CLINICAL STUDY PROTOCOL

Protocol Title	A Phase 1b-2 Study of the ROR1-Targeting Monoclonal Antibody, Cirmtuzumab (UC-961), and the Bruton Tyrosine Kinase Inhibitor, Ibrutinib, in Patients with B-Cell Lymphoid Malignancies
Investigational Product	Cirmtuzumab (UC-961) (INN: zilovertamab)
Protocol Number	CIRM-0001 (Oncternal Therapeutics, Inc)
Developmental Phase	Phase 1b-2 (Clinical Safety and Efficacy)
US IND Number	133131
Sponsor Name and Address	Oncternal Therapeutics, Inc 12230 El Camino Real, Ste 230 San Diego, CA 92130
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Confidentiality Statement

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Investigator: _____

Study Number: CIRM-0001

Product Name(s): Cirmtuzumab (UC-961) (INN: zilovertamab)

Study Title: A Phase 1b-2 Study of the ROR1-Targeting Monoclonal Antibody, Cirmtuzumab (UC-961), and the Bruton Tyrosine Kinase Inhibitor, Ibrutinib, in Patients with B-Cell Lymphoid Malignancies

Document Date: 15 April 2022

As Principal Investigator, I agree:

- To keep all documentation supplied to me or developed by me concerning this study, and that has not been previously published, in the strictest confidence. This documentation includes, but is not limited to, the Investigator's Brochure and Case Report Forms (CRFs)
- That the study will not commence without prior written approval of a properly constituted Institutional Review Board. No changes will be made to the study Protocol without prior written approval of Oncternal Therapeutics, Inc. and the Institutional Review Board, except where necessary to eliminate an immediate hazard to patients
- To implement and conduct the study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations
- To accurately transfer all required data from each patient's source document to the CRFs. The original CRFs will be submitted to the Sponsor in a timely manner at the completion of the trial, or as otherwise specified by the Sponsor
- To keep a complete and accurate accounting during and at the completion of the trial of all procedures performed with the drug provided by the Sponsor
- To allow authorized representatives of Oncternal Therapeutics, Inc. or regulatory authority representatives to conduct on-site visits to review, audit and copy trial documents. I will personally meet with these representatives at mutually convenient times to answer any trial-related questions
- To provide the Sponsor with an investigator's summary within 90 days of completion of the final trial visit for the last patient enrolled, or as designated by Sponsor
- To maintain all information supplied by the Sponsor in confidence and, when this information is submitted to an Institutional Review Board (IRB), Ethical Review Committee, or another group, it will be submitted with a designation that the material is confidential.

This protocol was designed and will be conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) guidelines. These guidelines are stated in United States federal regulations as well as "Guidance for Good Clinical Practice," International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

I have read this protocol in its entirety, including the preceding statements, and I agree to comply with all aspects of this trial.

_____
Investigator Printed Name

_____ _____
Investigator Signature Date

_____
Institution Name

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ALC	absolute lymphocyte count
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AV	Atrioventricular
Bcl2	B-cell lymphoma 2 (protein)
BTK	Bruton tyrosine kinase
BUN	blood urea nitrogen
CD	cluster of differentiation
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practices
CHO	Chinese hamster ovary (cells)
CI	confidence interval
CK	creatine kinase
Cl	clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum concentration
CMR	complete metabolic response
CR	complete response
CRi	complete response with incomplete blood count recovery
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450 (enzyme)
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	Electrocardiogram, electrocardiographic
eCl_{CR}	estimated creatinine clearance
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EMT	epithelial-mesenchymal transition
EU	European Union
FDA	Food and Drug Administration
FDAMA	Food and Drug Modernization Act of 1997
FDG	Fluorodeoxyglucose
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GTPase	guanosine-triphosphate-hydrolyzing enzyme
GVHD	graft-versus-host disease
HBc	hepatitis B core (antibody)
HBsAg	hepatitis B surface antigen

Abbreviation	Definition
HBV	hepatitis B virus
HCV	hepatitis C virus
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
Ig	Immunoglobulin
IL	Interleukin
IND	investigational new drug application
INN	International Nonproprietary Name
IRB	institutional review board
IV	intravenous, intravenously
LD or LDi	longest dimension
LDH	lactate dehydrogenase
LLQ	lower limit of quantitation
LPD	longest perpendicular dimension
LVD	longest vertical dimension
MCL	mantle cell lymphoma
MFI	mean fluorescent intensity
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MZL	marginal zone lymphoma
Na-EDTA	sodium-ethylenediaminetetraacetic acid
NCI	National Cancer Institute
NE	Nonevaluable
NHL	non-Hodgkin lymphoma
NK	natural killer (cells)
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PPD	product of the perpendicular diameters
PR	partial response
PR-L	partial response with lymphocytosis
PT	prothrombin time
Q4	once every
QD	once per day
QTc	cardiac QT interval corrected for heart rate
Rac1	Ras-related C3 botulinum toxin substrate
RDR	recommended dosing regimen
RhoA	Ras homolog gene family member A
RNA	ribonucleic acid
ROR1	receptor tyrosine kinase-like orphan receptor 1
R/R	Relapsed or Refractory
SAE	serious adverse event
SD	stable disease
SDi	shortest dimension
siRNA	small interfering ribonucleic acid
SLL	small lymphocytic lymphoma

Abbreviation	Definition
SPD	sum of the products of the diameters
SRC	safety review committee
SUSAR	suspected, unexpected, serious adverse reaction
$t_{1/2}$	elimination half-life
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
T_{max}	time of maximum concentration
TNT	time to next treatment
TTR	time to response
TTF	time to treatment failure
UC-961	alternate name for cirmtuzumab
UCSD	University of California, San Diego
ULN	upper limit of normal
V_d	volume of distribution
βHCG	beta human chorionic gonadotropin
λ_z	terminal elimination rate constant

STATEMENT OF COMPLIANCE

The study will be performed in accordance with the principles as set forth under the requirements of 21 Code of Federal Regulations (CFR) 50 and the ICH E6 GCP guideline.

The investigator will ensure that this study is conducted in accordance with 21 CFR parts 50 and 54 and ICH guidelines. For studies conducted under a US IND, the investigator will ensure adherence to the basic principles of GCP as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, Part 50, 1998, and 21 CFR, Part 56, 1998. This study is also subject to and will be conducted in accordance with 21 CFR, Part 320, 1993, "Retention of Bioavailability and Bioequivalence Testing Samples."

1. PROTOCOL SUMMARY

1.1. Synopsis

Investigational Product	Cirmtuzumab (UC-961) (INN: Zilovertamab)
Coadministered Drug	Ibrutinib
Study Title	A Phase 1b-2 Study of the ROR1-Targeting Monoclonal Antibody, Cirmtuzumab (UC-961), and the Bruton Tyrosine Kinase Inhibitor, Ibrutinib, in Patients with B-Cell Lymphoid Malignancies
Protocol Number	CIRM-0001 (Oncternal Therapeutics, Inc)
Study Background	Among the agents approved for the therapy of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL) or marginal zone lymphoma (MZL) is the Bruton tyrosine kinase (BTK) inhibitor, ibrutinib, which has provided durable tumor regressions in the majority of patients with these disorders. However, the proportion of patients experiencing complete response (CR) to ibrutinib monotherapy is low (<7% in CLL/SLL, ~15% in MCL and ~3% for MZL) and resistance to ibrutinib eventually develops in many patients. Collectively, these data support development of a new agent with a complementary mechanism of action that can safely combine with ibrutinib to enhance disease clearance and circumvent disease resistance. Receptor tyrosine kinase-like orphan receptor 1 (ROR1) is a cell surface protein that mediates signals from its ligand, the secreted glycoprotein, Wnt5a. Consistent with its role in influencing the fate of stem cells during embryogenesis, ROR1 expression is observed on invasive malignancies that revert to an embryonic transcriptional program, but is not observed on normal adult tissues, offering a favorable selectivity profile as a therapeutic target. ROR1 is expressed on the malignant cells in >90% of patients with CLL/SLL and >95% of patients with MCL and is also expressed on MZL [Barna 2011]. Oncternal Therapeutics, Inc. (Oncternal), in collaboration with The University of California, San Diego (UCSD) is developing the therapeutic monoclonal antibody, cirmtuzumab, for selective targeting of hematological and other cancers with high ROR1 expression. Cirmtuzumab is a humanized immunoglobulin (Ig) G1 monoclonal that shows high-affinity binding to ROR1. Cirmtuzumab is synergistic when tested together with ibrutinib, inhibiting the growth of CLL and MCL cells in vitro, and combination therapy was associated with substantially greater reductions in splenomegaly and leukemia-cell infiltration in splenic tissue in a murine CLL model than either single agent given alone. Clinical evaluation of cirmtuzumab has comprised a Phase 1a, sequential dose-escalation study in patients with CLL/SLL. Cirmtuzumab was very well tolerated over a dose range of 0.015 to 20 mg/kg. Adverse events (AEs) were largely attributable to patients' cancers or comorbidities and were primarily Grade 1 or 2 in intensity. No DLTs were observed, no serious adverse events (SAEs) occurred, and no maximum tolerated dose (MTD) was identified within the tested dose range. Pharmacodynamic data indicted decreases in ROR1-mediated signaling as manifest by decreased Rac1 and RhoA expression in circulating CLL cells. Individual signs of disease control over

	the 8-week drug administration period were observed, including reductions in circulating CLL cell numbers, lymphadenopathy, splenomegaly, and/or bone marrow infiltration. Many patients had persistent post-therapy disease stabilization. Collectively, these data provide context for the clinical development of the combination of cirmtuzumab and ibrutinib as therapy of CLL/SLL, MCL and MZL. It is hypothesized that coadministration of these 2 drugs will result in a higher proportion of patients achieving CR and experiencing longer progression-free survival (PFS). Given the exceptional clinical safety of both drugs, the combination is expected to be well tolerated. Accordingly, this clinical protocol will further characterize the safety, pharmacology, and activity of cirmtuzumab alone and when co-administered with ibrutinib in patients with recurrent or treatment-refractory CLL/SLL, MCL or MZL.
Study Design	This clinical trial is a Phase 1b-2 study of the safety, pharmacokinetics, pharmacodynamics, immunogenicity, and antitumor activity of the combination of cirmtuzumab and ibrutinib. The study will be conducted in 3 parts.
Part 1 Dose-Finding Cirmtuzumab → Cirmtuzumab + Ibrutinib	Part 1 comprises a Phase 1b, open-label, sequential allocation, dose-finding evaluation of the sequential administration of cirmtuzumab monotherapy followed by cirmtuzumab + ibrutinib combination therapy in patients with CLL/SLL or MCL. At the conclusion of Part 1 of the study, a recommended dosing regimen (RDR) of cirmtuzumab will be selected based primarily on safety, pharmacokinetic, and pharmacodynamic findings.
Part 2 Cohort Expansion Cirmtuzumab + Ibrutinib	Part 2 comprises a Phase 2 expansion and open-label evaluation of the concurrent administration of cirmtuzumab and ibrutinib based on the RDR derived from Part 1. Up to 18 evaluable patients with CLL/SLL will be enrolled. Up to 20 evaluable patients with MCL and up to 10 patients with relapsed/refractory (R/R) MZL will be enrolled into Part 2; a clinical review will then be performed to determine if additional patients are required to assess safety, efficacy, and exploratory biomarkers for further development.
Part 3 Efficacy Evaluation Cirmtuzumab + Ibrutinib versus Ibrutinib	Part 3 comprises a Phase 2 open-label, randomized, controlled, 2-arm, parallel-group evaluation of the clinical activity and safety of cirmtuzumab + ibrutinib versus ibrutinib alone. Patients with CLL/SLL will be randomized 2:1 to one of the following 2 regimens: • Arm A: cirmtuzumab + ibrutinib • Arm B: ibrutinib alone Approximately 30 patients will be enrolled and randomized into Part 3.

Study Objectives

Primary Objectives

- Part 1 (cirmtuzumab → cirmtuzumab + ibrutinib): To determine the RDR of cirmtuzumab when given alone and in combination with ibrutinib in patients with CLL/SLL or MCL
- Part 2 (cirmtuzumab + ibrutinib): To further characterize the safety, pharmacology, and clinical responses of cirmtuzumab + ibrutinib when administered using the RDR in patients with CLL/SLL, MCL, or MZL
- Part 3 (cirmtuzumab + ibrutinib versus ibrutinib): To further evaluate the CR rate associated with cirmtuzumab + ibrutinib when administered using the RDR in patients with CLL/SLL

Secondary Objectives

- To determine the drug administration, safety, and supportive care profiles of cirmtuzumab and the combination of cirmtuzumab + ibrutinib
- To evaluate the pharmacokinetic profile of cirmtuzumab alone and in combination with ibrutinib
- To assess the effects of cirmtuzumab and cirmtuzumab + ibrutinib on exploratory biomarkers/pharmacodynamic markers relating to drug mechanism, immune profile, and disease manifestations
- To characterize the immunogenicity of cirmtuzumab
- To characterize the antitumor activity of cirmtuzumab monotherapy and cirmtuzumab + ibrutinib combination therapy

Selection and Enrollment of Study Patients

Planned Number of Patients

Part 1 (Cirmtuzumab → Cirmtuzumab + Ibrutinib)

If 6 patients (3 patients with CLL/SLL and 3 patients with MCL) are enrolled at all 4 planned dose levels, 24 patients will be enrolled. If 2 additional dose levels are explored in 6 patients/dose level (3 patients with CLL/SLL and 3 patients with MCL), as many as 12 additional patients could be enrolled, bringing the potential sample size to 36 patients. To allow for the possibility that some patients may not be fully evaluable, up to 48 patients may be enrolled.

Part 2 (Cirmtuzumab + Ibrutinib)

It is planned that the RDR will be evaluated in up to 18 patients with CLL/SLL. To allow for the possibility that some patients may not be fully evaluable, up to 30 patients may be enrolled. The RDR will be the same for CLL/SLL, MCL and MZL. Up to 20 evaluable patients with MCL and up to 10 patients with R/R MZL will be enrolled into Part 2; a clinical review will then be performed to determine if additional evaluable patients are required to assess safety, efficacy, and exploratory biomarkers for further development. This review could lead to a further adjustment and increase in enrollment.

Part 3 (Cirmtuzumab + Ibrutinib vs Ibrutinib Alone)

Approximately 30 patients will be enrolled and randomized 2:1 into Part 3 (~20 patients will receive cirmtuzumab + ibrutinib and ~10 patients will receive ibrutinib alone).

Target Populations The target population comprises adult patients with adequate performance status and organ function who have CLL/SLL, MCL or MZL and are appropriate candidates for ibrutinib treatment.

1.2. Schema

Figure 1: Part 1 – Dose-Finding (Cirmtuzumab → Cirmtuzumab + Ibrutinib)

Drug	Dosing	Week															
		0	2	4	6	8	12	16	20	24	28	32	36	40	44	48	52
Cirmtuzumab	Dose levels: 2, 4, 8, or 16 mg/kg starting Week 0 Sequential dose allocation by disease type: CLL/SLL: 2→4→8→16→2→4→8→16→2→4→8→16 mg/kg MCL: 2→4→8→16→2→4→8→16→2→4→8→16 mg/kg	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ibrutinib	Fixed dose continuously starting Week 4 CLL/SLL: 420 mg QD MCL: 560 mg QD			X	X	X	X	X	X	X	X	X	X	X	X	X	X

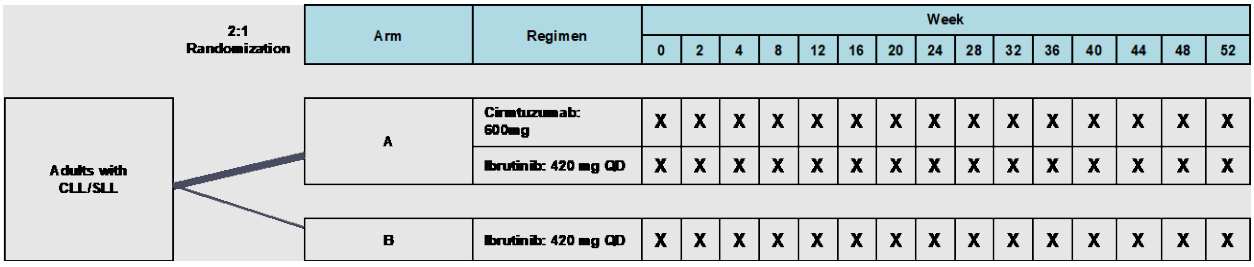
Patients exhibiting a PR or CR may be eligible to continue combination treatment beyond Week 52 as part of an extended therapy program.

Figure 2: Part 2 – Cohort Expansion (Cirmtuzumab + Ibrutinib)

Drug	Dosing	Week															
		0	2	4	6	8	12	16	20	24	28	32	36	40	44	48	52
Cirmtuzumab	Dose level: 600mg	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ibrutinib	Fixed dose continuously MCL/MZL :560mg QD or CLL/SLL 420mg QD	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Patients exhibiting a PR or CR may be eligible to continue combination treatment beyond Week 52 as part of an extended therapy program.

Figure 3: Part 3 – Efficacy Evaluation (Cirmtuzumab + Ibrutinib versus Ibrutinib)



Patients exhibiting a PR or CR may be eligible to continue combination treatment beyond Week 52 as part of an extended therapy program.

1.3. Schedule of Activities

Tabular schedules of study activities are presented in Section 8.2 (Part 1), Section 8.3 (Part 2), and Section 8.4 (Part 3).

2. INTRODUCTION

2.1. Lymphoid Cancers

B-cell lymphoid malignancies arise from the accumulation of monoclonal, neoplastic B lymphocytes in lymph nodes and often in organs such as blood, bone marrow, spleen, and liver. Among the variants of B-cell lymphoid cancers are chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), and marginal zone lymphoma (MZL). These disorders are characterized by disabling constitutional symptoms; lymphadenopathy and organomegaly that can induce life-threatening organ dysfunction; and myelosuppression and immunocompromise that can result in susceptibility to infection and bleeding [Zhang 2014b; Hallek 2015; Vose 2015; Cheah 2016]. Front-line use of multiagent chemoimmunotherapy is commonly successful in suppressing disease manifestations for prolonged periods [NCCN 2016a; NCCN 2016b]. However, these diseases are incurable, and patients require further therapy to maintain disease control.

2.2. Inhibition of Bruton Tyrosine Kinase in Lymphoid Cancers

Among the agents approved for the therapy of patients with relapsed or refractory CLL/SLL, MCL or MZL is the Bruton tyrosine kinase (BTK) inhibitor, ibrutinib (PCI-32765, Imbruvica™). Bruton tyrosine kinase (BTK) is a non-receptor enzyme in the TEC kinase family that is expressed among cells of hematopoietic origin, including B cells, myeloid cells, mast cells, and platelets, where it regulates multiple cellular processes including proliferation, differentiation, apoptosis, and cell migration [Khan 2001; Mohamed 2009; Bradshaw 2010]. Functional null mutations of BTK in humans cause the inherited disease, X-linked agammaglobulinemia, which is characterized by a lack of mature peripheral B cells [Vihinen 2000; Ponader 2014]. Conversely, BTK activation is implicated in the pathogenesis of several B-cell malignancies [Herman 2011; Buggy 2012; Herman 2014, Kil 2013; Woyach 2014a]. In addition, BTK-dependent activation of mast cells and other immunocytes in peritumoral inflammatory stroma has been shown to sustain the complex microenvironment needed for tumor maintenance and growth [Ponader 2012; de Rooij 2012].

Based on this pharmacology, ibrutinib was developed by Pharmacyclics, Inc (now a subsidiary of AbbVie, Inc) and Janssen, Inc as an orally delivered, small-molecule, irreversible inhibitor of BTK for the treatment of B-cell malignancies. Studies in patients with heavily pretreated CLL/SLL have demonstrated that chronic ibrutinib therapy can provide lasting antitumor activity for the majority of patients [Advani 2013; Byrd 2013; Byrd 2014; Farooqui 2015; O'Brien 2016; Winqvist 2016]. Similarly, in patients with substantial prior therapy for MCL and MZL, chronic ibrutinib monotherapy has offered tumor regressions and durable tumor control [Wang 2013; Dreyling 2016; Maruyama 2016; Noy 2017].

Ibrutinib has been generally well tolerated. For patients with lymphoid cancers receiving ibrutinib, clinical adverse events (AEs) (of any causality) have included: atrial fibrillation or atrial flutter; bleeding (primarily bruising and petechiae); infections; neutropenia, thrombocytopenia, or anemia; diarrhea, and rash. Such events have generally been infrequent and typically have been Grade 1 or 2 in intensity [Pharmacyclics 2020 and Ibrutinib Investigator Brochure 2021]. Across the tested ibrutinib dose range (through 1400 mg/day), no acute dose-limiting toxicities (DLTs) were identified and the recommended Phase 2 doses (420 mg/day for

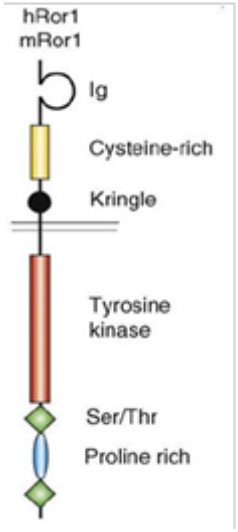
CLL/SLL and 560 mg/day for MCL and MZL) were established based on pharmacodynamic outcomes rather than safety limitations [Advani 2013]. The drug has also proved safe when administered as oral continuous monotherapy for periods of several years [Byrd 2015a; Wang 2015]. Rates of discontinuations due to adverse events have consistently been <10% across studies in CLL/SLL, MCL and MZL although they may approach ~20% in clinical practice [Mato 2016]. Further, ibrutinib has been readily combined with therapeutic monoclonal antibodies and cytotoxic agents used to treat CLL/SLL, MCL and MZL; because of a lack of overlapping toxicities with such drugs, it has been possible to administer both ibrutinib and the other agents at the full recommended dose levels [Burger 2014; Younes 2014; Brown 2015; Maddocks 2015a; Chanan-Khan 2016; Wang 2016]. Whether given alone or in combination, instances of tumor lysis syndrome (TLS) at the initiation of ibrutinib have been rare [Howard 2016]. Based on its efficacy and safety in patients with previously treated disease, ibrutinib has been approved for the therapy of previously untreated and previously treated CLL/SLL and for the therapy of previously treated MCL and MZL in the United States (US), the European Union (EU), and elsewhere [de Claro 2015; Pharmacyclics 2020].

While ibrutinib offers tumor regressions in the substantial majority of patients, the proportion of patients with CLL/SLL experiencing a complete response (CR) to ibrutinib monotherapy is consistently <5% within the first year of therapy [Byrd 2013; Byrd 2014; Farooqui 2015; Burger 2015; O'Brien 2016] and rises to only 7% after several years of treatment [Byrd 2015a]. In previously treated MCL, rates of CR have ranged from 12.5% to 23%, even with long-term therapy [Wang 2013; Dreyling 2016; Maruyama 2016; Wang 2015]. In relapsed/refractory MZL treated with prior rituximab or rituximab-based chemoimmunotherapy, rate of CR to ibrutinib monotherapy was 3.2% and ORR was 46% after 19.4 months of follow-up [Pharmacyclics 2020]. ORR rates increased to 58% after a median follow-up of 33.1 months [Noy 2020]. Progression-free survival (PFS) has been very long in most patients with CLL/SLL and has averaged 13 to 14.6 months in those with MCL [Wang 2015; Dreyling 2016]. For MZL, median PFS was 14.2 and 15.7 months, after a median follow-up of 19.4 and 33.1 months, respectively [Noy 2017; Noy 2020]. However, resistance to ibrutinib eventually develops in many patients with CLL and most patients with MCL [Chiron 2014; Furman 2014; Cheng 2015; Liu 2015; Burger 2016; Hamasy 2016]. Among those becoming resistant to ibrutinib, an aggressive natural history is common [Cheah 2015; Jain 2015; Maddocks 2015b; Stephens 2015; Martin 2016]. Collectively, these data support development of a new agent that targets a complementary mechanism of action and can safely be combined with ibrutinib to enhance disease clearance and circumvent disease resistance.

2.3. Receptor Tyrosine Kinase-like Orphan Receptor 1 (ROR1)

ROR1 is a type 1 transmembrane protein that shares homology to other receptor tyrosine kinases and shows high evolutionary conservation [Masiakowski 1992; Forrester 1999; Yoda 2003; Katoh 2005]. As shown in Figure 4, the extracellular portion contains immunoglobulin-like sequences, a cysteine-rich domain homologous to Frizzled receptors for various Wnt ligands, and a kringle domain. The cytoplasmic portion contains a tyrosine kinase-like domain followed by serine/threonine- and proline-rich motifs.

Figure 4. Structure of ROR1



Abbreviations: Ig=immunoglobulin, m/h ROR=mouse/human receptor tyrosine kinase-like orphan receptor 1, ser=serine, thr=threonine

Based on studies in rodents, ROR1 is an embryonic factor that is physiologically expressed during early embryogenesis and plays a critical role in neural, skeletal, and vascular organogenesis [Oishi 1999; Al-Shawi 2001; Matsuda 2001; Lyashenko 2010]. Functional studies in primary embryonic cells suggest that binding of the secreted glycoprotein ligand, Wnt5a, results in heterodimerization of ROR1 with ROR2 (the other member of the ROR family) and can stimulate neuronal synapse formation [Paganoni 2010]. During fetal development, the expression of ROR1 decreases [Masiakowski 1992; Al-Shawi 2001; Paganoni 2010]. With the exception of rare B-lymphocyte precursors known as hematogones (the non-neoplastic counterpart to precursor-B acute lymphoblastic leukemia (ALL) [Broome 2011], normal adult tissues lack surface expression of the ROR1 protein [Fukuda 2008; Hudecek 2010; Zhang 2012b; Liu 2015b].

