Activated:
Closed:

Version Date: 03/30/2017

A Phase 1 extension study to determine the safety of UC-961 (Cirmtuzumab) at the recommended phase 2 dose for retreatment of patients with Chronic Lymphocytic Leukemia treated previously with UC-961.

PRINCIPAL INVESTIGATORS

Catriona Jamieson, MD/PhD
Hematology/Oncology
3855 Health Sciences Drive, #0987
La Jolla, CA 92093-0987
Phone: 858-534-7128
Fax: 858-822-5399
e-mail: cjamieson@ucsd.edu

Michael Choi, MD (co-PI)
Hematology/Oncology
3855 Health Sciences Drive, #0820
La Jolla, CA 92093-0820
Phone: (858) 534-1765
Fax: (858) 534-5620
E-mail: mychoi@ucsd.edu

Protocol Number: HRPP #150851

Investigational Product: UC-961 (Cirmtuzumab)

IND Number: 117975

IND Holder: Thomas Kipps, MD/PhD

NCT Number: 02860676

LIST OF INVESTIGATORS

PRINCIPAL INVESTIGATORS

Catriona Jamieson, MD/PhD
Hematology/Oncology
3855 Health Sciences Drive, #0987
La Jolla, CA 92093-0987
Phone: 858-534-7128
Fax: 858-822-5399
e-mail: cjamieson@ucsd.edu

Michael Choi, MD (co-PI)
Hematology/Oncology
3855 Health Sciences Drive, #0820
La Jolla, CA 92093-0820
Phone: (858) 534-1765
Fax: (858) 534-5620
E-mail: mychoi@ucsd.edu

STUDY STATISTICIANS

Karen Messer, PhD
Biostatistics
3855 Health Sciences Drive, #0901
La Jolla, CA 92093-0901
Phone: 858-822-4334
e-mail: kmesser@ucsd.edu

Hongying Li, PhD
Biostatistics
3855 Health Sciences Drive, #0901
La Jolla, CA 92093-0901
Phone: 858-822-4818
Email: hol031@ucsd.edu

CO-INVESTIGATOR(S)

Januario Castro, MD
Hematology/Oncology
3855 Health Sciences Drive, #0960
La Jolla, CA 92093-0960
Phone: 858-822-6386
Fax: 858-822-6844
e-mail: jecastro@ucsd.edu

Thomas Kipps, MD/PhD
Hematology/Oncology
3855 Health Sciences Drive, #0820
La Jolla, CA 92093-0820
Phone: 858-534-5400
Fax: 858-534-5620
e-mail: tkipps@ucsd.edu

Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: _____

PI Signature: _____

Date: _____

TABLE OF CONTENTS

PROTOCOL SYNOPSIS

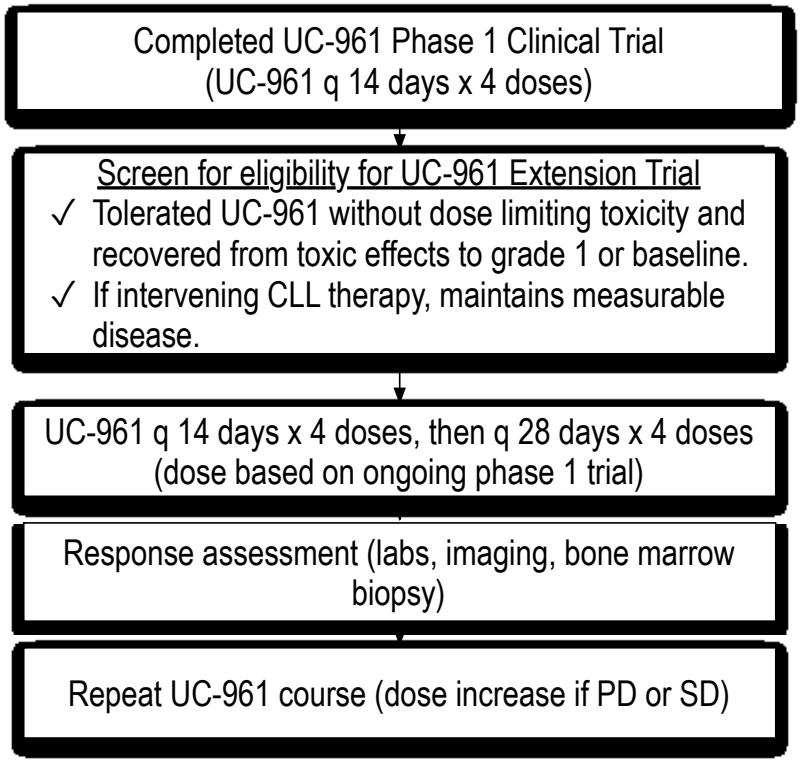
INVESTIGATIONAL AGENT	UC-961
TITLE	A Phase 1B Extension Study to Determine the Safety, Pharmacokinetics and Pharmacodynamics of UC-961 (Cirmtuzumab) at the recommended phase 2 dose for patients with Chronic Lymphocytic Leukemia Previously Treated with Cirmtuzumab (UC-961).
PROTOCOL NUMBER	
PHASE OF DEVELOPMENT	Phase IB
STUDY OBJECTIVES	*Primary Objective:* **1.** To determine the safety and tolerability of UC-961 when administered for an extended duration. *Secondary Objectives:* **2.** To determine the clinical activity of biweekly doses of UC-961, including overall response rate (2008 iwCLL guidelines) and progression free and overall survival (new clinical endpoint from the initial phase 1 trial). **3.** To assess the SD, PR, and MRD- rates *Exploratory Objectives:* **1.** To assess the mechanism of action through immunophenotypic (FACS, ELISA), nanoproteomic ROR1 signaling pathway analysis and pharmacodynamic studies including ROR1$^+$ cancer stem cell cycle and self-renewal assays.
STUDY ENDPOINTS	**Primary Endpoint** Safety and tolerability with extended dosing of UC-961 based on ongoing evaluation of AEs during treatment and 3 month follow up **Secondary Endpoints** 1. Overall response rate by IWCLL criteria following 6 months of biweekly dosing of UC-961 (Hallek *et al.*, 2008) 2. Progression free and overall survival (progression determined by IWCLL working group criteria) 3. SD, PR, and MRD- rates, as well as individual components of response (reduction in leukemia count, reduction in adenopathy and splenomegaly, and improvement in BM function), as determined by IWCLL working group criteria. **Exploratory Endpoints** 1. ROR1 receptor density on circulating bulk tumor cells and stem cells 2. Circulating UC-961 levels in peripheral blood 3. Level of circulating antibodies against UC-961 4. Assay of ROR1 signaling via nanoproteomics (CB1000) 5. Assay of cytokine signaling and other CLL signaling pathways via qPCR array. 6. Assay of associated proteins including phosphorylated AKT versus total AKT ratio by western blot 7. Assay of ROR1$^+$ cancer stem cell inhibition by stromal co-culture FUCCI2BL cell cycle, survival and self-renewal analysis
STUDY DESIGN	This is an open-label extension study to determine the safety and efficacy.

NUMBER OF PATIENTS	Patients enrolled in the initial phase 1 trial in CLL are eligible for enrollment in this extension trial. We anticipate that 33 patients will be enrolled, however, up to 75 patients may be eligible to be enrolled should the initial phase 1 trial require expansion to 6 patients for each dosing cohort.
INCLUSION CRITERIA	1. Ability to understand and the willingness to sign a written informed consent. 2. Clinical and phenotypic verification of B cell CLL and measurable disease. Immunophenotyping of the leukemic cells (blood or marrow) must demonstrate a monoclonal (or light chain positive) B cell population with immunophenotype consistent with CLL (e.g., co-expressing CD19 and CD5). 3. Recovered from toxic effects attributed to UC-961 to grade 1 levels, or baseline. 4. Must have measurable disease, including one of the following: absolute lymphocyte count greater than 5000/uL, lymphadenopathy greater than 1.5 cm in longest dimension, splenomegaly (palpable at least 1 cm below the costal margin or radiographically enlarged), bone marrow biopsy with residual CLL cells, or resultant bone marrow dysfunction (platelet count < 100k /uL, hemoglobin < 10 g/dL). 5. Women of childbearing potential (not postmenopausal for at least one year or not surgically incapable of bearing children) must agree not to become pregnant for the duration of the study. Both men and women must agree to use a barrier method of contraception for the duration of the study and until 10 weeks after the final dose of UC-961 (expected to be greater than 5 half-lives from pre-clinical data). 6. Subjects must have an ECOG performance status of 0-2. 7. Adequate hematologic function: • Platelet count ≥ 50,000/μL unless due to heavily infiltrated bone marrow (> 80% CLL cell infiltrate); AND • Hemoglobin ≥ 8.0 g/dL (may be supported by erythropoietin); AND • Absolute neutrophil count > 1000 /uL unless due to heavily infiltrated bone marrow (> 80% CLL cell infiltrate). 8. Adequate renal function: • Serum creatinine <1.5 times upper limit of normal; OR • Calculated Creatinine clearance (CrCl) ≥ 40 mL/min (based upon the Cockcroft-Gault Equation [CrCl = (140-age) * actual wt (in kg) * (0.85 if female) / (72 * Cr)]. 9. Adequate hepatic function: • Total bilirubin ≤ 2.5 times upper limit of normal; AND • ALT ≤ 2.5 times upper limit of normal. 10. Adequate coagulation tests: • Prothrombin time international normalized ratio (INR) ≤ 2; AND • Partial thromboplastin time ≤ 1.66 times upper limit of normal.
EXCLUSON CRITERIA	1. Pregnant or breast-feeding women will not be entered on this study due to risks of fetal and teratogenic adverse events as seen in animal/human studies. IgG may cross the placental barrier and cause fetal B- and T-lymphocyte depletion. Therefore, women of childbearing age must obtain a pregnancy test, and pregnant or breast feeding females are excluded.

