visit.

For Cycle 1, Day 1, 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

Copy produced by PhlexEview

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 and 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 cytomegalovirus (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 schedule, 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.

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.

6.3.3.2 Ofatumumab

Ofatumumab will be administered in accordance with the ARZERRA® Prescribing Information. Each subject assigned to ofatumumab will receive 12 doses as described in Table 3. Refer to Section 6.3.5 for recommended prophylactic treatment.

If the dose of ofatumumab is reduced, all reductions should be made per 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 and the ARZERRA® package insert.

6.3.4 Adverse Events

Any ongoing AEs from previous Study IPI-145-07 at Screening should be recorded in the subject's medical history.

Copy produced by PhlexEview

Collection of AEs will be performed from the signing of the ICF through 30 days after the last dose of either duvelisib or ofatumumab. SAEs will be sent to the Sponsor from the signing of the ICF through 30 days post last dose of study drug. See Section 8.2 for a full description of the collection and reporting of AEs during this study.

6.3.5 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.

- *Corticosteroids for the treatment of CLL/SLL-related disease symptoms:*

Copy produced by PhlexEview

Those subjects taking corticosteroids for the control of CLL/SLL-related disease symptoms at the time of study enrollment, must have their dose tapered to <20 mg QD (prednisone or equivalent) within 1 week following the first dose of study drug.

For subjects treated with ofatumumab

- *Premedication:*

Premedicate 30 minutes to 2 hours prior to each dose with oral acetaminophen 1000 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

6.3.5.1 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.

6.3.5.2 Prohibited: Immunosuppressants

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

6.3.5.3 Prohibited: PI3K or BTK Inhibitors

Subjects are not to have received any prior exposure to any BTK inhibitor or PI3K inhibitor (excluding investigation agent duvelisib) prior to study entry; these medications are prohibited while on-study.

6.3.5.4 Prohibited: Other Anticancer Therapy or Investigational Agents

During the Treatment Period subjects are not to receive any additional anticancer therapy or other investigational agents not outlined in the protocol.

6.3.5.5 Prohibited: (Duvelisib Subjects Only)

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

Copy produced by PhlexEview

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 CYP3A4 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 1is 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.

6.3.5.6 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 medications that are substrates for CYP2C8 or 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**.

Appendix 2 provides a list of medications known to be substrates of CYP3A4 or CYP2C8. Please note that Appendix 2 is not a comprehensive list of all medications which may be substrates of CYP3A4 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.

Copy produced by PhlexEview

6.3.5.7 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.

6.3.5.8 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 National Comprehensive Cancer Network [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.

6.3.5.9 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.

6.3.5.10 Photosafety

The effect of this medication on the skin, especially when in direct sunlight or with artificial 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.

6.3.6 Disease Response Assessments

Response will be measured by the following assessments as indicated in Table 4:

- Bone marrow aspirate and/or bone marrow biopsy
- CT scans of chest, abdomen and pelvis (See Section 6.3.6.1)
- CBC and differential count
- 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)

Copy produced by PhlexEview

These evaluations will be done until PD is documented, death occurs, or other anticancer therapy is initiated.

6.3.6.1 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 4. 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 12 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 Table 4 and Section 6.5.1.3.

6.3.6.2 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 8) and IWG response criteria for subjects with SLL (Table 9).

Copy produced by PhlexEview

Table 8: CLL Response Criteria (modified from IWCLL)[3, 4]

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

Copy produced by PhlexEview

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[3]
- 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)

Copy produced by PhlexEview

Table 9: SLL Response Criteria (modified from IWG)

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 progressive lymphocytosis in the setting of reduced lymph node size or organomegaly or improvement in hemoglobin/platelets 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
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 required)

At each scheduled Disease Response Assessment, the Investigator will be asked to provide a clinical response based on the parameters provided in Table 8 and Table 9 and assessment of disease-related constitutional symptoms.

6.4 EARLY TERMINATION OF DUVELISIB OR OFATUMUMAB

Subjects on duvelisib who discontinue treatment prior to Cycle 12 Day 1 or ofatumumab subjects prior to Cycle 7 will have an ETT visit within 7 days of last dose of study drug or the decision leading to treatment discontinuation, which will include the following assessments.