However, consistent with a role as an onco-embryonic factor, high levels of ROR1 protein expression have been found in multiple cancers, including both hematological malignancies [Daneshmanesh 2008; Baskar 2008; Hudecek 2010; Barna 2011; Uhrmacher 2011; Daneshmanesh 2013; Kotašková 2016] and solid tumors [Zhang 2012b; Liu 2015b]. Among lymphoid cancers, these studies indicate near universal expression of ROR1 expression in CLL/SLL and MCL and document evidence of ROR1 expression in some patients with ALL [Bicocca 2012], marginal zone lymphoma (MZL), and diffuse large B-cell lymphoma (DLBCL) [Barna 2011]. ROR1 expression and activation appears to be correlated with features of tumor aggressiveness in models of CLL, breast cancer, lung cancer, gastric cancer, and melanoma [Li 2010; Daneshmanesh 2012; Zhang 2012a; Daneshmanesh 2013; Gentile 2011; Yamaguchi 2012; Hojjat-Farsangi 2013a; Hojjat-Farsangi 2013b; O'Connell 2013; Ida 2016; Janovska 2016]. Elevated levels of ROR1 expression in patients and cell lines are associated with genes involved in epithelial-mesenchymal transition (EMT) [Cui 2013]. In patients with CLL, high levels of ROR1 expression are associated with shorter treatment-free survival and overall survival (OS) [Cui 2016]. Similarly, in patients with ovarian cancer, high ROR1 expression is associated with poor clinical outcomes [Zhang 2014a].

The potential functional significance of ROR1 signaling has been evaluated. In a gene therapy experiment in which 6 patients with CLL received infusion of adenovirus-CD145-transduced autologous CLL cells, it was noted that 3 of the patients made endogenous IgG that was reactive with ROR1 [Fukuda 2008]. In vitro studies indicated Wnt5a binding to ROR1 enhanced the survival of CLL cells in vitro, an effect that could be neutralized by sera from the anti-ROR1-positive patients. These results were supported by clinical data indicating that spontaneously developing anti-ROR1 immune responses in patients with CLL were associated with a better prognosis [Hojjat-Farsangi 2015]. In a mouse model, animals engineered to produce CLL-like B cells that were positive for ROR1 showed high transcriptome expression of subnetworks implicated in embryonic and tumor-cell proliferation, and relatively low levels of transcripts involved in cell-cell adhesion or cell death [Widhopf 2014]. These cells were also actively proliferating (as indicated by Ki-67-positivity) and showed relatively little spontaneous apoptosis.

Treatment of these mice with an anti-ROR1 monoclonal antibody (D10) resulted in ROR1 down-modulation, reduced down-stream signaling, and impaired engraftment of leukemia cells [Widhopf 2014]. Similarly, silencing of ROR1 with small interfering ribonucleic acid (siRNA) was observed to enhance apoptosis of human CLL cells [Choudhury 2010]. In nonclinical models of breast cancer, treatment with anti-ROR1 antibodies or siRNA reduced tumor growth and metastatic potential [Zhang 2012a; Cui 2013]. Likewise, treatment of melanoma with anti-ROR1 monoclonal antibodies resulted in apoptosis in ROR1-positive but not ROR1-negative cell lines [Hojjat-Farsangi 2013a].

Collectively, the accumulating data regarding its role in cancer and lack of expression in normal tissues indicate that ROR1 represents an attractive therapeutic target for cancer intervention.

2.4. Cirmtuzumab

2.4.1. Discovery

Given its tumor-specific expression and potential functional significance in oncogenesis, investigators at the University of California, San Diego (UCSD) initiated a drug discovery program to generate monoclonal antibodies for the treatment of ROR1-expressing hematological and solid tumors. Oncternal Inc (Oncternal) was formed to further develop the technology.

At UCSD, hybridomas were screened for production of monoclonal antibodies mimicking the activity of anti-ROR1 autoantibodies observed in patients vaccinated against transfected autologous leukemia cells [Fukuda 2008] and were tested in vivo using the TCL1 x ROR1 CLL mouse model [Widhopf 2014]. One murine monoclonal antibody, D10, was identified that could inhibit ROR1-mediated signaling and engraftment of $ROR1^{+}$ leukemia cells in this model. When tested in an immune-deficient murine xenograft, the D10 antibody consistently demonstrated potent, dose-dependent activity against human CLL patient samples. Mapping the epitope bound by the D10 antibody allowed generation of monoclonal antibodies with substantially higher affinity for ROR1. Humanization of the variable regions allowed identification of an antibody that maintained high binding affinity while minimizing the potential for immunogenicity. This clinical development candidate was designated UC-961 or cirmtuzumab [Choi 2015].

2.4.2. Chemistry

Cirmtuzumab is a recombinant humanized IgG1κ monoclonal antibody with specificity for an epitope in the Ig-like region of the extracellular domain of human ROR1 (see Figure 4 above). The antibody has 1,320 amino acids and a molecular weight of ~148 kilodaltons including N-linked glycosylation. The antibody is humanized except for amino acids adjacent to the borders of the complementarity-determining region and one of the framework regions, both of which are immune protected sites.

The protein is produced in Chinese hamster ovary (CHO) cells and is purified by a process that includes viral inactivation and removal steps. No animal sources are used in the production of the drug substance and culture media are serum-free and protein-free.

2.4.3. Clinical Experience with Cirmtuzumab

Clinical evaluation of cirmtuzumab has comprised a Phase 1a, sequential, dose-escalation study [Choi 2017]. Patients enrolled to the study have been adult men and women with relapsed or refractory CLL/SLL requiring treatment, Eastern Cooperative Group (ECOG) performance status ≤2, and adequate organ function. Study patients have received a total of 4 IV infusions of cirmtuzumab monotherapy, each to be administered every 2 weeks. Dose escalation has been performed with a 3+3 design with intrapatient dose escalation permitted in early dosing cohorts. Infusions have been given over 1.5 to 4 hours. The safety, pharmacokinetics, pharmaco-dynamics, and clinical effects of cirmtuzumab have been assessed.

In summary, the Phase 1a results with cirmtuzumab administration at dose levels of 0.015 to 20 mg/kg show the drug to be very well tolerated, with no obvious drug-related toxicity (including no DLTs, no Grade 4 AEs, no SAEs and no discontinuations due to AEs). Pharmacokinetic and pharmacodynamic data indicate systemic drug exposure and provide preliminary clinical evidence of expected drug mechanism. Details are provided in the Investigator Brochure.

2.4.4. Combination Studies of Cirmtuzumab and Ibrutinib

Given that ibrutinib now represents a standard-of-drug in the therapy of CLL/SLL and MCL, studies were performed to evaluate the therapeutic potential of combining cirmtuzumab with ibrutinib in nonclinical models of these diseases [Yu 2017; Yu 2018].

To evaluate the in vitro effects of ibrutinib on the ROR1 pathway, circulating mononuclear cells from patients who were taking ibrutinib at the standard dose of 420 mg once per day (QD) were evaluated [Yu 2017] or fresh CLL cells were incubated with ibrutinib in culture. The cells were examined for Wnt5a-induced Rac1 activation with or without ibrutinib and/or cirmtuzumab. The data showed that cirmtuzumab, but not ibrutinib, could inhibit Wnt5a-induced Rac1 activation in CLL cells and that ibrutinib did not block the capacity of cirmtuzumab to inhibit Wnt5a-induced Rac1 activation. To assess the combined effects of cirmtuzumab and ibrutinib on CLL proliferation, leukemic cells were co-cultured with HeLa cells expressing CD154 and recombinant interleukin (IL)-4 and IL-10 [Yu 2017]. Treatment of the CLL cells with cirmtuzumab, but not ibrutinib, could block Wnt5a-enhanced proliferation. A cell-cycle analysis found that Wnt5a stimulation significantly enhanced the fraction of leukemia cells in S/G2/M and that the proportion of cells in S/G2/M could be decreased by cirmtuzumab but not ibrutinib.

Collectively, these data demonstrate that cirmtuzumab can block ROR1-mediated leukemia-cell proliferation that is not affected by ibrutinib.

In vivo studies of the combination of cirmtuzumab and ibrutinib in several nonclinical models of CLL/SLL were performed [Yu 2017]. To assess the activity of cirmtuzumab and/or ibrutinib in xenografts derived from patients with CLL, leukemic cells from such patients were transferred into the peritoneal cavities of immunodeficient $Rag2^{-/-}\gamma_c^{-/-}$ mice. Following treatment with a single dose of cirmtuzumab or 7 days of ibrutinib administration, the percentages and total numbers of CLL cells in peritoneal lavage were significantly lower than in control mice. Coadministration of the 2 drugs resulted in an even greater antitumor effect than either drug administered alone. Similar combination effects were observed when ROR1 × TCL1 leukemia cell engraftment was evaluate in immunodeficient $Rag2^{-/-}\gamma_c^{-/-}$ mice or in immunocompetent human-ROR1 transgenic (ROR1-Tg) mice. Treatment with either single agent resulted in reductions in spleen size, and a lower mean proportion and number of leukemia cells in the spleen. However, treatment with both agents led to significantly greater antitumor effects than were observed with either monotherapy.

To determine the influence of the ROR1 signaling pathway in MCL, primary cells from patients with the disease were evaluated for evidence of ROR1 expression [Yu 2018]. All of the tested patient samples showed intense surface staining for ROR1; the median (±SD) values for mean fluorescence intensity relative to control (ΔMFI) were higher in patients with MCL (N=8, 87.5±18.5) than in sample patients with CLL (N=167, 38.5±18.5), and substantially higher than those in normal lymphocytes (<1). It was also notable that immunoassay evaluation of plasma samples from patients with MCL all showed high Wnt5a concentrations, further supporting the potential importance of the Wnt5a-ROR1 pathway in the pathogenesis of MCL.

As had be done with CLL cells, primary lymphoma cells from patients with MCL were examined for Wnt5a-induced, ROR1-dependent activation of the Rho-GTPase, Rac1 [Yu 2018]. As noted in CLL cells, Wnt5a induced activation of primary MCL cells in a ROR1-dependent fashion. Cirmtuzumab, but not ibrutinib, could inhibit the capacity of Wnt5a to induce Rac1 activation. To evaluate cirmtuzumab effects on lymphoma proliferation, MCL cells were co-cultured with HeLa cells expressing CD154, and recombinant IL-4 and IL-10 [Yu 2018]. The addition of exogenous Wnt5a to these co-cultures significantly enhanced the proportion of dividing MCL cells. Cell-cycle analysis showed that Wnt5a stimulation significantly increased the fraction of MCL cells in S/G2/M. The capacity of Wnt5a to enhance the proportion of primary MCL cells in S/G2/M could be inhibited by treatment with cirmtuzumab, but not with ibrutinib, as noted previously for CLL cells.

These data demonstrate the functional importance of ROR1 signaling in both CLL and MCL and the ability of cirmtuzumab to inhibit ROR1-mediated oncogenic activity in these disorders with a mechanism that complements BTK inhibition by ibrutinib.

2.5. Conclusions/Study Rationale

The conduct of this Phase 1b-2 study of the combination of cirmtuzumab and ibrutinib for patients with CLL/SLL, MCL and R/R MZL is founded on a current understanding of the natural history and current therapies for patients with lymphoid malignancies; knowledge of the importance of ROR1 and BTK cellular pathways in the pathophysiology of these diseases; and

nonclinical and clinical information regarding the efficacy and safety of the 2 study drugs. The collective data support the following conclusions:

- Relapsed or refractory CLL/SLL, MCL and MZL represent serious, disabling, and life-threatening disorders. Existing BTK inhibitor therapy demonstrates activity but only infrequently induces complete tumor regression and loses effectiveness over time. The development of cirmtuzumab with ibrutinib offers a potential method for enhancing antitumor immunotherapeutic activity, overcoming disease resistance, and improving both short- and long-term outcomes for patients with CLL/SLL, MCL and MZL.
- Clinical evaluation of cirmtuzumab in combination with ibrutinib in patients with B-cell lymphoid cancers has sound scientific rationale founded on the known efficacy of BTK inhibition in lymphoid cancers, the frequent expression and oncogenic potential of ROR1 in these malignancies, and the results of nonclinical pharmacology studies that demonstrate the therapeutic potential of the combination of cirmtuzumab and ibrutinib in lymphoid cancers.
- Advancing the development of cirmtuzumab together with ibrutinib in this study is well supported by nonclinical evaluations of cirmtuzumab pharmacology, pharmacokinetics, and toxicology; by Phase 1a safety, pharmacokinetic, and pharmacodynamic data obtained in patients with CLL/SLL receiving cirmtuzumab; and by extensive prior clinical experience with ibrutinib therapy. This collective information provides a basis for patient enrollment criteria; starting dose selection and dose escalation; administration of an appropriate dosing regimen; and for safety, pharmacodynamic, pharmacokinetic, and efficacy monitoring within this study.
- Given the seriousness of previously treated, progressive CLL/SLL, MCL and MZL and the aggregate potential benefits considered in the context of potential risks, clinical development of cirmtuzumab with ibrutinib in patients with hematological cancers is justified.

3. OBJECTIVES AND ENDPOINTS

3.1. Primary Objectives

- Part 1 (cirmtuzumab → cirmtuzumab + ibrutinib): To determine the RDR of cirmtuzumab when given alone and in combination with ibrutinib in patients with CLL/SLL or MCL
- Part 2 (cirmtuzumab + ibrutinib): To further characterize the safety, pharmacology, and clinical responses of cirmtuzumab + ibrutinib when administered using the RDR in patients with CLL/SLL MCL or R/R MZL
- Part 3 (cirmtuzumab + ibrutinib versus ibrutinib): To further evaluate the CR rate associated with cirmtuzumab + ibrutinib when administered using the RDR in patients with CLL/SLL

3.2. Secondary Objectives

- To determine the drug administration, safety, and supportive care profiles of cirmtuzumab and the combination of cirmtuzumab + ibrutinib
- To evaluate the pharmacokinetic profile of cirmtuzumab alone and in combination with ibrutinib
- To assess the effects of cirmtuzumab and cirmtuzumab + ibrutinib on exploratory biomarkers/pharmacodynamic markers relating to drug mechanism, immune profile, and disease manifestations
- To characterize the immunogenicity of cirmtuzumab
- To characterize the antitumor activity of cirmtuzumab monotherapy and cirmtuzumab + ibrutinib combination therapy

3.3. Primary Study Endpoints

- Part 1 (cirmtuzumab → cirmtuzumab + ibrutinib): RDR within the tested dose range
- Part 2 (cirmtuzumab + ibrutinib): RDR with the cirmtuzumab + ibrutinib combination
- Part 3 (cirmtuzumab + ibrutinib versus ibrutinib): CR rate, defined as the proportion of patients achieving a CR per pre-established CLL/SLL response criteria

3.4. Secondary Study Endpoints

3.4.1. Antitumor Activity and Survival

Efficacy will be evaluated using consolidated response criteria for CLL/SLL [Hallek 2018; Cheson 2012; Hallek 2008] and for lymphoma [Cheson 2014; Cheson 2007]. Efficacy will be evaluated as described in Section 8.5, Appendix 12.5, and Appendix 12.6. Efficacy endpoints will include:

- Overall response (OR), defined as achievement of complete response (CR), complete response with incomplete blood count recovery (CRi), partial response (PR), or partial

response with lymphocytosis (PR-L) for those with CLL/SLL; and the achievement of a CR or PR for those with MCL or MZL

- Complete response (CR), defined as achievement of CR or CRi for those with CLL/SLL; and the achievement of a CR for those with MCL or MZL
- Percent change in tumor dimensions, defined as the best (most negative) percent change from baseline in the sum of the products of the diameters (SPD) of index lesions
- Time to response (TTR), defined as the interval from the start of study therapy to the first documentation of an objective response
- Duration of response (DOR), defined as the interval from the first documentation of objective response to the earlier of the first documentation of disease progression or death from any cause
- Progression-free survival (PFS), defined as the interval from the start of study therapy to the earlier of the first documentation of disease progression or death from any cause
- Time to progression (TTP), defined as the time from the start of study therapy until objective tumor progression; TTP does not include deaths
- Time to treatment failure (TTF), defined as the interval from start of study therapy to the earliest of the first documentation of disease progression, the permanent cessation of study drug due to an AE, or death from any cause
- Time to next treatment (TNT), defined as the interval from start of study therapy to the start of a new regimen for CLL/SLL ,MCL or MZL due to study treatment failure
- Overall survival (OS), defined as the interval from the start of study therapy to death from any cause

3.4.2. Safety Profile

- Type, frequency, severity, timing of onset, duration, and relationship to study drugs of any treatment-emergent adverse events (TEAEs); laboratory abnormalities; vital sign abnormalities; adverse electrocardiogram (ECG) findings; SAEs; or AEs leading to interruption, modification, or discontinuation of study treatment

3.4.3. Pharmacokinetics

- Cirmtuzumab serum concentrations (as measured using a validated immunoassay)
- Derived pharmacokinetic parameters (including area under the serum concentration-time curve [AUC], maximum concentration [C_{max}], time of maximum concentration [T_{max}], volume of distribution [V_d], terminal elimination half-life [$t_{1/2}$], terminal elimination rate constant [λ_z], and clearance [Cl]) (as determined using noncompartmental methods)

3.4.4. Pharmacodynamics/Exploratory Biomarkers

- Evaluate pre- and post-regimen blood and bone marrow as well as any available CLL/SLL, MCL or MZL tumor biopsy samples for exploratory biomarkers that might be

predictive of tumor response and downstream effects of cirmtuzumab. Tests may include an examination of tumor receptor expression, gene activation, and blood cytokine levels.

- Changes in ROR1 cell surface expression and receptor occupancy
- Changes in ALC in peripheral blood (as assessed by standard cell counting methods)
- Changes in cancer stem cell parameters
- Changes in plasma concentrations of cytokines

3.4.5. Immunogenicity

Changes in titers and neutralizing capacity of circulating cirmtuzumab-reactive antibodies (as assessed using immunoassay methods)

4. STUDY DESIGN

This clinical trial is a Phase 1b-2 study of the safety, pharmacokinetics, pharmacodynamics, immunogenicity, and antitumor activity of the combination of cirmtuzumab and ibrutinib. The study will be conducted in 3 parts (see schema, Section 1.2).

4.1. Part 1 – Dose-Finding (Cirmtuzumab → Cirmtuzumab + Ibrutinib)

Part 1 comprises a Phase 1b, open-label, sequential allocation, dose-finding evaluation of the sequential administration of cirmtuzumab monotherapy followed by cirmtuzumab + ibrutinib combination therapy in patients with CLL/SLL or MCL. Patients will be administered study therapy as follows:

- Cirmtuzumab given by IV infusion every 2 weeks for 5 administrations (Weeks 0, 2, 4, 6, 8) and then every 4 weeks thereafter (Weeks 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52) at a dose of either 2, 4, 8, or 16 mg/kg. After establishment of safety at these dose levels, fixed doses of 300 and 600 mg IV per dose will be examined in patients with CLL/SLL.
- Ibrutinib self-administered orally, QD, continuously starting in Week 4 at a dose of either 420 mg/day (for patients with CLL/SLL) or at a dose of 560 mg/day (for patients with MCL).

Allocation to cirmtuzumab dose within each disease type (CLL/SLL or MCL) will be performed such that each successive patient with that disease is assigned to 2, 4, 8, and then 16 mg/kg in a sequence that is repeated 3 times, resulting in enrollment of 3 patients with CLL/SLL and 3 patients with MCL across each of the 4 dose levels. The fixed dose level cohorts will then be examined separately using a standard 3+3 design.

Patients exhibiting a PR or CR may continue combination treatment beyond Week 52 until disease progression or unacceptable toxicity as part of an extended therapy program. Patients who remain in a PR or CR at the end of the 2 year treatment period, may be eligible for Long-term Therapy and continue to receive cirmtuzumab and ibrutinib until they experience disease progression, unacceptable toxicity, or the study ends. Sites should discuss these cases with the sponsor in advance for approval.

For CLL/SLL patients, long-term follow-up consisting of patient contact every 6 months and collection of disease, treatment, and vital status data, will continue following the End of Treatment visit for up to 5 years. For MCL patients, long-term follow-up will occur every 3 months and include collection of disease, treatment, and vital status data for up to 5 years. Imaging reports may be requested by the sponsor for CLL/SLL or MCL patients in long-term follow-up. These data will be used to determine progression free survival (PFS), time to progression (TTP), and time to next treatment. Once a patient in long-term follow-up has progressed and received an alternate treatment for their disease, only vital status will be collected.

At the conclusion of Part 1 of the study, a recommended dosing regimen (RDR) of cirmtuzumab will be selected based primarily on safety, pharmacokinetic, and pharmacodynamic findings. This portion of the study has been completed and a 600 mg fixed dose of cirmtuzumab was determined to be the RDR for both CLL/SLL and MCL. [Choi 2019a, Choi 2019b].

4.2. Part 2 – Cohort Expansion (Cirmtuzumab + Ibrutinib)

Part 2 comprises a Phase 2 expansion, open-label evaluation of the concurrent administration of cirmtuzumab and ibrutinib based on the RDR derived from Part 1. Up to 18 evaluable patients with CLL/SLL will be enrolled. Up to 20 evaluable patients with MCL and up to 10 patients with MZL will be enrolled into Part 2; a clinical review will then be performed to determine if additional evaluable patients are required to complete any safety, efficacy, or biomarker analyses. This review could lead to a further adjustment or increase in enrollment.

Patients will be administered study therapy as follows:

- Cirmtuzumab given by IV infusion every 2 weeks for 3 administrations (Weeks 0, 2, 4) and then every 4 weeks thereafter (Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52) using the RDR of cirmtuzumab (600 mg fixed dose IV).
- Ibrutinib self-administered orally QD, continuously starting concurrently with cirmtuzumab in Week 0 at a dose of either 420 mg/day (for patients with CLL/SLL) or at a dose of 560 mg/day (for patients with MCL or MZL).

Patients exhibiting a PR or CR may continue combination treatment beyond Week 52 until disease progression or unacceptable toxicity as part of an extended therapy program. Patients who remain in a PR or CR at the end of the 2 year treatment period, may be eligible for Long-term Therapy and continue to receive cirmtuzumab and ibrutinib until they experience disease progression, unacceptable toxicity, or the study ends. Sites should discuss these cases with the sponsor in advance for approval.

For CLL/SLL patients, long-term follow-up consisting of patient contact every 6 months and collection of disease, treatment, and vital status data, will continue following the End of Treatment visit for up to 5 years. For MCL and MZL patients, long-term follow-up will occur every 3 months and include collection of disease, treatment, and vital status data for up to 5 years. Imaging reports may be requested by the sponsor for CLL/SLL, MCL or MZL patients in long-term follow-up. These data will be used to determine progression free survival (PFS), time to progression (TTP), and time to next treatment. Once a patient in long-term follow-up has progressed and received an alternate treatment for their disease, only vital status will be collected.

4.3. Part 3 – Efficacy Evaluation (Cirmtuzumab + Ibrutinib versus Ibrutinib)

Part 3 comprises a Phase 2 open-label, randomized, controlled, 2-arm, parallel-group evaluation of the clinical activity and safety of cirmtuzumab + ibrutinib versus ibrutinib alone. Patients with CLL/SLL will be randomized 2:1 to one of the following 2 regimens in blocks of 6 patients using a pre-generated randomization list:

- Arm A: cirmtuzumab + ibrutinib
- Arm B: ibrutinib alone

Approximately 30 patients will be enrolled and randomized into Part 3.

Patients exhibiting a PR or CR may continue treatment beyond Week 52 until disease progression or unacceptable toxicity as part of an extended therapy program. Patients who

remain in a PR or CR at the end of the 2 year treatment period, may be eligible for Long-term Therapy and continue to receive cirmtuzumab and ibrutinib until they experience disease progression, unacceptable toxicity, or the study ends. Sites should discuss these cases with the sponsor in advance for approval.

For CLL/SLL patients, long-term follow-up consisting of patient contact every 6 months and collection of disease, treatment, and vital status data, will continue following the End of Treatment visit for up to 5 years. Imaging reports may be requested by the sponsor for CLL/SLL patients in long-term follow-up. These data will be used to determine progression free survival (PFS), time to progression (TTP), and time to next treatment. Once a patient in long-term follow-up has progressed and received an alternate treatment for their disease, only vital status will be collected.

4.4. Rationale for Study Design

The study has been designed to provide critical dosing, safety, pharmacokinetic, pharmacodynamic, and early efficacy data in support of future clinical development of cirmtuzumab and cirmtuzumab + ibrutinib.

