STUDY PROTOCOL VS-0145-229

Protocol Title: A Phase 2, Randomized, Open-label, 2-Arm Study Comparing 2 Intermittent Dosing Schedules of Duvelisib in Subjects with Indolent Non-Hodgkin Lymphoma (iNHL)

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Compound: Duvelisib

Study Phase: Phase 2

Short Title: A Phase 2 Study of Intermittent Dosing Schedules of Duvelisib in Indolent Non-Hodgkin Lymphoma (iNHL)

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1. PROTOCOL SUMMARY

1.1. Synopsis

Study Title: A Phase 2, randomized, open-label, 2-arm study comparing 2 intermittent dosing schedules of duvelisib in subjects with indolent non-Hodgkin lymphoma (iNHL)
Protocol Number: VS-0145-229
Phase: 2
Rationale: Dosing with duvelisib 25 mg twice daily (BID) has been shown to be efficacious in multiple Phase 1-3 studies including subjects with iNHL. The efficacy, safety and tolerability of this dose supported the US approval of duvelisib for the treatment of adult patients with relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) after at least 2 prior therapies and accelerated approval in adult patients with R/R follicular lymphoma (FL) after at least 2 prior systemic therapies. The current study will evaluate whether efficacy can be achieved and maintained, with acceptable or improved safety and tolerability, by inclusion of pre specified 2-week drug holidays in 2 different 25 mg BID schedules in subjects with R/R iNHL.
Objectives and Endpoints

Objective	***Endpoint*** (see Section 9.4 for definitions)
Primary	
Evaluate the efficacy of duvelisib administered with prescribed drug holidays in subjects with iNHL	Overall Response Rate (ORR) according to the 2007 revised International Working Group (IWG) Criteria (Cheson 2007)
Secondary	
Evaluate supportive efficacy measures of duvelisib administered with prescribed drug holidays in subjects with iNHL	• ORR according to 2014 Lugano criteria (Cheson 2014) *Note: all additional secondary response endpoints as well as progression-free survival (PFS), will be assessed separately using 2007 revised IWG criteria (Cheson 2007) and 2014 Lugano criteria (Cheson 2014)* • ORR, at 6, 12, 18, and 24 months after first dose of study intervention • Progression-free Survival • Time to Treatment Failure (TTF) • Duration of Response (DOR) • Overall Survival (OS) • Lymph Node Response Rate (LNRR) • Time to the First Response (TTFR)

Evaluate the safety and tolerability of duvelisib administered with prescribed drug holidays in subjects with iNHL	Adverse events (AEs), serious AEs (SAEs), vital signs, physical examinations, and clinical laboratory values
Characterize the pharmacokinetics (PK) of duvelisib and metabolite IPI-656 when duvelisib is administered with prescribed drug holidays in subjects with iNHL	PK parameters for duvelisib and metabolite IPI-656
Exploratory	
Evaluate Quality of Life (QoL) in subjects with iNHL treated with duvelisib with prescribed drug holidays	• Eastern Cooperative Oncology Group (ECOG) Performance Score • EQ-5D-3L questionnaire responses
Evaluate potential biomarkers of clinical efficacy and/or safety of duvelisib administered with prescribed drug holidays in subjects with iNHL	• Blood assessments of immune cell populations, chemokines, cytokines, phosphorylated proteins, and/or circulating tumor ctDNA • Fecal assessments of protein, DNA, and or RNA • Tumor biopsy evaluation of biomarkers such as gene and copy number variation, RNA expression, protein expression, and/or immune cell content

Overall Design:

This is a Phase 2, randomized, open-label, 2-arm study designed to evaluate the efficacy and safety of prescribed drug holidays of duvelisib treatment in subjects with R/R iNHL who have received at least 1 prior systemic therapy.

Subjects will be stratified by number of prior therapies (1 or > 1), bulky disease status (longest diameter of baseline lesion < 5 cm or ≥ 5 cm) and time since last recurrence (≥ 24 months or < 24 months). Subjects will be randomized to Arm 1 or Arm 2 in a 1:1 fashion. Each treatment arm will be analyzed separately.

The study is a 2-stage design. **For each arm**: in the first stage, approximately 15 subjects will be enrolled. Responses will be assessed by the Investigator according to the 2007 revised IWG criteria (Cheson 2007) (primary endpoint) and 2014 Lugano criteria (Cheson 2014). The evaluation of the first stage will take place after the 15 enrolled subjects have been followed for a minimum of 3 cycles. If there are fewer than 6 responders (partial response [PR] or complete response [CR]) among the first 15 subjects in each arm, consideration may be given to stopping the arm. Otherwise, 36 additional subjects will be enrolled for a total of 51 per arm. Enrollment will be continuous between Stage 1 and Stage 2.

Number of Subjects:

Approximately 102 subjects will be enrolled and randomized at multiple sites globally. The study will employ a 2-stage approach with a planned enrollment of approximately 30 subjects for Stage 1 and up to approximately 72 additional subjects for Stage 2.

Intervention Groups and Duration:

- Arm 1: duvelisib 25 mg BID for one 10-week cycle followed by 25 mg BID in Weeks 3 and 4 of each subsequent 4-week cycles until disease progression, unacceptable toxicity, or withdrawal.
- Arm 2: duvelisib 25 mg BID on Weeks 1, 2, 5, 6, 9 and 10 of one 10-week cycle, then in Weeks 3 and 4 of each subsequent 4-week cycles until disease progression, unacceptable toxicity, or withdrawal.

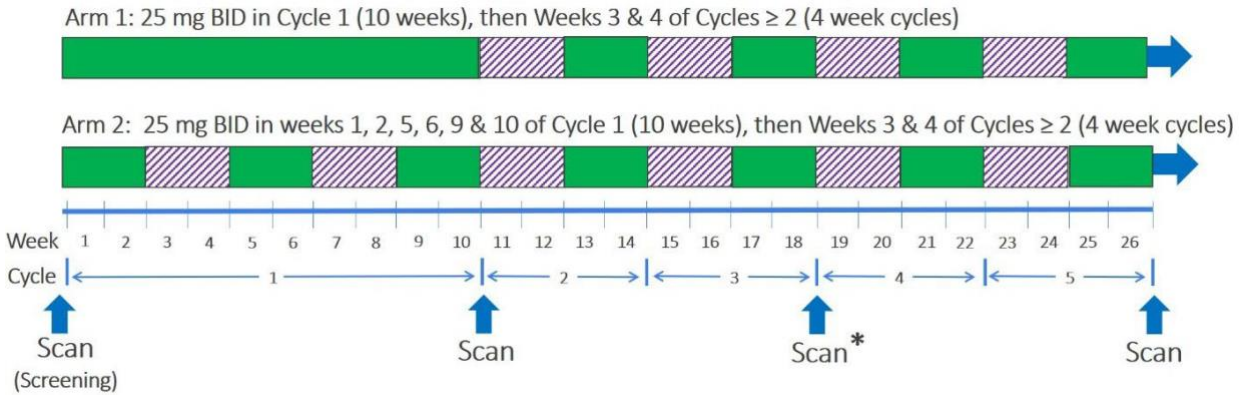
It is anticipated that the study enrollment will occur over approximately 2 years. The last subject visit will occur 2 years after the last subject is randomized. If the study is ended prior to all subjects discontinuing treatment, any subject continuing to receive benefit will be provided the opportunity to continue to receive duvelisib. Long-term continued treatment may be provided via an expanded access program consistent with local regulations, such as the Secura Bio NPP.

Data Monitoring Committee: None.

Disclosure Statement: This is a parallel-group unblinded treatment study with 2 arms.

1.2. Schema

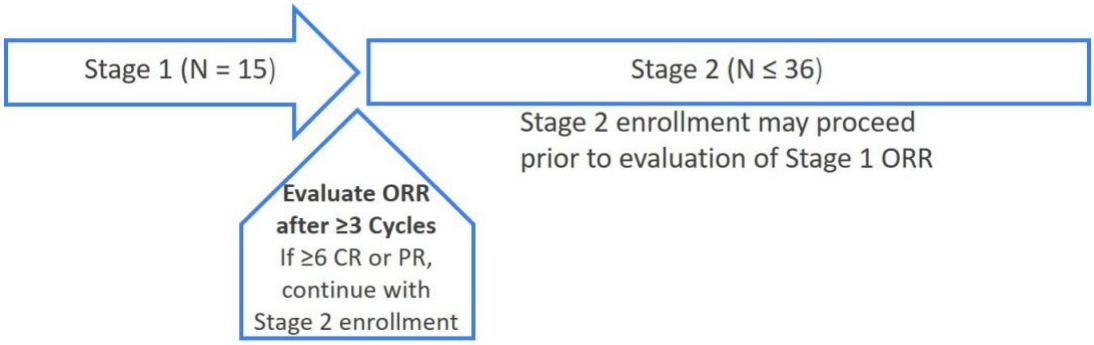
Figure 1: Treatment Scheme



Abbreviations: BID: twice daily.

Solid sections: duvelisib 25 mg BID; hashed sections: drug holiday. Subjects will be randomized 1:1 to Arms 1 and 2. Subjects will be assessed for disease response after approximately 10 weeks (i.e., within 7 days of the start of Cycle 2) and then within 7 days of the start of Cycles 4, 6, 9, 13, 17, and every 4th cycle thereafter until disease progression, unacceptable toxicity or withdrawal. (*): assessment of ORR after a minimum of 3 cycles of treatment in first-stage subjects (see Figure 2) to determine Stage 2 enrollment.

Figure 2: Two-stage Design for Each Arm



Abbreviations: CR: complete response; N: number of subjects; PR: partial response; ORR: overall response rate.

The decision to proceed to Stage 2 will be supported by the totality of data observed, including types of responses, safety data, and discontinuation rates. A treatment arm may also not proceed to the second stage if the totality of the data is compelling (e.g., accumulating enough data in Stage 1 to conclude the ORR exceeds 30%).

1.3. Schedule of Activities (SoA)

Table 1: Study Activities for Duvelisib Monotherapy (Cycle 1: 10 Weeks; Cycles ≥2: 4 Weeks)

Activity	Screening D-30 to D-1	Cycle 1					Cycle 2		Cycle 3+	EoT[a]	Safety F/U[b] 30d (+7) postdose		Notes
		D1	D14 (-3)	D29 (+3)	D43 (±3)	D57 (±3)	D1 (±3	D14 (-3)	D1 (±3)				
Informed Consent	X												Potentially eligible subjects must sign an 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.
Inclusion/Exclusion Criteria	X												
Randomization	X (D -7 to -1)												Subject must sign informed consent, meet inclusion/exclusion criteria, and complete all other screening activities prior to randomization.
Medical History, Demographics	X												Medical History includes histologic lymphoma diagnostic and prior treatment and response information, FLIPI-1 score
Archival Tumor Tissue	X												Tumor tissue is not required for enrollment, but should be submitted from all enrolled subjects, if available. Sample should be FFPE tissue and will be used to evaluate prognostic biomarkers.
Tumor Biopsy (optional)	X												If a transformation to a more aggressive subtype of lymphoma is suspected, a biopsy may be performed at Investigator's discretion. If this sample is collected, please see Archival Tumor Tissue instructions above.
Full Physical Examination	X	X											If performed within 7 days of C1D1, then screening results can be used for C1D1.
Focused Physical Examination			X	X	X	X	X	X	X	X			Disease-focused assessments including liver/spleen size, clinical assessment of tumor masses, and B symptoms.
Vital Signs	X	X	X	X	X	X	X	X	X	X			Vital signs measured in a semi-supine position after 5 minutes rest.
Computed Tomography (CT)	X									X			All subjects require CT or FDG-PET-CT scans. MRI may be used instead of CT scans if CT cannot

Activity	Screening D-30 to D-1	Cycle 1					Cycle 2		Cycle 3+		Safety F/U[b]		Notes
		D1	D14 (-3)	D29 (+3)	D43 (±3)	D57 (±3)	D1 (±3	D14 (-3)	D1 (±3)	EoT[a]	30d (+7) postdose		
Scans of the Chest, Abdomen and Pelvis			Day 1 of Cycles 2, 4, 6, 9, 13, 17, and Every 4th Cycle Thereafter (Window: Day -7 to Day 1 of Each Cycle)										be done, but the same method must be used throughout the study. A scan will be performed at the EoT if one was not performed within 30 days of the EoT Visit.
Response Assessment										X			Response will be assessed separately using 2007 revised IWG criteria (Cheson 2007) and 2014 Lugano criteria (Cheson 2014)
Bone Marrow Aspirate and/or Biopsy			As necessary to confirm CR										If a bone marrow/aspirate is performed within 60 days before C1D1 as part of standard of care, the pathology report will be provided to the Sponsor. If a radiologic CR according to 2007 revised IWG criteria (Cheson 2007) is observed during the course of the study, then a bone marrow biopsy should be done to confirm CR. The pathology report will be provided to the Sponsor.
ECG (12-lead)	X												QTc measurements (as measured by triplicate readings) will use the Fridericia's correction method. Additional on-treatment or follow-up ECGs may be performed at the Investigator's discretion as clinically indicated.
ECHO/ MUGA	X												ECHO or MUGA scan. Additional on-treatment or follow-up echocardiograms may be performed at the Investigator's discretion as clinically indicated.
Concomitant Medications and Procedures	X	X	X	X	X	X	X	X	X	X	X		
AE/SAE Assessment	X	X	X	X	X	X	X	X	X	X	X		
Coagulation tests	X												Prothrombin time, partial thromboplastin time and international normalized ratio
Viral screening	X												Hepatitis serology: HCV Ab, HBsAg, HBcAb. CMV/EBV serology or viral load. HIV test is not required if a prior negative test within 9 months is available.