Copy produced by PhlexEview

If performed within previous 14 days, do not need to be repeated:

- 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

If performed within previous 30 days, do not need to be repeated:

- Disease Response Assessments:
    - Focused physical exam /constitutional symptoms
    - Bone marrow biopsy/aspirate (if indicated)
    - Hematology
    - ECOG
    - CT scan

6.5 POST-TREATMENT PERIOD

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

6.5.1.1 Duvelisib

For subjects assigned to duvelisib, a visit should occur for 30+7 days after discontinuation of duvelisib administration 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 AE, 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 assessments as described in Table 2 and Table 4.

6.5.1.2 Ofatumumab

For subjects assigned 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 AE, in which case a clinical visit will be required. Assessments include:

- AEs/SAEs collection

Copy produced by PhlexEview

– Concomitant medications

Following the last dose of ofatumumab, subjects will continue follow-up as described in Table 3 and Table 4.

6.5.1.3 Follow-up

For subjects who completed treatment or discontinued treatment with duvelisib or ofatumumab early due to reasons other than disease progression and remain on study, CBC and differential count will be performed approximately 2 months after the last on-treatment Disease Response Assessment, and every 2 months thereafter through 18 cycles and every 3 cycles thereafter or until PD, subject withdrawal, or start of subsequent therapy. All other disease assessments should occur approximately 6 months after the last on-treatment Disease Response Assessment, and every 6 months thereafter until PD, subject withdrawal, or start of subsequent therapy. For subjects in the ofatumumab treatment arm, their final assessment will be at Cycle 24. The following assessments should be performed as outlined in Table 4.

Every 2 months

- CBC and differential count

Every 3 months (from Cycle 18)

- CBC and differential count

Every 6 months

- CT scans of chest, abdomen and pelvis
- Bone marrow biopsy and bone marrow aspiration
- Focused physical examination, ECOG performance status, and disease-related constitutional symptoms

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).

Copy produced by PhlexEview

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).

7.2.1.2 Ofatumumab

Subjects assigned to ofatumumab will receive treatment consistent with the approved product labeling: 8 weekly IV doses, starting with 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 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 will be taken daily BID (every 12±2 hours) in 28-day cycles, except Cycle 1 which is 21 days. 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.

Copy produced by PhlexEview

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 administered via infusion, as described in the ofatumumab (ARZERRA®) package insert.[1, 2] Please reference 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-145-12 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.

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 1000 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.

Copy produced by PhlexEview

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 TREATMENT ASSIGNMENT AND BLINDING

This is an open-label extension study for subjects who experience progressive disease while participating in Study IPI-145-07. Enrolled subjects will be assigned to receive the opposite treatment to what they were administered in Study IPI-145-07.

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 for up to 12 infusions as described in the package insert by the test article administrator.

Copy produced by PhlexEview

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 over-dosage with ofatumumab. Supportive care is to be given as indicated in the event of an ofatumumab over-dosage.

Copy produced by PhlexEview

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

Copy produced by PhlexEview

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 treated subjects will be recorded in the eCRF from the time of the signing of the 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.

Copy produced by PhlexEview

- 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

Copy produced by PhlexEview

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

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 the 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.

Copy produced by PhlexEview

- *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 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: [redacted]
- Hotline (Phone): [redacted] (USA)
- Fax: [redacted] (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 >2 x 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.

Copy produced by PhlexEview

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 / 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, including correspondence with Verastem and the IRB/EC on file.

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 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 5.2.1 and Section 6.2.1 for instructions on pregnancy testing and birth control).

Copy produced by PhlexEview

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): [redacted] (USA)
- Fax: [redacted] (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.

Copy produced by PhlexEview

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 protocol enables subjects to have access to duvelisib or ofatumumab following treatment with the alternative therapy in IPI-145-07. Therefore, no formal statistical sample size calculation was performed for this study. It is anticipated that approximately 150 subjects may be treated on this protocol. If the sample size for an arm is 75, then a two-sided 95% confidence interval will extend no further than ±12% from an observed ORR.

9.2 ANALYSIS SETS

All subjects who received at least one dose of study drug in this extension study will be included in the All-Treated (AT) Analysis Set. This analysis set will be the primary analysis set for all efficacy and safety endpoints.

Additional analysis sets may be defined in the SAP.

9.3 DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Baseline data will be summarized using mean, standard deviation, median, minimum, and maximum for continuous variables and frequency and percentage for categorical variables. Subject disposition will be summarized using frequencies and percentages.

