Abbreviated Title: IL-15+obinutuzumab in CLL
NIHProtocol #: 19C0024
CTEP Protocol #: 10241
Version Date: 09/14/2021
NCT Number: NCT03759184

Phase 1 Trial of Human IL-15 (rhIL-15) and Obinutuzumab for Relapsed and Refractory Chronic Lymphocyte Leukemia

NCI Principal Investigator: Kevin Conlon, M.D.
Center for Cancer Research (CCR)
National Cancer Institute
Building 10, Room 3B38
9000 Rockville Pike
Bethesda, MD 20892
Phone: 240-760-6087
Email: conlonkc@mail.nih.gov

Investigational Agents:

Drug Name(s):	rhIL-15 (NSC #745101)	Obinutuzumab (Gazyva® (NSC #793436)
IND Number:	140549	
Sponsor:	Center for Cancer Research (CCR), NCI	
Manufacturer(s):	Biopharmaceutical Development Program (BDP)/Leidos Biomedical Research, Inc. under contract with DCTD,NCI	Genentech, Inc.
Supplier:	BDP/DCTD, NCI	Commercial supply

PRÉCIS

Background:

- Of the several drugs and drug combinations approved for treatment of relapsed and refractory chronic lymphocytic leukemia (CLL), the reported complete response rates are no greater than 30%.
- Obinutuzumab is a glycoengineered, humanized type 2 anti-CD20 monoclonal antibody thought to engage the immune system by directly activating antibody-dependent, cell-mediated cytotoxicity (ADCC); it is approved for treatment of chronic lymphocytic leukemia in combination with chlorambucil.
- The key mediators of ADCC are polymorphonuclear neutrophils, monocytes, and natural killer (NK) cells.
- Recombinant human Interleukin-15 (rhIL-15) is a stimulatory cytokine that promotes the differentiation and activation of NK cells, monocytes, and long-term CD8+ memory T-cells. In a Phase I trial, administration of rhIL-15 as a 5-day continuous intravenous infusion (civ) was associated with up to 45-fold increase in the number of NK cells at well-tolerated dose levels.
- Preclinical murine lymphoid malignancy models have shown increased efficacy of monoclonal antibodies when administered together with rhIL-15; BL/6 mice inoculated with EL4-CD20 cells (a syngeneic lymphoma line); including significant prolongation of survival with the IL-15/Rituximab combination compared to either drug given as single agent (90% v. 30% alive at 75 days).

Objectives:

- To determine the safety, toxicity profile, dose-limiting toxicity (DLT) and the maximum tolerated dose (MTD) of civ rhIL-15 administration in combination with intravenous (IV) obinutuzumab treatment

Eligibility:

- Age $\geq$ 18 years old
- ECOG performance status $\leq$ 1
- Diagnosis of chronic lymphocytic leukemia (CLL) with $\geq$ 50% of B cells expressing CD20
- Patients must have measurable or evaluable disease
- Patients must have CLL that is refractory or relapsed following therapy with a Bruton's tyrosine kinase (BTK) inhibitor OR have relapsed/refractory CLL and are intolerant to BTK inhibitor therapy; patients with del(17p) must also be refractory or relapsed after, or intolerant to, therapy with venetoclax
- Adequate organ function parameters as defined within the protocol
- Active disease requiring treatment, as defined within the protocol

Design:

- This is a single institution non-randomized Phase I dose escalation study evaluating increasing doses of civ rhIL-15 in combination with obinutuzumab using a standard 3 + 3 dose escalation design.
- On days 1-5 of each 4-week cycle, rhIL-15 will be administered by civ at dose levels 0.5, 1, and 2 mcg/kg/day.

- During the first cycle, obinutuzumab will be administered at a dose of 100 mg by IV on day 4, 900 mg on day 5, 1,000 mg on day 11, and 1,000 mg on day 18; then 1,000 mg on day 4 of each subsequent cycle.
- Infusion reaction, antimicrobial, and tumor lysis syndrome prophylaxis will be administered per manufacturer's recommendations.
- Treatment will continue up to 6 cycles, or until unacceptable toxicity or progressive disease.
- Up to 24 patients will be enrolled in the study.

TABLE OF CONTENTS

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials 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 Institutional Review Board (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. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objectives

- To determine the safety, toxicity profile, dose-limiting toxicity (DLT) and the maximum tolerated dose (MTD) of civ rhIL-15 administration in combination with IV obinutuzumab treatment

1.1.2 Secondary Objectives

- To evaluate the potential antitumor activity of the combination of rhIL-15 and obinutuzumab by assessing the clinical response rate, minimal residual disease (MRD) status, progression-free survival, and overall survival in patients with relapsed and refractory CLL
- To define the effects of rhIL-15 on the ADCC mediated by obinutuzumab using ex vivo peripheral blood mononuclear cells (PBMCs)
- To characterize the biological effects of rhIL-15 administered with obinutuzumab on the percentages and absolute numbers of circulating lymphocytes (T and NK cells) and the T-cell subsets (including naïve, central, and effector memory subsets) by flow cytometry

1.1.3 Exploratory Objectives

- To identify biomarkers predictive of response to rhIL-15 and obinutuzumab treatment

1.2 BACKGROUND AND RATIONALE

1.2.1 Epidemiology and Pathophysiology of Chronic Lymphocytic Leukemia (CLL)

CLL is the most prevalent type of adult leukemia in Western countries, with an annual incidence of 4.7 per 100,000 and 1.3 per 100,000 deaths in the general population(1). The median age of diagnosis is between 67 and 72 years, and more men than women (1.7:1) are affected(2). Surveillance, Epidemiology, and End Results (SEER) database estimates 20,940 new cases and

4,510 deaths in 2018(1). As the incidence rises with age, the prevalence and mortality are expected to increase further due to the expected demographic changes in the coming decades.

The disease is defined by the clonal proliferation and accumulation of mature, typically CD5-positive B-cells in the blood, bone marrow, lymph nodes, and spleen. It grows and progresses slowly, and it may take years for symptoms to appear or for treatment to be needed. When there is no peripheral blood involvement and lymphadenopathy predominates, the disease may be called small lymphocytic lymphoma (SLL). The two diagnoses are considered a single entity in the WHO classification, and referred to as CLL/SLL, or simply as CLL (which is the term used in this protocol). Genetic features identified in CLL that impact prognosis vary with both recurrent cytogenetic abnormalities — del(13) (q14), trisomy 12, del(11), q(22.3), del(17), (p13.1), del(6), (q21) — and additional mutations — ATM, SF3B1, TP53, NOTCH1, XPO1, MYD88, and BIRC3(3, 4). Patients with del(11q), del(17p), and TP53 mutations frequently progress earlier to symptomatic disease requiring therapy and have shorter response durations with traditional CLL therapies.

The proliferation of leukemic cells is thought to be mediated by B-cell receptor (BCR) signaling, and different components of BCR and its downstream effectors are important for prognosis and treatment of CLL. For example, immunoglobulin heavy chain variable gene (IGHV) mutational status has been recognized as a prognostic marker, with those patients who have higher levels of somatic mutations experiencing longer progression-free survival (PFS) and overall survival (OS)(5). Kinases downstream of BCR, such as Bruton tyrosine kinase (BTK), have become important targets in treatment of CLL(6). The importance of kinases is not limited to BCR signaling: gene expression analysis has distinguished two major types of CLL with different survival types based on expression of ZAP-70, a tyrosine kinase normally associated with the zeta chain of the T-cell receptor(7). Patients with CLL that express ZAP-70 have an average survival of 9.3 years, while those negative for ZAP-70 have an average survival of more than 24.4 years(8).

1.2.2 Diagnosis and Staging of CLL

According to the 2008 International Workshop on Chronic Lymphocytic Leukemia (IWCLL)(9), updated in 2018(10), diagnosis of CLL requires meeting two criteria:

- presence of at least $5x10^9$ /L morphologically mature-appearing small lymphocytes in the peripheral blood (PB), and
- circulating monoclonal B lymphocytes defined by PB flow cytometry; the characteristic pattern of CLL immunophenotype is: expression of the T-cell surface antigen (CD5), expression of B-cell surface (CD19, CD20, and CD23), and low-level expression of surface Ig with either κ or λ (but not both) light chains.

Two staging systems are widely used: the Rai system(11), and the Binet system(12), both of which are simple and inexpensive owing to their reliance solely on a physical exam and standard laboratory tests (**Table 1**).

Table 1: Rai Staging System

Stage	Risk	Manifestation	Median survival (months)
0	Low	Lymphocytosis	120
I	Intermediate	Lymphocytosis with adenopathy	108
II		Lymphocytosis with hepato/splenomegaly	94

Stage	Risk	Manifestation	Median survival (months)
III	High	Lymphocytosis with anemia (Hemoglobin <11 g/dL)	60
IV		Lymphocytosis with thrombocytopenia (platelets <100,000 / μL)	60

As Rai staging cannot identify patients with aggressive clinical phenotypes who are at risk for treatment-refractory disease or early relapse, many prognostic and predictive marks have been developed, including IGHV mutation status(5), ZAP-70(7), and β2microglobulin(13).

Newly diagnosed patients with asymptomatic early stage disease (Rai 0, Binet A) should be monitored without intervention unless there is an evidence of rapid disease progression. Symptomatic patients with advanced stage (Rai 3 or 4, Binet B or C) stages usually benefit from treatment. 2008 IWCLL defines active disease by following criteria(9):

- Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia
- Massive (i.e., at least 6 cm below the left costal margin) or progressive or symptomatic splenomegaly
- Massive (i.e., at least 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy
- Progressive lymphocytosis with an increase of more than 50% over a 2-month period or lymphocyte doubling time (LDT) of less than 6 months. LDT can be obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of 2 weeks over an observation period of 2 to 3 months. In patients with initial blood lymphocyte counts of less than $30x10^9$/L (30,000/μL), LDT should not be used as a single parameter to define a treatment indication. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL (i.e., infections) should be excluded.
- Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy
- Constitutional symptoms, defined as any one or more of the following disease-related symptoms or signs:
    - Unintentional weight loss of 10% or more within the previous 6 months
    - Significant fatigue (i.e., ECOG performance status 2 or worse; inability to work or perform usual activities)
    - Fevers higher than 100.5°F or 38.0°C for 2 or more weeks without other evidence of infection
    - Night sweats for more than 1 month without evidence of infection

1.2.3 Treatment of CLL

An initial treatment regimen that contains fludarabine, cyclophosphamide, and rituximab (known as FCR) has demonstrated high overall and complete response rates of 90% and 44% respectively(14), with improvement in overall survival on long-term follow-up(15). Another well-validated chemoimmunotherapy is bendamustine plus rituximab (BR), which has been shown to be less effective than FCR, but more tolerable with regard to toxicity (particularly in patients older than 65 years)(16). Single-agent alemtuzumab (Campath) has also been approved for use in treatment of CLL(17), after a study of 297 newly diagnosed patients randomly assigned to either

alemtuzumab or chlorambucil showed superior progression-free survival (PFS HR 0.58 [0.43-0.77]) and response rate (ORR 83% v. 55% [CR 24% v. 2%]) in the alemtuzumab arm(18).

