UNIVERSITY OF UTAH
HUNTSMAN CANCER INSTITUTE

A Phase Ib/II Trial of Combination Camonsertib (RP-3500) and Olaparib in DNA Damage Repair Pathway Deficient Relapsed/Refractory Chronic Lymphocytic Leukemia (CORONADO CLL)

Principal Investigator	Boyu Hu, MD Huntsman Cancer Institute 2000 Circle of Hope Salt Lake City, UT 84112 Boyu.Hu@hci.utah.edu
Statistician	Kenneth M. Boucher, PhD Huntsman Cancer Institute 2000 Circle of Hope Room 1710 Kenneth.Boucher@hci.utah.edu
Sponsor	Huntsman Cancer Institute
Coordinating Center	Huntsman Cancer Institute 2000 Circle of Hope Salt Lake City, UT 84112 Compliance@hci.utah.edu
Investigational Product	Camonsertib (RP-3500)
Commercial Agent	Olaparib
Drug Manufacturer	Repare Therapeutics AstraZeneca
Drug Manufacturer Protocol ID	

IND	160108
NCT number	NCT05405309
HCI IRB number	141431
Protocol Version	Version 4: 28AUG2023

DOCUMENT HISTORY

Document	Date	Overall Rationale
Original Protocol	29APR2022	Not applicable
Amendment 1	06OCT2022	IB updates, eligibility clarifications, SAE reporting updates
Amendment 2	09MAY2023	Updated inclusion criteria to allow CrCl ≥45 mL/min, increased screening window to 42 days
Amendment 3	28AUG2023	Updated cycle length and dosing Schedule

Table of Contents

List of Figures

List of Tables

List of Appendices

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

PROTOCOL SIGNATURE

I confirm that I have read this protocol, and I will conduct the study as outlined herein and according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practice, and the applicable laws and regulations of the federal government. I will promptly submit the protocol to the IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modifications made during the study must first be approved by the IRB prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

This document is signed electronically through submission and approval by the Principal Investigator at Huntsman Cancer Institute in the University of Utah IRB Electronic Research Integrity and Compliance Administration (ERICA) system. For this reason, the Principal Investigator at Huntsman Cancer Institute will not have a hand-written signature on this signature page.

Instructions to multi-site Principal Investigators at locations other than Huntsman Cancer Institute: SIGN and DATE this signature page and PRINT your name. Return the original, completed and signed, to the HCI Research Compliance Office. Retain a copy in the regulatory binder.

_____ _____

Signature of Principal Investigator Date

_____

Principal Investigator Name (Print)

_____

Name of Institution

ABREVIATIONS

Abbreviation	Definition/Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AV	Atrioventricular
BCVA	Best-corrected distance visual acuity
BICR	Blinded Independent Central Review
β-HCG	Beta-human chorionic gonadotropin
BID	Twice daily
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CLL	Chronic lymphocytic leukemia
CL_{cr}	Creatinine clearance
C_{max}	Maximum observed concentration
C_{min}	Trough observed concentration
CMP	Comprehensive metabolic panel
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CYP	Cytochrome P450
CQ	Chloroquine

Abbreviation	Definition/Explanation
DILI	Drug-Induced Liver Injury
DoR	Duration of Response
DSMB	Data Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ECG	Electrocardiogram
Eg	Exempli Gratia (for example)
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyltransferase
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
i.e.	Id est (that is)
IEC	Independent ethics committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional review board
iwCLL	International Working Group on Chronic Lymphocytic Leukemia
LDH	Lactate dehydrogenase
MRI	Magnetic resonance imaging
NIH	National Institute of Health
PD	Pharmacodynamic(s)
PDAC	Pancreatic Ductal Adenocarcinoma
PFS	Progression-Free Survival
PK	Pharmacokinetic(s)

Abbreviation	Definition/Explanation
PO	Per os (administered by mouth)
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QTc	QT interval corrected
QTcF	QT interval corrected using Fredericia equation
RBC	Red blood cell
RP2D	Recommended Phase 2 Dose
SAE	Serious adverse event
SD	Stable disease
SD-OCT	Spectral-domain ocular coherence tomography
$T_{1/2}$	Terminal elimination half-life
TdP	Torsades de Pointes
T_{max}	Time of maximum observed concentration
ULN	The upper limit of normal
VF	Visual field
WBC	White blood cell

1 PROTOCOL SUMMARY

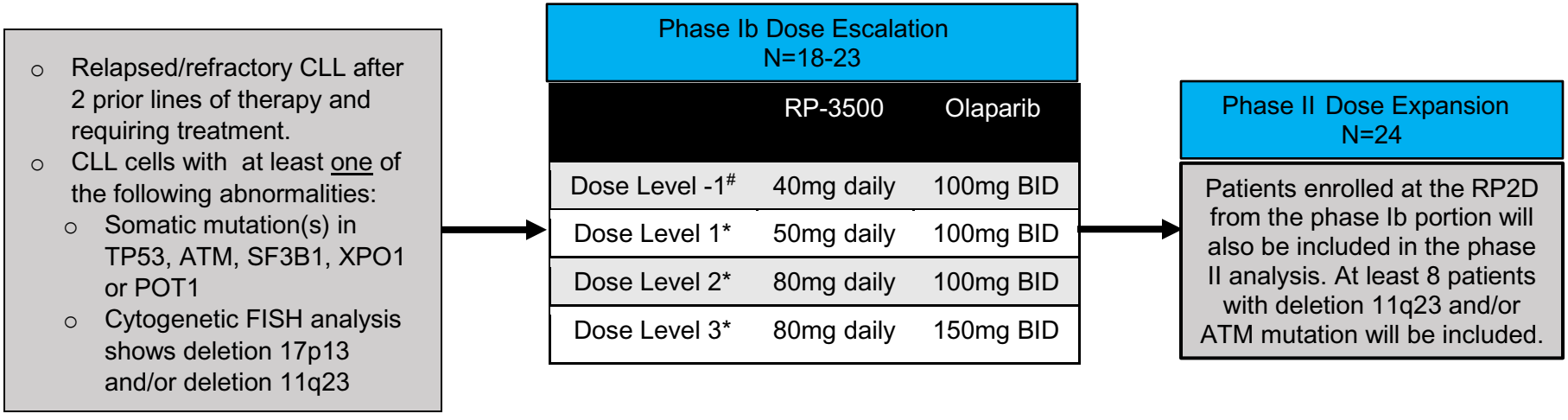
1.1 Synopsis

Title:	Phase Ib/II Trial of Combination RP-3500 and Olaparib in DNA Damage Repair Pathway Deficient Relapsed/Refractory Chronic Lymphocytic Leukemia (CORONADO CLL)
Protocol Short Title	CORONADO CLL
Study Description:	Open label, multi-center clinical trial to determine the safety and efficacy of combination camonsertib (RP-3500) and olaparib in DNA damage repair pathway deficient relapsed/refractory chronic lymphocytic leukemia.
Phase:	Ib/II
Objectives:	Primary Objective: • Phase Ib: To assess the maximum tolerated dose (MTD) and determine the recommended phase 2 dose (RP2D) of combination RP-3500 and olaparib in subjects with relapsed/refractory chronic lymphocytic leukemia with DNA damage repair deficiencies. • Phase II: To assess the overall response rate (ORR) of combination RP-3500 and olaparib in subjects with relapsed/refractory chronic lymphocytic leukemia with DNA damage repair deficiencies. Secondary Objectives: • To assess the safety and tolerability of RP-3500 and olaparib in the study population. • To assess progression-free survival (PFS) in the study population • To assess overall survival (OS) in the study population • To assess the duration of response (DoR) of the study population
Endpoints:	Primary Endpoint: • Phase Ib: The rate of dose-limiting toxicities (DLTs) during the DLT evaluation period. • Phase II: Overall response rate (ORR) will be defined by the proportion of subjects achieving any confirmed partial (PR)

	and complete remission (CR) as assessed by 2018 International Working Group on Chronic Lymphocytic Leukemia (iwCLL) response criteria.
	Secondary Endpoints: • The frequency of adverse events and serious adverse events characterized by type, severity (as defined by NIH CTCAE v5.0), seriousness, duration, and relationship to study treatment. • PFS as defined as the time from study drug initiation to the time documented disease progression (as assessed by 2018 iwCLL criteria) or death from any cause. • OS as defined as the time from registration until death from any cause. • DoR as defined as the interval of time from the date of initial documented response (PR or better as per 2018 iwCLL criteria for response) to the time of progression from the best response, the start of a new therapy, or death from any cause.
Study Population:	Key Inclusion Criteria: 1. Diagnosis of CLL according to the NCI/IWCLL criteria. 2. Repeat testing of somatic mutations and FISH analysis must be performed after progression is noted from most recent line of therapy and within 6 months of screening. Primary CLL cells must harbor at least <u>one</u> of these abnormalities: • Somatic gene mutation testing shows mutation(s) in TP53, ATM, SF3B1, XPO1 and/or POT1, • Cytogenetic FISH analysis shows deletion 17p13 and/or deletion 11q22.3, 3. Relapsed or refractory after at least 2 prior lines of therapy, and in the opinion of the treating Investigator are either not eligible for other approved therapies or no approved therapies are expected to have sustained therapeutic benefit. 4. Patients in need of treatment as per iwCLL criteria. • Patients on BTK, PI3K or BCL2 inhibitors may enroll without meeting iwCLL criteria for treatment as long as there is clinical evidence of progression (i.e. increasing lymphocytosis, worsening anemia/thrombocytopenia attributable to CLL disease progression, increasing lymphadenopathy, or worsening patient symptoms) and require change in treatment at the discretion of the treating provider. 5. Absolute neutrophil count ≥1000/μL and platelet count ≥50K/μL (unless documented CLL bone marrow involvement). 6. ECOG performance status between 0-2 7. Patients must be able to receive xanthine oxidase inhibitor and/or rasburicase for tumor lysis syndrome prophylaxis.

	Key Exclusion Criteria: 1. Patients who are currently receiving any other investigational drug. 2. Prior ATR inhibitor use, but prior PARP inhibitor use for any reason is allowed on study. 3. Evidence of active Richter's Transformation 4. Disease states requiring steroids (e.g. adrenal insufficiency, autoimmune conditions) are allowed as long as the steroid dose is ≤10mg of prednisone or equivalent dose of another steroid. Steroids premedications to prevent iodine contrast allergy for CT scans are allowed. 5. Patients who have undergone autologous stem cell transplant ≤4 weeks or allogeneic stem cell transplant ≤12 weeks prior to cycle 1 day 1 or have active graft-versus-host disease are excluded. 6. Patients with active known central nervous system (CNS) involvement of CLL. Patients with a history of CNS CLL now in remission are eligible for the trial. 7. Patients with conditions significantly affect gastrointestinal function.
Study Intervention:	Camonsertib (RP-3500) PO Olaparib PO
Study Duration:	36 months
Participant Duration:	13 months

1.2 Schema



*Both drugs are given with intermittent dosing of 2 days per week.

1.3 Schedule of Events

Protocol Activities	Screening [1]	On-Treatment Period: One Cycle = 2 1 days									Post Treatment Period	
		Cycle 1					Cycle 2		Cycle s 3 & 4	Cycle 5-18	EOT[2]	Follow - Up[3]
Day of Cycle (Visit Window)		1	2	3	8 (± 1 day)	15 (±1 day)	1 (± 2 days)	8 (± 2 days)	1 (± 3 days)	1 (± 7 days)	(+28 days)	(+14 days)
Informed Consent	X											
Demographics	X											
Medical History[4]	X	X										
Cancer History[5]	X											
Eligibility Criteria	X											
Registration[6]	X											
Clinical Assessments												
Vital Signs[7]	X	X			X	X	X	X	X	X	X	X
Height/ Weight	X	X					X		X	X	X	X
Physical Exam	X	X			X	X	X	X	X	X	X	X
ECOG Performance Status	X	X			X	X	X	X	X	X	X	X
ECG[8]	X	X		X								
Adverse event collection		Continuous										
Concomitant medications	X	Continuous										
Laboratory Studies												
Hematology[9]	X	X			X	X	X	X	X	X	X	X
Chemistry[10]	X	X	X	X	X	X	X	X	X	X	X	X
TLS Labs[11]	X	X	X	X	X	X	X					
24 Hour Urine[12]	(X)											
Pregnancy Test[13]	X											
HIV and Hepatitis Serologies[14]	X											

Protocol Activities	Screening [1]	On-Treatment Period: One Cycle = 2 1 days									Post Treatment Period	
		Cycle 1					Cycle 2		Cycles 3 & 4	Cycle 5-18	EOT[2]	Follow - Up[3]
Day of Cycle (Visit Window)		1	2	3	8 (± 1 day)	15 (±1 day)	1 (± 2 days)	8 (± 2 days)	1 (± 3 days)	1 (± 7 days)	(+28 days)	(+14 days)
IGHV Mutational Status[15]	X											
CLL FISH Analysis[16]	X											
Somatic mutation testing[17]	X											
PB CLL MRD by Flow Cytometry[18]										X[18]	X	
BMA CLL MRD by Flow Cytometry[19]		X[19]									X[19]	
Disease Assessments												
CT Scans	X									X[20]	X	
Peripheral blood immunophenotyping	X									ACI[21]	X	
Bone marrow biopsy and aspirate	X[22]									(X)[23,24]	X[24]	
Correlative Studies												
Measurement of DNA damage and apoptosis[25]		X			X	X	X	X		X	X	
Pharmacokinetics[26]		X	X		X	X				X[26]		
PB CLL MRD by NGS[27,28]	(X)									X	X	
BM CLL MRD by NGS[28]	(X)	X									X	
Treatment Compliance												
Dispense olaparib		X					X		X	X		
Dispense camonsertib (RP-3500)		X					X		X	X		
Xanthine Oxidase Inhibitor		X[29]										
Dosing diary		X					X		X	X		

[1] Screening procedures must be completed ≤ 42 days prior to C1D1 unless noted otherwise.

[2] The end of treatment visit should occur when the patient discontinues treatment *for any reason*. This may be due but not limited to unacceptable toxicity from the combination therapy, patient/treating physician preference, progressive disease or completion of 18 cycles of combination therapy (whichever comes first). If this visit overlaps with a regularly scheduled visit, only the procedures listed in the calendar for the EOT visit will be performed. All end of treatment procedures should be completed ≤ 28 days after discontinuation of treatment.

[3] A follow-up visit will occur 28 (+14) days post the last dose of study treatment. The focused history and physical should discuss residual/lingering adverse events experienced by the subject during treatment.. The visit can be performed remotely should the Investigator or subject desire. For remote visits, vital signs, height/weight, and laboratory examinations are not required.

[4] Initial medical history at time of screening should include: baseline symptoms; a detailed history of prior cancer therapies including start and stop dates, disease progression during or after therapy, as well as discontinuations due to intolerability or any other serious illness; family and social history;.

[5] History of the patient's CLL course will be collected at the screening visit with special attention to prior treatment regimens (duration of therapy, best response on therapy, date of discontinuation, toxicities encountered on treatment and reason for discontinuation) and sequence.

[6] To register eligible subjects on study, complete a Clinical Trials Office Subject Registration Form and submit to CTORegistrations@hci.utah.edu.

[7] Vital signs include systolic/diastolic blood pressure, heart rate, respiration rate, pulse oximetry, and body temperature.

[8] ECGs will be performed in triplicate at each time-point; ECG recordings should be completed approximately one minute apart. Patient must rest in supine position for at least 5 minutes prior to ECG recording. ECGs should be recorded prior to any blood draw required at the same time-point.

[9] Hematology includes CBC with differential and platelets.

[10] Chemistry includes a Complete Metabolic Panel (Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin, Calcium, Carbon Dioxide, Creatinine, Chloride, Glucose, Total Potassium, Protein, Sodium, and Urea Nitrogen).

[11] Tumor lysis syndrome (TLS) labs: lactate dehydrogenase, phosphorus, and uric acid

[12] Optional and can be performed to calculate creatinine clearance instead of the estimated creatinine clearance through Cockroft-Gault equation.

[13] Pregnancy test (serum or urine) must be obtained at screening ≤ 3 days prior to C1D1 for all women of childbearing potential and as clinically indicated while on treatment.

[14] Must be conducted within 6 months of registration.

[15] If the subject has had successful testing in the past, this will be accepted and repeat *IGHV* mutational status will not be required.

[16] Should be performed after progression is noted from most recent line of therapy and within 6 months of screening and should include deletion 13q14, trisomy 12, deletion 11q22.3, deletion 17p13.

[17] Should be performed after progression is noted from most recent line of therapy and within 6 months of screening. At a minimum, the following somatic mutations must be tested: *TP53, ATM, SF3B1, POT1* and *XPO1*. While not required, the following genes are strongly encouraged to be tested as well: *NOTCH1, BIRC3, BRAF, KRAS, DDX3X, MYD88 and CXCR4.*

[18] CLL MRD testing by flow cytometry should be performed on peripheral blood on C5D1, C9D1 and EOT.

[19] BM MRD testing by flow cytometry through a local lab should be performed on any BM aspirate obtained after screening. An additional aspirate sample should be collected and processed for correlative studies.

[20] At C5D1 (±7 days): CT scans of the neck, chest, abdomen and pelvis should be performed with contrast agents unless contraindicated for medical reasons. Should this CT show that the patient has achieved an iwCLL 2018 defined complete remission and absolute lymphocyte count is <4000, then a bone marrow biopsy should be performed at this time to confirm the complete remission. At any other study time point beyond C5D1 (excluding end of treatment): If patient achieves hematologic recovery or the treating physician suspects the patient has achieved a complete remission per the 2018 iwCLL criteria, then a peripheral blood immunophenotype should be ordered. Should this show no evidence of circulating CLL cells, then a complete remission can be confirmed with CTs of the neck, chest, abdomen and pelvis along with a bone marrow biopsy. If CTs and bone marrow biopsy are indicated, studies need to be performed within 28 days.

[21] If subject achieves hematologic recovery or the treating physician suspects the patient has achieved a complete remission as per the 2018 iwCLL criteria, then a peripheral blood immunophenotype should be ordered. Please refer to reference **20** for sequencing of testing to confirm a complete remission.

[22] The bone marrow biopsy performed at screening should be after progression is noted from most recent line of therapy and within 6 months of screening. If a bone marrow biopsy is not performed at screening, an archival tissue maybe requested at the discretion of the PI. BM CLL MRD by NGS should be performed on any BM aspirate obtained after screening.

[23] Should peripheral blood immunophenotying show no evidence of circulating CLL cells, then a complete remission can be confirmed with CTs of the neck, chest, abdomen and pelvis and a bone marrow biopsy. Please refer to reference **20** for sequencing of testing to confirm a complete remission.

[24] BMBx at screening and EOT are the only ones required on study. If a prior bone marrow biopsy showed the patient to be in a complete remission, a repeat bone marrow biopsy is not required unless progression of disease is suspected.

[25] Samples should be collected prior to dosing of the drugs. Samples should be collected on C1D1, C1D8, C1D15, C2D1, C2D8 and at time of progression.

[26] Refer to section **1.5.1** for time points

[27] PB CLL MRD by NGS should be performed on peripheral blood on C5D1, C9D1 and EOT as tracking samples..

[28] The treating physician may choose to collect the identification sample for MRD by NGS on either the PB or BM at screening depending on which compartment has CLL cells present. Thus, two samples (one from PB and one from BM) for MRD by NGS at screening are not required.

[29] Xanthine oxidase inhibitor agent must be given at least 72 hours prior to C1D1 and during the first cycle of study therapy.

1.4 Long Term Follow -Up

Activities [1]	Year 1	Year 2-5[2]	Year 6-10[2]
Office visit for history and physical[3]	Every 3 months (±14 days)	Every 3-6 months (±14 days)	Every 3-12 months (±28 days)
Labs[4]	Every 3 months (±14 days)	Every 3-6 months (±14 days)	Every 3-12 months (±28 days)

[1] Long term follow-up is calculated from the last date that the patient took any study drug.
[2] Follow up length in years 2-10 is at the discretion of the treating physician.
[3] An abbreviated history and physical can be performed, but should include signs or symptoms of CLL relapse or disease progression. This includes B-symptoms (fevers, drenching night sweats, unintentional weight loss), new palpable lymphadenopathy and/or hepatosplenomegaly, new or progressive symptoms from the patient's last visit.
[4] Hematology includes CBC with differential and platelets. Chemistry includes a Complete Metabolic Panel (Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin, Calcium, Carbon Dioxide, Creatinine, Chloride, Glucose, Total Potassium, Protein, Sodium, and Urea Nitrogen).

1.5 Correlative Study Calendar

1.5.1 Pharmacokinetic

Cycle 1	Day 1						Day 3	Day 8 (±1 day)					Day 15 (±1 day)					
Time of Collection (hours after drug dosing)	Pre	0.5	1	2	4	24	Pre	Pre	0.5	1	2	4	Pre	0.5	1	2	4	24
Time Window for Collection (min)		±5	±10	±15	±15	±120			±5	±10	±15	±15		±5	±10	±15	±15	±120
PK Blood Draw	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
ECG[1]				X			X											

Cycle 5	Day 1			
Time of Collection (hours after drug dosing)	Pre	0.5	1	2
Time Window for Collection (min)		±5	±10	±15
PK Blood Draw	X	X	X	X

[1] ECGs will be performed in triplicate at each time-point; ECG recordings should be completed approximately one minute apart. Patient must rest in supine position for at least 5 minutes prior to ECG recording. ECGs should be recorded prior to any blood draw required at the same time-point.

2 OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

2.1.1 Phase Ib: To assess the maximum tolerated dose (MTD) and determine the recommended phase 2 dose (RP2D) of combination RP-3500 and olaparib in subjects with relapsed/refractory chronic lymphocytic leukemia with DNA damage repair deficiencies.

Primary endpoint: The rate of dose-limiting toxicities (DLTs) during the DLT evaluation period.

2.1.2 Phase II: To assess the overall response rate (ORR) of combination RP-3500 and olaparib in subjects with relapsed/refractory chronic lymphocytic leukemia with DNA damage repair deficiencies.

Primary endpoint: Overall response rate (ORR) will be defined by the proportion of subjects achieving any confirmed partial (PR) and complete response (CR) as assessed by 2018 International Working Group on Chronic Lymphocytic Leukemia (iwCLL) response criteria.

2.2 Secondary Objectives

2.2.1 To assess the safety and tolerability of RP-3500 and olaparib in the study population.

Secondary Endpoint: The frequency of adverse events (AEs) and serious adverse events (SAEs) characterized by type, severity (as defined by the NIH CTCAE, version 5.0), seriousness, duration, and relationship to study treatment.

2.2.2 To assess progression-free survival (PFS)

Secondary Endpoint: Progression-free survival (PFS) as defined as the time from study drug initiation to the time documented disease progression (as assessed by 2018 iwCLL criteria) or death from any cause.

2.2.3 To assess overall survival (OS) in this study population

Secondary Endpoint: OS as defined as the time from registration until death from any cause.

2.2.4 To assess the duration of response (DoR) of the study population.

Secondary Endpoint: DoR as defined as the interval of time from the date of initial documented response (PR or better as per 2018 iwCLL criteria for response) to the time of progression from the best response, the start of a new therapy, or death from any cause.

2.3 Exploratory Objecti ves

2.3.1 To evaluate protein expression levels of γH2AX, annexin V, cleaved PARP1 and cleaved caspase 3 during treatment with combination RP-3500 and olaparib as markers of DNA damage and apoptosis.

Exploratory Endpoint #1: Correlation of protein expression levels to best overall response and minimal residual disease status.

Exploratory Endpoint #2: Trend of protein expression levels at the beginning of therapy as compared to at the time of suspected relapse.

2.3.2 To assess the effects of combination of RP-3500 and olaparib on minimal residual disease status.

Exploratory Endpoint: Proportion of patients achieving undetectable minimal residual disease as assessed by either flow cytometry and/or next generation sequencing methods.

2.3.3 To determine the pharmacokinetic properties of combination RP-3500 and olaparib in relapsed/refractory chronic lymphocytic leukemia.

Exploratory Endpoint: Peripheral blood RP-3500 and olaparib concentrations when each are given at varying doses.

2.3.4 To correlate ORR, PFS and OS to DNA damage repair gene alterations

Exploratory Endpoint: ORR, PFS and OS according to each DNA damage repair gene alterations for which the patient was enrolled.

3 BACKGROUND AND RATIONALE

3.1 Chronic Lymphocytic L eukemia

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia with approximately 21,000 new cases per year[1]. The disease is still generally considered incurable with an estimated 3930 deaths in the United States for the year 2019[1]. Recent advances in the characterization of the biological drivers of the disease have shifted CLL treatments from chemo-immunotherapy to targeted and specific small molecule inhibitors (i.e. ibrutinib and venetoclax). While these targeted therapies are effective at controlling relapsed/refractory (R/R) disease, progression and relapse are inevitable with many of these patients eventually dying[2,3]. Therefore, new treatment strategies are desperately needed. Over the years, genomic and chromosomal profiling of these R/R CLL patients have shown a predominance of somatic mutations and/or cytogenetic abnormalities within the DNA damage repair (DDR) pathways[4,5]. While these intrinsic deficiencies in the CLL's DDR system offer the disease a survival advantage, they can also be exploited for therapeutic benefit.