Activity	Screening D-30 to D-1	Cycle 1					Cycle 2		Cycle 3+		Safety F/U[b]		Notes
		D1	D14 (-3)	D29 (+3)	D43 (±3)	D57 (±3)	D1 (±3	D14 (-3)	D1 (±3)	EoT[a]	30d (+7) postdose		
CMV Reactivation Monitoring			Subjects with a history of CMV infection/reactivation or viremia should be monitored for reactivation by PCR or antigen test at least monthly										
C-Reactive Protein	X		Obtain when Grade ≥ 2 diarrhea or any colitis occurs										
Endocrine function	X												Free thyroxine and thyroid-stimulating hormone
HLA Typing	X												Testing for HLA types A, B, C, DRB1, and DQB1. Do not need to perform if previous typing results are available.
Serum hCG Pregnancy Test	X			X		X	X		X	X			For WCBP, a serum pregnancy test must be performed within 7 days of C1D1. At subsequent time points, serum testing is preferred but urine testing is allowed if a blood draw for other assessments is not performed. A positive urine test must be confirmed by a serum test.
Clinical Chemistry, including Liver Function Tests	X	X	X	X		X	X		X	X			Liver function tests include LDH, serum ALT, serum AST, total and direct bilirubin, and ALP. Testing must be conducted, and results available, within 7 days prior to administration of first dose of duvelisib. Screening test results can be used for C1D1 if tests are performed within 7 days of C1D1.
Immunoglobulin blood levels	X			X			X		X (even # cycles)				IgA, IgG, IgM
Hematology	X	X	X	X	X	X	X		X	X			Hematology panel plus a 5-part differential. Testing must be conducted, and results available, within 7 days prior to administration of first dose of duvelisib. Screening test results can be used for C1D1 if tests are performed within 7 days of C1D1.
Urinalysis	X	X		X			X		X	X			Qualitative analysis for protein performed at Screening, at C1D1, C2D1 and C6D1. If positive, quantitative analysis is needed if not previously noted as part of medical history. Testing must be conducted, and results available, within 7 days

Activity	Screening D-30 to D-1	Cycle 1					Cycle 2		Cycle 3+	EoT[a]	Safety F/U[b]		Notes
		D1	D14 (-3)	D29 (+3)	D43 (±3)	D57 (±3)	D1 (±3	D14 (-3)	D1 (±3)		30d (+7) postdose		
													prior to administration of first dose of duvelisib. Screening test results can be used for C1D1 if tests are performed within 7 days of C1D1.
ECOG Performance Status	X	X		X			X		X	X			If the ECOG Performance Status assessed at Screening is performed within 7 days of C1D1, the Screening assessment can be used and does not need to be repeated at C1D1 (predose).
EQ-5D-3L Questionnaire	X	X		X			X		X	X			Administered predose and prior to other procedures during treatment visits
Pharmacokinetic and Biomarker Assessments		X	X	X		X	X	X	X see note				For Cycles ≥ 3, obtain stool sample if subject has Grade ≥ 3 diarrhea or colitis. Request representative fragment of tissue and/or representative section of paraffin block from biopsy if taken for colitis or Grade ≥ 3 diarrhea.
			See Table 2 for detailed schedule										
Duvelisib Self-Administration Diary		X		X	X	X	X	X	X				First year on treatment only
Duvelisib Administration (Please see required and recommended prophylaxis in Section 6.6.1)		X (C1D14 AM dose in clinic)		X	X	X	X	X	X				Administration of the first dose should be scheduled to occur within 1 week after randomization. See Section 6.1 for dosing schedule.

Abbreviations: AE/SAE: adverse event/serious adverse event; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BID: twice daily; CxDx: Cycle x, Day x; CMV: cytomegalovirus; CR: complete response; CT: computed tomography; EBV: Epstein-Barr virus; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; ECHO: echocardiogram; EoT: end of treatment; FDG-PET: ^{18}fluoro-2-deoxy-d-glucose-positron emission tomography; FFPE: formalin-fixed paraffin-embedded; FLIPI-1: Follicular Lymphoma International Prognostic Index; F/U: follow-up; HBcAb: hepatitis B core antibody; HBsAg: hepatitis B surface antigen; HCVAb: hepatitis C antibody; hCG: human chorionic gonadotropin; HIV: human immunodeficiency virus; HLA: human leukocyte antigen; ICF: informed consent form; iNHL: indolent non-Hodgkin lymphoma; IWG: international working group; LDH: lactate dehydrogenase; MRI: magnetic resonance imaging; MUGA: multi-gated acquisition; PCR: polymerase chain reaction; WCBP: women of childbearing potential.

a. An EoT Visit will be performed for all subjects who permanently discontinue study intervention within 7 days following the decision to discontinue study intervention. EoT assessments need not be repeated if performed within the previous 14 days, or 30 days for CT scan.

b. Safety follow-up visit to be performed 30 + 7 days from last dose. If possible, this visit should occur prior to the initiation of any subsequent anticancer therapy. This can be performed by telephone call if the subject does not require laboratory and/or other procedures related to any new or ongoing AEs, in which case a clinical visit will be required.

Table 2: Pharmacokinetic and Biomarker Sampling[a,b]

Cycle	Study Day	Time Points	Whole blood for PK[c]	Whole blood for pharmacodynamic biomarkers (U.S. sites only)	Serum and plasma for biomarkers	Whole blood for immune cell analysis	Stool sample for biomarker analysis
1	1	Predose	X	X	X	X	X[e]
		1 hour (± 5 min) postdose	X	X			
		2 hours (± 10 min) postdose	X	X			
		4 hours (± 10 min) postdose	X				
	14 (-3)[d]	Predose	X	X			
		1 hour (± 5 min) postdose	X				
		2 hours (± 10 min) postdose	X				
		4 hours (± 10 min) postdose	X				
	29 (+3)[d]	Predose	X				
		1 hour (± 5 min) postdose	X				
		2 hours (± 10 min) postdose	X				
		4 hours (± 10 min) postdose	X				
	57 (±3)[d]	Predose			X	X	
2	1 (±3)	Anytime during visit			X	X	X[e]
	14 (-3)	Anytime during visit			X	X	
3+	Any	Anytime during visit					X[e]

Abbreviations: CR: complete response; CxDx: Cycle x Day x; PK: pharmacokinetics

a. Any changes to this sampling plan (e.g., reductions in the number of sample collections) will be provided in the study lab manual.
b. In addition to the samples shown in this table, provide (if feasible) a sample of any colon biopsies taken for colitis or Grade ≥ 3 diarrhea
c. PK sampling must occur on a dosing day. After a subject has had a dose reduction and received ≥ 10 consecutive days of the reduced dose (not including scheduled dose holidays), PK sampling as shown for C1D1 will be repeated.
d. On C1D14, C1D29 and C1D57, the morning dose of study medication will be administered in the clinic to accommodate PK and/or biomarker sampling.
e. The C1D1 stool sample may be collected up to 7 days prior to C1D1. C2D1 stool samples may be collected up to 3 days prior to these visits. Stool samples may be collected either predose or postdose. Obtain additional stool sample if subject has colitis or Grade ≥ 3 diarrhea.

2. INTRODUCTION

Duvelisib (VS-0145) is a synthetic orally-active small molecule dual inhibitor of phosphoinositide 3-kinase (PI3K)-δ and PI3K-γ that is being developed by Secura Bio, Inc. (Secura Bio; study Sponsor) for the treatment of follicular lymphoma (FL) and other indolent non-Hodgkin lymphomas (iNHLs), T-cell lymphoma and other hematological malignancies, and solid tumor malignancies.

2.1. Study Rationale

The registrational studies for duvelisib 25 mg twice daily (BID) in chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL; the DUO study) and for iNHL, including FL (the DYNAMO study), were positive with respect to their primary endpoints of progression-free survival (PFS; DUO) and overall response rate (ORR; DYNAMO) and included subjects who received at least 1 prior treatment regimen. Ultimately duvelisib (COPIKTRA®) 25 mg BID was approved by the United States (US) Food and Drug Administration (FDA) for the treatment of adult patients with relapsed or refractory (R/R) FL and SLL after ≥ 2 prior systemic therapies. The overall risk-benefit profile was greatest in the setting of ≥ 2 prior systemic therapies, which supported the approval in this specific subset of subjects. Although several other regimens (e.g., autologous transplantation for younger patients, repetition of the first-line treatment, bendamustine plus obinutuzumab or rituximab) are currently recommended by the European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines in the second-line setting, relapses are common, and the unmet medical need remains high in this patient population (ESMO 2019, NCCN 2019).

The post-hoc analysis of the DUO study showed that response to duvelisib was improved or maintained in most subjects who had ≥ 1 dose interruption (DI) for > 1 week (84%) or > 2 weeks (82%), then followed by ≥ 3 weeks on duvelisib. PFS was also similar between subjects with ≥ 1 DI and those without DI for > 1 week or > 2 weeks within the first 3 months of therapy (median PFS: > 1 week, 17.8 vs 16.3 months; > 2 weeks, 17.8 vs 16.3 months) (Flinn 2019). These data support the hypothesis that prespecified 2-week DIs would not impact efficacy.

This study (VS-0145-229) is a proof-of-concept study that will evaluate whether duvelisib 25 mg BID efficacy can be achieved and maintained, with acceptable or improved safety and tolerability, by inclusion of prespecified 2-week drug holidays in 2 different schedules in subjects with R/R iNHL after failure of at least 1 line of prior therapy.

2.2. Background

2.2.1. Non-Hodgkin Lymphoma

Non-Hodgkin lymphoma (NHL) is one of the most common malignancies in the US, Europe, and Asia. It is expected that about 74,200 people will be diagnosed with NHL in the US in 2019 with about 19,970 projected deaths from this disease (NCI-SEER 2019). Indolent NHL (iNHL) accounts for approximately one third of all NHL cases. Follicular lymphoma (FL) is the most common iNHL type, followed by SLL, and marginal zone B-cell lymphoma (MZL, that includes

nodal and splenic marginal zone), which occur in approximately 30%, 7%, and 4% of all NHL cases, respectively (Swerdlow 2016).

The course of iNHL is variable. While some patients can remain asymptomatic for extended periods, others may require immediate intervention. Rituximab-based regimens are common front-line treatment choices in patients with FL and MZL, and ibrutinib or venetoclax in combination with obinutuzumab are preferred choices in patients with SLL (NCCN 2019).

Although most patients with iNHL have durable responses to initial treatment with prolonged remission, relapses, requiring serial retreatment, are common. Almost all patients will eventually progress or have a disease recurrence, and advanced-stage iNHL remains incurable (Cheson 1998, Hitz 2011, Sehn 2016). Recent data show that patients with FL who progress within 2 years of initial diagnosis also have a lower 5-year overall survival (OS) rate (50%) than patients without early progression (90%) after front-line combination therapy with rituximab plus cyclophosphamide, doxorubicin, and prednisone (R-CHOP) (Casulo 2015).

Despite the availability of several treatment options for relapsed iNHL, major challenges remain, which include cumulative toxicities from multiple therapies and resistance or transformation to aggressive or high-grade lymphomas (Coutre 2015, Federico 2000). While allogeneic stem cell transplantation could be potentially curative, only a small number of patients are eligible for this therapy, and there is unmet medical need for new therapies.

2.2.2. PI3 Kinases

PI3Ks catalyze the production of phosphatidylinositol (3, 4, 5)-trisphosphate, leading to activation of downstream effector pathways important for cellular survival, differentiation, and function. There are 4 mammalian isoforms of class 1 PI3Ks: PI3K-α, β, δ (class 1a), and PI3K-γ (class 1b) (Fruman 2017).

PI3K-α and PI3K-β are widely expressed and are important mediators of signaling from cell surface receptors, while the PI3K-δ and PI3K-γ isoforms are more narrowly expressed in hematopoietic lineage cells, immune cells, and malignant hematopoietic cells. Pathways mediated by PI3K-δ and PI3K-γ are involved in diverse processes of cell growth, survival, proliferation, migration, differentiation, and metabolism. Since central regulatory roles for either or both enzymes have been demonstrated in B cells, T cells, macrophages/monocytes, mast cells, and natural killer (NK) cells, both PI3K-δ and PI3K-γ are believed to be important for the development and persistence of autoimmune disease and hematologic malignancies (Curran 2014, Ortiz-Maldonado 2015, Steele 2014, Westin 2014).

PI3K-δ, and PI3K-γ activity supports the growth and maintenance of cancer cells and the supportive tumor microenvironment. Data from nonclinical in vitro and in vivo studies show that inhibition of PI3K-δ, and PI3K-γ results in significant efficacy against hematologic malignancies and solid tumors. Duvelisib is being developed due to its ability to inhibit PI3K-δ and PI3K-γ and reduce their cancer-promoting effects. The direct effect of duvelisib on primary malignant hematologic tumor cells was demonstrated by duvelisib-mediated growth inhibition of both primary CLL cells and cell lines derived from transformed FL, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), multiple myeloma, and T-cell lymphoma/leukemia (Dong 2014, Faia 2015).

2.2.3. Duvelisib in Hematologic Malignancies

Duvelisib has shown clinical activity in various hematologic malignancies, including CLL, iNHL, and cutaneous and peripheral T-cell lymphoma (CTCL and PTCL, respectively). In the Phase 1 study in hematologic malignancies, including iNHL (Flinn 2018), the recommended Phase 2 dose (RP2D) was determined to be 25 mg BID with maculopapular rash, alanine aminotransferase/aspartate aminotransferase (ALT/AST) elevation, neutropenia, and cellulitis observed as dose-limiting toxicities.

As of 19 July 2018, approximately 1378 subjects have been exposed to duvelisib as monotherapy or in combination with another agent, including approximately 814 subjects with hematologic malignancies in Company- or Investigator-sponsored studies. Indications include NHL subtypes of mature B-cell lymphomas (e.g., FL, CLL/SLL, DLBCL, marginal zone lymphoma, MCL) and mature T-cell lymphomas (e.g., PTCL, CTCL), acute myeloid leukemia, and multiple myeloma. Studies have been conducted globally in countries including the US, Canada, the United Kingdom, Austria, France, Germany, Georgia, Hungary, Italy, Spain, Belarus, Belgium, Bulgaria, Czech Republic, and Australia.