Despite long-lasting remissions after chemoimmunotherapy with a median PFS of >6 years in some subgroups(19), most patients will eventually relapse after chemoimmunotherapy and may develop chemotherapy- or rituximab-refractory disease. Treatment of CLL in the relapsed /refractory setting represents a challenge. Several combination and targeted therapies have been evaluated in clinical trials of patients with relapsed/refractory CLL (**Table 2**). Byrd et al. studied rituximab monotherapy in 33 rituximab-naïve patients with relapsed/refractory CLL at escalating doses, up to 375 mg/m^2 3 times weekly for 4 weeks. ORR was 45%, with 3% CRs(20). In 284 patients who received FCR, ORR was 74% with CR 30%(21). A study of bendamustine and rituximab (BR) in 78 patients showed ORR of 59%, 9% of which were CR(22). More recently, the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib has been introduced for patients with CLL. In a study of 137 patients with relapsed/refractory CLL with del(17p), investigator-assessed ORR was 83%, with 63% having a partial response (PR), 17% PR with lymphocytosis, and 2% CR (of which 1%, or 3 patients, with incomplete marrow recovery). 24-month PFS was 63%, and OS was 75%, with 79% of patients having sustained hematological improvement(23). Ibrutinib is now approved both for relapsed/refractory CLL, and for newly diagnosed CLL with del(17p).

Two more targeted agents, the Bcl-2 inhibitor venetoclax and the phosphoinositol-3-kinase inhibitor idelalisib, are also approved for treatment of relapsed/refractory CLL, both in combination with rituximab for patients who are not candidates for any other treatment. In a Phase III trial of 220 patients receiving rituximab with either idelalisib or placebo, ORR was 81% v. 13% (odds ratio 29.92), with no CRs in either group(24). Venetoclax received limited approval after 107 patients with del(17p) enrolled in a Phase II single-arm trial showed ORR 79%, with 8% CRs(25); approval was expanded in 2018 to include all patients with relapsed/refractory CLL regardless of cytogenetics after the MURANO trial showed 2-year PFS benefit of 84.9% versus 36.6% seen in the comparison arm (bendamustine-rituximab).

Table 2: Drugs and Combination Regimens Approved for Relapsed/Refractory (R/R) CLL

Drug	Indication	Patients	ORR	CR	Reference
FCR	R/R	284	74%	30%	Badoux et al.(21)
BR	R/R	78	59%	9%	Fischer et al.(22)
Venetoclax	R/R, with rituximab	194	92%	27%	Seymour et al.(26)
Ibrutinib	R/R, 1st line with del(17p)	85	71%	2%	Byrd et al.(27)
Idelalisib	R/R, with rituximab	110	81%	0%	Furman et al.(24)
Ofatumumab	R/R, 1st line with chlorambucil	33	50%	0%	Coiffier et al.(28)
FCR, fludarabine, cyclophosphamide, rituximab; BR, bendamustine, rituximab					

1.2.4 Design and Function of Obinutuzumab

Obinutuzumab is a humanized anti-CD20 monoclonal antibody that was approved under the trade name Gazyva by the U.S. FDA in 2013 in combination with chlorambucil for the treatment of

patients with newly diagnosed CLL, and as a second line treatment for follicular lymphoma. It binds to CD20 on B-CLL cells and causes these cells to be destroyed by engaging in the adaptive immune system directly activating intracellular ADCC and activating the complement system(29).

CD20 is an integral protein specific to B-lymphocytes and therefore an attractive target for B-cell malignancies and B-cell-mediated autoimmune diseases. It is a transmembrane receptor, although the natural ligand is not known yet, and its physiological role is not completely understood(30). It is suspected that it is involved in the regulation of B-cell activation and proliferation and that it is crucial for B-cell immune response(31). Depending on the targeted epitope, CD20 antibodies can have different affinities and induce varying immune responses.

CD20 monoclonal antibodies are classified into Type I and Type II based largely on their ability to redistribute CD20 into lipid rafts. Type I antibodies such as rituximab and ofatumumab bind to CD20 and induce a quick redistribution of the antibody–antigen complex into a lipid raft(32). This complex leads to weak direct cell death (apoptosis), as well as strong complement-dependent cytotoxicity (CDC) by recruiting C1q(33). In contrast, type II antibodies such as obinutuzumab do not localize the antibody–antigen complex into lipid rafts and therefore induce only very weak CDC that is 10- to 100-fold weaker than that with rituximab or ofatumumab(34). However, reduced FcγRIIb-mediated CD20 internalization increases the capacity to bind and activate natural killer (NK) cells and subsequent immune effector function(35, 36). Additionally, obinutuzumab causes cell death via homotypic aggregation, meaning the aggregation of malignant B-cells by antibodies and subsequent nonapoptotic cell death without the involvement of immune effector cells(37).

Obinutuzumab was initially designed by removal of one fucose from the glycan tree that is attached to the amino acid asparagine 297(38, 39). This led to an increased affinity to FcγRIIIa and FcγIIIb, which then increased the recruitment of FcγRIII expressing effector cells (i.e., neutrophil granulocytes, NK cells and macrophages), and more intense signaling was observed.(34) ADCC was increased in comparison to fully fucosylated antibodies, while antibody dependent cellular phagocytosis (ADCP) seemed to be comparable. In comparison to rituximab, NK degranulation was two- to four-fold more efficient with obinutuzumab(40). This unique process of glycoengineering was standardized by raising antibodies in Chinese hamster ovary (CHO) cells that constitutively overexpress the heavy and light chains of obinutuzumab together with β-1,4-N-acetyl- glucosaminyltransferase III and Golgi α-mannosidase II, both of which reduce fucose and thereby remove fucose from the glycan tree of obinutuzumab(41).

1.2.5 Clinical Pharmacology of Obinutuzumab Monotherapy

The clinical pharmacology properties of obinutuzumab have been characterized in several clinical studies in patients with CLL or NHL. These studies include two Phase I/II monotherapy studies (BO20999 and BO21003); two Phase I monotherapy studies in Japanese patients with NHL (JO21900) and Chinese patients with FL, DLBCL, or CLL (YP25623); two Phase Ib combination studies (BO21000 and GAO4779g); two Phase II studies (a combination study GAO4915g and a monotherapy study GAO4768g at 1000 mg and 2000 mg); and two Phase III combination studies (BO21004/CLL11 and GAO4753g). A serum sampling scheme for the quantitation of obinutuzumab was undertaken in these studies to enable population PK analysis, which demonstrated that a two-compartment PK model comprising both a linear clearance pathway and a non-linear time-varying clearance pathway adequately described serum obinutuzumab concentration data. The initial clearance of obinutuzumab was 2 × higher than the steady-state clearance, which is consistent with a decrease in the time-varying clearance component, which is

high at the start of treatment and declines with repeated cycles of obinutuzumab treatment. The time-varying clearance pathway is consistent with target-mediated drug disposition such that, at the start of treatment when there is a large quantity of CD20+ cells, it binds obinutuzumab. With repeated dosing of obinutuzumab, the pool of CD20+ cells is saturated, thereby reducing this component in clearance. The linear clearance pathway is consistent with catabolism of IgG antibodies and is therefore independent of CD20+ cells. Analysis further supports the need to minimize the time-varying clearance component quickly and has led to the proposed dose and regimen of 1000 mg in both induction and extended treatment.

Consistent with the mechanism of action of obinutuzumab, extensive B-cell depletion was observed both in patients with NHL and CLL. In most patients receiving obinutuzumab monotherapy, there was no notable increase in complement levels during or following an infusion. Changes in the levels of interleukins IL-6 and IL-8 were observed, i.e., increases during the course of the first infusion followed by a decrease to pre-infusion levels 7 days later.

1.2.6 Clinical Efficacy of Obinutuzumab Monotherapy in CLL

Obinutuzumab was first tested in the Phase I/II GAUGUIN trial, which enrolled 33 patients with relapsed/refractory CLL(42). The trial was separated into a dose escalation phase and a fixed dose phase. Patients initially received 400–1,200 mg of obinutuzumab in Phase I and a fixed dose of 1,000 mg in Phase II. In the Phase I portion, 22 patients with treatment-refractory CD20-positive CLL or non-Hodgkin lymphoma had ORR 32%, with 1 CR(43). Response rate was 15% in the second phase; no complete remissions (CRs) were observed. The difference in response rates between the trial phases was attributed to an imbalance in tumor burden between the two patient cohorts.

Further investigation on obinutuzumab dosage was done in the GAGE trial, which compared 1,000 vs 2,000 mg obinutuzumab (100 mg IV day 1, 900 [1,900] mg day 2, 1,000 [2,000] mg days 8 and 15 in cycle 1; 1,000 [2,000] mg day 1 over 7 further cycles)(44). Eighty treatment-naïve patients were enrolled for this Phase II study. With regard to the primary end point, ORR was higher in the 2,000 mg cohort (67% vs 49%) as well as CR (20% vs 5%). Despite this dose effect on response, no difference in PFS was observed.

In the updated results of the CLL11 study upon which the FDA approval was based (NCT01010061), median PFS of patients given obinutuzumab and chlorambucil was better than rituximab in the same combination at 29.2 months versus 15.4, HR 0.40 (0.33-0.50), with median OS not yet reached in either group(45). Obinutuzumab monotherapy for treatment of patients with follicular lymphoma is approved as a second line treatment to a regimen containing rituximab.

1.2.7 Clinical Safety of Obinutuzumab Monotherapy in CLL

As of 2 July 2015 (the safety data cutoff date for all studies except MO28543), obinutuzumab has been administered to a total of 3386 patients, including 1281 patients with CLL and 2105 patients with NHL, from doses of 50 mg to 2000 mg as monotherapy or in combination with CHOP, FC, bendamustine, or chlorambucil (Clb). Overall, the safety of monotherapy obinutuzumab, or obinutuzumab combination therapy with CHOP, FC, bendamustine, or Clb, was manageable.