3.2 Poorly Prognostic Genetic Aberrations in R/R CLL

CLL is a clinically heterogeneous disease with highly variable outcomes. Somatic gene mutations and chromosomal abnormalities have been identified as underlying risk factors for resistance to therapy and shortened survival in CLL patients[1-3]. Specifically, the CLL genetic landscape is represented by a high prevalence of mutations affecting DDR genes, including TP53, ATM, SF3B1, XPO1 and POT1 (Table 1. Prevalence of DNA damage repair gene mutations and cytogenetic abnormalities in R/R CLL.)[1-4], which conveys resistance to both upfront and salvage treatments and portends worse survival outcomes[1-3,5-8]. Compared to newly diagnosed patients, these high-risk genetic defects are enriched in R/R patients, and result in poor progression-free survival (PFS) and overall survival (OS) of 6-9 and 20-30 months, respectively, when treated with chemotherapy or lenalidomide-based therapies[1-4]. Furthermore, chromosomal abnormalities have been frequently shown to co-occur with some of these gene mutations such as deletion 17p13 [del(17p)] with TP53 mutation and deletion 11q22.3 [del(11q)] with ATM and SF3B1 mutations[1,3,4,6]. These concurrent chromosomal and genetic alterations help to explain the poor prognoses and almost absent responses to chemotherapy in CLL patients harboring these cytogenetic abnormalities[9,10]. Due to the poor clinical outcomes in R/R CLL patients with DDR deficient gene mutations and cytogenetic aberrations, these patients remain an area of unmet need.

Table 1. Prevalence of DNA damage repair gene mutations and cytogenetic abnormalities in R/R CLL.

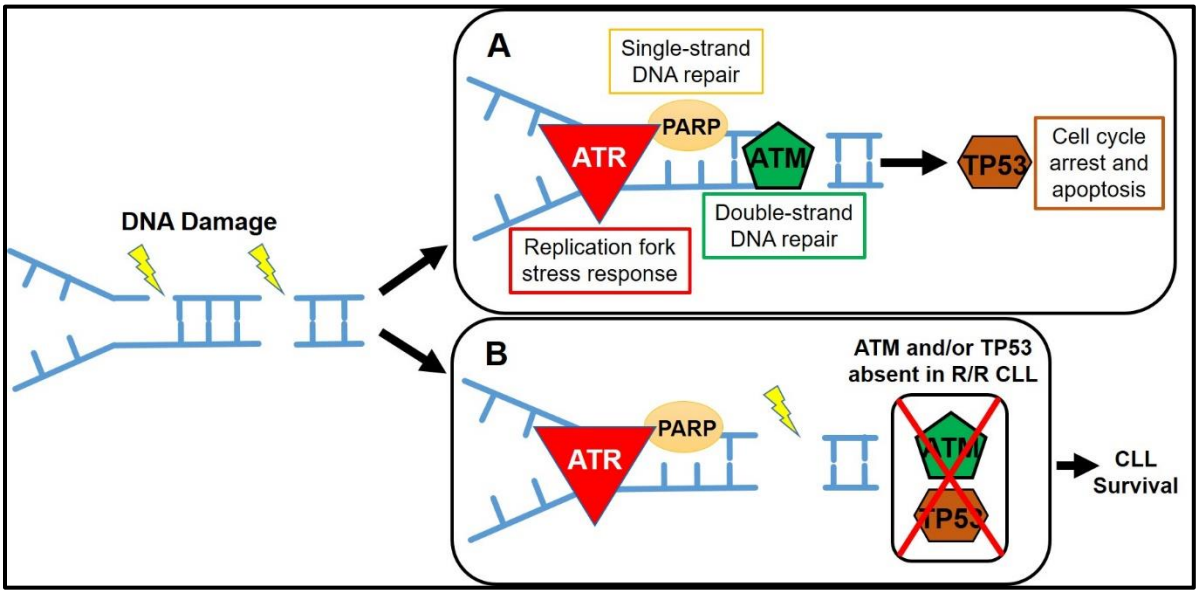
Gene Mutation	Prevalence
TP53	15-25%
ATM	10-15%
SF3B1	10-15%
XPO1	~5%
POT1	~5%
Cytogenetic Abnormality	**Prevalence**
Deletion 17p13	15-25%
Deletion 11q22.3	10-20%
Total	50-70%*

* Patients may harbor mutational and cytogenetic co-occurrences such as del(17p) with TP53 mutation, del(11q) with ATM and SF3B1 mutations, which is why the predicted total prevalence of these abnormalities is 50-70%

3.2.1 DDR and Cell Cycle Checkpoint Mechanisms in Non-Malignant Cells

Ataxia telangiectasia and Rad3 related (ATR) protein is an essential kinase for cell viability. DNA damage at the replication fork is recognized by ATR to ensure mitotic arrest, allowing sufficient repair of the damage prior to re-initiation of replication[11]. Single-strand DNA breakage (SSB) repair is led by poly (ADP-ribose) polymerase (PARP) while double-strand DNA breakage (DSB) repair is directed by ATM[12-14]. Crosstalk between DDR and cell cycle checkpoint proteins is mediated by TP53 to halt cellular division and if needed, to trigger apoptosis (Figure 1. DNA damage triggers recruitment of DNA damage repair proteins.)[14]. While non-malignant cells utilize all of these mechanisms for DDR and cell cycle checkpoints, R/R CLL patients with DDR deficiencies are dependent on ATR and PARP for DDR, genomic stability and cell survival (Figure 1. DNA damage triggers recruitment of DNA damage repair proteins.).

Figure 1. DNA damage triggers recruitment of DNA damage repair proteins.
A) ATR regulates replication fork initiation to maintain genomic integrity. PARP is required for single-strand DNA damage repair whereas ATM is required for double-strand repair. If excessive DNA damage is present, TP53 is activated to initiate cell cycle arrest and apoptosis. B) Since relapsed/refractory CLL patients are deficient in either ATM and/or TP53, genomic integrity and DNA damage repair are solely dependent on ATR and PARP.



3.3 Rationale for Combined Inhibition of ATR and PARP

Treatment of cell and murine models of TP53- or ATM-deficient CLL with an ATR inhibitor (ATRi) or a PARP inhibitor (PARPi) have shown significant single-agent activity. The use of the PARPi, olaparib, increased DNA damage and mitotic catastrophe in ATM-deficient CLL cell lines, which led to decreased proliferation and increased cytotoxicity as compared to ATM-proficient cells[15]. Notably, the drug had almost no activity in the ATM-wildtype control cell lines and showed no noticeable escalation of DNA damage. Similarly in mice, ATM-deficient CLL mice treated with olaparib had a statistically significant decrease in circulating CLL cells and in spleen volume as well as prolonged survival when compared to the control mice[16]. In contrast, the ATM-proficient control mice showed no difference in the measured parameters when treated with either vehicle or olaparib, suggesting that ATM-deficient CLL is dependent on PARP for survival. Similarly, the use of the ATRi, AZD6738, showed significant responses in ATM- and TP53-mutated CLL cell lines as compared with wildtype ATM and TP53 CLL cells and healthy donor lymphocytes[17]. However, a small phase I clinical trial using olaparib single agent for the treatment of 9 CLL patients showed a modest benefit for ATM-deficient patients with a non-statistically significant improvement in overall survival by 103 days as compared to wildtype patients[18]. This study highlights the challenges of PARPi treatment due to the high prevalence of acquired or innate resistance to single-agent PARPi. Preclinical data in solid tumors have shown these resistance mechanisms to include reversion of DDR mutations to wildtype, promoter demethylation of suppressed DDR genes, mitigation of replication stress and mutations in PARP[19,20].

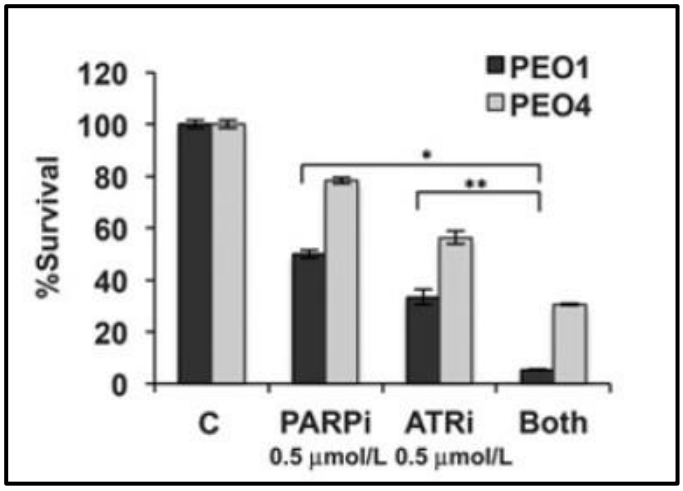


Figure 2. PEO1 and PEO4 are both BRCA2 mutated ovarian cancer cell lines.
Treatment with combination PARPi and ATRi showed synergy as compared to single agent therapy.

In order to overcome PARP resistance, the addition of ATRi to a PARPi has shown both preclinical efficacy and synergy. In breast and ovarian cancer patients with germline deficiencies of DSB repair proteins, such as BRCA1/BRCA2, treatment with PARPi is highly efficacious and improves survival in these diseases as compared to conventional chemotherapy[21-23]. These pivotal clinical trials in breast and ovarian cancer patients have proven the concept of synthetic lethality in which the loss of function of one component of cell survival (i.e. BRCA1/BRCA2) does not have significant impact on cancer fitness, but the combined deficit of two vital and inter-dependent elements (i.e. PARP and BRCA1/BRCA2) leads to tumor death[24]. Combination strategies to incite improved synthetic lethality have been explored in BRCA1/BRCA2 mutated ovarian cell lines in which the combination of ATRi and olaparib was synergistic in producing increased apoptosis and cell death (Figure 2. PEO1 and PEO4 are both BRCA2 mutated ovarian cancer cell lines.)[25]. Furthermore, PARPi resistant BRCA-deficient cell lines show an increased reliance on ATR signaling fork stabilization and PARP sensitivity can be restored by using a combination ATRi and PARPi strategy[26]. Therefore, we hypothesize that the rational combination of an ATRi in combination with a PARPi would be highly efficacious and potentially synergistic in high-risk CLL patients carrying somatic mutations in TP53, ATM, SF3B1, XPO1 and POT1 or cytogenetic abnormalities such as del(17p) and del(11q).

3.4 Other CLL Somatic Mutations Affecting the DDR System

While the use of PARPi in CLL patients with mutations in TP53 and ATM is apparent, its use in SF3B1, XPO1 and POT1 mutated patients are also scientifically rational. SF3B1 is a part of the mRNA spliceosome and has been shown to co-occur with both del(11q) and ATM mutations[4,6,27,28]. Its effects on the DDR system is due to decreased synthesis of various DDR proteins in a manner that is independent of ATM downregulation, leading to increased DNA breakage and decreased apoptosis[28]. Therefore, SF3B1 co-occurrence with del(11q)/ATM gene mutation leads to genomic instability by increasing DNA damage and decreasing DDR. In a similarly indirect manner, XPO1 transports tumor suppressor proteins out of the nucleus in the absence of DNA damage, but its recurrent hotspot mutation at E571 most likely enhances its binding to DDR proteins and inappropriately sequesters them in the cytoplasm, rendering them ineffective[4,29,30]. This leads to increased DNA stress and damage with decreased capacity for DDR[29]. Lastly, POT1 is a critical protein for maintaining DNA telomere stability and POT1 loss-of-function mutations lead to reduced telomere capping, fusion and lengthening, which then decreases DNA integrity and increases genomic instability[31,32]. While mutations in additional DDR

genes have been implicated in CLL, the ones specifically chosen here have a clinically significant frequency of at least 5% in R/R CLL patients[4].

3.5 Current Treatment Landscape in CLL and Remaining Unmet Needs

Recent approvals of targeted therapies such as Bruton's Tyrosine Kinase inhibitors (BTKi) and venetoclax for both the frontline and salvage treatments of CLL have dramatically changed the treatment paradigms for the disease[33-36]. Specifically, these drugs have become standard for high-risk patients with del(17p) and TP53 mutation as prior studies have shown that treatment of these patients with chemotherapy leads to almost absent responses and poor survival outcomes[1-3]. Recent real world data collected between 2015-2019 showed that ~45% of previously untreated and ~60% of R/R of CLL patients were treated with targeted therapies[37]. The majority of this data was abstracted before the FDA approvals of frontline venetoclax in May/2019 and acalabrutinib in November/2019 for the treatment of CLL patients. Therefore, present day use of targeted agents for the frontline treatment of CLL patients far exceeds the prior reported 45%. Furthermore, multiple clinical trials have investigated the efficacy of combination ibrutinib and venetoclax in the frontline (NCT02910583, NCT03701282, NCT03737981) and R/R settings[38]. Therefore, R/R CLL patients with DDR pathway deficiencies who have failed both BTKi and venetoclax have no known effective treatments.

3.5.1 Safety Profile of BTKi and Venetoclax Limit Their Use in Patients with Comorbidities

Toxicities associated with BTKi and venetoclax treatment limit its use. In a 5-year follow up of ibrutinib-treated patients showed only 55% of treatment-naïve patients remained on drug due to progression, intolerable side effects or patient preference while 72% of R/R patients had discontinued[5]. In the MURANO trial investigating rituximab/venetoclax for R/R CLL patients, 33% of patients discontinued treatment prior to finishing the 2-years of therapy with 15% of patients coming off study due to adverse events[34,36]. While overall response rates are high with ibrutinib, complete responses (CR) in R/R CLL patients are only 10%[5]. Since CLL is a disease of the elderly with a median age at diagnosis of 70 years old, many patients with CLL have concurrent comorbidities. For example, patients with chronic kidney disease and high CLL tumor burden are at increased risk for tumor lysis syndrome when treated with venetoclax therapy, making venetoclax difficult to administer safely[39]. BTKi have high rates of cardiac toxicities and bleeding[5,40,41]. The use of BTKi in CLL patients with cardiac comorbidities or who require anticoagulation or anti-platelet therapies can be difficult and result in sudden cardiac death or major bleeding[42]. Therefore, alternative effective therapies are required for these patients, especially if they concurrently harbor high-risk CLL genetic aberrations.

3.5.2 Inclusion of High-Risk CLL Patients With No Known Effective or Safe Treatments

Altogether, the high-risk CLL patient who has discontinued chemotherapy, BTKi and/or venetoclax due to either disease progression or intolerable side effects will remain a challenge to treat in the future as there are currently no effective therapies.

Combination RP-3500 and olaparib treatment can fulfill these unmet needs within the R/R CLL treatment landscape: 1) currently approved targeted therapies for CLL treatment are heavily being used in upfront treatment as most clinicians are no longer treating with chemo-immunotherapy. Multiple current and former clinical trials are investigating combination BTKi and venetoclax in

frontline and R/R settings, thus exhausting these treatments earlier in the CLL patient's disease course. 2) BTKi are not as effective in treating CLL patients with high-risk cytogenetic abnormalities such as del(17p) and del(11q). BTKi treatments rarely induce CRs and uMRD status and therefore, need to be given life-long, which adds to both patient cost and dissatisfaction. 3) Venetoclax-based treatments are also less effective for CLL patients with high-risk cytogenetic abnormalities. While venetoclax-based treatments are for a fixed duration, efficacy of venetoclax re-challenge due to progressive disease after treatment discontinuation is unknown, which is especially relevant when venetoclax is being increasingly used in the frontline setting. 4) Toxicities associated with BTKi and venetoclax leading to treatment discontinuation can be high especially in an elderly CLL patient population with comorbidities, making either class of drugs not safe to use. Due to these unmet needs in the CLL treatment paradigm, combination RP-3500 and olaparib treatment can be a highly effective, fixed-duration treatment for R/R CLL patients with high-risk genetic aberrations related to DNA damage repair (i.e. del(17p), del(11q); gene mutations in TP53, ATM, SF3B1, XPO1 and POT1).

3.6 Olaparib

Olaparib is an oral PARPi that inhibits PARP's function by competitively binding to the NAD+ binding site, which PARP requires as a cofactor to operate. This leads to decreased recruitment of PARP's downstream substrates and also traps PARP onto the DNA so that other components of the SSB complex cannot bind to the damaged site[43]. Olaparib has multiple FDA approved indications in DDR-deficient solid tumors including ovarian, breast, pancreatic and prostate cancers[21,44-49]. Compared to other PARPi, olaparib has moderate potency, leading to a more favorable cytopenia-related toxicity profile with grades 3-4 anemia, neutropenia and thrombocytopenia occurring in 7-20%, 3-11%, and 1-4% of patients treated with continuous 300mg or 400mg BID dosing, respectively[21,44-49].

3.7 RP-3500

RP-3500 is a highly potent and selective ATRi and has demonstrated significant preclinical activity. Pharmacokinetic (PK) and pharmacodynamic marker analysis from tumor xenografts demonstrates target engagement and a dose-responsive increase in double-strand DNA breaks leading to tumor cell death in vivo. RP-3500 is a potent ATR kinase inhibitor with a Ki of 0.022 nM determined in a biochemical ATR assay using p53 as a substrate. RP-3500 induced cell death in the low nM range in a panel of cancer cell lines with ATM or BRCA1/2 pathway defects in 5-day cell-based cytotoxicity assays (Table 2. Single-Agent Activity of RP-3500 in ATM and BRCA1/2 Pathway Deficient Human Cancer Cell Lines).

Table 2. Single-Agent Activity of RP-3500 in ATM and BRCA1/2 Pathway Deficient Human Cancer Cell Lines

Cell Line	Cancer Type	Genetic Aberration	IC_{50} (nM)[a]
Lovo	Colon adenocarcinoma	MRE11 (Del exon 5)	29±10
NCI-H23	Non-small cell lung adenocarcinoma	ATM (Q1919P)	13±4
CW-2	Colon adenocarcinoma	ATM (A2843V)	17±5
Capan-1	Pancreatic adenocarcinoma	BRCA2 (6174delT)/-	57±4
SUM-149-PT	Triple-negative breast cancer	BRCA1 (2288delT)/-	7±3

Granta-519	Mantle cell lymphoma	ATM (R2832C)	8.3±2

a. IC_{50} values are the mean ± standard deviation of n≥3 independent experiments.

RP-3500 is also highly selective for ATR and does not compete an ATP binding pocket probe on >300 kinases probed in a cell lysate binding assay at 300 nM. Kinases that bind to RP-3500 at higher concentrations represent members of the closely related PIKK family. In biochemical assays measuring inhibitory activity of the related PIKK family of kinases, RP-3500 exhibits at least a 120-fold selectivity over mTOR, ATM, DNA-PK, and PI3Ka. Furthermore, RP-3500 is >31-fold selective for ATR kinase over mTOR and >2000-fold over ATM, DNA-PK, and PI3Ka in cell-based kinase assays.

3.7.1 Intermittent Dosing Rationale

Significant preclinical activity of RP-3500 was demonstrated in Granta-519 mantle cell lymphoma xenograft model in which intermittent dosing schedule of the drug at 30 mg/kg QD 3 days per week showed the best efficacy and least toxicity (Figure 3).

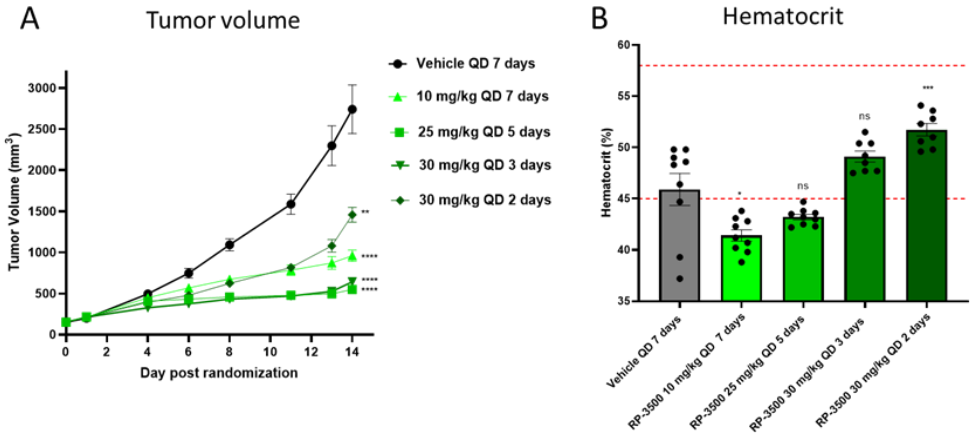


Figure 3. Preclinical activity of RP-3500 in Granta-519 mantle cell lymphoma xenograft model

A) Tumor xenograft volume and (B) Hematocrit from female NOD-SCID mice bearing Granta-519 tumors treated PO with RP-3500 at MTD on different weekly dosing schedules as indicated. RP-3500 was administered QD in 0.5% MC/0.02% SLS vehicle in sequence followed by a recovery phase for the remainder of the week. Results are expressed as mean ± SEM, N=9/group. Tumor volumes were measured by electronic caliper; volume = $0.52*L*W^2$. Blood parameters including hematocrit were measured on day 14 at termination and are expressed as the mean ± SEM. Blood samples from some mice were not available. Red dashed lines indicate reference hematocrit range from female age and strain matched mice (Charles River). Statistical significance relative to vehicle control was established by Student's T-test (GraphPad Prism v8); ns; not significant; *p <0.05; **p <0.01; *** p <0.001; **** p<0.0001.

3.7.2 RP-3500 Clinical Pharmacokinetics

In an ongoing Phase 1 dose escalation study of RP-3500 (NCT04497114) in patients with advanced cancer, the PK has been evaluated at doses from 5 mg to 20 mg QD. The available

bioanalytical data as of 11 November 2021 were analyzed in a draft noncompartmental analysis (NCA) using nominal sampling times to determine the PK. The results of the draft analysis indicated a half-life ranging from 2.7 to 23.0 hours with a mean half-life across all QD dose groups of 6.4 hours. Across all cohorts, the Tmax is in the range of 0.5 to 4 hours in the fasted state. Additionally, both Cmax and area under the plasma concentration-time curve from time 0 to time of last quantifiable concentration (AUC0-t) have increased in roughly a dose-linear fashion. The mean ± standard error (SE) Cmax at the therapeutic dose levels of 120 mg and 160 mg QD are 5.17 ± 0.25 µg/mL and 7.36 ± 0.25 µg/mL, respectively. The mean AUC0-t ± SE at these dose levels was 34.2 ± 15.8 µg•hr/mL and 47.8 ± 20.7 µg•hr/mL, respectively.

3.7.3 RP-3500 Drug-Drug Interactions

Definitive in vitro drug-drug interaction studies have been conducted as per the recommendations of the Food and Drug Administration (FDA) Guidance for Industry (FDA, 2020). In definitive in vitro studies, RP-3500 did not appreciably inhibit CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5 [testosterone as substrate], or CYP3A4/5 [midazolam as substrate] with a half maximal inhibitory concentration [IC50] >100 µM), and was found to be a weak direct inhibitor of CYP2C8 (IC50 = 44 µM) in these same studies. RP-3500 was not a preincubation or time-dependent inhibitor of all CYP isoforms evaluated. Incubations of human hepatocytes with RP-3500 showed only minor increases in CYP2B6 and CYP3A4 messenger RNA that did not exceed more than 20% of the associated positive control values. Experiments using cell systems have shown that RP-3500 is not an inhibitor of the uptake transporters organic anion transporting polypeptide 1B1 (OATP1B1), organic anion transporting polypeptide 1B3 (OAT1B3), organic anion transporter 1 (OAT1), organic anion transporter 3 (OAT3), organic cation transporter 1 (OCT1), or multidrug and toxin extrusion protein 2-K (MATE2-K). RP-3500 is a weak inhibitor of multidrug and toxin extrusion protein-1 (MATE-1; 44% inhibition at 5 µM), multidrug resistance 1 (MDR1; 40% inhibition at 100 µM), and breast cancer resistance protein (BCRP; IC50 = 17.4 µM). Together the data suggest that RP-3500 has a low potential to be a perpetrator of drug-drug interactions with co-administered transport substrates, however depending on the dose, RP-3500 may inhibit BCRP in the gastrointestinal tract and increase the absorption of BCRP substrates. Additionally, based on the current data, RP-3500 is not expected to be a perpetrator of drug-drug interactions at the levels of inhibition, or induction of CYP isoforms.