	2. May have had intervening therapy since completion of initial UC-961 dosing, but excluding the following: a. Within 14 days, or 5 half-lives (if known), whichever is shorter, of UC-961 restart: small molecule kinase inhibitor (eg: ibrutinib, idelalisib, AVL-292, IPI-145); b. Within 28 days of UC-961 restart: chemotherapy (e.g., purine analogues, alkylating agents), corticosteroids, radiation therapy, or participation in any other investigational drug treatment (besides UC-961); c. Within 56 days UC-961 restart: previous UC-961 dosing; d. Within 8 weeks of UC-961 restart**:** monoclonal antibody therapy directed against CLL (eg. rituximab, ofatumumab, obinutuzumab, alemtuzumab**).** 3. Current infection requiring parenteral antibiotics. 4. Active infection with HIV, HBV, or HCV. 5. Concurrent malignancy or prior malignancy within the previous 3 years (other than completely resected carcinoma in situ, prostate cancer, or localized non-melanoma skin cancer). 6. Known central nervous system (CNS) involvement by malignancy. 7. Untreated autoimmunity such as autoimmune hemolytic anemia, or immune thrombocytopenia. 8. Uncompensated hypothyroidism (defined as TSH greater than 2x upper limit of normal not treated with replacement hormone). 9. Presence of more than 55% pro-lymphocytes in peripheral blood. Patients with Richter's transformation are not excluded. 10. Insufficient recovery from surgical-related trauma or wound healing. 11. Impaired cardiac function including any of the following: • Myocardial infarction within 6 months of starting study drug; • A past medical history of clinically significant ECG abnormalities, eg: QTc 481 ms or greater. • Other clinically significant heart disease (e.g. uncontrolled congestive heart failure, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen) 12. Patients who in the opinion of the investigator may be unable to comply with the safety monitoring requirements of the study.
DURATION OF INVESTIGATIONAL AGENT ADMINISTRATION AND STUDY PARTICIPATION	Duration of UC-961 administration is until disease progression, treatment intolerance, or lack of clinical benefit. Patients may remain on the clinical trial protocol until one of the following: • Clinical or radiographic progressive disease (See Section 12). • Adverse Events requiring removal from study (See Section 13). • Refusal of further protocol therapy by patient/parent/guardian • Non-compliance that in the opinion of the investigator does not allow for ongoing participation. • Physician determines it is in the patient's best interest to discontinue participation in the clinical trial. • Completion of all clinical trial procedures.

	Participation in the study and long-term follow-up will continue until one of the following: • Death. • Loss to follow-up. • Withdrawal of consent for any further data submission. • Progression requiring initiation of subsequent therapy.
STUDY DRUG ADMINISTRATION	UC-961 is administered by intravenous infusion on day 1, 15, 29, 43, 57, 85, 113, and 141, after which responses will be assessed. Patients with an objective response (meeting working group criteria for partial response or complete response) will continue at the same dose and schema. Patients with stable disease or progressive disease are eligible to increase the dose of UC-961 for another 6-month course.
CRITERIA TO EVALUATE SAFETY	Safety will be determined by Principal Investigator, and will be assessed according to the NCI Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03) for non-hematologic toxicity and modified iwCLL criteria for hematologic toxicity.
CRITERIA TO EVALUATE EFFICACY	Overall response rate is the percentage of patients meeting criteria for partial response, nodular partial response, or complete response based on iwCLL criteria. Progression free survival is according to iwCLL definition.

SCHEMA



1.0 BACKGROUND

1.1 Introduction/Rationale for Development

Chronic Lymphocytic Leukemia (CLL) is the most prevalent hematologic cancer in the western hemisphere (Gribben and O'Brien, 2011). At this time, it is considered incurable. Treatment regimens that combine chemotherapy and immunotherapy (eg: Fludarabine + Cyclophosphamide + Rituximab) have produced high response rates and have been associated with an improved overall survival (Hallek et al., 2010). However, patients inevitably relapse and there is no standard of care therapy in the relapsed or refractory setting. Moreover, many patients cannot tolerate chemoimmunotherapy regimens in the relapsed/refractory setting due to age, comorbidities, or compromised bone marrow function (Brown, 2011). Obinutuzumab (GA-101) in combination with chlorambucil was approved by the FDA in November 2013 based on efficacy as front-line therapy for patients older than 65. However, responses were not durable with this treatment either (ASH 2013, abstract 6). Oral agents that inhibit B-cell receptor associated tyrosine kinases, including Ibrutinib (which has been FDA approved for mantle cell lymphoma and CLL) may be approved for CLL by the FDA as well. However, it does not appear that these agents are capable of consistently inducing complete remissions, eradicating minimal residual disease (Byrd et al., 2013) or a dormant malignant stem cell population. Thus, development, testing, and optimization of novel therapeutic strategies are required to provide more tractable clinical responses.

ROR1 (receptor tyrosine kinase-like orphan receptor 1) is a transmembrane protein that is expressed on the surface of CLL cells, from nearly all patients with CLL (94% based on flow

cytometry analysis of the CLL research consortium) (Fukuda et al., 2008). It shares homology with other receptor tyrosine kinases, and is believed to participate in Wnt signaling, based on homology to the Wnt receptor, Frizzled. However, its precise function is unknown, and although the protein has a putative kinase domain, it may be a pseudo-kinase serving as a cofactor for other signaling proteins, leading to phosphorylation of Akt.

Importantly, ROR1 is not expressed on the surface of normal adult tissues, with the possible exception of a rare subset of precursor B cells, called hematogones, which are typically observed in the marrow of pediatric patients or patients recovering from myeloablative therapy, but are found in minute levels (<1% of mononuclear cells) in the marrow of healthy adults (Broome et al., 2011). ROR1 plays a key role in fetal development, but based on exhaustive profiling studies in human hematopoietic stem cells, it is no longer detectable by the second trimester fetal liver stage, and is not on marrow stem cells or normal adult tissues (Fukuda et al., 2008, Hudecek et al., 2010, Masiakowski and Carroll, 1992, Matsuda et al., 2001, Zhang et al., 2012). As such, it represents an ideal target for immunotherapy, due to a potential lack of cross-reactivity with normal adult tissues, reduced immunosuppression based on lack of targeting or normal myeloid or lymphoid cells.

UC-961 (Cirmtuzumab) is a fully humanized monoclonal antibody designed to bind the extracellular immunoglobulin-like domain of ROR1 with high-affinity. Initial preclinical studies (described below) show that it is an ideal potential therapy due to the following features:

- High affinity for cell-surface ROR1
- Activity against cancer cells that express ROR1, which include cancer-stem cells, with a mechanism of cell death that appears to be due to inhibition of Wnt5a/ROR1 mediated Akt signaling and non-canonical Wnt signaling, both important pathways for the survival of CLL cells (*Fukuda et al.*, 2008, *Cui et al.*, 2013, *Widhopf et al.*, 2014).
- Lack of cross reactivity with normal adult tissues
- Reduced immunosuppressive potential based on lack of targeting most normal lymphoid or myeloid cells
- Low immunogenic potential due to substantial humanization of the mAb framework

Based on this biological rationale and the preclinical activity, an open label, phase I clinical trial is ongoing and will determine safety and efficacy of UC-961 for the treatment of patients with relapsed or refractory CLL. This phase I trial uses a 3+3 phase 1 dose escalation design, and a relatively short treatment duration of 2 months to evaluate for immediate adverse effects. See Section 1.3 for details.

The study proposed herein will allow patients who wish to continue UC-961 therapy to receive continued UC-961 at the biologically active dose or recommended phase 2 dose (RP2D). It will also allow patients that were initially treated at doses below the RP2D to increase their dose of UC-961. It will also allow for improved data regarding long-term safety and safety with prolonged dosing of UC-961 at the R2PD.

1.2 UC-961 Development and preclinical activity in CLL models

UC-961 is the result of testing and optimization of anti-human ROR1 monoclonal antibodies initially generated by classical hybridoma and phase display technologies. Initially, mice were inoculated with DNA, protein, adenoviral constructs of ROR1, cytokines, and immune stimulatory agents to generate anti-human ROR1 antibodies. These initial murine anti-ROR1 monoclonal

antibodies (designated 1-1-4A5 and 3-D10) have been tested using *in vivo* and *in vitro* test systems. When tested in an immune deficient murine model, 3-D10 consistently demonstrated potent activity against human CLL patient samples. At this time, the 3-D10 mAb has been tested against human primary CLL cells in hundreds of mice and has consistently eliminated the human cells in a dose dependent manner. Mouse models have included immune-deficient mice with CLL cell xenografts, as well as immune competent transgenic models that spontaneously generate leukemic cells expressing the human ROR1 protein. In these models, the 3-D10 mAb, but not control IgG or 1-4A5, was able to inhibit the development and expansion of the ROR1 positive leukemic B cells in the blood and spleen of recipient animals. A dose of 10mg/kg was used.

To improve binding affinity, chimeric truncated ROR1 screening proteins were then used to pan for high affinity anti-human ROR1 mAbs generated through the use of a proprietary enhanced phage library (Alere, Inc., San Diego, CA). High affinity antibodies that bind to the same epitope as 3-D10 and more importantly exhibit the same anti-leukemic activity of this prototypical mAb were identified. After cell line and animal testing and kinetic binding analysis, we chose a single antibody designated UC-99961 (UC-m961) for advancement in pre-clinical development.