In Part 1 of the study, the intrapatient comparison of sequential administration of cirmtuzumab monotherapy followed by cirmtuzumab + ibrutinib combination therapy generates a rigorous evaluation of the pharmacology of cirmtuzumab at fixed repeated doses with and without ibrutinib. Such an evaluation is important for cirmtuzumab given knowledge that ibrutinib can increase pharmacokinetic exposure to therapeutic monoclonal antibodies (eg, rituximab) that have tumor cells as a major mediator of drug clearance [Cramer 2016]. The intent is to obtain critical information regarding pharmacokinetic and pharmacodynamic dose-response and dose-exposure relationships and any potential drug-drug interaction to support selection of a RDR for use in Parts 2 and 3 of this study and in other trials of both single-agent and combination cirmtuzumab-based therapy. Introduction of ibrutinib within 4 weeks of starting the study ensures that study patients transition rapidly to established therapy for their CLL/SLL, MCL or MZL.

The planned rotating, sequential dose-assignment process in Part 1 of the trial provides an efficient and impartial method of assigning dose levels while offering safety and simplicity advantages over conventional ascending-dose or randomized designs. A standard ascending-dose design is not warranted given the substantial safety and lack of DLTs for either cirmtuzumab and ibrutinib within the tested dose range, the lack of overlapping toxicities between the agents, and historical knowledge that ibrutinib can be combined with multiple types of intensive chemoimmunotherapy without the need for modification of either the ibrutinib or chemoimmunotherapy doses [Burger 2014; Younes 2014; Brown 2015; Maddocks 2015a; Chanan-Khan 2016; Wang 2016]. Randomized dose allocation is not necessary because it would introduce complexity that would be disproportionate to the modest size and exploratory goals of Part 1 of the trial.

Part 2 of the study provides a confirmatory characterization of the safety and pharmacology of the cirmtuzumab + ibrutinib combination when administered using the provisional RDR defined from Part 1 of the trial. Interpatient comparisons between cohorts receiving cirmtuzumab alone during the first 2 infusions in Part 1 and cohorts receiving ibrutinib together with cirmtuzumab

during the first 2 infusions in Part 2 will strengthen an understanding of the pharmacological consequences of adding ibrutinib to cirmtuzumab.

Part 3 of the trial offers a Phase 2 assessment of cirmtuzumab + ibrutinib activity that will be important as a basis for Phase 3 planning. The randomized, add-on design in Part 3 is customary in the comparative evaluation of new therapies for cancer; such a design documents the incremental benefit and safety of the investigational therapy (cirmtuzumab) in the context of a controlled clinical trial while ensuring that all participants receive potentially active treatment (ibrutinib). Randomization is an accepted means to reduce bias and allows for the highest standard of evidence in documenting a treatment effect. Use of a 2:1 allocation enlarges the clinical experience with the investigational cirmtuzumab + ibrutinib combination.

Involvement of a coordinating SRC is considered appropriate to ensure safety and general study conduct oversight of this exploratory, open-label Phase 1b-2 trial; each study center may follow local standard operating procedures relating to institutional review of safety data at that study center.

4.5. Rationale for Study Drug Doses

The cirmtuzumab starting dose levels to be evaluated in this study were selected based on data from a Phase 1a study showing that cirmtuzumab was very well tolerated in the range of 0.015 to 20 mg/kg and that dose levels of ≥2 mg/kg have the potential to induce pharmacodynamic inhibition of ROR1-mediated signaling [Choi 2017]. The specific doses (2, 4, 8, and 16 mg/kg) to be evaluated in the current clinical trial were selected with the intent of defining the shape of the dose-response and exposure-response profiles and to determine the minimal dose associated with maximal continuous ROR1 inhibition. The planned schedule of cirmtuzumab administration (2 infusions at 2-week intervals followed by subsequent infusions at 4-week intervals) builds on pharmacokinetics findings with the every-2-week schedule used in the Phase 1a study; the schedule in the current trial is intended to achieve early ROR1 inhibition with maintenance of target coverage during chronic therapy. The initial 90-minute cirmtuzumab infusion time considered the lack of infusion toxicities observed in the Phase 1a cirmtuzumab experience and safety information developed with the therapeutic monoclonal antibody, rituximab, showing the feasibility of this approach [Dakhil 2014, Genentech 2016]. Guidelines for the administration of cirmtuzumab are detailed in the Pharmacy manual. In general, the first infusion will be given over 90 minutes. If no adverse reactions are observed, the infusion time may be shortened with each subsequent administration as tolerated, following the guidelines in the Pharmacy Manual.

The doses and schedule of ibrutinib (420 mg QD for patients with CLL/SLL and 560 mg QD for patients with MCL or MZL) and the dose modification provisions for ibrutinib are consistent with those recommended in product labeling [Pharmacyclics 2020].

5. STUDY POPULATION: RECRUITMENT AND SELECTION OF STUDY PATIENTS

5.1. Planned Number of Patients

5.1.1. Part 1 (Cirmtuzumab → Cirmtuzumab + Ibrutinib)

If 6 patients (3 patients with CLL/SLL and 3 patients with MCL) are enrolled at all 4 planned dose levels, 24 patients will be enrolled. If 2 additional dose levels are explored in 6 patients/dose level (3 patients with CLL/SLL and 3 patients with MCL), as many as 12 additional patients could be enrolled, bringing the potential sample size to 36 patients. To allow for the possibility that some patients may not be fully evaluable, up to 48 patients may be enrolled.

5.1.2. Part 2 (Cirmtuzumab + Ibrutinib)

The RDR derived from Part 1 will be evaluated in up to 18 patients with CLL/SLL. Up to 20 evaluable patients with MCL and up to 10 evaluable patients with MZLwill be enrolled into Part 2; a clinical review will then be performed to determine if additional evaluable patients are required. This review could lead to a further adjustment and an increase in enrollment.

5.1.3. Part 3 (Cirmtuzumab + Ibrutinib versus Ibrutinib)

Approximately 30 patients will be enrolled and randomized 2:1 into Part 3 (~20 patients will receive cirmtuzumab + ibrutinib and ~10 patients will receive ibrutinib alone).

5.2. Enrollment of Study Patients

Inclusion and exclusion criteria will be reviewed for each potential patient by qualified study center personnel. If the consented study candidate is considered eligible for study participation, the study center will transmit an enrollment request to Oncternal (or designee).

Oncternal (or designee) will acknowledge receipt of the enrollment request and will assign the study part, the cirmtuzumab dose (Part 1), and the appropriate ibrutinib dose (for CLL/SLL, MCL or MZL). Once the study center has received this information, the patient can begin treatment.

Study candidates who fail screening will be noted on a screening and enrollment log maintained by site staff. Their data will not be entered into the EDC system (eCRF).

5.3. Patient Selection Criteria

This clinical trial can fulfill its objectives only if appropriate participants are enrolled. The protocol-specified eligibility criteria are designed to select patients for whom study participation is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a study candidate. Eligibility criteria may not be waived by the investigator and conformance to the eligibility criteria will be reviewed in the case of a GCP or a regulatory authority audit. Any questions regarding a study candidate's eligibility should be discussed with the medical monitor before enrollment.

5.3.1. Inclusion Criteria

Study candidates must meet all of the following inclusion criteria to be eligible for participation in this study:

1. Men and women of age ≥18 years.
2. ECOG performance status of 0, 1, or 2 (see Appendix 12.1).
3. Histological diagnosis of CLL/SLL, MCL or MZL (including splenic,nodal and extranodal subtypes) as documented in medical records (pathology reports and slides or blocks should be available for review or additional testing).
4. MCL has been previously treated and has relapsed after or progressed during prior therapy. CLL/SLL may have been previously treated or are treatment naïve but now require therapy. MZL has been previously treated and has relapsed after or progressed during at least one prior anti-CD20 -based therapy
5. A medically appropriate candidate for ibrutinib treatment (based on the judgement of the clinical investigator).
6. Patients who have received prior BTK inhibitor therapy are eligible, unless they demonstrated primary or acquired resistance to a BTK inhibitor or experienced a serious or severe adverse event attributed to BTK inhibitor therapy.
7. Presence of radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of ≥1 non-biopsied, non-irradiated lesion that measures >1.5 cm in the longest dimension [LD] and ≥1.0 cm in the longest perpendicular dimension [LPD] as assessed by computed tomography [CT] or magnetic resonance imaging [MRI]).
8. Current medical need for therapy due to disease-related symptoms, lymphadenopathy, organomegaly, extranodal organ involvement, or progressive disease.
9. Completion of all previous therapy (including any Bcl-2 or PI3K inhibitor therapy, surgery, radiotherapy, chemotherapy, immunotherapy, or investigational therapy) for the treatment of cancer ≥1 week (or ≥3 half-lives of the previous drug) before the start of study therapy.
10. All acute toxic effects of any prior antitumor therapy resolved to Grade ≤1 before the start of study therapy (with the exceptions of alopecia, or neurotoxicity [Grade 1 or 2 permitted], or selected laboratory parameters [Grade 1 or Grade 2 permitted with exceptions as noted below]).
11. Adequate bone marrow function:
    a. Absolute neutrophil count (ANC) ≥1.0 × 10^9/L.
    b. Platelet count ≥50 × 10^9/L.
    c. Hemoglobin ≥8.0 g/dL maintained for ≥1 week from any prior transfusion.

    Note: Grade ≥3 neutropenia, thrombocytopenia, or anemia is permitted if the abnormality is related to bone marrow involvement with hematological malignancy (as documented by bone marrow biopsy/aspirate obtained since the last prior therapy).
12. Adequate hepatic profile:
    a. Serum alanine aminotransferase (ALT) ≤3 × upper limit of normal (ULN).

b. Serum aspartate aminotransferase (AST) ≤3 × ULN.

c. Serum bilirubin ≤1.5 × ULN unless elevated due to Gilbert syndrome.

13. Adequate renal function:

a. Estimated creatinine clearance (eCl_{CR}) >30 mL/minute (with eCl_{CR} to be calculated by the Cockcroft-Gault formula [see Appendix 12.2]), or

b. Measured creatinine clearance >30 mL/minute (as assessed with a 24-hour urine collection).

14. Adequate coagulation profile:

a. Prothrombin time (PT) ≤1.5 × ULN.

b. Activated partial thromboplastin time (aPTT) ≤1.5 × ULN.

15. Negative viral serology:

a. Negative human immunodeficiency virus (HIV) antibody.

b. Negative hepatitis B surface antigen (HBsAg) and negative hepatitis B core (HBc) antibody or undetectable hepatitis B (HBV) deoxyribonucleic acid (DNA) by quantitative polymerase chain reaction (PCR) testing.

c. Negative hepatitis C virus (HCV) antibody or negative HCV RNA by quantitative PCR.

16. For female patients of childbearing potential, a negative urine or serum pregnancy test prior to the start of study therapy.

17. For female patients of childbearing potential, willingness to use a highly effective method of contraception from the start of the screening period until ≥3 months after the last dose of cirmtuzumab and ≥1 month after the last dose of ibrutinib, whichever is later. ***Note: A female patient is considered to be of childbearing potential unless she has had a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy; has medically documented ovarian failure (with serum estradiol and follicle-stimulating hormone [FSH] levels within the institutional laboratory postmenopausal range and a negative serum or urine beta human chorionic gonadotropin [βHCG]); or is menopausal (age ≥50 years with amenorrhea for ≥6 months)***.

18. For male patients who can father a child and are having intercourse with females of childbearing potential who are not using adequate contraception, willingness to use an effective method of contraception from the start of study therapy until ≥3 months after the last dose of cirmtuzumab and ≥3 months after the last dose of ibrutinib, whichever is later and to refrain from sperm donation from the start of study therapy until ≥3 months after administration of the final dose of either of the study drugs. ***Note: A male patient is considered able to father a child unless he has had a bilateral vasectomy with documented aspermia or a bilateral orchiectomy***.

19. In the judgment of the investigator, participation in the protocol offers an acceptable benefit-to-risk ratio when considering current disease status, medical condition, and the potential benefits and risks of alternative treatments for the patient's cancer.

20. Willingness and ability of the patient to comply with scheduled visits, drug administration plan, protocol-specified laboratory tests, other study procedures, and study restrictions.

21. Evidence of a personally signed informed consent indicating that the patient is aware of the neoplastic nature of the disease and has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential risks and discomforts, potential benefits, and other pertinent aspects of study participation.

5.3.2. Exclusion Criteria

Study candidates who meet any of the following criteria will not be eligible for participation in this study:

1. Known histological transformation to an aggressive lymphoma (ie, Richter transformation). ***Note: Biopsy documentation of the absence or presence of transformation is not required.***
2. Known central nervous system malignancy. ***Note: Central nervous system imaging is only required in patients with suspected central nervous system malignancy.***
3. Presence of another cancer with disease manifestations or therapy that could adversely affect patient safety or longevity, create the potential for drug-drug interactions, or compromise the interpretation of study results.
4. Significant cardiovascular disease (eg, myocardial infarction, arterial thromboembolism, cerebrovascular thromboembolism) within 3 months prior to start of study therapy; angina requiring therapy; symptomatic peripheral vascular disease; New York Heart Association Class 3 or 4 congestive heart failure; or uncontrolled Grade ≥3 hypertension (diastolic blood pressure ≥100 mmHg or systolic blood pressure ≥160 mmHg) despite antihypertensive therapy.
5. Significant screening ECG abnormalities, including unstable cardiac arrhythmia requiring medication, atrial fibrillation/flutter, left bundle branch block, 2nd-degree atrioventricular (AV) block type II, 3rd-degree AV block, or Grade ≥2 bradycardia.
6. Gastrointestinal disease (eg, gastric or intestinal bypass surgery, pancreatic enzyme insufficiency, malabsorption syndrome, symptomatic inflammatory bowel disease, chronic diarrheal illness, bowel obstruction) that might interfere with drug absorption or with interpretation of gastrointestinal AEs.
7. Contraindication for ibrutinib use because of a bleeding diathesis.
8. Evidence of an ongoing systemic bacterial, fungal, or viral infection (including upper respiratory tract infections) at the time of start of study therapy. ***Note: Patients with localized fungal infections of skin or nails are not precluded from participation.***
9. In patients with prior hematopoietic progenitor cell transplantation, evidence of ongoing graft-versus-host disease (GVHD).
10. Pregnancy or breastfeeding.
11. Major surgery within 4 weeks before the start of study therapy.
12. Prior solid organ transplantation.
13. Prior anti-ROR1 therapy within 12 weeks prior to the start of study therapy.
14. Use of a moderate or strong inhibitor or inducer of cytochrome P450 (CYP) 3A4 within 7 days prior to the expected start of ibrutinib therapy (see Appendix 12.3).

15. Concurrent participation in another therapeutic or imaging clinical trial.
16. Any illness, medical condition, organ system dysfunction, or social situation, including mental illness or substance abuse, deemed by the investigator to be likely to interfere with a patient's ability to provide informed consent, adversely affect the patient's ability to cooperate and participate in the study, or compromise the interpretation of study results.

6. STUDY INTERVENTION

6.1. Cirmtuzumab

6.1.1. Known Potential Risks: Cirmtuzumab (zilovertamab)

The safety profile (N = 31) of cirmtuzumab in combination with ibrutinib in subjects with MCL was recently presented (Lee, 2021). The overall safety profile of cirmtuzumab plus ibrutinib was similar to the known safety profile of ibrutinib alone, with no dose reductions and no SAEs attributed to cirtuzumab. Most TEAEs were Grades 1 and 2. Few subjects had a Grade 3 or above AE.

6.1.2. Known Potential Benefits: Cirmtuzumab (zilovertamab)

The efficacy data from 26 evaluable subjects with MCL enrolled in Study CIRM-0001 is summarized in Section 3.1 of the Cirmtuzumab Investigator Brochure, and was presented at ASH 2021 (Lee, 2021). The ORR of 80.8%, CR rate of 34.6%, and median PFS of 35.9 months (95% CI: 16.5 to 35.9 months) for evaluable subjects with MCL in Study CIRM-0001 compare favorably to the reported ORR of 66%, CR rate of 20%, and PFS of 12.8 months (95% CI: 8.5 to 16.6 months) for 370 subjects with MCL in a merged analysis of 3 studies of single agent ibrutinib (Rule, 2017).

The interim safety results from Study CIRM-0001 suggest that myelosuppression associated with ibrutinib monotherapy, especially neutropenia, may occur less frequently when ibrutinib is administered in combination with cirmtuzumab therapy. TEAEs related to myelosuppression appeared to be slightly lower than expected for ibrutinib treatment, so quantitative analysis of complete blood count data for MCL was undertaken. Grade 3 or greater neutrophil decrease and platelets decreased of 9.7%, respectively, for cirmtuzumab plus ibrutinib appear to be qualitatively lower than the 29% Grade 3 or greater neutrophils decreased and 17% platelets decreased reported for the ibrutinib MCL registration study (Ibrutinib Investigator Brochure 2021). This could be related to the observation that residual tumor cells during ibrutinib treatment express ROR1, which is activated by its ligand Wnt5a, leading to cross-activation of inflammatory pathways including JAK/stat and secretion of inflammatory chemokines and cytokines including IL6 and IFN gamma. Cirmtuzumab has been shown to inhibit this inflammatory activity (Chen, 2019). These Grade 3 and above hematologic toxicities associated with monotherapy BTK inhibitor therapy may have contributed to dose reductions, delays, or treatment discontinuation that may be associated with monotherapy BTK inhibitor therapy administration, potentially reducing optimal dosing and efficacy.

6.1.3. Description

Cirmtuzumab is manufactured under current Good Manufacturing Practices (cGMP) and is supplied in vials nominally containing 300 mg of drug substance (40 mg/mL) in 7.5 mL of formulation buffer containing the excipients sodium citrate, trehalose, polysorbate 80, and sodium-ethylenediaminetetraacetic acid (Na-EDTA). The drug product appears as a clear to slightly opalescent, colorless to slightly yellow liquid and essentially free of visible particulates. The solution has a target pH of 5.2. The drug product is for IV administration. A pharmacy manual outlining the preparation of the cirmtuzumab infusion bag will be provided to the site personnel.

6.1.4. Source

Cirmtuzumab will be provided by Oncternal.

6.1.5. Packaging and Labelling

Cirmtuzumab drug product is filled into sterile 10-ml Type I, clear, borosilicate glass vials with butyl siliconized rubber stoppers and aluminum seals.

Labels for cirmtuzumab vials meet all applicable requirements of the FDA, Annex 13 of cGMP (Manufacture of Investigational Medicinal Products, July 2003), and/or other local regulations, as applicable.

6.1.6. Shipping, Storage, and Stability

During shipping and storage, vials should remain refrigerated at temperatures of 2 to 8°C [35.6 to 46.4°F]).

After dilution and prior to use, cirmtuzumab should be maintained at 2 to 8°C [35.6 to 46.4°F]) and is stable for at least 24 hours after dilution. However, cirmtuzumab contains no antimicrobial preservative and so should be administered as soon as possible after preparation.

6.1.7. Cirmtuzumab Administration

Cirmtuzumab will be given by IV infusion at dose levels and intervals as specified in Sections 4.1-4.3. Intrapatient dose escalation to dose levels above the dose level assigned to a patient will not be permitted.

A qualified person (eg, nurse or physician with experience in monitoring the administration of therapeutic agents used in patients with cancer) will be responsible for infusing cirmtuzumab.

The initial cirmtuzumab infusion will be administered over a planned infusion time of ~90 minutes, with 20% of the total dose to be administered in the first ~30 minutes and the remaining 80% of the total protein dose to be administered in the subsequent ~60 minutes. For patients who prove able to tolerate infusions without infusion-related toxicity, the infusion time may be shortened with each subsequent administration as tolerated following the guidelines in the Pharmacy Manual. Infusion times may be extended as necessary to accommodate individual patient tolerance of treatment.

6.1.7.1. Transient Lymphocytosis

An asymptomatic lymphocytosis has been observed in patients with CLL/SLL treated with cirmtuzumab [see Cirmtuzumab Investigator Brochure; Choi 2017]. This effect may represent a positive pharmacodynamic effect of cirmtuzumab to redistribute malignant cells from sanctuary sites in lymph nodes and spleen and should not be considered a drug-related AE or sign of disease progression unless other evidence of disease progression is also present.

6.1.7.2. Cirmtuzumab Infusion Reactions

Cirmtuzumab administration has been well-tolerated and only rare Grade 1 or 2 infusion reactions have been reported in 3 patients (considered at least possibly related in 2 patients, unrelated in 1 patient) [see Cirmtuzumab Investigator Brochure]. However, other monoclonal antibodies used in the treatment of CLL/SLL, MCL or MZL (eg, rituximab, ofatumumab,

obinutuzumab) can cause severe infusion reactions with manifestations that may include dyspnea, bronchospasm, laryngeal edema, pulmonary edema, acute respiratory distress syndrome, tachycardia, hypertension, hypotension, syncope, dizziness, cardiac ischemia/infarction, pyrexia, headache, chills, back pain, rigors, nausea, vomiting, abdominal pain, diarrhea, flushing, rash, urticaria, and angioedema. While infusion reactions are not expected with cirmtuzumab, the following guidelines for managing infusion reactions are provided as a precaution:

- If a Grade 1-2 infusion reaction occurs, the infusion may be temporarily slowed or interrupted and then can be restarted at half of the previous rate when the patient's condition has stabilized. After resuming the infusion, the infusion rate may be increased consistent with patient tolerance.
- If an infusion reaction Grade ≥3 occurs, the infusion must be interrupted. Medical management (eg, oxygen, epinephrine, bronchodilators, corticosteroids) may be instituted as needed. After the severity of the reaction has decreased to Grade ≤2 the investigator may restart the infusion at a rate no higher than the initial rate for this cirmtuzumab dose. After resuming the infusion, the infusion rate may be increased consistent with patient tolerance.

6.1.7.3. Overdose Precautions

An overdose is defined as a dose taken (accidentally or intentionally) exceeding the overdose limit. In the case of a discrepancy in drug accountability, an overdose will be established only when it is clear that the patient has received an excess dose, or the investigator has reason to suspect that the patient has received an excess dose.

There is no experience with overdose of cirmtuzumab. For this protocol, an overdose of cirmtuzumab is defined as administration of a dose that is ≥2-fold higher than that prescribed for the patient or exceeds 20 mg/kg (whichever is smaller).

In a patient who experiences an overdose that is discovered during drug infusion, the cirmtuzumab infusion may be interrupted or modified, as appropriate. Depending upon the degree of an overdose, it may be necessary to delay administration of subsequent cirmtuzumab infusions. Observation for any symptomatic side effects may be instituted, and safety laboratory parameters may be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects may be initiated, as needed.

The medical monitor should be contacted if a study drug overdose occurs. The occurrence of an overdose does not preclude further protocol therapy if the patient appears to be safely benefiting from treatment and the circumstances that led to the initial overdose are unlikely to recur.

6.1.7.4. Inadvertent Exposure Precautions

As noted in the cirmtuzumab investigator brochure, cirmtuzumab is not expected to be acutely toxic, irritating, or genotoxic at levels that are likely to result from inadvertent exposure. Personnel handling the drug should use reasonable precautions to avoid eye contact, skin contact, inhalation, ingestion, or injection of cirmtuzumab.

6.2. Ibrutinib

6.2.1. Known potential risks: Ibrutinib

In the Ibrutinib Investigator Brochure 2021, guidance regarding the following AEs associated with ibrutinib administration in patients with B-cell malignancies are conveyed:

- Hemorrhage: Fatal bleeding events have occurred in patients who received ibrutinib. Use of either anticoagulant or antiplatelet agents concomitantly with ibrutinib increases the risk of major hemorrhage.
- Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with ibrutinib therapy. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections.
- Cytopenias: In 645 patients with B-cell malignancies who received ibrutinib as a single agent, Grade 3 or 4 neutropenia occurred in 23% of patients, Grade 3 or 4 thrombocytopenia in 8% and Grade 3 or 4 anemia in 3%, based on laboratory measurements. Monitor complete blood counts monthly.
- Cardiac Arrhythmias and Cardiac Failure: Fatal and serious cardiac arrhythmias and cardiac failure have occurred with ibrutinib. At baseline and then periodically, monitor patients clinically for cardiac arrhythmias and cardiac failure. Obtain an electrocardiogram (ECG) for subjects who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea.
- Hypertension: Hypertension occurred in 19% of 1,476 patients who received ibrutinib in clinical trials. Monitor blood pressure in subjects treated with ibrutinib and initiate or adjust antihypertensive medication throughout treatment with ibrutinib as appropriate.
- Second Primary Malignancies: Other malignancies (10%), including non-skin carcinomas (4%), occurred among the 1,476 patients who received ibrutinib in clinical trials.
- Tumor Lysis Syndrome: Tumor lysis syndrome (TLS) has been infrequently reported with ibrutinib. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.
- Embryo-Fetal Toxicity: Based on findings in animals, ibrutinib can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with ibrutinib and for 4 weeks after the last dose.

Ibrutinib is primarily metabolized by CYP3A4, so some patients treated with moderate or strong CYP3A4 inhibitors or inducers are not eligible for ibrutinib therapy unless these drugs are discontinued > 7 days before the first dose of ibrutinib (See Section 6.4.6 for more details and Appendix 12.3 for list of potent inhibitors and inducers of CYP3A4).

Lymphocytosis has been observed after the administration of ibrutinib, and patients with MCL who develop lymphocytosis greater than 400,000/mcL have developed intracranial hemorrhage,

lethargy, gait instability, and headache. However, some of these cases were in the setting of disease progression (Ibrutinib Investigator Brochure 2021).