The most frequent causes of death were disease progression and adverse events of infectious diseases. This is consistent with the study population and the disease being treated.

Of particular interest, infusion-related reactions (IRRs) were observed consistently in all obinutuzumab trials. In patients with CLL (study BO21004), the highest incidence of IRR was at

the first infusion with the incidence decreasing rapidly with subsequent infusions. The incidence of IRRs observed with combination therapy (FC, CHOP, or bendamustine) appears similar to that observed with monotherapy. Furthermore, the incidence of IRRs appears to be higher with CLL compared with NHL, and higher in patients who received obinutuzumab compared with patients who received rituximab based on evidence from studies BO21003 and BO21999. There is no clear relationship between obinutuzumab dose and the incidence of IRRs based on data from Study GAO4768g. In Stage 2 of the pivotal Phase III study, BO21004, investigating G-Clb vs. R-Clb in patients with CLL, the incidence of IRRs, Grade 3-4 IRRs, and IRRs leading to discontinuation was higher in the G-Clb arm compared with the R-Clb arm. This study implemented several measures to minimize the risk of IRRs, including: use of corticosteroids, withdrawal of antihypertensive treatments, slow infusion, and split dosing. The evidence suggests that these risk-minimization measures decreased the risk of IRRs (all grades); however, the impact on the incidence of Grade 3-4 events and treatment discontinuations due to IRRs was limited.

Adverse events of special interest include IRRs, TLS, thrombocytopenia (including acute thrombocytopenia), neutropenia (including late-onset and prolonged neutropenia), prolonged B-cell depletion, infections including progressive multifocal leukoencephalopathy (PML) and hepatitis B virus (HBV) reactivation, worsening of pre-existing cardiac conditions, gastrointestinal (GI) perforation, and secondary malignancies(46). Details on the safety concerns and mitigation plan for obinutuzumab are provided in Section **3.5**.

1.2.8 Interleukin-15

IL-15 is a 14-15kDA member of the 4-alpha-helix bundle family of cytokines that acts through a heterotrimeric receptor involving IL-12/IL-15R beta subunit shared with IL-2, the common gamma chain (γc) shared with IL-2, IL-4, IL-9, IL-21, and IL-15 specific receptor subunit IL-15R alpha (CD215)(47). IL-15 acts as a cell-surface molecule as part of an immunological synapse with IL-15 and IL-15R alpha produced *in trans* on adjacent mononuclear cells like monocytes and DCs which have been stimulated with interferon (and/or) CD40 ligation. IL-15 has been shown in many model systems to be a potent stimulator of T and NK-cell functions and in contrast to IL-2 does not activate Tregs and participates less in the capillary leak syndrome(48). Several studies in murine models suggested that IL-15 may prove to be of value in the therapy of neoplasia. The safety of IL-15 was evaluated in rhesus macaques(49, 50). A 12-day bolus intravenous administration of 20 µg/kg/day of IL-15 to rhesus macaques was associated with a 4 to 8-fold increase in the number of circulating NK cells. When administered by continuous intravenous infusion at 20 µg/kg/day for 10 days it led to a 10-fold increase in the number of circulating NK cells, a 15-fold increase in the number of circulating monocytes and a massive 80 to 100-fold increase in the number of circulating effector memory CD8 T-cells. Subcutaneous infusions at 20 µg/day for 10 days led to a 10-fold expansion in the number of circulating effector memory CD8 T-cells. On the basis of animal and laboratory trials of IL-15, great interest was generated among leading immunotherapeutic experts participating in the NCI Immunotherapy Agent Workshop who ranked IL-15 as the most promising unavailable immunotherapeutic agent to be brought to therapeutic trials.

1.2.9 Clinical Trials Using IL-15 Monotherapy in the Treatment of Cancer

We initiated, executed and reported a first in-human Phase I study of bolus administered intravenous rhIL-15 in adults with refractory metastatic malignant melanoma and metastatic renal cell cancer(51) (NCI Protocol ID Number: 10-C-0021 A Phase I Study of Intravenous Recombinant Human IL-15 [rhIL-15] in Adults with Refractory Metastatic Melanoma and

Metastatic Renal Cell Cancer NCT01021059). This study was initially planned as a Phase I dose-escalation trial starting with an initial dose of 3 mcg/kg/day for 12 days. However, after the initial patient developed grade 3 hypotension and another patient of the 5 at 3 mcg/kg/day studied developed grade 3 thrombocytopenia the protocol was amended to add the two lower doses of 1.0 and 0.3 mcg/kg/day. Two of four patients given 1.0 mcg/kg/day dose developed persistent grade 3 alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations that were dose limiting. All 9 patients with IL-15 at 0.3 mcg/kg/day received 12 doses without a DLT, and the MTD of rhIL-15 was defined as 0.3mcg/kg/day.

There was a consistent temporal pattern of post-treatment adverse events in patients receiving 3 mcg/kg/day doses of IL-15 with fever and rigors beginning 2 ½ to 4 hours following the start of IV infusions, and a drop in blood pressure 2 to 3 hours after the infusion to a nadir approximately 20 mm/Hg below pretreatment levels. These changes were concurrent with a maximum of 50-fold elevation of circulating IL-6 and IFN- γ concentrations.

Flow cytometry of peripheral blood lymphocytes in patients receiving 3 mcg/kg/day revealed a dramatic efflux of NK and memory CD8 T-cells from the circulation within minutes of IL-15 administration, followed by an influx and hyperproliferation yielding a 10-fold expansion in the number of NK cells that ultimately returned to baseline. There was a modest effect on the number of CD8+ T-cells but by day 8 of the infusion virtually all CD8+ T-cells expressed high levels of Ki67, CD38 and HLA-DR. In this first-in-human Phase I trial there were no responses with stable disease as the best response. However, 5 patients manifested a decrease of between 10% and 30% of their marker lesions and 2 had clearing of lung lesions.

1.2.10 Clinical Trials Involving IL-15 Administered by Alternate Dosing Strategies

Ultimately, we concluded that it proved too difficult to administer IL-15 as an intravenous bolus infusion because of clinical toxicities produced by intense cytokine secretion that occurred within the first 2 hours after treatment. There were exceedingly high IL-15 C_{max} levels initially after bolus infusions that were sufficient to signal through the IL-2/IL-15R beta and γc receptor pair that IL-15 shares with IL-2, thereby contributing to the toxicities observed. To reduce the C_{max}, the toxicity and increase the period of time when IL-15 is at an optimal concentration for high-affinity IL-15 receptors we evaluated alternative dosing strategies, first in rhesus macaques. By administering IL-15 by civ or subcutaneously (SC) to these nonhuman primates the exceedingly high C_{max} observed by bolus infusion was avoided. In particular, with bolus intravenous infusions to rhesus macaques at 20 mcg/kg/day, the C_{max} was 720 pg/mL, in contrast with SC infusion of 20 mcg/kg/day the C_{max} was 50 pg/mL and with civ at 20 µg/kg/d the IL-15 C_{max} was between 2 and 4 pg/mL throughout the 10-day study period.

1.2.10.1 A Phase I Study of Subcutaneous Recombinant Human IL-15 (rhIL-15) in Adults with Metastatic Cancer (NCT01727076; NCI CC#13-C-0045)

To translate this observation in collaboration with the Cancer Immunotherapy Trials Network (CITN), we completed a Phase I trial of subcutaneous recombinant human IL-15 in cycles consisting of 5 daily injections of rhIL-15 given Monday-Friday for 2 weeks, then 2 weeks of observation with potential for additional cycles. Three patients each were enrolled in 0.25, 0.5, 1.0, and 2.0 mcg/kg/day dose levels and six patients were evaluated at 3.0 mcg/kg/day. Eighteen patients completed at least one cycle with one DLT at 3.0 mcg/kg/day and one serious adverse event pancreatitis at 2.0 mcg/kg/day. Flow-cytometry data indicated a consistent increase in the frequency of CD56bright CD3- negative NK cells peaking at day 15 (day 12 = last dose). The mean fold increase with 3 mcg/kg/day of IL-15 in circulating NK cell numbers peaked at 10.8-

fold. The maximum fold increase in circulating CD8 + T cells was 3.3-fold. It was concluded that subcutaneous IL-15 was well tolerated and that the 3 mcg/kg/day dose level expansion dose was safe for outpatient use.

1.2.10.2 A Phase I Study of a Continuous Intravenous Infusion of Recombinant Human Interleukin IL-15 (rhIL-15) in Adults with Metastatic Cancers (NCT01572493)

In a parallel clinical trial that we performed in the Clinical Center NIH, rhIL-15 was administered at progressively increasing doses to 3 patients each of 0.25, 0.5, 1.0, 2.0 and 4.0 mcg/kg/day to patients with metastatic malignancy by civ infusion for 10 days. Two dose-limiting toxicities were observed at 4.0 mcg/kg/day, one hepatotoxicity and the other visceral arterial ischemia. Therefore, an expansion group study of 9 patients at the MTD of 2.0 mcg/kg/day was completed. This 2.0 mcg/kg/day dose level was well tolerated. None of the patients in this trial developed anti-IL-15 antibodies.

The pharmacokinetic pattern when IL-15 was administered by civ was quite distinct from that observed with bolus infusion. With bolus infusions of 3 mcg/kg/day the arithmetic mean C_{max} of 30,420 pg/mL was observed at the onset of the IL-15 administration, followed by a rapid decline in serum IL-15 levels. When IL-15 was administered by subcutaneous infusion the C_{max} at 4 hours after the subcutaneous administration of 3.0 mcg/kg/day was 6,480 pg/mL. With continuous intravenous infusion, there was a progressive increase of serum IL-15 levels with a C_{max} at 12 to 48 hours of 1,510 pg/mL, markedly lower than that observed with bolus infusions. The lower C_{max} observed with subcutaneous and continuous intravenous infusions was paralleled inversely by a 10-fold greater MTD at these levels compared to that with the bolus infusion. In the civ trial following the C_{max} at 12 to 48 hours there was a gradual decline to 8% of the maximum level by days 8-10 despite the fact that the IL-15 infusions were continued. Our hypothesis for this decline in serum IL-15 concentration is that one factor was the induction by IL-15 of an increase in the number of IL-15 receptor bearing cells as well as the number of receptors especially IL-2/IL-15Rβ (CD122) receptors, per cell that acted as a sink, binding some of the IL-15 administered. The time course of the increase in host lymphoid cells showed an interesting pattern with civ. Within 1 to 3 days of the infusion initiation there was a rapid decline in the number of circulating NK cells, followed by a gradual increase till the termination of infusions. Of interest, during the 1 to 3 days immediately following termination of the infusion there was a dramatic 30-fold increase in the number of circulating NK cells and an over 350-fold increase in the number of CD56bright NK cells (**Figure 1**). The rate of proliferation of different subsets of NK cells assessed by Ki67 was consistent with their levels of CD122 (IL-2/IL-15Rβ) expression with CD56bright > CD56dim, CD94high, > CD56dim, CD94low. The functional capacity of the dominant CD56bright subset was augmented following IL-15 administration and was associated with an increase in their expression of perforin and granzyme. Furthermore, although the specific lytic activity of CD56bright cells was not as great as that of CD56dim cells, their lytic activity was markedly increased by IL-15 treatment including activity associated with antibody-dependent cellular cytotoxicity (ADCC), assessed with CD20 antibody coated Raji cells, natural cytotoxicity to K562 cells, mediated by NKp30 and NKp46 as well as by MICA/NKG2D-mediated cytotoxicity(52). These observations on the effect of IL-15 on NK subsets and their function support the proposed trials described below that involve the combinations of IL-15 with antitumor monoclonal antibodies to increase their ADCC and antitumor efficacy.