UC-m961 was humanized by BioAtla, Inc. (San Diego, CA), who employed a proprietary recombinant framework grafting technology to generate humanized antibodies that retain the biologic activities of the parent mAb. Over 20 different light and heavy chain humanized variant ROR1 targeting mAbs were screened.

After conducting head-to-head analyses of several candidate humanized anti-ROR1 mAb, a final humanized mAb construct, designated UC-h961, was selected. This humanized mAb is essentially humanized except for a few amino acids adjacent to the CDR borders and framework 4, which for the most part are tucked under CDR3 in an immune protected site. UC-h961 will hereafter be referred to as UC-961 or Cirmtuzumab.

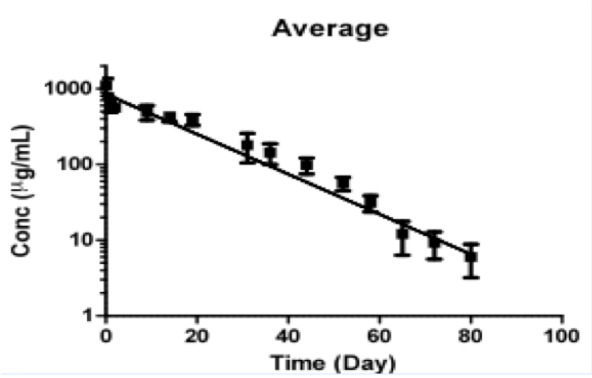
1.2.1 Pre-Clinical Pharmacology and Toxicology

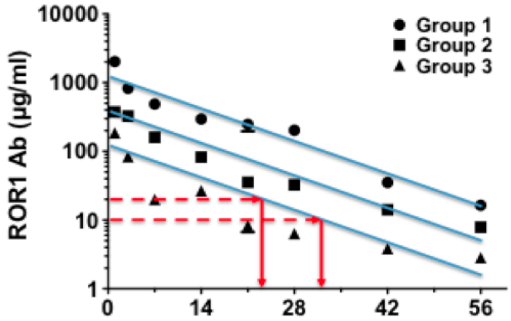
To support the UC-961 phase I clinical trial, a comprehensive single-species pharmacology/toxicology study was conducted in rats. In this study, groups of animals (15 of each sex) received UC-961 at doses of 40, 120 and 400 mg/kg given weekly for 5 doses over 28 days. Three days following the final product administration, 20 animals (10 of each sex) in each dosing cohort were sacrificed and the remaining animals in the recovery phase sacrificed on day 56. During the study, parameters measured included twice-daily clinical signs, food consumption, weekly body weights, ophthalmic examinations (pretreatment, after last dose and last week of drug-free period) urinalysis (prior to sacrifice) and clinical pathology indices including serum chemistries, hematology and coagulation studies (prior to sacrifice). Safety pharmacology measurements including functional observation batteries were conducted weekly. Finally, full necropsy and a complete microscopic analysis was performed on all animals in all groups and a select panel of organs including the liver, spleen, heart, kidneys, brain and ovaries were weighed.

In all dosing cohorts, the UC-961 drug product was well tolerated by the treated rats. No adverse events were noted during the conduct of the study. At terminal sacrifice gross pathologic exams were normal and no untoward effects of product administration were noted.

1.2.2 Pre-Clinical Pharmacokinetics and Metabolism

Comprehensive pharmacokinetic studies were conducted in both immune deficient mice and in Wistar rats. Immune deficient mice (Rag2g-/-) were injected i.v. (1 mg/mouse), blood was drawn at different time points (left panel) and levels in plasma were measured by ELISA. One-compartment PK description of average data reveals that t1/2 = 11.4 days V= 1.18 mL (47 mL/kg) and CL = 0.072 mL/day (0.12 mL/hr/kg). For studies in rats, cohorts of animals received 200, 60 and 20 mg/kg of UC-961 mAb and were screened at 14, 28, 42 and 56 days after treatment. The results (right panel) indicate that the UC-961 was removed from the rats with an apparent half-life of 7 days irrespective of the initial dose of administered mAb.





1.3 Initial Clinical Trial Results

The phase 1 trial of cirmtuzumab (UC-961) initiated in August 2014. Eligible patients have relapsed or refractory CLL or SLL, not amenable to approved treatment options. As April 2016, 18 patients have received doses of UC-961 as part of the ongoing phase 1 clinical trial. Doses are administered every 14 days for a total of 4 doses with an intrapatient dose escalation scheme in place through cohort 4. Per the protocol design, any grade 2 adverse events (unless definitely not due to UC-961), triggered a cessation of intrapatient dose escalation, and conversion of the protocol to a standard 3+3 design starting at the dose at which the AE occurred.

Cohort 1: 3 patients received 2 doses of 15 mcg/kg and 2 doses of 30 mcg/kg. 1 patient in the first cohort had progressive disease and stopped after only 1 infusion of UC-961.

Cohort 2: 3 patients received 2 doses of 60mcg/kg and 2 doses of 240mcg/kg.

Cohort 3: 3 patients received 2 doses of 500mcg/kg and 2 doses of 1mg/kg.

Cohort 4: 2 patients received 2 doses of 2mg/kg and 2 doses of 4mg/kg. 1 patient in this cohort had progressive disease and stopped after only 1 infusion of UC-961 2mg/kg and therefore required replacement. The subsequent patient in this cohort received 2 doses of 2mg/kg and then had a grade 2 urinary tract infection associated with grade 2 neutropenia, thrombocytopenia, and confusion. These events were assessed to be unlikely related to UC-961. However, they triggered halting of intrapatient dose escalation. This patient received 1 additional dose of 2mg/kg and then elected to discontinue with stable disease to pursue other treatment options. Because 3 patients had received at least 28 days of UC-961 2mg/kg without dose limiting toxicity, the 2mg/kg dose level was determined to be safe. An additional patient was then enrolled in this cohort and received 4 doses of 4mg/kg to complete the 4mg/kg dose level (including the 2 patients that had been observed for 28 days at that dose earlier in the cohort).

Cohort 5: As of 4/8/16, 1 patient received 4 doses of 8 mg/kg. 2 patients are currently receiving 8 mg/kg, and will pass the DLT observation period in April 2016.

Cirmtuzumab was well tolerated with the majority of adverse events being grade 1 in severity. One patient had a grade 2 urinary tract infection associated with grade 2 neutropenia, thrombocytopenia, and confusion; these were assessed to be unlikely related to cirmtuzumab. All AEs, regardless of attribution, are listed in table 4. The most common AEs were anemia (6 pts), thrombocytopenia (5 pts), neutropenia (4 pts), restlessness (4 pts), bloating (3 pts), nausea (3 pts), and diarrhea (3 pts). All hematologic AEs are attributed to underlying disease, and not to cirmtuzumab.

AE summary that were probably, possibly, or unlikely due to UC-961, as of 4/1/16.

	Gr1	Gr2
Anemia	6	
Thrombocytopenia	4	1
Neutropenia	3	1
Restlessness	4	
Nausea	3	
Bloating	3	
Diarrhea	3	
Lipase Increased	1	1
Bilirubin increased	2	
Dizziness	2	
Flushing	2	
Vomiting	2	
Amylase Increased		1
Confusion		1
ALT increased	1	
AST increased	1	
Atrial fibrillation	1	
Constipation	1	
Cough	1	
Creatinine increased	1	
Dry mouth	1	
Fatigue	1	
Fecal incontinence	1	
Headache	1	
Hoarseness	1	
Hot flashes	1	
Hyperkalemia	1	
Hypokalemia	1	
Hypernatremia	1	
Insomnia	1	
Urinary frequency	1	

1.4 Rationale for Dose Selection

Each extension course consists of 8 infusions. A patient may repeat the course, and therefore receive a total of 16 infusions on the extension study. Each individual patient will receive the same

dosage of UC-961 for each of the 8 infusions of each course. The dosage of UC-961 may be increased for the 2nd set of 8 infusions (if a higher dose has been shown to be safe on the phase 1 trial AND there is Progressive Disease or Stable Disease after the first course of extension.

The dose administered on this extension study will be the highest safe dose, or once established, the biologically active dose or the recommended phase 2 dose from the phase 1 trial. To date, the 8 mg/kg dose level has been completed and determined to be safe. Therefore, patients on this extension study will begin at the 8 mg/kg dose level. Should subsequent dose levels be determined to be safe in the Phase 1 trial, the dose utilized in this trial may increase for subsequent patients.

Planned dose levels (starting dose is the highest safe dose administered to a patient in the phase 1 trial):

Potential Dose Level	Dose
-1	4 mg/kg
1 (start)	8 mg/kg
2	16 mg/kg (or max 2000 mg dose)
3	20 mg/kg (or max 2000 mg dose)

1.5 Overview of Proposed Study

UC-961 will be examined for safety and tolerability in patients who enrolled and completed UC-961 infusions on the phase 1 first-in-man clinical trial without dose limiting toxicity at doses at or below the RP2D, and receive retreatment with UC-961 at the established biologically active dose or MTD. The primary endpoint of this phase I trial will be assessment of adverse events during continued treatment. In addition there will be assessment of clinical activity according to iwCLL working group criteria and progression free survival. Additionally, pharmacokinetic parameters will be assessed and blood samples will be collected for correlative analysis.