Serious (Grade ≥ 3) hematologic effects (neutropenia, anemia, thrombocytopenia), pneumonia, and lymphocytosis are associated with the use of all approved BTK inhibitor therapies for the treatment of subjects with MCL, including ibrutinib.

6.2.2. Description

Ibrutinib is manufactured and formulated under cGMP. The drug product for investigational use is supplied as gray opaque Size 0, gelatin capsules that contain 140 mg ibrutinib as the active ingredient. Inactive compendial ingredients include: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The capsule shell contains gelatin, titanium dioxide and black iron oxide.

Further information regarding Imbruvica® (ibrutinib) as supplied for commercial use can be obtained in product labelling [Pharmacyclics 2020 and Ibrutinib Investigator Brochure 2021]. In addition, a pharmacy manual will be provided to site personnel with additional information.

6.2.3. Source

It is intended that sufficient investigational ibrutinib for a planned duration of study treatment in each patient will be supplied by the drug manufacturer (Pharmacyclics, LLC) and distributed by Oncternal.

6.2.4. Packaging and Labelling

Ibrutinib capsules are supplied in high-density polyethylene (HDPE) bottles, each of which is closed with an induction seal and a child-resistant, plastic screw cap. Each bottle contains either 92 or 120 capsules per bottle (as indicated on the label).

6.2.5. Shipping, Storage, and Stability

Bottles of ibrutinib should be stored at 15 to 25°C (59 to 77°F). Excursions are permitted to 30°C (86°F). It is recommended that the capsules be retained in the original package until ingestion. Stability information will be provided to study center personnel.

6.2.6. Dispensing

For the investigational product, a pharmacist or other qualified staff member will dispense bottles containing ibrutinib capsules. Sufficient bottles will be dispensed to the patient to provide an adequate drug supply (with a modest overage) until the patient's next planned clinic visit.

For ibrutinib doses that are taken in the study center, patients will take the dose from the drug dispensed to them for that specific dispensing interval. All other ibrutinib doses will be taken at home.

6.2.7. Return and Compliance Assessment

At the completion of each dispensing interval, empty, partially used, or full bottles of ibrutinib should be retrieved from the patient. The quantities of unused ibrutinib and the date when these study supplies are returned by the patient should be recorded in the study drug accountability

records. Appropriate site personnel should confirm the number of capsules taken through an interview with the patient. Returned bottles of investigational product may be redispensed to the same patient but not to another patient. Returned capsules bottles may be destroyed according to the site's standard operating procedures (see Section 10.11).

Interruptions in treatment, for any reason, that result in missed doses of >7 days (sequential days or total days, for example 3 days and 4 days) during a 28 day period should be reported to the Sponsor as soon as possible.

6.2.8. Ibrutinib Administration

As described in Sections 4.1-4.3, ibrutinib will be started at a dose of 420 mg (for patients with CLL/SLL) or at a dose of 560 mg (for patients with MCL or MZL) on Day 28 (Study Part 1) or on Day 0 (Study Parts 2 and 3) with the first dose of ibrutinib administered ~30 minutes prior to the start of the cirmtuzumab infusion on that day. Thereafter, patient should self-administer ibrutinib at approximately the same time each day, ideally at ~24-hour intervals (eg, ~7 AM every day). While it is realized that variations in dosing schedule may occur in the outpatient setting, the prescribed regimen should be followed as closely as possible.

At each dose administration, the required number of 140-mg capsules should be removed from the storage bottle and swallowed whole. Patients should be instructed not to bite or chew on the capsules. In case of breakage of the capsules in the oral cavity, additional water should be taken as a rinse.

Ibrutinib may be given without regard to food, however ingestion of the drug following a meal may be desirable to enhance drug exposure [de Jong 2015; Marostica 2015].

Patients who have a delay in administration of a dose of ibrutinib of <12 hours should take the planned dose as soon as possible after the intended time of administration. For patients who have a delay in administration of ibrutinib of ≥12 hours, the dose should not be taken. The planned timing of subsequent ibrutinib dosing should not be altered.

For patients who vomit shortly after taking ibrutinib, the vomited dose should not be replaced. The planned timing of subsequent ibrutinib dosing should not be altered.

6.2.8.1. Overdose Precautions

There are limited data on the effects of ibrutinib overdose. No MTD was reached in a Phase 1 study in which patients received up to 12.5 mg/kg/day (1400 mg/day) [Advani 2013]. One healthy patient who received a dose of 1680 mg experienced reversible Grade 4 increases in serum ALT and AST [Pharmacyclics 2020, Ibrutinib Investigator Brochure 2021].

For this protocol, an overdose of ibrutinib is defined as administration of a daily dose ≥700 mg. In a patient who experiences an overdose, consideration should be given as to whether ibrutinib administration should be temporarily interrupted. If the overdose is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered. Observation for any symptomatic side effects may be instituted, and safety laboratory parameters may be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management should be instituted if needed to mitigate adverse effects. There is no specific antidote for ibrutinib.

The medical monitor should be contacted if a study drug overdose occurs. The occurrence of an overdose does not preclude further protocol therapy if the patient appears to be safely benefiting from treatment and the circumstances that led to the initial overdose are unlikely to recur.

6.2.8.2. Inadvertent Exposure Precautions

Based on available data, ibrutinib is not expected to be acutely toxic, irritating, or genotoxic at levels that are likely to result from inadvertent exposure. However, personnel handling the drug should use reasonable precautions to avoid eye contact, skin contact, inhalation, or ingestion of ibrutinib. Patients should be instructed to keep the drug secured such that it is out of the reach of children and is not inadvertently taken by others.

6.3. Dose Modifications

Recommendations for modifications of the dosing regimens for each of the study drugs are based on current knowledge regarding the safety profiles of these agents. Recommendations comprise only guidelines; variations from these recommendations may be warranted based on an investigator's individual judgment in considering potential risks, benefits, and therapeutic alternatives available to each patient.

6.3.1. Dose adjustments for Cirmtuzumab

The Investigator is encouraged to discuss modifications in the dosing regimen with the Medical Monitor. For an AE that is attributed primarily to cirmtuzumab and requires a dose modification, the dose of cirmtuzumab should be reduced by 1 dose level to 300 mg per dose. Successive adjustments to progressively lower dose levels (ie, 150→100 mg fixed dose) can be made. If the patient cannot tolerate cirmtuzumab at a dose of 100 mg per dose, then the patient should be discontinued from cirmtuzumab therapy and from the study overall unless continued treatment is permitted by the medical monitor.

After the cirmtuzumab or ibrutinib dose is reduced, the dose can be maintained at that dose level, even if there is minimal or no toxicity with the reduced dose. However, if the patient tolerates the drug at a reduced dose for ≥4 weeks, then the dose may be re-escalated to the next higher dose level at the discretion of the investigator (particularly if the AE comprised TLS or if further evaluation reveals that the AE that led to the dose reduction was primarily related to the underlying malignancy, an intercurrent illness, a comorbid condition, or a concomitant medication). Successive adjustments to progressively higher dose levels can be made at intervals of ≥4 weeks with the condition that the escalated dose level of either cirmtuzumab or ibrutinib cannot exceed the starting dose level for that patient.

6.3.2. Treatment interruptions for Cirmtuzumab

During the course of the study, treatment may be interrupted due to unforeseen causes including the COVID-19 pandemic. If the interruption was not due to a safety event and the PI and sponsor believe that the patient may safely continue therapy, the patient may be able to continue as long as the missed treatment interval is ≤ 60 days. If the patient's missed treatment interval is >60 days and due to extenuating circumstances, the patient may only be allowed to continue after discussion with the sponsor and written approval.

If a patient misses cirmtuzumab doses, treatment may resume following the guidelines below.

- Resuming therapy: If one dose of cirmtuzumab is missed AND the interval between last dose administered and planned next dose is <45 days:
  - Administer 1 dose as soon as possible
  - Continue with scheduled administrations after that
- Reloading doses to reach optimal drug levels quickly: If one dose of cirmtuzumab is missed AND the interval between last dose administered and planned next dose is 45-60 days OR if two sequential doses of cirmtuzumab are missed:
  - Administer 1 dose as soon as possible
  - Administer a second dose 14 days later to ensure that cirmtuzumab serum concentrations are brought back to appropriate levels as fast as possible
- If the missed treatment interval is >60 days, the reloading procedure will be determined by the sponsor based on the patient situation.

Continue with scheduled doses after the patient has been reloaded. These guidelines may not cover all potential scenarios or circumstances. Please discuss with Oncternal all cases where such interruption in treatment is anticipated. Please refer to the Pharmacy manual for details.

6.3.3. Dose modifications for Ibrutinib

Recommendations for modifications of the dosing regimens for ibrutinib are based on current knowledge regarding its safety profile and in alignment with guidance in marketing authorization documents and the Ibrutinib Investigator Brochure 2021 for ibrutinib as a second-line or subsequent treatment of patients with CLL/SLL, MCL and MZL.

6.3.3.1. Dosage modifications for Adverse Reactions

Ibrutinib therapy should be interrupted for any Grade 3 or 4 non-hematological toxicities, Grade 3 or 4 neutropenia with infection or fever, or Grade 4 hematological toxicities. Once the adverse reaction has improved to Grade 1 or baseline (recovery), ibrutinib may be reinitiated at the current dose. If the adverse reaction reoccurs (Table 1), the dose should be reduced by 140 mg per day. Further dose reductions by 140 mg should be considered by the Investigator, as needed. If these adverse reactions persist or recur following two dose reductions, ibrutinib should be discontinued.

Table 1: Dose Adjustments for Ibrutinib

Toxicity Occurrence	Dose Modification for MCL and MZL After Recovery Starting Dose = 560 mg Dose	Dose Modification for CLL After Recovery Starting Dose = 420 mg Dose
First	Restart at 560 mg daily	Restart at 420 mg daily
Second	Restart at 420 mg daily	Restart at 280 mg daily
Third	Restart at 280 mg daily	Restart at 140 mg daily
Fourth	Discontinue ibrutinib	Discontinue ibrutinib

If the ibrutinib dose is reduced due to non-cardiac events, the dose can be maintained at that dose, even if there is minimal or no toxicity with the reduced dose. However, if the subject tolerates the drug at a reduced dose without toxicity for ≥ 8 weeks, then the dose may be re-escalated to the next higher dose at the discretion of the Investigator (if the AE comprised TLS, as defined by Howard, 2011 or if further evaluation reveals that the AE that led to the dose reduction was primarily related to the underlying malignancy, an intercurrent illness, a comorbid condition, or a concomitant medication). Dose re-escalation to progressively higher doses can be made at intervals of ≥ 4 weeks if clinically indicated. For a change in ibrutinib dose, the appropriate study center personnel should dispense ibrutinib for the new dose and instruct the subject/caregiver about the change in dose.

6.4. Concomitant Therapy

If considered necessary for the patient's well-being, drugs for concomitant medical conditions or for symptom management may be given at the discretion of the investigator. The investigator's decision to authorize the use of any drug other than study drug will take into account patient safety, the medical need, the potential for drug interactions, the possibility for masking symptoms of a more significant underlying event, and whether use of the drug will compromise the outcome or integrity of the study.

Patients will be instructed about the importance of the need to inform the clinic staff of the use of any drugs or remedies (whether prescribed, over-the-counter, or illicit) before and during the study.

6.4.1. Cirmtuzumab Infusion-Reaction Prophylaxis

Based on the available experience, clinically significant infusion reactions are not expected in patients receiving cirmtuzumab. Thus, premedication for infusion-reaction prophylaxis should be avoided on Day 0 (and on Day 28 in Part 1 of the study) unless infusion reactions become a safety concern during the study.

Patients who develop infusion-related toxicities may be premedicated before subsequent cirmtuzumab infusions with an antipyretic and an antihistamine to reduce the incidence and severity of infusion reactions, for example an oral or IV antipyretic (acetaminophen 650 to 1,000 mg or equivalent) and an oral or IV antihistamine (cetirizine, 10 mg or equivalent) both given 30 to 60 minutes prior to each cirmtuzumab infusion.

6.4.2. Tumor Lysis Syndrome (TLS) Prophylaxis

Based on the available experience in CLL/SLL, cirmtuzumab does not specifically pose a risk of TLS and ibrutinib monotherapy in patients with CLL/SLL, MCL or MZL is only rarely associated with TLS [Howard 2016]. However, patients who are at intermediate to high risk of TLS can be considered for medical prophylaxis of TLS depending upon physician judgement or if evidence of TLS is observed during the study. The general risk for TLS can be characterized according to the following criteria, considering established algorithms [Cairo 2010, MDACC 2016, Roberts 2016]:

- Low-risk: Serum lactate dehydrogenase (LDH) ≤ULN, all measurable lymph nodes <5 cm, and ALC <25 × 10^9/L.
- Intermediate risk: Serum LDH >1 to ≤2 × ULN, ≥1 measurable lymph node with an LD of ≥5 but <10 cm, or ALC ≥25 × 10^9/L.
- High risk: Serum LDH >2 × ULN, ≥1 measurable lymph node with a LD of ≥10 cm, or both ≥1 measurable lymph node with an LD of ≥5 but <10 cm and ALC ≥25 × 10^9/L.
- An institutional TLS prophylaxis regimen may be used, or the following prophylaxis regimens may be considered:
- Intermediate Risk of TLS: These patients may receive allopurinol, 100 to 300 mg orally daily starting ≥24 to 48 hours before the initial administration of ibrutinib; in addition, patients who develop hyperuricemia may receive rasburicase, 3 to 4.5 mg by IV infusion.
- High Risk of TLS: These patients may receive allopurinol, 100 to 300 mg orally daily starting ≥24 to 48 hours before the initial administration of ibrutinib; in addition, high-risk patients may receive rasburicase, 3 to 4.5 mg by IV infusion, administered 3 to 4 hours prior to the first dose of ibrutinib.

6.4.3. TLS Management

Information regarding TLS prophylaxis is provided in Section 6.4.2.

Patients who develop TLS may experience hyperkalemia, hypocalcemia, hyperuricemia, hyperphosphatemia, cardiac dysrhythmias, and acute renal failure; thus, close monitoring of electrolytes is important after initial therapy.

Patients with TLS should receive IV hydration, rapid reversal of hyperkalemia, antihyperuricemic agents, and appropriate cardiac and renal support, including dialysis as indicated. Upon recovery to baseline functioning and as medically appropriate, such patients should continue with protocol therapy to maintain tumor control.

6.4.4. Anticancer Therapies Other than the Study Drugs

No systemic anticancer therapies (including chemotherapy, antibody therapy, hormonal therapy, immunotherapy, or other experimental therapies) for the patient's cancer are permitted while the patient is receiving study treatment. Patients are not allowed to participate concurrently in any other therapeutic clinical or imaging study.

The use of palliative radiotherapy should be minimized given the potential of such treatment to confuse assessments of cirmtuzumab + ibrutinib safety or therapeutic effect. However, in a

patient participating in Part 1 of the study, administration of limited-fraction radiotherapy is permitted after Week 8 to control local tumor-related symptoms if irradiation is unlikely to induce major organ toxicity or affect target lesions being followed for tumor response and progression.

If required to maintain disease control, study drugs may be continued with caution during radiotherapy administration given that phototoxicity with cirmtuzumab is unlikely and has not been observed with ibrutinib in relevant in vitro studies.

6.4.5. Anticoagulants

Fatal bleeding events have occurred in patients treated with ibrutinib. Grade 3 or higher bleeding events (intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with ibrutinib [Pharmacyclics 2020, Ibrutinib Investigator Brochure 2021]. The mechanism for the bleeding events is not well understood, although ibrutinib may impair platelet function.

Ibrutinib may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies. Such agents should be administered with caution, and patients should be monitored for signs of bleeding. However, for patients who develop atrial fibrillation, it has been suggested that additional anticoagulation not be administered unless they are at substantial risk of thromboembolism based on the presence of comorbid conditions [Vrontikis 2016].

6.4.6. Drugs with Potential for Drug-Drug Interactions with Ibrutinib

Ibrutinib is primarily metabolized by CYP3A4. In healthy subjects, coadministration of a strong CYP3A4 inhibitor, increased ibrutinib plasma exposure by >20-fold ibrutinib and coadministration of a strong CYP3A4 inducer decreased ibrutinib exposures by ≥10-fold [Pharmacyclics 2020, Ibrutinib Investigator Brochure 2021]. Based on these findings, protocol candidates who require therapy with the moderate or strong CYP3A4 inhibitors or inducers listed in Appendix 12.3 should not be enrolled into the study. If medically justified, protocol candidates may be enrolled if such inhibitors or inducers can be discontinued or alternative drugs that do not affect this enzyme can be substituted >7 days before the first dose of ibrutinib.

During study participation, coadministration of ibrutinib with moderate or strong CYP3A4 inhibitors or inducers listed in Appendix 12.3 should be avoided, if possible. However, a patient who develops a condition that may require use of such drugs is not required to discontinue ibrutinib if the patient is experiencing clinical benefit and other options for treating the patient's cancer are limited. If medically appropriate, investigators may wish to use a therapeutic alternative that would not be expected to affect these enzymes. For patients who require temporary use of a drug that does affect these enzymes (eg, treatment with a systemic antifungal agent), ibrutinib therapy may be temporarily interrupted and then resumed after completion of the other drug. For patients who require initiation of chronic therapy with a moderate or strong inhibitor of CYP3A4, the dose of ibrutinib should be reduced to 140 mg QD and the patient should be monitored closely for signs of ibrutinib toxicity.

6.4.7. Drugs Known to Prolong the QT Interval

To satisfy regulatory requirements, the clinical potential of cirmtuzumab to prolong the QT interval was assessed in CLL Parts 1 and 2 and MCL Part 1 of this study. Protocol candidates who were taking drugs at screening known to prolong the QT interval were not enrolled into those parts of the study. As of Amendment 6, MCL or MZL patients in Part 2, and for CLL/SLL patients in Part 3, the exclusion criteria restricting the enrollment of patients with QTc abnormalities or taking drugs known to prolong the QT interval is removed.

6.4.8. Procedures/Surgery

The extent to which cirmtuzumab may affect wound healing, enhance the risk of infection, or increase the risk of bleeding is unknown. Ibrutinib causes inhibition of platelet function (see Section 6.4.5). Considering parameters such as ANC, platelet count, and PT/aPTT, investigators may use clinical discretion in deciding whether to interrupt cirmtuzumab therapy before and after surgery or other invasive procedures. Depending upon the type of procedure or surgery and the risk of bleeding, investigators may wish to withhold ibrutinib for 3 to 7 days before and after surgery.

6.5. Study Restrictions

6.5.1. Breast Feeding

There is no information regarding the presence of cirmtuzumab, ibrutinib, or ibrutinib metabolites in human milk. The effects of these drugs on the breastfed infant or on milk production are unknown.

For these reasons, women who are nursing are not eligible to participate in this study. Lactating women who do participate in this clinical trial must discontinue nursing during protocol therapy and for ≥ 3 months after the last dose of cirmtuzumab and for ≥ 1 month after the last dose of ibrutinib, whichever is later.

6.5.2. Contraception

The effects, if any, of cirmtuzumab or ibrutinib on ovarian or testicular function are unknown.

Sexually active females of childbearing potential must agree to use a highly effective method of contraception during heterosexual intercourse from the start of the screening period until ≥3 months after the last dose of cirmtuzumab and ≥1 month after the last dose of ibrutinib, whichever is later.

In the context of this protocol, a female patient is considered to be of childbearing potential unless she has had a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy; has medically documented ovarian failure (with serum estradiol and FSH levels within the institutional laboratory postmenopausal range and a negative serum or urine beta βHCG); or is menopausal (age ≥50 years with amenorrhea for ≥6 months).

Sexually active male patients who can father a child and are having intercourse with females of childbearing potential who are not using adequate contraception must agree to use an effective method of contraception from the start of study therapy until ≥3 months after the last dose of cirmtuzumab and ≥3 months after the last dose of ibrutinib, whichever is later. Male patients

should also refrain from sperm donation from the start of study therapy until ≥3 months after administration of the final dose of either of the study drugs.

In the context of this protocol, a male patient is considered able to father a child unless he has had a bilateral vasectomy with documented aspermia or a bilateral orchiectomy.

6.5.3. Diet

Because ibrutinib is a sensitive substrate of CYP3A4, patients should be advised to avoid ingestion of grapefruit, grapefruit juice, or Seville oranges (which contains a potent CYP3A4 inhibitor) and should not use St. John's wort, which is a potent CYP3A4 inducer. No other specific dietary restrictions are required.

7. STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Duration of Study Drug Administration and Study Participation

Patients exhibiting a PR or CR may continue combination treatment beyond Week 52 until disease progression or unacceptable toxicity as part of an extended therapy program.

Patients who remain in a PR or CR at the end of the 2 year treatment period, may be eligible for Long-term Therapy and continue to receive cirmtuzumab and/or ibrutinib until disease progression, unacceptable toxicity, or the study ends. Sites should discuss these cases with the sponsor in advance for approval.

For CLL/SLL patients, long-term follow-up consisting of patient contact every 3-6 months and collection of disease, treatment, and vital status data will continue following the End of Treatment visit for up to five years. For MCL or MZL patients, long-term follow-up will occur every 3 months and include collection of disease, treatment, and vital status data for up to five years. Imaging reports may be requested by the sponsor. These data will be used to establish PFS, TTP, and time to next treatment. Once a patient in long-term follow-up has progressed and received an alternate treatment for their disease, only vital status will be collected.

For patients actively receiving study drug therapy, the occurrence of any of the following events requires treatment discontinuation:

- Patients who withdraw from either ibrutinib or cirmtuzumab treatment will be withdrawn from the study.
- Documented objective evidence of cancer progression while receiving combination study treatment
- Intolerable toxicity despite appropriate supportive care and/or dose modification
- The development of intercurrent illness or other substantial change in the patient's condition or circumstances that would place the patient at unacceptable risk as determined by the study investigator in consultation with the medical monitor
- Initiation of treatment for the patient's cancer with an off-study therapeutic regimen
- Pregnancy or breastfeeding
- Substantial noncompliance with study drug administration, study procedures, or study requirements in circumstances that increase risk or substantially compromise the interpretation of study results
- Discontinuation of the study by the study center, Oncternal, relevant regulatory agencies, or the IRB

Patients in Part 1 who experience disease progression while receiving cirmtuzumab monotherapy should not be discontinued from study therapy solely for that reason; if otherwise medically appropriate, they should continue on study to receive combination cirmtuzumab + ibrutinib treatment.

Unless they withdraw consent, patients will enter long-term follow-up. Patients who discontinue study therapy will be followed for acquisition of safety information through ≥30 days after the

last dose of study treatment, and for up to five years for further collection of information regarding subsequent anti-cancer therapies and vital status.

7.2. Patient Replacement

Patients who do not have the necessary baseline and on-study measurements to provide interpretable results for safety, pharmacodynamic, pharmacokinetics, or efficacy parameters may be replaced at the discretion of the sponsor. In general, this will mean that patients who do not complete study drug administration and protocol evaluation through Week 16 of therapy in Part 1 or through Week 12 of therapy in Parts 2 or 3 of the study will be considered for replacement. The replacement patient will be assigned to the same treatment cohort as the original patient. Accrual of additional patients to a treatment cohort may also be considered at the discretion of the SRC. A replacement patient or an additional patient may be accrued if there is agreement that treatment of such a patient is unlikely to constitute an unacceptable safety risk.

7.3. Study Discontinuation

Both the investigator and Oncternal reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures. The investigator will be responsible for notifying the relevant study center IRB. Oncternal will be responsible for notifying the appropriate regulatory authorities. In terminating the study, the investigator and Oncternal will assure that adequate consideration is given to the protection of the patients' interests. As directed by Oncternal, all study materials must be collected and all eCRFs completed to the greatest extent possible.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Study Activities

The specific study procedures and time of activities to be conducted for each patient enrolled in the study are presented in tabular form in Section 8.2 (Part 1), Section 8.3 (Part 2), and Section 8.4 (Part 3) below.

To provide necessary medical care to the patient while on study, additional types of clinical evaluations and laboratory studies or more frequent assessments may be performed if clinically indicated, even if not specified in the protocol. Physical examinations may be performed consistent with appropriate medical care for the patient, but physical examination data considered not clinically significant or an AE will not be routinely collected in the eCRF.

To optimize scheduling convenience for the patient and for the study center staff, screening procedures may be performed over as many days as necessary provided that screening is completed within 28 days before initiation of treatment. For scheduled visits after Day 1, permitted visit windows are indicated in the table.

For procedures to be performed at a specified time post-dose, the acceptable margin for actual time is the specified time ±15 minutes. If multiple procedures are to be done at the same time point, the preferred order is vital signs, blood sampling, and then ECG, with blood sampling (particularly for pharmacokinetics) occurring as close as possible to the specified time.

Missed procedures or evaluations should be performed as close to the originally scheduled date/time as possible. Based on the investigator's judgment, an exception can be made when rescheduling becomes medically unnecessary because it is too close in time to the next scheduled procedure or evaluation. In that case, the missed evaluation may be omitted.

If necessary, remote/telemedicine visits and local laboratories are allowed to ensure continued safety monitoring.