A trial of IL-15 by continuous intravenous infusion for 5 days has been initiated and in the 10 patients studied following treatment there was a 21 to 44-fold increase in the number of circulating NK cells, and up to an 8.9-fold increase in the number of CD8+ T cells (**Table 3**, **Figure 1**).

1.2.11 Preclinical Trials of IL-15 with Anticancer Monoclonal Antibodies to Augment their ADCC

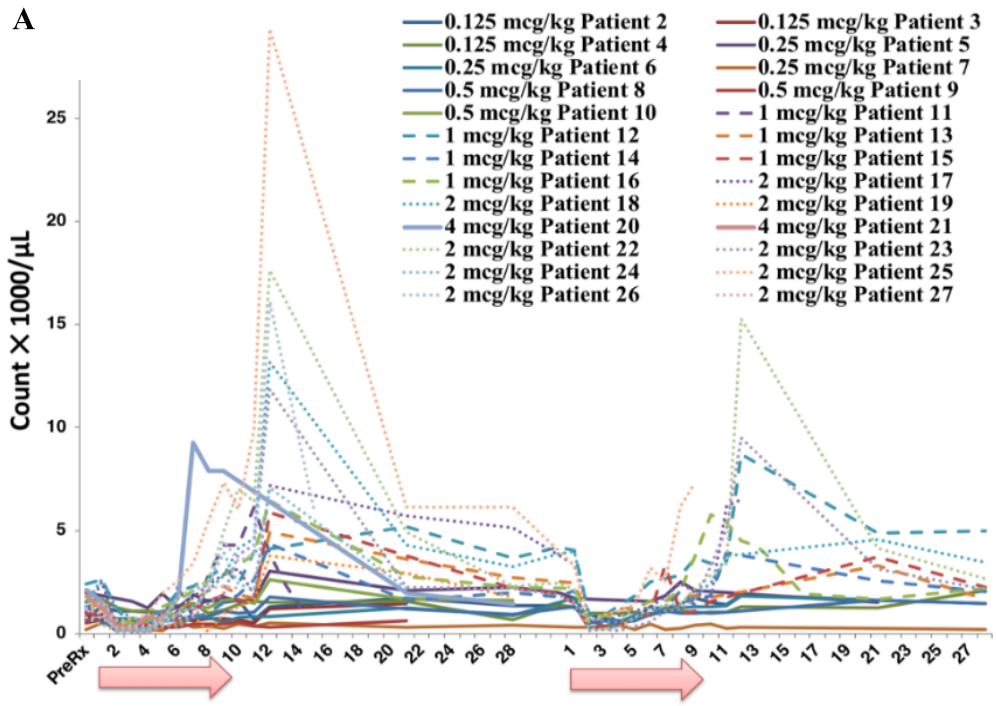
While the in vivo effects of IL-15 in cancer patients are still not entirely clear, the initial clinical data has demonstrated that to achieve its potential in the treatment of cancer IL-15 will have to be used in combination with other therapeutic agents. Considering the data from preclinical animal models and clinical trials of the capacity of IL-15 to increase the number of activated NK cells, T cells and monocytes, this information supports the administration of IL-15 with antitumor monoclonal antibodies to augment their ADCC against tumor cells. To further investigate this strategy, the Waldmann Laboratory used an immunocompetent syngeneic mouse model of B-cell lymphoma to investigate the combination of IL-15 with rituximab. Wild-type CD56 and BL/6 mice were inoculated intravenously with EL4-CD20 cells, a mouse lymphoma line transfected with CD20, and the mice were distributed into 4 treatment groups (control, IL-15 alone, rituximab alone and the combination) of 10 mice each. IL-15(5 μg/mouse) was administered 5 x per week for 4 weeks beginning 3 days after EL4-CD20 inoculation. In cohorts receiving rituximab, the monoclonal antibody was given once per week for 4 weeks starting 5 days after EL4-CD20 inoculation. As seen in **Figure 2** below, IL-15 or rituximab monotherapy prolonged survival of mice when compared to the control group ($p < 0.05$) but the combination of IL-15 and rituximab showed the greatest prolongation of survival compared to monotherapies (< 0.01) so that 75 days after tumor inoculation 90% of the combination treatment group were still alive in contrast to 30% survival from the monotherapy groups and no surviving mice in the control group (**Figure 2**). In a parallel preclinical trial, the Waldmann Group administered a combination therapy of alemtuzumab with rhIL-15 in the MET-1 bearing xenograft model in wild-type SCID/NOD mice (**Figure 3**, A). Again, there was an augmentation of survival of the combination of IL-15 with alemtuzumab compared to either element alone. The efficacy was lost in FcRγ-/- mice supporting the hypothesis that the efficacy was due to augmented ADCC.

In a prospective analysis which compared *ex vivo* NK cell phenotype and function in patients with CLL and healthy controls, CD56dim NK cells in CLL patients displayed reduced expression of the NKG2D activating receptor and increased CD27 expression, indicating declines in mature cells. In addition, NK cells from CLL patients showed reduced degranulation responses toward transformed B cells both alone and with rituximab, and were more sensitive to activation-induced cell death(53).

In another study of *ex vivo* PBMCs of patients with CLL, rhIL-15 alone induced NK cell activation and proliferation, leading to improved B leukemic cell depletion(54). Level of depletion increased with the addition of rituximab, and increased even further with obinutuzumab (**Figure 4**). The evidence therefore suggests that IL-15 alone may show efficacy in CLL by increasing NK cell number and activation, and that this efficacy can be increased further by the addition of a tumor-directed monoclonal antibody whose mechanism of action includes ADCC, such as obinutuzumab.

Table 3: Characteristics and Outcomes of 11 Patients Treated with a 5-day civ rhIL-15 Infusion

Diagnosis	Age	Gender	Dose level (mcg/kg)	No. of doses	NK cell increase (fold)	CD8+ T-cell increase (fold)
Melanoma	63	M	5	5	32.01	4.21
Small bowel	69	M	5	10	39.13	4.74
Colorectal	60	F	5	4	-	-
Small bowel	51	F	5	10	32.03	5.66
Colorectal	66	F	4	10	44.90	3.65
Renal cell	56	M	4	15	43.65	8.94
Esophageal	60	M	4	10	39.63	2.01
Colorectal	67	F	3	20	21.40	1.65
Colorectal	56	F	3	15	23.66	2.03
Endometrial	70	F	3	3	-	-
Colorectal	47	F	3	10	24.15	1.66



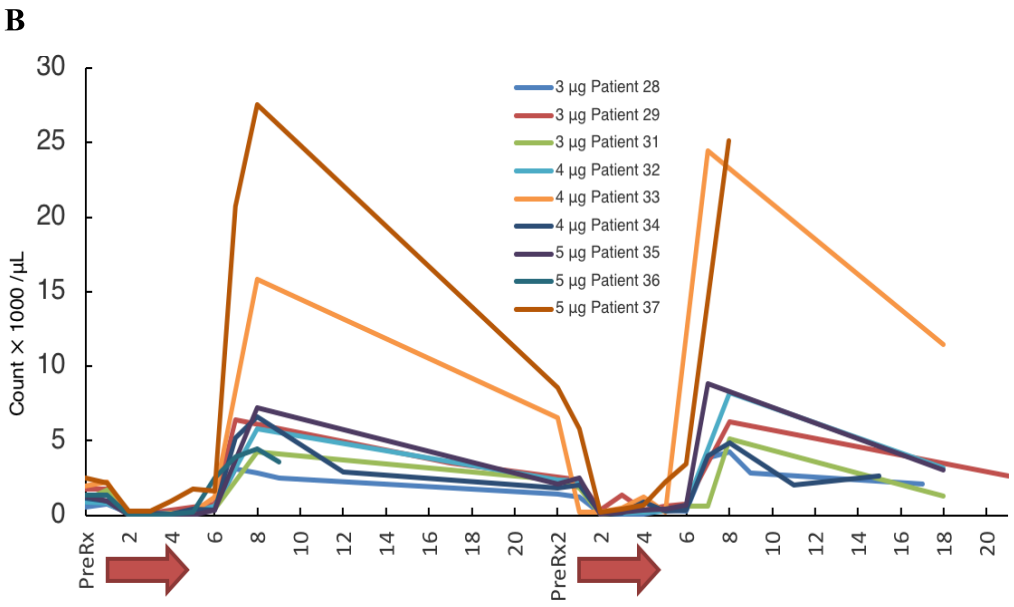


Figure 1: Increase in lymphocytes, predominantly NK cell count, during continuous infusion of rhIL-15. rhIL-15 was administered at progressively increasing doses of 0.25, 0.5, 1.0, 2.0 and 4.0 mcg/kg/day by 10-day civ infusion (A) and 5-day civ. infusion (B) to patients with metastatic malignancy. Patients 2-4 received 0.125 mcg/kg, patients 5-7 received 0.25 mcg/kg, patients 8-10 received 0.5 mcg/kg, patients 11-16 received 1.0 mcg/kg and patients 17-19 received 2.0 mcg/kg.Following termination of the treatment (red arrow) there was a dramatic 30-fold increase in the number of circulating lymphocytes predominantly NK cell count and an over 350-fold increase in the number of circulating CD56bright NK cells in the 10-day cohort, and an up to 44-fold increase (33-fold mean increase) in the number of circulating NK cells in the 5-day cohort.