Duvelisib was approved by the FDA in September 2018 for the treatment of patients with R/R CLL/SLL after at least 2 prior therapies and received accelerated approval for R/R FL after at least 2 prior systemic therapies (COPIKTRA 2018). Please see the Duvelisib Investigator's Brochure (IB) for detailed descriptions of nonclinical and clinical safety and efficacy results. These data, together with the available safety data, support the ongoing evaluation of duvelisib in subjects with hematologic malignancies.

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

As of 19 July 2018, in 588 subjects treated with duvelisib monotherapy in hematologic malignancy studies (see Section 6.3.4.1.2 in the IB), the most frequent treatment-emergent adverse events (TEAEs) (≥ 20% of subjects) reported were diarrhea/colitis (49.0%), neutropenia (34.7%), rash (34.7%), fatigue (33.2%), pyrexia (30.3%), cough (26.7%), nausea (26.0%), transaminase elevation (22.8%), musculoskeletal pain (22.6%), anemia (22.4%), upper respiratory tract infection (22.3%), and pneumonia (21.6%). The most frequently reported TEAEs, diarrhea and neutropenia, are amenable to early recognition and intervention. These events infrequently resulted in treatment discontinuation with management, including dose modifications and supportive care. Many of the more severe TEAEs, such as infections and hematologic abnormalities, are commonly observed in subjects with advanced B-cell malignancies. Adverse events (AEs) of special interest (AESIs), such as diarrhea, colitis, pneumonitis, rash, and transaminase elevations, have been well-described with the use of PI3K-δ inhibitors and immuno-oncology therapies. The most commonly occurring AEs infrequently resulted in treatment discontinuation, representing a manageable safety profile in subjects with advanced hematologic malignancies.

The identified risks for duvelisib treatment are infections, diarrhea/colitis, cutaneous reactions, pneumonitis, transaminase elevations, and neutropenia. Potential risks are hepatotoxicity and reproductive toxicity. Guidance on management of these AEs, including duvelisib dose interruptions and modifications, is provided in Section 6.6 and Section 6.7. Detailed information

about the known and expected risks and reasonably expected AEs of duvelisib may be found in the IB.

2.3.2. Benefit Assessment

Subjects may derive benefit due to improvements in symptoms and tumor control. Duvelisib treatment produced clinical activity in subjects with hematologic malignancies, including CLL/SLL, FL, and PTCL. In the pivotal CLL/SLL study (Study IPI-145-07), duvelisib monotherapy resulted in statistically significant improvement in PFS (16.4 months vs 9.1 months) and ORR (78% vs 39%) compared to ofatumumab in subjects who had received at least 2 prior therapies. Reductions in target lymph nodes were observed in Study IPI-145-07 in most subjects treated with duvelisib (85%), representing a statistically significant treatment effect over ofatumumab (16%). In subjects with FL in a Phase 2 study in iNHL (IPI-145-06), the ORR was 42.2%, meeting the primary endpoint ($p < 0.0001$ against the null hypothesis that ORR was ≤ 30% per Independent Review Committee [IRC]). In subjects with PTCL in a Phase 1 dose escalation study (IPI-145-02), the observed ORR was 53.3%. More detailed information about the clinical efficacy observed in duvelisib studies can be found in the IB.

2.3.3. Overall Benefit: Risk Conclusion

Clinical study results to date support a favorable benefit-risk of duvelisib for subjects with hematologic malignancies. Efficacy has been seen in multiple studies, including significant improvements in ORR and PFS relative to the comparator in a pivotal study in R/R CLL/SLL (Study IPI-145-07) and positive ORR and duration of response (DOR) in a single-arm FL study (Study IPI-145-06). Important identified risks include infections, diarrhea/colitis, cutaneous reactions, pneumonitis, neutropenia, and ALT/AST elevations. The efficacy and safety profile of duvelisib, as detailed in the IB, indicates that the benefits of duvelisib therapy outweigh the risks. In addition, the alternative dosing schedules being evaluated in the current study may improve the safety profile while maintaining the efficacy benefit, potentially increasing the benefit:risk for subjects in this study.

3. OBJECTIVES AND ENDPOINTS

Table 3: Objectives and Endpoints

Objective	Endpoint (see Section 9.4 for definitions)
Primary	
Evaluate the efficacy of duvelisib administered with prescribed drug holidays in subjects with iNHL	Overall Response Rate (ORR) according to the 2007 revised International Working Group (IWG) Criteria (Cheson 2007)
Secondary	
Evaluate supportive efficacy measures of duvelisib administered with prescribed drug holidays in subjects with iNHL	• ORR according to 2014 Lugano criteria (Cheson 2014) *Note: all additional secondary response endpoints, as well as progression-free survival (PFS), will be assessed separately using 2007 revised IWG criteria (Cheson 2007) and 2014 Lugano criteria (Cheson 2014)* • ORR, at 6, 12, 18, and 24 months after first dose of study intervention • Progression-free Survival • Time to Treatment Failure (TTF) • Duration of Response (DOR) • Overall Survival (OS) • Lymph Node Response Rate (LNRR) • Time to the First Response (TTFR)
Evaluate the safety and tolerability of duvelisib administered with prescribed drug holidays in subjects with iNHL	Adverse events (AEs), serious AEs (SAEs), vital signs, physical examinations, and abnormal laboratory values
Characterize the pharmacokinetics (PK) of duvelisib and metabolite IPI-656 when duvelisib is administered with prescribed drug holidays in subjects with iNHL	PK parameters for duvelisib and metabolite IPI-656
Exploratory	
Evaluate Quality of Life (QoL) in subjects treated with duvelisib with prescribed drug holidays	• ECOG Performance Score • EQ-5D-3L questionnaire responses
Evaluate potential biomarkers of clinical efficacy and/or safety of duvelisib administered with prescribed drug holidays in subjects with iNHL	• Blood assessments of immune cell populations, chemokines, cytokines, proteins and/or circulating tumor (ctDNA)

	• Assessments of protein, DNA, and or RNA in fecal microbiota • Tumor biopsy evaluation of biomarkers such as gene and copy number variation, RNA expression, protein expression, and/or immune cell content

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, randomized, open-label, 2-arm study designed to evaluate the efficacy and safety of alternative dosing schedules of duvelisib treatment in subjects with R/R iNHL who have received at least 1 prior systemic therapy. This is a multi-site global study.

Subjects will be stratified by number of prior therapies (1 or > 1), bulky disease status (longest diameter of baseline lesion < 5 cm or ≥ 5 cm) and time since last recurrence (≥ 24 months or < 24 months).

Subjects will be randomized to Arm 1 or Arm 2 in a 1:1 fashion.

- Arm 1: duvelisib 25 mg BID for one 10-week cycle followed by 25 mg BID on Weeks 3 and 4 of each subsequent 4-week cycles until disease progression, unacceptable toxicity, or withdrawal.
- Arm 2: duvelisib 25 mg BID on Weeks 1, 2, 5, 6, 9 and 10 of one 10-week cycle, then on Weeks 3 and 4 of each subsequent 4-week cycles until disease progression, unacceptable toxicity, or withdrawal.

The study has a 2-stage design (see Figure 2). For each arm: in the first stage, 15 subjects will be enrolled. Responses will be assessed by the Investigator according to the 2007 revised IWG criteria (Cheson 2007) (primary endpoint) and the 2014 Lugano criteria (Cheson 2014). The evaluation of the first stage will take place after the enrolled subjects have been followed for a minimum of 3 cycles. If there are fewer than 6 responders (partial response [PR] or complete response [CR]) among the first 15 subjects per arm, consideration may be given to stopping that arm. Otherwise, approximately 36 additional subjects will be enrolled for a total of 51 per arm. Enrollment will be continuous between Stage 1 and Stage 2. If fewer than 22 (43%) responders (PR or CR) are observed in 51 subjects, consideration may be given to concluding that the treatment schedule does not warrant further study in this population.

It is anticipated that study enrollment will occur over approximately 2 years. The last subject visit will occur 2 years after the last subject is randomized.

4.2. Scientific Rationale for Study Design

Dosing with duvelisib 25 mg BID has been shown to be efficacious in multiple Phase 1-3 studies including subjects with iNHL. Data from the pivotal Phase 3 CLL/SLL study (DUO) and Phase 2 FL study (DYNAMO) showed that most tumor responses occurred by the end of Cycle 4 of duvelisib 25 mg BID treatment, and the majority of DIs for toxicity occurred primarily after 4 cycles. The post-hoc analysis of the DUO study showed that response to duvelisib was improved or maintained in most subjects who had ≥ 1 DI for > 1 week (84%) or > 2 weeks (82%), then followed by ≥ 3 weeks on duvelisib. PFS was also similar between subjects with ≥ 1 DI and those without DI for > 1 week or > 2 weeks within the first 3 months of therapy (median PFS: > 1 week, 17.8 vs 16.3 months; > 2 weeks, 17.8 vs 16.3 months) (Flinn 2019). These data support the hypothesis that prespecified 2-week drug holidays used in this study would not impact efficacy. Based on these results, the VS-0145-229 study will examine the effects of prespecified 2-week dose holidays on tumor responses (i.e., is uninterrupted dosing required in early cycles to

achieve responses, or can comparable tumor responses be achieved starting with alternating 2-week periods of dosing and holidays?) and safety/tolerability (i.e., will the holidays reduce the frequency, severity, and/or duration of AEs, allowing subjects to stay on treatment longer?).

4.3. Justification for Dose

The duvelisib 25 mg BID dose was selected as the current Recommended Phase 2 Dose (RP2D) based on the pharmacokinetics (PK), pharmacodynamics, clinical activity, and safety observed in a Phase 1 dose escalation study (IPI-145-02) in subjects with hematologic malignancies, including iNHL. The efficacy, safety, and tolerability of this RP2D was confirmed in a Phase 2 study (IPI-145-06) in subjects with iNHL and is currently the approved label dose for CLL/SLL and FL patients. Please see the IB for detailed descriptions of duvelisib clinical study results and the selection of the RP2D.

4.4. End of Study Definition

A subject is considered to have completed the study if he/she has completed the last scheduled procedure shown in the Schedule of Activities (SoA) (Section 1.3).

The end of the study is defined as the date of the last scheduled procedure shown in the SoA (Section 1.3) for the last subject in the study globally. This will occur 2 years after the last subject is randomized.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Subjects may be eligible for inclusion in the study if they meet the following criteria:

1. Male or female subjects ≥ 18 years of age
2. Histologically confirmed diagnosis of iNHL. Histologic subtypes include FL Grades 1 to 3a, marginal zone lymphoma (splenic, nodal, or extranodal), or SLL
3. Must have received at least 1 prior systemic regimen for iNHL
4. Must have documented radiologic evidence of disease progression, at least 1 bidimensionally measurable lesion ≥ 1.5 cm (which has not been previously irradiated), according to 2007 revised IWG criteria (Cheson 2007), and be a candidate for a subsequent line of therapy
5. Must have adequate organ function defined by the following laboratory parameters:
   a. Absolute neutrophil count (ANC) ≥ 1.0×10^9/L
   b. Platelet count ≥ 75×10^9/L
   c. Hemoglobin ≥ 8 g/dL
   d. Estimated creatinine clearance (eCCr) ≥ 60 mL/min, as determined by the Cockcroft-Gault method (Cockcroft 1976)
   e. Total bilirubin ≤ 1.5 × upper limit of normal (ULN) (exception: subjects with Gilbert's Syndrome may have a bilirubin > 1.5 × ULN)
   f. Aspartate transaminase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) and alanine aminotransferase (ALT)/serum pyruvic transaminase (SGPT) ≤ 3.0 × ULN
6. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
7. Male and female subjects of reproductive potential (i.e., not surgically sterile or female subjects who are not postmenopausal) must be willing to use highly effective methods of contraception (see Section 10.4) for the duration of the study intervention and for 3 months after the last dose of duvelisib
8. Negative serum human chorionic gonadotropin (hCG) pregnancy test within 7 days before first dose of study intervention if the subject is a woman of childbearing potential (WCBP) (defined in Section 10.4)
9. Signed and dated institutional review board (IRB)/independent ethics committee (IEC)-approved informed consent form before any study specific-screening procedures are performed

5.2. Exclusion Criteria

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

1. Anticancer treatment, major surgery, or use of any investigational drug within 28 days before the start of study intervention; palliative radiation therapy is allowed if > 7 days before planned first dose of study interventions and any toxicity is Grade ≤ 1
2. Clinical or histological evidence of transformation to a more aggressive subtype of lymphoma or grade 3b FL or Richter's transformation or CLL
3. Received prior allogeneic hematopoietic stem cell transplant (HSCT)
4. Previous treatment with a PI3K inhibitor
5. Known hypersensitivity to duvelisib and/or its excipients
6. History or concurrent condition of interstitial lung disease of any severity and/or severely impaired lung function
7. Prior history of drug-induced colitis or drug-induced pneumonitis
8. History of tuberculosis treatment within the 2 years prior to randomization
9. Administration of a live or live attenuated vaccine within 6 weeks of randomization
10. Ongoing treatment with chronic immunosuppressants (e.g., cyclosporine) or systemic steroids > 20 mg of prednisone (or equivalent) per day
11. Ongoing treatment for systemic bacterial, fungal, or viral infection at screening
    - Note: Subjects on antimicrobial, antifungal, or antiviral prophylaxis are not specifically excluded if all other inclusion/exclusion criteria are met
12. Active cytomegalovirus (CMV) or Epstein-Barr virus (EBV) infection (i.e., subjects with detectable viral load)
13. Unable to receive prophylactic treatment for pneumocystis, herpes simplex virus (HSV), or herpes zoster (VZV) at screening
14. Infection with hepatitis B, hepatitis C, or human immunodeficiency virus (HIV)
    - Subjects with a positive hepatitis B surface antigen [HBsAg] or hepatitis C antibody [HCV Ab] will be excluded
    - Subjects with a positive hepatitis B core antibody (HBcAb) must have negative hepatitis B virus (HBV) deoxyribonucleic acid (DNA) to be eligible and must be periodically monitored for HBV reactivation by institutional guidelines
    - Investigators who strongly believe that a positive HBcAb is false due to passive immunization from previous immunoglobulin infusion therapy should discuss the potential to defer HBV prophylaxis with the Medical Monitor
15. Concurrent administration of medications or foods that are strong inhibitors or inducers of cytochrome P450 3A (CYP3A). No prior use within 2 weeks before the start of study intervention.
16. Subjects with clinically significant medical condition of malabsorption, inflammatory bowel disease, chronic conditions which manifest with diarrhea, refractory nausea, vomiting, or any other condition that will interfere significantly with drug absorption