8.2. Schedule of Activities – Part 1 MCL and CLL/SLL (Cirmtuzumab → Cirmtuzumab + Ibrutinib)

Period	Screen	Treatment																				End of Tx	Follow-up	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20+	22+		Safety FU	Long-term
Week	-4	0	0	2	4	4	6	8	12	16	20	24	28	32	36	40	44	48	52	56+	64+	104		
Study Day	Within 28 Days	0	1	14	28	29	42	56	84	112	140	168	196	224	252	280	308	336	364	Q 4 weeks [bb]	Q 12 weeks [bb]	728 [bb]	Within +30 days	To ≤5 years
Visit Window, days				±2	±2	±2	±2	±2	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7	
General Eligibility/Safety Assessments																								
Written informed consent [b]	X																							
Height [c]	X																							
Weight/Vital signs [d]	X	X*	X	X*	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Performance status [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Medical history [f]	X																							
Adverse Event (AE) assessment [g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
12-lead ECG [i]	X	X*	X	X*																		X	X	
Drug Administration/Dispensing/Return																								
TLS prophylaxis [j]					X																			
Ibrutinib administration in the clinic [k]					X																			
Cirmtuzumab administration [l]		X		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Dispensing of ibrutinib [m]					X			X	X	X	X	X	X	X	X	X	X	X		X	X			
Ibrutinib compliance check [m]								X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Laboratory Assessments ##																								
Serum virology [n]	X																							
Serum chemistry [o]	X	X[(a)]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology [p]	X	X[(a)]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis [q]	X	X[(a)]	X	X	X	X		X		X			X			X			X		X	X	X	
Coagulation [r]	X	X[(a)]			X	X		X		X			X			X			X		X		X	
Serum or urine pregnancy test [s]	X	X[(a)]			X					X			X			X			X		X			
Serum for cirmtuzumab pharmacokinetics [t]		X*	X	X*	X*[(k)]	X		X		X			X			X			X			X[t]	X[t]	
Blood for ROR1 [u]		X*	X	X*	X*[(k)]	X		X		X			X			X			X					
MCL ONLY: Blood for exploratory biomarkers[v]		X	X	X	X[(k)]	X		X		X			X			X			X					
Serum for cirmtuzumab-reactive antibodies [w]		X											X						X		X			
Disease Assessments																								
Radiology examination [x]	X				X					X			X			X			X		X	X[X]		
Blood and Bone marrow biopsy/aspirate [y]		X								---------- If required to document complete response ----------														
Posttherapy Follow-up																								
Posttherapy safety assessment [z]																							X	
Long-term follow-up [aa]																								X

Footnotes – Part 1	
Note:	***For procedures to be performed at a specified time postdose, the acceptable margin for actual time is the specified time ±15 minutes. If multiple procedures are to be done at the same time point, the preferred order is vital signs, blood sampling, and then ECG, with blood sampling occurring as close as possible to the specified time.***
##	General safety lab assays will be done utilizing your CLIA approved local lab. Other required labs will utilize a central laboratory, so samples will need to be prepared and shipped according to the study lab manual.
a.	If obtained within 7 days prior to the start of therapy, urinalysis and serum pregnancy, serum chemistry, hematology, and coagulation studies collected during Screening need not be repeated on Day 0.
b.	Written informed consent will be obtained before any study procedures are performed that are not part of routine medical care.
c.	Height (in centimeters) will be obtained at Screening only.
d.	Weight (in kilograms) and vital signs (blood pressure, pulse, and temperature) will be assessed prior to the cirmtuzumab infusion, and at any time if no infusion that day. * - on Days 0, 14, and 28 vital signs will also be assessed immediately after the end of the cirmtuzumab infusion.
e.	Performance status will be assessed using ECOG scale (see Appendix 12.1).
f.	Medical history to include recording of cancer history, previous therapy for cancer, clinically significant past and ongoing medical conditions, review of systems, and relevant social history and will be obtained at Screening only.
g.	Description of all AEs using concise medical terminology, including whether the AE is serious, the date of onset, the date of resolution, the severity based on the CTCAE, Version 4.03, a description of the potential relatedness to study drug or to a study procedure, the action taken, and the outcome (see Section 8.6).
h.	Concomitant medication assessments should include information regarding all prescription, nonprescription, illicit, and alternative medications.
i.	12-lead ECGs will be obtained with the patient resting in a supine position. * - on Days 0 and 14 ECGs will also be assessed one hour after the end of the cirmtuzumab infusion.
j.	Based on the risk of TLS (low, intermediate, or high), patients at intermediate or high risk should be considered for TLS prophylaxis (see Section 6.4.2).
k.	The first dose of ibrutinib will be administered to the patient in the study center after collection of the predose blood samples and ~30 minutes prior to the start of the cirmtuzumab infusion (with recording of the date and actual clock time of the ibrutinib administration).
l.	Cirmtuzumab will be infused as indicated in Section 6.1.5, with recording of the date and actual clock time of the start and end of the infusion. Record any cirmtuzumab infusion reaction as an adverse event(s) in the eCRF, and record any supportive care provided. If infusion prophylaxis is required for subsequent infusions, see Section 6.4.1.
m.	A supply of ibrutinib will be dispensed to the patient with instructions for self-administration at home. At subsequent visits, empty, partially used, or full bottles of ibrutinib will be retrieved from the patient and drug compliance will be assessed.
n.	Virology evaluation to include serum HIV antibody, HBsAg antibody, HBc antibody, HCV antibody. Patients with a positive antibody evaluation for HBc or HCV should undergo evaluation for HBV DNA and for HCV RNA to determine if the antibody test may be falsely positive.
o.	Serum chemistry to include sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphorus, magnesium (screening only), total protein, albumin, ALT, AST, ALP, LDH, and total bilirubin.
p.	Hematology to include hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils; platelet count.
q.	Urinalysis to include specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase as assessed by dipstick, and microscopic urinalysis evaluating white blood cells, red blood cells, epithelial cells, bacteria, cast and crystals.
r.	Coagulation studies to include PT and aPTT.
s.	Serum or urine pregnancy testing will be performed in women of childbearing potential only. See Section 8.6.6 for reporting requirements in the event of a pregnancy.
t.	Serum for cirmtuzumab pharmacokinetics will be collected on the indicated days prior to the cirmtuzumab infusion, and at any time if no infusion that day. * - on Days 0, 14 and 28 serum for cirmtuzumab pharmacokinetics will also be collected one hour after the end of the cirmtuzumab infusion. Serum for cirmtuzumab pharmacokinetics may also be collected with any unscheduled blood draw if indicated. Optional PK collection at select sites: on the day of the last infusion, 1 sample post infusion should be collected and, if possible, 1 additional sample every 28 days x4 (post last infusion).

u.	Blood for ROR1 cell surface expression and receptor occupancy will be collected on the indicated days prior to the cirmtuzumab infusion, and at any time if no infusion that day. * - on Days 0, 14 and 28, blood for ROR1 cell surface expression and receptor occupancy will also be collected one hour after the end of the cirmtuzumab infusion.
v.	MCL Patients Only: Blood for exploratory biomarkers, such as cytokines and stem cell gene profile, will be collected on the indicated days prior to the cirmtuzumab infusion. On Day 28 the blood must be collected prior to ibrutinib administration. (The samples collected for each Part of the study will be described in the lab manual.) Tumor samples (unstained slides, tissue/cells or blocks) obtained pre-treatment or post-treatment, if available, may be requested for biomarker testing.
w.	Serum for cirmtuzumab-reactive antibodies will be collected on the indicated days prior to the cirmtuzumab infusion.
x.	Radiology examination to include contrast-enhanced CT or MRI imaging of neck, chest, abdomen, and pelvis and may include FDG-PET/CT for MCL. The same method of assessment (CT, MRI, FDG-PET/CT) and the same technique should be used, whenever possible, to characterize each identified and reported lesion at Screening and while on study. Evaluations may be performed within the 7 days prior to the indicated day. Baseline examination should be within 14 days of Day 0. For details see Section 8.5, Appendix 12.5, and Appendix 12.6. For patients having an End of Treatment visit and evaluations, if radiology imaging studies were last performed > 8 weeks before the End of Treatment visit, then they should be performed as part of this visit. For patients ending treatment due to radiographic confirmation of disease progression following cirmtuzumab + ibrutinib combined therapy, the End of Treatment visit should occur ≤4 weeks after the documentation of progression and the imaging studies do not need to be performed.
y.	A bone marrow aspirate, biopsy and peripheral blood sample should be obtained prior to Day 0 and before the cirmtuzumab infusion for exploratory biomarkers, with a biopsy for disease assessment if no biopsy results are available in the preceding 45 days. Subsequent bone marrow aspirate and biopsy plus peripheral blood sample, including samples for exploratory biomarkers, will only be obtained as needed to confirm a clinical/radiologic complete response. A blinded bone marrow sample may be sent for central review/confirmation.
z.	The End of Treatment visit will be performed after permanent cessation of study therapy. The Safety Follow-up visit will occur either 30 days after the last dose of study treatment or upon resolution/stabilization of any ongoing drug-related AEs and/or SAEs, whichever occurs later. AE/SAE follow-up may be obtained in person, by telephone, or by e-mail contact.
aa.	Long-term follow-up information will be obtained for up to 5 years in all surviving patients who permanently discontinue study therapy. Long term follow-up data should be obtained every 6 months for CLL patients. Long term follow-up data should be collected every 3 months for MCL patients. Data on the timing of disease progression and post-study cancer therapies (including ibrutinib) will be collected. Once a patient has progressed and received a subsequent cancer therapy, only vital status will be collected. Reports of imaging studies performed during long-term follow-up may be requested by the sponsor for review.
bb.	For patients continuing beyond Week 52, the combination treatment will continue at the same dose and schedule as year 1. Assessments will continue to be performed with visits and infusions every 4 weeks and scans and other additional assessments every 12 weeks, as indicated in the SOA.

Abbreviations: AE=adverse event, ALP=alkaline phosphatase, ALT=alanine aminotransferase, aPTT=activated partial thromboplastin time, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CLL/SLL=chronic lymphocytic leukemia/small lymphocytic lymphoma, CR=complete response, CT=computed tomography, DNA=deoxyribonucleic acid, ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, FDG=fluorodeoxyglucose, HBc antibody=anti-hepatitis B core antibody, HBsAg=hepatitis B surface antigen, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, LDH=lactate dehydrogenase, MCL=mantle cell lymphoma, MRD=minimal residual disease, MRI=magnetic resonance imaging, OS=overall survival, PD=progressive disease, PET=positron emission tomography, PT=partial thromboplastin time, RNA=ribonucleic acid, ROR1= receptor tyrosine kinase-like orphan receptor 1, SAE=serious adverse event, TLS=tumor lysis syndrome, Tx=treatment.

8.3. Schedule of Activities – Part 2 MCL, MZL and CLL/SLL (Cirmtuzumab + Ibrutinib)

Period	Screen	Treatment																		End of Tx	Follow-up	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18+**	**19+**		**Safety FU**	**Long-term**
Week	**-4**	**0**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56+**	**60+**	**104**		
Study Day	**Within 28 Days**	**0**	**1**	**14**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**	**Q 4 weeks [bb]**	**Q 12 weeks [bb]**	**728 [bb]**	**Within +30 days**	**To ≤5 years**
Visit Window, days				**±2**	**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+7**	
General Eligibility/Safety Assessments																						
Written informed consent [b]	X																					
Height [c]	X																					
Weight/Vital signs [d]	X	X*	X	X*	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Performance status [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Medical history [f]	X																					
Adverse Event (AE) assessment [g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
12-lead ECG [i]	X																			X		
Drug Administration/Dispensing/Return																						
TLS prophylaxis [j]		X																				
Ibrutinib administration in the clinic [k]		X																				
Cirmtuzumab administration [l]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Dispensing of ibrutinib [m]		X			X	X	X	X	X	X	X	X	X	X	X	X[cc]	X	X	X			
Ibrutinib compliance check [m]					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Laboratory Assessments ##																						
Serum virology [n]	X																					
Serum chemistry [o]	X	X[(a)]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology [p]	X	X[(a)]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis [q	X	X[(a)]	X	X	X		X			X			X			X			X	X	X	
Coagulation [r]	X	X[(a)]			X		X			X			X			X			X	X	X	
Serum or urine pregnancy test [s]	X	X[(a)]			X		X			X			X			X			X			
Serum for cirmtuzumab pharmacokinetics [t]		X*[(k)]		X	X					X*			X			X				X[t]	X[t]	
Blood for ROR1 [u]		X[(k)]		X	X					X			X			X				X		
Blood for exploratory biomarkers [v]		X[(k)]			X					X			X			X			X	X		
Serum for cirmtuzumab-reactive antibodies [w]		X[(k)]								X						X			X		X	
Disease Assessments																						
Radiology examination [x]	X						X			X			X			X			X	X[X]		
Blood and Bone marrow biopsy/aspirate [y]		X					---------- If required to document complete response ----------															
Posttherapy Follow-up																						
Posttherapy safety assessment [z]																					X	
Long-term follow-up [aa]																						X

Footnotes – Part 2	
Note:	***For procedures to be performed at a specified time postdose, the acceptable margin for actual time is the specified time ±15 minutes. If multiple procedures are to be done at the same time point, the preferred order is vital signs, blood sampling, and then ECG, with blood sampling occurring as close as possible to the specified time.***
##	General safety lab assays will be done utilizing your CLIA approved local lab. Other required labs will utilize a central laboratory, so samples will need to be prepared and shipped according to the study lab manual.
a.	If obtained within 7 days prior to the start of therapy, urinalysis and serum pregnancy, serum chemistry, hematology, and coagulation studies collected during Screening need not be repeated on Day 0.
b.	Written informed consent will be obtained before any study procedures are performed that are not part of routine medical care.
c.	Height will be obtained once at Screening.
d.	Weight (in kilograms) and vital signs (blood pressure, pulse, and temperature) will be assessed prior to the cirmtuzumab infusion, and at any time if no infusion that day. * - on Days 0, 14, and 28 vital signs will also be assessed immediately after the end of the cirmtuzumab infusion and on Day 0 only, vital signs should also be assessed one hour post infusion to ensure no delayed reaction occurs following the first infusion.
e.	Performance status will be assessed using ECOG scale (see Appendix 12.1) once on each designated day.
f.	Medical history to include recording of cancer history, previous therapy for cancer, clinically significant past and ongoing medical conditions, review of systems, and relevant social history and will be obtained at Screening only.
g.	Description of all AEs using concise medical terminology, including whether the AE is serious, the date of onset, the date of resolution, the severity based on the CTCAE, Version 4.03, a description of the potential relatedness to study drug or to a study procedure, the action taken, and the outcome (see Section 8.6).
h.	Concomitant medication assessments should include information regarding all prescription, nonprescription, illicit, and alternative medications .
i.	12-lead ECGs will be obtained with the patient resting in a supine position. If ECG abnormalities such as QT prolongation are observed compared to baseline following study treatment, the test result should be confirmed and ECG repeated at the Safety Follow-up visit (post the End of Treatment visit).
j.	Based on the risk of TLS (low, intermediate, or high), patients at intermediate or high risk should be considered for TLS prophylaxis (see Section 6.4.2).
k.	The first dose of ibrutinib will be administered to the patient in the study center after collection of the predose blood samples and ~30 minutes prior to the start of the cirmtuzumab infusion (with recording of the date and actual clock time of the ibrutinib administration).
l.	Cirmtuzumab will be infused as indicated in Section 6.1.5, with recording of the date and actual clock time of the start and end of the infusion. Record any cirmtuzumab infusion reaction as an adverse event(s) in the eCRF, and record any supportive care provided. If infusion prophylaxis is required for subsequent infusions, see Section 6.4.1.
m.	For patients receiving investigational ibrutinib, a supply of ibrutinib will be dispensed to the patient with instructions for self-administration at home. At subsequent visits, empty, partially used, or full bottles of ibrutinib will be retrieved from the patient and drug compliance will be assessed.
n.	Virology evaluation to include serum HIV antibody, HBsAg antibody, HBc antibody, HCV antibody. Patients with a positive antibody evaluation for HBc or HCV should undergo evaluation for HBV DNA and for HCV RNA to determine if the antibody test may be falsely positive.
o.	Serum chemistry to include sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphorus, magnesium (screening only), total protein, albumin, ALT, AST, ALP, LDH, and total bilirubin.
p.	Hematology to include hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils; platelet count.
q.	Urinalysis to include specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase as assessed by dipstick, and microscopic urinalysis evaluating white blood cells, red blood cells, epithelial cells, bacteria, cast and crystals.
r.	Coagulation studies to include PT and aPTT.
s.	Serum or urine pregnancy testing will be performed in women of childbearing potential only. See Section 8.6.6 for reporting requirements in the event of a pregnancy.

t.	Serum for cirmtuzumab pharmacokinetics will be collected on the indicated days prior to the cirmtuzumab infusion. * - In addition, on Day 0 and Day 168 a sample should be drawn at the end of the cirmtuzumab infusion. Optional PK collection at select sites: on the day of the last infusion, 1 sample post infusion should be collected and, if possible, 1 additional sample every 28 days x4 (post last infusion).
u.	Blood for ROR1 cell surface expression and receptor occupancy will be collected on the indicated days prior to the cirmtuzumab infusion, and at any time if no infusion that day. Additional timepoints may be requested, should it be needed to complete the dataset.
v.	Blood for exploratory biomarkers will be collected on the indicated days prior to the cirmtuzumab infusion. Additional timepoints may be requested, should it be needed to complete the dataset. Tumor samples (unstained slides, tissue/cells or blocks) obtained pre-treatment or post-treatment, if available, may be requested for biomarker testing.
w.	Serum for cirmtuzumab-reactive antibodies will be collected on the indicated days prior to the cirmtuzumab infusion.
x.	Radiology examination to include contrast-enhanced CT (preferred) or MRI imaging of neck, chest, abdomen, and pelvis (for MCL and MZL FDG-PET/CT, is preferred). The same method of assessment (CT, MRI, FDG-PET/CT) and the same technique should be used, whenever possible, to characterize each identified and reported lesion at Screening and while on study. Evaluations may be performed within the 7 days prior to the indicated day. Baseline examination should be within 14 days of Day 0. For details see Section 8.5, Appendix 12.5, and Appendix 12.6. For patients having an End of Treatment visit and evaluations, if radiology imaging studies were last performed > 8 weeks before the End of Treatment visit, then they should be performed as part of this visit. For patients ending treatment due to radiographic confirmation of disease progression following cirmtuzumab + ibrutinib combined therapy, the End of Treatment visit should occur ≤4 weeks after the documentation of progression and the imaging studies do not need to be performed.
y.	A bone marrow aspirate, biopsy and peripheral blood sample should be obtained prior to Day 0 and before the cirmtuzumab infusion for exploratory biomarkers, with a biopsy for disease assessment if no biopsy results are available in the preceding 45 days. Subsequent bone marrow aspirate and biopsy plus peripheral blood sample, including samples for exploratory biomarkers, will only be obtained as needed to confirm a clinical/radiologic complete response. As the data for exploratory biomarkers develops, additional samples may be requested to better analyze and confirm the results of these tests. A blinded bone marrow sample may be sent for central review/confirmation.
z.	The End of Treatment visit will be performed after permanent cessation of study therapy. The Safety Follow-Up visit will occur the later of either 30 days after the last dose of study treatment or until resolution/stabilization of any ongoing drug-related AEs and/or SAEs. AE/SAE follow-up may be obtained in person, by telephone, or by e-mail contact.
aa.	Long-term follow-up information will be obtained for up to 5 years in all surviving patients who permanently discontinue study therapy. Long term follow-up data should be obtained every 6 months for CLL patients. Long term follow-up data should be collected every 3 months for MCL and MZL patients. Data on the timing of disease progression and post-study cancer therapies (including ibrutinib) will be collected. Once a patient has progressed and received a subsequent cancer therapy, only vital status will be collected. Reports of imaging studies performed during long-term follow-up may be requested by the sponsor for review.
bb.	For patients continuing beyond Week 52, the combination treatment will continue at the same dose and schedule as year 1. Assessments will continue to be performed with visits and infusions every 4 weeks and scans and other additional assessments every 12 weeks, as indicated in the SOA.
cc.	Ibrutinib can be dispensed if documented intention is for patient to extend and scans are planned or pending.
Abbreviations: ALP=alkaline phosphatase, ALT=alanine aminotransferase, aPTT=activated partial thromboplastin time, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CLL/SLL=chronic lymphocytic leukemia/small lymphocytic lymphoma, CR=complete response, CT=computed tomography, DNA=deoxyribonucleic acid, ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, FDG=fluorodeoxyglucose, HBc antibody=anti-hepatitis B core antibody, HBsAg=hepatitis B surface antigen, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, LDH=lactate dehydrogenase, MCL=mantle cell lymphoma, MRD=minimal residual disease, MRI=magnetic resonance imaging,MZL= Marginal Zone Lymphoma, OS=overall survival, PD=progressive disease, PET=positron emission tomography, PT=partial thromboplastin time, RNA=ribonucleic acid, ROR1= receptor tyrosine kinase-like orphan receptor 1, SAE=serious adverse event, SOA=schedule of activities, TLS=tumor lysis syndrome, Tx=treatment.	

8.4. Schedule of Activities – Part 3 CLL/SLL (Cirmtuzumab + Ibrutinib versus Ibrutinib)

Period	Screen	Treatment																	End of Tx	Follow-up	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17+**	**18+**		**Safety FU**	**Long-term**
Week	**-4**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56+**	**60+**	**104**		
Study Day	**Within 28 Days**	**0**	**14**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**	**Q 4 weeks [z]**	**Q 12 weeks [z]**	**728 [z]**	**Within +30 days**	**To ≤5 years**
Visit Window, days			**±2**	**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+7**	
General Eligibility/Safety Assessments																					
Written informed consent [b]	X																				
Height [c]	X																				
Weight/Vital signs [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Performance status [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Medical history [f]	X																				
Adverse Event (AE) assessment [g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
12-lead ECG [i]	X																		X		
Drug Administration/Dispensing/Return																					
TLS prophylaxis [j]		X																			
Ibrutinib administration in the clinic [k]		X																			
Cirmtuzumab administration (Arm A) [l]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Dispensing of ibrutinib [m]		X		X	X	X	X	X	X	X	X	X	X	X	X[aa]	X	X	X			
Ibrutinib compliance check [m]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Laboratory Assessments																					
Serum virology [n]	X																				
Serum chemistry [o]	X	X[(a)]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology [p]	X	X[(a)]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis [q]	X	X[(a)]	X	X		X			X			X			X			X	X	X	
Coagulation [r]	X	X[(a)]				X			X			X			X			X	X	X	
Serum or urine pregnancy test [s]	X	X[(a)]				X			X			X			X			X			
Serum for cirmtuzumab-reactive antibodies and cytokines, and blood for exploratory biomarkers [t]		X										X			X			X	X	X	
Disease Assessments																					
Rai stage [u]	X																				
Radiology examination [v]	X					X			X			X			X			X	X[v]		
Bone marrow biopsy/aspirate [w]		X	---------- If required to document complete response -------																		
Posttherapy Follow-up																					
Posttherapy safety assessment [x]																				X	
Long-term follow-up [y]																					X

Footnotes – Part 3	
Note:	***For procedures to be performed at a specified time postdose, the acceptable margin for actual time is the specified time ±15 minutes. If multiple procedures are to be done at the same time point, the preferred order is vital signs, blood sampling, and then ECG, with blood sampling occurring as close as possible to the specified time.***
a.	If obtained within 7 days prior to the start of therapy, urinalysis and serum pregnancy, serum chemistry, hematology, and coagulation studies collected during Screening need not be repeated on Day 0.
b.	Written informed consent will be obtained before any study procedures are performed that are not part of routine medical care.
c.	Height will be measured once during Screening.
d.	Weight (in kilograms) and vital signs (blood pressure, pulse, temperature) will be assessed at Screening and on each subsequent study day prior to cirmtuzumab treatment, and at any time if no infusion that day.
e.	Performance status will be assessed using ECOG scale (see Appendix 12.1) once on each designated day.
f.	Medical history to include recording of cancer history, previous therapy for cancer, clinically significant past and ongoing medical conditions, review of systems, and relevant social history and will be obtained at Screening only.
g.	Description of all AEs using concise medical terminology, including whether the AE is serious, the date of onset, the date of resolution, the severity based on the CTCAE, Version 4.03, a description of the potential relatedness to study drug or to a study procedure, the action taken, and the outcome (see Section 8.6).
h.	Concomitant medication assessments should include information regarding all prescription, nonprescription, illicit, and alternative medications.
i.	12-lead ECGs will be obtained with the patient resting in a supine position. ECGs will be collected at Screening and at End of Treatment visits. If ECG abnormalities such as QT prolongation are observed compared to baseline following study treatment, the test result should be confirmed and ECG repeated at the Safety Follow-up visit (post the End of Treatment visit).
j.	Based on the risk of TLS (low, intermediate, or high), patients at intermediate or high risk should be considered for TLS prophylaxis (see Section 6.4.2).
k.	The first dose of ibrutinib will be administered to the patient in the study center ~30 minutes prior to the start of the cirmtuzumab infusion (with recording of the date and actual clock time of the ibrutinib administration).
l.	Cirmtuzumab will be infused as indicated in Section 6.1.5, with recording of the date and actual clock time of the start and end of the infusion. Record any cirmtuzumab infusion reaction as an adverse event(s) in the eCRF, and record any supportive care provided. If infusion prophylaxis is required for subsequent infusions, see Section 6.4.1.
m.	For patients receiving investigational ibrutinib, a supply of ibrutinib will be dispensed to the patient with instructions for self-administration at home. At subsequent visits, empty, partially used, or full bottles of ibrutinib will be retrieved from the patient and drug compliance will be assessed.
n.	Virology evaluation to include serum HIV antibody, HBsAg antibody, HBc antibody, HCV antibody. Patients with a positive antibody evaluation for HBc or HCV should undergo evaluation for HBV DNA and for HCV RNA to determine if the antibody test may be falsely positive.
o.	Serum chemistry to include sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphorus, magnesium (screening only), total protein, albumin, ALT, AST, ALP, LDH (screening only), and total bilirubin.
p.	Hematology to include hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils; platelet count.
q.	Urinalysis to include specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase as assessed by dipstick, and microscopic urinalysis evaluating white blood cells, red blood cells, epithelial cells, bacteria, cast and crystals.
r.	Coagulation studies to include PT and aPTT.
s.	Serum or urine pregnancy testing will be performed in women of childbearing potential only. See Section 8.6.6 for reporting requirements in the event of a pregnancy.
t.	Serum for cirmtuzumab-reactive antibodies and cytokines, and blood for exploratory biomarkers will be collected on the indicated days prior to the cirmtuzumab infusion. Tumor samples (unstained slides, tissue/cells or blocks) obtained pre-treatment or post-treatment, if available, may be requested for biomarker testing.