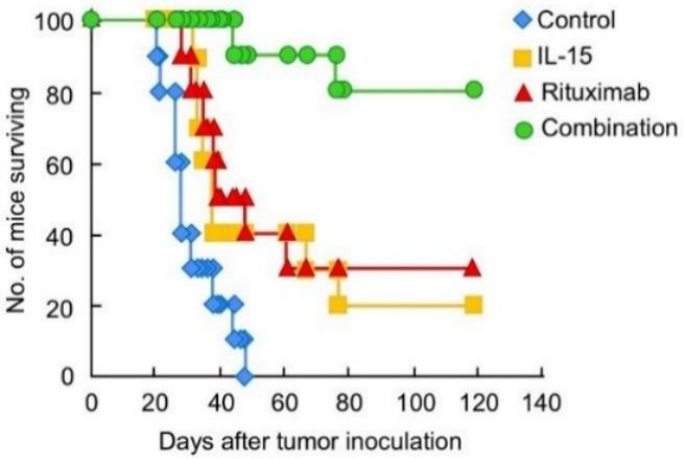


Figure 2: Addtion of IL-15 increased ADCC and the antitumor efficacy of cancer-directed monoclonal antibodies. EL4 leukemic cells were transfected with human CD20 and administered intravenously into immunologically intact mice**.** Mice treated with either IL-15 alone (yellow) or rituximab (anti-CD20) alone (red) showed modest prolongation of survival. This prolongation was markedly augmented when the two agents were administered together (green).

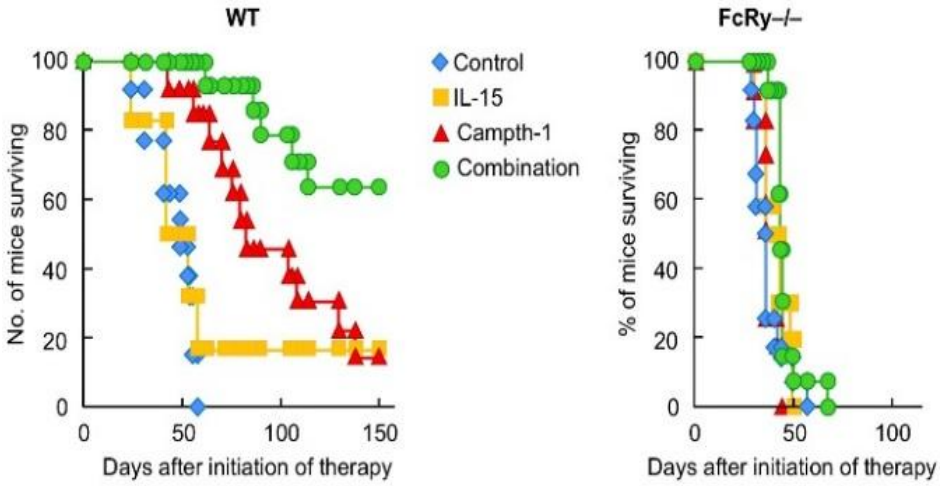


Figure 3: Combination alemtuzumab and rhIL-15 in a xenograft model of MET-1 ATL Leukemia. Left: SCID/NOD mice bearing the MET-1 ATL leukemia receiving either alemtuzumab (CAMPATH) (red) or IL-15 alone (yellow) had only modest efficacy that was markedly augmented by the combination of IL-15 plus alemtuzumab (green). Right: This efficacy was lost in FcR$\gamma^{-/-}$ mice supporting the hypothesis that the efficacy was due to ADCC.

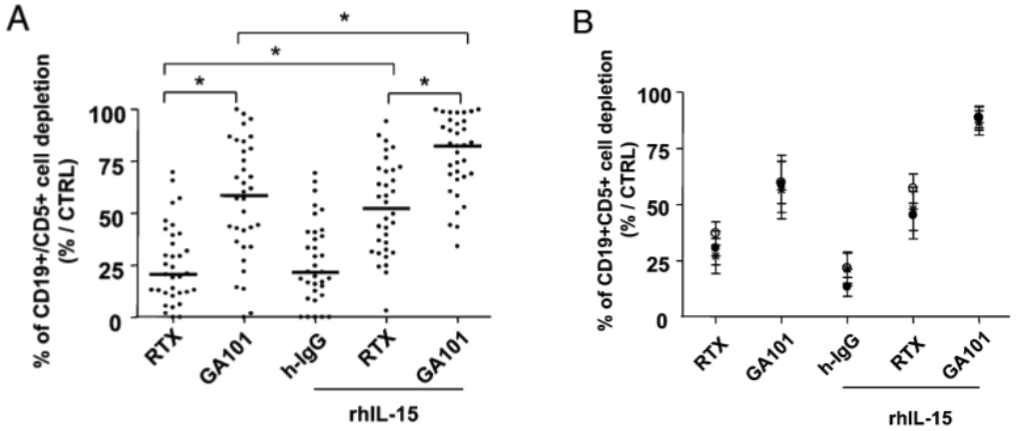


Figure 4: B leukemic cell depletion induced by mAbs and rhIL-15 in *ex vivo* CLL samples. After 7 days of treatment, B leukemic cell depletion as a percentage (A) and mean percentage (B) compared with h-IgG-treated cells; RTX, rituximab, GA101, obinutuzumab (from Laprevotte E, et al. 2013)

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Patients must have a confirmed diagnosis of chronic lymphocytic leukemia/small lymphocytic lymphoma that expresses CD20 as confirmed by new/fresh peripheral blood sample collection and review by Laboratory of Pathology, NCI

2.1.1.2 Measurable or evaluable disease (see Section **6.3**)

2.1.1.3 Patients must have received prior treatment required as follows: CLL that is refractory or relapsed following therapy with a BTK inhibitor OR have relapsed/refractory CLL and are intolerant of BTK inhibitor therapy; in addition, patients with del(17p) must also be refractory or relapsed after, or intolerant to, therapy with venetoclax; patients who have received prior obinutuzumab are eligible regardless of response to the drug.

2.1.1.4 Active disease requiring treatment, as defined by at least one of the following (per IWCLL 2018 consensus criteria):

- Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia (Hb <10 g/dL) and/or thrombocytopenia (platelet counts $<100 \times 10^9$/L).
- Massive (i.e., ≥6 cm below the left costal margin) or progressive or symptomatic splenomegaly.
- Massive nodes (i.e., ≥10 cm in longest diameter) or progressive or symptomatic lymphadenopathy.
- Progressive lymphocytosis with an increase of ≥50% over a 2-month period, or lymphocyte doubling time (LDT) <6 months.
- Autoimmune complications including anemia or thrombocytopenia poorly responsive to corticosteroids.
- Symptomatic or functional extranodal involvement (eg, skin, kidney, lung, spine).
- Disease-related symptoms as defined by any of the following:
  - Unintentional weight loss ≥10% within the previous 6 months.
  - Significant fatigue (ie, ECOG performance scale 2 or worse; cannot work or unable to perform usual activities).
  - Fevers 38.0°C for 2 or more weeks without evidence of infection.
  - Night sweats for ≥1 month without evidence of infection.

2.1.1.5 ≥18 years of age on day of signing informed consent

NOTE: Because no dosing or adverse event data are currently available on the use of rhIL-15 in combination with obinutuzumab in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials

2.1.1.6 ECOG performance status ≤1 (Karnofsky ≥80%; see **APPENDIX A**) or ≤2 (Karnofsky ≥60%) if the decrease in the performance status is CLL-related and constitutes a criterion for active treatment (see **2.1.1.4**)

1.1.1.1 Adequate organ function as evidenced by the following laboratory parameters:

• Absolute neutrophil count (ANC)	≥ 750 /mcL
• Platelets	≥ 50,000 / mcL (transfusions not permitted)
• Hemoglobin	≥ 9 g/dL (transfusions permitted)
• Serum creatinine	≤ 1.5 X upper limit of normal (ULN)
• Serum total bilirubin	≤ 1.5 X ULN **OR** Direct bilirubin ≤ ULN for patients with total bilirubin levels > 1.5 ULN
• AST (SGOT) and ALT (SGPT)	≤ 3 X ULN

2.1.1.7 Women of child-bearing potential (WOCBP) and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study treatment, and for at least 18 months after the last dose of obinutuzumab. The effects of rhIL-15 and obinutuzumab on the developing human fetus are unknown. Additionally, CD20-depleting agents are known to produce opportunistic infections, causing fetal B-cell depletion in animal studies, and may be teratogenic. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

NOTE: WOCBP is defined as any female who has experienced menarche and who has not undergone successful surgical sterilization or who is not postmenopausal. WOCBP must have a negative pregnancy test (HCG blood or urine) during screening.

2.1.1.8 Ability of patient to understand and the willingness to sign a written informed consent document.

2.1.2 Exclusion Criteria

2.1.2.1 Current or prior anti-cancer treatment prior to the first dose of rhIL-15 as defined below:

- Chemotherapy, targeted small molecule therapy, or other anti-cancer treatment not otherwise specified below within 2 weeks
- Radiation therapy within 2 weeks
- Anti-cancer monoclonal antibody (mAb) treatment within 4 weeks
- Use of an investigational agent (e.g., biologic, drug, or other) within 4 weeks
- Allogeneic stem cell transplant within 100 days
- Systemic treatment for graft versus host disease (GVHD), including but not limited to oral or parenteral corticosteroids, ibrutinib, and extracorporeal phototherapy, within the last 12 weeks

2.1.2.2 Persisting toxicity related to prior therapy (including GVHD) of grade > 1, with the exception of the following: alopecia or sensory neuropathy grade ≤ 2, or other grade ≤ 2 not constituting a safety risk based on investigator's judgment

2.1.2.3 Current use of immunosuppressive medication, EXCEPT for the following:

- Intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection);
- Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent; or,
- Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)

2.1.2.4 Presence of Richter's transformation.

2.1.2.5 Patients requiring immediate cytoreduction, if they had no prior treatment with a drug that has an established clinical benefit.