17. Central nervous system non-Hodgkin lymphoma (NHL); lumbar puncture not required unless central nervous system involvement is clinically suspected
18. Baseline QTcF > 500 ms (average of triplicate readings). NOTE: This criterion does not apply to subjects with a right or left bundle branch block.
19. Concurrent active malignancy other than non-melanoma skin cancer or carcinoma in situ of the cervix, bladder cancer, or prostate cancer not requiring treatment. Subjects with previous malignancies are eligible if they have been disease-free for 2 years or more.
20. History of chronic liver disease, veno-occlusive disease/sinusoidal obstruction syndrome, alcohol abuse, or illicit drug use
21. History of stroke, unstable angina, myocardial infarction, or ventricular arrhythmia requiring medication or mechanical control within the last 6 months prior to first dose of study intervention
22. Unstable or severe uncontrolled medical condition (e.g., unstable cardiac function, unstable pulmonary condition). Any important medical illness or abnormal laboratory finding that would, in the Investigator's judgment, increase the subject's risk to participating in this study.
23. Female subjects who are pregnant or breastfeeding

5.3. Lifestyle Considerations

- Male and female subjects of reproductive potential (i.e., not surgically sterile or female subjects who are not postmenopausal) must use highly effective contraception for the duration of the study intervention and for at least 3 months after the last dose of duvelisib. Please see Section 10.4 for detailed contraceptive requirements.
- Subjects should be advised to use appropriate protective measures to minimize exposure to direct sunlight or ultraviolet light sources during the treatment period and for at least 30 days after the last dose of duvelisib. Please see the IB for additional details on the potential for phototoxicity.
- Refrain from consumption of grapefruit juice and St. John's Wort, and other foods and herbal products that are strong inhibitors or inducers of CYP3A during treatment with duvelisib. Please see Section 6.6.3 for additional information on restrictions on the use of CYP 3A inhibitors, inducers, and substrates, and Section 10.2 for lists of CYP3A inhibitors, inducers, and substrates. The IB contains additional details on potential interactions with foods.

5.4. Definition of Enrolled

"Enrolled" means a subject's agreement to participate in a clinical study following completion of the informed consent process. Potential subjects who are pre-screened for the purpose of determining eligibility for the study but do not sign an informed consent form (ICF) are not considered enrolled.

5.5. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date. Please note that repeating of clinical laboratory assessments during screening does not constitute rescreening.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study subject according to the study protocol.

6.1. Study Intervention(s) Administered

Table 4: Study Intervention Arms

	Arm 1	Arm 2
Intervention Name	Duvelisib	
Type	Investigational Drug	
Drug Substance Description	White to off-white crystalline powder	
Dose Formulation	Capsule	
Unit Dose Strength(s)	25 mg 15 mg (dose reductions only)	
Formulation Excipients	Excipients (diluent, glidant, disintegrant, and lubricant) that are listed in the United States (US) Food and Drug Administration (FDA) Inactive Ingredients Database for approved drug products and/or Generally Regarded as Safe (GRAS).	
Dosage Level(s) and Frequency	25 mg BID for one 10-week cycle followed by 25 mg BID on Weeks 3 and 4 of each subsequent 4-week cycles until disease progression, unacceptable toxicity, or withdrawal	25 mg BID on Weeks 1, 2, 5, 6, 9 and 10 of one 10-week cycle, then on Weeks 3 and 4 of each subsequent 4-week cycles until disease progression, unacceptable toxicity, or withdrawal
Route of Administration	Oral	
Use	Experimental	
Investigational Medicinal Product (IMP) or Non-Investigational Medicinal Product (NIMP)	IMP	
Sourcing	Provided by the Sponsor	
Packaging and Labeling	Packaging and labeling will be prepared to meet all regulatory requirements.	
Current/Former Name(s) or Alias(es)	VS-0145, IPI-145	

6.2. Administration

Duvelisib should be swallowed whole with a glass of water (approximately 8 ounces or 240 mL). Advise subjects not to open, break, or chew the capsules. Duvelisib may be administered without regard to meals, however, subjects must avoid grapefruit and grapefruit juice while on duvelisib.

Refer to the Pharmacy Manual for additional instructions regarding study intervention administration.

6.3. Preparation/Handling/Storage/Accountability

Dispensing and storage instructions for duvelisib will be provided in the Pharmacy Manual. On receipt at the investigative site, duvelisib should remain in the packaging as provided until use or dispensation. The packaged product should be stored at the investigative site at 20° to 25°C (68° to 77°F), with excursions permitted at 15° to 30°C (59° to 86°F). Temperature excursion procedures are provided in the Pharmacy Manual. Expired drug is not to be dispensed.

Only subjects enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.4. Measures to Minimize Bias: Randomization and Blinding

This is an open-label randomized study. Subjects will be stratified by number of prior therapies (1 or > 1), bulky disease status (longest diameter of baseline lesion < 5 cm or ≥ 5 cm) and time since last recurrence (≥ 24 months or < 24 months).

Subjects will be assigned a unique number in ascending numerical order at each study site. This is an open-label study; however, the specific arm for a subject will be assigned using an interactive web response system (IWRS). The site will contact the IWRS prior to the start of study intervention administration for each subject. The site will record the arm assignment on the applicable case report form (CRF). Potential bias will be reduced by central randomization.

6.5. Study Intervention Compliance

When subjects are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When subjects self-administer study intervention at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by reviewing subject diaries (first year on treatment only) and counting returned capsules during the site visits and documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

A record of the number of duvelisib capsules dispensed to and taken by each subject must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the CRF.

6.6. Concomitant Therapy

Any other medication (e.g., supportive care) that is considered necessary for the subject's welfare and is not expected to interfere with the evaluation of duvelisib may be given at the discretion of the Investigator.

Any medication that the subject is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6.1. Required and Recommended Prophylaxis

6.6.1.1. Antimicrobial and Antiviral Prophylaxis

Based on the duvelisib clinical experience to date the following are required or recommended:

- Subjects are required to receive pneumocystis prophylaxis concomitant with study intervention treatment per institutional guidelines. Following completion of duvelisib treatment, continue prophylaxis until the absolute CD4+ T-cell count is greater than 200 cells/μL.
- HSV and VZV infections have been observed with duvelisib; therefore, herpes (HSV/VZV) prophylaxis concomitant with treatment is recommended, per Investigator discretion according to institutional guidelines.
- Subjects with a history of CMV infection/reactivation or viremia should be monitored for reactivation by polymerase chain reaction (PCR) or antigen test at least monthly. Prophylactic treatment per institutional guidelines is recommended for subjects considered by Investigators to be at high risk for CMV reactivation.
- Antimicrobial prophylaxis and pneumococcal pneumonia vaccine are recommended for subjects with history of or considered at high risk for infections and during periods of severe neutropenia. Choice of antimicrobial agent (antifungal, antibiotic, antiviral) is per Investigator discretion, but the restrictions on the use of CYP3A inducers, inhibitors, and substrates should be considered (see Section 6.6.3).

6.6.2. Supportive Care and Management of Toxicities

Supportive care should be provided as clinically indicated. Granulocyte colony-stimulating factor (G-CSF) may be used according to the American Society of Clinical Oncology (ASCO)

guidelines (Smith 2015). Transfusions may be used at any time as clinically indicated, and according to ASCO guidelines. Subjects on a stable dose of erythropoietin to treat baseline anemia may continue this therapy at this dose.

Recommendations for the management of non-hematologic and hematologic AEs with supportive care, treatment hold, dose reduction, or discontinuation of duvelisib are found in Table 5. Additional information regarding management of toxicities can be found in the Summary of Data and Guidance to the Investigator section of the IB.

Table 5: Recommendations for the Management of Toxicities

Toxicity	Adverse Reaction Grade	Recommended Management
Non-hematologic Adverse Reactions		
Infections	Grade 3 or higher infection	• Withhold duvelisib until resolved • Resume at the same or reduced dose (see Table 8)
	Clinical CMV infection or viremia (positive PCR or antigen test)	• Withhold duvelisib until resolved • Resume at the same or reduced dose (see Table 8) • If duvelisib is resumed, monitor subjects for CMV reactivation (by PCR or antigen test) at least monthly
	PJP	• For suspected PJP, withhold duvelisib until evaluated • For confirmed PJP, discontinue duvelisib
Non-infectious Diarrhea or colitis	Mild/moderate diarrhea (Grade 1-2, up to 6 stools per day over baseline) and responsive to antidiarrheal agents, OR Asymptomatic (Grade 1) colitis	• No change in dose • Initiate supportive therapy with antidiarrheal agents as appropriate • Monitor at least weekly until resolved
	Mild/moderate diarrhea (Grade 1-2, up to 6 stools per day over baseline) and unresponsive to antidiarrheal agents	• Withhold duvelisib until resolved • Initiate supportive therapy with enteric acting steroids (e.g., budesonide) • Monitor at least weekly until resolved • Resume at a reduced dose (see Table 8)
	Abdominal pain, stool with mucus or blood, change in bowel habits, peritoneal signs, OR Severe diarrhea (Grade 3, > 6 stools per day over baseline)	• Withhold duvelisib until resolved • Initiate supportive therapy with enteric acting steroids (e.g., budesonide) or systemic steroids • Monitor at least weekly until resolved • Resume at a reduced dose (see Table 8) • For recurrent Grade 3 diarrhea or recurrent colitis of any grade, discontinue duvelisib
	Life-threatening	• Discontinue duvelisib

Toxicity	Adverse Reaction Grade	Recommended Management
Cutaneous reactions	Grade 1-2	• No change in dose • Initiate supportive care with emollients, anti-histamines (for pruritus), or topical steroids • Monitor closely
	Grade 3	• Withhold duvelisib until resolved • Initiate supportive care with emollients, anti-histamines (for pruritus), or topical steroids • Monitor at least weekly until resolved • Resume at reduced dose (see Table 8) • If severe cutaneous reaction does not improve, worsens, or recurs, discontinue duvelisib
	Life-threatening	• Discontinue duvelisib
	SJS, TEN, DRESS (any grade)	• Discontinue duvelisib
Pneumonitis without suspected infectious cause	Moderate (Grade 2) symptomatic pneumonitis	• Withhold duvelisib • Treat with systemic steroid therapy • If pneumonitis recovers to Grade 0 or 1, duvelisib may be resumed at reduced dose (see Table 8) • If non-infectious pneumonitis recurs or subject does not respond to steroid therapy, discontinue duvelisib
	Severe (Grade 3) or life-threatening pneumonitis	• Discontinue duvelisib • Treat with systemic steroid therapy
ALT/AST elevation	3 to 5 × ULN (Grade 2)	• Maintain duvelisib dose • Monitor at least weekly until return to < 3 × ULN
	> 5 to 20 × ULN (Grade 3)	• Withhold duvelisib and monitor at least weekly until return to < 3 × ULN • Resume duvelisib at same dose (first occurrence) or at a reduced dose for subsequent occurrence (see Table 8)
	> 20 × ULN (Grade 4)	• Discontinue duvelisib
Hematologic Adverse Reactions		
Febrile neutropenia	Grade 3-4	• Interrupt duvelisib until afebrile and resolution of Grade 3 or Grade 4 neutropenia to Grade ≤2
Neutropenia	ANC 0.5 to 1.0 Gi/L	• Maintain duvelisib dose • Monitor ANC at least weekly
	ANC less than 0.5 Gi/L	• Withhold duvelisib • Monitor ANC until > 0.5 Gi/L • Resume duvelisib at same dose (first occurrence) or at a reduced dose for subsequent occurrence (see Table 8)

Toxicity	Adverse Reaction Grade	Recommended Management
Thrombocytopenia	Platelet count 25 to < 50 Gi/L (Grade 3) with Grade 1 bleeding	• No change in dose • Monitor platelet counts at least weekly
	Platelet count 25 to < 50 Gi/L (Grade 3) with Grade 2 bleeding or Platelet count < 25 Gi/L (Grade 4)	• Withhold duvelisib • Monitor platelet counts until ≥ 25 Gi/L and resolution of bleeding (if applicable) • Resume duvelisib at same dose (first occurrence) or resume at a reduced dose for subsequent occurrence (see Table 8)

Abbreviations: ALT: alanine aminotransferase; ANC: absolute neutrophil count; AST: aspartate transaminase; CMV: cytomegalovirus; DRESS: drug reaction with eosinophilia and systemic symptoms; Gi: 1 x 10^9; PCR: polymerase chain reaction; PJP: *Pneumocystis jiroveci* pneumonia; SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis; ULN: upper limit of normal.

6.6.3. Concomitant Therapies Restrictions

Table 6: Prohibited Concomitant Therapies

Prohibited Concomitant Therapy	Guidance
Use of Vaccines	For all subjects, the use of live or live attenuated vaccines is prohibited within 6 weeks prior to C1D1, during the treatment with duvelisib, and for 3 months after the last dose of study drug. The use of inactivated (or killed) vaccines (such as pneumococcal pneumonia vaccine) is allowed during the study, however subjects and their physicians should be aware that the effectiveness of any vaccine administered concomitantly with duvelisib may be diminished. The ability to generate an immune response to any vaccine following the administration of duvelisib has not been studied.
Immunosuppressants	Subjects are not to receive ongoing treatment with chronic immunosuppressants (e.g., cyclosporine) or systemic steroids for > 1 week at doses > the equivalent of 20 mg prednisone QD. Note: Acute treatment for underlying autoimmune disorders (e.g., reactive airway disease, rheumatoid arthritis, etc.) with corticosteroid doses > 20 mg prednisone or equivalent QD for ≤ 1 week is permitted during the study. Corticosteroid doses of ≤ 20 mg prednisone or equivalent QD are permitted during the study for physiological replacement or chronic treatment for underlying autoimmune disorders (e.g., reactive airway disease, rheumatoid arthritis, etc.).
Other Anticancer Therapy or Investigational Agents	During study intervention period, subjects are not to receive any additional anticancer therapy or other investigational agents not outlined in the protocol.