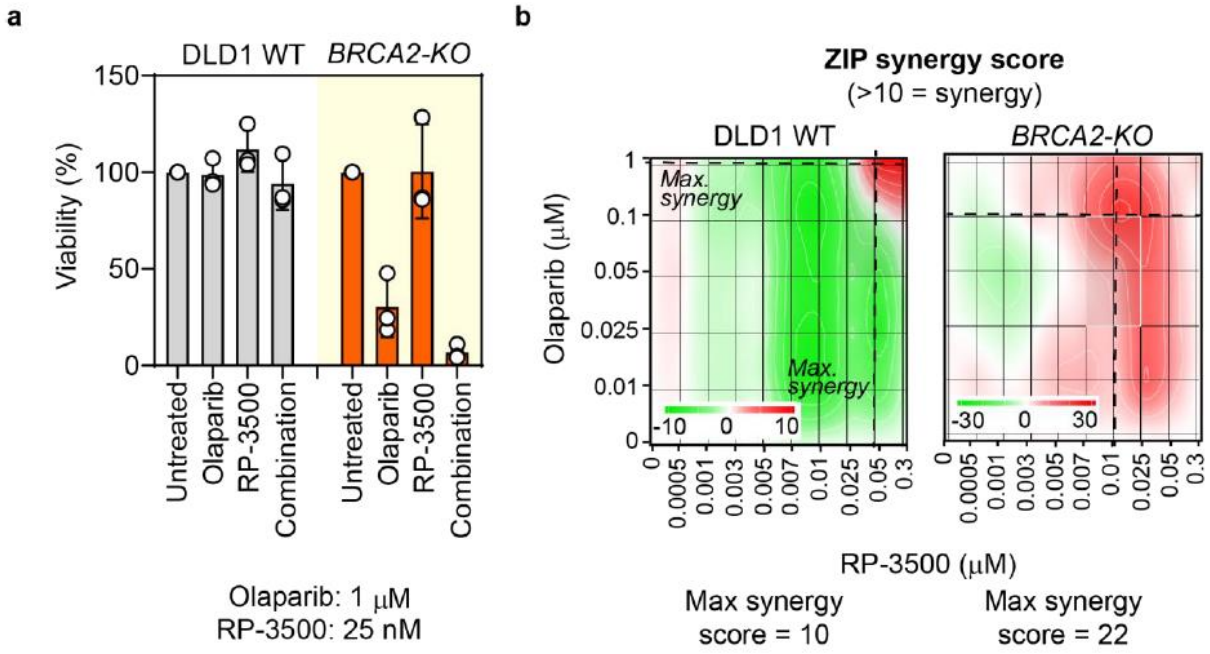
The current data from in vitro experiments suggests that that RP-3500 is a substrate of both P-glycoprotein (P-gp) and BCRP drug transporters, and CYP3A4 and CYP2C8 appear to be the major isoforms responsible for the CYP-mediated metabolism of RP-3500 in vitro. Based on the currently available data, it is recommended that administration of strong P-gp and BCRP inhibitors as well as strong CYP3A inhibitors and/or inducers including food and herbal sources should be excluded while on study and at least 14 days prior to initiating treatment with RP-3500 until further clinical evaluation is available.

3.8 Combination RP-3500 and Olaparib Shows Preclinical Efficacy and Synergy

Using an isogenic DLD1 colorectal cancer cell line system, combination RP-3500 and olaparib at sub-lethal doses was profoundly cytotoxic to breast cancer type 2 susceptibility protein-knockout (BRCA2-KO) cells, while minimally affecting the viability of wild type (WT) cells (after 8 or 6 days

of treatment, respectively) (Figure 4A). The combination also showed a strong synergistic effect on viability at markedly lower concentrations in BRCA2-KO cells than WT (Figure 4B).

Figure 4. BRCA2-deficient cells are sensitive to RP-3500 and olaparib.



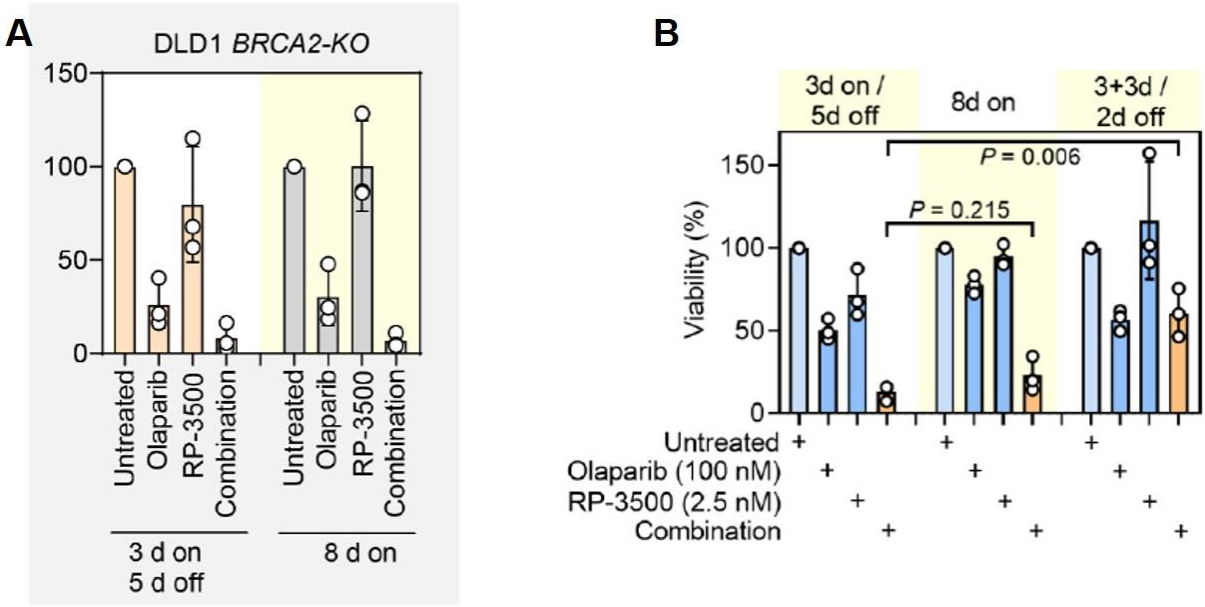
Abbreviations: *BRCA2* = breast cancer type 2 susceptibility protein; *BRCA2-KO* = breast cancer type 2 susceptibility protein-knockout; SD = standard deviation; WT = wild type

a. When combined, sub-lethal doses of RP-3500 and olaparib eliminate *BRCA2*-deficient cells. DLD1 WT and

3.9 Intermittent Dosing of Comb ination RP -3500 and Olaparib Is Equally Efficacious as Continuous Dosing

In the same DLD1 BRCA2-KO cell model, reducing the treatment time of combination RP-3500 and olaparib to 3 days followed by removal of the compounds for 5 days was equally as efficacious in killing BRCA2-KO cells as 8 days of continuous treatment (Figure 5A). These findings were confirmed using a different cell model of SUM149PT, which are BRCA1-mutated triple negative breast cancer cells. Intermittent dosing of the drug combination (3 days on 5 days off) produced equal efficacy as compared to continuous 8 day dosing and increased efficacy as compared to sequential dosing (i.e. olaparib treatment for 3 days alone followed by RP-3500 treatment for 3 days alone followed by 2 days off) (Figure 5B). These findings support intermittent dosing of the drug combination.

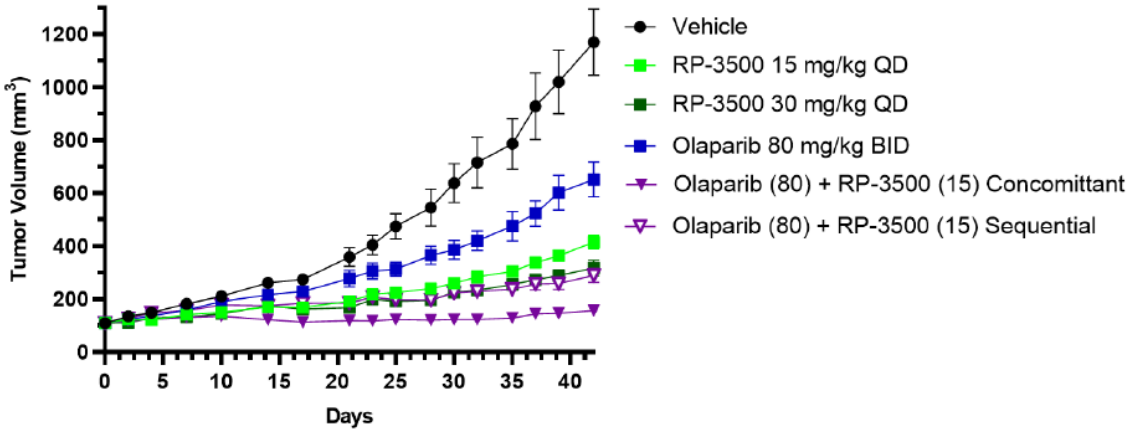
Figure 5. Intermittent dosing of combination RP-3500 and olaparib produced equal efficacy as compared to continuous and sequential dosing.
A) DLD1 BRCA2-KO and B) SUM149PT (BRCA1-mutated triple negative breast cancer) cell models



3.10 Combination RP-3500 and Olaparib is More Efficacious at Reduced Doses than RP-3500 Monotherapy at Higher Doses

Dosing strategies for combination RP-3500 and olaparib were explored in SUM149PT xenograft mice models. Concomitant administration of RP-3500 with olaparib for 3 days weekly resulted in higher efficacy than sequential administration (Figure 6). Furthermore, intermittent administration of RP-3500 and olaparib was well tolerated with <5% body weight loss over the course of the experiment compared to continuous concomitant dosing schedules (data not shown). The olaparib doses selected in this study represent exposure levels of ~11 µM, which is comparable to ~40% of the circulating free drug exposure levels of olaparib at steady state in humans taking 300 mg BID daily. This dose is less than the maximum tolerated dose (MTD) of 400mg BID as previously determined[50]. However, prior pharmacokinetic and efficacy data comparing 200mg BID versus 400mg BID in phase I and phase II trials have not shown major differences between the two dosing strategies[50,51]. Notably, the lower dose of 200mg BID led to decreased grade 3-4 anemia of 6% as compared to 13% in patients treated with 400mg BID[51].

Figure 6. Efficacy of intermittent sequential versus concomitant RP-3500 plus olaparib in the SUM149PT breast cancer xenograft model (BRCA1-deficient),



Abbreviations: BID = twice daily; *BRCA1* = breast cancer type 1 susceptibility protein; MC = methylcellulose; NOD-SCID = non-obese diabetic severe combined immunodeficiency; PO = oral; QD = once daily; SEM = standard error of measure; SLS = sodium lauryl sulfate

Tumor xenograft volume in mice treated with RP-3500 (QD) and olaparib (BID) PO 3 days weekly (either concomitant or sequential). Olaparib was administered on Days 1-3 weekly and RP-3500 Days 1-3 in all groups except the sequential schedule where RP-3500 was administered on Days 4-6; treatment lasted for 5 weeks (Day 35) for all groups. Olaparib and RP-3500 were administered as suspensions in 0.5% MC/0.02% SLS. Results are expressed as mean ± SEM, N=9/group in female NOD-SCID mice.

RP-3500 at 15 mg/kg is 50% of the MTD on a 3 day on/4 day off dosing schedule. The combination of low dose RP-3500 administered concomitantly with low dose olaparib given on an intermittent schedule led to superior efficacy when compared to either single agent at full dose (Figure 6).

3.11 Rationale for Starting Doses of RP -3500 and Olaparib

The currently presented data supports the administration of RP-3500 and olaparib with intermittent dosing (3 days per week) and at reduced doses from the previously determined monotherapy MTDs. Furthermore, dosages of RP-3500 and olaparib must also account for the potential drug-drug interaction between RP-3500 and olaparib as previous in vitro data has shown olaparib to be an inhibitor of the two major metabolic proteins for RP-3500, including CYP3A4 and UGT1A1. Therefore, the proposed starting dose of RP-3500 at 50mg daily and olaparib at 100mg BID administered with intermittent 2 days per week dosing was based on preclinical PK data and prior toxicity experience with both drugs to help reduce toxicity while maintaining efficacy.

3.12 Rational e for Allowing Creatinine Clearance (CrCl) Between 45 and 59 mL/min

In an analysis of 154 solid tumor patients treated with RP-3500, there were small changes in the PK clearance of RP-3500 among patients with normal renal function (N=62), mild renal impairment (N=49) and moderate renal impairment (N=13) defined as CrCl between 45 and 59 mL/min (Table 3). However, the analysis is confounded by the lower mean body weights in the moderate renal impaired patients, but still supports little effect of renal impairment on the PK of RP-3500.

Table 3. PK Clearance of RP-3500 Among Patients with Normal, Mild, and Moderate Renal Impairment

	Normal (N=61)	Mild (N=49)	Moderate (45-59 ml/min) (N=13)	Moderate (<45 ml/min) (N=4)	Missing (N=7)	Overall (N=134)
Weight (kg)						
Mean (SD)	85.6 (19.9)	68.7 (14.5)	65.5 (13.7)	52.8 (6.94)	NA (NA)	76.0 (19.5)
Median [Min, Max]	85.2 [53.1, 148]	66.9 [45.0, 113]	61.4 [50.3, 97.9]	53.9 [44.5, 58.9]	NA [NA, NA]	76.5 [44.5, 148]
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7 (100%)	7 (5.2%)
Dose Normalized $AUC_{0-6,ss}$ of RP-3500 (ng.h/mL/mg)						
Mean (SD)	168 (78.6)	180 (69.3)	221 (88.3)	239 (63.2)	180 (86.8)	180 (77.4)
Median [Min, Max]	154 [66.6, 554]	158 [66.6, 373]	190 [107, 435]	225 [179, 325]	156 [93.2, 353]	163 [66.6, 554]
Dose Normalized $AUC_{0-12,ss}$ of RP-3500 (ng.h/mL/mg)						
Mean (SD)	237 (129)	253 (112)	318 (148)	328 (100)	252 (136)	254 (126)
Median [Min, Max]	220 [75.6, 905]	227 [75.4, 597]	268 [132, 678]	299 [241, 471]	227 [112, 522]	227 [75.4, 905]
Dose Normalized $C_{max,ss}$ of RP-3500 (ng/mL/mg)						
Mean (SD)	49.1 (17.1)	54.2 (16.9)	63.7 (17.5)	71.8 (15.9)	54.6 (17.6)	53.3 (17.6)
Median [Min, Max]	47.0 [19.0, 117]	52.6 [26.9, 87.2]	61.8 [39.5, 104]	72.0 [55.0, 88.1]	54.0 [32.0, 90.0]	50.8 [19.0, 117]
Dose Normalized $C_{min,ss}$ of RP-3500 (ng/mL/mg)						
Mean (SD)	3.04 (5.62)	3.88 (4.89)	4.38 (3.67)	3.94 (2.91)	4.52 (6.82)	3.58 (5.17)
Median [Min, Max]	1.65 [0.157, 43.7]	2.67 [0.189, 21.5]	3.80 [0.736, 13.5]	2.83 [1.86, 8.26]	2.22 [0.519, 19.8]	2.11 [0.157, 43.7]
Daily Dose Normalized AUC_{24} of RP-3500 (ng.h/mL/mg)						
Mean (SD)	115 (67.6)	128 (87.7)	154 (75.2)	135 (76.4)	116 (58.3)	124 (76.0)
Median [Min, Max]	98.8 [30.6, 345]	115 [30.2, 565]	162 [56.7, 263]	101 [89.7, 249]	108 [47.1, 201]	108 [30.2, 565]
Daily Dose Normalized C_{avg} of RP-3500 (ng/mL/mg)						
Mean (SD)	5.46 (3.22)	6.10 (4.18)	7.34 (3.58)	6.43 (3.64)	5.53 (2.78)	5.91 (3.62)
Median [Min, Max]	4.71 [1.46, 16.4]	5.46 [1.44, 26.9]	7.72 [2.70, 12.5]	4.80 [4.27, 11.9]	5.12 [2.24, 9.57]	5.14 [1.44, 26.9]

Reassuringly, the modest PK effects of renal impairment did not translate to increased observed toxicities including anemia, neutropenia and treatment-emergent significant adverse events (TESAE) (Table 4,

Table 5, Table 6)

Table 4. Summary Anemia by Renal Function Categories (CrCL)

	Normal (N=61)	Mild (N=49)	Moderate (45-59 ml/min) (N=13)	Moderate (<45 ml/min) (N=4)	Missing (N=7)	Overall (N=134)
Adverse Event						
No Anaemia	23 (37.7%)	10 (20.4%)	2 (15.4%)	0 (0%)	2 (28.6%)	37 (27.6%)
Anaemia	38 (62.3%)	39 (79.6%)	11 (84.6%)	4 (100%)	5 (71.4%)	97 (72.4%)

Table 5. Summary Neutropenia by Renal Function Categories (CrCL)

	Normal (N=61)	Mild (N=49)	Moderate (45-59 ml/min) (N=13)	Moderate (<45 ml/min) (N=4)	Missing (N=7)	Overall (N=134)
Adverse Event						
No Neutropenia	47 (77.0%)	35 (71.4%)	9 (69.2%)	2 (50.0%)	4 (57.1%)	97 (72.4%)
Neutropenia	14 (23.0%)	14 (28.6%)	4 (30.8%)	2 (50.0%)	3 (42.9%)	37 (27.6%)

Table 6. Summary TESAE by Renal Function Categories (CrCL)

	Normal (N=61)	Mild (N=49)	Moderate (45-59 ml/min) (N=13)	Moderate (<45 ml/min) (N=4)	Missing (N=7)	Overall (N=134)
Adverse Event						
No TESAE	47 (77.0%)	35 (71.4%)	9 (69.2%)	2 (50.0%)	4 (57.1%)	97 (72.4%)
TESAE	14 (23.0%)	14 (28.6%)	4 (30.8%)	2 (50.0%)	3 (42.9%)	37 (27.6%)

While Olaparib is affected by CrCl, the package insert for olaparib does not recommend any dose modifications for CrCl between 51-80 mL/min.[52] If a patient has moderate renal impairment, defined as CrCl 31-50mL/min, the package insert recommendation is to decrease Olaparib to 200mg BID. However, due to the anticipated synergy between RP-3500 and Olaparib, the starting dose of Olaparib for this trial is 100mg BID at dose level 1 with a maximum dose of Olaparib at 150mg BID for dose levels 2 and 3, which are all below the recommended reduced 200mg BID for moderate renal impairment.

4 STUDY DESIGN

This is an open-label, multicenter, phase Ib/II study of the combination of camonsertib (RP-3500) and olaparib in R/R CLL patients with DDR deficiencies.

4.1 Justification for New Dosing Schema and Dose Escalation

At the previous dose level 1, five R/R CLL patients were treated with camonsertib (RP-3500) 40mg daily and olaparib 100mg BID dosed 3 days per week. One patient met the definition of a dose limiting toxicity due to persistent grade 4 thrombocytopenia lasting ≥7 days. Cytopenias were the most common AEs with 2/5 (40%) of patients experiencing grade 4 thrombocytopenia as per the iwCLL criteria. Grade ≥3 neutropenia occurred in 2/5 (40%) of patients with one patient experiencing a grade 3 neutropenic fever outside of the DLT window.

In the ongoing parallel ATTACC study (NCT04972110) of combination camonsertib (RP-3500) and PARPi combinations (either niraparib or olaparib) in patients with molecularly selected cancers (i.e. DDR-deficient solid tumors), similar cytopenias were observed with the 3 days per week dosing. However, better tolerance of the combination was observed when patients were dosed only 2 days per week. In preliminary data, reduction of the dosing to 2 days per week significantly reduced ≥grade 3 toxicities by 5-fold as compared to 3 days per week dosing at similar dosages of combination RP-3500 and olaparib. The 2/5 (i.e. 2 days on and 5 days off) dosing strategy is supported by previous preclinical data generated in DDR-deficient bladder cancer cell lines in which shortening the treatment of the cells to 48 hours had no significant effect on the IC_{50} as compared to continuous dosing (Refer to RP-3500 Investigator Brochure Section 4.2.1.4.2.1). Furthermore, treating various DDR-deficient solid tumor cell lines with RP-3500 and various PARPi dosed with a 2/5 strategy in vitro demonstrated strong synergy with the combination treatments (Refer to RP-3500 Investigator Brochure Section 4.2.1.5.1). Given the prior clinical experience of RP-3500 and olaparib with the 2/5 dosing strategy in solid tumor patients along with the existing preclinical data to support this dosing method, we propose to amend the phase Ib of combination RP-3500 and olaparib in R/R CLL patients to be dosed with a 2/5 treatment strategy to improve the tolerability of the combination.

4.2 Phase Ib Dose Escalation

4.2.1 The Phase Ib part of the trial will seek to assess the MTD of camonsertib (RP-3500) in combination with olaparib. Given the potential overlapping toxicities of RP-3500 and olaparib, a keyboard phase I design, a novel Bayesian method that typically underestimates the MTD,[53] will be employed. The target toxicity is 30% with an equivalence interval between 25-33% of patients. With an anticipated 3 dose levels (DL) and an option for a DL-1, up to 18 patients may be required to determine the MTD. A maximum of 12 patients will be treated at a DL.

The first 5 patients treated at the previous DL1 (camonsertib 40mg daily and olaparib 100mg BID dosing 3 days per week) determined that this dosing strategy may not be appropriate for R/R CLL patients and reduced dosing may be necessary to increase safety of the combination therapy. Therefore, the newly proposed DLs will seek to enroll an additional 18 patients.

4.2.2 Dose Escalation

During dose escalation, four DLs of combination therapy of RP-3500 and olaparib may be explored (Table 7. Dose levels of RP-3500 and olaparib in phase Ib portion of the trial.). Subjects will be enrolled in cohorts of three starting with DL 1. Enrollment will be placed on hold to allow for all members of a cohort to complete the Dose Limiting Toxicity (DLT) period. Once all subjects in a cohort have completed the defined DLT evaluation period, the assignment of the dose level for the following cohort will follow the decision algorithm in Table 8. Dose escalation rules according to the keyboard phase I design. Doses may be escalated (E) to the next highest dose level, de-escalated (D) to a lower dose level, or stay (S) at the same dose level (Table 8. Dose escalation rules according to the keyboard phase I design.).

Table 7. Dose levels of RP-3500 and olaparib in phase Ib portion of the trial.

*Both drugs are given with intermittent dosing of 2 days per week.

Dose Level	RP-3500	Olaparib
-1[#]	40mg daily	100mg BID
1*	50mg daily	100mg BID
2*	80mg daily	100mg BID
3*	80mg daily	150mg BID

As long as there are not any unacceptably (U) high toxicities encountered with the enrolled patients as according to the keyboard algorithm, then the trial can continue enrollment in cohorts of 3 patients. Each cohort will complete the DLT window at which point it will trigger the Data Safety Monitoring Committee (DSMC) and the Principal Investigator of the trial to convene and determine the appropriate DL for the following cohort(s). The DSMC and Principal Investigator can also make the recommendation to enroll in cohorts of 1-2 patients if a slower enrollment is required to ensure the safety of the drug combination. All patients enrolled in these smaller cohorts must complete the DLT window prior to the determination of the number of patients to enroll in the next cohort and at which DL. Should a DL accumulate enough DLTs so that the keyboard algorithm dictates a U, the remaining cohorts will be de-escalated to the next lowest DL and no more patients will be treated at the DL with U toxicities.

Table 8. Dose escalation rules according to the keyboard phase I design.

Depending on the number of patients treated on the current dose level and the number of dose-limiting toxicities encountered, the algorithm will dictate dose escalation (E) to the next highest dose, de-escalation (D) to the next lowest dose or stay (S) at the current dose level. Should any DL encounter an unacceptable (U) toxicity in the decision table, future cohorts will be D to next lowest dose and no further patients will be treated at this DL.

4.2.3 Determination of The MTD and RP2D

After successful enrollment of 18 patients who have completed the DLT window, then the phase Ib portion of the trial will be complete. An exception to this is if any DL enrolls 12 patients and the keyboard algorithm dictates to stay at the current dose level. The MTD and RP2D will be determined to be the DL in which the 12 patients are enrolled as the chances of additional patients treated at the current DL altering the decision table of the keyboard design would be low. Therefore, the phase Ib portion of the trial may be completed before the enrollment of 18 total patients. If a DL reaches 8 patients and 2 DLTs are noted, the keyboard decision table dictates an S at the current DL. The Principal Investigator or DSMC can determine to enroll 4 additional patients at the current DL if the 4 additional patients do not put the total number of patients enrolled into the phase Ib portion over 18.

After the phase Ib portion is completed, final DLT rates at each dose level will be estimated by isotonic regression[54]. The weighted least squares regression model will assume monotonic non-decreasing DLT rates with increasing dose and use the empirical (observed) DLT rates at each DL as responses and DL sample sizes as weights, along with the pool adjacent violators algorithm (PAVA) to estimate the DLT rate at each dose level. Given the DLT estimates for each dose level, all tried dose levels that have not been previously declared to be unsafe with a U decision according to the keyboard decision table will be considered for the RP2D. With this constraint, the MTD will be determined as the dose level with the DLT estimate closest to the target toxicity level of 30%.

	Number of Patients Treated At Current Dose Level												
# of DLTs Observed	0	1	2	3	4	5	6	7	8	9	10	11	12
0	S	E	E	E	E	E	E	E	E	E	E	E	E
1		D	D	D	S	E	E	E	E	E	E	E	E
2			D	D	D	D	D	S	S	E	E	E	E
3				U	U	D	D	D	D	D	S	S	S
4					U	U	U	D	D	D	D	D	D
5						U	U	U	U	U	D	D	D
6							U	U	U	U	U	U	D
7+								U	U	U	U	U	U

Each dose level may enroll approximately 3 to 12 subjects in order to further inform RP2D decision. Enrollment to the highest open dose level will be prioritized if multiple dose levels are open for enrollment. The RP2D will be selected with approval from all investigators and the DSMC after considering the cumulative safety, PK/Pd (as available) and efficacy data from subjects treated in dose escalation.

4.2.4 Definition of Dose Limiting Toxicities

DLTs will be assessed for each patient within the DLT window. The DLT window is defined as the time from Cycle 1 Day 1 to Cycle 1 Day 21. Common terminology criteria for adverse events (CTCAE) v5.0 will be used to grade all adverse events (AE) and to provide management guidelines for administrational toxicity. Any of the following AEs which cannot be incontrovertibly attributed to CLL or CLL disease progression will be defined as a DLT.