2.1.2.6 Presence of uncontrolled intercurrent illnesses including but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, cognitive impairment, active substance abuse, or psychiatric illness/social situations that in the view of the Investigator would preclude safe treatment and limit compliance with study requirements

2.1.2.7 Presence of active bacterial infections, documented HIV infection, PCR evidence for active or chronic hepatitis B or hepatitis C, or positive screening HBV/HCV serology without documentation of successful curative treatment (see Section **3.5.2.1** for data on obinutuzumab administration in patients with HBV, and Section **12.5** for IL-15 administration in HIV-positive patients)

2.1.2.8 Asthma requiring chronic inhaled or oral corticosteroids, or history of asthma requiring mechanical ventilation; patients with a history of mild asthma that are on or can be switched to non-corticosteroid bronchodilator regimens are eligible

2.1.2.9 Active or history of any autoimmune disease thought to be unrelated to their CLL

2.1.2.10 Inability or refusal to practice effective contraception during therapy or the presence of pregnancy or active breastfeeding. Because there is no significant preclinical information regarding the risks to a fetus or a newborn infant, all pregnant or breastfeeding woman will be excluded from participation in this trial

2.1.2.11 Received a live vaccine within 30 days of planned start of study therapy. **NOTE:** Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed

2.1.2.12 History of allergic reactions attributed to compounds of similar chemical or biologic composition to rhIL-15 or obinutuzumab, unless felt to be in the best interests of the patient in the opinion of the investigator

2.1.2.13 Known additional malignancy that requires active systemic treatment

2.1.3 Recruitment Strategies

Study participants will be recruited from the population of patients screened in the lymphoid malignancies clinic of the National Institutes of Health (NIH). These will include both referrals from outside physicians as well as patient self-referrals. This study will be posted on NIH websites and on NIH social media forums. Study-specific public service announcements and informational

fliers will be used for recruitment activities. All information to be posted or distributed publicly will be submitted to the IRB for review and approval in advance of use.

2.2 SCREENING EVALUATION

Screening evaluation testing/procedures are conducted under the separate screening protocol, 01-C-0129 (Eligibility Screening and Tissue Procurement for the NIH Intramural Research Program Clinical Protocols).

NOTE: Assessments and procedures to confirm study eligibility should be completed within 28 days prior to registration (unless otherwise noted). See also the Study Calendar (Section **3.9**).

- Clinical Evaluations
  - Disease history, including: diagnosis, treatment (e.g., systemic treatments, radiation and surgeries), status, and significant prior/ongoing side effects and symptoms
  - Complete medical history, including: all active conditions considered to be clinically significant by the treating investigator
  - Physical examination, including: height (screening only), weight, vital signs (i.e., temperature, pulse, respiratory rate, and blood pressure); review of concomitant medications and symptoms/side effects; and, assessment of performance status
- Laboratory Evaluations

  NOTE: Results from outside NIH are accepted.
  - CBC with differential
  - Chemistry panels (as noted) or specific analyte required for eligibility, including: Creatinine (i.e., or Acute Care Panel); serum calcium, phosphate, magnesium and albumin (i.e., Mineral Panel); ALT, AST, total and direct (if required) bilirubin (i.e., or Hepatic Panel); and, 24-hour urine creatinine clearance (if needed to measure CrCl in cases where serum creatinine >1.5mg/dl)
  - Coagulation panel, including: PT/INR and aPTT
  - Thyroid function tests, including: thyroid stimulating hormone (TSH) with reflex total triiodothyronine (T3) and free thyroxine (T4) per DLM policy
  - Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody, Hepatitis C antibody (HCV) [qualitative] (within 3 months), HIV 1/2 antibody (qualitative) (at any time, or within 3 months in patients with high risk or clinical suspicion for HIV as determined by PI) **NOTE:** For individuals with a positive hepatitis B core antibody, HBV DNA PCR will be performed to screen for subclinical infection.
  - Urine and/or serum HCG in women of childbearing potential
  - Urinalysis (with microscopic examination if abnormal)
- Imaging Studies

  NOTE: Results from outside NIH are accepted. Other body areas may be imaged if clinically indicated.
  - CT neck, chest, abdomen and pelvis (CT should be performed with IV and PO contrast, unless patient is allergic or has renal insufficiency; other imaging may be substituted at the discretion of the investigator [such as MRI])
  - MRI of brain (in patients with known or suspected involvement of CNS)

- Other Procedures
  - Pathologic review/confirmation of diagnosis by Laboratory of Pathology, NCI (no time limit). A fresh peripheral blood sample is required for this evaluation.
  - Electrocardiogram (EKG) (within 3 months)

2.3 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g. when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found **here**.

2.3.1 Treatment Assignment Procedures

NOTE: The following for NCI CCR patient registration purposes only.

2.3.1.1 Cohorts

Number	Name	Description
1	RR CLL	Patients with relapsed/refractory CLL (Up to 24 patients)

2.3.1.2 Arms

Number	Name	Description
1	Dose Escalation	IL-15 by civ infusion at escalating doses of 0.5, 1, and 2 mcg/kg/day on days 1-5 of each 4-week cycle (max 6 cycles), with obinutuzumab by IV infusion at a dose of 100 mg on day 4, 900 mg on day 5, 1,000 mg on day 11, and 1,000 mg on day 18 of the first cycle; then 1,000 mg on day 4 of each subsequent cycle, to determine the MTD
2	Dose Expansion	An additional 3 to 6 patients to receive IL-15 by civ infusion at the MTD on days 1-5 of cycles 1-6 with obinutuzumab by IV infusion at a dose of 100 mg on day 4, 900 mg on day 5, 1,000 mg on day 11, and 1,000 mg on day 18 of the first cycle; then 1,000 mg on day 4 of each subsequent cycle (Total 9 patients at MTD)

2.3.1.3 Treatment Assignment

The study is single-arm, open-label and non-randomized; i.e., subjects in Cohort 1 are directly assigned to Arm 1 or Arm 2 based on the dose level/arm open to enrollment.

2.4 BASELINE EVALUATION

The following should be performed prior to the first dose of rhIL-15 unless otherwise noted; tests performed as part of screening do not need to be repeated if they were performed within the specified window prior to the first dose of rhIL-15.

2.4.1 Clinical Evaluations

- Required within 28 days:
  - Medical history (interim)
  - Physical examination, including weight, and vital signs (i.e., temperature, pulse, respiratory rate, and blood pressure); review of concomitant medications and symptoms/side effects; and, assessment of performance status

2.4.2 Laboratory Evaluations

NOTE: Results from outside NIH are accepted.

- Required within 7 days:
  - Urine and/or serum HCG in WOCBP
- Required within 14 days:
  - CBC with differential
  - Chemistry panels, including: Acute Care Panel (sodium, potassium, chloride, CO_2, glucose, BUN, creatinine), Mineral Panel (serum calcium, phosphate, magnesium and albumin), Hepatic Panel (alkaline phosphatase, ALT, AST, total and direct bilirubin), and 24-hour urine creatinine clearance (if needed measure CrCl if serum creatinine >1.5mg/dl)
  - Others: LDH, Uric acid, Total protein
  - Coagulation panel, including: PT/INR and aPTT
  - TSH with reflex T3 and free T4
  - Urinalysis (with microscopic examination if abnormal)
  - HLA typing (A, B, C, DR, DQ)
  - Serum protein electrophoresis with immunofixation (SPEP)
  - Serum free light chains, quantitative serum immunoglobulin (IG) levels
  - C-reactive protein (CRP)
  - Beta-2 microglobulin (B2M)
  - Haptoglobin, direct antiglobulin test (DAT)
  - Iron panel (includes ferritin, transferrin, iron), folate, vitamin B12
  - Viral studies (serologies CMV and EBV).
- Required within 28 days:
  - Lymphocyte Phenotype: T, B and NK cell subsets
  - Anti-Nuclear Antibody (ANA)
  - Glucose-6-phosphate dehydrogenase (G6PD)
- Required within 3 months:
  - PB interphase FISH panel with probes for ATM (11q22.3), D12Z3 (12 cen), D13S319 (13q14.3), LAMP1 (13q34) and TP53 (17p13.1)
  - Karyotype
- Required, from any time point post-diagnosis (i.e., no time limit):
  - IGVH mutation analysis

2.4.3 Imaging Studies

NOTE: Results from outside NIH are accepted. Other body areas may be imaged if clinically indicated.

- CT neck, chest, abdomen and pelvis (CT should be performed with IV and PO contrast, unless patient is allergic or has renal insufficiency; other imaging may be substituted at the discretion of the investigator [such as MRI])
- MRI of brain * (in patients with known or suspected involvement of CNS)

*NOTE: The MRIs to be done in this study may involve the use of the contrast agent gadolinium, if clinically indicated. The risks associated with MRIs and contrast are discussed in the consent form and section 12.5.2

2.4.4 Other Procedures

- Flow cytometry will be performed on peripheral blood for both diagnostic and staging purposes (only NIH results accepted; NCI Laboratory of Pathology)
- Bone marrow aspiration and biopsy (within 3 months)

2.4.5 Research Correlates

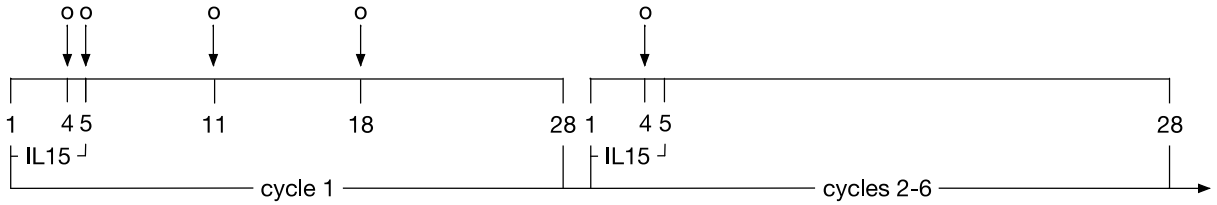
NOTE: See Section **5** for additional information. The following sample types will be collected for correlative research studies:

- Required:
  - Blood samples for lymphocyte subset testing and circulating tumor DNA
  - Blood, buccal swab, or saliva for germline DNA
- Optional:
  - Blood samples for ADCC of obinutuzumab, tissue immune cell subset comparison
  - Bone marrow biopsy
  - Tumor biopsy

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

To determine the MTD, and safety and toxicity profile of the combination of civ IL-15 and obinutuzumab, a non-randomized, open-label, single arm, single institution Phase I study will be conducted at the NCI. Each cycle of treatment is 28 days or 4 weeks, and a maximum of 6 cycles will be administered. Patients will be treated with civ IL-15 at dose levels of 0.5,1 or 2 mcg/kg/day on days 1-5 of cycles 1-6. Obinutuzumab (IV) will be administered at a dose of 100 mg on day 4, 900 mg on day 5, 1,000 mg on day 11, and 1,000 mg on day 18 of cycle 1; then 1,000 mg on day 4 of each subsequent cycle.