Prohibited Concomitant Therapy	Guidance
Medications or Foods that Strongly Inhibit or Induce CYP3A4	Use of a strong CYP3A inhibitor or inducer is prohibited. Co-administration with a strong CYP3A inhibitor increases duvelisib exposure which may increase the risk of duvelisib toxicities. Co-administration with a strong CYP3A inducer decreases duvelisib exposure which may reduce duvelisib efficacy. Section 10.2 provides a list of medications and foods known to inhibit (Table 15) or induce (Table 16) CYP3A. Please note that these tables do not provide a comprehensive list of all medications which may modulate CYP3A activity.

Abbreviations: CYP3A: cytochrome P450 3A; QD: once daily.

Table 7: Concomitant Therapies: Use with Caution

Concomitant Therapy: Use with Caution	Guidance
Medications or Foods that Weakly or Moderately Inhibit or Induce CYP3A4	Please discuss use of weak or moderate CYP3A inhibitors and inducers with the Medical Monitor. Section 10.2 provides a list of medications and foods known to inhibit (Table 15) or induce (Table 16) CYP3A. Please note that these tables do not provide a comprehensive list of all medications which may modulate CYP3A activity.
Medications that are Substrates of CYP3A	Co-administration with duvelisib decreases AUC of a sensitive CYP3A4 substrate which may decrease the efficacy of these drugs. Consider finding an alternative drug that is not a substrate of CYP3A4. Table 17 in Section 10.2 provides a list of medications known to be substrates of CYP3A. Please note that Table 17 is not a comprehensive list of all medications which may be substrates of CYP3A. The Sponsor should be contacted with any questions regarding concomitant use of medications that are CYP3A substrates.

Abbreviations: AUC: area under the curve; CYP3A: cytochrome P450 3A; QD: once daily.

6.6.4. Contraception and Pregnancy

The effects of duvelisib on conception, pregnancy, and lactation are unknown.

At Screening, all male and female subjects of reproductive potential (i.e., not surgically sterile or female subjects who are not postmenopausal) must be willing to use highly effective methods of contraception for the duration of the study intervention and for 3 months after the last dose of duvelisib. See Section 10.4 (Appendix 4) for Contraceptive Guidance including examples of highly effective contraceptive methods. Pregnancy testing will be performed throughout the study as shown in SoA (Table 1).

6.6.5. COVID-19 Vaccines

Subjects who have received, or receive while active in the trial, a regulatory-approved COVID-19 vaccine may participate in the study with no restrictions. Any vaccine-related AEs reported by study subjects will be recorded on the appropriate CRF.

6.7. Dose Modification

For dose modifications and dose level recommendations refer to Table 8. Duvelisib may be held up to 42 days for toxicity. Doses held for > 42 days due to treatment-related toxicity will result in permanent discontinuation from duvelisib. Any subject who requires a dose level reduction to below 15 mg BID due to treatment-related toxicities will be permanently discontinued from duvelisib treatment.

If duvelisib treatment is permanently discontinued due to an AE, subjects should be followed for disease response and survival as outlined in the SoA (Table 1).

Dosing levels for duvelisib are shown in Table 8.

Table 8: Duvelisib Dosing Levels

Dose Level	Duvelisib Dosing Levels
1	25 mg BID
-1	15 mg BID
-2	Discontinue duvelisib if subject is unable to tolerate 15 mg BID

Abbreviations: BID: twice daily

Subjects who have a dose reduction due to a toxicity will not be eligible for a dose re-escalation.

6.8. Intervention after the End of the Study

If the study is ended prior to all subjects discontinuing treatment, any subject continuing to receive benefit will be provided the opportunity to continue to receive duvelisib. Long-term continued treatment may be provided via an expanded access program consistent with local regulations, such as the Secura Bio NPP.

7. DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Duvelisib will be discontinued for any of the following reasons:

- Subject withdrawal of informed consent
- Protocol-specified disease progression
- Clinical deterioration (at the discretion of the Investigator)
- Study intervention interruption for > 42 days due to duvelisib-related toxicity (unless approved by study Medical Monitor)
- Unacceptable toxicity
- Pregnancy
- Termination of the study by the Sponsor
- Death
- Other reasons, including major protocol violation or noncompliance

The Investigator must determine the primary reason for a duvelisib discontinuation and record this information on the CRF.

See the SoA for data to be collected at the time of discontinuation of study intervention and for any further evaluations that need to be completed.

7.2. Subject Withdrawal from the Study

- A subject may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- At the time of withdrawing from the study, if possible, an End of Treatment (EoT) Visit should be conducted, as shown in the SoA. See SoA (Table 1) for data to be collected at the EoT Visit and follow-up, and for any further evaluations that need to be completed. Additional visits may be conducted as necessary for any abnormal findings that require medical follow-up.
- The subject will be permanently discontinued from the study intervention and withdrawn from the study at that time.
- If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.3. Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject. These contact attempts (e.g., 3 phone calls followed by a certified letter) should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are described in Section 10.6.8.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Table 1 and Table 2). Protocol waivers or exemptions are not allowed.
- Urgent safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. Repeat lab assessments during the screening period do not constitute rescreening. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screen failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will be described in the ICF. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

Assessment of disease response and progression status in all subjects will be evaluated by the Investigator using 2007 IWG criteria (Cheson 2007) and 2014 Lugano criteria (Cheson 2014). Response and progression will be evaluated using the following procedures, as indicated in the SoA (Table 1).

- Focused physical examination (PE) (including assessment of liver and spleen and review of disease-related constitutional symptoms) (see Section 8.2.1.2)
- Imaging scans of chest, abdomen, and pelvis (see Section 8.1.1)
- Bone marrow biopsy/aspirate (see Section 8.1.2)

These evaluations will be done until progressive disease (PD) is documented, other anticancer therapy is initiated, or death occurs. For subjects who discontinue study intervention for reasons other than radiologic disease progression, response assessments will be performed during long-term follow-up (Section 8.1.4).

8.1.1. Imaging Scans

All subjects require CT or ^{18}Fluoro-2-deoxy-d-glucose (FDG) positron emission tomography (PET)-CT (PET-CT) scans of the chest, abdomen, and pelvis. Magnetic resonance imaging (MRI) may be used instead of CT scans if CT cannot be done, but the same method must be used

throughout the study. Other scans may be performed (e.g., neck/head) if clinically indicated or if the area is a site of known disease. Any new abnormal findings outside disease measurements should be captured as an AE.

8.1.2. Bone Marrow Biopsy/Aspirate

If a bone marrow/aspirate is performed within 60 days before C1D1 as part of standard of care, the pathology report will be provided to the Sponsor. If a radiologic CR according to 2007 revised IWG criteria (Cheson 2007) is observed during the course of the study, then a bone marrow biopsy should be done to confirm a CR. The pathology report will be provided to the Sponsor.

8.1.3. Investigator Assessment of Response and Progression Status

Assessment of response and progression status will be evaluated by the Investigator at each scheduled disease response assessment as outlined in the SoA (Table 1). Assessment of response and progression status in all subjects will be evaluated using the definitions from the 2007 revised IWG criteria (Cheson 2007) for clinical decision-making and assessment of response. Secondarily, response will also be assessed using the 2014 Lugano criteria (Cheson 2014). Please see Section 10.1 for detailed descriptions of these response criteria.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 1). Additional visits may be conducted as necessary for any abnormal findings that require medical follow-up.

8.2.1. Physical Examinations and Vital Signs

8.2.1.1. Full Physical Examination

The full PE will include assessment of liver/spleen size, clinical assessment of tumor masses (if evaluable by PE), review of disease-related constitutional symptoms (B symptoms: symptoms of fever [i.e., temperature > 38°C/100.4°F] without evidence of infection, weight loss, and drenching night sweats without evidence of infection), neurologic exam, height, and weight.

Any pre-existing PE abnormality deemed clinically significant by the Investigator during Screening will be reported as medical history. Any PE abnormality that emerges or has worsened after signing of the ICF and that is assessed as clinically significant by the Investigator will be reported as an AE.

8.2.1.2. Focused Physical Examination

Each focused PE is to include assessment of liver and spleen size, clinical assessment of tumor masses and evaluation for the presence of disease-related constitutional symptoms (B symptoms: symptoms of fever [i.e., temperature > 38°C/100.4°F] without evidence of infection, weight loss, and drenching night sweats without evidence of infection).

Results from the focused PEs and assessments of ECOG performance status (Section 8.4.1) will be used for assessment of disease response and safety. Additionally, any new or ongoing abnormal findings will be assessed. Any new clinically significant abnormality from baseline should be recorded as an AE.

8.2.1.3. Vital Signs

Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate.

8.2.2. Electrocardiogram and Echocardiogram/Multi-gated Acquisition Scan

At Screening, a standard 12-lead electrocardiogram (ECG) will be conducted following an approximate 10-minute rest period. QTc measurements (as measured by triplicate readings) will use the Fridericia's correction method (QTcF).

To measure left ventricular ejection fraction (LVEF), an echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan will be administered at the Screening Visit.

Additional ECGs and ECHO/MUGA scans may be performed as clinically indicated per Investigator's judgment.

8.2.3. Concomitant Medication and Procedures

Concomitant medications and procedures will be assessed and recorded in the CRF during Screening (including those occurring within 30 days prior to randomization) and at each visit.

8.2.4. Clinical Safety Laboratory Assessments

- See Table 18 for the list of clinical laboratory tests to be performed and the SoA (Table 1) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or the Medical Monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.
    - All protocol-required laboratory assessments, as defined in Table 18, must be conducted in accordance with the Laboratory Manual and the SoA (Table 1).
    - If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the CRF.

8.3. Adverse Event Management

8.3.1. Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a subject administered a medicinal product that does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the study (investigational) product. This includes an exacerbation of pre-existing conditions or events, concurrent illnesses, drug interaction, or the significant worsening of the indication under investigation. Anticipated fluctuations of pre-existing conditions, including the disease under study that does not represent a clinically significant exacerbation or worsening, need not be considered AEs.

Symptoms of the disease under study/lack of efficacy/disease progression should not be classified as an AE if they are within the normal day-to-day fluctuation or expected progression of the disease.

It is the responsibility of the Investigator to document all AEs that occur during the study. AEs should be reported on the appropriate CRF.

8.3.2. Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence at any dose (including after the ICF is signed and prior to dosing) that:

- Results in death
- Is life-threatening (subject is at immediate risk of death from the event as it occurred)
- Requires inpatient or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect

Important medical events that may not result in death, are not immediately life-threatening, or do not require hospitalization may be considered SAEs when, based on 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 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.

For SAE reporting purposes, hospitalization is defined as inpatient hospital stay. Hospitalizations for elective surgery or other medical procedures that are not related to a TEAE are not considered SAEs. Hospitalization, which in the opinion of the Investigator, is unrelated to the study intervention, and due to purely non-medical circumstances (e.g., respite care, lack of a caretaker at home, lack of transportation home) are also not considered to be SAEs. PD under study (including signs and symptoms of progression) if documented by use of appropriate methods, should not be reported as an SAE unless the outcome of the PD is fatal during the study or within the safety reporting period (see Section 8.3.3, Reporting of Adverse Events and Serious

Adverse Events). If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event should be reported using the term "disease progression" with a Common Terminology Criteria for Adverse Events (CTCAE) severity of Grade 5.

Death should not be reported as an SAE. The primary reason for a subject's death should be reported as an SAE, with death reported as the outcome.

8.3.3. Reporting of Adverse Events and Serious Adverse Events

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

Elective or previously scheduled hospitalizations for pre-existing conditions that have not worsened after initiation of treatment should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE.

All AEs should be recorded individually unless, in the opinion of the Investigator or designated physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be reported rather than each individual sign or symptom. 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 AE or SAE as appropriate on the relevant form(s) (SAE Report Form and/or AE CRF). If a diagnosis is subsequently established, it should be reported as follow-up information becomes available. If a diagnosis is determined after the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

Each AE will be evaluated for duration, severity, seriousness, and causal relationship to the investigational drug. The action taken with study intervention and the outcome must also be recorded.

All SAEs, regardless of relationship to the study intervention, must be reported immediately (within 24 hours of awareness of event by Investigator) to the Sponsor and Contract Research Organization (CRO) pharmacovigilance group. Initial SAE notification should be made by e-mailing or faxing the SAE report form to the e-mail or fax number provided on the SAE report form.

An initial SAE Report may be sent without the Investigator's signature but must be followed by a report signed by the Investigator within 48 hours of becoming aware of the event. Follow-up SAE reports must be submitted by the Investigator as new information becomes available.

The Medical Monitors for this study may be contacted for advice or assistance. Contact details will be provided in the study contact list.

8.3.4. Severity of Adverse Events

The severity of the AE will be graded according to the National Cancer Institute (NCI) CTCAE, version 5.0 (see web page https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50 for details). AEs not listed in the CTCAE should be graded as summarized in Table 9.

Table 9: CTCAE AE Grading

CTC Grade	Equivalent To:	Definition
Grade 1	Mild	Discomfort noticed but no disruption of normal daily activity
Grade 2	Moderate	Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated although this could improve the overall well-being or symptoms of the subject
Grade 3	Severe	Inability to work or perform normal daily activity; treatment or medical intervention is indicated to improve the overall well-being or symptoms; delaying the onset of treatment is not putting the survival of the subject at direct risk
Grade 4	Life-threatening/ disabling	An immediate threat to life or leading to a permanent mental or physical condition that prevents work or performing normal daily activities; treatment or medical intervention is required to maintain survival
Grade 5	Death	AE resulting in death

Abbreviations: AE: adverse event, CTC: Common Terminology Criteria; CTCAE: Common Terminology Criteria for Adverse Events.