u.	For patients with CLL/SLL, Rai stage will be calculated (see Appendix 12.4).
v.	Radiology examination to include contrast-enhanced CT (preferred) or MRI imaging of neck, chest, abdomen, and pelvis (and may include FDG-PET/CT, if relevant). The same method of assessment (CT, MRI, FDG-PET/CT) and the same technique should be used, whenever possible, to characterize each identified and reported lesion at Screening and while on study. Evaluations may be performed within the 7 days prior to the indicated day. Baseline examination should be within 14 days of Day 0. For details see Section 8.5, Appendix 12.5, and Appendix 12.6. For patients having an End of Treatment visit and evaluations, if radiology imaging studies were last performed > 8 weeks before the End of Treatment visit, then they should be performed as part of this visit. For patients ending treatment due to radiographic confirmation of disease progression following cirmtuzumab + ibrutinib combined therapy, the End of Treatment visit should occur ≤4 weeks after the documentation of progression and the imaging studies do not need to be performed.
w.	A bone marrow aspirate, biopsy and peripheral blood sample should be obtained prior to Day 0 and before the cirmtuzumab infusion for exploratory biomarkers, with a biopsy for disease assessment if no biopsy results are available in the preceding 45 days. Subsequent bone marrow aspirate and biopsy plus peripheral blood sample, including samples for exploratory biomarkers, will only be obtained as needed to confirm a clinical/radiologic complete response. A blinded bone marrow sample may be sent for central review/confirmation.
x.	The End of Treatment visit will be performed after permanent cessation of study therapy. The Safety Follow-up visit will occur either 30 days after the last dose of study treatment or upon resolution/stabilization of any ongoing drug-related AEs and/or SAEs, whichever occurs later. AE/SAE follow-up may be obtained in person, by telephone, or by e-mail contact.
y.	Long-term follow-up information will be obtained for up to 5 years in all surviving patients who permanently discontinue study therapy. Long term follow-up data should be obtained every 6 months. Data on the timing of disease progression and post-study cancer therapies (including ibrutinib) will be collected. Once a patient has progressed and received a subsequent cancer therapy, only vital status will be collected. Reports of imaging studies performed during long-term follow-up may be requested by the sponsor for review.
z.	For CLL/SLL patients continuing beyond Week 52, they will continue with the assigned treatment at the same dose and the same assessments will be performed with visits and infusions every 4 weeks and scans and other additional assessments every 12 weeks.
aa.	Ibrutinib can be dispensed if documented intention is for patient to extend and scans are planned or pending.
Abbreviations: AE=adverse event, ALP=alkaline phosphatase, ALT=alanine aminotransferase, aPTT=activated partial thromboplastin time, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CLL/SLL=chronic lymphocytic leukemia/small lymphocytic lymphoma, CT=computed tomography, DNA=deoxyribonucleic acid, ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, FDG=fluorodeoxyglucose, HBc antibody=anti-hepatitis B core antibody, HBsAg=hepatitis B surface antigen, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, LDH=lactate dehydrogenase, MCL=mantle cell lymphoma, MRD=minimal residual disease, MRI=magnetic resonance imaging, OS=overall survival, PD=progressive disease, PET=positron emission tomography, PT=partial thromboplastin time, RNA=ribonucleic acid, SAE=serious adverse event, TLS=tumor lysis syndrome	

8.5. Efficacy Assessments

8.5.1. Overview

Tumor response and progression will be assessed using standard criteria appropriate for each hematological malignancy. During the course of the study, investigators will periodically determine general disease status based on radiographic and laboratory evaluations (supplemented by physical examination, as appropriate). Treatment decisions by the investigator in this study will be based, in part, on these assessments. The investigator assessment of tumor control endpoints will be used for the primary analyses in all Parts of the study.

8.5.2. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

8.5.2.1. Tumor Assessment Criteria

The determination of CLL/SLL response and progression will be based on standardized criteria iwCLL [Hallek 2008], as recently updated [Hallek 2018; Cheson 2012]. A detailed description of response assessment for this study is presented in Appendix 12.5.

8.5.2.2. Method of Assessment

Imaging-based evaluation will be used in this study in all patients enrolled. CT scan is the preferred method for radiographic tumor assessment. MRI scanning may be used at the investigator's discretion in patients for whom this may be a preferred alternative to CT scanning; however, if MRI is performed, a non-contrast CT of the chest should be performed. Contrast-enhanced scanning is preferred, but iodine-containing or gadolinium contrast material may be omitted in patients for whom use of a contrast agent would be medically contraindicated. Chest x-ray, ultrasound, endoscopy, laparoscopy, PET, radionuclide scans, or tumor markers will not be considered for response assessment.

For radiographic evaluations, the same method of assessment and the same technique (eg, scan type, scanner, patient position, dose of contrast, injection/scan interval) should be used, whenever possible, to characterize each identified and reported lesion at screening and during study treatment and follow-up. However, if a patient is imaged without contrast at screening, subsequent assessments should be performed with contrast, unless the patient cannot tolerate the contrast.

All relevant radiographic and clinical information required to make each tumor status assessment must be made available for source verification and review.

8.5.2.3. Timing of Assessments

During screening, imaging-based and laboratory assessments should be performed within the specified screening period. On-study tumor assessments should be scheduled as indicated in Section 8. For patients having an End of Treatment visit and evaluations, if radiology imaging studies were last performed > 8 weeks before the End of Treatment visit, then they should be performed as part of this visit. For patients ending treatment due to radiographic confirmation of disease progression following cirmtuzumab + ibrutinib combined therapy, the End of Treatment visit should occur ≤4 weeks after the documentation of progression and the imaging studies do

not need to be performed. If a patient permanently discontinues study drug prior to objective documentation of CLL/SLL progression, investigators should attempt to obtain further follow-up at ~12-week intervals until CLL/SLL progression is documented or until the initiation of a new post-study therapy for the patient's CLL/SLL.

8.5.3. Lymphoma

8.5.3.1. Tumor Assessment Criteria

The determination of response and progression for MCL and MZL will be based on standardized criteria [Cheson 2007] as recently updated [Cheson 2014]. A detailed description of response assessment for this study is presented in Appendix 12.6.

8.5.3.2. Method of Assessment

Imaging-based evaluation will be used in this study as the primary basis of lymphoma assessment. Preferred methods for radiographic tumor assessment are diagnostic CT (with contrast enhancement) or PET/CT. If CT is performed, contrast-enhanced scanning is preferred, but contrast material may be omitted in patients for whom use of a contrast agent becomes medically contraindicated or if the CT is obtained in conjunction with PET scanning. If available, PET scan data will be considered in response and progression assessment; however, PET scanning will not be a required component of assessment in this study. As required by the protocol or as otherwise necessary, bone marrow aspirate/biopsy (eg, for confirmation of CR) or cytological/histological evaluation of lymph nodes, effusions, ascites, or other organ abnormalities) will be also be considered. Clinical palpation, chest x-ray, ultrasound, endoscopy, laparoscopy, radionuclide scan, or tumor markers will not be considered for response assessment. MRI scanning is not advised but may be used at the investigator's discretion in patients for whom this becomes a necessary alternative to CT scanning.

For radiographic assessments, the same method of assessment and the same technique (eg, scan type, scanner, patient position, dose of contrast, injection/scan interval) should be used, whenever possible, to characterize each identified and reported lesion at screening and during study treatment and follow-up. CT of the neck, chest, abdomen, and pelvis should be performed with cuts of ≤0.5 mm in slice thickness contiguously. If performed, whole-body FDG PET-CT scanning should be extended from the base of the skull to mid-thigh.

All relevant radiographic and clinical information required to make each tumor status assessment must be made available for source verification and review.

8.5.3.3. Timing of Assessments

During screening, imaging-based and laboratory assessments should be performed within the specified screening period. On-study tumor assessments should be scheduled as indicated in Section 8. For patients having an End of Treatment visit and evaluations, if radiology imaging studies were last performed > 8 weeks before the End of Treatment visit, then they should be performed as part of this visit. For patients ending treatment due to radiographic confirmation of disease progression following cirmtuzumab + ibrutinib combined therapy, the End of Treatment visit should occur ≤4 weeks after the documentation of progression and the imaging studies do not need to be performed. If a patient permanently discontinues treatment prior to objective documentation of lymphoma progression, investigators should continue further follow-up of

tumor status with assessments at ~12-week intervals until disease progression is documented or until the initiation of a new post-study therapy for the patient's lymphoma.

8.6. Safety Assessments

8.6.1. Definitions

8.6.1.1. Adverse Event

An AE can be any unfavorable and unintended sign or symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug. 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 product, whether or not considered related to the medicinal product.

In this study, any of the following events will be considered an AE:

- Any preexisting condition that increases in severity or changes in nature during or as a consequence of study drug administration. Worsening manifestations of the underlying cancer (eg, increase in pain, tumor flare reaction, TLS) may be considered AEs in this study but should be reported as disease progression.
- Any injury or accident. If a medical condition is known to have caused the injury or accident (eg, a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate AEs.
- Any abnormality in physiological testing or a physical examination finding that requires clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test).
- Any laboratory (eg, clinical chemistry, hematology, urinalysis) or investigational abnormality (eg, ECG, X-ray) independent of the underlying medical condition that requires clinical intervention, results in further investigation (beyond ordering a repeat [confirmatory] test), or leads to investigational medicinal product interruption or discontinuation unless it is associated with an already reported clinical event. If the laboratory abnormality is part of a syndrome, the syndrome or diagnosis (eg, anemia) not the laboratory result (eg, decreased hemoglobin) should be recorded.
- A complication related to pregnancy or termination of a pregnancy (see Section 8.6.6 for additional information).
- However, none of the following events is considered an AE:
- Asymptomatic lymphocytosis
- Cancer progression without worsening disease manifestations. In cases of SAEs, cancer progression may be reported if there is no alternative term that can be satisfactorily substituted. In such cases, the AE description should match the SAE description.
- Laboratory abnormalities not requiring clinical intervention or further investigation. Such abnormalities will be captured as part of laboratory monitoring.

- A diagnostic, medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, transfusion). However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE and the resulting appendectomy should be recorded in the source documents.
- A preexisting disease or condition or laboratory abnormality present or detected before the initial screening visit and that does not worsen.
- An intervention not associated with an untoward medical occurrence (eg, hospitalization for elective surgery or for social and/or convenience reasons).
- An overdose without clinical sequelae.

8.6.1.2. Serious Adverse Event

An SAE is defined as an untoward medical occurrence that results in any of the following outcomes:

- Death (ie, all deaths occurring from the time of the first drug administration to within 30 days after last study drug administration), including deaths due to cancer progression if no other event more satisfactorily explains the reason for death. Deaths that occur as a result of an AE that started during the study period should be reported. Death is not an SAE term; the reported AE should be the event that caused the death. Death is the outcome of this SAE.
- Life-threatening situation (ie, with an immediate risk of death from the event as it occurred but not including an event that, had it occurred in a more serious form, might have caused death).
- In-patient hospitalization or prolongation of existing hospitalization. Of note, an untoward medical occurrence that occurs during hospitalization is an AE but a complication that prolongs hospitalization is an SAE. Inpatient hospitalization comprises formal admission to a hospital for medical reasons, for any length of time, whether or not hospitalization extends overnight. However, hospital admissions for administration of the study drug or procedures required by the study protocol, diagnostic observations or procedures, logistical issues (eg, lengthy travel), or the convenience of the patient or clinical personnel are not considered serious.
- Persistent or significant disability/incapacity.
- Congenital anomaly/birth defect in the offspring of a patient who received the investigational medicinal product.
- Other medically significant event. Such events may not be immediately life-threatening or result in death or hospitalization, but based upon appropriate medical and scientific judgment, may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events might include:
    - Allergic bronchospasm requiring intensive treatment in an emergency room or at home
    - New cancers or blood dyscrasias

- Convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

8.6.1.3. Unexpected Adverse Event

An unexpected AE is defined as an event that has a nature, severity, or specificity that is not consistent with the applicable investigator brochure, or that is symptomatically and pathophysiologically related to a known toxicity but differs because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed and reported rather than an experience that has not been anticipated based on the pharmacological properties of the study drug.

8.6.1.4. Treatment-Emergent Adverse Event

A TEAE is defined as an AE that occurs or worsens in the period from the first dose of study drug administration to 30 days after the final dose of study drug administration.

8.6.1.5. Adverse Events of Special Interest

The AEs of special interest in this protocol will be:

- Grade ≥3 infusion reactions
- TLS
- Major hemorrhage (defined as any of hemorrhagic TEAEs of Grade ≥3, treatment-emergent hemorrhagic SAEs of any grade, or treatment-emergent central nervous system hemorrhage of any grade).
- Covid-19 infection (in addition, if the patient withdraws due to fear of contracting Covid-19 at the treatment site, due to travel, or other causes associated with trial, please note this as a reason for discontinuation.)

In addition to description in listings and tables, these types of events will be characterized in narratives.

8.6.2. Grading of the Severity of an Adverse Event

The severity of AEs will be graded using the CTCAE, Version 4.03 [NCI 2010]. For each episode, the highest severity grade attained should be reported.

If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the AE. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 2.

Table 2: Grading of Adverse Event Severity

Grade	Adjective	Description
Grade 1	Mild	Sign or symptom is present, but it is easily tolerated, is not expected to have a clinically significant effect on the patient's overall health and well-being, does not interfere with the patient's usual function, and is not likely to require medical attention.
Grade 2	Moderate	Sign or symptom causes interference with usual activity or affects clinical status, and may require medical intervention.
Grade 3	Severe	Sign or symptom is incapacitating or significantly affects clinical status and likely requires medical intervention and/or close follow-up.
Grade 4	Life-threatening	Sign or symptom results in a potential threat to life.
Grade 5	Fatal	Sign or symptom results in death.

The distinction between the seriousness and the severity of an AE should be noted. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events (as listed in Section 8.6.1.2).

8.6.3. Describing Adverse Event Relationship to Study Drug

The investigator will evaluate the causal relationship of each AE to a study drug and record that relationship on the appropriate CRFs. Causality will be assessed considering whether the AE is reasonably related to the study drug or whether the AE is not reasonably related to the study drug considering the definitions in Table 3.

Table 3: Relationship of Study Drug to Adverse Event

Relationship	Description
Definite	A clinical event in which a relationship to the use of the study drug seems definite because of such factors as consistency with known effects of the drug; a clear temporal association with the use of the drug; lack of alternative explanations for the event; improvement upon withdrawal of the drug (de-challenge); and recurrence upon resumption of the drug (rechallenge).
Probable	A clinical event in which a relationship to the study drug seems probable because of such factors as consistency with known effects of the drug; a reasonable temporal association with the use of the drug; lack of alternative explanations for the event; and improvement upon withdrawal of the drug (de-challenge).
Possible	A clinical event with a reasonable temporal association with administration of the study drug, and that is not likely to be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking.
Unlikely	A clinical event with a temporal relationship to study drug administration that makes a causal relationship improbable and for which other factors suggesting an alternative etiology exist. Such factors might include a known relationship of the clinical event to a concomitant drug, past medical history of a similar event, the patient's disease state, intercurrent illness, or environmental factors.
Unrelated	A clinical event in which a relationship to the study drug seems improbable because of factors such as inconsistency with known effects of the study drug; lack of a temporal association with study drug administration; lack of association of the event with study drug withdrawal or rechallenge; and/or presence of alternative explanations for the event. Alternative explanations might include a known relationship of the clinical event to a concomitant drug, past medical history of a similar event, the patient's disease state, intercurrent illness, or environmental factors.

8.6.4. Adverse Event Reporting Period

The start of the AE reporting for a study patient will coincide with study day 0, upon the start of dosing. After the first administration of study drug, all AEs (serious and nonserious, related and unrelated) should be reported. Unless a patient withdraws consent for follow-up, each patient must be followed until the end of the AE reporting period at 30 days after the final cirmtuzumab administration or when any ongoing drug-related AEs and/or SAEs have resolved or become stable. The investigator should use appropriate judgment in ordering additional tests as necessary to monitor the resolution of events. The medical monitor or Oncternal may request that certain AEs be followed longer.

Investigators are not obligated to actively seek information regarding the occurrence of new SAEs beginning after the 30-day post-cirmtuzumab period. However, if the investigator learns of such an SAE and that event is deemed relevant to the use of cirmtuzumab, he/she should promptly document and report the event. A longer reporting period applies in the case of pregnancy (see Section 8.6.6).

8.6.5. Adverse Event Reporting Requirements

Whether completing a paper SAE form or entering the SAE through the EDC system, SAEs must be reported to the sponsor or designee within 24 hours of first awareness.

Investigators must also submit written safety reports as required by the IRB within timelines set by their IRBs. The study site should retain documentation of the submission of expedited safety reports to the IRB, and their receipt.

The following minimum information is required when reporting the SAE to the sponsor or designee:

- Patient identification (ie, patient number, sex, age)
- Description of the SAE (diagnosis preferred, symptoms, etc.)
- Study drug and causal relationship of the SAE to the study drugs
- Investigator name

The original SAE form and any follow-up forms must be kept on file at the study site. An SAE is followed until it is considered resolved, it returns to baseline, is chronically ongoing, or explained otherwise by the principal investigator.

Contact information for reporting an SAE to Oncternal (or designee) is provided in Table 4.

Table 4: Contact Information for Reporting Serious Adverse Events or Pregnancies

Function	Contact Information
Vigilare International	E-mail: SAEONTX@vigilareintl.com

8.6.6. Pregnancy and Reporting

Each female patient should be instructed to inform the investigator immediately if she becomes pregnant at any time between the start of study screening until 30 days after the last administration of study drug.

The investigator should counsel the patient regarding the possible effects of study drug exposure on the fetus and the need to inform the study center, the medical monitor, and Oncternal (or designee) of the outcome of the pregnancy.

Neither the pregnancy itself nor an induced elective abortion to terminate the pregnancy without medical reasons is considered an AE; such occurrences should be reported on the appropriate pregnancy report forms. However, if the outcome of the pregnancy meets the criteria for classification as an SAE (ie, spontaneous abortion, induced abortion due to complications, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the investigator should follow the procedures for reporting SAEs (ie, report the event to Oncternal [or designee] and follow up by submission of the appropriate AE eCRFs (see Section 8.6.5).

Information regarding any pregnancy in a study patient or the female partner of a male patient must be documented on a pregnancy report form and forwarded to Oncternal (or designee) within 24 hours of becoming aware of the pregnancy. Monitoring of the pregnancy in both female study patients and female partners of male study patients should continue until the conclusion of the pregnancy. For female partners of male study patients, such monitoring applies if they became pregnant in the period from the patient's start of study drug until 30 days after the patient's last dose of study drug. The outcome of the pregnancy should be reported on the pregnancy outcome report form within 5 days of the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported to Oncternal (or designee).

Contact information for reporting a pregnancy to Oncternal (or designee) is provided in Table 4.

8.6.7. Sponsor Reporting Requirements

Each SAE or special situation report received from the investigator will be evaluated by Oncternal (or designee). Oncternal (or designee) will assess the seriousness of the event the expectedness of the event, and the relationship to participation in the study. Oncternal (or designee) will also indicate whether there is concurrence with the details of the report provided by the investigator.

Oncternal (or designee) will provide information for reporting of suspected, unexpected, serious adverse reactions (SUSARs) to the FDA per US FDA CFR. SUSARS will be reported to within 7 calendar days for life-threatening and fatal events, or 15 calendar days for all others. These timeframes begin with the first notification of the event from the reporting investigator to Oncternal (or designee), which represents the start of the regulatory clock (Day 0). .

9. STATISTICAL CONSIDERATIONS

9.1. Analysis Plan

Details of the statistical analyses will be fully described in a statistical analysis plan to be finalized prior to the analyses.

9.1.1. Pharmacokinetics

Pharmacokinetic parameters will be calculated using non-compartmental methods. Only serum concentrations greater than or equal to the validated lower limit of quantitation (LLQ) will be used in the pharmacokinetic analyses. Per-protocol times will be used to calculate mean serum concentrations for graphical displays. Actual blood sampling times will be used in all pharmacokinetic analyses.

9.1.2. Pharmacodynamics

For each pharmacodynamic variable, the value at each assessment will be described. Changes from baseline to each assessment and the most extreme changes from baseline during the study will be summarized using tabular and graphical methods. The data may also be described by baseline variables such as sex, age, weight, body-mass index, and disease type (CLL/SLL, MCL or MZL).

As appropriate, changes in the pharmacodynamic parameters will be assessed using paired t-tests or analysis of covariance (ANCOVA) with baseline values as covariates; in these analyses, both changes from baseline to each subsequent time point and most extreme on study changes will be evaluated.

9.1.3. Efficacy Analyses

Tumor control will be documented at each assessment by response category (eg, CR, PR, PR-L, SD, PD, or NE), as defined for each response parameter, the SPDs, percentage change in the SPDs from the pre-cirmtuzumab and pre-ibrutinib baselines (Part 1), or pretreatment baseline (Parts 2 and 3); percentage change in the SPDs from the nadir, date that response is first documented, date that response is confirmed, and date of tumor progression. Evaluable patients for efficacy are those who have completed treatment and have had the planned 3 month post cirmtuzumab + ibrutinib combination therapy imaging studies or had documented or clinical PD following 28 days of therapy. These analyses will be further described in the Statistical Analysis Plan.

9.1.4. Other Analyses

Using appropriate regression techniques, possible relationships between patient characteristics (eg, sex, race, age, weight, tumor characteristics, dose) and outcome measures (eg, pharmacodynamic and pharmacokinetic parameters) may be assessed. Similarly, associations between outcome measures (eg, relationships between pharmacokinetic and pharmacodynamic parameters) may be evaluated.

9.2. Timing of Analyses

9.2.1. Interim Analyses

During Parts 1 and 2, conference calls among the members of the SRC will be conducted periodically to discuss study progress, exchange study information, and review safety events, determine whether additional dose levels should be evaluated, and discuss potential amendments to the protocol. It is expected that these discussions will be scheduled at intervals of ~4 weeks unless accrual to the study and decisions regarding study conduct or transitions between the dosing cohorts indicate the need for an alternate schedule of reviews. As needed for scientific or business reasons, Oncternal may collate and summarize available study results during conduct of the study.

During Part 2 of the study, interim futility analyses are planned that will evaluate whether there is sufficient antitumor activity to warrant further development of the cirmtuzumab + ibrutinib combination in the selected disease types (CLL/SLL and MCL). The interim analysis will be performed when: ≥9 evaluable patients with either disease type from Part 1 and Part 2 of the study (eg, ≥6 from Part 1 and ≥3 from Part 2) have: a) received treatment using a dose of cirmtuzumab that is at or below the RDR for the combination, and, b) have ≥24 weeks of evaluable efficacy data on combination treatment.

In patients with CLL/SLL, the target CR rate of interest with cirmtuzumab + ibrutinib is an increment of ≥25% over that expected with ibrutinib alone. Thus, for CLL/SLL a CR rate of ≥30% is targeted with the combination based on knowledge of an anticipated CR rate of ≤5% with ibrutinib monotherapy [Byrd 2013; Byrd 2014; Farooqui 2015; Burger 2015, O'Brien 2016]. Futility will be tested using a 1-sided exact binomial CI upper bound of 90% considering all evaluable patients meeting the criteria (a and b) described above. Assuming the minimum futility sample for CLL/SLL, if 0/9 evaluable patients experience a CR, then a population CR rate of ≥30% can be ruled out with >90% certainty (1-sided exact binomial 90% CI upper bound=22.5%). The interim analysis of this study presented at ASCO 2020 showed that the CLL/SLL data did not satisfy the hypothesis that cirmtuzumab + ibrutinib would produce a CR rate 25% greater than that for ibrutinib alone [Lee 2020]. Therefore, the number of patients to be enrolled and randomized into Part 3 was reduced to include approximately 30 patients.