Study treatment will continue for as long as:

- Subject is deriving clinical benefit (complete remission [CR], partial remission [PR], or stable disease [SD]), and
- Subject is not experiencing any unacceptable toxicity (i.e., dose-limiting toxicity as found in Section **3.2** or toxicity requiring hold as defined in Section **3.5** lasting longer than two weeks)

3.2 DOSE-LIMITING TOXICITY

Dose-limiting toxicities are defined as: any grade 3, 4, or 5 toxicity if not incontrovertibly due to disease progression or an extraneous cause, and deemed possibly, probably or definitely related to IL-15 or obinutuzumab by the PI or designee during the first 28 days of treatment, with the following exceptions:

3.2.1 Hematological Exceptions

- Grade 3 or 4 lymphocytopenia without clinical signs of infection grade 2 or above.
- Grade 3 or 4 neutropenia without clinical signs of infection grade 2 or above.
- Grade 3 or 4 thrombocytopenia lasting fewer than 5 days and not associated with bleeding or purpura.
- Grade 3 leukocytosis (WBC > 100,000/mm3) in the absence of signs of leukostasis or other toxicities possibly related to the expansion of activated cells.

3.2.2 Non-Hematological Exceptions

- Transient (< 24 hours) grade 3 hypoalbuminemia, hypokalemia, hypomagnesemia, hyponatremia or hypophosphatemia which responds to medical intervention.
- Non-sustained (< 7 days) grade 3 liver function test (ATL, AST, alkaline phosphatase, total or direct bilirubin) abnormalities in the absence of clinical signs of hepatic dysfunction (lethargy, confusion, anorexia, pruritus, tremor); for patients with baseline grade 1 elevations, any increase ≥ 10 x baseline will be considered dose-limiting and these patients will be closely monitored for liver function abnormalities.
- First grade 3 infusion reaction associated with obinutuzumab administration (occurring

within 24 hours of the dose). Infusion reactions will be managed as outlined in Section **3.5**.

- Grade 3 tumor lysis syndrome (TLS) and non-sustained (<7 days) grade 3-4 metabolic abnormalities related to TLS. TLS will be managed as outlined in Section **3.5**.

Management and dose modifications associated with the above adverse events are outlined in Section **3.5**. Occurrence of any of the adverse events listed above after the first 28 days of treatment will lead to permanent discontinuation of protocol therapy, but will not be deemed a DLT for purposes of dose escalation.

3.3 DOSE ESCALATION

Dose escalation will proceed according to the following schedule (**Table 4**) and guidelines (**Table 5**). Dose-limiting toxicity (DLT) is defined above. Each patient will continue treatment at the dose level they were enrolled — there will be no intra-patient dose escalation.

The MTD is the dose level at which no more than 1 of up to 6 patients experience DLT during the DLT evaluation window(s), or the dose below that at which at least 2 (of ≤6) patients have DLT. If a patient did not experience a DLT and did not finish treatment during the DLT window, he or she will not be evaluable for toxicity and will be replaced in that dose level. The protocol will be amended to note the MTD once determined.

Table 4: IL-15 Dose Escalation Schedule

Dose Level	rhIL-15 (all cycles) (mcg/kg/day)	Obinutuzumab** (mg)
Level 1	0.5 on day 1-5	1000
Level 2	1 on day 1-5	1000
Level 3	2 on day 1-5	1000
*Doses are stated as exact dose in units (e.g., mg/m^2, mcg/kg, etc.) rather than as a percentage. ** Each dose of obinutuzumab is 1000mg IV on day 4, with the exception of infusions in Cycle 1, which are administered on day 4 (100 mg) and day 5 (900 mg), day 11 (1,000 mg) and day 18 (1,000 mg).		

Table 5: Dose Escalation Guidelines

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended Phase II dose. At least 6 patients must be entered at the recommended Phase II dose.

3.4 DRUG ADMINISTRATION

Each cycle of treatment is 28 days (4 weeks). The minimum window between initiation of new cycles is 26 days; a cycle delay due to scheduling or other administrative reasons (i.e., reasons other than toxicity/dose management as defined below) is 7 days.

Treatment will be administered on an inpatient basis during week 1 of the first cycle, and as outpatient during subsequent weeks and cycles unless decided otherwise by the principal investigator based on clinical judgment. Reported adverse events and potential risks are described in Section **14**. Appropriate dose modifications are described in Section **3.5**. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Regimen Description				
Agent	**Premedications; Precautions**	**Schedule**	**Dose**	**Route**
rhIL-15	Premedicate with acetaminophen and/or ibuprofen	Cycles 1-6 Days 1-5	** in *** mL D5W with 0.1% HSA	IV over 24 hours
Obinutuzumab	Infusion reaction and tumor lysis syndrome prophylaxis*	Cycle 1 Day 4	** in 100 mL NS	IV at 25 mg/hr over 4 hours
		Cycle 1 Day 5	** in 250 mL NS	IV at 50 mg/hr (if no infusion reaction during prior infusion) OR 25 mg/hr (if an infusion reaction occurred during prior infusion); may escalate in increments of up to 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr
		Cycle 1 Day 11	** in 250 mL NS	If no infusion reaction occurred during the previous infusion and the final infusion rate was 100 mg/hr or faster, IV infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. If an infusion reaction occurred
		Cycle 1 Day 18	** in 250 ml NS	
		Cycles 2-6 Day 4	** in 250 mL NS	

Regimen Description				
Agent	**Premedications; Precautions**	**Schedule**	**Dose**	**Route**
				during the previous infusion, administer IV at 50mg/hr. The rate of infusion can be escalated in increments of 50mg/hr every 30 minutes to a maximum rate of 400mg/hr.
*See Section **3.4.2**. **Doses as appropriate for assigned dose level. *** Infusion volume of rhIL-15 per calculation in **APPENDIX C: IL-15 Dilution Instructions**				

Infusions may be done peripherally or via central venous access device (if present; not required to be placed by the study). When administered on an outpatient basis, rhIL-15 will be infused via an ambulatory infusion pump. On days that both rhIL-15 and obinutuzumab are given together (i.e., Day 4 and 5 of Cycle 1, and Day of of each subsequent Cycle), rhIL-15 infusion will be held up to two hours prior to, and up to two hours following the obinutuzumab infusion.

3.4.1 Prophylactic and Supportive Care for rhIL-15

Patients will be given acetaminophen 500-650 mg IV or orally 30 to 60 minutes prior to each IL-15 infusion as first line, and ibuprofen 400 mg or 600 mg orally depending on reactions with acetaminophen as a premedication

3.4.2 Prophylactic and Supportive Care for Obinutuzumab

As hypotension may occur during obinutuzumab infusions, antihypertensive treatments may be held for 12 hours prior to and throughout each obinutuzumab infusion and for the first hour after administration.

Premedication to reduce the risk of infusion reactions is outlined below.

Premedication for obinutuzumab infusion to reduce infusion-related reactions (IRR)			
Day of treatment cycle	**Patients requiring premedication**	**Premedication**	**Administration**
Cycle 1, Day 4 AND Cycle 1, Day 5	All patients	IV glucocorticoid: 20 mg dexamethasone OR 80mg methylprednisolone	Completed at least 1 hour prior to obinutuzumab infusion
		650-1000 mg acetaminophen	At least 30 minutes before obinutuzumab infusion
		Anti-histamine (e.g., 50 mg diphenhydramine)	
All subsequent infusions	All patients	650-1000 mg acetaminophen	At least 30 minutes before obinutuzumab infusion
	Patients with an IRR (Grade 1-2) with prior infusion	650-1000 mg acetaminophen	At least 30 minutes before obinutuzumab infusion
		Anti-histamine (e.g., 50 mg diphenhydramine)	

Premedication for obinutuzumab infusion to reduce infusion-related reactions (IRR)			
Day of treatment cycle	**Patients requiring premedication**	**Premedication**	**Administration**
	Patients with a grade 3 IRR with the previous infusion OR ALC > 25 X 10^9/L prior to next treatment	IV glucocorticoid: 20 mg dexamethasone OR 80mg methylprednisolone	Completed at least 1 hour prior to obinutuzumab infusion
		650-1000 mg acetaminophen	At least 30 minutes before obinutuzumab infusion
		Anti-histamine (e.g., 50 mg diphenhydramine)	

As the effects of combined treatment with rhIL-15 and obinutuzumab in CLL are unknown, all patients on the protocol will receive tumor lysis syndrome prophylaxis during Cycle 1. They will be premedicated with anti-hyperuricemics (e.g., allopurinol or rasburicase) at least 24 hours prior to each obinutuzumab infusion, with adequate hydration ensured. Prophylaxis will be continued for each subsequent cycle in patients with high tumor burden, ALC > 25 X 10^9 /L, and renal impairment (creatinine >1.5 X ULN)

3.4.3 Antimicrobial Prophylaxis

Patients with Grade 3 to 4 neutropenia lasting more than one week will receive antimicrobial prophylaxis until resolution of neutropenia to Grade 1 or 2. Antiviral and antifungal prophylaxis will be considered in patients with history of viral and fungal infections.

3.4.4 Other Modalities or Procedures

Patients will be observed in the day hospital or the inpatient unit for at least 60 minutes after administration of obinutuzumab for potential infusion-related reactions.

Patients with Grade 3-4 neutropenia may receive granulocyte colony-stimulating factor until ANC ≥ 5 X 10^9 /L.

3.5 Assessment of Safety and Dose Modifications

3.5.1 rhIL-15-specific Adverse Events

Please refer to the Comprehensive Adverse Event and Potential Risk list (CAEPR) for rhIL-15 presented in Section **14.1.8**.

Dose of rhIL-15 is based on the dose level and patient's weight at the beginning of each cycle, and can only be modified for rounding and/or consistency with prior cycles, and not for adverse events or renal/hepatic dysfunction. Infusion may continue during correction of electrolyte and other laboratory abnormalities listed in Section **3.2**. Infusion may be interrupted for other reasons for up to two hours each day (in addition to interruptions due to administration of obinutuzumab) but treatment should end 120 (±1) hours after initiation on Day 1.

3.5.2 Obinutuzumab-specific Adverse Events

Important risks identified in clinical investigations with obinutuzumab were: IRRs, TLS, thrombocytopenia (including acute thrombocytopenia), neutropenia (including prolonged and late onset neutropenia), prolonged B-cell depletion, infections (including hepatitis B reactivation and PML), worsening of pre-existing cardiac conditions GI perforation, and secondary malignancies. Obinutuzumab dose may be held as specified below, but not otherwise modified.