General
a. Treatment delays > 21 days. b. Any grade 5 event.
Non-hematologic
a. Any grade ≥ 4 event. b. Any grade ≥ 3 non-hematologic toxicity with the following exceptions: i. Grade 3 fatigue, asthenia, anorexia, fever, or constipation. ii. Grade 3 nausea, vomiting or diarrhea not requiring tube feeds, TPN or hospitalization. iii. Grade 3 or 4 non-clinically significant and transitory laboratory abnormalities that resolve to ≤ grade 1 or baseline within 7 days, except for any possible Hy's Law event (Refer to 8.3.2) iv. Alopecia v. Tumor lysis syndrome not requiring dialysis vi. DVT responsive to anticoagulation
Hematologic
a. For patients with baseline/screening absolute neutrophil count (ANC) ≥1000/mm^3, grade 4 neutropenia [ANC <500/mm^3] not responsive to optimal supportive care or G-CSF administration lasting ≥5 days. For patients with baseline/screening ANC <1000/mm^3, DLT here is defined as a ≥75% reduction from baseline ANC not responsive to optimal supportive care or G-CSF administration lasting ≥5 days. b. Any grade febrile neutropenia.

c. For patients with baseline/screening platelet count ≥100,000/mm^3, grade 4 thrombocytopenia (platelet count <25,000/mm^3) lasting ≥7 days. For patients with baseline/screening platelet count <100,000/mm^3, DLT here is defined as a ≥75% reduction from baseline platelet counts lasting for ≥7 days.

d. Grade ≥3 thrombocytopenia-associated bleeding.

Subjects will be considered eligible for DLT assessment if they have received at least 1 dose of RP-3500 and 1 dose of olaparib.

4.2.5 Consideration of Alternative Dosing Strategies

Alternative dosing strategies including extended intermittent dosing will be considered should any dose level be deemed unacceptably toxic. A meeting between all investigators, the sponsor, and DSMC will be held to determine and approve alternative DLs. Any alternative DLs evaluated will only do so with an amendment to the protocol and appropriate justification.

If a majority of the review committee deem the combination too toxic at any DL, then the trial may be terminated at that time.

4.2.5.1 Dose Level -1 is Deemed Unacceptable Toxicity

If the number of DLTs incurred at DL-1 is deemed U by the keyboard design decision table, alternative dosing schedules and strategies will be considered. These include adding additional DLs in which RP-3500 is dosed at either 20mg, 30mg, 40mg, or 50mg daily. Depending on the DLTs encountered at DL-1 and if these were attributed to either RP-3500 or olaparib administration, olaparib for these additional DLs can be dosed between 100-200mg BID. The new DLs may have either similar intermittent dosing schedule of the combination with 2 days on and 5 days off or an alternative dosing strategy of the combination of 2 weeks on and 1 week off. Other considerations would include a 28 day cycle in which the dosing would alternate between the 4 weeks (i.e. first week on, second week off, third week on, fourth week off) with dosing being 2-3 days in the “on” weeks.

4.2.5.2 Exploration of Extended Intermittent Dosing

Should DLTs occur at at any DL so that the keyboard algorithm deems that DL unacceptably toxic, an extended intermittent dosing schedule can be considered. While subsequent patients would enroll with the same RP-3500 and olaparib dosages at the current DL, an extended intermittent dosing schedule can be explored in which patients would dose for 2 weeks on and then have a 1 week rest period within a 21-day cycle. In the 2 weeks that patients dose, RP-3500 and olaparib will be administered 2 days during the week with 5 days off (Table 10).

Table 9. Modification of Dosing Schedule for Toxicity with Every Week Dosing

Dose Level	RP-3500	Olaparib	Dosing Schedule
-1	40mg daily	100mg BID	2 days on/5 days off, every week

-1A	40mg daily	100mg BID	2 days on/5 days off; 2 weeks on/1 week off
1	50mg daily	100mg BID	2 days on/5 days off, every week
1A	50mg daily	100mg BID	2 days on/5 days off; 2 weeks on/1 week off
2	80mg daily	100mg BID	2 days on/5 days off, every week
2A	80mg daily	100mg BID	2 days on/5 days off; 2 weeks on/1 week off
3	80mg daily	150mg BID	2 days on/5 days off, every week
3A	80mg daily	150mg BID	2 days on/5 days off; 2 weeks on/1 week off

If patients enrolled at the extended intermittent dosing DLs clear a DL, dose escalation may continue but must follow the outlined A DLs in Table 9. Modification of Dosing Schedule for Toxicity with Every Week Dosing(i.e. DL -1A, DL 1A, DL 2A, DL 3A).

4.2.5.3 Escalation Beyond DL3

If enrollment of patients reaches DL3 and this DL is deemed safe, consideration for a DL4 in which RP-3500 is dosed at 120mg daily and olaparib is dosed at 150mg BID (2 days per week) will be considered. In this case, 6 additional patients will be added to the phase Ib cohort for a maximum of 24 patients.

4.2.5.4 Continuous Dosing

In any of the original and alternative DLs, continuous RP-3500 and/or olaparib dosing (i.e. no days off) may be explored pending the PK, PD and toxicity assessments, and with the approval of the DSMC and amendment to the protocol.

4.2.5.5 Intra-patient Dose Escalation

At the discretion of the treating investigator, phase Ib patients enrolled at a lower DL may have their doses of camonsertib (RP-3500) and/or olaparib escalated to the next highest DL that has cleared the DLT window and deemed acceptably safe by the DSMC. Patients may not escalate if they have encountered a decrease in dosages or dose schedule due to treatment-related AEs, or have not been able to maintain their assigned DL dosages and dosing schedule for at least 6 weeks. However, if a patient required a dosing schedule modification (i.e. reduction from every week dosing to 2 weeks on/1 week off) and has not experienced significant treatment-related AEs grade >2 on the new dosing schedule for at least 6 weeks, and the next cleared DL is also a

dosing schedule of 2 weeks on/1 week off, the patient may still escalate their dosages of RP-3500 and/or olaparib to the newly cleared DL.

4.3 Phase II Dose Expansion

After completion of the phase Ib portion and assignment of the RP2D, continuous enrollment of patients may commence into the phase II dose expansion portion. All patients enrolled at the RP2D during the phase Ib dose-escalation portion of the trial can be carried over into the phase II analysis. The maximum number of patients that can be carried over from the dose escalation to the dose-expansion portion is 12.

The phase II dose expansion will consist of two separate cohorts of subjects: an enrichment cohort and a cohort for all other eligible subjects. All subjects enrolled into the enrichment cohort must have a del(11q) and/or ATM mutation. Eight subjects will be enrolled into the enrichment cohort and 16 will be enrolled into the second cohort for a total phase II cohort of 24 patients.

4.4 Study Duration and Sample Size

With cohorts of 3 patients and possible early completion of the dose-escalation due to a DL accruing 12 patients, then the minimum time to accrue 4 cohorts is 4 months. Due to potential delays in patient enrollment and variability in dose escalation cohort size, the maximum enrollment time frame for the dose escalation portion is anticipated to be 24 months. Expansion at the RP2D is anticipated to be between 6-12 months as a portion of the dose escalation cohort treated at the RP2D will be rolled into the expansion cohort. Therefore, the total study duration is between 12-36 months, which is inclusive of the phase Ib and phase II durations.

On average, we expect 33 patients to be enrolled, assuming that 9 patients in the phase Ib portion will be treated at the MTD and rolled into the dose expansion phase. If the dose escalation portion enrolls patients only at the RP2D and all of these patients are rolled into the dose-expansion cohort, then the minimum number of patients required would be 24 for the entire trial. The maximum number of patients required would be 39 assuming that only 3 patients roll over from the dose escalation to the dose expansion.

4.5 End of Study

A subject is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Events

The study will end when the last subject completes the last visit or last contact, discontinues from the study, or is lost to follow-up, whichever occurs first. In addition, the sponsor may terminate the study at any time. If at any time, the sponsor terminates the study any subjects receiving clinical benefit from the study intervention may roll over to an expanded access protocol to ensure continued access to the study medication.

4.5.1 Continuation of Study Protocol Treatment Beyond 18 Cycles

If a subject completes 18 cycles of study protocol treatment and is still deriving clinical benefit, the patient may remain on study treatment and follow up at the discretion of the treating provider

indefinitely. Patients may discontinue follow up and treatment as per section 6.9.1 and discontinue the study as per section 6.9.2. All required "EOT" assessments should be performed at the completion of C18D21 including laboratory, imaging and bone marrow assessments. The post-treatment "follow-up" 28 days later is not required.

After cycle 18, the patient should be monitored every 1-3 cycles with physical exam, ECOG PS, vital signs, height/weight and laboratory assessments that are required on previous day 1s (e.g. cycle 4 day 1). Camonsertib (RP-3500) and olaparib may be dispensed to the patient in 1-3 month allotments depending on the intended follow up as determined by the treating investigator. Repeat imaging and bone marrow biopsies are not mandatory during this extended treatment period and should be performed as clinically indicated, following the step-wise approach outlined in footnote 20 of the Schedule of Events.

4.6 Duration of Follow Up for PFS and DoR

Patients will be followed for PFS until progression of disease noted or death, whichever occurs first. Patients will be followed for DoR until progression is noted from the best response, start of a new therapy, or death from any cause. Refer to section 1.1 for long-term follow up time points. In the first year, patients will be followed every 3 months. Between years 2 to 5, the patient will be followed every 3-6 months at the discretion of the treating provider. After 5 years, the patient will be followed every 3-12 months at the discretion of the treating provider. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of adverse event. Follow up data will be required unless consent is withdrawn. Overall survival follow up for patients who have progressed will be completed according to section 6.9.4.

5 STUDY POPULATION

Potential study participants must meet all inclusion criteria and no exclusion criteria to be deemed eligible for trial participation. To ensure subject safety, all subjects must be deemed eligible at the time of study registration and must continue to meet eligibility criteria up to cycle one day one dosing. This eligibility checklist is used to determine subject eligibility and will be filed with the enrolling investigator's signature in the subject research chart.

5.1 Inclusion Criteria

5.1.1 _____ Diagnosis of CLL according to the NCI/IWCLL criteria.

This includes previous documentation of:

a. Biopsy-proven small lymphocytic lymphoma/CLL

OR

b. Diagnosis of CLL according to the NCI/IWCLL criteria as evidenced by all of the following:

1. Peripheral blood monoclonal B cell population of greater than $5x10^9$/L

2. Immunophenotype consistent with CLL defined as:

- The predominant population of lymphocytes share both B cell antigens [CD19, CD20 (typically dim expression), or CD23] as well as CD5 in the absence of other pan-T-cell markers (CD3, CD2, etc).

- Clonality as evidenced by **κ** or **λ** light chain restriction (typically dim immunoglobulin expression)

c. Negative FISH analysis for t(11;14)(IgH/CCND1) on peripheral blood or tissue biopsy (e.g. marrow aspirate), or negative immunohistochemical stains for cyclin D1 on involved tissue biopsy (e.g. marrow aspirate or lymph node biopsy).

5.1.2 _____ Repeat testing of somatic mutations and FISH analysis must be performed by a CLIA certified laboratory after progression is noted from most recent line of therapy and within 6 months of screening. Primary CLL cells must harbor at least one of these abnormalities:

- Somatic gene mutation testing shows mutation(s) in TP53, ATM, SF3B1, XPO1 and/or POT1

- Cytogenetic FISH analysis shows deletion 17p13 and/or deletion 11q22.3

5.1.3 _____ Relapsed or refractory after at least 2 prior lines of therapy, and in the opinion of the treating Investigator are either not eligible for other approved therapies or no approved therapies are expected to have sustained therapeutic benefit.

5.1.4 _____ Patient in need of treatment or change in treatment per iwCLL criteria.

i. Patients on BTK, PI3K or BCL2 inhibitors may enroll without meeting iwCLL criteria for treatment as long as there is clinical evidence of progression (i.e. increasing lymphocytosis, worsening anemia/thrombocytopenia attributable to CLL disease progression, increasing lymphadenopathy, or worsening patient symptoms) and require change in treatment at the discretion of the treating provider. Patients must still meet all other inclusion/exclusion criteria for enrollment including appropriate washout periods (5.2.2) and relapsed disease after 2 prior lines of therapy with no other approved therapies that are expected to have sustained therapeutic benefit (5.1.3).

5.1.5 _____ Age ≥18 years

5.1.6 _____ ECOG performance status between 0-2

5.1.7 _____ Expected life expectancy of at least 12 months per the investigator.

5.1.8 _____ The following laboratory or clinical values obtained ≤ 42 days prior to enrollment:

- Absolute neutrophil count ≥1000/μL (G-CSF support is allowed) unless documented bone marrow involvement of CLL
- Platelets of ≥50K/μL unless documented bone marrow involvement of CLL
- Creatinine Clearance (CrCl) ≥ 45 mL/minute as measured by a 24 hour urine collection or calculated by the Cockcroft-Gault Formula:
  - Males: $\frac{(140-age)\times weight[kg]}{serum\ creatinine\left[\frac{mg}{dL}\right]\times 72}$
  - Females: $\left(\frac{(140-age)\times weight[kg]}{serum\ creatinine\left[\frac{mg}{dL}\right]\times 72}\right)\times 0.85$
- Total bilirubin ≤ 1.5 x institutional ULN unless due to Gilbert's disease. For those patients with previous history of Gilbert's disease, a direct bilirubin should be performed and must be <1.5mg/dL.
- SGOT (AST)/SGPT (ALT) ≤3.0 x the institutional ULN
- QTcF ≤470 msec
  - For patients with prolonged AT interval due to bundle branch block, a "corrected value" ≤470 msec and confirmation by cardiologist that patient is asymptomatic and that no other cardiac conduction or cardiac abnormality is present would pose any safety issues for the patient.
  - Recommended correction of QT for patients with bundle branch block are as follows: Patient's QRS is 160 msec, and the measured QT is 510 msec. As the normal QRS is ~120 msec, subtract 120 msec from the measured QRS of the patient (160-120 = 40 msec) and then subtract this result from the measured QT (510-40=470 msec).
- Pulse oximetry reading of ≥90% on room air

5.1.9 _____ Able to adhere to study visit schedule and other protocol requirements

5.1.10 _____ Patients must be able to swallow capsules

5.1.11 _____ Patients must be able to receive xanthine oxidase inhibitor and/or rasburicase for tumor lysis syndrome prophylaxis.

5.1.12 _____ Patients with a history of hepatitis B (surface antigen or core antibody-positive and PCR positive) must take lamivudine or equivalent drug during study therapy and for one year after completion of all therapy. Patients on IVIG who are core antibody-positive but PCR negative are not mandated to take prophylaxis.

5.1.13 _____ Patients who are HIV+ are eligible under the following circumstances:

- Undetectable HIV viral load (laboratory value obtained within the last 6 months prior to enrollment)
- CD4 count ≥200 (laboratory value obtained within the last 6 months prior to enrollment)
- Actively taking antiretroviral therapy (ART)
- Current ART therapy cannot have significant interactions with RP-3500 or Olaparib (Refer to Appendix 5). If current medications do interact, patients should receive alternative ART.

5.1.14 __ ___ Recovery to baseline or ≤ Grade 1 CTCAE v5.0 from toxicities related to any prior cancer therapy, unless considered clinically not significant by the treating investigator.

5.1.15 _____ Female patients capable of reproduction or males who have partners capable of reproduction must agree to the use of an effective contraceptive method during the course of the study and for 6 months following the completion of their last treatment.

5.1.16 _____ Females of childbearing potential must have a negative serum β-Hcg pregnancy test result within 3 days of the first study dose. Female patients who are surgically sterilized or who are >45 years old and have not experienced menses for >2 years may have β-Hcg pregnancy test waived.

5.2 Exclusion Criteria

5.2.1 _____ Patients who are currently receiving any other investigational drug. Patients who are or have received therapies for the prevention, treatment or management of COVID-19 under the FDA emergency use authorization are allowed to enroll.

5.2.2 _____ Patients who have received:

- Radiation or chemotherapy ≤2 weeks prior to registration.
- Immunotherapy or targeted therapy ≤2 weeks prior to registration.
    i. Patients currently on BCR pathway antagonists (i.e. BTK and PI3K inhibitors, etc) require a 2 day wash out period prior to starting combination therapy with RP-3500 and olaparib as these subjects progress quickly after treatment discontinuation.
- Strong CYP3A inhibitors or inducers, p-glycoprotein inhibitors, or BCRP inhibitors within five half-lives or 14 days of registration, whichever is shorter (See Appendix 5).

5.2.3 _____ Prior ATR inhibitor use, but prior PARP inhibitor use for any reason is allowed on study.

5.2.4 _____ Major surgery 4 weeks prior to C1D1 or who have not fully recovered from major surgery.

5.2.5 _____ Evidence of active Richter's Transformation

5.2.6 _____ Disease states requiring steroids (e.g. adrenal insufficiency, autoimmune conditions) are allowed as long as the steroid dose is ≤10mg of prednisone or equivalent dose of another steroid. Steroids premedications to prevent iodine contrast allergy for CT scans are allowed.

5.2.7 _____ Patients who have undergone autologous stem cell transplant ≤4 weeks or allogeneic stem cell transplant ≤12 weeks prior to cycle 1 day 1 or have active graft-versus-host disease are excluded.

5.2.8 _____ Patients who have active, clinically significant hepatic impairment (≥ moderate hepatic impairment according to the NCI/Child-Pugh classification)

5.2.9 _____ Prior history of another malignancy except for the following:

- Patients with current history of basal or squamous skin carcinoma, cervical carcinoma in situ, localized breast cancer requiring hormonal therapy, or localized prostate cancer (Gleason score <6) are allowed.
- Previously treated malignancies (with chemotherapy, radiation, and/or surgery) currently deemed to have been in complete remission for at least 24 months.

5.2.10 _____ Patients with active known central nervous system (CNS) involvement of CLL. Patients with a history of CNS CLL now in remission are eligible for the trial.

5.2.11 _____ Patients with uncontrolled concurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, extensive bilateral interstitial lung disease, unstable angina pectoris, or psychiatric illness/social situations that would limit compliance with study requirements.

- Patients with a history of pneumonitis or pulmonary disease that could predispose them to development of ILD and/or underlying respiratory conditions should be excluded.

5.2.12 _____ Known prior severe hypersensitivity to RP-3500, olaparib, or any component in its formulations (NCI CTCAE v5.0 Grade ≥ 3).

5.2.13 _____ Female patients who are pregnant or actively breast feeding

5.2.14 _____ Patients with conditions significantly affecting gastrointestinal function including, but not limited to:

- Significant resection of the stomach or small bowel
- Symptomatic inflammatory bowel disease
- Partial or complete bowel obstruction

5.3 Registration

Subjects must meet all of the eligibility requirements before registration. Study-related screening procedures can only begin once the subject has signed the consent form. Subjects must not begin protocol treatment prior to registration.

Treatment should start within 14 days after registration.

To register eligible subjects on study, complete a Clinical Trials Office Subject Registration Form and submit to CTORegistrations@hci.utah.edu.

For sites outside of Huntsman Cancer Institute, submit registration forms to MultisiteRegistrations@hci.utah.edu

5.4 Life Style Considerations

5.4.1 Diet

Due to CYP3A4 interactions, subjects will be advised to avoid grapefruit, Seville oranges, pomelos, and star fruit including products containing these fruits (e.g. juices, jams, marmalades, etc.).

5.4.2 Contraception

Due to the unknown abortifacient and teratogenic effects of RP-3500 and olaparib, a form of highly effective contraception is required for the duration of study therapy. Female subjects of childbearing potential must use a form of highly effective contraception from the start of study therapy until 6 months after the last dose of study therapy. Male subjects with a partner of childbearing potential must agree to use a method of highly effective contraception from the start of study therapy until 6 months after the last dose of study therapy.

Acceptable highly effective contraceptive methods include:

- Bilateral tubal occlusion
- Vasectomized partner
- Intra-uterine devise (IUD) or hormone-releasing system (IUS)
- Any hormonal (estrogen combined with progesterone or progesterone alone) contraception associated with inhibition of ovulation: implanted, oral, intravaginal, transdermal, or injectable.
- Spermicide with a compatible barrier method (i.e. diaphragm, sponge, or male or female condoms).
- Abstinence from heterosexual intercourse.

It is unknown whether RP-3500 and olaparib can produce drug transfer through seminal fluid. Therefore, male subjects must agree to use a condom during any form of intercourse from the start of study therapy until 6 months after the last dose of study therapy.

5.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but do not meet subject eligibility criteria. These subjects will not be entered into the study or begin study intervention. However, minimal information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements. Minimal information includes, but may not be limited to, demography, screen failure details, eligibility criteria, and any serious adverse event (SAE) experienced during

screening, but prior to being deemed ineligible. Adverse events and SAEs will not be collected after a subject is deemed ineligible.

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened at the Investigator's discretion.

5.6 Strategies for Recruitment

Investigators will identify potential subjects in the setting of their outpatient clinics. This study will be posted on clinicaltrials.gov for help in recruitment. Investigators will perform local and regional outreach to patients and physicians. Furthermore, we will enlist the help of patient education and advocacy forums such as national cooperative groups, Lymphoma Research Foundation, The CLL Society and Leukemia & Lymphoma Society for advertisement of the trial.

5.7 Number of Study Sit es

This is a two-institution study including The University of Utah/Huntsman Cancer Institute (Salt Lake City, UT) and MD Anderson Cancer Center (Houston, TX).

If trial recruitment is anticipated to be greater than the expected maximum of 36 months, then additional CLL specialty centers will be asked to participate in this trial.

6 STUDY INTERVENTION

6.1 Administration Schedule

Treatment will be administered on an outpatient basis. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's CLL.

Regimen Description					
Agent	Precautions	Dose	Route	Schedule	Cycle Length
RP-3500	Take with 8 oz of water at approximately the same times each day (±2 hours)	Capsule*	Oral	Once daily; intermittent weekly dosing of 2 days on and 5 days off	21 days (3 weeks)
Olaparib	Take with 8 oz of water at approximately the same times each day (±2 hours)	Capsule*	Oral	Twice daily; intermittent weekly dosing of 2 days on 5 days off	
* Doses as appropriate for assigned dose level					

Study medications should be taken at approximately the same time every day. Study medication should not be crushed, chewed, or altered in any way. Subjects should not take extra medication for any reason nor should they re-administer in the case of vomiting after

administration. If a dose is missed outside of the dosing window, the dose should not be made up but rather dosing should continue at their regularly scheduled time.

6.1.1 Preparation and Dispensing

The investigator or qualified personnel will prepare and dispense all investigational supplies. Subjects will be dispensed enough medication to last a full cycle of both study medications. Appropriate records will be kept to accurately show all dispensing activates and Investigational Product (IP) will be supplied only to subjects deem eligible for study therapy. IP may not be dispensed to subjects who have not been enrolled in the trial.

6.1.2 Accountability and Compliance

Information pertaining to study drug compliance (i.e., date time, and dose) will be recorded by subjects on the drug diary (see Appendix 3) and recorded in the corresponding electronic case report form (eCRF) by the study team. A member of the study team will review subject drug compliance at the end of each cycle and provide subject re-education as required. Any reason for non-compliance will be documented in the subject's research chart and the corresponding eCRF. At the discretion of the principal investigator, a subject may be discontinued from the trial for non-compliance with study visits or study drug.

Subjects will be required to return any unused medication or empty bottles at the end of every cycle. Excess or unused study drug should be returned to the investigative site for accounting and destroyed in accordance with GCP after drug accountability has been performed. The total number of tablets dispensed, returned, and documented as taken will be reconciled to support drug accountability. Treatment compliance will be calculated and recorded separately for each drug. It will be recorded as a percentage defined as the number of doses taken divided by the expected number of doses taken multiplied by 100%.

6.2 Olaparib

6.2.1 Investigational Product Supplies

Olaparib will be supplied by Repare Therapeutics as either 150mg or 100mg tablets.

• 150 mg: green to green/grey, oval, bi-convex, film-coated, with debossment 'OP150' on one side and plain on the reverse side.

• 100 mg: yellow to dark yellow, oval, bi-convex, film-coated, with debossment 'OP100' on one side and plain on the reverse side.

Olaparib will be stored at 20ºC to 25ºC (68ºF to 77ºF), excursions permitted to 15ºC to 30ºC (59ºF to 86ºF). Tablets will be stored in original bottle to protect from moisture.

The Principal Investigator will ensure appropriately trained and delegated personnel will receive, inventory, and stored all investigational products per applicable laws and regulations.

6.3 Camonsertib (RP-3500)

6.3.1 Investigational Product Supplies

RP-3500 will be supplied by Repare Therapeutics as capsules containing 5 mg or 40 mg (free base equivalent) of RP-3500 hydrogen sulfate salt. Capsules are packaged in induction-sealed HDPE bottles fitted with child-resistant polypropylene caps. The study drug should be stored in the original bottles tightly closed in a dry place at 15 to 25°C (59 to 77°F). The capsules should not be frozen.

6.4 Dose Interruptions

Dose interruptions for study treatment-related AEs are allowed as per the dose modification recommendations in Section 6.6. In addition to dose interruption, the need for a dose reduction at the time of treatment resumption should also be considered based on the dose modification recommendations. If a toxicity-related dose delay lasts for >28 days, treatment will be discontinued permanently and the subject should be removed from study treatment. If a subject requires a dose hold for > 28 days for a non-treatment-related adverse event or situation (i.e. radiation therapy or COVID-19 infection) the subject may continue on study only after approval and discussion with the Principal Investigator and Medical Monitor.