For MCL, a CR rate of ≥50% is targeted with the combination based on knowledge of an anticipated CR rate of ≤23 to 27% with ibrutinib monotherapy [Wang 2013; Dreyling 2016, Maruyama 2016; Wang 2015, Rule 2019]. Pooled analyses of large single agent ibrutinib studies in MCL indicate an overall CR rate of 27% with a 23% CR rate in those previously receiving 2 or more prior treatments [Rule 2019]. The interim analysis of this study presented at ASCO 2020 [Lee 2020] indicates that a complete response rate of 58% was achieved in heavily pre-treated patients with MCL. Because of the promising clinical results from this interim analysis, the sample size of the MCL expansion study was increased.

9.2.2. Final Analyses

9.2.2.1. Part 1 (Cirmtuzumab → Cirmtuzumab + Ibrutinib) and Part 2 (Cirmtuzumab + Ibrutinib))

Parts 1 and 2 of the study may be reported separately from Part 3. Final study reporting for these components of the study is expected to occur after all Part 1 and 2 patients have completed planned cirmtuzumab treatment and have been followed for ≥30 days thereafter.

9.2.2.2. Part 3 (Cirmtuzumab + Ibrutinib versus Ibrutinib)

Final study reporting for Part 3 of the study is expected to occur after all Part 3 patients have discontinued study treatment or ≥72 weeks after accrual of the final patient (whichever occurs earlier).

9.3. Basis for the Planned Sample Sizes

9.3.1. Part 1 (Cirmtuzumab → Cirmtuzumab + Ibrutinib) and Part 2 (Cirmtuzumab + Ibrutinib)

Sample sizes for Part 1 and Part 2 of the study are not based on formal statistical hypotheses but on experience from similar types of Phase 1b dose-ranging studies and Phase 2 expansion cohorts of patients treated with the same regimen.

9.3.2. Part 3 (Cirmtuzumab + Ibrutinib versus Ibrutinib)

In patients with CLL/SLL receiving ibrutinib, rates of CR have been ≤5% [Byrd 2013; Byrd 2014; Farooqui 2015; Burger 2015, O'Brien 2016]. Based on these data, it is assumed that in Part 3 of this trial, the CR rate in patients with CLL/SLL receiving ibrutinib monotherapy will be ≤5%. A ≥25% absolute improvement in CR rate (to ≥30%) is targeted for patients with CLL/SLL treated with cirmtuzumab + ibrutinib, with testing of this hypothesis using Fisher's exact test with a 1-sided significance level of ≤0.05.

The interim analysis performed for ASCO 2020 showed that the CLL/SLL data did not satisfy the hypothesis that cirmtuzumab + ibrutinib would produce a CR rate 25% greater than that for ibrutinib alone [Lee 2020]. Therefore, the number of patients to be enrolled and randomized into Part 3 was reduced to include approximately 30 patients.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Study Conduct

Oncternal will serve as the regulatory sponsor for the study and will maintain the investigational new drug (IND) applications with the FDA. The current and future protocol amendments will be submitted to Oncternal's IND (IND#133131) for cirmtuzumab and the trial design has been and will be subject to review by the FDA.

Oncternal will serve as the operational coordinator for all aspects of the study and will oversee conduct of the study at participating study centers and through contract research organization (CROs). The CROs will perform activities relating to pharmacovigilance, site monitoring, data collection, data management and study reporting, sample handling, centralized performance of pharmacokinetic and pharmacodynamic assays, and centralized assessments of drug efficacy (Part 3 only).

10.2. Study Committees

During Parts 1, 2, and 3 of the study, assessments of safety and trial conduct will be performed by a safety review committee (SRC) comprising the investigators, the medical monitor, and the Oncternal study director. AEs and SAEs will be reviewed on an ongoing basis to identify any safety concerns. Conference calls among the members of the SRC will be conducted periodically to discuss study progress, exchange study information, and review safety events (in particular, SAEs and AEs leading to dose interruption, dose reduction, or therapy discontinuation), determine whether the dose range should be restricted or whether additional dose levels should be evaluated based on emerging safety data, and discuss potential amendments to the protocol.

10.3. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

10.4. Institutional Review Board (IRB)

This protocol and any accompanying material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IRB. Approval from the IRB must be obtained before starting the study and should be documented in a letter from the IRB to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

Any modifications or amendments made to the protocol or informed consent document after receipt of the initial IRB approval must also be submitted to the IRB for approval before implementation. Only changes necessary to eliminate apparent immediate hazards to the patients may be initiated prior to IRB approval. In that event, the investigator must notify the IRB, the medical monitor, and Oncternal in writing within 5 working days after implementation. If a change to the protocol in any way increases the risk to the patient or changes the scope of the

study, then written documentation of IRB approval must be received by Oncternal before the amendment may take effect.

10.5. Informed Consent

The investigator, or designee (designee must be listed on the Study Personnel Responsibility/Signature Log), must explain to each patient the purpose and nature of the study, the study procedures, the possible adverse effects, and all other elements of consent as defined in 21 CFR Part 50 and other applicable national and local regulations governing informed consent. Each patient must provide a signed and dated informed consent before enrollment into this study. Signed consent forms must remain in each patient's study file and be available for verification by study monitors at any time.

10.6. Confidentiality

Every effort will be made to maintain the anonymity and confidentiality of all patients during this clinical study. However, because of the experimental nature of this study drug, the investigator agrees to allow the IRB, representatives of Oncternal and its designated agents, and authorized employees of appropriate regulatory agencies to inspect the facilities used in this study and, for purposes of verification, allow direct access to the study center records of all patients enrolled into this study. This includes providing by fax, email, or regular mail de-identified copies of clinical, laboratory, ECG, radiology, pathology, and/or other test results when requested by Oncternal. A statement to this effect will be included in the informed consent and a permission form authorizing the use of protected health information will also be included.

In accordance with local and national patient privacy regulations, the investigator or designee must explain to each patient that in order to evaluate study results, the patient's protected health information obtained during the study may be shared with IRBs, Oncternal and its designees, and regulatory agencies. It is the investigator's or designee's responsibility to obtain written permission to use protected health information from each patient. If a patient withdraws permission to use protected health information, it is the investigator's responsibility to obtain the withdrawal request in writing from the patient and to ensure that no further data will be collected from the patient. Any data collected on the patient before withdrawal will be used in the analysis of study results. Oncternal will only use or disclose the patient's protected health information as defined in the informed consent document.

The investigator must assure that each patient's anonymity will be strictly maintained, and that each patient's identity is protected from unauthorized parties. Only patient initials, date of birth, and an identification code (but no patient names) should be recorded on any form or biological sample submitted to the IRB, to Oncternal or its designees (eg, laboratories), or to regulatory authorities. However, sufficient information must be retained at the study center to permit sample data and data in the database to be connected with the unique patient number assigned to each study participant.

The investigator agrees that all information received from Oncternal, including but not limited to the study drug, the investigator brochure, this protocol, the eCRFs, and any other study information remain the sole and exclusive property of Oncternal during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written

consent from Oncternal. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study center to any third party or otherwise into the public domain.

10.7. Sample Shipping, Storage, and Retention

Routine clinical safety samples (for serum virology, serum pregnancy test, serum chemistry, hematology, and coagulation) will be analyzed at the CLIA certified clinical laboratory at the study center and will not be shipped.

Other samples (serum for pharmacokinetics, blood, bone marrow, and plasma for pharmacodynamics, serum for immunogenicity, and blood and bone marrow for disease characterization, exploratory biomarkers, and MRD assessment) will be prepared following the instructions outlined in the clinical study laboratory manual.

These samples will be shipped to Oncternal, UCSD or the contract analytical laboratories using a shipping service designated by Oncternal and as specified in the study laboratory manual. For the duration of the sample analysis campaign, samples will be stored at these contract laboratory facilities or sent for long-term storage at a storage facility designated by Oncternal.

10.8. Study Files and Retention of Records and Biological Samples

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified by the IRB, representatives of Oncternal and its designated agents, and authorized employees of appropriate regulatory agencies. These documents should be classified into at least the following 2 categories: (1) investigator's study file, and (2) patient clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF and query forms, the IRB and governmental approval with correspondence, signed informed consent documents, drug accountability records, staff curriculum vitae and authorization forms (eg, Form FDA 1572), and other appropriate documents and correspondence pertaining to the conduct of the study.

The required source data referenced in the monitoring plan for the study should include sequential notes containing at least the following information for each patient:

- Patient identification (name, date of birth, gender)
- Documentation that the patient meets eligibility criteria, eg, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)
- Participation in trial (including trial number)
- Trial discussed and date of informed consent
- Dates of all visits
- Documentation that protocol-specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of study drug (including relevant drug dispensing information)

- Record of all AEs and other safety parameters (including start and end date, causality and intensity)
- Concomitant medications (including start and end date and dose if relevant dose changes occur)
- Date of trial completion and reason for discontinuation, if applicable

All clinical study documents must be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region (ie, the United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified or for 15 years, whichever is longer. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with Oncternal. The investigator must notify Oncternal and obtain written approval from Oncternal before destroying any clinical study records. The investigator will promptly notify Oncternal in the event of accidental loss or destruction of any study records. Oncternal will inform the investigator of the date that study records may be destroyed or returned to Oncternal.

Oncternal must be notified in advance and must provide express written approval of any change in the maintenance of the foregoing documents if the investigator wishes to move study records to another location or assign responsibility for record retention to another party.

If the investigator cannot guarantee this archiving requirement at the study center for any or all of the documents, special arrangements must be made between the investigator and Oncternal to store these in sealed containers outside of the study center so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the study center.

Any biological samples retained by the investigator that have not been collected by the CROs will be stored and maintained by the investigator until notification is received from Oncternal that the retained samples and records no longer need to be retained. The investigator must obtain written permission from Oncternal before disposing of any retained samples. The investigator should promptly notify Oncternal in the event of accidental loss or destruction of any study samples. With the permission of Oncternal, the retained samples may be transferred to an acceptable designee, such as another investigator, another institution, a contract laboratory, a contract storage site, or to Oncternal.

10.9. Modifications of the Protocol

Protocol modifications, except those intended to reduce immediate risk to study participants, will be made only by Oncternal. All protocol modifications must be submitted to the IRB in accordance with local requirements. Except as noted in Section 10.4, IRB approval must be obtained before changes can be implemented.

10.10. Case Report Forms

Authorized study center personnel will submit all required information into a central electronic case report form (eCRF) designed for this study and maintained by Oncternal's CRO, according

to the completion guidelines that will be provided. An eCRF is required and must be completed for each enrolled patient, with all required study data accurately recorded such that the information matches the data contained in medical records (eg, physicians' notes, nurses' notes, study center charts, or other study-specific source documents). The investigator will ensure that the eCRFs are accurate, complete, legible, and completed in a timely fashion after each patient's visit. If a patient withdraws from the study, the reason must be noted on the eCRF and thorough efforts should be made to clearly document outcome.

The eCRFs for this study will exist within a web-based electronic data capture (EDC) system.

10.11. Study Drug Accountability

The disposition of all investigational cirmtuzumab and ibrutinib should be documented from the time of receipt at the study center through patient administration. An investigational drug accountability log must be maintained for drug accountability. It is acceptable to use a protocol-specific form or a study center form that captures the relevant information. Within the drug accountability log, the responsible study center personnel must maintain accurate records of the receipt of all cirmtuzumab and ibrutinib shipped by Oncternal (or its designee), including, but not limited to, the date received, lot number, amount received, pertinent details about the condition of the study drug upon receipt based on visual inspection, and the disposition of the drug (eg, to storage). If a cirmtuzumab or ibrutinib drug shipment arrives damaged, or if there are any other complaints relating specifically to the drug, a product complaint should be emailed to the sponsor or the sponsor's representative. Cirmtuzumab and ibrutinib accountability records must also be maintained that include the patient number to whom the study drug was administered and the date, quantity and lot number of the cirmtuzumab administered.

Study personnel must ensure that cirmtuzumab and ibrutinib are kept in a secure locked area with access limited to authorized personnel. The study drugs must not be used outside the context of this protocol. Under no circumstances should the investigator or study center personnel supply cirmtuzumab or ibrutinib designated for this study to other investigators, patients, or clinics, or allow the study drugs to be used other than as directed by this protocol without the prior authorization from Oncternal.

Depending upon the decision of Oncternal, remaining unused cirmtuzumab and ibrutinib supplies will be returned to Oncternal or its designee after the study is completed or will be discarded or destroyed at the study center. After investigational product accountability has been performed, cirmtuzumab and ibrutinib may be returned or destroyed on an ongoing basis during the study if appropriate. If the study drug is discarded or destroyed at the study center, standard institutional policy should be followed. At study initiation, the monitor will evaluate the study center's standard operating procedure for study drug disposal/destruction in order to ensure that it complies with Oncternal requirements. At the end of the study, following final drug inventory reconciliation by the monitor, the study center will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the study center cannot meet Oncternal requirements for disposal, arrangements will be made between the study center and Oncternal or its representative for destruction or return of unused study drug supplies.

All study drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study. Study drug accountability records must be

readily available for inspection by the study monitor or other representatives of Oncternal or by regulatory authorities.

10.12. Monitoring

Representatives of Oncternal or its designee will monitor this study until completion at appropriate intervals. Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete and verifiable and the conduct of the trial is in compliance with the currently approved protocol/amendment(s), and within ICH guidelines and the CFR.

In accordance with GCP, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the eCRFs for consistency. Because of constraints caused by the COVID-19 pandemic, Oncternal has determined that remote and centralized monitoring of study data is acceptable. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

10.13. Inspections

The source documents for this trial must be made available to appropriately qualified personnel from Oncternal or its representatives, to IRBs, and to regulatory authority or health authority inspectors as a part of their responsibility to protect human subjects in research. The investigator agrees to provide access to records, facilities, and personnel for the effective conduct of any inspection or audit to representatives of Oncternal and regulatory agencies. It is important that the investigator and relevant institutional personnel are available during monitoring visits and possible audits or inspections and that sufficient time is devoted to the process. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify Oncternal immediately.

10.14. Data Management

The eCRFs for this study will exist within a web-based electronic data capture (EDC) system.

During the data collection process, automated quality assurance programs will be used to identify missing data, out-of-range data, and other data inconsistencies. Requests for data clarification or correction will be forwarded to the investigative study center for resolution.

Quality assurance and quality control systems will be implemented and maintained according to written standard operating procedures to ensure that the data are generated, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirements. Data collection and storage systems will provide audit trail, security mechanisms, and electronic signature capabilities that meet the requirements of FDA Title 21 of CFR Part 11 regarding electronic records and electronic signatures.

10.15. Communications with Regulatory Authorities

Oncternal (or its designee) will have responsibility for interactions with the FDA and any other relevant regulatory authorities. Oncternal will maintain their IND for the development of cirmtuzumab in support of the study in the US. In fulfilling these responsibilities, Oncternal (or a

designee) will collect and assemble all required regulatory documents (eg, Form FDA 1572, investigator financial disclosure forms, protocol and protocol amendments, investigator brochures, informed consent documents, annual reports) as required by regulation. Oncternal (or a designee) will assume primary responsibility for AE reporting to regulatory authorities (as described in Section 8.6.7).

10.16. Public Notification of Study Conduct

Consistent with Section 113 of the Food and Drug Modernization Act of 1997 (FDAMA) and to ensure meeting the requirement of the International Committee of Medical Journal Editors (ICMJE) as a condition of consideration for publication of study results, Oncternal will register this protocol at the ClinicalTrials.gov website (or equivalent). Oncternal will appropriately update the information at the website relating to study design and conduct during the course of the study. In order to facilitate this process, investigators will need to supply Oncternal with appropriate contact information for study center personnel.

10.17. Study Reporting and Publication

Oncternal may make information obtained during this study available in order to further the scientific or business needs of the company or as required by law or regulation. In this regard, Oncternal may provide study information to private or public organizations (eg, business partners, collaborators, consultants, CROs, investors, other physicians who are conducting similar studies, funding organizations, regulatory authorities, or other government authorities). The results may also be used for papers, abstracts, posters or other material presented at scientific meetings or published in professional journals or as part of an academic thesis.

Oncternal will prepare a clinical study report for submission to relevant regulatory agencies. Oncternal will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). An abbreviated report may be prepared in certain cases, as appropriate.

Oncternal intends that the data from this study will be presented and published. Because the study will ultimately part of a multicenter clinical trial, data from all study centers will be pooled and analyzed for a primary publication of the study results. Oncternal will coordinate and prepare this primary publication. The investigator agrees that the primary publication, which will be coordinated by Oncternal, will be the first publication to present the pooled study results. Other ancillary publications or presentations relating to the pooled data from this study may be suggested by the investigator but can only be published with the express consent of Oncternal and the other investigators; such ancillary publications will also be coordinated by Oncternal.

After the primary publication, or if the primary publication is not published within 2 years of termination of the study, the investigator may freely publish or present the results of his or her work conducted under the clinical trial agreement, subject to providing Oncternal with the opportunity to review the contents of any proposed presentation, abstract, or publication about such work, including any results of this study, in advance of any presentation or submission for publication. Within that advance notice period, Oncternal may review the proposed publication to identify patentable subject matter and/or any inadvertent disclosure of its confidential information, which must be redacted from any final publication or presentation. If necessary, to permit the preparation and filing of patent applications, Oncternal may elect an additional review

period. The durations of the review periods will be specified in a contractual agreement between each study center and Oncternal.

In most cases, the principal investigators at the study centers with the highest accruals of eligible patients and/or who have provided significant intellectual input into the study design, shall be listed as lead or senior authors on publications and presentations of study results. Oncternal clinical personnel, lead statistician, scientific personnel, or other staff members meeting the requirements for authorship may also be included in the list of authors. This custom can be adjusted upon mutual agreement of the authors and Oncternal.

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12. APPENDICES

12.1. ECOG Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light 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

Reference: [Oken 1982]

12.2. Cockcroft-Gault Method for Estimating Creatinine Clearance

Formulas for calculating the estimated creatinine clearance (eC_{lCR}) are provided below. The formula appropriate to the units in which serum creatinine was measured and the patient's sex should be used.

Cockcroft-Gault Formulas for Calculating Estimated Creatinine Clearance		
Serum Creatinine Units	**Sex**	**Formula**
mg/dL	Males	eCl_{CR} [mL/min] = $\frac{(140\text{-patient age [years]}) \times \text{patient weight [kilograms]} \times 1.0}{72 \times \text{patient serum creatinine [mg/dl]}}$
	Females	eCl_{CR} [mL/min] = $\frac{(140\text{-patient age [years]}) \times \text{patient weight [kilograms]} \times 0.85}{72 \times \text{patient serum creatinine [mg/dl]}}$
µM/dL	Males	eCl_{CR} [mL/min] = $\frac{(140\text{-patient age [years]}) \times \text{patient weight [kilograms]} \times 1.23}{\text{Patient serum creatinine [µM/dL]}}$
	Females	eCl_{CR} [mL/min] = $\frac{(140\text{-patient age [years]}) \times \text{patient weight [kilograms]} \times 1.04}{\text{Patient serum creatinine [µM/dL]}}$

Abbreviation: eCl_{CR}=estimated creatinine clearance

12.3. Potent Inhibitors and Inducers of CYP3A4

Effect on CYP3A	Drug Class	Medications
Moderate to Strong CYP3A Inhibitors	**Antibiotics**	chloramphenicol, ciprofloxacin, clarithromycin, erythromycin, telithromycin
	Antiemetic	aprepitant
	Antifungals	ketoconazole, fluconazole, itraconazole, posaconazole, voriconazole
	Antiviral protease inhibitors	amprenavir, atazanavir, boceprevir, cobicistat, darunavir, elvitegravir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, telaprevir, tenofovir, tipranavir
	Calcium-channel blockers	diltiazem, mibifradil, verapamil
	Foods/herbs	grapefruit, grapefruit juice, Seville oranges
	Serotonin antagonist	nefazodone
	Tyrosine kinase inhibitor	imatinib
	Vasopressin antagonist	conivaptan
Moderate to Strong CYP3A Inducers	**Antibiotics**	nafcillin, rifampin
	Anticonvulsants	carbamazepine, phenobarbital, phenytoin
	Antiviral reverse transcriptase inhibitors	efavirenz, etravirine
	Endothelin receptor antagonist	bosentan
	Foods/herbs	St. John's wort
	Wakefulness-promoting agent	modafinil

Reference: [FDA 2014]
Abbreviation: CYP=cytochrome P450 enzyme

12.4. RAI Staging System for CLL/SLL

Grade	Disease Manifestations
0	• Absolute lymphocytosis (>15 × 10^9/L) • No lymphadenopathy, splenomegaly, hepatomegaly, anemia (hemoglobin <11 g/dL), or thrombocytopenia (platelet count <100 × 10^9/L)
1	• Lymphadenopathy with or without absolute lymphocytosis (>15 × 10^9/L) • No splenomegaly, hepatomegaly, anemia (hemoglobin <11 g/dL), or thrombocytopenia (platelet count <100 × 10^9/L)
2	• Absolute lymphocytosis (>15 × 10^9/L) • Splenomegaly and/or hepatomegaly with or without absolute lymphocytosis (>15 × 10^9/L) and/or lymphadenopathy • No anemia (hemoglobin <11 g/dL) or thrombocytopenia (platelet count <100 × 10^9/L)
3	• Absolute lymphocytosis (>15 × 10^9/L) • Anemia (hemoglobin <11 g/dL) with or without absolute lymphocytosis (>15 × 10^9/L), lymphadenopathy, splenomegaly, and/or hepatomegaly • No thrombocytopenia (platelet count <100 × 10^9/L)
4	• Thrombocytopenia (platelet count <100 × 10^9/L) with or without absolute lymphocytosis (>15 × 10^9/L), lymphadenopathy, splenomegaly, hepatomegaly, and/or anemia (hemoglobin <11 g/dL)

Reference: [Rai 1975]

12.5. Efficacy Assessments – CLL/SLL

The determination of CLL/SLL response and progression will be based on standardized criteria [Hallek 2008], as recently updated [Hallek 2018; Cheson 2012].

12.5.1. Identification and Measurement of Tumor Lesions and Organomegaly

12.5.1.1. Index Lesions

At screening, up to 6 lymph nodes should be selected as index lesions that will be used to quantitate the status of the disease during study treatment. Ideally, the index lesions should be located in disparate regions of the body. Only peripheral nodes need be selected as index lesions. However, it is optimal if mediastinal and retroperitoneal areas of disease are assessed whenever these sites are involved.

Index lesions will be measured and recorded at screening and at the stipulated intervals. The cross-sectional dimensions (the largest cross-sectional diameter, ie, the LD × LPD) will be recorded (in cm) for each index lesion. The product of the perpendicular diameters (PPD) (in cm^2) for each index lesion and SPD (in cm^2) for all index lesions will be calculated and recorded. The screening SPD will be used as references by which objective tumor response will be characterized during treatment. The nadir LD of individual lesions and the nadir SPD will be used as references by which CLL/SLL progression will be characterized. All LD and LPD diameters will be reported in centimeters and all PPDs and SPDs will be reported in centimeters squared.

A nodal mass may be selected as a nodal index lesion if it is both abnormal and measurable at screening. A lymph node lesion is considered abnormal if it has a single diameter that is >1.5 cm

and is considered measurable if it has 2 perpendicular diameters that can be accurately measured in cross section with the LD being ≥1.0 cm and the LPD also being ≥1.0 cm.

Index lesions measuring >1.5 cm in the LD, regardless of the measurement of the LPD, will be prioritized during screening index lesion selection.

At follow-up timepoints, the LDs for individual lesions and the SPD of all nodal index lesions will be considered. Because nodal index lesions that have one or both diameters >0 cm and <1.0 cm cannot be reliably measured, a default value of 1.0 cm will be assigned for each diameter that meets these criteria and the resulting PPD will be used in SPD calculations. Based on this convention, a CR may be achieved even if an SPD value is >0 cm^2, (ie, if all lymph nodes measure <1.0 cm^2).

A new node that measures ≥1.5 cm in any diameter will be considered progressive disease [Hallek 2018].

In cases in which a large lymph node mass has split into multiple components, only those elements that are >1.0 cm in ≥1 diameter will be considered abnormal and used in calculating the SPD. Progression of the lesion can only be based on the SPD of abnormal sub-components. Lesion sub-components that are considered normal but measurable will have the true PPDs calculated, with the result used only for calculating an accurate nadir. Similarly, lesion sub-components that are visible but neither abnormal nor measurable will have the default PPD of 1.0 cm^2 (1.0 cm × 1.0 cm) stored only for the purposes of calculating the nadir SPD value.

If lesions merge, a boundary between the lesions will be established so the LD of each individual lesion can continue to be measured. If the lesions have merged in a way that they can no longer be separated by this boundary, the newly merged lesion will be measured bi-dimensionally.

12.5.1.2. Spleen and Liver

Both the spleen and liver will be assessed by CT/MRI scan at screening and at the stipulated intervals during treatment. The screening and nadir values for the longest vertical dimension (LVD) of each organ will be used as reference to further characterize the objective tumor response of the measurable dimensions of the CLL/SLL during treatment. All spleen and liver LVD measurements should be recorded in centimeters.

By imaging, the spleen will be considered enlarged if it is >13 cm in LVD [Bezerra 2005; Asghar 2011], with the LVD being obtained by multiplying the number of sections on which the spleen is visualized by the thickness of the sections (eg, if the spleen is seen in 14 contiguous cross-sectional images with 0.5-cm thickness, the LVD is recorded as 7 cm).