2.0 STUDY OBJECTIVES AND ENDPOINTS:

2.1 Primary Objective:

2.1.1 To determine the safety and tolerability of UC-961 when administered for an extended duration.

2.2 Secondary Objectives:

2.2.1 To determine the clinical activity of biweekly doses of UC-961, including overall response rate (2008 iwCLL guidelines) and progression free and overall survival (new clinical endpoint from the initial phase 1 trial).

2.2.2 To assess the SD, PR, and MRD- rates

2.3 Exploratory Objectives:

2.3.1 To assess the mechanism of action through immunophenotypic (FACS, ELISA), nanoproteomic ROR1 signaling pathway analysis and pharmacodynamic studies including ROR1$^+$ cancer stem cell cycle and self-renewal assays.

2.4 Primary Endpoint

2.4.1 Safety and tolerability with extended dosing of UC-961 based on ongoing evaluation of AEs during treatment and 3 month follow up

2.5 Secondary Endpoints

2.5.1 Overall response rate by IWCLL criteria following 6 months of biweekly dosing of UC-961 (Hallek *et al.*, 2008)

2.5.2 Progression free and overall survival (progression determined by IWCLL working group criteria)

2.5.3 SD, PR, and MRD- rates, as well as individual components of response (reduction in leukemia count, reduction in adenopathy and splenomegaly, and improvement in BM function), as determined by IWCLL working group criteria.

2.6 Exploratory Endpoints

2.6.1 ROR1 receptor density on circulating bulk tumor cells and stem cells

2.6.2 Circulating UC-961 levels in peripheral blood

2.6.3 Level of circulating antibodies against UC-961

2.6.4 Assay of ROR1 signaling via nanoproteomics (CB1000)

2.6.5 Assay of cytokine signaling and other CLL signaling pathways via qPCR array.

2.6.6 Assay of associated proteins including phosphorylated AKT versus total AKT ratio by western blot

2.6.7 Assay of ROR1$^+$ cancer stem cell inhibition by stromal co-culture FUCCI2BL cell cycle,

survival and self-renewal analysis

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

Subjects must meet all of the inclusion criteria to participate in this study.

1. Ability to understand and the willingness to sign a written informed consent.

2. Clinical and phenotypic verification of B cell CLL and measurable disease. Immunophenotyping of the leukemic cells (blood or marrow) must demonstrate a monoclonal (or light chain positive) B cell population with immunophenotype consistent with CLL (e.g., co-expressing CD19 and CD5).

3. Recovered from toxic effects attributed to UC-961 to grade 1 levels, or baseline.

4. Must have measurable disease, including one of the following: absolute lymphocyte count greater than 5000/uL, lymphadenopathy greater than 1.5cm in longest dimension, splenomegaly (palpable at least 1 cm below the costal margin or radiographically enlarged), bone marrow biopsy with residual CLL cells, or resultant bone marrow dysfunction (platelet count < 100k /uL, hemoglobin < 10 g/dL).

5. Women of childbearing potential (not postmenopausal for at least one year or not surgically incapable of bearing children) must agree not to become pregnant for the duration of the study. Both men and women must agree to use a barrier method of contraception for the duration of the study and until 10 weeks after the final dose of UC-961 (expected to be greater than 5 half-lives from pre-clinical data).

6. Subjects must have an ECOG performance status of 0-2.

7. Adequate hematologic function:

- Platelet count ≥ 50,000/μL unless due to heavily infiltrated bone marrow (> 80% CLL cell infiltrate); AND
- Hemoglobin ≥ 8.0 g/dL (may be supported by erythropoietin); AND
- Absolute neutrophil count > 1000 /uL unless due to heavily infiltrated bone marrow (> 80% CLL cell infiltrate).

8. Adequate renal function:

- Serum creatinine <1.5 times upper limit of normal; OR
- Calculated Creatinine clearance (CrCl) ≥ 40 mL/min (based upon the Cockcroft-Gault Equation [CrCl = (140-age) * actual wt (in kg) * (0.85 if female) / (72 * Cr)].

9. Adequate hepatic function:

- Total bilirubin ≤ 2.5 times upper limit of normal; AND
- ALT ≤ 2.5 times upper limit of normal.

10. Adequate coagulation tests:

- Prothrombin time international normalized ratio (INR) ≤ 2; AND
- Partial thromboplastin time ≤ 1.66 times upper limit of normal.

3.2 Exclusion Criteria

Subjects meeting any of the exclusion criteria at baseline will be excluded from study participation.

1. Pregnant or breast-feeding women will not be entered on this study due to risks of fetal and teratogenic adverse events as seen in animal/human studies. IgG may cross the placental barrier and cause fetal B- and T-lymphocyte depletion. Therefore, women of child-bearing age must obtain a pregnancy test, and pregnant or breast feeding females are excluded.

2. May have had intervening therapy since completion of initial UC-961 dosing, but excluding the following:
    a. Within 7 days of UC-961 restart, or 5 half-lives (if known), whichever is shorter: small molecular tyrosine kinase inhibitor (eg: ibrutinib, idelalisib, AVL-292, IPI-145);
    b. Within 28 days of UC-961 restart: chemotherapy (e.g., purine analogues, alkylating agents), corticosteroids, radiation therapy, or participation in any other investigational drug treatment (besides UC-961)
    c. Within 56 days UC-961 restart: previous UC-961 dosing
    d. Within 56 days of UC-961 restart**:** monoclonal antibody therapy directed against CLL (eg. rituximab, ofatumumab, obinutuzumab, alemtuzumab**).**
3. Current infection requiring parenteral antibiotics.
4. Active infection with HIV, HBV, or HCV.
5. Concurrent malignancy or prior malignancy within the previous 3 years (other than completely resected carcinoma in situ, prostate cancer, or localized non-melanoma skin cancer).
6. Known central nervous system (CNS) involvement by malignancy.
7. Untreated autoimmunity such as autoimmune hemolytic anemia, or immune thrombocytopenia.
8. Uncompensated hypothyroidism (defined as TSH greater than 2x upper limit of normal not treated with replacement hormone).
9. Presence of more than 55% pro-lymphocytes in peripheral blood. Patients with Richter's transformation are not excluded.
10. Insufficient recovery from surgical-related trauma or wound healing.
11. Impaired cardiac function including any of the following:
    - Myocardial infarction within 6 months of starting study drug;
    - A past medical history of clinically significant ECG abnormalities.
    - Other clinically significant heart disease (e.g. uncontrolled congestive heart failure, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen)
12. Patients who in the opinion of the investigator may be unable to comply with the safety monitoring requirements of the study.

4.0 INVESTIGATIONAL TREATMENT PLAN

4.1 Dose Assignment

The dose of UC-961 is currently undergoing evaluation in a phase 1 study.

During the extension treatments, patients will be assigned to receive the highest safe dose from an ongoing phase 1 study, or the established maximum tolerated dose/ recommended phase 2 dose (which may increase as the phase 1 trial accrues additional patients). Patients will receive the same dose of UC-961 for 1 course, which consists of 8 doses (every 14 days for 4 doses, then every 28 days for 4 doses). As of April 2016, the highest safe dose is 8 mg/kg.

Following 1 course, patients will be assessed for response, and then are eligible to receive a second course. Patients with a complete response or partial response will continue at the same

dose. Patients with stable disease or progressive disease will receive a higher dose of UC-961, if a higher safe dose has been established in the concurrent CLL Phase 1 trial by that time.

4.2 Dose Limiting Toxicity

Dose-Limiting Toxicity (DLT) is defined as any of the following adverse events that are considered by the investigator to be possibly, probably, or definitely related to the study agent UC-961 within the 28 days of the start investigational treatment:

- CTCAE Grade 3 or higher non-hematologic toxicity, except for: Grade 3 infections lasting < 7 days that have resolved, or one occurrence of Grade 3 infusion reaction; or
- Grade 4 or higher hematologic toxicity (by modified iwCLL criteria); or
- Any AE requiring a dose delay of greater than 28 days;

4.3 Recommended Pre-Medications and Concomitant Medications

1. Antibiotics: per investigator discretion.

2. Tumor lysis syndrome prophylaxis: allopurinol or other uric acid lower agent per investigator discretion.

3. Infusion reaction prophylaxis:

    - Acetaminophen 325-1000 mg PO prior to UC-961 administration, or per investigator discretion.
    - Benadryl 50 mg IV or PO, or other antihistamine per investigator discretion, prior to UC-961 administration.
    - Optional: Hydrocortisone 100 mg IV bolus (or infusion over 30 +/-10 minutes) or other equivalent corticosteroid, prior to UC-961 infusion.

4.4 UC-961 infusion plan

Initial Infusion (Cycle 1, Day 1, or if longer than 56 day since prior UC-961 infusion)

1. **Test Dose:** Infuse 8 mg/hour for 10 minutes, then stop infusion (or sooner if not tolerated prior to 10 minutes). 10 minutes (+/-5 minutes) following completion of test dose, monitor for any signs or symptoms of infusion reaction, including: hypotension (greater than 30 mm Hg drop in systolic blood pressure from baseline); fever (temperature greater than 101.3 degrees Fahrenheit); rigors. Management / supportive measures for these events is per institutional standards.
2. In the absence of any of vital sign instability or signs/symptoms of infusion reaction, or after normalization of them, begin infusion:

    - Initiate infusion at 25 mg/hr x 30 min (+/- 5 minutes)
    - Check vital signs every 30 minutes (+/- 5 minutes).
    - If vitals signs are stable (SBP is within 20 mm Hg of baseline, HR > 60 or < 120 beats per minute or within 20% of baseline, and temperature <101.3 F) and without sign/symptoms of infusional toxicity, the rate of infusion is doubled every 30 minutes (+/- 5 minutes) to a maximum of 800 mg/hr for remainder of infusion.