All doses that were missed for any reason will not be replaced.

6.5 Dose Reductions

In dose-escalation, toxicities that occur within the DLT window that are deemed DLTs (Section 4.1.3 Definition of Dose Limiting Toxicities) will result in protocol removal. Adverse events that are not defined as DLTs, or occur after the DLT window, or occur in patients enrolled in the dose-expansion cohort may lead to dose delays and modifications as detailed in section 6.6. No dose reduction below RP-3500 20mg daily and olaparib 100mg BID will be allowed. Should the protocol dictate a dose reduction of olaparib below 100mg BID and/or RP-3500 below 20mg daily, the patient will be taken off of the protocol therapy. While these are suggested dosing schedule modifications and dosage reductions, the optimal dosing and dosing schedule for each patient should be individualized, and may not always fall into a step-wise fashion. Consultation with the study PI and medical monitor is recommended to determine the optimal dosing for each patient after significant AEs.

6.6 Dose Modifications and Supportive Care Guidelines

Subjects experiencing AEs attributed to study drug may undergo dose modifications for toxicity management. Dose modification guidelines are provided below for AEs considered to be related to study medication.

6.6.1 Dosing Schedule Modifications

The dose modifications will first alter the dosing schedules. The dosages of camonsertib (RP-3500) and olaparib will remain the same as the dose to which the patient was originally assigned:

Table 10.: Dosing Schedule Modifications

Dose Level	Schedule (21 -Day Cycles)	Camonsertib (RP -3500) and Olaparib dosing
Starting	3 weeks on	2 days on/5 days off
-1	2 weeks on/1 week off	2 days on/5 days off during dosing weeks
-2	1 week on/2 weeks off	3 days on/4 days off during dosing weeks

Should the patient require further dose reductions for toxicities, decreases in either camonsertib and/or olaparib dosages can be considered while maintaining the current dosing schedule or concurrently with a dosage decrease and a change in the dosing schedule. The study PI and medical monitor should be contacted for help in determining optimal dosing and dosing schedule for the patient. Some example patient scenarios are presented below:

- Patient experiences grade 3 neutropenic fever for a second time while receiving camonsertib (RP-3500) 50mg daily and olaparib 150mg BID on a dosing schedule of 2 days per week every week (i.e. no off weeks). Dose reduction of camonsertib to 40mg daily and olaparib to 100mg BID can be considered while maintaining the 2 days per week every week (i.e. no off weeks) dosing schedule.
- Patient experiences grade 4 neutropenic fever while receiving camonsertib (RP-3500) 50mg daily and olaparib 150mg BID on a dosing schedule of 2 days per week every week (i.e. no off weeks). Dose reduction of camonsertib to 40mg daily and olaparib to 100mg BID along with reduction of the dosing schedule to 2 weeks on/1 week off may be considered while maintaining the 2 days per week treatment during the dosing/on weeks.

6.6.2 Drug Dosage Modifications

After dosing schedule modifications, dosage reductions of either camonsertib and/or olaparib can considered independently or concurrently with dosing schedule modifications. If either camonsertib (RP-3500) or olaparib requires reductions to below DL 1 for toxicity management, study therapy will be discontinued:

Table 11. Dose Reduction Levels

Dose Level	Camonsertib (RP-3500)
1	20mg daily
2	30mg daily

3	40mg daily
4	50mg daily
5	80mg daily

Dose Level	Olaparib
1	100mg BID
2	150mg BID

6.6.3 Hematologic and Infectious Toxicities

Optimal supportive care should be offered to the patient in order to mitigate toxicities. Where appropriate, this includes administration of G-CSF, GM-CSF and blood/platelet transfusions as per institutional guidelines. At the start of each cycle, hold therapy until ANC ≥500/mm^3 and platelet count is ≥25,000/mm^3. Lymphopenia is an expected toxicity of CLL treatments and therefore should be graded and recorded as per CTCAE v5.0, but treatment holds and dose changes are not needed.

This study will utilize the 2018 IWCLL grading scale for hematologic adverse events in patients with baseline platelet count <100,000/mm^3 and/or baseline hemoglobin less than the lower limit of normal[55]. Grading of ANC is at the nadir within the cycle, and patients who have an ANC <1 x 10^9/L before therapy will not be evaluable for toxicity. These criteria account for baseline cytopenias secondary to CLL and are detailed in Table 12 below.

Table 12. iwCLL Hematologic Grading

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

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

The order in which dose reductions will occur will be change in dosing schedule (Table 10.: Dosing Schedule Modifications) with either sequential (preferred) or concurrent changes in drug dosages (Table 11). If drug dosage changes are required, the order in which dose reductions will occur will be camonsertib (RP-3500) first followed by olaparib if the AE continues to occur. If at any time a dose reduction would leave camonsertib (RP-3500) or olaparib doses less than DL 1 (Table 11. Dose Reduction Levels), the patient will be taken off protocol. Treatment delays for adverse events exceeding 21 days will lead to protocol removal. If reduction of the dosing schedule and/or drug doses resolves the patient's toxicity to grade ≤1 for at least 3-6 weeks, increasing camonsertib (RP-3500) and/or olaparib back to the prior dose or dosing schedule is permitted after discussion with the study PI.

Table 13. Management and dose modification guidelines for hematologic toxicities encountered with combination camonsertib (RP-3500) and olaparib.

Event Name	Neutropenia	
Grade of Event	Management/Next Dose for RP - 3500	Management/Next Dose for Olaparib
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose
Grade 3	No change in dose	No change in dose
Grade 4	Hold until ANC∫ is ≥1000/mm^3. G-CSF administration is recommended. At first occurrence, no change in dose or dosing schedule. If toxicity recurs, follow reductions in dosing schedule and drug dosages as per sections 6.6.1 and 6.6.2 only if grade 4 neutropenia lasts ≥7 days with optimal supportive care.	Hold until ANC∫ is ≥1000/mm^3. G-CSF administration is recommended. At first occurrence, no change in dose or dosing schedule. If toxicity recurs, follow reductions in dosing schedule and drug dosages as per sections 6.6.1 and 6.6.2 only if grade 4 neutropenia lasts ≥7 days with optimal supportive care and

		RP-3500 dosage already decreased for the same toxicity.
∫Only for patients with baseline ANC ≥1000. For patients with baseline ANC <1000, hold until ANC ≥500/mm^3		
Event Name	Thrombocytopenia	
Grade of Event	Management/Next Dose for RP - 3500	Management/Next Dose for Olaparib
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose
Grade 3	Hold until platelets∫ ≥50,000/mm^3. At first occurrence, no change in dose or dosing schedule. If toxicity recurs, follow reductions in dosing schedule and drug dosages as per sections 6.6.1 and 6.6.2.	Hold until platelets∫ ≥50,000/mm^3. At first occurrence, no change in dose or dosing schedule. If toxicity recurs, follow reductions in dosing schedule and olaparib dosages as per sections 6.6.1 and 6.6.2 if RP-3500 dosage already decreased for the same toxicity.
Grade 4	Same management as grade 3	Same management as grade 3
∫Only for patients with baseline platelets ≥100,000/mm^3. For patients with baseline platelets <100,000/mm^3, hold until platelets have recovered to at least 50% of baseline value.		
Event Name	Neutropenic Fever	
Grade of Event	Management/Next Dose for RP - 3500	Management/Next Dose for Olaparib
Grade 3	Hold until resolution of toxicity. G-CSF administration required. At first occurrence, no change in dose or dosing schedule. If toxicity recurs, follow reductions in dosing schedule and drug dosages as per sections 6.6.1 and 6.6.2.	Hold until resolution of toxicity. G-CSF administration required. At first occurrence, no change in dose or dosing schedule. If toxicity recurs, follow reductions in dosing schedule and olaparib dosages as per sections 6.6.1 and 6.6.2 if RP-3500 dosage already decreased for the same toxicity.

Grade 4	Hold until resolution of toxicity. G-CSF administration required. Follow reductions in dosing schedule and olaparib dosages as per sections 6.6.1 and 6.6.2.	Hold until resolution of toxicity . G-CSF administration required. Follow reductions in dosing schedule and olaparib dosages as per sections 6.6.1 and 6.6.2.if RP-3500 dosage already decreased for the same toxicity.
Event Name	Anemia	
Treat per institutional guidelines including blood transfusions and/or erythropoietins. Consider transfusing for symptoms with hemoglobin >8 g/dL (Grade <3) or for any Grade 3 (hemoglobin <8 g/dL). If possible, maintain RP-3500 and olaparib doses as long as patient is clinically stable, but if a dose reduction or interruption is desired, consult with the Medical Monitor.		

6.6.4 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) has been associated with the treatment of CLL and other B-cell neoplasms, including venetoclax treatment which requires a dose escalation of the drug over 5 weeks to mitigate TLS risk[56]. It is unknown whether combination RP-3500 and olaparib will induce TLS upon initiation of treatment. Therefore, TLS prophylaxis with a xanthine oxidase inhibitor will be administered at least 72 hours prior to C1D1 and during the first cycle of study therapy.

TLS blood chemistry monitoring are mandated at screening, C1D1, C1D2, C1D3, C1D8, C1D15, and C2D1. After which, TLS monitoring is at the discretion of the treating provider. If rasburicase is being considered for the treatment of hyperuricemia, it is recommended to check for red blood cell levels of glucose-6-phosphate dehydrogenase (G6PD) as rasburicase administration in G6PD-deficient patients may cause severe hemolysis.

For blood chemistry changes or symptoms suggestive of TLS in cycle 1:

Event	Hyperkalemia (including rapidly rising potassium)
Potassium ≥ 0.5 mmol/L increase from prior value (and ≤ULN)	• Hold RP-3500 and olaparib. Recheck potassium, phosphorous, uric acid, calcium, and creatinine in 1 hour. • If additional ≥ 0.2 mmol/L increase in potassium, but still ≤ upper limit of normal (ULN), manage per potassium > ULN. ○ If < 0.2 mmol/L increase in potassium and potassium ≤ ULN and no other evidence of tumor lysis, resume camonsertib (RP-3500) and olaparib per protocol..

Potassium > ULN but < 6 mmol/L (6.0mEq/L) and asymptomatic (e.g. muscle cramps, weakness,	• Hold camonsertib (RP-3500) and olaparib until resolution to ≤ ULN.
	• Perform ECG; administer calcium gluconate 100-200 mg/kg IV slowly if there is evidence of life-threatening arrhythmias
	  ○ Administer Kayexalate/Resonium 60g if available
	  ○ Administer furosemide 20mg

paresthesias, nausea, vomiting, and diarrhea)	○ Recheck potassium, phosphorous, uric acid, calcium and creatinine in 1 hour after administration of calcium gluconate, keyexalate/resonium, furosemide and ECG. If potassium ≤ULN 1 hour later, repeat potassium, phosphorous, uric acid, calcium, and creatinine 1, 2, and 4 hours later, if no other evidence of tumor lysis.
Potassium ≥ 6 mmol/L (6.0mEq/L) and symptomatic (e.g. muscle cramps, weakness, paresthesias, nausea, vomiting, and diarrhea)	• Hold camonsertib (RP-3500) and olaparib until resolution to ≤ ULN. • Perform ECG; administer calcium gluconate 100-200 mg/kg IV slowly if there is evidence of life-threatening arrhythmias ○ Administer Kayexalate/Resonium 60g if available ○ Administer furosemide 20mg IV ○ Administer insulin 0.1 U/kg IV + D52 2 mL/kg IV ○ Administer sodium bicarbonate 1 to 2 mEq/kg IV. Rasburicase should not also be used as this may exacerbate calcium phosphate precipitation. ○ Recheck potassium, phosphorous, uric acid, calcium and creatinine every hour.
Event	Hyperuricemia
Uric acid ≥ 8.0 mg/dL (476 µmol/L)	• Hold camonsertib (RP-3500) and olaparib until resolution to < 8.0 mg/dL (476 µmol/L) • Give rasburicase (as per local guidelines). Sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Recheck potassium, phosphorous, uric acid, calcium, and creatinine in 1 hour after rasburicase administration.
Uric acid ≥ 10 mg/dL (595 µmol/L) OR Uric acid ≥ 8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027 mmol/L) from predose level.	• Hold camonsertib (RP-3500) and olaparib until resolution • Give rasburicase (as per local guidelines). Sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Recheck potassium, phosphorous, uric acid, calcium, and creatinine in 1 hour after rasburicase administration. • If uric acid < 8.0 mg/dL 1 hour later, repeat potassium, phosphorous, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Event	Hypocalcemia
Corrected calcium ≤ 7.0 mg/dL (1.75 mmol/L) OR Patient symptomatic (e.g., muscle cramps,	• Hold camonsertib (RP-3500) and olaparib until resolution of calcium to > 7.0 mg/dL (1.75 mmol/L) or resolution of symptoms related to hypocalcemia.

hypotension, tetany, cardiac arrhythmias) in the presence of hypocalcemia	• Administer calcium gluconate 50 to 100 mg/kg IV slowly with ECG monitoring unless hyperphosphatemia in which case should address in consultation with nephrology. • Recheck potassium, phosphorous, uric acid, calcium, and creatinine in 1 hour after administration of calcium gluconate. If calcium normalizes 1 hour later, repeat potassium phosphorous, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Event	Hyperphosphatemia
Phosphate ≥ 0.5 mg/dL (1.615 mmol/L) with ≥ 5.0 mg/dL (0.16 mmol/L) increase	• Hold camonsertib (RP-3500) and olaparib until resolution to < 5.0 mg/dL (1.615 mmol/L). • Administer a phosphate binder (e.g., aluminium) • Recheck potassium, phosphorous, uric acid, calcium, and creatinine in 1 hour after administration of phosphate binder. If calcium normalizes 1 hour later, repeat potassium phosphorous, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.

For blood chemistry changes or symptoms suggestive of TLS outside of cycle 1:

- Withhold the next day's dose of RP-3500 and olaparib. If it resolves within 48 hours of last dose resume at the same dose and then proceed with planned therapy.
- For any blood chemistry changes requiring > 48 hours to resolve and TLS attributable to RP-3500 and olaparib treatment, resume both drugs at one DL lower.
- For any events of clinical TLS and attributable to RP-3500 and olaparib treatment, hold both drugs and provide best supportive care. When resolved, resume both drugs at one DL lower.

If TLS does not re-occur after 2 weeks of treatment at the reduced doses, increase of both drugs to the prior DL can be considered. Should laboratory or clinical TLS re-occur after re-escalation to the higher DL, and is attributable to RP-3500 and olaparib treatment, both drugs should be permanently lowered to one DL lower.

6.6.5 Non-hematologic Toxicities

Specific guidelines are provided below for selected non-hematologic toxicities. In AEs that have guidelines for both RP-3500 and olaparib, follow the guideline for the most likely causative agent. If the causative agent cannot be determined, hold both RP-3500 and olaparib and follow the guidelines for both drugs.

If a patient experiences several adverse events, and there are conflicting recommendations, the investigator should use the recommended dose adjustment that reduces the dose to the lowest level. Treatment delays for adverse events exceeding 21 days will lead to protocol removal. If reduction of the drug doses resolves the patient's toxicity to grade ≤1 for at least 3 weeks,

increasing RP-3500 and/or olaparib back to the prior dose is permitted. No dose below dose level 1 (Table 11) for either drug is allowed and should protocol dictate another dose reduction below dose level 1, the patient will be removed from study.

Table 14. Management and dose modification guidelines for non-hematologic toxicities encountered with combination RP-3500 and olaparib.

Event Name	Nausea	
Grade of Event	Management/Next Dose for RP - 3500	Management/Next Dose for Olaparib
≤ Grade 1	No change in dose	5-HT3-antagonists, D2-antagonists or NK1 antagonists, and benzodiazepines administration can prevent or treat nausea in the majority of patients. Consider additional anti-emetics as per the NCCN Clinical Practice Guideline for antiemesis[57]. Advise patient to take one or more anti-nausea medications 30-60min prior to taking olaparib.
Grade 2	No change in dose. Modify dosing schedule of RP-3500 concurrently with olaparib.	Implement one or more combinations of anti-nausea medications including dexamethasone pre-medication given 30-60 min prior to taking RP-3500 and olaparib. Consider additional anti-emetics as per the NCCN Clinical Practice Guideline for antiemesis[57]. Advise patient to take one or more anti-nausea medications 30-60min prior to taking olaparib. Olanzapine 2.5 to 5mg every morning, as per NCCN guidelines, can mitigate nausea/vomiting. If nausea persists at grade 2 for ≥7 days, hold olaparib. May resume olaparib at the same dose if nausea becomes ≤ grade 1. If grade 2 nausea reoccurs for ≥7 days for a second occurrence despite maximal supportive care, then follow reductions in dosing schedule and drug dosages as per sections 6.6.1 and 6.6.2. If patient's nausea is grade ≤1 for 3 weeks, then the dose or dosing schedule of olaparib may

		be increased back to the previous dose/schedule.
Grade 3	No change in dose. Modify dosing schedule of RP-3500 concurrently with olaparib.	Hold drug and implement one or more combinations of anti-nausea medications including dexamethasone pre-medication given 30-60 min prior to taking RP-3500 and olaparib. Consider additional anti-emetics as per the NCCN Clinical Practice Guideline for antiemesis[57]. May restart olaparib at the same dose level once nausea becomes ≤ grade 1 and advise the patient to take one or more anti-nausea medications 30-60min prior to taking olaparib. Olanzapine 2.5 to 5mg every morning, as per NCCN guidelines, can mitigate nausea/vomiting. If grade 3 nausea reoccurs, hold drug until nausea resolves to ≤ grade 1 and resume olaparib with a dose reduction following reductions in dosing schedule and drug dosages as per sections 6.6.1 and 6.6.2. If patient's nausea is grade ≤1 for 3 weeks at the reduced dose/schedule, then olaparib may be increased back to the previous dose/schedule.
Event Name	Vomiting	
Grade of Event	Management/Next Dose for RP - 3500	Management/Next Dose for Olaparib
≤ Grade 2	No change in dose	No change in dose. Implement one or more combinations of anti-nausea medications including dexamethasone pre-medication given 30-60 min prior to taking RP-3500 and olaparib. Consider additional anti-emetics as per the NCCN Clinical Practice Guideline for antiemesis[57]. Advise patient to take one or more anti-nausea medications 30-60min prior to taking olaparib. Olanzapine 2.5 to 5mg every morning, as per NCCN guidelines, can mitigate nausea/vomiting.

Grade 3	No change in dose. Modify dosing schedule of RP-3500 concurrently with olaparib.	Hold until toxicity ≤ grade 1 and resume treatment with reduction of dosing following reductions in dosing schedule and drug dosages as per sections 6.6.1 and 6.6.2. Implement maximal supportive care measures including dexamethasone pre-medication 30-60 min prior to taking RP-3500 and olaparib. Olanzapine 2.5 to 5mg every morning, as per NCCN guidelines, can mitigate nausea/vomiting. If patient's vomiting is grade ≤1 for 3 weeks at the reduced dose/schedule, then olaparib may be increased back to the previous dose/schedule.
Event Name	Diarrhea	
Grade of Event	Management/Next Dose for RP - 3500	Management/Next Dose for Olaparib
≤ Grade 1	No change in dose	Rule out other causes of diarrhea, including infectious etiologies and drug effects. At the first sign of loose or abnormal stool, it is recommended that the patient be treated according to institutional standard of care. Maintain dose of olaparib.
Grade 2	No change in dose. Modify dosing schedule of RP-3500 concurrently with olaparib.	If diarrhea is present despite maximal anti-diarrheal medications, rule out other causes of diarrhea, including infectious etiologies and drug effects. Reduce olaparib following reductions in dosing schedule and drug dosages as per sections 6.6.1 and 6.6.2(i.e. dosing schedule with either sequential or concurrent decrease in olaparib dose level) until resolved to grade ≤1, then increase olaparib to prior dose and/or schedule. If toxicity recurs at grade ≥2, then reduce olaparib following reductions in dosing schedule and drug dosages as per sections 6.6.1 and 6.6.2. If patient is stable and diarrhea resolves (grade 0 or

		baseline) for 3 weeks, olaparib may be re-escalated to prior dose/schedule.
≥ Grade 3	No change in dose. Modify dosing schedule of RP-3500 concurrently with olaparib.	If diarrhea is present despite maximal anti-diarrheal medications, rule out other causes of diarrhea, including infectious etiologies and drug effects. Hold olaparib until toxicity is grade ≤1, then restart olaparib following reductions in dosing schedule and drug dosages as per sections 6.6.1 and 6.6.2 (i.e. dosing schedule with either sequential or concurrent decrease in olaparib dose level). If patient is stable and diarrhea resolves (grade 0 or baseline) for 3 weeks, olaparib may be re-escalated to prior dose/schedule.
Event Name	Fatigue	
Grade of Event	Management/Next Dose for RP - 3500	Management/Next Dose for Olaparib
Grade 1	Maintain dose. Rule out other causes. If found to be anemic and symptomatic, consider transfusing even with hemoglobin >8g/dL. Consider adding dexamethasone 4-8mg pre-medication on days of RP-3500/olaparib administration.	Maintain dose. Rule out other causes. If found to be anemic and symptomatic, consider transfusing even with hemoglobin >8g/dL. Consider adding dexamethasone 4-8mg pre-medication on days of RP-3500/olaparib administration.
Grade 2 lasting ≤7 days	As per NCCN guidelines, consider stimulants such as methylphenidate 5mg QD in the morning only. Consider adding dexamethasone 4-8mg pre-medication on days of RP-3500/olaparib administration.	As per NCCN guidelines, consider stimulants such as methylphenidate 5mg QD in the morning only. Consider adding dexamethasone 4-8mg pre-medication on days of RP-3500/olaparib administration.
Grade 2 lasting >7 days or grade ≥3	Rule out other causes. If found to be anemic and symptomatic, consider transfusing even for hemoglobin >8 g/dL. As per NCCN guidelines, consider stimulants such as methylphenidate 5mg QD in the morning only. Hold RP-3500 dosing until resolved to ≤ grade 1 or	Rule out other causes. If found to be anemic and symptomatic, consider Transfusing even for hemoglobin >8 g/dL. As per NCCN guidelines, consider stimulants such as methylphenidate 5mg QD in the morning only. Hold olaparib dosing until resolved to ≤ grade 1 or baseline. For first occurrence, restart

	baseline. For first occurrence, restart RP-3500 at current dose and schedule. For second occurrence, reduce RP-3500 and olaparib treatments following reductions in dosing schedule and drug dosages as per sections 6.6.1 and 6.6.2. Consider adding dexamethasone 4-8mg pre-medication on days of RP-3500/olaparib administration. If patient is stable and fatigue resolves (≤ grade 1 or baseline) for 3 weeks, RP-3500 may be re-escalated to prior dose.	olaparib at current dose and schedule. For second occurrence, reduce olaparib and RP-3500 treatment following reductions in dosing schedule and drug dosages as per sections 6.6.1 and 6.6.2. Consider adding dexamethasone 4-8mg pre-medication on days of RP-3500/olaparib administration. If patient is stable and fatigue resolves (≤ grade 1 or baseline) for 3 weeks, olaparib may be re-escalated to prior dose.
Event Name	Dyspnea	
Grade of Event	Management/Next Dose for RP - 3500	Management/Next Dose for Olaparib
Grade 1	No change in dose	Rule out other causes, including infection, primary pulmonary causes (i.e. embolism, effusion and edema), cardiac etiologies and drug effects. Consider transfusing even if patient's hemoglobin is >8g/dL. Maintain dose.
≥ Grade 2	No change in dose. Modify dosing schedule of RP-3500 concurrently with olaparib.	Rule out other causes, including infection, primary pulmonary causes (i.e. embolism, effusion and edema), cardiac etiologies and drug effects. Consider transfusing even if patient's hemoglobin is >8g/dL. Hold olaparib until toxicity resolves to grade ≤1. Resume olaparib at the same dose and schedule. If toxicity reoccurs despite maximal supportive care or treatment of underlying cause, reduce olaparib and RP-3500 following reductions in dosing schedule and drug dosages as per sections 6.6.1 and 6.6.2. If patient's dyspnea is grade ≤1 for 3 weeks at the reduced dose, then olaparib may be increased back to the previous dose/schedule.
Other Non-Hematologic Toxicity		
≥ Grade 3	Hold the causative agent until toxicity is ≤ grade 1 or baseline. Implement maximal supportive care and rule out other potential causes of that toxicity. If treatment delay is ≤7 days, restart at same dose or at a lower dose level	

	upon investigator discussions. If treatment delay is >7 days but ≤21 days, restart treatments following reductions in dosing schedule and drug dosages as per sections 6.6.1 and 6.6.2 in which changes in dosing schedule of both drugs should first be implemented with either sequential or concurrent reductions in drug dosages. If treatment delay >21 days, discontinue study.

6.7 Concomitant Medications and Therapies

All administered concomitant medications (including herbal supplements) and non-medicinal therapies (including transfusions) used 28 days prior to Cycle One Day One, and until 30 days after the last dose of study therapy will be recorded in the subject's research chart and corresponding eCRF. All medications, including those used to treat adverse events, chronic conditions or diseases, or as supportive therapy should be documented in the eCRF.