For patients with splenomegaly at screening or at the splenic LVD nadir, respective response and progression evaluations of the spleen will consider only changes relative to the enlargement of the spleen (ie, the portion of the LVD that is >13 cm by imaging) at screening or nadir, not changes relative to the total splenic LVD.

A 50% decrease from screening (minimum decrease of 2 cm) in the enlargement of the spleen in its LVD or to ≤13 cm by imaging is required for declaration of a splenomegaly response. Conversely, an increase in splenic enlargement by ≥50% (minimum increase of 2 cm) from nadir is required for declaration of splenic progression. Patients with a normal spleen LVD (ie, a LVD

of ≤12 cm by imaging) at nadir will only be considered to have progressed if the spleen attains a LVD of >14 cm by imaging.

There is no firmly established international consensus of the size of a normal liver. For this study, an increase in the liver size of ≥50% of the extent enlargement of the liver below the costal margin defined by palpation, or the de novo appearance of hepatomegaly by imaging compared to baseline should be considered. However, given the impact of numerous medical conditions, liver size by physical examination or by CT scan is not a reliable measure of hepatic involvement by CLL and should only be counted if hepatomegaly is clearly attributable to lymphoid involvement [Hallek 2018].

A 50% decrease from screening (minimum decrease of 2 cm) in the enlargement of the liver in its LVD or to ≤18 cm by imaging is required for declaration of a hepatomegaly response. Conversely, an increase in liver enlargement by ≥50% (minimum increase of 2 cm) from nadir is required for declaration of hepatic progression.

12.5.1.3. Non-Index Lesions

Any other measurable and abnormal nodal lesions not selected for quantitation as index lesions may be considered non-index lesions. In addition, non-measurable evidence of CLL/SLL such as nodal lesions with both diameters <1.0 cm, extranodal lesions, bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusions, lymphangitis of the skin or lung, abdominal masses that are not confirmed and followed by imaging techniques, cystic lesions, previously irradiated lesions, and lesions with artifacts may be considered as non-index disease.

The presence or absence of non-index disease should be recorded at screening and at the stipulated intervals during treatment. If present at screening, up to 6 non-index lesions should be recorded. The non-index disease at screening will be used as a general reference to further characterize regression or progression of CLL/SLL during assessments of the objective tumor response during treatment. Measurements are not required, and these lesions should be followed as “present” or “absent”.

12.5.1.4. Bone Marrow

Bone marrow assessments will be based on morphologic evaluation of bone marrow biopsies. Immunohistochemistry may be used to assess response if the sample is indeterminate by morphology.

12.5.2. Definitions of Tumor Response and Progression

Responses will be categorized as complete response (CR), complete response with incomplete blood count recovery (CRi), partial response (PR), partial response with lymphocytosis (PR-L), stable disease (SD), or progressive disease (PD). In addition, a response category of nonevaluable (NE) is provided for situations in which there is inadequate information to otherwise categorize response status. A summary of response criteria is provided in Table 5.

The best overall response will be determined. The best overall response is the best response recorded from the start of treatment until PD/recurrence. The screening measurement will be taken as a reference for determinations of response. The nadir measurement will be taken as a reference for PD; this measurement constitutes the smallest measurement recorded, including the

screening measurement if this is the smallest measurement. Where imaging data are available, these data will supersede physical examination data in determining tumor status.

Table 5: Summary of Response Criteria for CLL/SLL Patients

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

Source: Hallek 2018
*Sum of the products of 6 or fewer lymph nodes (as evaluated by CT scans and physical examination in clinical trials or by physical examination in general practice).
†Spleen size is considered normal if <13 cm. There is no firmly established international consensus of the size of a normal liver; therefore, liver size should be evaluated by imaging and manual palpation in clinical trials and be recorded according to the definition used in a study protocol.
CR, complete remission (all of the criteria have to be met); PD, progressive disease (at least 1 of the criteria of group A or group B has to be met); PR, partial remission (for a PR, at least 2 of the parameters of group A and 1 parameter of group B need to improve if previously abnormal; if only 1 parameter of both groups A and B is abnormal before therapy, only 1 needs to improve); SD, stable disease (all of the criteria have to be met; constitutional symptoms alone do not define PD).

12.5.2.1. Complete Response and Complete Response with Incomplete Blood Count Recovery

To satisfy criteria for CR or CRi, all of the following conditions must be attained:

- No evidence of new disease
- ALC in peripheral blood of <4 x 10^9/L
- Regression of all index nodal masses to normal size <1.5 cm in the LD
- Normal spleen and liver size
- Regression to normal of all nodal non-index disease and disappearance of all detectable non-nodal, non-index disease
- Morphologically negative bone marrow defined as <30% of nucleated cells being lymphoid cells and no lymphoid nodules in a bone marrow sample that is normocellular for age
- Peripheral blood meeting all of the following criteria:
  - ANC ≥1.5 x 10^9/L without need for exogenous growth factors (eg, G-CSF)
  - Platelet count ≥100 x 10^9/L without need for exogenous growth factors

- Hemoglobin ≥110 g/L (11.0 g/dL) without red blood cell transfusions or need for exogenous growth factors (eg, erythropoietin)

Note: Patients who fulfill all the criteria for a CR (including bone marrow criteria) but who have a persistent anemia, thrombocytopenia, or neutropenia or a hypocellular bone marrow that is related to prior or ongoing drug toxicity (and not to CLL/SLL) will be considered as a CRi.

12.5.2.2. Partial Response

To satisfy criteria for a PR, all of the following conditions must be attained:

- No evidence of new disease
- A change in disease status meeting ≥2 of the following criteria, with 2 exceptions in which only 1 criterion is needed: (1) Only lymphadenopathy is present at screening; or (2) only lymphadenopathy and lymphocytosis are present at screening; in these 2 cases, only lymphadenopathy must improve to the extent specified below:
  - Decrease in peripheral blood ALC by ≥50% from screening
  - A decrease by ≥50% from the screening in the SPD of the index nodal lesions
  - In a patient with enlargement of the spleen at screening, a splenomegaly response as defined in Section 12.5.1.2
  - In a patient with enlargement of the liver at screening, a hepatomegaly response as defined in Section 12.5.1.2
  - A decrease by ≥50% from screening in the CLL/SLL bone marrow infiltrate or in B-lymphoid nodules
- No index, splenic, liver, or non-index disease with worsening that meets the criteria for definitive PD
- Peripheral blood meeting ≥1 of the following criteria:
  - ANC ≥1.5 x 10^9/L or ≥50% increase over screening without need for exogenous growth factors (eg, G-CSF)
  - Platelet count ≥100 x 10^9/L or ≥50% increase over screening without need for exogenous growth factors
  - Hemoglobin ≥110 g/L (11.0 g/dL) or ≥50% increase over screening without red blood cell transfusions or need for exogenous growth factors (eg, erythropoietin)

12.5.2.3. Partial Response with Lymphocytosis

To satisfy criteria for a PR-L, the following conditions must be attained:

- No evidence of new disease
- All criteria for PR achieved (per Section 12.5.2.2) except for the lack of a decrease in peripheral blood ALC by ≥50% from screening

12.5.2.4. Stable Disease

To satisfy criteria for SD, the following conditions must be attained:

- No evidence of new disease
- There is neither sufficient evidence of tumor shrinkage to qualify for PR nor sufficient evidence of tumor growth to qualify for definitive PD

12.5.2.5. Progressive Disease

The occurrence of any of the following events indicates PD:

- Evidence of any new disease:
  - A new node that measures >1.5 cm in any diameter
  - New splenomegaly as defined in Section 12.5.1.2
  - New hepatomegaly as defined in Section 12.5.1.2
  - New non-index disease (eg, effusions, ascites, or other organ abnormalities related to CLL/SLL)

Note: Isolated new effusions, ascites, or other organ abnormalities are not sufficient evidence alone of PD unless histologically confirmed. Thus, a declaration of PD should not be made if this is the only manifestation of apparently new disease.

- Evidence of worsening of index lesions, spleen or liver, or non-index disease:
  - Increase from the nadir by ≥50% from the nadir in the SPD of index lesions
  - Increase from the nadir by ≥50% in the LD of an individual node or extranodal mass that now has an LD of >1.5 cm and an LPD of > 1.0 cm
  - Splenic progression as defined in Section 12.5.1.2
  - Hepatic progression as defined in Section 12.5.1.2
    - Unequivocal increase in the size of non-index disease (eg, effusions, ascites, or other organ abnormalities related to CLL/SLL)
    - Transformation to a more aggressive histology (eg, Richter syndrome) as established by lymph node biopsy (with the date of the lymph node biopsy being considered the date of CLL/SLL progression if the patient has no earlier objective documentation of CLL/SLL progression)
- Decrease in platelet count or hemoglobin that is attributable to CLL/SLL, is not attributable to an autoimmune phenomenon, and is confirmed by bone marrow biopsy showing an infiltrate of clonal CLL/SLL cells
  - The current platelet count is <100 x 10^9/L and there has been a decrease by >50% from the highest on-study platelet count
  - The current hemoglobin is <110 g/L (11.0 g/dL) and there has been a decrease by >20 g/L (2 g/dL) from the highest on-study hemoglobin

Note: If there is uncertainty regarding whether there is true progression, the patient should continue study treatment and remain under close observation (eg, evaluated at 4-week intervals) pending confirmation of progression status. In particular, worsening of constitutional symptoms in the absence of objective evidence of worsening CLL/SLL will not be considered definitive disease progression; in such patients, both CLL/SLL-related and non-CLL/SLL-related causes for the constitutional symptoms should be considered. Worsening of disease during temporary interruption of study treatment (eg, for intercurrent illness) is not necessarily indicative of resistance to study treatment. In these instances, CT/MRI or other relevant evaluations should be considered in order to document whether definitive disease progression has occurred. If subsequent evaluations suggest that the patient has experienced persistent definitive CLL/SLL progression, then the date of progression should be the timepoint at which progression was first objectively documented.

12.5.2.6. Nonevaluable

In a patient who does not have evidence of PD, the response status of NE will be assigned when there are no images or inadequate or missing images to visualize index, non-index or splenic disease.

In addition, the following occurrence indicates a response status of NE:"Clinically significant" contemporaneous period of interruption of study drug administration or other event that in the opinion of the investigator suggests there is some uncertainty as to whether there is true progression.

Note: When there is uncertainty of true progression, the response status of NE should not be used more than one time in succession. The prior and subsequent tumor assessments must not demonstrate PD for the NE assessment to stand. If the radiographic response is PD for the subsequent evaluation, even if there was an interruption to study drug administration or uncertainty remains about true progression, PD will be assessed (not NE) in both cases. The date of PD should be the date the progression was first suspected. These cases should be discussed in advance with the Sponsor.

12.5.2.7. Lymphocytosis during Therapy

Lymphocytosis early in cirmtuzumab or ibrutinib therapy may not represent disease progression in patients who have persistent control of other CLL/SLL-related signs and symptoms [Cheson 2012]. ***In the absence of other objective evidence of disease progression, lymphocytosis alone will not preclude patients from meeting the criteria for PR if other criteria for PR are met and will not be considered evidence of PD if occurring in isolation.*** Patients with lymphocytosis should be continued on study drug until the occurrence of definitive disease progression (ie, disease progression that is manifest by worsening CLL/SLL-related signs other than lymphocytosis alone), or the occurrence of another reason to discontinue study therapy as described in Section 7.1.

12.6. Efficacy Assessment – Lymphoma

The determination of response and progression for MCL and MZL will be based on standardized criteria [Cheson 2007] as recently updated [Cheson 2014]. A summary of updated response criteria is provided in Table 6.

12.6.1. Identification and Follow-up of Tumor Lesions and Organomegaly

12.6.1.1. Index Lesions

Up to 6 lesions (eg, lymph nodes, liver or spleen nodules, and/or other circumscribed extranodal masses) should be selected as index lesions that will be used to quantitate the status of the disease during study treatment. Ideally, the index lesions should be located in disparate regions of the body and include mediastinal, abdominal, and retroperitoneal areas of disease whenever these sites are involved. For patients with FDG-avid lymphomas undergoing PET, selection of FDG-avid lesions is preferred. The IWG criteria for reviewing PET scans were based on visual interpretation and intended for end-of-treatment evaluation, using mediastinal blood pool as the comparator. The current recommendation is to use the Deauville 5-point scale, both for clinical trials including interim analysis and for end-of-treatment assessment.

Index lesions will be measured and recorded at screening and at the stipulated intervals during treatment. The largest cross-sectional dimensions (ie, the LDi × shortest dimension [SDi] will be recorded (in cm) for each index lesion. Using the LD and SDi, the product of the perpendicular diameters (PPD) for each index lesion will be calculated. The PPDs and the SPDs for all index lesions will be calculated and recorded. The screening and nadir PPDs of individual lesions and the screening and nadir SPDs will be used as references by which objective tumor response and progression will be characterized during treatment. All PPD and SPD measurements will be reported in centimeters squared.

12.6.1.2. Nodal Index Lesions

A nodal mass may be selected as a nodal index lesion if it is measurable at screening. A lymph node lesion is considered measurable if it has 2 perpendicular diameters (LDi and SDi) that can be accurately measured in cross section. A measurable node must have an LDi greater than 1.5 cm [Cheson 2014]. Nodal index lesions measuring >1.5 cm in the LD, regardless of the measurement of the LPD, will be prioritized during screening index lesion selection.

At follow-up timepoints, the PPDs for individual nodal lesions and the SPD of all nodal index lesions will be considered.

A new node that measures >1.5 cm in any diameter will be considered PD. Criteria for response assessments are detailed below and in Table 6 [Cheson 2014].

In cases in which a large lymph node mass has split into multiple components, the individual PPDs of the nodes will be summed together to represent the PPD of the split lesion; this PPD will be added to the sum of the PPDs of the remaining lesions to measure response. If subsequent growth of any or all of these discrete nodes occurs, the nadir of each individual node will be used to determine PD (as if each individual node was selected as a target lesion at baseline).

If nodal lesions merge, the PPD of the current confluent mass will be compared with the sum of the PPDs of the individual nodes, with >50% increase in the PPD of the confluent mass compared with the sum of individual nodes necessary to indicate PD.

12.6.1.3. Extranodal Index Lesions

An extranodal mass may be selected as an index lesion if it is measurable at screening. It is considered measurable at screening if it has 2 perpendicular diameters that can be accurately measured in cross section with the LD being >1.0 cm.

At follow-up timepoints, the PPD of each single extranodal index lesion and the SPD of all extranodal index lesions will be considered. Because extranodal index lesions that have one or both diameters <0.5 cm and >0 cm cannot be reliably measured, a default value of 0.5 cm will be assigned for each diameter that meets these criteria and the resulting PPD will be used in SPD calculations. If an extranodal lesion is no longer clearly visible, it will be considered resolved and its PPD will be defined as 0 cm^2.

If an extranodal lesion that had resolved (ie, had a PPD of 0 cm^2) subsequently reappears and reaches >1.0 cm in LDi, the patient will be considered to have PD. Criteria for response assessments are detailed below and in Table 6 [Cheson 2014].

12.6.1.4. Non-Index Lesions

Any other measurable and abnormal nodal or extranodal lesions not selected for quantitation as index lesions may be considered non-index lesions. In addition, non-measurable evidence of lymphoma such as abnormal, non-measurable nodal lesions, extranodal lesions with both diameters <1.0 cm, bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusions, lymphangitis of the skin or lung, abdominal masses that are not confirmed and followed by imaging techniques, cystic lesions, previously irradiated lesions, or lesions with artifacts may be considered as non-index disease.

If present at screening, up to 10 non-index lesions should be recorded. Measurements are not required.

Non-index disease will be used as a general reference to further characterize regression or progression of lymphoma during assessments of the objective tumor response during treatment. These lesions should be followed as “present” or “absent”.

12.6.1.5. Spleen

Assessments of the sizes of the spleen will be performed. For patients with splenomegaly at screening or at the nadirs for assessments of the spleen, evaluations will consider only changes relative to the enlargement of the organ (ie, the portion of the LVD that is >13 cm by imaging for the spleen) at screening or nadir, not changes relative to the total splenic LVD.

By imaging, the spleen will be considered enlarged if it is >13 cm in LVD [Cheson 2014]. In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond the LVD normal of 13 cm (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline.

12.6.1.6. Bone Marrow

Bone marrow assessments will be based on morphologic evaluation of bone marrow biopsies. Immunohistochemistry or flow cytometry may be used to assess response if the sample is indeterminate by morphology. The recommendation for bone marrow response is that histologically normal bone marrows with a small (< 2%) clonal B-cell population detected by

flow cytometry should be considered normal, given that definitive clinical studies that demonstrate an inferior outcome are lacking [Cheson 2007]. (Note: Blinded independent review may be used to determine responses.)

In a patient who has a screening bone marrow biopsy showing bone marrow lymphoma or does not have a screening bone marrow examination, declaration of an on-study CR requires bone marrow biopsy documentation of the absence of bone marrow lymphoma. In a patient who has a screening bone marrow biopsy showing no evidence of lymphoma, declaration of an on-study CR does not require bone marrow examination as long as other criteria for CR are met. Of note, in patients with an FDG-PET avid lymphoma, declaration of an on-study CR can be based on FDG-PET documentation of the absence of bone marrow involvement, even if a bone marrow biopsy is not available, or if by blinded, independent pathologic review a marrow is reported as normal or indeterminant.

12.6.1.7. Lymph Node Biopsy

During study participation, a patient who has a lymph node biopsy indicating transformation to a more aggressive lymphoma (eg, DLBCL) will be considered to have PD even in the absence of other evidence of PD. If the patient has no earlier objective documentation of PD, the date of the lymph node biopsy will be considered the date of PD.

12.6.2. Definitions of Tumor Response and Progression

Responses will be categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). In addition, a response category of nonevaluable (NE) is provided for situations in which there is inadequate information to otherwise categorize response status.

The best overall response will be determined. The best overall response is the best on-treatment response from screening recorded from the start of treatment until PD/recurrence. The screening measurement will be taken as a reference for determinations of response. The nadir measurement will be taken as a reference for PD; this measurement constitutes the smallest measurement recorded, including the screening measurement if this is the smallest measurement. For FDG-avid tumors, metabolic criteria for response by PET-CT will take precedence over anatomic criteria for response by contrast CT when assessing CR.

12.6.2.1. Complete Response

To satisfy criteria for CR, all of the following conditions must be attained:

- No evidence of new disease
- Regression of all index nodal lesions to ≤1.5 cm in the LDi
- Regression to ≤1.5 cm of all nodal non-index disease
- Disappearance of all detectable extranodal index and non-index disease
- Normal spleen size by imaging studies
- If PET performed, no evidence of residual disease – ie, score of 1 (no uptake above background), 2 (uptake ≤mediastinum), or 3 (uptake > mediastinum but ≤liver) on the Deauville 5-point scale, with or without a residual mass [Cheson 2014]. [Note: In

Waldeyer's ring or in extranodal sites (eg, gastrointestinal tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors)].

- Negative for bone marrow involvement by PET for a PET-avid tumor or by morphological assessment of a unilateral core biopsy; if the bone marrow biopsy is indeterminate by morphology, it should be negative by immunohistochemistry or flow cytometry. Due to its greater accuracy, in this study priority is given to flow cytometry analyses when available. The recommendation for bone marrow response is that histologically normal or indeterminant bone marrows with a small (< 2%) clonal B-cell population detected by flow cytometry should be considered normal, given that definitive clinical studies that demonstrate an inferior outcome are lacking [Cheson 2007].
- A complete metabolic response (CMR) based on PET-CT would be attained if a score of 1, 2, or 3 with or without a residual mass on the Deauville 5-point scale is observed in lymph node or extralymphatic sites, no new lesions, and no evidence of FDG-avid disease in marrow.

12.6.2.2. Partial Response

To satisfy criteria for PR, all of the following conditions must be attained:

- No evidence of new disease
- A ≥50% decrease from screening in the SPD of the index nodal and extranodal lesions
  - When a lesion is too small to measure on CT, assign 5 mm x 5 mm (0.25 cm2) as the default value
  - When no longer visible, 0 x 0 mm
  - For a node > 5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
- No increase from the nadir in the size of non-index disease
- In a patient with enlargement of the spleen at screening, a splenomegaly response as defined in Section 12.6.1.5
- If PET performed:
  - Typically, FDG-avid lymphoma: Score of 4 or 5 on the Deauville 5-point scale with reduced uptake compared with baseline and residual mass(es) of any size.
  - Variably FDG-avid lymphoma/FDG-avidity unknown: if no pretreatment PET scan or if the pretreatment PET scan was negative for lymphoma, CT criteria should be used in assessing the tumor during treatment. If the PET scan was positive before therapy, the on-treatment PET is positive in ≥1 previously involved site.

Bone Marrow: If PET performed, residual uptake should be higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed) [Cheson 2014].

12.6.2.3. Stable Disease

To satisfy criteria for SD, all of the following conditions must be attained:

- No evidence of new disease
- Neither sufficient tumor shrinkage from screening to qualify for PR nor sufficient evidence of tumor growth to qualify for PD
- If PET performed, the results show a score of 4 (uptake moderately >liver) or score of 5 (uptake markedly >liver) on the Deauville 5-point scale with no significant change in uptake compared with screening or end of treatment [Cheson 2014].

12.6.2.4. Progressive Disease

The occurrence of any of the following events indicates progressive disease (PD):

- Evidence of any new disease that was not present at screening:
  - A new node that measures >1.5 cm in any diameter
  - Reappearance of an extranodal lesion that had resolved (ie, had previously been assigned a PPD of 0 cm^2)
  - A new extranodal lesion >1.0 cm. If < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma.
  - New non-index disease (eg, effusions, ascites, or other organ abnormalities) of any size unequivocally attributable to lymphoma (usually requires PET, biopsy, cytology, or other non-radiologic confirmation to confirm disease attributable to lymphoma). ***Note: Isolated new effusions, ascites, or bone lesions are not sufficient evidence alone of PD unless histologically confirmed. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are usually benign. Thus, a declaration of PD should not be made if this is the only manifestation of an apparently new lesion.***
  - New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If there is uncertainty regarding the etiology of new lesions, biopsy or interval scan may be considered.
  - New or recurrent bone marrow involvement with lymphoma by PET or by bone marrow biopsy if prior PET or bone marrow biopsy performed as part of the study was negative for lymphoma.
- Evidence of worsening of nodal or extranodal index lesions:
  - Increase from the nadir by ≥50% in the SPD of index lesions
  - Evidence of worsening of individual index lymph nodes or nodal masses with an increase from the nadir by ≥50% in the PPD for any individual node if the node now has an LDi of >1.5 cm, an increase by ≥50% from the nadir PPD, and an increase in LDi or SDi from the nadir by:
    - ≥0.5 cm for lesions measuring ≤2.0 cm (in LDi or SDi) or
    - ≥1.0 cm for lesions measuring >2.0 cm (in LDi or SDi)

- Unequivocal increase in the size of non-index disease
- Unequivocal worsening in the size of the spleen as defined in Section 12.6.1.5

- Transformation to a more aggressive NHL histology as established by lymph node biopsy
- If PET performed, there is a score of 4 (uptake moderately >liver) or score of 5 (uptake markedly >liver) on the Deauville 5-point scale with an increase in uptake compared with the nadir in conjunction with an anatomic increase in lesion size consistent with PD.

Note: Study patients undergoing PET for lymphoma assessment can experience transient disease flare on imaging before having subsequent therapy-induced tumor regression. Worsening of constitutional symptoms or performance status in the absence of objective evidence of worsening lymphoma (eg, due to infection) may not represent definitive disease progression. Further, transient worsening of disease during temporary interruptions of study therapy (eg, for drug-related toxicity or inter-current illness) may not indicate definitive progressive lymphoma. If there is uncertainty regarding whether there is true lymphoma progression and if medically appropriate, the patient may continue or resume study treatment and remain under close observation (eg, evaluated at 4-week intervals) while relevant radiographic, clinical, and/or laboratory assessments are performed to document whether tumor control can be maintained or whether disease progression has truly occurred. If subsequent evaluations suggest that the patient has experienced persistent definitive disease progression, then the date of progression will be the timepoint at which progression was first objectively documented.

12.6.2.5. Nonevaluable

In a patient who does not have evidence of PD, the response status of NE will be assigned when there are no images or inadequate or missing images to visualize index, non-index, or splenic disease.

In addition, the following occurrence indicates a response status of NE: “Clinically significant” contemporaneous period of interruption of study drug administration or other event that in the opinion of the investigator suggests there is some uncertainty as to whether there is true progression.

Note: When there is uncertainty of true progression, the response status of NE should not be used more than one time in succession. The prior and subsequent tumor assessments must not demonstrate PD for the NE assessment to stand. If the radiographic response is PD for the subsequent evaluation, even if there was an interruption to study drug administration or uncertainty remains about true progression, PD will be assessed (not NE) in both cases. The date of PD should be the date the progression was first suspected. These cases should be discussed in advance with the Sponsor.

Table 6: Summary of Response Criteria for MCL and MZL Patients

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, 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	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured 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
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	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
Nonmeasured 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	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 end-of-treatment 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 (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

(continued on following page)

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	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; 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 trials 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 six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 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.

Source: Cheson 2014