- If a patient is unable to tolerate faster rate, continue infusion at the best tolerated rate until infusion is completed. Monitor for acute infusion-related reactions during and for 30 minutes (+/- 5 minutes) after infusion completed.
- Hold infusion and immediately notify MD if any of the following occur: hypotension (greater than 30 mm Hg drop in systolic blood pressure from baseline); fever (temperature greater than 101.3 degrees Fahrenheit); rigors. Management / supportive measures for these events is per institutional standards. Infusion of UC-961 is resumed at half the previous rate once vital signs and symptoms have returned to baseline.

Subsequent Infusions

1. Test dose is not required.
2. Initiate infusion at rate of 50 mg/hr (or at highest previously tolerated rate if it is lower than 50 mg/hr). Remainder of infusion, vital sign monitoring, and management of infusion reaction as above.

4.5 Criteria for dosing

Doses are administered on day 1, 15, 29, 43, 57, 85, 113, and 141 (+/-3 days) if the patient is without ongoing Grade 3 non-hematologic or Grade 4 hematologic toxicities attributable to UC-961.

4.6 Dose Modifications and Dosing Delays

Each patient will be assessed for the development of toxicity according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.03 for non-hematologic toxicity or modified iwCLL criteria (section 7.1.2) for hematologic toxicity. Patients experiencing a DLT as defined in section 4.2 will be discontinued from study treatment. Otherwise, dose adjustments should be made according to the system showing the greatest degree of toxicity, as per 4.6.1, unless the adverse event is definitely unrelated to the study drug. Dose levels are listed in section 1.4.

4.6.1 Dose Modification Guidelines

Toxicity – NCI CTCAE Grade (Hematologic- modified iwCLL)	**Occurrence**	**Dose Modification**
Autoimmune anemia or autoimmune thrombocytopenia		
Grade ≥ 2	any	Withhold study treatment until resolved to Grade ≤ 1. Resume study treatment at same dose level.
Tumor Lysis Syndrome		
Grade ≥ 3	1st	Withhold study treatment until clinical and laboratory signs resolved to baseline. Resume study treatment at same dose level.
	Repeat	Discontinue therapy
Confusion / Delirium		

Grade ≥ 2	1st	Withhold study treatment until resolved to Grade ≤ 1. Resume study treatment at the next lower dose level.
	Repeat	Discontinue therapy
Pneumonitis		
Grade ≥ 2	1st	Withhold study treatment until resolved to Grade ≤ 1. Resume study treatment at the next lower dose level.
	Repeat	Discontinue therapy
Acute kidney injury		
Grade ≥ 2 (serum creatinine > 2 x baseline)	1st	Withhold study treatment until resolved to Grade ≤ 1. Resume study treatment at the next lower dose level.
	Repeat	Discontinue therapy
Other Non-hematologic		
Grade ≥ 3	1st	Withhold study treatment until resolved to Grade ≤ 2. Resume study treatment at the next lower dose level.
	Repeat	Discontinue therapy.
Hematologic*		
ANC <500/mm^3; Hemoglobin < 6.5 gm/dL; Platelet count ≥75% decrease from baseline (and/or platelet count ≤ 25,000/mm^3)	1st	Withhold study treatment until resolved to ANC ≥500/mm^3 and platelet count ≥25,000/mm^3. Resume study treatment at same dose.
	2nd	Withhold study treatment until resolved to ANC ≥500/mm^3 and platelet count ≥25,000/mm^3. Resume study treatment at the next lower dose level.
	3rd	Permanently discontinue study treatment.
*Dose adjustments or dose holds for hematologic toxicity will apply even if the baseline values are lower than these thresholds due to heavily infiltrated marrow. In those cases, growth factors and/or blood product transfusion may be administered prior to continuing with UC-961.		

Notes:

1. If any of the above is noted, the patient will be re-assessed within 7 days by the treating physician or investigator. Isolated laboratory abnormalities may be re-evaluated by laboratory draw only, or based on physician or investigator discretion.
2. UC-961 infusions can be delayed for a maximum of 28 days; if not restarted in that time-span, study treatment will be permanently discontinued.

3. If dose is decreased for Grade 3 or 4 toxicity, dose re-escalation is not planned.
4. For invasive procedures, not including biopsies or venous catheter placement: withhold study treatment for 1 week prior to procedure, and at least 1 week following surgery until satisfactory wound healing has been achieved.

4.6.2 Modifications for Infusion Reactions

Patients will be monitored for the presence of infusion-related reactions. Treatment for infusion-related reactions will be managed according to the following guidelines:

Infusion Reaction	Occurrence	Management Guidelines
Grade ≤ 2	any	Institute supportive measures. When resolved, resume study treatment at same dose level. Infusion rate adjustment per 4.4.
Grade 3	1st	Institute supportive measures. When resolved, resume study treatment at the same dose level. Infusion rate adjustment per 4.4. Pre-medications listed in protocol are mandatory for re-challenge.
	2nd	Institute supportive measures. Permanently discontinue study treatment.
Grade 4	any	Institute institutional procedures for adult medication reaction/anaphylactic response. Permanently discontinue study treatment.

4.7 Permitted concomitant therapy

Supportive Care
Appropriate antibiotics, anti-emetics, fluids, electrolytes and general supportive care are to be used as necessary.

Blood Products and Growth Factors
Blood products or myeloid growth factors can be administered for grade 4 toxicities (DLT), per investigator discretion for patient safety. The Principal Investigator (C. Jamieson, MD PhD or M. Choi, MD) should be called before growth factors are initiated. Erythropoietin or thrombopoietin mimetics are not to be used, unless continuation of a therapy that started ≥ 1 day prior to Cycle 1, Day 1.

4.8 Prohibited concomitant therapy

Concurrent Anticancer Therapy
Concurrent cancer therapy, including chemotherapy, radiation therapy, immunotherapy, or biologic therapy may NOT be administered to patients receiving study drug. Corticosteroids administration, even if for treatment of conditions other than CLL, at doses greater than

prednisone 20 mg daily (or equivalent dose of other steroids) are prohibited for greater than 14 days. If these treatments are administered the patient will be removed from study.

Investigational Agents
No other investigational agents may be given while the patient is on study.

4.9 Duration of Therapy

The investigational agent UC-961 will be administered until:

a) Clinical or radiographic progressive disease.
b) Unacceptable toxicities.
c) Refusal of further protocol therapy by patient.
d) Non-compliance that in the opinion of the investigator does not allow for ongoing participation.
e) Completion of therapy.
f) Physician determines it is in the patient's best interest to discontinue study agent.

Clinical Study Stopping Rules: Enrollment will be held pending review and approval by the UC San Diego Moores Cancer Center Data Safety Monitoring Board (DSMB) in the event of either of the following:

- Death, or
- 2 or more non-hematologic Grade 4 events at least possibly attributable to the study drug.

4.10 Duration of Follow Up

Patients removed from study treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Patients will be followed after removal from study treatment every 28 days (+/-7 days) for 8 visits, then every 56 days (+/- 7 days) until death, lost to follow-up, withdrawal of consent, or initiation of subsequent therapy for disease progression (*see Section 5 for assessments*).

4.11 Criteria for Removal from Study

Patients can be taken off the study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

a) Death.
b) Loss to follow-up.
c) Withdrawal of consent for any further data submission.
d) Disease progression requiring initiation of subsequent therapy.

5.0 STUDY PROCEDURES

5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to

determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 30 days prior to Cycle 1 Day 1 of the study unless otherwise stated. The screening procedures include:

5.1.1 Complete history and physical examination including vital signs (blood pressure, heart rate, temperature, weight) and organ measurements (i.e., lymph nodes, spleen, liver).

5.1.2 Current medications will be recorded in the subject's medical record but not captured in case report forms.

5.1.3 12 lead ECG. ECG is required on screening. Subsequent ECG will be performed during the study as clinically indicated.

5.1.4 Laboratory examinations: hematology (CBC w/differential), comprehensive metabolic panel (Na+, Cl-, K+, CO2, BUN, Creatinine, Glucose, Ca2+, total protein, albumin, total bilirubin, SGPT, SGOT, alkaline phosphatase), phosphorous, magnesium, uric acid, LDH, amylase, lipase.

5.1.5 Coagulation parameters: PT/PTT.

5.1.6 If female of child-bearing potential: serum pregnancy test within 14 days of Cycle 1 Day 1.

5.1.7 Subjects will have bone marrow aspirate and biopsy with samples sent for differential, morphology, and flow cytometry for MRD within 90 days prior to Cycle 1 Day 1, so long as there has been no intervening CLL therapy.

5.1.8 Disease staging to include CT, MRI, and/or PET scan as clinically indicated (typically including chest, abdomen, pelvis to measure non-palpable lymph nodes) within the last 60 days prior to Cycle 1 Day 1 if there has been no intervening CLL treatment. Any appropriate radiological and radioisotope examinations should be performed as clinically indicated.

5.1.9 Research Tests: peripheral blood and serum collection for one or more of the following (i) Leukemia cell immunophenotype, (ii) T and B cell immune response, (iii) plasma cytokine levels. (see Correlative Studies Section 5.9).

5.2 UC-961 Extension Course 1:

UC-961 doses are administered on Days 1, 15, 29, 43, 57, 85, 113, and 141; all +/- 3 days). The following are to be completed on the day of each infusion.