6.7.1 Prohibited Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the active treatment period (Refer to Appendix 5). Subjects are prohibited from receiving the following therapies during the treatment phase of this trial:

- Anti-cancer systemic chemotherapy or biological therapy;
- Other investigational agents;
    - Exception: therapies given for the prevention, treatment or management of COVID-19 under the FDA emergency use authorization are allowed.
- Radiation therapy >10 Gy to any one lesion;
- Any live-attenuated vaccine therapies for the prevention of infectious disease (e.g. MMR, or rotavirus);
    - Exception: Vaccines for the prevention of COVID-19 are allowed.
- Herbal remedies known to potentially interfere with major organ function (e.g. hypericin);
- Strong P-glycoprotein inhibitors (P-gp);
- Breast Cancer Resistance Protein (BCRP) inhibitors;
- Strong CYP3A4 inhibitors and/or inducers.

If a subject requires treatment with one or more of the listed prohibited medications, the subject may need to be taken off study therapy. Each case will be considered and if possible, the investigator should discuss with the DSMC and Medical Monitor prior to initiating prohibited therapy.

6.8 Recommended Infectious Prophylaxis

The use of infectious prophylaxis medications are strongly recommended given the immunocompromised state of CLL patients and potential for leukopenia/neutropenia while being treated with RP-3500 and olaparib. While prophylaxis regimens can be determined by the treating

provider and according to institutional guidelines, Table 15 summarizes the recommended regimens for infectious prophylaxis and appropriate alternatives. If the patient is allergic to all of the medications listed for each specific type of infection, then an infectious disease physician should be consulted for help in management.

G-CSF administration and formulation are as per institutional standard.

Table 15. Recommended infection prophylaxis medications.

Prophylaxis	Preferred Medication	Alternative Medication	Duration
Viral • Herpes Simplex • Varicella Zoster	Acyclovir* 400mg to 800mg PO BID	Valacyclovir* 500mg to 1000mg PO daily	Entirety of treatment and trial
Bacterial (if neutropenia with ANC <1,000/μL is expected to last ≥7 days)	• G-CSF administration is strongly recommended • Levofloxacin* 500mg PO/IV daily	• G-CSF administration is strongly recommended • Cefpoxodime* 200mg PO BID or, • Ciprofloxacin* 500mg PO BID	Until ANC >500/μL for 3 consecutive days
Immunoglobulin replacement therapy	Hypogammaglobulinemia is common in CLL patients. Replacement with IVIG may be indicated for patients with IgG levels <500 and recurrent infections. However, some patients may benefit from IVIG replacement even if IgG is ≥500 if recurrent infections were common in their prior clinical history.		
*Adjust for renal function			

6.9 Duration of Therapy

Subjects will receive combined treatment until treatment discontinuation criteria is met. Upon meeting treatment discontinuation criteria, subjects will continue on the study in follow-up until study discontinuation criteria are met.

6.9.1 Criteria for the Discontinuation of Treatment

Subjects may withdraw from treatment or the study overall at any time at their request, or they may be withdrawn at the discretion of the Investigator or Sponsor for safety, behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures. In addition to the drug-specific discontinuation criteria listed in section 7, the following will result in treatment discontinuation:

- The subject requests to discontinue the study treatment and/or study procedures;

- Clinical deterioration that, in the opinion of the investigator, increases the risk to the subject;
- Confirmed disease progression based on iwCLL 2018 criteria (Section 7.5.3);
- Adverse events or intercurrent illness that in the opinion of the investigator warrants the subject's withdrawal from study treatment;
- Significant noncompliance with the protocol schedule or treatment administration in the opinion of the investigator;
- Pregnancy;

6.9.2 Criteria for the Discontinuation of Study

Subjects will be taken off study for the following:

- Completed study follow-up period;
- Participant or legally authorized representative requests to be fully withdrawn from the study;
- If, in the investigator's opinion, the continuation of the trial would be harmful to the subject's well-being;
- The subject is lost to follow-up;
- Screen failure;
- Death.

6.9.3 Withdrawal of consent

Subjects are free to withdraw from the study at any time without prejudice to further treatment. Subjects who withdraw consent for further participation in the study will not receive any further study medications or further study observation.

If a subject withdraws consent, they will be specifically asked if they are withdrawing consent to all further participation in the study including any further follow-up (e.g., survival contact telephone calls). Survival status may be obtained from public records for subjects who have withdrawn from any further follow-up contact.

6.9.4 Long Term Follow-Up for OS

Subjects that discontinue study treatment for any reason other than disease progression, must continue to have disease assessments until disease progression or the initiation of subsequent anticancer therapy per Section 4.5.

Upon discontinuation of study therapy, subjects will be followed for OS for 10 years from the date of study therapy initiation. Subjects or their legally authorized representatives will be contacted every 6 months (±14 days) during the first 5 years and then yearly (±28 days) during the following years thereafter until death, end of the study, or subject withdrawal of consent, whichever comes first. Survival and subsequent treatment status may be collected by public records, medical

records, or by contacting the subject or their legally authorized representative by phone. All efforts should be made to contact the subject at these time points. Refer below for Lost to Follow-Up guidelines.

6.9.4.1 Lost to Follow-Up

Subjects will be considered lost to follow-up only if no contact has been established by the time the study is completed, such that there is insufficient information to determine the subject's status at that time. Subjects who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing subjects throughout the study period. If contact with a missing subject is re-established, the subject should not be considered lost to follow-up and evaluations should resume according to the protocol.

When a subject is lost to follow-up, site personnel should check hospital records, the subjects' current physician, and a publicly available death registry to obtain a current survival status.

In the event that the subject has actively withdrawn consent, the survival status of the subject can be obtained by site personnel from publicly available death.

7 STUDY ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that there may be circumstances, outside of the control of the Investigator that may make it unfeasible to perform the test. In these cases, the Investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the Investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible.

7.1 General Assessments

7.1.1 Participant Consent

Before the initiation of any study procedures, all potential subjects or their legal representative must be fully informed of the risks and potential benefits of trial participation and demonstrate understanding. An informed consent document must be signed and dated by the participant or their legal representative indicating that they understand the risks and consent to participation and treatment on the study. The Principal Investigator or their appropriately trained and delegated study personnel conducting the informed consent discussion must also sign and date the document. A copy of the signed document should be provided to the subject.

Procedures, laboratory tests, or imaging performed as part of the standard of care prior to subject consent may contribute to the assessment of eligibility and/or screening procedures if performed during the screening period.

7.1.2 Medical History

The investigator or appropriately trained and delegated study personnel will collect medical history to the extent that supports the assessment of eligibility. The medical history will include any active

conditions and any conditions deemed to be clinically significant by the treating investigator. The use of symptom terms should be discouraged; if possible, terms describing the principal condition or syndrome should be used.

When collecting the initial medical history at screening, specific attention should be given to:

- Baseline symptoms
- A detailed history of prior cancers and cancer therapies including start and stop dates (duration of therapy), disease progression during or after therapy, discontinuation of therapies due to intolerability or any other serious illness, and length of remission.
- Past surgical, family, and social histories
- Past medical history as well as currently managed medical problems and their treatments
- ECOG performance status

When collecting medical history at subsequent study visits, specific attention should be given to:

- New symptoms related to potential adverse events
- Status of disease
- Management of previously documented adverse events and their current grade

7.1.3 Cancer History

The oncologic history of the patient's CLL will be collected at the screening visit and will include:

- CLL status at initial diagnosis (if known)
  - Date of diagnosis
  - Age at diagnosis
  - Relevant laboratory measures including but not limited to complete blood count with differential, CLL FISH, beta 2 microglobulin, CLL NGS, IGHV mutational status, karyotype, CLL flow cytometry markers.
  - Rai and Binet stages
  - Presence of B-symptoms
- Time to first treatment – defined as days from date of initial diagnosis to date of first treatment initiation
- Prior treatment regimens
  - Treatment name and type
  - Duration of therapy (if available, start and stop dates)
  - Best response on therapy
  - Reason for discontinuation
  - Sequence of therapies
  - Toxicities encountered while on each treatment regimen
  - Length of remission

- Current indication for treatment

7.1.4 Concomitant Medications

All medications currently being used by a study participant, regularly or as needed, must be reviewed and documented by the investigator or qualified designee. Specific attention should be given to medications with a protocol required washout as described in the exclusion criteria and any medication taken 28 days prior to cycle one day one. Refer to Section 6.7 for prohibited medications.

During protocol therapy, any medications taken by the patient or used to treat an adverse event will be documented in the subject's research chart and the corresponding eCRF. If a new anticancer therapy is initiated during study follow-up, the new therapy should also be recorded in the subject's research chart and corresponding eCRF.

7.1.5 CLL FISH Testing

It is required that all subjects have CLL FISH analysis after progression is noted from the most recent line of therapy and within 6 months of screening. Testing will be accepted from either peripheral blood and/or bone marrow samples. FISH probes should be directed to detect deletion 13q14, trisomy 12, deletion 11q22.3, and deletion 17p13. The CLL FISH testing must be confirmed by a Clinical Laboratory Improvement Amendments (CLIA) approved test. All FISH abnormalities should be recorded along with whether the deletion 13q14 was monoallelic or biallelic. If a patient has multiple FISH abnormalities, hierarchal FISH should be used[9].

7.1.6 Mutation Testing

It is required that all subjects have documentation of the necessary somatic mutations through local laboratory testing. Somatic mutation testing must be performed after progression is noted from the most recent line of therapy and within 6 months of screening. Testing will be accepted from either peripheral blood and/or bone marrow samples. At a minimum, the following somatic mutations should be tested: TP53, ATM, SF3B1, POT1, and XPO1. While not required, the following genes are strongly encouraged to be tested: NOTCH1, BIRC3, BRAF, KRAS, DDX3X, MYD88, and CXCR4. All detected gene mutations and their respective variant allele frequency (VAF) percentage should be recorded. The mutational status must be confirmed by a CLIA approved test.

7.2 Safety Assessments

7.2.1 Physical Examinations and Vital Signs

Subjects will have physical examinations to include major body systems, vital signs (blood pressure, heart rate, respiration rate, pulse oximetry, and body temperature), assessment of ECOG performance status (see Appendix 1), weight, and height at the time points described in the Schedule of Events. Particular attention should be paid to lymph nodes, spleen and liver. Documentation of lymph nodes should include location(s) and size (in centimeters) as noted in two orthogonal directions. Liver size should be documented as enlargement of the liver below the costavertebral angle as measured from the right mid-supraclavicular line in centimeters. Spleen

size should be documented as enlargement of the spleen below the costaverteral angle as measured from the left mid-supraclavicular line in centimeters.

7.2.2 Adverse Events

Adverse events experienced during trial participation will be collected per the Schedule of Events and Adverse Events Section. Each study participant will be questioned about the occurrence of adverse events in a non-leading manner. Should the treating investigator feel that the adverse event is attributed to study therapy, dose modification guidelines in the Dose Modification Section will be followed.

7.2.3 Laboratory Assessments

Samples for all laboratory assessments will be drawn at the time points indicated in the Schedule of Events and when clinically indicated. All safety laboratory analyses will be performed by the local laboratory for each study center. When applicable, all safety laboratory assessments must be reviewed by the treating investigator before study drug administration. When applicable, results from the pregnancy test must also be available for review before dosing.

Table 16: Laboratory Assessments

Laboratory Assessments	

Complete Blood Count with Platelet Count and Differential	• White Blood Cell Count
	• Hemoglobin
	• Platelets
	• Manual or automated white blood cell count differential including:
	  ○ Absolute Neutrophil Count
	  ○ Absolute Lymphocytes

Chemistry	• Complete Metabolic Panel
	  ○ Sodium
	  ○ Potassium
	  ○ Chloride
	  ○ Carbon Dioxide
	  ○ Alkaline Phosphatase
	  ○ Aspartate Aminotransferase
	  ○ Alanine Aminotransferase
	  ○ Urea Nitrogen
	  ○ Glucose
	  ○ Creatinine
	  ○ Calcium
	  ○ Protein
	  ○ Albumin
	  ○ Total Bilirubin

Tumor Lysis Syndrome (TLS)	• Lactate dehydrogenase • Phosphorus • Uric acid

Urine	• 24 hour urine

HIV and Hepatitis Serologies	• Hepatitis B Virus (HBV):
	  ○ Hepatitis B surface antigen (HBsAg)
	  ○ Antibody to hepatitis B core antigen (anti-HBc)
	  ○ Antibody to hepatitis B surface antigen (anti-HBs)
	  ○ HBV DNA quantification (for subjects who are anti-HBs positive)
	• Hepatitis C Virus (HCV):
	  ○ Antibody to Hepatitis C (anti-HCV)
	  ○ HCV-RNA (for subjects who are anti-HCV positive)
	• HIV
	  ○ Human Immunodeficiency Virus (HIV) Combo Antigen/Antibody (HIV-1/O/2)

Pregnancy	• Beta-hCG Qualitative Urine or Serum

7.3 12-Lead Electrocardiograms

Standard 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs. All subjects will require triplicate 12-lead ECG measurement with tracings approximately one-minute apart which will be performed according to the Schedule of Events. The parameters to be recorded are QT, QTc, PR, and QRS. All ECGs should be conducted pre-dose and Fridericia's formula will be used for all QT correction calculations. The mean QTcF from these ECGs should be recorded.

7.4 Efficacy Assessments

7.4.1 Disease Assessment

Disease assessments will include complete blood count with differential, CT scans of the neck, chest, abdomen, and pelvis, peripheral blood immunophenotyping, and bone marrow biopsy and aspirate at the time points indicated on the Schedule of Events.

7.4.2 Disease Assessment Algorithm

All patients should have a CT scan of the neck, chest, abdomen, and pelvis with IV contrast at the time of screening or up to 28 days prior to C1D1. CTs are required at C4D1 (± 7 days). Should this CT show that the patient has achieved an iwCLL 2018 defined complete remission (CR) and absolute lymphocyte count is <4000, then a bone marrow biopsy should be performed to confirm CR.

At any other study time point beyond C4D1 excluding end of treatment, the patient may have a disease assessment if the subject achieves hematologic recovery or the treating physician suspects the patient has achieved a CR as per the 2018 iwCLL criteria. At that time, a peripheral blood immunophenotype should be ordered. If the peripheral blood

immunophenotype shows no evidence of circulating CLL cells, then CTs of the neck, chest, abdomen, and pelvis should be performed. Should the CT also confirm CR, then a bone marrow biopsy should be performed to confirm CR. The study team has 28 days to complete all necessary testing required to confirm a CR from the time a CR is suspected by the treating physician. During this time, protocol treatment may continue as prescribed.

7.4.3 End of Treatment Assessment

Patients who come off study for any reason should have an end of treatment assessment as outlined in the Schedule of Events.

7.4.4 Patients with Iodine Contrast Allergy

If a patient has a history of an allergy to iodine contrast as required by the CTs, then premedications should be offered to the patient. Premedications can follow institutional guidelines or the offered schedule below:

- 13 hours prior to CT: 50 mg PO prednisone
- 7 hours prior to CT: 50 mg PO prednisone
- 1 hour prior to CT: 50 mg PO prednisone and 50 mg PO Benadryl

If a patient refuses iodine contrast allergy even when premedications are offered, then CTs may be performed without iodine contrast.

7.4.5 Peripheral Blood Immunophenotyping

Peripheral blood immunophenotyping are required at screening and to confirm a CR as outlined on the Schedule of Events. This is a flow cytometry based test to confirm markers present on CLL cells. These markers include but are not limited to CD5, CD10, CD19, CD20, CD23, CD200 and kappa/lambda light chain restriction. The percentage of CLL cells that make up the total population of leukocytes should be recorded. The peripheral blood immunophenotyping must be confirmed by a CLIA approved test.

7.4.6 Bone Marrow Biopsy

At a minimum, marrow core and aspirate testing should include pathological review of the core sample, leukocyte and lymphocyte flow cytometry and minimal residual disease testing by flow cytometry (as per institutional standard). Other testing is at the discretion of the treating provider. The CLL FISH and CLL NGS required at the time of screening may be performed on either peripheral blood or bone marrow biopsy as long as the test produces a successful result. If the presence of lymphoid nodules are noted by the pathologist, immunohistochemistry of these nodules should be performed to define whether these are primarily T cells, B cells other than CLL cells or CLL cells. The following data points should be recorded in the corresponding eCRF.

- Lymphocyte percentage and count
- Presence of lymphoid of nodules – If presence is noted, additional immunohistochemistry tests should be performed on these nodules to define whether these nodules comprise primarily T cells, B cells other than CLL cells or CLL cells

- Percent cellularity
- Percent of CLL cells detected on flow cytometry
- Percent of CLL cells comprising the entire marrow if detected by morphology and immunohistochemistry
- CLL MRD by flow cytometry (if performed)
- CLL MRD by NGS (if performed and resulted)
- Bone marrow fibrosis grade (if performed)
- Any NGS identified mutations (if performed)
- Cytogenetics (if performed)
- CLL FISH (if performed)

If the patient has had a previous bone marrow biopsy that has demonstrated a CR while on trial, a repeat bone marrow biopsy is not required while the subject is still enrolled on trial unless the treating provider suspects progression of disease.

7.5 Definition of Response and Progression

Disease response assessments will be according to the 2018 iwCLL definitions of response and progression. It is summarized in Table 17.

Table 17. Response definitions and criteria.

Parameter	Complete remission (CR)*	Partial remission (PR)*	Progressive disease (PD)*	Stable disease (SD)*
	All criteria below must be met	At least 2 of the parameters of group A and 1 parameter of group B must improve if previously abnormal; if only 1 parameter of both groups A and B is abnormal before therapy, only 1 must improve	At least 1 of the criteria of group A or group B must be met; constitutional symptoms alone do not define PD	All of the criteria must be met
Group A				

Parameter	Complete remission (CR)*	Partial remission (PR)*	Progressive disease (PD)*	Stable disease (SD)*
Lymph nodes	None > 1.5 cm	Decrease ≥ 50% (from baseline)*	Increase ≥ 50% from best response	Change of -49% to +49% from baseline
Liver and/or spleen size**	Spleen size < 13; liver size normal	Decrease ≥ 50% (from baseline)	Increase ≥ 50% from best response	Change of -49% to +49% from baseline
Constitutional Symptoms	None	Any	Any	Any
Circulating lymphocyte count	Normal	Decrease ≥ 50% (from baseline)	Increase ≥ 50% over baseline	Change of -49% to +49% from baseline
Group B				
Platelet count	≥ 100,000/mcL	> 100,000/mcL or increase ≥ 50% over baseline	Decrease of ≥ 50% from baseline secondary to CLL	Change of -49% to +49% from baseline
Hemoglobin	≥ 11.0 g/dL	> 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-lymnphoid 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

7.5.1 Complete Remission

CR requires all of the following criteria:

- Peripheral blood lymphocytes (evaluated by blood and differential count) below 4 x 10^9/L (4,000/mm^3).
- Absence of significant lymphadenopathy (i.e., lymph nodes >1.5 cm in diameter) and hepatosplenomegaly by physical examination.
- CT scan of the abdomen, pelvis, and thorax should be performed, showing no lymph nodes larger than 1.5 cm in diameter and no hepatosplenomegaly with spleen size <13cm.
- Absence of disease-related constitutional symptoms.
- Blood counts above the following values:

- Neutrophils ≥1.5 x 10^9/L (1,500/mm^3).
- Platelets ≥100 x 10^9/L (100,000/mm^3).
- Hemoglobin ≥110 g/L (11.0 g/dL) without red blood cell transfusion.

- Bone Marrow Aspirate/Biopsy:
  - For a CR, the cytological or pathological evaluation of the bone marrow smear or biopsy must be at least normocellular for age, without evidence for typical CLL lymphocytes by morphological criteria.
  - If the marrow is hypocellular, a repeat determination should be performed after 4 weeks, when peripheral blood counts have recovered. However, this time interval should not exceed 6 months after the last treatment. A marrow biopsy should be compared with that of pretreatment marrow.
  - The quality of the CR should be assessed for MRD by flow

For patients who fulfill the criteria for a CR, but have a persistent anemia, thrombocytopenia or neutropenia apparently unrelated to CLL, but related to drug toxicity, these patients should be labeled as a CR with incomplete marrow recovery (CRi). A bone marrow evaluation must be performed with scrutiny and not show any clonal disease infiltrate.

7.5.2 Partial Remission (PR)

PR is defined by achieving at least 2 of the criteria described in Sections 7.4.1a, 7.4.1b, or 7.4.1c (if abnormal before therapy), as well as one or more of the features listed in section 7.2d. If only 1 parameter in Sections 7.4.1a, 7.4.1b, 7.4.1c, 7.4.1d were abnormal before therapy, only 1 needs to improve.

- A decrease in the number of blood lymphocytes to 50% or less from the value recorded immediately prior to initial dose of therapy.
- Reduction in lymphadenopathy compared with baseline by palpation as defined by the following: (Additional assessment of response by CT scan of abdomen, pelvis, and thorax should be performed per study calendar.):
  - A decrease in lymph node size by 50% or more either in the sum of the longest diameters of the enlarged lymph node(s) selected at baseline as assessed by physical examination (an established number has been a maximum of 6) or the sum products of the same enlarged lymph nodes selected at baseline as assessed by imaging (an established number in clinical trials of lymph nodes has been up to 6).
  - No increase in any lymph node, and no new enlarged lymph node. In small lymph nodes (longest diameter < 1.5 cm), an increase <25% is not considered significant.
- A regression ≥ 50% of the extent of enlargement of the spleen below the costal margin defined by palpation, or normalization in size. When assessed by CT, scan spleen size

must have regressed by ≥ 50% in length beyond normal. A persistence of splenomegaly posttherapy may have limited influence on outcome in CLL.

- A regression of ≥ 50% of the extent of enlargement of the liver below the costal margin defined by palpation, or normalization in size. Given the impact of numerous medical conditions, liver size by physical examination or 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.
- The blood count should show one of the following results:
    - Platelet counts greater than 100 × 109/L (100,000/mcL) or 50% improvement over baseline.
    - Hemoglobin greater than 110 g/L (11.0 g/dL) or 50% improvement over baseline without requiring red blood cell transfusions

Patients who achieve a CR as per section 7.5.1 but bone marrow examination shows residual lymphoid nodules deemed related to CLL residual disease will be labeled as having achieved a nodular partial remission (nPR).

7.5.3 Progressive Disease

Progressive disease during or after therapy is characterized by at least one of the following:

- Lymphadenopathy: Progression of lymphadenopathy as confirmed by physical examination. Disease progression occurs if one of the following events is observed:
    - Appearance of any new lesion, such as enlarged lymph nodes (≥ 1.5 cm), splenomegaly, hepatomegaly, or other organ infiltrates.
    - An increase by 50% or more in greatest determined diameter of any previous site.
- Splenomegaly: An increase in the spleen size by ≥ 50% of the extent of enlargement of the spleen below the costal margin or the de novo appearance of splenomegaly defined by palpation. If no prior splenomegaly was observed at baseline or if splenomegaly has resolved with treatment, the spleen must increase by at least 2 cm from baseline.
- 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. 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.
- An increase in the number of blood lymphocytes by 50% or more with at least 5 x 10^9/L B lymphocytes.
- Transformation to a more aggressive histology (e.g., Richter syndrome or Richter transformation). Whenever possible, this diagnosis should be established by lymph node biopsy.

- Occurrence of cytopenia (neutropenia, anemia, or thrombocytopenia) directly attributable to CLL and unrelated to autoimmune cytopenias.
    - During Therapy: Cytopenias may occur as a side effect of many therapies and should be assessed according to CTCAE criteria. During therapy, cytopenias cannot be used to define disease progression. Dose reductions for cytopenias are outlined in Section 6.
    - After Treatment: The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of Hb levels by ≥ 20 g/L (2 g/dL) or < 100 g/L (10 g/dL), or by a decrease of platelet counts by ≥ 50% or to < 100 x 10^9/L, which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells and is not considered treatment-related toxicity.

7.5.4 Stable Disease

Patients who have not achieved a CR, or PR and who have not exhibited progressive disease, will be considered to have stable disease (which is equivalent to a nonresponse).

7.6 Correlative Studies

To support exploratory objectives and correlative studies, blood and bone marrow aspirate will be collected at the time points indicated on the Schedule of Events. After completion of the described correlative studies, any remaining blood or bone marrow aspirate will be stored for future unspecified cancer research. With the participant's approval and as approved by the Institutional Review Board (IRB), de-identified biological samples will be stored at Huntsman Cancer Institute's Biorepository.

At the time of consent, subjects will be given the opportunity to authorize the biobanking of their remaining samples for use in future undisclosed research. During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, the withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

7.6.1 Peripheral Blood Samples For Correlatives

Up to 40mLof blood will be collected at the time points listed in the Schedule of Events. See the lab manual for collection, processing, and storage instructions.

7.6.1.1 Measurement of DNA Damage and Repair Markers

The peripheral blood specimens will be assessed for DNA damage by quantitation of γH2AX and cleaved PARP1 in $CD5^+/CD19^+$ cells by flow cytometry. The sample obtained prior to drug administration on C1D1 for each patient will serve as the baseline for that patient and follow-up samples will be compared back to that baseline. We will calculate the change from baseline for each patient and aggregate the data for all patients to look for common outcomes.