9.4 EFFICACY ANALYSES

ORR, DOR and PFS will be based on response and progression statuses as determined by investigators according to the IWCLL Response Criteria or revised IWG criteria, with modification for treatment-related lymphocytosis.

ORR will be summarized for each treatment arm using a point estimate along with a 95% confidence interval employing the exact binomial method. The proportion of subjects in each response category will also be presented. In the primary analysis of ORR, any subjects not exhibiting a response (eg, CR, CRi, PR, and PRwL) are classified as nonresponders. Additional sensitivity analyses based on other analysis sets or responder definitions may be conducted.

DOR and PFS will be presented for each treatment arm using the Kaplan-Meier method. A 2-sided 95% confidence interval for the median of each of the 2 endpoints will be presented for each treatment arm. Censoring for DOR and PFS will be identical to the method employed for PFS in study IPI-145-07.

Copy produced by PhlexEview

9.5 SAFETY ANALYSES

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 INTERIM ANALYSIS

No interim analysis is planned.

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 patient ICF for modification, as appropriate, by the Investigator. The ICF must include all elements required by ICH, GCP, and must adhere to the governing 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 patient prior to enrollment. The Investigator or designee will obtain written, informed consent. The patient 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 patient will be asked if they are willing to sign and personally date an ICF. Only if the patient voluntarily agrees to sign the ICF and has done so, may he/she enter the study. A copy of the signed and dated ICF will be provided to the patient. The signed ICF is to remain in the Investigator's file, per local requirements.

The ICF and any other written information provided to the patients will be revised whenever important new information becomes available that may be relevant to the patient's consent, or if there is an amendment to the protocol which necessitates a change to the content of the patient's

Copy produced by PhlexEview

ICF. The Investigator will inform the patient of changes in a timely manner and will ask the patient to confirm continuation of their participation in the study by their signature on the revised ICF (if applicable). Any written informed consent form 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 ICFs, should be maintained in strict confidence by the Investigator.

10.4 INSTITUTIONAL REVIEW BOARD/INDEPENDENT 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. The protocol must be re-approved by the IRB/IEC annually.

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

10.5 CASE REPORT FORMS AND SOURCE DOCUMENTATION

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

10.6 SPONSOR MONITORING

During the conduct of the study, a monitor from Verastem or a representative of Verastem, 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.

Copy produced by PhlexEview

- 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

A Data Monitoring Committee will not be chartered for this study. Study IPI-145-12 is an open-label, non-randomized extension study of patients who previously enrolled in the Phase 3 Study IPI-145-07. Therefore, Verastem may present potential safety findings arising from Study IPI-145-12 to the Study IPI-145-07 Independent DMC for further review, as necessary.

10.8 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.

10.9 STUDY OR SITE TERMINATION

Verastem, 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 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.

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

Study enrollment will continue as long as Study IPI-145-07 remains ongoing. The maximum length of study participation is 24 cycles for ofatumumab subjects. Study treatment is expected to be approximately 11 months per subject treated with duvelisib (with some subjects continuing on duvelisib if they have shown clinical benefit) and 7 months per subject treated with ofatumumab, followed by a 30-Day Post-Treatment Visit for both treatment arms.

Copy produced by PhlexEview

10.11 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/IEC, 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.

10.12 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.

Copy produced by PhlexEview

11 REFERENCES

1. ARZERRA (Ofatumumab) [Summary of Product Characteristics]. Novartis Europharm Limited, Frimley Business Park, Camberley GU16 7SR, United Kingdom 2016: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001131/WC500093091.pdf.

2. ARZERRA (ofatumumab) Injection for intravenous infusion [Package Insert]. Novartis Europharm Limited, Frimley Business Park, Camberley GU16 7SR, United Kingdom; 2016; Available from: http://www.pharma.us.novartis.com/product/pi/pdf/arzerra.pdf.

3. Cheson BD, Byrd JC, Rai KR, Kay NE, O'Brien SM, Flinn IW, et al. Novel targeted agents and the need to refine clinical end points in chronic lymphocytic leukemia. J Clin Oncol. 2012 Aug 10;30(23):2820-2.

4. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–Working Group 1996 guidelines. Blood. 2008 June 15, 2008;111(12):5446-56.

Copy produced by PhlexEview

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.

Copy produced by PhlexEview

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.

Copy produced by PhlexEview

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

Copy produced by PhlexEview

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

Copy produced by PhlexEview

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.

Copy produced by PhlexEview

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