5.2.1 Complete history and physical examination including vital signs (blood pressure, heart rate, temperature, weight) and organ measurements (i.e., lymph nodes, spleen, liver).

5.2.2 Current medications will be recorded in the subject's medical record but not captured in case report forms.

5.2.3 Adverse events assessment and grading per patient reporting.

5.2.4 Standard laboratory examinations: hematology (CBC w/differential), comprehensive metabolic panel (Na+, Cl-, K+, CO2, BUN, Creatinine, Glucose, Ca2+, total protein, albumin, total bilirubin, SGPT, SGOT, alkaline phosphatase), phosphorous, magnesium, uric acid, LDH. Also: amylase; lipase.

5.2.5 Collection of PK samples.

5.2.6 Collection of correlative lab samples.

5.2.7 If criteria met for start of cycle (section 4.5), proceed with pre-medications (section 4.3) and UC-961 infusion (dose per section 4.1; infusion procedure per section 4.4)

5.2.8 Post-infusion monitoring: patients will be observed for at least 1 hour following the infusion of UC-961, with continued measurement of blood pressure, pulse, temperature every 30 minutes (+/- 10 minutes).

5.2.9 Peripheral blood draw 1 hour after the end of the infusion (+/- 10 minutes), including comprehensive metabolic panel (CMP), phosphorous, uric acid, LDH.

5.3 Day 169 +/- 7 days: Response Assessment:

Not all activities are required on the same day.

5.3.1 Complete history and physical examination including vital signs (blood pressure, heart rate, temperature, weight) and organ measurements (i.e., lymph nodes, spleen, liver).

5.3.2 Adverse events grading and reporting.

5.3.3 Standard laboratory examinations: hematology (CBC w/differential), comprehensive metabolic panel (Na+, Cl-, K+, CO2, BUN, Creatinine, Glucose, Ca2+, total protein, albumin, total bilirubin, SGPT, SGOT, alkaline phosphatase), phosphorous, magnesium, uric acid, LDH. Also: amylase; lipase.

5.3.4 Collection of correlative lab samples.

5.3.5 Flow cytometry of peripheral blood for T-cell subtypes and CLL MRD.

5.3.6 CT scan or MRI or PET of chest, abdomen, and pelvis.

5.3.7 Bone marrow biopsy if clinically indicated to evaluate complete response / minimal residual disease.

5.4 UC-961 Extension Course 2:

UC-961 doses are again administered every 14 days for the first 4 doses, then every 28 days for 4 doses (Days 197, 211, 225, 239, 253, 281, 309, 337; all +/- 3 days).

5.4.1 Complete history and physical examination including vital signs (blood pressure, heart rate, temperature, weight) and organ measurements (i.e., lymph nodes, spleen, liver).

5.4.2 Current medications will be recorded in the subject's medical record but not captured in case report forms.

5.4.3 Adverse events assessment and grading per patient reporting.

5.4.4 Standard laboratory examinations: hematology (CBC w/differential), comprehensive metabolic panel (Na+, Cl-, K+, CO2, BUN, Creatinine, Glucose, Ca2+, total protein, albumin, total bilirubin, SGPT, SGOT, alkaline phosphatase), phosphorous, magnesium, uric acid, LDH. Also: amylase; lipase.

5.4.5 Collection of PK samples.

5.4.6 Collection of correlative lab samples.

5.4.7 If criteria met for start of cycle (section 4.5), proceed with pre-medications (section 4.3) and UC-961 infusion (section 4.4)

5.4.8 Post-infusion monitoring: patients will be observed for at least 1 hour following the infusion of UC-961, with continued measurement of blood pressure, pulse, temperature every 30 minutes (+/- 10 minutes).

5.4.9 Peripheral blood draw 1 hour after the end of the infusion (+/- 10 minutes), including comprehensive metabolic panel (CMP), phosphorous, uric acid, LDH.

5.5 Long term follow-up

Every 28 days (+/- 7 days) for 8 visits then every 56 days (+/- 7 days), until discontinuation of trial participation:

5.5.1 Complete history and physical examination including vital signs (blood pressure, heart rate, temperature, weight) and organ measurements (i.e., lymph nodes, spleen, liver).

5.5.2 Adverse events grading and reporting.

5.5.3 Standard laboratory examinations: hematology (CBC w/differential), comprehensive metabolic panel (Na+, Cl-, K+, CO2, BUN, Creatinine, Glucose, Ca2+, total protein, albumin, total bilirubin, SGPT, SGOT, alkaline phosphatase), phosphorous, magnesium, uric acid, LDH.

5.5.4 Collection of correlative lab samples.

5.6 Pharmacokinetic (PK) Studies

Serum samples will be banked for analysis. HPLC–based assay used in antibody production will also be utilized for serum antibody levels. Limited PK studies are planned, with collection of serum **prior to and 1 hour after** each dose of UC-961.

Sample Collection and Handling Instructions

Blood samples (up to 10 ml) will be collected in heparinized tubes at a site distant from the infusion for pharmacokinetic evaluation. Samples cannot be drawn from the 2nd lumen of a multi-lumen catheter through which drug is being administered. The exact time that the sample is drawn along with the exact time that the drug is administered should be recorded.

Sample Processing: Plasma will be isolated in the translational laboratory (Kipps) and stored at minus 20 degrees.

Sample Labeling

Each tube must be labeled with the patient's de-identified study number, and the date and time the sample was drawn. Data should be recorded on the Pharmacokinetic Study Form, which must accompany the sample(s).

Sample Shipping Instructions

Samples may be shipped to third-party vendor for PK analysis. Samples will be shipped as per assay manufacturer recommendations.

5.7 Correlative Studies

Studies will be performed in the Kipps laboratory, to correlate with PK and clinical responses. Samples will be taken at baseline/screening, during treatment and after treatment. However, not all assays will be performed for all time points for all patients, based on sample availability and leukemic cell number. Specimens will be banked in the CLL research consortium tissue repository (see below).

Assays from patient serum may include:
- Measurement of cytokine levels (IL2, IL12, and TNFα) and Wnt5a levels.
- Assessment for anti-UC-961 antibody production.

Isolation of leukemic cells by Ficoll-hypaque separation and assessment, which may include:
- UC-961 antibody binding, ROR1 expression and receptor occupancy
- ZAP-70, CD38, and Immunoglobulin heavy chain variable region (IgVH) mutation in CLL cells
- Assessment of down-stream signaling by multiplex qPCR
- Measurement of Akt and phospho-Akt levels prior to and after therapy.
- Expression of co-stimulatory molecules (CD80 and CD86), apoptosis related receptors (CD95 and DR5), and expression of genes and proteins related to apoptosis, from pre-treated and post-treated samples.

5.7.1 Sample Collection Guidelines

Sampling Schedule

Blood sample for correlative studies will be collected at the following time points:
- Screening
- Day 1 of each cycle, pre-treatment and 1 hour after each UC-961 infusion
- End of Treatment visit
- Response assessment
- Long-Term Follow-up visits

Sample Collection and Handling Instructions

Blood samples (approximately 15-20 ml) will be collected in anticoagulated (ACD) tubes at a site distant from the infusion for pharmacokinetic evaluation. Samples cannot be drawn from the 2nd lumen of a multi-lumen catheter through which drug is being administered. The exact time that the sample is drawn along with the exact time that the drug is administered should be recorded.

Sample Processing

Samples will be processed in the translational lab of Dr. Thomas Kipps, with separation of plasma, followed by isolation of mononuclear cells or neutrophils by Ficoll or Percoll differential centrifugation, respectively.

Sample Labeling

Each tube must be labeled with the patient's study number and the date and time the sample was drawn. Data should be recorded on the Correlative Study Form, which must accompany the sample(s).

5.7.2 Specimen Banking

Patient samples collected for this study will be retained at the UCSD School of Medicine (Kipps Laboratory). Specimens will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the patient, best efforts will be made to stop any additional studies and to destroy the specimens. Samples will be labeled with the subject's de-identified study number and collection date. The link between study number and medical record number will be viewed over a password secured encrypted server-client.

Drs. Kipps will be responsible for reviewing and approving requests for research specimens from potential research collaborators outside of UCSD. Collaborators will be required to complete an agreement (a Material Transfer Agreement or recharge agreement) that states specimens will only be released for use in disclosed research. Any data obtained from the use of clinical specimens will be the property of UCSD for publication and any licensing agreement will be strictly adhered to.

The study research coordinator will review the subject's medical record for demographic and clinical information pertaining to the subject's general medical history, diagnosis, and outcomes of any treatments received. Samples and data extracted from the subject's medical record will be coded with a de-identified study number, and the subject's name and identifying information will be removed. A log that links the subject's name and identifiers to the study number will be maintained in a secure database distinct from the secure database into which the subject's clinical information will be entered

The specimens and their derivatives may have significant therapeutic or commercial value. The Informed Consent form contains this information and informs the subject that there is the potential for financial gain by UCSD, the investigator or a collaborating researcher or entity.