7.6.1.2 Apoptosis Markers

Apoptosis will be assessed at the time points listed on the Schedule of Events. See the lab manual or correlative specimen for collection, processing and storage instructions.

7.6.1.3 Minimal Residual Disease

At any time point in which a MRD specimen is required from the peripheral blood as according to the Schedule of Events two samples should be collected. One sample will be collected and analyzed as according to the institution's CLL flow cytometry MRD assay specifications. A second sample should be collected and processed for correlative studies. See the lab manual or correlative specimen for collection, processing and storage instructions.

7.6.2 Bone Marrow Aspirate

Any time a bone marrow biopsy is performed on this study after screening, at least two tubes of bone marrow aspirate will be collected for MRD testing. One sample will be collected and analyzed for CLL MRD by flow cytometry according to the institution's laboratory specifications. A second sample should be collected and processed for correlative studies. See the lab manual or correlative specimen for collection, processing and storage instructions.

Refer to the lab manual for sample collection and processing instructions.

7.6.3 Pharmacokinetic Studies

Plasma samples will be collected at defined time points in section 1.5.1 to assess the pharmacokinetics of RP-3500 and olaparib.

7.6.3.1 On C1D1 and C1D15, blood samples will be collected at pre-dose and 0.5, 1, 2, 4, and 24 hours post dose. Patients will take their doses of RP-3500 and olaparib in the infusion room or clinic after the pre-dose PK blood draw has occurred and at the instruction of the research team. For the 24 hour post dose collection, patients will have PK study blood drawn prior to taking their C1D2 and C1D16 drug doses.

7.6.3.2 On C1D8, blood samples will be collected at pre-dose, 0.5, 1, 2, and 4 hours post dose. Patients will take their doses of RP-3500 and olaparib in the infusion room or clinic after the pre-dose PK blood draw has occurred and at the instruction of the research team.

Blood samples will be processed to plasma and RP-3500 and olaparib will be analyzed by validated LC/MS-MS bioanalytical methods. PK parameters for RP-3500 and olaparib will be calculated using non-compartmental analysis: area under the concentration-time curve (AUC) from time 0 to last quantifiable concentration ($AUC_{0\text{-last}}$); AUC from time 0 to infinity ($AUC_{0\text{-inf}}$); maximum observed plasma concentration (C_{max}); time to reach Cmax (T_{max}) and terminal elimination half-life ($t_{1/2}$). The effect of olaparib on the $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ and C_{max} of RP-3500 will be compared to respective monotherapy doses from other studies performed with RP-3500. RP-3500 and olaparib may also be analyzed using population PK methods.

7.7 Remote Visits/Telehealth

Some study visits and/or procedures may be conducted remotely in the following circumstances:

- Telehealth visits do not present an increased risk to the participant.
- All necessary data for the trial can be collected.
- Procedures do not include research related imaging, lab samples, and/or pathology which should be conducted in person.

The method of telehealth should be documented in the paricipants' charts.

8 ADVERSE EVENTS

8.1 Definitions

8.1.1 Adverse events

21 CRF 312.32, ICH GCP, and OHRP define an adverse event as any untoward medical occurrence whether or not considered treatment-related. This definition extends to the worsening of any preexisting condition or symptom. All adverse events experienced during trial participation should be documented in the subject's research chart and corresponding eCRF

Laboratory abnormalities should not be listed as adverse events unless deemed clinically significant by the investigator or qualified designee. An abnormal test result or findings should not be recorded as an adverse event unless the following conditions are met:

- Associated with clinical symptoms; and/or
- Requires intervention (medical, surgical, or additional diagnostic testing); and/or
- Results in a change in study drug dosing; and/or
- Deemed by the investigator or qualified designee to be an adverse event.

While disease progression should be noted in the subject's research chart, it should not be reported as an adverse event.

8.1.2 Serious Adverse Events

A serious adverse event is defined as any untoward event that is:

- Fatal;
- Life-threatening;(ie. the subject is at immediate risk of death, not at risk only if the event worsens or fails to respond to intervention)
- Results in persistent or significant disability/incapacity;
- Medically significant;
- Causes a congenital abnormality or birth defect;
- Requires or prolongs inpatient hospitalization.

Investigator judgment must be used to assess an event as medically significant. The event may not be life-threatening or cause disability but may jeopardize the subject and require intervention to prevent the other SAE outcomes.

The following situations should not be reported as an SAE:

- Death due to disease progression;
- Hospitalization for signs and symptoms associated with disease progression;
- Hospital admission not associated with a precipitating AE such as:
    - Treatment for a preexisting condition not associated with a new AE or the worsening of a preexisting condition;
    - Admission for social or administrative reasons;
    - Optional admission or elective surgery;
    - Observation;
    - Preplanned treatments or surgical procedures as noted at baseline;
    - Admission for the administration of blood products.

8.2 Adverse Event Reporting

The investigator and qualified designees are responsible for the detection, documentation, reporting, and follow-up of all adverse events experienced by subjects during trial participation. AEs and SAEs will be recorded from the initiation of study therapy until 28 days after the last dose of study medication or until new cancer therapy is started. The following information will be required for each adverse event:

- Event term;
- For non-hematologic toxicities and patients with normal baseline platelet, hemoglobin and ANC, event severity as graded by the CTCAE v.5;
- For patients with baseline cytopenias (i.e. platelet count <100,000/mm^3 and/or hemoglobin less than the lower limit of normal), hematologic toxicity event severity as graded by 2018 iwCLL criteria (Refer to section 6.6.3)
- The causality assessment to study medication per the below definitions;
- Expectedness;
- Event duration;
- Any action taken to treat or manage the event;
- Event outcome.

8.2.1 Severity Assessment

The severity of adverse events should be assessed by CTCAE v.5. If an event is not listed in CTCAE v.5 then the assessment of severity should follow the general guidelines listed in Table 18.

Table 18: Severity assessment

Grade	Severity Description
1	Mild event that generally does not require intervention.
2	Moderate event that may require intervention.
3	Severe event that requires intervention.
4	Life-threatening event that requires urgent intervention.
5	Death.

Events meeting grade 4 or 5 severity description should be reported promptly as SAEs unless otherwise indicated in Section 8.1.

8.2.2 Causality Assessment

The Investigator should assess the causality or relationship of AEs and SAEs to study therapy. The Investigator should consider if there is evidence that the investigational product caused the event taking into consideration timing, organ system affected, type of event, and possible alternative etiologies. The relationship of the AE to study treatment will be reported as listed below. These categories will be defined as follows:

- Definitely related (D) – a clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to the withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
- Probably related (PR) – a reasonable time sequence to the administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- Possibly related (PO) – a reasonable time sequence to administrations of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- Unlikely related (UL) –a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
- Not related (NR) – there is no evidence of a causal relationship between the study drug and the event and in which other drugs, chemicals or underlying disease explain the event.

Adverse events reported as definitely, probably, and possible, related to study therapy will be reported as related. In cases when the Investigator is unsure of the causality of an AE, the event will be considered related to study therapy unless deemed otherwise by the DSMC.

8.2.3 Expectedness

The Investigator will be responsible for determining whether or not an adverse event was expected or unexpected. Expected adverse events are those adverse events that are listed or characterized in the Package Insert (PI) or Reference Safety Information (RSI) of the current Investigator Brochure (IB). Unexpected adverse events are those not listed in the PI or current IB or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the PI or IB. For example, under this definition, hepatic necrosis would be unexpected if the PI or IB only referred to elevated hepatic enzymes or hepatitis.

8.2.4 Action Taken and Outcome

Start and stop dates will be required for all adverse events and serious adverse events. The action taken in response to the event should also be recorded in the subject's research chart and corresponding eCRF. Event action terms include none, medication administered, non-drug therapy administered, surgery, hospitalization, or other with the option to specify. If a new medication is added the medication should also be added to the concomitant medications log.

All adverse events should be followed until stabilization or resolution. Event outcomes may be classified as resolved, resolved with sequelae, ongoing, or death.

8.2.5 Reporting Serious Adverse Events

All serious adverse events should be reported as soon as possible but no later than one business day after the Investigator becomes aware. All SAEs must be reported via the HCI CTMS (OnCore) and submitted to HCI-RCO@utah.edu. The HCI Clinical Site Monitor will in turn, submit the report to the Medical Monitor. The RCO will summarize and present all reported SAEs according to the Data and Safety Monitoring Plan at the monthly DSMC meeting.

At a minimum, initial SAE reports must include a description of the event, assessment of event causality, event grade, and the expectedness of the event. Although the Investigator may not know all the information at the time of the event, the available information should be reported. An SAE follow-up may be submitted at a later date once more information is known. It is required that follow-up reports be submitted until the SAE is resolved.

Follow-Up Information

It is recommended that follow-up reports be submitted as new information becomes available, however, a follow-up report should be submitted within 7 days of knowledge of event resolution. Follow-up information will be added to the SAE in OnCore and submitted to the DSMC via RCO.

8.2.6 FDA Notifications

Per 21 CRF 312.32 adverse events and serious adverse events will be reported on a MedWatch 3500A form to the FDA. Reportable events will be reported by the RCO according to the following guidelines:

8.2.6.1 MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic (Section A) and suspect medication information (Section C & D), the report should include the following information within the Event Description (Section B.5) of the MedWatch 3500A form:

- Protocol number and title description
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics (Section B.6)
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication
- Expectedness of the event (i.e., expected or unexpected event).

8.2.6.2 FDA Reporting Timelines:

- 7 Calendar Day Report:

  Any event that is fatal or life-threatening, unexpected, and definitely, probably or possibly related to study medication will be reported to the FDA by telephone or fax within seven calendar days of first learning of the event.

- 15 Calendar Day Report:

  Any event that is serious, unexpected, and definitely, probably or possibly related to study medication will be reported to the FDA in an IND safety report within 15 calendar days of first learning of the event.

  In accordance with 21 CFR 312.32, an Analysis of Similar Events should be included in the IND Safety Report. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

  FDA fax number for IND Safety Reports:

  Fax: 1 (800) FDA 0178

8.2.7 IRB Notification

The University of Utah IRB requires any unanticipated problems that may increase the risk to research participants be promptly reported. All study-therapy related, unexpected adverse events whose nature, severity, or frequency is not consistent with either:

- The unknown or foreseeable risk of adverse events that are described in the protocol related-documents, such as the IRB-approved research protocol, applicable investigator brochure, the current IRB-approved informed consent document, and/or other relevant sources of information, such as product labeling and package inserts; or
- The expected natural progression of any underlying disease or condition of the subject(s) experiencing the adverse event.

Adverse events meeting this criterion must be promptly reported to the IRB within 10 business days of awareness.

8.2.8 Drug Manufacturer Notifications

SAEs, regardless of causal relationship, as outlined in section 8.1 must be reported to Repare Therapeutics within one (1) business day of the Investigator's knowledge of the event by submitting a completed SAE report form to rp-3500-safety@reparerx.com and reparesafety@navitaslifesciences.com.

All Serious Unexpected Serious Adverse Reactions (SUSAR) shall be submitted to Repare Therapeutics at least 4 calendar days prior to the safety report (7/15 Day Safety Reports) due date. SUSARS should be reported to rp-3500-safety@reparerx.com, reparesafety@navitaslifesciences.com, and pvg@drugsafetynavigator.com.

8.3 Special Situations

8.3.1 Pregnancy or Breastfeeding

Although pregnancy is not considered an adverse event, any exposure to the investigational products during pregnancy or breastfeeding must be reported promptly. Exposure may occur by a woman actively receiving study therapy or the partner of a male subject actively receiving study therapy becomes pregnant. Any possible pregnancy or breastfeeding exposure during study therapy and up to 28 days after the last dose of study therapy or up to the start of subsequent anticancer therapy (whichever happens first) must be reported within one business day of awareness regardless of the occurrence of an SAE. Should a woman on study therapy become pregnant, she should immediately discontinue study treatment.

Women exposed to IP during pregnancy or while breastfeeding will be followed for pregnancy outcome and neonate health. Pregnancy outcomes may meet criteria as an SAE if ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly occurs. Congenital anomalies that occur in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death should be reported as an SAE. Any neonatal deaths that occur up to 30 days after birth or breastfeeding exposure should be reported as an SAE. Further follow-up on birth outcomes and neonate health will be handled on a case-by-case base.

Pregnancies and any associated SAEs will be reported to Repare Therapeutics within one (1) business day of the Investigator's knowledge of the pregnancy.

8.3.2 Hy's Law Cases

It is important to identify possible cases of Drug-Induced Liver Injury (DILI) early. Total bilirubin, AST, and ALT should be regularly monitored for elevations indicative of liver damage. Subjects who experience a transaminase elevation above three times the ULN should be monitored frequently to determine if the elevation is transient. Transient elevations are an indication of adaption and these subjects may be identified as "adaptors." However, should a transaminase elevation be followed by total bilirubin (TBili) increase, a DILI could be occurring. Any laboratory abnormalities meeting the following criteria should be reported within 24 hours of awareness:

- AST or ALT elevation > 3 x ULN; and

- Total bilirubin > 2 x ULN; and
- Absence of cholestasis; and
- No alternative explanation for the elevations (e.g., impaired glucuronidation capacity caused by genetic [Gilbert syndrome]; viral hepatitis A, B, or C, preexisting or acute liver disease; or another drug capable of causing the observed injury).

Investigators should conduct reasonable investigations to rule out other possible etiologies. Investigators should take into consideration the subject's use of ethanol, acetaminophen, recreational drugs, herbal supplements, and medical history. A potential Hy's Law case will not be considered a confirmed case until all results and considerations have excluded alternative etiologies.

Possible cases of DILI will be promptly reported to the FDA and Repare Therapeutics prior to full work up to rule out other etiologies. Reporting should be completed on a MedWatch 3500A form and should include all available information, including the likelihood that the drug caused the event. Subjects should be closely followed until the resolution of the event.

Subjects who experience possible DILI should be managed per the Dose Modification Guidelines.

8.4 Data Safety Monitoring Committee

A Data Safety Monitoring Committee (DSMC) at HCI is charged with ensuring the risk/benefit balance for subjects undergoing study therapy. The purpose of the DSMC is to ensure subject safety and make recommendations for study conduct to ensure subject safety and data integrity. The DSMC is chaired by a medical oncologist and may include, but is not limited to, representatives from medical oncology, oncological sciences, biostatistics, and pharmacy.

The roles and responsibilities of the DSMC are described in the NCI-approved Data and Safety Monitoring (DSM) plan. The activities of the committee include reviewing adverse events (including SAEs), deviations, important medical events, and approving cohort/dose escalations. Amendments that increase risk, increase treatment exposure, or impact study objectives will also be reviewed by the DSMC. If the DSMC and/or the PI have concerns about unexpected safety issues or AE trends, the study may be stopped and an unplanned safety data analysis may be conducted. Enrollment will not resume until the issues are resolved. The DSMC also reviews and approves audit reports generated by the Research Compliance Office.

All trials will be assigned and an oncologist member of the DSMC to serve as a medical monitor. In rare cases, an external medical monitor may be assigned. The Medical Monitor will be notified of all serious adverse events (SAEs). Specific notifications will also be issued when a dose-limiting toxicity is encountered and when the RP2D is defined. Approval from the Medical Monitor is required for all dose escalations. All serious adverse events (SAEs) occurring in subjects treated at HCI or its affiliates will also be reviewed by the full DSMC monthly.

Each trial is assigned a research compliance officer who will be responsible for monitoring the trial and reporting to the DSMC. The assessed risk level of the trial will determine the frequency with which monitoring occurs. The Research Compliance Officer monitor will review the study status and summarize enrollment, toxicities, SAEs, dose-escalation, statistical endpoints (e.g.,

stopping rules), deviations, and any other pertinent information for the full DSMC membership at the regularly scheduled meetings.

Audits will be conducted for all trials one year after enrollment begins and annually thereafter. Audits may be conducted more frequently as requested by the DSMC, Institutional Review Board (IRB), Protocol Review and Monitoring Committee (PRMC), Research Compliance Office management, or the Principal Investigator.

DSMC oversite will be tailored to the assessed risk level of the trial. Trials are categorized amongst three risk levels: high, moderate, and low.

This trial has been classified as high risk and therefore will be monitored by RCO and reviewed by DSMC after the first subject is enrolled and then quarterly thereafter.

9 STATISTICAL CONSIDERATIONS

9.1 Sample size determination

9.1.1 Number of Patients Required for Dose Expansion

Prior to amendment v. 28AUG2023, five patients were treated at the previous DL1 (camonsertib 40mg daily and olaparib 100mg BID dosing 3 days per week). It was determined that this dosing strategy may not be appropriate for R/R CLL patients and reduced dosing may be necessary to increase safety of the combination therapy. These patients will be replaced and will not be included in the analysis.

The planned sample size for dose expansion is 24 evaluable patients with a primary endpoint of overall response rate (ORR). In a recent phase I/II study of pirtobrutinib enrolling a similar CLL patient population, the ORR of the drug was 63%[58]. Therefore, the target ORR for the dose expansion portion of the trial will be 60%. ORR will be summarized by the observed proportion and an exact one-sided 95% confidence interval (Clopper-Pearson method). The estimated ORR and lower bounds of the confidence interval with 24 patients and ORR near 60% is presented in Table 19. With 24 evaluable patients, the lower bound of the confidence interval will be approximately 17-20% below the observed proportion for observed ORR near 60%, which is an acceptable level of precision in a dose expansion cohort.

Table 19: Lower Bound of a One-sided 95% Confidence Interval for ORR with N = 24 Patients

Lower Bound of a One-sided 95% Confidence Interval for ORR with N = 24 Patients		
Number of Objective Responses	Observed ORR	Lower Bound of one sided 95% Confidence Interval
10	42%	24%
11	46%	28%
12	50%	31%

13	54%	35%
14	58%	39%
15	63%	43%
16	67%	47%
17	71%	52%
18	75%	56%

9.1.1.1 Enrichment of Dose Expansion with del(11q) and ATM Mutated Patients

An enrichment cohort of 8 patients with either del(11q) and/or ATM mutation will be included in the arm A dose expansion cohort. If 8/8 patients in the enrichment cohort are responders, the lower bound of the exact one-sided 95% confidence interval will be 68.7%. If 7/8 are responders, the lower bound is 52.9%.

9.2 Populati on for Analyses

A modified intent-to-treat data set will be used for both safety and efficacy endpoint analysis. All subjects who havereceived one dose of study medication will be included in all efficacy and safety data sets. Subjects who fail to begin study therapy will be replaced.

9.2.1 DLT Evaluable Population

For dose-finding, subjects who receive at least one dose of any study drug during the DLT evaluation period will be considered evaluable for a DLT event. Only subjects who have experienced a DLT event or received 80% of the expected doses during the DLT period will be included when evaluating dose level changes.

9.2.2 Population for Sensitivity Analyses

9.2.2.1 Per Protocol Analysis

An additional analysis will be conducted including all subjects who have had an on treatment response assessment including imaging studies. All subjects without an on treatment response assessment will be excluded from this analysis.

9.2.2.2 As-treated Analysis

An as-treated analysis will be conducted including all subjects who have maintained at least 75% medication compliance. Subjects who have missed over 25% of the required doses during study therapy for any reason other than for the management of treatment-related toxicities will not be evaluable for this analysis.

9.3 Stopping Rules

The trial will be evaluated quarterly for excess toxicity. A rate of 20% grade 3 or higher non-hematological toxicity is acceptable, while a rate of 35% is unacceptable. Stopping boundaries were calculated using the R function “toxbdry” in the package “clinfun”. The trial will be stopped if more than 2/4, 3/8, 4/12, 5/16, 6/20, 7/24, 8/28 or 9/34 patients experience grade 3 or higher non-hematologic adverse events attributed to study therapy during the 12 month evaluation period.

The operating characteristics of the stopping rule are difficult to determine precisely because up to 12 patients from the phase Ib portion will contribute to the phase II. We evaluated the operating characteristics in two ways. First, we present operating characteristics of the stopping rule calculated by toxbdry(0.16, 0.4, c(4,8,12,16,20,24,28,34),cP0=0.1, cP1=0.9, ngrid=7) in Table 20. This table assumes the operating characteristics are unaffected by the patients carried over from phase Ib to phase II. Second, we explore the effect of the rollover from phase Ib to phase II with a scenario in which the dose selection has a relatively large effect (Table 21). There are 3 assumptions: 1) 12 patients from the phase Ib portion contribute to phase II, 2) all of the grade 3 or higher non-hematologic toxicity occurred in the 28 day DLT period of phase Ib, and 3) the observed toxicity in the 12 rollover patients is in the target range of 25-35%. It is noted that the stopping probability in Table 21 is higher than the corresponding stopping probability in Table 20 when the true toxicity is lower than the target, and lower when the true toxicity is higher than the target.

Table 20: Operating Characteristics of Stopping Rule from toxbdry (N = 34)

Operating Characteristics of Stopping Rule Calculated by toxbdry			
Probability of DLT	Probability of Crossing Boundary	Probability of Stopping Before Last Patient	Expected Sample Size
0.16	8.9%	7.9%	32.3
0.20	21.1%	18.0%	30.4
0.24	38.9%	32.8%	27.6
0.28	58.4%	50.1%	24.1
0.32	75.5%	66.7%	20.5
0.36	87.6%	80.2%	17.2
0.40	94.6%	89.6%	14.3

Table 21: Operating Characteristics of Stopping Rule Under Scenario (N = 34)

Operating Characteristics of Stopping Rule under the Scenario Described Above

Probability of DLT	Probability of Crossing Boundary	Probability of Stopping Before Last Patient
0.16	13.7%	11.3%
0.20	26.3%	20.7%
0.24	41.9%	32.9%
0.28	58.9%	47.3%
0.32	73.3%	60.6%
0.36	84.4%	72.8%
0.40	91.4%	82.3%

Should a treatment-related death occur on study, the trial will be stopped until all investigators and the DSMC can meet and determine appropriate actions. The event will be reported to the FDA.

9.4 Primary Endpoint s

9.4.1 Dose-Finding

The primary objective is to assess the RP2D and the rate of DLTs will be used to determine RP2D. All subjects who receive any study treatment will be included in the final summaries and listings of safety data.

9.4.2 Overall Response Rate

Overall response rate (ORR) will be calculated as the sum of subjects achieving any complete response (including CR and CRi) or any partial response (including PR and nPR) divided by the total number of response evaluable subjects. Subjects without a baseline/screening tumor assessment or at least one on-treatment assessment will be considered non-responders. Each value will be reported along with a one-sided 95% exact binomial confidence interval. No hypothesis testing will be performed for ORR.

9.4.2.1 Rationale to Use ORR as Endpoint

The decision to use ORR as the endpoint is based on multiple phase III clinical trials that have not shown a correlation between PFS and OS outcomes to CR rates. In Burger et al, elderly treatment-naïve CLL patients were randomized to receive either ibrutinib or chlorambucil[35]. CR rates for ibrutinib were 4% and 2% for chlorambucil yet ibrutinib had improved 18-month PFS and 24-month OS by 38% (hazard ratio [HR] 0.16; 95% confidence interval [CI] 0.09 – 0.28; p<0.001) and 14% (HR 0.16; 95% CI 0.05 – 0.56; p=0.001), respectively. Similarly in R/R CLL patients, a phase III trial comparing ibrutinib vs. ofatumumab showed low CR rates of 2% and 1%, respectively[33]. In an updated analysis, ibrutinib-treated patients had a median PFS of 44.1 months as compared to 8.1 months for ofatumumab-treated patients (HR 0.148; 95% CI 0.113 – 0.196; p<0.001)[59]. Rituximab/venetoclax vs. rituximab/bendamustine was studied in the MURANO trial for R/R CLL patients[34]. Independent-review committee CR rates for rituximab/venetoclax was

8.2% as compared to 3.6% for patients treated with rituximab/bendamustine. An updated 36 month median follow up showed an improvement in 36 month PFS of 56.2% (HR 0.16; 95% CI 0.12 – 0.23; p<0.001) for patients treated with rituximab/venetoclax as compared to patients treated with rituximab/bendamustine as well as 36 month OS of 87.9% vs. 79.5% (HR 0.50; 95% CI 0.30 – 0.85; p=0.0093). Lastly, precedence to use ORR as the primary endpoint for a R/R CLL phase II trial exists with venetoclax[60].

9.5 Secondary Endpoints

9.5.1 Safety and Tolerability

All subjects who receive any study treatment will be included in the final summaries and listings of safety data. The detailed information collected for each AE will include a description of the event, duration, severity, relatedness to study drugs, action taken, and clinical outcome. The severity of the AEs will be graded according to the CTCAE v5.0. The statistical analysis of the safety data will be descriptive and tabular.

9.5.2 Duration of Response

The duration of response (DoR) will be defined as the time from the first documented response (CR, CRi, PR or nPR per iwCLL) until the time of progression, the start of a new therapy, or death from any cause. Kaplan-Meier methods will be used to analyze DoR and will be presented with 95% confidence intervals. Table 22 defines the date of progression or censoring that will be utilized for the analysis. No formal hypothesis testing will be performed.