8.3.5. Relationship of Adverse Events to Study Intervention

The Investigator will make a judgment regarding whether or not the AE was related to study intervention, as outlined below:

- **Definitely related:** This category applies when, after careful medical consideration, there is almost no consideration of other causation.
- **Probably related:** There is a clinically plausible time sequence between onset of the AE and study intervention administration. The AE is unlikely to be caused by a concurrent or underlying illness, other drugs, or procedures. If applicable, the AE follows a clinically consistent resolution pattern upon withdrawal of study intervention.
- **Possibly related:** There is a clinically plausible time sequence between onset of the AE and study intervention administration, but the AE could also have been caused by the concurrent or underlying illness, other drugs, or procedures. Information regarding study intervention withdrawal may be lacking or unclear. "Possible" should be used when study intervention administration is one of several biologically plausible causes of the AE.

- **Unlikely related:** The AE is most likely due to a cause not related to study intervention administration. However, association with the study intervention cannot be completely ruled out.
- **Unrelated:** Another cause of the AE is most plausible, and a clinically plausible temporal sequence is inconsistent with the onset of the AE and study intervention administration and/or a causal relationship is considered biologically implausible.

For the purpose of regulatory reporting requirements, causal relationships of definite, probable, and possible will be considered treatment-related, while unlikely and unrelated will be considered not treatment-related.

8.3.6. Clinical Laboratory Adverse Events

A clinical laboratory AE is any laboratory value that is deemed clinically significant by the Investigator. The Investigator should decide, based upon the AE criteria and the clinical condition of the subject, whether a change in a laboratory parameter is clinically significant and therefore represents an AE.

The following items may be considered when determining clinical significance:

- Severity of the laboratory abnormality (i.e., greater than Grade 2 in severity)
- Laboratory abnormality requires a medical intervention
- Laboratory abnormality requires a change or suspension of study intervention
- Laboratory abnormality is accompanied by clinical symptoms

Laboratory abnormalities that are not considered clinically significant should not be recorded as AEs and will be captured and reported in the laboratory section of the clinical study report. If a medical intervention occurs, it should be recorded as a treatment with the abnormal laboratory finding as the AE (e.g., anemia with treatment required and blood transfusion recorded as a procedure, hyperglycemia with treatment required and change in insulin dose recorded on concomitant medications).

If, at the end of the treatment phase with the study intervention, there are pathological laboratory values which were not present at Baseline, further clinical or laboratory investigations should be performed until the values return to within reference range or until a plausible explanation (i.e., concomitant disease) is found for the pathological laboratory values.

8.3.7. Regulatory Aspects of Adverse Event Reporting

The Sponsor is responsible for submitting reports of SAEs associated with the use of the study intervention to the appropriate Regulatory Authority (e.g., the US FDA), Investigators, and IRB/IEC/Central Ethics Committee (CEC) in accordance with all applicable regulations and guidelines.

It is the responsibility of the Investigator to notify the IRB of all SAEs that occur at his or her site. Investigators will be notified of all suspected, unexpected serious adverse reactions (SUSARs; 7 / 15 Day Safety Reports) that occur during any clinical studies that are using the investigative compound. Each site is responsible for notifying their IRB/IEC/CEC of these additional SUSARs in accordance with local regulations.

8.3.8. Overdose

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

For this study, overdose is defined as a daily dose of duvelisib higher than the prescribed daily dose. Overdoses will not be considered SAEs unless the outcome of the overdose meets seriousness criteria as defined in Section 8.3.2. In the event of an overdose that causes an SAE, the Sponsor should be notified within 24 hours of Investigator's knowledge. The subject should be carefully monitored for potential adverse reactions and symptomatic treatment instituted as per institutional standards of care. The Investigator will determine if and when dosing should resume.

8.3.9. Pregnancy

Any pregnancy must be reported to the Sponsor or designee within 24 hours of the Investigator's knowledge of the pregnancy using a Pregnancy Report Form.

Pregnancy per se is not considered an AE unless there is cause to believe that the study intervention may have interfered with the effectiveness of a contraceptive medication or if the outcome of the pregnancy meets SAE criteria (miscarriage or congenital anomaly/birth defect, etc.), in which case it should be reported in the same manner and timelines as an SAE. 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 intervention should also be reported as an SAE. Hospitalization for normal delivery of a healthy newborn is not an SAE.

Since duvelisib has not been evaluated in pregnant or nursing women, the treatment of pregnant women or WCBP who are not using highly effective contraception is contraindicated (see Table 18 and Section 10.4 for instructions on pregnancy testing and contraception).

Pregnancies occurring in subjects or partners of male subjects during the study intervention period until 30 days after the subject's last dose of study intervention are considered immediately reportable events. If a pregnancy occurs in a subject, study intervention must be discontinued immediately. The pregnant woman should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. The Investigator will observe the pregnant woman until completion of the pregnancy and must notify the Sponsor of the outcome within 24 hours of the Investigator's knowledge of the pregnancy outcome using a Pregnancy Outcome Form. This notification includes pregnancies resulting in live, "normal" births.

8.4. Quality of Life Assessments

8.4.1. ECOG Performance Status

ECOG Performance Status will be assessed at Screening. If the ECOG Performance Status assessed at Screening is performed within 7 days of Cycle 1 Day 1, the Screening assessment can be used and does not need to be repeated at Cycle 1 Day 1 (predose). Please see SoA Table 1 for the schedule of ECOG Performance Status during study treatment and follow-up.

8.4.2. Subject Self-reported Health-related Quality of Life

Subject self-reported health-related quality of life (QoL) will be assessed at Screening, during study treatment, and, when possible, upon treatment discontinuation for any reason. Subject-reported health-related QoL will be assessed using the EQ-5D-3L questionnaire. Questionnaire should be administered predose and prior to other procedures during treatment visits.

8.5. Pharmacokinetics

- Blood samples will be collected to evaluate the PK of duvelisib and metabolite IPI-656 at the visits and timepoints defined in SoA Table 2.
- Predose samples are preferred, therefore on the days that include PK assessments the morning dose of duvelisib should be administered in the clinic to facilitate collection of samples prior to dosing. However, the sample should still be collected even if the morning dose of duvelisib has already been taken. The date and time of the sample collection and date and time of the previous duvelisib dose must be recorded for all collected samples.
- Additional PK samples beyond those listed in SoA (Table 2) may be requested (when feasible) for any unusual safety event. (i.e., an AE different in type and severity from that which is expected in the setting of duvelisib use).
- Specific instructions on sample collection and handling will be provided in a separate Laboratory Manual.
- Retained duplicate PK samples may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Genetic analyses will not be performed on these PK samples.
- Subject confidentiality will be maintained.

8.6. Pharmacodynamics

Pharmacodynamic biomarkers will be assessed using blood samples collected at sampling timepoints in the SoA (Table 2) and are described under Biomarkers (Section 8.8).

8.7. Genetics

Normal germline genetic studies are not evaluated in this study. Tumor genomic studies may be conducted as part of exploratory biomarker research (Section 8.8).

8.8. Biomarkers

Biomarker samples will be collected according to the SoA (Table 2) and assessments may be conducted to evaluate potential biomarkers as described in Table 10.

Table 10: Biomarker Samples and Assessments

Sample	Assessments
Blood for pharmacodynamics	Pharmacodynamic assays evaluate phosphorylated protein levels in several cell types.
Serum and plasma for biomarker analysis	Protein (e.g., cytokines, chemokines) and/or ctDNA
Blood for immunophenotyping	Immune cell population profiling (e.g., B T- funcDNA, and/or RNA analysis)
Stool for biomarker analysis	Protein, DNA, and/or RNA analysis to evaluate correlations with gastrointestinal toxicities
Archival tumor tissue (if available)	Tumor markers that may predict clinical response to duvelisib. PI3K pathway and/or disease-specific biomarkers (e.g. PTEN, PI3K isoforms) by immunohistochemistry and/or in situ hybridization. Tumor genomic studies may be performed (e.g. DNA sequencing, DNA copy number analysis, RNA expression profiling) to explore whether specific genomic features correlate with response or resistance to duvelisib in iNHL.
Colon biopsies taken as standard of care to assess colitis (if available)	Pharmacodynamic analysis, immune cell and immune cell function, protein and genomics analyses

Abbrevia tions: ctDNA: circulating tumor deoxyribonucleic acid; iNHL: indolent non-Hodgkin lymphoma; PI3K: phosphoinositide 3-kinase; PTEN: phosphatase and tensin homolog; RNA: ribonucleic acid

In addition, C-reactive protein levels in blood (a clinical safety laboratory assessment) will be evaluated as a potential biomarker and will be assessed at Screening and whenever Grade ≥ 2 diarrhea or any colitis occurs.

8.9. Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL METHODOLOGY

A detailed description of the statistical methodology for this study can be found in the Statistical Analysis Plan (SAP). Deviations from the statistical analyses outlined in this protocol will be indicated in the SAP; any further modifications will be noted in the final clinical study report.

9.1. Statistical Hypotheses

This study will test the null hypothesis that the ORR for each arm is ≤ 30% against the alternative that ORR is ≥ 55%.

9.2. Sample Size Determination

The sample size for each arm was calculated using a 2-stage approach.

For each arm: in the first stage, 15 subjects will be randomized. The evaluation of the first stage will take place after the 15 enrolled subjects have been followed for a minimum of 3 cycles (18 weeks).

If there are fewer than 6 responders (PR or CR) among the first 15 subjects, consideration may be given to terminating the treatment arm. The decision to proceed to Stage 2 will be based on the totality of data observed, including types of responses, safety data, and discontinuation rates. The treatment arm may also not proceed to the second stage if the totality of the data is viewed as compelling; such scenarios could include (but are not limited to) accumulating enough data in Stage 1 to conclude the ORR exceeds 30%. If the treatment arm proceeds to the second stage, up to 36 additional subjects will be enrolled for a total of 51. If fewer than 22 (43%) responders (PR or CR) are observed in 51 subjects, consideration may be given to concluding that the treatment schedule does not warrant further study in this population. The final evaluation of each schedule will be based on the totality of data observed, including types of responses, safety data, and discontinuation rates. This design yields 90% power under the assumptions described above; the alpha level (type I error rate) for the study will be controlled at 0.025.

Subjects will be stratified by number of prior therapies (1 or > 1), bulky disease status (longest diameter of baseline lesion < 5 cm or ≥ 5 cm) and time since last recurrence (≥ 24 months or < 24 months).

9.3. Populations for Analyses

The modified intent-to-treat (mITT) analysis set will include all subjects who receive at least 1 dose of duvelisib. The mITT analysis set will serve as the primary analysis set for all endpoints and baseline characteristics.

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and secondary endpoints.

9.4.1. General Considerations

Each treatment arm will be evaluated separately; no formal comparisons between treatment arms are planned. Hypothesis testing will be used for the primary efficacy endpoint of ORR for each treatment arm. No formal hypothesis testing will be used for any other endpoints or other study data, such as demographics and safety data.

Tabulations will be produced for appropriate disposition, demographic, baseline, efficacy, and safety parameters. For categorical variables, summary tabulations of the number and percentage of subjects within each category (with a category for missing data) of the parameter will be presented, as well as 2-sided 95% CIs, unless stated otherwise. For continuous variables, the number of subjects, mean, median, standard deviation, minimum, and maximum values will be presented. Time-to-event data will be summarized using Kaplan-Meier (KM) methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% CIs, as well as number and percentage of censored observations.

The Investigator's assessments of disease response will be used as the basis for the evaluation of the primary and secondary efficacy endpoints.

9.4.1.1. Procedures for Handling Missing, Unused, and Spurious Data

All available efficacy and safety data will be included in data listings and tabulations. In general, missing data will be treated as missing and no data imputation will be applied, unless otherwise specified. Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures. Details of procedures for handling missing, unused or spurious data can be found in the SAP.

9.4.2. Primary Endpoint Efficacy Analysis

The ORR (proportion of subjects achieving a CR or PR) will be estimated, along with the 2-sided 95% exact CI. Responses for the primary ORR analysis will be assessed using the 2007 revised IWG criteria (Cheson 2007). Missing data will be imputed by assuming that any subjects not exhibiting a response (CR or PR) are non-responders.

9.4.3. Secondary Efficacy Endpoints Analyses

- ORR according to 2014 Lugano criteria (Cheson 2014)

Note: all additional secondary response endpoints will be assessed separately using 2007 revised IWG criteria (Cheson 2007) and 2014 Lugano criteria (Cheson 2014)

- ORR, at 6, 12, 18, and 24 months after first dose of study intervention, defined as the proportion of subjects achieving CR or PR at each of these time points.
- PFS will be assessed using KM methods from time of first dose of study intervention to PD or death.
- TTF will be calculated as the time from first dose of study intervention until discontinuation for any reason and will be summarized using KM methods.
- DOR will be calculated for those subjects with a CR or PR from the time of first response to PD using KM methods.

- OS will be assessed using KM methods from time of first dose of study intervention to death.
- LNRR will be calculated as the proportion of subjects achieving ≥ 50% decrease in the sum of the product of the diameters (SPD) of target lymph nodes.
- TTFR will be calculated for those subjects with a CR or PR from the time of first dose of study intervention to time of first CR or PR.

9.4.4. Secondary Safety Endpoints Analyses

- Safety analyses will be performed on the mITT population, and safety endpoints will be tabulated and presented.
- AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) for purposes of summarization. All AEs occurring during the study will be included in by-subject data listings and tabulated by MedDRA system organ class and preferred term, and in selected cases, High Level Group Term and High Level Terms. AEs will be summarized overall, by relationship and by severity. Events leading to death, SAEs, and events resulting in treatment discontinuation will be listed and, if warranted by the data, tabulated.
- AEs of special interest (AESI) will be defined for analysis purposes in the SAP and will be summarized using the methods as described in the above bullet.
- Exposure to duvelisib, including the proportion of expected doses received, will be tabulated.
- Changes from baseline over time for vital sign measurements (including diastolic and systolic blood pressure) will be summarized. By-subject listings of vital sign measurements will be prepared.
- Individual subject laboratory parameter values and summary statistics over time will be prepared using descriptive statistics. Severity of select clinical laboratory measures will be determined using NCI CTCAE criteria and Grade 3 or 4 laboratory values will be presented in a separate table and listing.
- The use of concomitant medications, coded using World Health Organization Drug Dictionary, will be tabulated and included in a by-subject listing.
- Additional safety analyses may be performed to more clearly enumerate rates of toxicities and to further define the safety profile of duvelisib.