The following information obtained from the subject's medical record may be provided to research collaborators when specimens are made available:

- Diagnosis
- Collection time in relation to study treatment
- Clinical outcome – if available
- Demographic data

6.0 Schedule of Events

Treatment Cycle	Screening	Extension Course 1	Response Assessment 1	Extension Course 2	Response Assessment 2	Long-Term Follow-up
Visit Day		1, 15, 29, 43, 57, 85, 113, 141	169 [6]	197, 211, 225, 239, 253, 281, 309, 337 [7]	365 [6]	Q28d x8, then q56d
Visit window	≤ 30 days prior to visit 2	±3d	±7d	±3d	±7d	±7d
Informed Consent	X					
Eligibility Checklist	X					
History and Symptoms	X	X	X	X	X	X
VS/Ht and Wt	X	X	X	X	X	X
Comprehensive PE	X	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X
CBC and differential	X	X	X	X	X	X
Blood chemistry panel[1]	X	X	X	X	X	X
ECG	X					
Adverse Events Screen		X	X	X	X	X
Concomitant Medication		X	X	X	X	X
UC-961 Administration		X		X		
CT scan Chest/ Abdomen/ Pelvis [2]	within 60 days of C1D1		X		X	
Bone marrow aspirate and biopsy [3]	within 90 days of C1D1		X		X	
Cytogenetics/FISH from bone marrow or peripheral blood [4]	X		X		X	
Serum hCG for female of child bearing potential	within 14 days of C1D1					
Quantitative T-cell subsets	X		X		X	

Treatment Cycle	Screening	Extension Course 1	Response Assessment 1	Extension Course 2	Response Assessment 2	Long-Term Follow-up
Visit Day		1, 15, 29, 43, 57, 85, 113, 141	169 [6]	197, 211, 225, 239, 253, 281, 309, 337 [7]	365 [6]	Q28d x8, then q56d
Visit window	≤ 30 days prior to visit 2	±3d	±7d	±3d	±7d	±7d
PT/aPTT	X					
Collection of Pharmacokinetic and Pharmacodynamic Samples [5]	X	X	PD only	X	PD only	PD only

1. Chemistry panel to include: comprehensive metabolic panel (Na+, Cl-, K+, CO2, BUN, Creatinine, Glucose, Ca2+, total protein, albumin, total bilirubin, SGPT, SGOT, alkaline phosphatase), phosphorous, magnesium, uric acid, LDH, amylase, and lipase. NOTE: amylase and lipase are not measured in long-term follow-up unless clinically indicated.
2. Or MRI or PET scan.
3. In the case of a CR, an additional bone marrow will be taken two months after patient first achieves CR
4. Chromosome analysis and FISH Panel to include 11q, 12p, 13q, 17p analysis.
5. Blood samples are collected for PK and/or PD analysis (refer to section 5.8 and 5.9)
6. May be done earlier if progressive disease is suspected.
7. Or 28 days after Response Assessment 1.

7.0 Measurement of Effect

7.1 Safety/tolerability

7.1.1 Common Terminology Criteria for Adverse Events (CTCAE)

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 4.03 (http://ctep.cancer.gov/reporting/ctc.html) for reporting of non-hematologic adverse events.

7.1.2 International Working group for Chronic Lymphocytic Leukemia (IWCLL) criteria for hematologic toxicity

As is the case with virtually all of the hematological malignancies, an evaluation of the hematological toxicity in patients with CLL must consider the high frequency of marrow involvement and consequent medullar compromise at the initiation of therapy. A substantial proportion of patients will have hematological parameters within the range of Grade 2 – 4 hematological toxicity before therapy is given; therefore, a modified schema will be used to monitor hematological toxicity in patients with CLL. The modified hematological toxicity schema is displayed:

Modified Grading Scale for Hematological Toxicity in CLL Studies

Grade[1]	Decrease in platelets (nadir) from pretreatment value (%)[2]	ANC/µl (nadir)[3]	Hemoglobin[4]
0 (not AE)	10%, or above lower limit of normal for institution.	≥ 1800, or above lower limit of normal for institution.	Baseline or higher, or above lower limit of normal for institution.
1	11-24%	≥ 1500 and < 1800	> 10.0 g/dL and below baseline
2	25-49%	≥ 1000 and < 1500	< 10.0 – 8.0 g/dL and less than baseline
3	50-74%	≥ 500 and < 1000	< 8.0 – 6.5 g/dL and less than baseline
4	≥75% or ≤ 25,000/mm3 [2]	< 500	< 6.5 g/dL and less than baseline

*This schema concurs with the CTEP CTCAE 4.03, except for the platelet values are taken from the iwCLL-WG guidelines working group criteria and hemoglobin toxicity modified from CTCAE only to account for low baseline values in CLL patients. No hematologic toxicity will be registered unless hemoglobin falls below baseline level.

[1] Grades: 1, mild; 2, moderate; 3, severe; 4, life threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from pretreatment will be recorded as a Grade 5.

[2] Treatment will be held for platelet count ≤ 25,000/mm3, even if it does not meet grade 4 criteria based on percent decrease. See section 4.6.1 for dose hold/adjustment guidelines.

[3] If baseline ANC is <1,500/µL, neutrophil toxicity cannot be evaluated. In that case, if

the neutrophil count is less than 500/μL, it is still recommended to hold therapy until ANC is greater than 500/μL.

[4] If baseline Hemoglobin is < 10.0, hemoglobin toxicity cannot be evaluated. In that case, if the hemoglobin is less than 6.5, it is still recommended to hold therapy until Hgb is greater than 6.5.

7.2 Response Criteria for Patients with Chronic Lymphocytic Leukemia

Criteria for response will utilize the IWCLL Guidelines for response, which includes clinical, hematological, and bone marrow features as outlined below (Hallek et al., 2008).

Minimal Residual Disease negative: less than 0.01% CLL cell involvement by 4-color flow cytometry of bone marrow aspirate (less than 1 in 10,000 events) and meeting all other criteria for complete response.

Complete response: Requires all of the following for a period of at least two months from completion of therapy:

- Absence of significant lymphadenopathy (e.g. >1.5cm in diameter) on physical exam;
- No hepatomegaly or splenomegaly on physical exam;
- Absence of constitutional symptoms;
- Blood counts corresponding to the following values: Lymphocytes < 4,000/uL, polymorphonuclear leukocytes >1500/μL, platelets >100,000/μL, hemoglobin >11.0 g/dL (untransfused)
- Bone marrow aspirate and biopsy must be normocellular for age with <30% of nucleated cells being lymphocytes. Lymphoid nodules must be absent. If the marrow is hypocellular, a repeat determination should be performed in one month.
- The marrow should be analyzed by flow cytometry and/or immunohistochemistry to demonstrate that the marrow is free of clonal B- CLL cells.
- A CT scan or MRI documenting absence of significant lymphadenopathy should be performed if previously abnormal.
- Patients who fulfill the criteria for CR with the exception of a persistent cytopenia that is believed to be treatment related will be considered CR with incomplete bone marrow recovery (CRi). Additionally, patients who fulfill the criteria of CR with exception of having bone marrow lymphoid nodules will be considered a nodular PR.

Partial response: Requires at least 2 of the following criteria from group A, and at least one of the criteria from group B, and for a period of at least 2 months:

Group A:

- ≥50% decrease in peripheral absolute lymphocyte count from pretreatment value, or less than 4,000/uL.
- ≥50% reduction in lymphadenopathy by examination or scan, or less than 1.5cm in size.
- ≥50% reduction in splenomegaly (cm below costal margin) by examination or scan
- ≥50% reduction hepatomegaly (total liver span) by examination or scan
- ≥50% reduction in marrow infiltrate or B-lymphoid nodules

Group B:

- Polymorphonuclear leukocytes ≥1,500/μL or 50% improvement from pre-treatment value;
- Platelets >100,000/μL or 50% improvement from pre-treatment value;
- Hemoglobin >11.0 g/dl (un-transfused) or 50% improvement from pre-treatment value.

Progressive Disease: Characterized by any one of the following events:

- ≥50% increase in the products of at least two lymph nodes on two consecutive determinations two weeks apart (at least one lymph node must be ≥2 cm); appearance of new palpable lymph nodes.
- ≥50% increase in the size of the liver and/or spleen as determined by measurement below the respective costal margin; appearance of palpable hepatomegaly or splenomegaly, which was not previously present.
- An increase in the number of blood lymphocytes by 50% or more with at least 5000 B lymphocytes per microliter.
- Transformation to a more aggressive histology (i.e., Richter's syndrome or prolymphocytic leukemia with ≥56% prolymphocytes).
- *During therapy,* patients not fulfilling the above criteria for progressive disease but demonstrating a decrease in hemoglobin >2 gm/dL, decrease >50% in platelet or granulocyte count will not be rated as progressive disease because these may occur as both a consequence of therapy. A bone marrow biopsy in such settings is strongly encouraged. Furthermore, during therapy, patients with progressive lymphocytosis but not any other findings of hemoglobin, platelet count, lymph node size, or spleen size meeting criteria for progressive disease will not be rated as progressive disease as agents that target the akt pathway have been demonstrated to induce a redistributive lymphocytosis as part of the mechanism of action (Byrd et al., 2013).
- *After treatment,* The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of Hgb levels by more than 20 g/L (2 g/dL) or to less than 100 g/L (10 g/dL), or by a decrease of platelet counts by more than 50% or to less than 100×10^9/L (100 000/μL), which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells.

Stable Disease: Patients who do not fulfill the criteria for complete or partial response as defined above but do not exhibit progressive disease will be considered as having stable disease.

7.2.1 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment until objective tumor progression or death.

8.0 ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an

experimental intervention, whether or not related to the intervention.

8.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

As far as possible, each adverse event should be evaluated to determine:

- duration (start and end dates)
- severity (grade)
- seriousness
- relationship to study agent
- action taken (i.e., none, study agent modification, medical intervention)
- outcome (i.e., resolved without sequelae, resolved with sequelae, ongoing)

All patients experiencing an adverse event, regardless of its relationship to study drug, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

8.2 Severity

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE v4.03 is available at http://ctep.cancer.gov/reporting/ctc.html. All hematologic adverse events will be graded according to the modified iwCLL criteria.