Table 22: Duration of Response Censoring Criteria

Situation	Date of Progression or Censoring	Outcome
Incomplete or no baseline tumor assessments	Date of registration	Censored
Progression documented between scheduled visits	Earliest of: • Date of progression assessment showing new lesion (if progression is based on new lesion); or • Date of last progression assessment.	Progressed
No progression	Date of last progression assessment with no documented progression	Censored
Treatment discontinuation for undocumented progression	Date of last progression assessment with no documented progression	Progressed
New anticancer treatment started	Date of last progression assessment with documented non-progression before the start of new treatment	Progressed

Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after more than one missed visit	Date of last progression assessment with documented non-progression	Progressed

9.5.3 Progression-Free Survival

Progression-free survival (PFS) will be defined as the time from treatment initiation until documented clinical or radiographic progression or death from any cause. Kaplan-Meier methods will be used to analyze PFS and will be presented with 95% confidence intervals. Table 23 defines the date of progression or censoring that will be utilized for the analysis. No formal hypothesis testing will be performed.

Table 23: PFS Censoring Criteria

Situation	Date of Progression or Censoring	Outcome
Incomplete or no baseline tumor assessments	Date of treatment initiation	Censored
Progression documented between scheduled visits	Earliest of: • Date of progression assessment showing new lesion (if progression is based on new lesion); or • Date of last progression assessment.	Progressed
No progression	Date of last progression assessment with no documented progression	Censored
Treatment discontinuation for undocumented progression	Date of last progression assessment with no documented progression	Progressed
New anticancer treatment started	Date of last progression assessment with documented non-progression before the start of new treatment	Progressed
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed

Death or progression after more than one missed visit	Date of last progression assessment with documented non-progression	Progressed

9.5.4 Overall Survival

Overall Survival (OS) will be assessed as the time between treatment initiation and death of any cause. Subjects will be followed for OS for at least seven years after the initiation of therapy until death from any cause. Subjects lost to follow-up will be censored at the time of last known follow-up. Subjects still alive will be censored after five years from the date of study therapy initiation. Kaplan-Meier methods will be used to analyze OS. No hypothesis formal testing will be performed for OS.

10 ETHICAL AND REGULATORY CO NSIDERATIONS

10.1 Human Subjects Protection

The study will be conducted in accordance with the protocol, 21 CFR, HIPAA regulations, the Belmont Principles, ICH Guidelines for Good Clinical Practice (GCP), and the Declaration of Helsinki. Informed consent will be obtained from all research participants or their legally authorized representative before performing any study procedures using the most recent IRB approved version.

10.1.1 Personal Data Protection

All parties will take all necessary actions required for the protection of subject personal data. Subjects enrolled in the study will be assigned a subject number and will be reference by this number. Directly identifiable data will be omitted from reports, publications, and other disclosures. All personal data will be store at the study site in encrypted electronic and/or paper form stored in a locked and secured facility. The site will be responsible for maintaining a list of subjects linking each subject with their subject number. Data will only be accessed by appropriate personnel and will be password protected or securely stored in a locked room. In the case of a potential breach of personally identifiable data, the site will take responsibility to ensure appropriate action is taken according to institutional practice and applicable laws and regulations.

10.2 Institutional Review

Before the initiation of the study, the Investigator will have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, (e.g., recruitment advertisements, questionnaires, if applicable), from the IRB. All correspondence with the IRB should be retained in the Investigator's regulatory file. Changes to the protocol or approved documents may not be made until IRB approval has been received. However, if a change is necessary to eliminate immediate hazards to the subjects, prospective approval is not necessary.

The investigator or designee should provide the IRB with reports, updates and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

10.3 Investigator Responsibilities

The Investigator is responsible for ensuring the trial is conducted in compliance with the current IRB approved version of the protocol, GCP, the Declaration of Helsinki, and any applicable national and local laws and regulations.

10.4 Protocol Amendments

Any amendments or administrative changes to an IRB approved protocol will not be initiated without submission of an amendment for IRB review and approval. However, prospective IRB approval will not be sought when an amendment is required to eliminate immediate risk to subjects on study. In these cases, amendments will be retrospectively submitted to the IRB for review and approval.

Any amendments to the protocol that significantly affect the safety of subjects, the scope of the investigation, or the scientific quality of the study will be submitted to the FDA for review.

10.5 Protocol Deviations

A deviation will be defined as any noncompliance with ICH GCP or the clinical protocol requirements. The noncompliance may be either on the part of the participant, the Investigator, or the study staff. As a result of the deviation, a corrective action must be implemented to ensure future deviation does not occur. It is the Investigator's responsibility to identify and report deviations from ICH GCP or protocol requirements. These deviations and corrective action should be documented in the subject's research chart, the associated eCRF, and reported to the IRB per their policy.

10.6 FDA Reporting

As applicable and in accordance with 21 CRF 312.33, an annual progress report will be submitted to the FDA within 60 days of the anniversary of the date the IND went into effect.

11 DATA HANDLING

11.1 Recording and Collection of Data

Primary source documentation will come directly from the subject's medical record. All source documentation should be attributable, legible, contemporaneous, original, accurate, complete, and available. All documentation should be signed and dated by applicable personnel. Relevant source data will be transcribed into the electronic case report forms (eCRFs) and should be completed as soon as possible after data availability. The eCRFs will be part of a computerized database grounded in the protocol requirements and study objectives. The database will be designed to comply with 21 CFR Part 11.

The Investigator has ultimate responsibility for ensuring that all data collected and recorded is accurate and consistent. He/she will need to sign off on all eCRFs to attest that all data recorded on them is true. A separate screening log of all the subjects screened for participation in the study must also be maintained and should include gender, age, eligibility status, the reason for ineligibility (if applicable), and study allocated subject number (if applicable).

11.2 Data Management

To accommodate evaluations, inspections, and/or audits from regulatory authorities, the Investigator must maintain all study records including subject identity, source documentation, original signed consent form, safety reporting forms, monitoring logs, IP accountability records, relevant correspondence (e.g., letters, emails, meeting minutes, etc.), and any other documents pertaining to the conduct of the study. The Investigator must also agree to the maintain source documents for a minimum of two years after regulatory approval of the investigational product per 21 CFR 312.57. For the duration of record maintenance, records must be stored in a secure location and protected from the elements. If for any reason the Investigator at another participating institution is no longer able to retain study records, the HCI Investigator Sponsor should be notified before any destruction so that the records can be transferred to an acceptable designee. Once retention requirements have been met, the participating site Investigator must get HCI Investigator Sponsor approval before the destruction of any records.

12 PUBLICATION PLAN

In accordance with U.S. regulations and the best interest of research ethics and transparency, this study will be registered on ClinicalTrials.gov before subject enrollment. US Basic Results will also be reported and available on ClinicalTrials.gov within one year of the primary completion date, regardless of formal journal publication. All results will be reported objectively, accurately, balanced, and completely, regardless of the study outcome.

13 REFERENCES

1. Landau DA, Tausch E, Taylor-Weiner AN, et al: Mutations driving CLL and their evolution in progression and relapse. Nature 526:525-30, 2015

2. Herling CD, Klaumunzer M, Rocha CK, et al: Complex karyotypes and KRAS and POT1 mutations impact outcome in CLL after chlorambucil-based chemotherapy or chemoimmunotherapy. Blood 128:395-404, 2016

3. Takahashi K, Hu B, Wang F, et al: Clinical implications of cancer gene mutations in patients with chronic lymphocytic leukemia treated with lenalidomide. Blood 131:1820-1832, 2018

4. Hu B, Patel KP, Chen HC, et al: Routine sequencing in CLL has prognostic implications and provides new insight into pathogenesis and targeted treatments. Br J Haematol 185:852-864, 2019

5. O'Brien S, Furman RR, Coutre S, et al: Single-agent ibrutinib in treatment-naive and relapsed/refractory chronic lymphocytic leukemia: a 5-year experience. Blood 131:1910-1919, 2018

6. Wang L, Lawrence MS, Wan Y, et al: SF3B1 and other novel cancer genes in chronic lymphocytic leukemia. N Engl J Med 365:2497-506, 2011

7. Nadeu F, Delgado J, Royo C, et al: Clinical impact of clonal and subclonal TP53, SF3B1, BIRC3, NOTCH1, and ATM mutations in chronic lymphocytic leukemia. Blood 127:2122-30, 2016

8. Oscier DG, Rose-Zerilli MJ, Winkelmann N, et al: The clinical significance of NOTCH1 and SF3B1 mutations in the UK LRF CLL4 trial. Blood 121:468-75, 2013

9. Dohner H, Stilgenbauer S, Benner A, et al: Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med 343:1910-6, 2000

10. Eichhorst B, Fink AM, Bahlo J, et al: First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol 17:928-942, 2016

11. Zeman MK, Cimprich KA: Causes and consequences of replication stress. Nat Cell Biol 16:2-9, 2014

12. O'Connor MJ: Targeting the DNA Damage Response in Cancer. Mol Cell 60:547-60, 2015

13. Lord CJ, Ashworth A: BRCAness revisited. Nat Rev Cancer 16:110-20, 2016

14. Roos WP, Thomas AD, Kaina B: DNA damage and the balance between survival and death in cancer biology. Nat Rev Cancer 16:20-33, 2016

15. Weston VJ, Oldreive CE, Skowronska A, et al: The PARP inhibitor olaparib induces significant killing of ATM-deficient lymphoid tumor cells in vitro and in vivo. Blood 116:4578-87, 2010

16. Knittel G, Rehkamper T, Korovkina D, et al: Two mouse models reveal an actionable PARP1 dependence in aggressive chronic lymphocytic leukemia. Nat Commun 8:153, 2017

17. Kwok M, Davies N, Agathanggelou A, et al: ATR inhibition induces synthetic lethality and overcomes chemoresistance in TP53- or ATM-defective chronic lymphocytic leukemia cells. Blood 127:582-95, 2016

18. Pratt G, Yap C, Oldreive C, et al: A multi-centre phase I trial of the PARP inhibitor olaparib in patients with relapsed chronic lymphocytic leukaemia, T-prolymphocytic leukaemia or mantle cell lymphoma. Br J Haematol 182:429-433, 2018

19. Pilie PG, Tang C, Mills GB, et al: State-of-the-art strategies for targeting the DNA damage response in cancer. Nat Rev Clin Oncol 16:81-104, 2019

20. Ashworth A, Lord CJ: Synthetic lethal therapies for cancer: what's next after PARP inhibitors? Nat Rev Clin Oncol 15:564-576, 2018

21. Robson M, Goessl C, Domchek S: Olaparib for Metastatic Germline BRCA-Mutated Breast Cancer. N Engl J Med 377:1792-3, 2017

22. Robson M, Im SA, Senkus E, et al: Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med 377:523-533, 2017

23. Litton JK, Rugo HS, Ettl J, et al: Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. N Engl J Med 379:753-763, 2018

24. Lord CJ, Ashworth A: PARP inhibitors: Synthetic lethality in the clinic. Science 355:1152-1158, 2017

25. Kim H, George E, Ragland R, et al: Targeting the ATR/CHK1 Axis with PARP Inhibition Results in Tumor Regression in BRCA-Mutant Ovarian Cancer Models. Clin Cancer Res 23:3097-3108, 2017

26. Yazinski SA, Comaills V, Buisson R, et al: ATR inhibition disrupts rewired homologous recombination and fork protection pathways in PARP inhibitor-resistant BRCA-deficient cancer cells. Genes Dev 31:318-332, 2017

27. Wan Y, Wu CJ: SF3B1 mutations in chronic lymphocytic leukemia. Blood 121:4627-34, 2013

28. Te Raa GD, Derks IA, Navrkalova V, et al: The impact of SF3B1 mutations in CLL on the DNA-damage response. Leukemia 29:1133-42, 2015

29. Turner JG, Dawson J, Sullivan DM: Nuclear export of proteins and drug resistance in cancer. Biochem Pharmacol 83:1021-32, 2012

30. Jeromin S, Weissmann S, Haferlach C, et al: SF3B1 mutations correlated to cytogenetics and mutations in NOTCH1, FBXW7, MYD88, XPO1 and TP53 in 1160 untreated CLL patients. Leukemia 28:108-17, 2014

31. Poncet D, Belleville A, t'kint de Roodenbeke C, et al: Changes in the expression of telomere maintenance genes suggest global telomere dysfunction in B-chronic lymphocytic leukemia. Blood 111:2388-91, 2008

32. Ramsay AJ, Quesada V, Foronda M, et al: POT1 mutations cause telomere dysfunction in chronic lymphocytic leukemia. Nat Genet 45:526-30, 2013

33. Byrd JC, Brown JR, O'Brien S, et al: Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med 371:213-23, 2014

34. Seymour JF, Kipps TJ, Eichhorst B, et al: Venetoclax-Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. N Engl J Med 378:1107-1120, 2018

35. Burger JA, Tedeschi A, Barr PM, et al: Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia. N Engl J Med 373:2425-37, 2015

36. Fischer K, Al-Sawaf O, Bahlo J, et al: Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions. N Engl J Med 380:2225-2236, 2019

37. Mato AR, Barrientos JC, Ghosh N, et al: Prognostic Testing and Treatment Patterns in Chronic Lymphocytic Leukemia in the Era of Novel Targeted Therapies: Results From the informCLL Registry. Clin Lymphoma Myeloma Leuk 20:174-183 e3, 2020

38. Hillmen P, Rawstron AC, Brock K, et al: Ibrutinib Plus Venetoclax in Relapsed/Refractory Chronic Lymphocytic Leukemia: The CLARITY Study. J Clin Oncol 37:2722-2729, 2019

39. Wierda WG, Byrd JC, Abramson JS, et al: NCCN Guidelines Insights: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 2.2019. J Natl Compr Canc Netw 17:12-20, 2019

40. Burger JA, Sivina M, Jain N, et al: Randomized trial of ibrutinib vs ibrutinib plus rituximab in patients with chronic lymphocytic leukemia. Blood 133:1011-1019, 2019

41. Byrd JC, Hillmen P, Ghia P, et al: Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results of the First Randomized Phase III Trial. J Clin Oncol:JCO2101210, 2021

42. Brown JR: How I treat CLL patients with ibrutinib. Blood 131:379-386, 2018

43. Pommier Y, O'Connor MJ, de Bono J: Laying a trap to kill cancer cells: PARP inhibitors and their mechanisms of action. Sci Transl Med 8:362ps17, 2016

44. Moore K, Colombo N, Scambia G, et al: Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med 379:2495-2505, 2018

45. Ray-Coquard I, Pautier P, Pignata S, et al: Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. N Engl J Med 381:2416-2428, 2019

46. Pujade-Lauraine E, Ledermann JA, Selle F, et al: Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 18:1274-1284, 2017

47. Ledermann J, Harter P, Gourley C, et al: Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med 366:1382-92, 2012

48. Golan T, Hammel P, Reni M, et al: Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer. N Engl J Med 381:317-327, 2019

49. de Bono J, Mateo J, Fizazi K, et al: Olaparib for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med 382:2091-2102, 2020

50. Fong PC, Boss DS, Yap TA, et al: Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med 361:123-34, 2009

51. Kaye SB, Lubinski J, Matulonis U, et al: Phase II, open-label, randomized, multicenter study comparing the efficacy and safety of olaparib, a poly (ADP-ribose) polymerase inhibitor, and pegylated liposomal doxorubicin in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer. J Clin Oncol 30:372-9, 2012

52. LYNPARZA® (olaparib) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2020.

53. Yan F, Mandrekar SJ, Yuan Y: Keyboard: A Novel Bayesian Toxicity Probability Interval Design for Phase I Clinical Trials. Clin Cancer Res 23:3994-4003, 2017

54. Ji Y, Liu P, Li Y, et al: A modified toxicity probability interval method for dose-finding trials. Clin Trials 7:653-63, 2010

55. Hallek M, Cheson BD, Catovsky D, et al: iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood 131:2745-2760, 2018

56. Roberts AW, Davids MS, Pagel JM, et al: Targeting BCL2 with Venetoclax in Relapsed Chronic Lymphocytic Leukemia. N Engl J Med 374:311-22, 2016

57. Berger MJ, Ettinger DS, Aston J, et al: NCCN Guidelines Insights: Antiemesis, Version 2.2017. J Natl Compr Canc Netw 15:883-893, 2017

58. Mato AR, Shah NN, Jurczak W, et al: Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. Lancet 397:892-901, 2021

59. Munir T, Brown JR, O'Brien S, et al: Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. Am J Hematol 94:1353-1363, 2019

60. Stilgenbauer S, Eichhorst B, Schetelig J, et al: Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. Lancet Oncol 17:768-778, 2016

61. Oken MM, Creech RH, Tormey DC, et al: Toxicity and response criteria of the Eastern Cooperative Oncology Group. American journal of clinical oncology 5:649-655, 1982

Appendix 1: ECOG Performance Status [61]

Score	Definition
0	Fully active, able to carry on all pre-disease activities 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 or 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 hour
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. Confined to bed or chair
5	Dead

Appendix 2: Rai and Binet Staging System

Risk Level	Rai Stage	Description
Low-Risk Disease	0	Lymphocytosis; no enlargement of the lymph nodes, spleen, or liver; red blood cell and platelet counts are near normal.
Intermediate Risk	I	Lymphocytosis; enlarged lymph nodes; spleen and liver are not enlarged; red blood cell and platelet counts are near normal.
	II	Lymphocytosis; enlarged spleen (and maybe an enlarged liver); lymph nodes may or may not be enlarged; red blood cell and platelet counts are near normal.
High Risk	III	Lymphocytosis; lymph nodes, spleen, or liver may or may not be enlarged; red blood cell counts are low (anemia); platelet counts are near normal.
	IV	Lymphocytosis; enlarged lymph nodes, spleen, or liver; red blood cell counts may be low or near normal; platelet counts are low (thrombocytopenia).

Binet Stage	Description
A	Two or less lymphoid bearing areas enlarged*
B	Three or more lymphoid bearing areas enlarged*
C	Presence of anemia (hemoglobin <10 g/dL) or thrombocytopenia (platelet count <100,000/mm^3)
* Five lymphoid beraing areas are possible: cervical, axillary, inguino-femoral, spleen and liver.	

Appendix 3: Subject Dosing Diary

Subject Number: _____ Date: _____

Cycle #:_____

Please record how many tablets you take of the study medications, the time you take them, and bring the completed diary as well as your study drug supply, including empty bottles, to every study visit. This diary will help us keep track of your study drug and how well you are tolerating it.

Storage Instructions:

RP-3500- Store at room temperature. Keep out of reach of children.

Olaparib- Store at room temperature. Keep out of reach of children.

Administration Instructions:

RP-3500- Take with 8 oz of water at approximately the same time each day (±2 hours).

Olaparib- Take with 8 oz of water at approximately the same time each day (±2 hours).

General Instructions:

Study medication should not be crushed, chewed, or altered in any way. Do not take extra medication for any reason nor should you re-administer in the case of vomiting after administration. If a dose is missed outside of the dosing window, the dose should not be made up but rather take your next dose at you regularly scheduled time.

You will take the following number of tablets each time (per dose) as listed in the table below:

Study Drug Name	# of tablets to take per time/dose	# of times/doses each day	Time of Dose (To be completed below)
RP-3500	_____ tablet(s) (____mg)	Once daily; 2 days on and 5 days off	____:____ ☐ a.m. ☐ p.m.
Olaparib	_____ tablets (____mg)	Twice daily; 2 days on and 5 days off	____:____ ☐ a.m. ☐ p.m. ____:____ ☐ a.m. ☐ p.m.

Date	Medication	Number of Tablets Taken	Time of Dose	Number of Tablets Taken	Time of Dose
	RP-3500		_____:_____ ☐ a.m. / ☐ p.m. ☐ Dose Not Taken		
	Olaparib		_____:_____ ☐ a.m. / ☐ p.m. ☐ Dose Not Taken		_____:_____ ☐ a.m. / ☐ p.m. ☐ Dose Not Taken
	Comments:				
	RP-3500		_____:_____ ☐ a.m. / ☐ p.m. ☐ Dose Not Taken		
	Olaparib		_____:_____ ☐ a.m. / ☐ p.m. ☐ Dose Not Taken		_____:_____ ☐ a.m. / ☐ p.m. ☐ Dose Not Taken
	Comments:				
	RP-3500				
	Olaparib				
	Comments:				
	RP-3500				

Date	Medication	Number of Tablets Taken	Time of Dose	Number of Tablets Taken	Time of Dose
	Olaparib				
	Comments:				
	RP-3500				
	Olaparib				
	Comments:				
	RP-3500				
	Olaparib				
	Comments:				
	RP-3500				
	Olaparib				
	Comments:				

Date	Medication	Number of Tablets Taken	Time of Dose	Number of Tablets Taken	Time of Dose
	RP-3500		_____:_____ ☐ a.m. / ☐ p.m. ☐ Dose Not Taken		
	Olaparib		_____:_____ ☐ a.m. / ☐ p.m. ☐ Dose Not Taken		_____:_____ ☐ a.m. / ☐ p.m. ☐ Dose Not Taken
	Comments:				
	RP-3500		_____:_____ ☐ a.m. / ☐ p.m. ☐ Dose Not Taken		
	Olaparib		_____:_____ ☐ a.m. / ☐ p.m. ☐ Dose Not Taken		_____:_____ ☐ a.m. / ☐ p.m. ☐ Dose Not Taken
	Comments:				
	RP-3500				
	Olaparib				
	Comments:				

Date	Medication	Number of Tablets Taken	Time of Dose	Number of Tablets Taken	Time of Dose
	RP-3500				
	Olaparib				
	Comments:				
	RP-3500				
	Olaparib				
	Comments:				
	RP-3500				
	Olaparib				
	Comments:				
	RP-3500				
	Olaparib				
	Comments:				

Date	Medication	Number of Tablets Taken	Time of Dose	Number of Tablets Taken	Time of Dose
	RP-3500		_____:_____ ☐ a.m. / ☐ p.m. ☐ Dose Not Taken		
	Olaparib		_____:_____ ☐ a.m. / ☐ p.m. ☐ Dose Not Taken		_____:_____ ☐ a.m. / ☐ p.m. ☐ Dose Not Taken
	Comments:				
	RP-3500		_____:_____ ☐ a.m. / ☐ p.m. ☐ Dose Not Taken		
	Olaparib		_____:_____ ☐ a.m. / ☐ p.m. ☐ Dose Not Taken		_____:_____ ☐ a.m. / ☐ p.m. ☐ Dose Not Taken
	Comments:				
	RP-3500				
	Olaparib				
	Comments:				
	RP-3500				

Date	Medication	Number of Tablets Taken	Time of Dose	Number of Tablets Taken	Time of Dose
	Olaparib				
	Comments:				
	RP-3500				
	Olaparib				
	Comments:				
	RP-3500				
	Olaparib				
	Comments:				
	RP-3500				
	Olaparib				
	Comments:				

Date	Medication	Number of Tablets Taken	Time of Dose	Number of Tablets Taken	Time of Dose
	RP-3500		_____:_____ ☐ a.m. / ☐ p.m. ☐ Dose Not Taken		
	Olaparib		_____:_____ ☐ a.m. / ☐ p.m. ☐ Dose Not Taken		_____:_____ ☐ a.m. / ☐ p.m. ☐ Dose Not Taken
	Comments:				
	RP-3500		_____:_____ ☐ a.m. / ☐ p.m. ☐ Dose Not Taken		
	Olaparib		_____:_____ ☐ a.m. / ☐ p.m. ☐ Dose Not Taken		_____:_____ ☐ a.m. / ☐ p.m. ☐ Dose Not Taken
	Comments:				
	RP-3500				
	Olaparib				
	Comments:				
	RP-3500				

Date	Medication	Number of Tablets Taken	Time of Dose	Number of Tablets Taken	Time of Dose
	Olaparib				
	Comments:				
	RP-3500				
	Olaparib				
	Comments:				
	RP-3500				
	Olaparib				
	Comments:				
	RP-3500				
	Olaparib				
	Comments:				

Participant/Caregiver Signature: _____ Date:_____

Appendix 4: Examples of Strong CYP3A Inhibitors and Inducers, P -GP Inhibitors and BCRP Inhibitors

Strong CYP3A Inhibitors

Inhibitor	Therapeutic Class
ritonavir	Protease Inhibitors
cobicistat (GS-9350)	None
ketoconazole	Antifungals
troleandomycin	Antibiotics
telaprevir	Antivirals
itraconazole	Antifungals
indinavir	Protease Inhibitors
voriconazole	Antifungals
mifepristone	Antiprogestins
clarithromycin	Antibiotics
posaconazole	Antifungals
telithromycin	Antibiotics
grapefruit juice	Food Products
ceritinib	Kinase Inhibitors
conivaptan	Diuretics
nefazodone	Antidepressants
nelfinavir	Protease Inhibitors
saquinavir	Protease Inhibitors
ribociclib	Kinase Inhibitors
idelalisib	Kinase Inhibitors
boceprevir	Antivirals

Strong CYP3A Inducers

Inducers	Therapeutic class
rifampin	Antibiotics
mitotane	Other Antineoplastics
avasimibe	Other Antilipemics
rifapentine	Antibiotics

Inducers	Therapeutic class
apalutamide	Antiandrogens
ivosidenib	Cancer Treatments
phenytoin	Anticonvulsants
carbamazepine	Anticonvulsants
enzalutamide	Antiandrogens
St John's Wort extract	Herbal Medications
lumacaftor	Cystic Fibrosis Treatments
phenobarbital	Anticonvulsants

P-gp Inhibitors:

amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, propafenone, quinidine, ranolazine, ritonavir, telaprevir, verapamil

BCRP Inhibitors:

curcumin, cyclosporine A, eltrombopag