9.4.5. Secondary PK Endpoints Analyses

- PK analyses will be conducted on the mITT population.
- Blood samples will be taken for the analyses of duvelisib and metabolite IPI-656 in plasma at the time points defined in the SoA (Table 2). The relevant PK parameters will be determined using bioanalytical data. The PK data will be summarized using descriptive statistics and will be listed and summarized in tabular and/or graphical form.

- A separate PK analysis plan may be developed.

9.4.6. Exploratory QoL Endpoints Analyses

- Changes from baseline over time for ECOG performance status will be summarized. A by-subject listing of ECOG performance status data will be prepared.
- Changes from baseline over time for EQ-5D-3L scores will be summarized. By-subject listings of EQ-5D-3L will be prepared.

9.4.7. Exploratory Pharmacodynamic and Biomarker Endpoints Analyses

- Pharmacodynamic analyses will be conducted on the mITT population.
- Prognostic markers such as genetic variation, ctDNA, immunophenotype, functional immune assays, gene expression, and circulating protein, will be evaluated relative to baseline levels and change to baseline levels.
- Additional exploratory analyses identified by the Sponsor also may be performed.
- Listing of individual subject and summary statistics for duvelisib effects on biomarkers and graphs of changes versus time will be prepared.
- Biomarker effects will be summarized using descriptive statistics and associations with clinical efficacy and/or safety outcomes may be explored.

9.5. Interim Analyses

There is no formal interim analysis. Study data for each arm will be evaluated at the end of Stage 1 to determine whether a study arm should be terminated or continued to Stage 2. Please see additional details of the 2-stage design in Section 9.2.

9.6. Data Monitoring Committee (DMC)

This study will not use a DMC.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS: APPENDICES

Table 11: Appendices

Appendix	Title	Section
1	Overview of Disease Response Criteria	10.1
2	CYP3A Inhibitors, Inducers, and Substrates	10.2
3	Clinical Laboratory Tests	10.3
4	Contraceptive Guidance	10.4
5	ECOG Performance Status	10.5
6	Regulatory, Ethical, and Study Oversight Considerations	10.6
7	Abbreviations	10.7
8	Protocol Summary of Changes and Version History	10.8

10.1. Appendix 1: Overview of Disease Response Criteria

10.1.1. 2007 Revised IWG Criteria

Table 12: Revised Response Criteria for Malignant Lymphoma (Cheson 2007)

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; 1 or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than 1 node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR: complete remission; CT: computed tomography; FDG: [^{18}F] fluorodeoxyglucose; PD: progressive disease; PET: positron emission tomography; PR: partial remission; SD: stable disease; SPD: sum of the product of the diameters.

10.1.2. 2014 Lugano Response Criteria

PET-CT images will be assessed using the 5-point scale (5PS) (Table 13), a semi-quantitative analysis that is a pragmatic yet robust predictor of subject outcome, then disease response will be assessed using the Lugano response criteria (Table 14).

Table 13: 5-Point Scale for Positron Emission Tomography Assessment (Barrington 2014)

Score	Criterion
1	No uptake above background
2	Uptake ≤ mediastinum
3	Uptake > mediastinum, but ≤ liver
4	Uptake moderately > liver*
5	Uptake markedly higher than liver and/or new lesions*
X	(New) areas of uptake unlikely to be related to lymphoma

*It is suggested according to published data that score 4 be applied to uptake greater than the maximum standardized uptake value (SUV) in a large region of normal liver and score 5 to uptake 2× to 3× greater than the maximum SUV in the liver.

Table 14: Lugano Response Criteria for Malignant Lymphoma (Cheson 2014)

Response and Site	PET-CT-based Response	CT-based Response
Complete Response	**Complete metabolic response**	**Complete radiologic response (requires all of the following)**
Lymph nodes and extralymphatic sites	Score of 1, 2, or 3* with or without a residual masson 5PS (Table 13) It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease
Non-measured lesions	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in bone marrow	Normal by morphology; if indeterminate, IHC negative
Partial Response	**Partial metabolic response**	**Partial remission (all of the following)**
Lymph nodes and extralymphatic sites	5PS score 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size During treatment, these findings suggest responding disease At EoT, these findings indicate residual disease	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value When no longer visible, 0 × 0 mm

Response and Site	PET-CT-based Response	CT-based Response
		For a node × 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Non-measured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by ≥ 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
Stable disease (no response)	**No metabolic response**	**Stable disease**
Target nodes/nodal masses, extranodal lesions	5PS score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Non-measured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive Disease	**Progressive metabolic disease**	**Progressive disease requires at least 1 of the following:**
Individual target nodes/nodal masses	5PS score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or EoT assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly

Response and Site	PET-CT-based Response	CT-based Response
Non-measured lesions	None	New or clear progression of pre-existing non-measured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS: 5-point scale; CT: computed tomography; EoT: end of treatment; FDG: fluorodeoxyglucose; IHC: immunohistochemistry; LDi: longest transverse diameter of a lesion; MRI: magnetic resonance imaging; PET: positron emission tomography; PPD: cross product of the LDi and perpendicular diameter; SDi: shortest axis perpendicular to the LDi; SPD: sum of the product of the perpendicular diameters for multiple lesions.
*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in studies involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 2 diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), gastrointestinal (GI) involvement, cutaneous lesions, or those noted on palpation. Non-measured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extra nodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

10.2. Appendix 2: CYP3A Inhibitors, Inducers, and Substrates

10.2.1. Medications or Foods Known to Inhibit CYP3A

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

https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.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.

Table 15: Classification of In Vivo Inhibitors of CYP3A

Strong Inhibitors[1]	Moderate inhibitors[2]	Weak inhibitors[3]
Boceprevir, cla rithromycin, conivaptan, grapefruit juice[4], indinavir, itraconazole, ketoconazole, lopina vir/ritonavir, mibefradil[5] nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, tela previr, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltia zem, erythromycin, fluconazole, fosamprenavir, gra pefruit juice[4], ima tinib, verapamil	Alpra zolam, amiodarone, amlodipine, atorvastatin, bica lutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo[6], goldenseal[6], isonia zid, nilotinib, oral contraceptives, ranitidine, ranolazine, tipra navir/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 ≥ 5-fold, or results in a > 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 < 5-fold but ≥2-fold or results in a 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 < 2-fold but ≥1.25-fold or results in a 20-50% decrease in CL.
4. 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 prepa ration was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another prepa ration was used (e.g., low dose, single strength).
5. Withdrawn from the United States market because of safety reasons.
6. Herbal product.

10.2.2. Medications Known to Induce CYP3A

Table 16: 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[2,3]	Bosentan, efavirenz, etravirine, modafinil, nafcillin	Amprenavir, aprepitant, armodafinil, Echinacea[3] pioglitazone, prednisone, rufinamide

Abbreviations: AUC: area under the curve; CYP3A: cytochrome P450 3A.

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

10.2.3. Medications Known to Be CYP3A Substrates

Known sensitive CYP3A substrates and CYP3A substrates with a narrow therapeutic range are listed in Table 17. Drugs or foods that are substrates of CYP3A should only be used if medically necessary and therapeutic alternatives do not exist.

Additional information can be found at:

- https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

Table 17: Cytochrome P450 3A (CYP3A) Substrates

Sensitive CYP3A Substrates	
budesonide	midazolam
buspirone	saquinavir
eplerenone	sildenafil
eletriptan	simvastatin
felodipine	triazolam
fluticasone	vardenafil
lovastatin	
CYP3A Substrates with a Narrow Therapeutic Range	
alfentanil	fentanyl
astemizole	pimozide
cisapride	quinidine
cyclosporine	sirolimus
dihydroergotamine	tacrolimus
ergotamine	terfenadine

10.3. Appendix 3: Clinical Laboratory Tests

- The tests detailed in Table 18 will be performed by the local laboratory. The timing and frequency are detailed in SoA Table 1.
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.
- The results of each test must be entered in the CRF.

Table 18: Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count		RBC Indices: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) % Reticulocytes	White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Red blood cell (RBC) Count			
	Hemoglobin			
	Hematocrit			
Clinical Chemistry[1]	Blood urea nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (non-fasting)	Calcium	Alkaline phosphatase (ALP)	Lactate dehydrogenase (LDH)
Quantitative serum immunoglobulins (Ig)	IgA, IgG, IgM			

Laboratory Assessments	**Parameters**
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if dipstick is abnormal)
Pregnancy	• Highly sensitive serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2]
Other Screening Tests	• Viral screening: serology (hepatitis B surface antigen [HBsAg], hepatitis B core antibody [HBcAb], hepatitis C virus antibody [HVC Ab], Epstein-Barr virus [EBV] antibody, human immunodeficiency virus [HIV] antibody); cytomegalovirus (CMV) via serology or viral load detection via polymerase chain reaction (PCR). Subjects with a negative HBsAg and positive HBcAb require an undetectable/negative hepatitis B DNA test (e.g., PCR test) to be enrolled. o HIV testing is required for subjects without documentation of a prior negative test result from within the last 9 months. Results will be analyzed locally and will not be captured in the study database. Only subjects with negative results will be eligible to enroll. • Coagulation tests: prothrombin time (PT), partial thromboplastin time (PTT) and international normalized ratio (INR) • C-reactive protein • Endocrine function tests: Free thyroxine (T4) and thyroid-stimulating hormone (TSH) • Human leukocyte antigen (HLA) typing: types A, B, C, DRB1, and DQB1

NOTES:

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are provided in Table 5. All liver-related SAEs must be reported as described in Section 8.3.3.
2. A serum pregnancy test must be performed within 7 days of C1D1. At subsequent time points, serum testing is preferred but urine testing is allowed if a blood draw for other assessments is not performed. A positive urine test must be confirmed by a serum test.

10.4. Appendix 4: Contraception Guidance

The effects of duvelisib on conception, pregnancy, and lactation are unknown. Every woman of childbearing potential (WCBP) and male subjects with a partner who is a WCBP must use highly effective methods of contraception as described below in Section 10.4.1. A woman is considered to be a WCBP following menarche and until becoming postmenopausal (i.e., > 55 years and postmenopausal for at least 1 year), unless permanently sterile.

At Screening, all male and female subjects of reproductive potential (i.e., not surgically sterile or female subjects who are not postmenopausal) must agree to use highly effective methods of contraception for the duration of the study intervention, and for at least 3 months after the last dose of duvelisib. Male subjects must also refrain from donating sperm during their participation in the study and for at least 3 months after the last dose of duvelisib.

The use of contraceptive methods is not required if the male subject or the male partner (of the female subject) has a documented history of a vasectomy or if the female subject or the female partner (of the male subject) has a documented history of bilateral oophorectomy, hysterectomy, or tubal ligation, or if she is > 55 years of age and postmenopausal for at least 1 year.

Section 8.3.9 for requirements for pregnancy reporting.

10.4.1. Highly Effective Methods of Contraception

Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation[1]:
  - oral
  - injectable
  - implantable[2]
- intrauterine device (IUD)[2]
- intrauterine hormone-releasing system (IUS)[2]
- bilateral tubal occlusion[2]
- vasectomized partner[2,3]
- sexual abstinence[4]

[1]Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.

[2]Contraception methods that are considered to have low user dependency

[3]Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WCBP study participant and that the vasectomized partner has received medical assessment of the surgical success.

[4]Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.

10.5. Appendix 5: Eastern Cooperative Oncology Group (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, e.g., light housework, 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: (Oken 1982).

10.6. Appendix 6: Regulatory, Ethical, and Study Oversight Considerations

10.6.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.6.2. Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.6.3. Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of informed consent that meets the requirements of 21

CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements (where applicable), and the IRB/IEC or study site.

- Subjects who are detained by administrative or judicial order will be excluded from participating in the study.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject.
- A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date.

10.6.4. Subject Data Protection

- Subjects will be assigned a unique identifier during screening. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information that would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.6.5. Dissemination of Clinical Study Data

The Sponsor will comply with current regulatory requirements for disclosure and submission of study results. The Sponsor's policy on publication of study results is described in Section 10.6.9.

10.6.6. Data Quality Assurance

- All subject data relating to the study will be recorded in the electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements (including handling of noncompliance issues and monitoring techniques [central, remote, or on-site monitoring]) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 2 years after study completion, for a period of 2 years after a marketing application is approved for duvelisib in the study population, until 2 years after shipment and delivery of the drug for investigational use is discontinued, or as long as required by local regulations, whichever is longer. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.6.7. Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in ICH guidance for industry E6 GCP: Consolidated Guidance.

10.6.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of subjects.

The first act of recruitment is the first site open and will be the study start date.