If no grading is available, the severity of an AE is graded as follows:

Mild (grade 1): the event causes discomfort without disruption of normal daily activities.

Moderate (grade 2): the event causes discomfort that affects normal daily activities.

Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.

Life-threatening (grade 4): the patient was at risk of death at the time of the event.

Fatal (grade 5): the event caused death.

8.3 Seriousness

A “serious” adverse event is defined in regulatory terminology as any untoward medical

occurrence that:

1. Results in death.
   If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
2. Is life-threatening.
   (the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
3. Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
4. Results in persistent or significant disability or incapacity.
5. Is a congenital anomaly/birth defect
6. Is an important medical event
   Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".

   For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

8.4 Relationship

Attribution categories for adverse events in relationship to protocol therapy are as follows:

Definite – The AE *is clearly related* to the study treatment.
Probable – The AE *is likely related* to the study treatment.
Possible – The AE *may be related* to the study treatment.
Unlikely – The AE *is doubtfully related* to the study treatment.
Unrelated – The AE *is clearly NOT related* to the study treatment.

8.5 Prior experience

Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is <u>not</u> listed in the toxicities listed in the agent information section of this protocol.

8.6 Reporting Requirements for Adverse Events

8.6.1 Expedited Reporting

- The **Principal Investigator** must be notified <u>within 24 hours of learning of any serious adverse events</u>, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.
- The **UCSD Human Research Protections Program (HRPP)** must be notified <u>within 10 business days</u> of "any unanticipated problems involving risk to subjects or others" (UPR).

  The following events meet the definition of UPR:

1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
5. Any breach in confidentiality that may involve risk to the subject or others.
6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

- The **FDA** should be notified within 7 calendar days of any unexpected fatal or life-threatening adverse event with possible relationship to study drug, and 15 calendar days of any adverse event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

8.6.2 Routine Reporting Requirements

- The UCSD HRPP will be notified of any adverse events that are not unanticipated problems involving risk to subjects or others (non-UPRs) at the time of the annual Continuing Review.
- The FDA will be notified of all non-serious adverse events annually at the time of the annual report.

9.0 AGENT INFORMATION

9.1 UC-961 (Cirmtuzumab)

Please refer to Investigator's Brochure for more comprehensive information.

Structure: Monoclonal antibody

Supplied by: UC-961 will be produced at Pacific GMP (San Diego, CA) in compliance with cGMP standards.

Formulation

The agent is supplied as a liquid formulation at a concentration of 40 mg/ml protein, with 7.2 to 7.8 mL/vial. Each ml of the formulation contains 40 mg UC-961, 14.7 mg sodium citrate, 10 mg trehalose, 216 µg Polysorbate 80, 15 µg sodium EDTA and adjusted to pH 5.2 ± 0.2.

UC-961 will be filled into 10ml clear borosilicate Type 1 glass vials with 20 mm grey butyl siliconized rubber stopper and 20 mm aluminum royal blue flip off seals.

Storage
UC-961 is to be kept refrigerated (2-8°C) until use, in single use vials.

Solution Preparation
To prepare the agent for administration, it will be dissolved in normal saline to the following final concentrations:

- 100 µg/mL for doses 15 µg/kg to 240 µg/kg
- 500 µg/mL for doses 500 µg/kg to 2 mg/kg
- 1 mg/mL dose 4 mg/kg
- 2 mg/mL for dose 8 mg/kg
- 4 mg/mL for doses 16mg/kg and 20 mg/kg

Administration
The drug will be administered by intravenous infusion with infusion rate according to section 4.4.

Toxicities and tolerability
No toxicities have been yet identified in the ongoing first-in-man study. The agent has been well tolerated. There is no off-target binding identified in initial preclinical assays. Infusion reaction, fluid retention, tumor lysis syndrome, and immunogenicity are possible class effects of monoclonal antibody therapy. Depletion of precursor B cells and B cell lymphopenia are possible as well. Other ROR1 antibodies, distinct from UC-961, have demonstrated binding to pancreatic islet cells and adipose tissue (Hudecek et al., 2010). Glucose levels and body weight will therefore be monitored.

10.0 STATISTICAL CONSIDERATIONS

The primary aim of the study is to determine the safety of UC-961 therapy given at the currently used, biologically active dose, or RP2D for an extended duration.

Safety will be assessed through summaries of adverse events, clinical laboratory abnormalities, and changes in physical exam and vital signs. All subjects who receive a single dose of study medication will be considered evaluable for safety.

Adverse events will be listed, documenting the course, outcome, severity, and relationship to the study treatment. Incidence rates of AEs and the proportion of subjects prematurely withdrawn from the study due to AEs will be shown.

The primary endpoint of this study is the rate of dose-limiting toxicity (DLT).

SECONDARY ANALYSIS
Secondary Endpoints are overall response rate by IWCLL criteria following 6 months of biweekly dosing of UC-961 (Hallek *et al.*, 2008) ; Progression free and overall survival (progression determined by IWCLL working group criteria); and SD, PR, and MRD-rates, as well as individual components of response (reduction in leukemia count, reduction in adenopathy and splenomegaly, and improvement in BM function), as determined by IWCLL working group criteria.

These secondary endpoints will be summarized by dose cohort, clinical characteristics and overall using percentages, means and median survival estimates as appropriate. Data will also be presented graphically with Kaplan Meier plots, box plots, and bar charts. All statistics will be presented with 95% confidence intervals. The analysis will be descriptive; thus no correction for multiple analyses will be made and no formal tests of hypothesis will be done.

11.0 STUDY MANAGEMENT

11.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed according to UCSD conflict of interest policy.

11.2 Institutional Review Board (IRB) Approval and Consent

The IRB should approve the consent form and protocol prior to any study-related activities. It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

11.3 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), subjects who have provided written informed consent must also sign a subject authorization to release medical information to the study Sponsor and allow a regulatory authority, or Institutional Review Board access to subject's medical information relevant to the study.

11.4 Data and Safety Monitoring

In addition to adverse event monitoring and clinical oversight by the principal investigator and co-investigators, quality assurance of the study will be performed by the clinical trials office internal monitor.

This study will also use the UCSD Moores Cancer Center Data Safety and Monitoring Board (DSMB) to provide oversight in the event that this treatment approach leads to unforeseen toxicities. Data from this study will be reported after every 6 months, or sooner if required for clinical study stopping rules (Section 4.9), and will include:

1) the protocol title, IRB protocol number, and the activation date of the study.
2) the number of patients enrolled to date
3) the date of first and most recent patient enrollment
4) a summary of all adverse events regardless of grade and attribution
5) a response evaluation for evaluable patients when available
6) a summary of any recent literature that may affect the ethics of the study.

11.5 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

11.6 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

12.0 REFERENCES

1. Hallek M, Cheson BD, Catovsky D et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood*. 2008;111 (12):5446-5456.
2. Gribben JG, O'Brien S. Update on therapy of chronic lymphocytic leukemia. *J Clin Oncol*. 2011;29 (5):544-550.
3. Hallek M, Fischer K, Fingerle-Rowson G et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet*. 2010;376 (9747):1164-1174.
4. Brown JR. The treatment of relapsed refractory chronic lymphocytic leukemia. *Hematology Am Soc Hematol Educ Program*. 2011;2011 (110-118.
5. Byrd JC, Furman RR, Coutre SE et al. Targeting BTK with Ibrutinib in Relapsed Chronic Lymphocytic Leukemia. *N Engl J Med*. 2013
6. Fukuda T, Chen L, Endo T et al. Antisera induced by infusions of autologous Ad-CD154-leukemia B cells identify ROR1 as an oncofetal antigen and receptor for Wnt5a. *Proc Natl Acad Sci U S A*. 2008;105 (8):3047-3052.
7. Broome HE, Rassenti LZ, Wang HY et al. ROR1 is expressed on hematogones (non-neoplastic human B-lymphocyte precursors) and a minority of precursor-B acute lymphoblastic leukemia. *Leuk Res*. 2011;35 (10):1390-1394.
8. Hudecek M, Schmitt TM, Baskar S et al. The B-cell tumor-associated antigen ROR1 can be targeted with T cells modified to express a ROR1-specific chimeric antigen receptor. *Blood*. 2010;116 (22):4532-4541.
9. Masiakowski P, Carroll RD. A novel family of cell surface receptors with tyrosine kinase-like domain. *J Biol Chem*. 1992;267 (36):26181-26190.
10. Matsuda T, Nomi M, Ikeya M et al. Expression of the receptor tyrosine kinase genes, Ror1 and Ror2, during mouse development. *Mech Dev*. 2001;105 (1-2):153-156.
11. Zhang S, Chen L, Wang-Rodriguez J et al. The onco-embryonic antigen ROR1 is expressed by a variety of human cancers. *Am J Pathol*. 2012;181 (6):1903-1910.
12. Cui B, Zhang S, Chen L et al. Targeting ROR1 inhibits epithelial-mesenchymal transition and metastasis. *Cancer Res*. 2013;73 (12):3649-3660.
13. Widhopf GFn, Cui B, Ghia EM et al. ROR1 can interact with TCL1 and enhance leukemogenesis in Emu-TCL1 transgenic mice. *Proc Natl Acad Sci U S A*. 2014;111 (2):793-798.

13.0 APPENDICES

Appendix A. Performance Status

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