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason (e.g., as necessary for patient safety) at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the Investigator

Circumstances that may warrant premature termination of the entire study by the Sponsor include but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects, including:
  - the occurrence of AEs with character, severity, or frequency that are new in comparison to the existing risk profile
  - data derived from other clinical studies or toxicological studies that negatively influence the risk/benefit assessment
- Failure to enter subjects at an acceptable rate
- Plans to modify, suspend, or discontinue the development of the study intervention

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

10.6.9. Publication Policy

- The results of this study may be published or presented at scientific meetings with prior approval of the Sponsor. The Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multi-site studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement between the Sponsor and the Investigators.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.7. Appendix 7: Abbreviations

Table 19: List of Abbreviations and Definitions

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
BID	Twice daily
CEC	Central Ethics Committee
CI	Confidence interval
CxDx	Cycle x Day x
CLL	Chronic lymphocytic leukemia
CMV	Cytomegalovirus
CR	Complete response
CRF	Case report form
CRO	Contract research organization
CTCL	Cutaneous T-cell lymphoma
CYP3A	Cytochrome P450 3A
DI	Dose interruption
DNA	Deoxyribonucleic acid
DOR	Duration of response
DRESS	Drug reaction with eosinophilia and systemic symptoms
EBV	Epstein-Barr virus
eCCr	Estimated creatinine clearance
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FDG	^{18}fluoro-2-deoxy-d-glucose
FFPE	Formalin-fixed paraffin-embedded

Abbreviation	Definition
FL	Follicular lymphoma
GCP	Good Clinical Practice
Gi	Giga (1×10^9) or 1 billion
HBcAb	Hepatitis B core antibody
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus;
HLA	Human leukocyte antigen
HSV	Herpes simplex virus
IHC	Immunohistochemistry
iNHL	indolent non-Hodgkin lymphoma
IB	Investigator's Brochure
ICF	Informed consent form
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IWG	International Working Group
IRB	Institutional Review Board
KM	Kaplan-Meier
L	Liter
LDH	Lactate dehydrogenase
LNRR	Lymph node response rate
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mITT	Modified intent-to-treat
MUGA	Multi-gated acquisition
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NPP	Named Patient Program
ORR	Overall response rate
OS	Overall survival
PCR	Polymerase chain reaction

Abbreviation	Definition
PD	Progressive disease
PE	Physical examination
PET	Positron emission tomography
PFS	Progression-free survival
PI3K	Phosphoinositide 3-kinase
PJP	*Pneumocystis jiroveci* pneumonia
PK	Pharmacokinetics
PR	Partial response
PTCL	Peripheral T-cell lymphoma
PTEN:	Phosphatase and tensin homolog
QD	Once daily
QTcF	QT interval corrected with Fridericia's method
RBC	Red blood cell
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
R/R	Relapsed or refractory
SAE	Serious adverse event
SD	Stable disease
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum pyruvic transaminase
SJS	Stevens Johnson syndrome;
SLL	Small lymphocytic lymphoma
SoA	Schedule of Activities
SPD	Sum of the product of the diameters
TEAE	Treatment-emergent adverse event
TEN	Toxic epidermal necrolysis
TTF	Time to treatment failure
TTFR	Time to the first response
ULN	Upper limit of normal
VZV	Herpes zoster
WBC	White blood cell
WCBP	Woman of childbearing potential

10.8. Appendix 8: Protocol Summary of Changes and Version History

10.8.1. Protocol Version 4.0 (Amendment 5), 18 May 2021

10.8.1.1. Amendment Rationale and Summary of Changes

The primary purpose for this amendment was to remove the Long-Term and Survival F/U visits, while continuing to provide the opportunity for patients experiencing long term benefit to receive study drug. Changes were made in the Schedule of Assessments and in the body text. Additionally, the study duration was modified to end 2 years after the last subject is randomized. COVID-19 vaccine information was also added.

Minor language and format corrections were also done throughout the document.

The revised protocol, Version 4.0, dated 18 May 2021 will be submitted by the Investigator(s) to all applicable IRBs, IECs, or CECs, and by Secura Bio, Inc. (or designee) to all applicable Regulatory Authorities.

Table 20: Summary of Changes for Version 4.0

Section(s)	Description of Change	Rationale for the Change
Global	Updated the version number and date of protocol from Version 3.2 dated 08 December 2020 to Version 4.0 dated 18 May 2021	Administrative change
Global	Minor corrections to grammar/spelling	Administrative changes
Synopsis Section 1.3 Section 4.1 Section 4.4 Section 6.8 Section 7.1	Removed Long-Term and Survival F/U visits, and revised study end date to be 2 years after last subject randomized	Removed the Long-Term and Survival F/U visits, which required a revision to the study end date
Table 2	Removed all PD/Biomarker sampling after Cycle 2	Re-evaluated need for additional sample collection after Cycle 2
Section 6.6.5	Added COVID-19 vaccines as allowed Concomitant Medications	Global rollout of COVID-19 vaccines addressed with this addition
Section 8.4	Section removed as part of Long-Term and Survival F/U removal	Harmonizing protocol with prior removal of the Long-Term and Survival F/U visits

10.8.2. Protocol Version 3.2 (Amendment 4), 08 December 2020

10.8.2.1. Amendment Rationale and Summary of Changes

Secura Bio, Inc. acquired the global rights in Oncology for the Investigational Medicinal Product (IMP), duvelisib (also referred to as Copiktra®) from Verastem. Updates were made in this document in all sections, as applicable, to reflect that Secura Bio is now the Sponsor for this study. This is an administrative change that does not affect the planned study.

In addition, minor language and format corrections were also done throughout the document.

The revised protocol, Version 3.2, dated 08 December 2020 will be submitted by the Investigator(s) to all applicable IRBs, IECs, or CECs, and by Secura Bio, Inc. to all applicable Regulatory Authorities.

10.8.3. Protocol Version 3.1 (Amendment 3), 25 February 2020

10.8.3.1. Amendment Rationale and Summary of Changes

The primary purpose for this amendment was to make minor administrative changes to the protocol. Specifically, to provide a consistent and correct date of the amendment throughout the document. In Version 3.0, the date of the amendment was not correct in some footers and text (28 January 2019 instead of 28 January 2020). In addition, a minor change to the ECG note in the Schedule of Assessments and Section 8.2.2 was made to indicate that "QTc measurements will be *as measured by triplicate readings*" for consistency with the text of Exclusion Criterion #18.

10.8.4. Protocol Version 3.0 (Amendment 2), 28 January 2020

10.8.4.1. Amendment Rationale

The primary purpose for this amendment was to incorporate changes made in 3 country-specific amendments to address requests from Regulatory Authorities after their review of Version 1.0.

The revised protocol, Version 3.0, dated 28 January 2020 will be submitted by the Investigator(s) to all applicable IRBs, IECs, or CECs, and by Secura Bio, Inc. to all applicable Regulatory Authorities.

A summary of key changes that were made to protocol Version 1.0, including the rationales for these changes, is provided in Table 20.

Table 21: Summary of Changes for Version 3.0

Section(s)	Description of Change	Rationale for the Change
Global	Updated the version number and date of protocol from Version 1.0 dated 04 April 2019 to Version 3.0 dated 28 January 2020	Administrative change
Global	Minor corrections to grammar/spelling	Administrative changes
Synopsis Section 3	Specified the metabolite of duvelisib as IPI-656	To clarify that the only metabolite analyzed in PK data analysis is PI-656

Section(s)	Description of Change	Rationale for the Change
Section 8.5 Section 9.4.5		
Section 1.2	Legend for Figure #1 revised to provide correct disease response frequency to be consistent with Table 1 (Schedule of Assessments)	Correction of error
Section 1.3	Minor corrections/clarifications and reorganizations to Table 1 (Schedule of Assessments)	Correction of errors (incorrect or missing information), addition of clarifications, and elimination of sub-header rows
Section 1.3	Added an optional tumor biopsy at Screening	To allow the Investigator, at their discretion, to perform a tumor biopsy during Screening to confirm diagnosis if they suspect transformation to a more aggressive lymphoma.
Section 1.3	Added details (e.g., "Day 1" and "Window" to describe timing of CT assessment	Clarification
Section 1.3	Merge cells for Bone Marrow Biopsy and/or Aspirate	To correct omission, as biopsy may be required at any visit during the course of the study, including LTFU, to confirm CR
Section 1.3	Added guidance text to indicate that additional ECGs and echocardiograms may be conducted at the Investigator's discretion as clinically indicated	For consistency with body of the protocol (existing guidance text in Section 8.2.4)
Section 1.3	Add C1D43 visit, with Hematology, Conmeds, focused PE, vitals, AEs, drug diary, and self-admin of drug	To provide for additional neutrophil count monitoring consistent with US Prescribing Information and ensure safety monitoring at this visit
Section 1.3	Added note to Clinical Chemistry, Hematology, and Urinalysis assessments that tests must be conducted, and results available, within 7 days prior to the first dose of duvelisib	To ensure that key laboratory parameters are assessed within a short time frame before first dose of study drug
Section 1.3 Section 5.2 Section 10.3	Removal of human T-lymphotrophic virus type 1 (HTLV-1) testing at Screening and from exclusion criterion #14	This testing is not relevant for this clinical study
Section 1.3 Section 8.1.1	Modified text describing requirements for imaging scans	To clarify that CT or PET-CT is required but MRI may be used instead of CT if CT cannot be done

Section(s)	Description of Change	Rationale for the Change
Section 1.3 Section 8.1.2 (Section 8.1.3 in prior version)	Changed bone marrow biopsy guidance for submission of available pathology reports from "most recent" to "within 60 days before C1D1"	If a patient had bone marrow biopsy/aspirate prior to the first dose of the study drug as a part of standard of care; the pathology report data within 60 days of C1D1 are more medically relevant than results from an earlier time point
Section 1.3 Section 8.2.1	Modified schedule of assessments to include Full Physical Examination (PE) at C1D1, and Focused PE and Vital Signs at every visit. Re-ordered SoA rows and text sections to present full PE, focused PE, and Vital Sign assessments sequentially. Align SoA notes and text descriptions.	To increase frequency of vital signs measurements and provide additional safety monitoring. Re-ordering and text alignment was done for clarity
Section 1.3 Section 10.3	Removed cortisol testing at Screening	Not needed for this clinical study
Section 1.3 Section 10.3	Added description of HLA types included in the HLA assessment at Screening	To provide additional assessment details for clarity
Section 2.1 Section 2.2 Section 4.2 Section 11	Added information to Rationale, Background, and Scientific Rationale sections, with supporting references	To provide justification for study design and population, as well as additional information on indication and available therapies
Section 5.1	Modified inclusion criterion #4 to indicate that subjects are required to be candidates for a subsequent line of therapy	To clarify eligibility requirements
Section 5.1	Modified inclusion criterion #5 to indicate that subjects must have hemoglobin level $\geq$ 8 g/dL	To clarify the eligibility based on hemoglobin levels
Section 5.1 Section 11	Modified inclusion criterion #5 to indicate that renal function will be measured by estimated creatinine clearance rather than serum creatinine level	To more accurately assess eligibility based on renal function
Section 5.1 Section 5.3 Section 6.6.4 Section 8.3.9 Section 10.4	Modified inclusion criterion #7 and contraception guidance to indicate that highly effective methods of contraception must be used	To align contraception guidance with the Clinical Trials Facilitation Group (CFTG) guidance
Section 5.2	Modified exclusion criterion #14 to remove requirement for HBV viral prophylaxis with entecavir (or equivalent) concomitant with	Monitoring for reactivation of HBV is a sufficient precaution against active HBV infection for

Section(s)	Description of Change	Rationale for the Change
	duvelisib treatment for subjects who have positive HBcAB and negative DNA	subjects who have positive HBcAB and negative DNA
Section 5.4 (new)	Moved definition of enrolled from the Sample Size Determination section (Section 9.2) to a new section (Definition of Enrolled)	To improve clarity
Section 5.5	Deleted text stating that rescreened subjects should be assigned the same subject number as for the initial screening	To align with current practice
Section 6.6.2 Section 10.7	Added definition for the term "Gi" as 1 X 10^9 (1 billion cells or giga)	To clearly distinguish the "Gi" abbreviation from the "GI" abbreviation
Section 6.6.3	Modified text to indicate that, in addition to during treatment, live vaccines are prohibited within 6 weeks of C1D1 and for 3 months after last dose of study drug	To provide additional safety protection for study subjects after treatment discontinuation
Section 6.8	Added the following statement: "Long-term continued treatment will be provided either in a separate clinical study or expanded access program consistent with local regulations"	To clarify how subjects who are still receiving treatment at the end of the study will access duvelisib after the end of the study
Section 8 Section 8.2.1	Deleted text describing timing of Screening activities, including the following statement: "A full PE will be conducted at Screening."	To align with the protocol template by limiting descriptions for the timing of assessments to the SoA
Section 8.1.1 (Section 8.1.2 in prior version)	Modified text describing PET-CT	To align with SoA
Section 8.3.6	Modified Clinical Laboratory Adverse Event section to remove language that restricts the constitution of abnormal laboratory values as AEs	To align with ICH Guideline E.2.A
Section 8.3.8	Clarified that only cases of overdose that cause an SAE are required to be reported within 24 hours, and that Investigator will determine if and when dosing should resume	To clarify and expand overdose guidance
Section 5.4 (new, statement was moved from Section 9.2 in prior version) Section 10.6.3	Deleted references to subject's legal representative	To address request by regulatory authorities to limit participation to subjects who are capable of providing informed consent

Section(s)	Description of Change	Rationale for the Change
Section 9.2	Reworded the power statement in terms of significance level alpha	To clarify the significance level
Section 10.1.2	Corrected PET to PET-CT and deleted "(PET)" from title of Table 13	To align with nomenclature in published response criteria
Section 10.2.1	Footnote 3: corrected the definition of a weak CYP inhibitor based on FDA definition	To correct a textual error
Section 10.6.3	Clarified that patients who are detained by administrative or judicial order will be excluded from participating in the study	To provide information regarding the eligibility of patients who are detained by administrative or judicial order
Section 10.6.8	Provided additional details regarding study termination criteria, particularly termination due to safety concerns	To clarify criteria for premature termination of the study
Section 10.7	Updated Abbreviations list	To reflect updated protocol
Section 10.8.1	Added Summary of Changes made in Version 3.0	Administrative change
Section 10.8.2	Updated version history	Administrative change

10.8.5. Version History

Table 22: Primary Reason for Each Version

Version	Primary Reason for Version
4.0	To revise study assessments/sample collection and incorporate COVID-19 vaccine approvals
3.2	Administrative amendment to update the Sponsor contact information and to correct minor errors in Version 3.1
3.1	Administrative amendment to correct minor errors in Version 3.0
3.0	To incorporate Version 2.0 country-specific changes into a global amendment
2.0 (3 country-specific amendments)	To address country-specific requests from Czech Republic/Italian, German, and United Kingdom regula tory authorities after their review of global Version 1.0. There was no global Version 2.0.
1.0	Original version

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