3.5.2.1 Hepatitis B Reactivation

HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with anti-CD20 antibodies such as obinutuzumab. HBV reactivation has been reported in patients who are HBsAg positive and also in patients who are HBsAg negative but are anti-HBc positive. Reactivation has also occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg negative, anti-HBc positive, and hepatitis B surface antibody [anti-HBs] positive). HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels and, in severe cases, increase in bilirubin levels, liver failure and death.

All patients will be screened for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with obinutuzumab. As noted in Section **2.1.2.7**, patients who show evidence of hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive) will be excluded from the study due to to the risk of HBV reactivation.

3.5.2.2 Progressive Multifocal Leukoencephalopathy (PML)

JC virus infection resulting in PML, which can be fatal, was observed in patients treated with obinutuzumab. Consider the diagnosis of PML in any patient presenting with new onset or changes to preexisting neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain magnetic resonance imaging and lumbar puncture. Discontinue obinutuzumab therapy and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML.

3.5.2.3 Infusion-Related Reactions (IRRs)

Obinutuzumab can cause severe and life-threatening IRRs; 65% of patients with CLL experienced a reaction to the first 1000 mg infused of obinutuzumab, and 38% of iNHL patients experienced a reaction on Day 1 of obinutuzumab infusion. IRRs within 24 hours of receiving obinutuzumab have occurred. IRRs can also occur with subsequent infusions. Symptoms may include hypotension, tachycardia, dyspnea, and respiratory symptoms (e.g., bronchospasm, larynx and throat irritation, wheezing, and laryngeal edema). Most frequently reported symptoms include nausea, fatigue, dizziness, vomiting, diarrhea, hypertension, flushing, headache, pyrexia, and chills.

If a patient experiences an infusion reaction during obinutuzumab infusion, adjust the infusion as follows:

- **Grade 4 (life-threatening):** Stop all infusions immediately and permanently discontinue protocol therapy.
- **Grade 3 (severe):** Interrupt all infusions and manage symptoms. Upon resolution of symptoms, restart rhIL-15 infusion at prior rate, consider restarting obinutuzumab infusion at no more than half the previous rate (the rate being used at the time that the infusion reaction occurred) and, if patient does not experience any further infusion reaction symptoms, obinutuzumab infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose (the Cycle 1 Day 4 infusion rate may be increased back up to 25 mg/hr after 1 hour but not increased further). Permanently discontinue treatment if patients experience a Grade 3 infusion-related symptom at rechallenge.

- **Grade 1-2 (mild to moderate):** Reduce obinutuzumab infusion rate or interrupt obinutuzumab infusion and treat symptoms. Upon resolution of symptoms, continue or resume infusion and, if patient does not experience any further infusion reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose (the Day 1 infusion rate may be increased back up to 25 mg/hr after 1 hour but not increased further).

3.5.2.4 Tumor Lysis Syndrome (TLS)

TLS, including fatal cases, has been reported in patients receiving obinutuzumab. Patients with high tumor burden, high circulating lymphocyte count (> 25 X 10^9/L) or renal impairment are at greater risk for TLS and should receive appropriate tumor lysis prophylaxis with antihyperuricemics (e.g., allopurinol or rasburicase) and hydration prior to the infusion of obinutuzumab. Continue prophylaxis prior to each subsequent obinutuzumab infusion, as needed.

During the initial days of obinutuzumab treatment, monitor the laboratory parameters of patients considered at risk for TLS. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.

3.5.2.5 Infections

Serious, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of obinutuzumab therapy. Fatal infections have been reported. Do not administer obinutuzumab to patients with an active infection. Patients with a history of recurring or chronic infections may be at increased risk of infection.

Non-neutropenic patients who require antibiotic treatment may continue therapy with rhIL-15 and obinutuzumab.

3.5.2.6 Neutropenia

Severe and life-threatening neutropenia, including febrile neutropenia, has been reported during treatment with obinutuzumab. Patients with Grade 3 - 4 neutropenia should be monitored frequently with regular laboratory tests until resolution. Anticipate, evaluate, and treat any symptoms or signs of developing infection. Granulocyte colony stimulating factors (G-CSF) may be administered in patients with Grade 3 or 4 neutropenia.

Neutropenia can also be of late onset (occurring more than 28 days after completion of treatment) and/or prolonged (lasting longer than 28 days).

Each cycle may be delayed by up to two weeks until resolution of Grade 3 or 4 neutropenia to Grade 1 or 2. Patients with severe and long lasting (> 1 week) neutropenia are strongly recommended to receive antimicrobial prophylaxis until resolution of neutropenia to Grade 1 or 2. Antiviral and antifungal prophylaxis should be considered.

3.5.2.7 Thrombocytopenia

Severe and life-threatening thrombocytopenia has been reported during treatment with obinutuzumab in combination with chlorambucil or bendamustine. Fatal hemorrhagic events during Cycle 1 have also been reported in patients with CLL treated with obinutuzumab.

Monitor all patients frequently for thrombocytopenia and hemorrhagic events, especially during the first cycle. In patients with Grade 3 or 4 thrombocytopenia, monitor platelet counts more frequently until resolution and consider subsequent dose delays of obinutuzumab and chemotherapy or dose reductions of chemotherapy. Transfusion of blood products (i.e., platelet

transfusion) may be necessary. Consider withholding concomitant medications which may increase bleeding risk (platelet inhibitors, anticoagulants), especially during the first cycle.

Each cycle may be delayed by up to two weeks until resolution of Grade 3 or 4 thrombocytopenia to Grade 1 or 2. If grade 3-4 thrombocytopenia occurs during Cycle 1, Day 4 and Day 5 doses of Obinutuzumab may still be administered, and Day 11 and Day 18 doses of Obinutuzumab delayed by up to a week until resolution of thrombocytopenia to Grade 1 or 2.

3.5.2.8 Immunization

The safety and efficacy of immunization with live or attenuated viral vaccines during or following obinutuzumab therapy have not been studied. Immunization with live-virus vaccines is not allowed during treatment and until B-cell recovery.

3.6 On Study Assessments/Evaluations

After Cycle 1, pre-dose assessments may be performed up to 3 days prior to Day 1 of a cycle, except where otherwise noted. The results from all procedures/tests must be reviewed prior to initiation of each cycle of treatment for consideration of dose modifications and delay of therapy.

Treatment with rhIL-15 and obinutuzumab will continue for six cycles or until disease progression, absent clinical benefit, unacceptable treatment-related toxicity, or other reasons outlined in Section **3.10.1**.

Refer to the Study Calendar (Section **3.9**) for all tests and procedures to be conducted on study/during treatment. See also Section **5** for all samples to be collected for correlative research. During treatment, it is expected that all laboratory and clinical assessments be conducted at the NIH (including post-treatment imaging evaluations); results from outside NIH will only be accepted at the discretion of the investigator.

3.7 Post-Treatment Evaluations

Post-treatment evaulations will be performed at the end of treatment (3-5 weeks after the last dose of protocol treatment). If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30-day safety follow-up visit must occur before the first dose of the new therapy.

Unless otherwise noted, follow-up will occur at the following time points: every 3 months (±2 weeks) for first year after completion of therapy, every 6 months for years 2-5 (±4 weeks), and then annually thereafter (±6 weeks) at the discretion of the investigator. Any other evaluations and tests should be performed as clinically indicated.

Upon disease progression or initiation of other anti-cancer therapy, contact will be for survival only until the subject is off study (i.e., every 3 months [±4 weeks]); unless otherwise clinically indicated. See Study Calendar (Section **3.9**) for additional information. Any adverse events which are present at the time of discontinuation should be followed in accordance with the safety requirements.

3.8 Follow-Up Evaluations

The following follow-up phases apply to this study at the time points and windows noted above and per the Study Calendar (Section **3.9**). Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

3.8.1 30-Day Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Patients with an ongoing, treatment-related AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1, stabilization of the AE in the opinion of the investigator, or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 30 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

3.8.2 Follow-Up Visits – Prior to Disease Progression

Patients who complete trial treatment without evidence of disease progression will move into the Follow-Up Phase and may be assessed at approximately 6 months and annually thereafter at the discretion of the investigator by radiologic imaging or other clinical assessments to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, or end of the study.

3.8.3 Follow-Up Visits – Survival/Post-Disease Progression

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted (e.g., phone, email, etc.; in-person visit not required) at least every 3 to 6 months collect information on new anti-cancer treatments received and to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first (see Study Calendar).

3.9 STUDY CALENDAR

Procedure	**Screening**	**Baseline**	**Study Cycles**									**End of Treatment and Disease Progression**	**Post-Treatment Follow-Up**		
			C1						C2-6				Safety	Follow-Up (Prior to PD)	Survival (Post-PD)
Scheduling Window (Days):	-28 to -1[1]		-14[2]	4 (-1)	5 (-1)	8	11 (-1)	18 (-1)	1 (-3)	4	8	Treatment discon/PD[3]	Day 30 (+7)	Every 3, 6, or 12 months[4]	Every 3 months[5]
Confirmation of Diagnosis	X														
Physical Exam and ECOG PS[6]	X	X		X	X		X	X	X	X		X	X	X	
CBC with Differential	X	X	X	X	X		X	X	X	X		X	X	X	
Reticulocyte Count	X	X	X	X	X		X	X	X	X		X	X	X	
Chemistry Panels[7]	X	X	X	X	X		X	X	X	X		X	X	X	
LDH, Uric Acid, Total Protein		X	X	X	X		X	X	X	X		X	X	X	
PT/INR and aPTT	X	X	X						X			X	X	X	
Thyroid Function (TSH, reflex T3, T4)	X	X	X						X			X			
Urinalysis	X	X	X						X			X			
Pregnancy Test (urine/serum; WOCBP)	X	X	X												
Hepatitis B and C, HIV Antibody,and Karyotype Testing	X														
HLA typing (A, B, C, DR, DQ), Anti-nuclear antibody (ANA), G6PD		X													
CMV, EBV, SPEP, C-reactive Protein (CRP), IGVH mutation analysis, PB interphase FISH panels[8]		X										X (PD only)			
Iron panels, Folate, and B12		X	X												
Serum free light chains, Quantitative IgG		X	X									X	X	X	
Beta-2 microglobulin, Haptoglobin, DAT		X	X						X			X	X	X	
T, B, NK cell subsets		X							X			X	X	X	
CT Scans, Brain MRI[9]	X	X										X		X	
Flow Cytometry, Bone Marrow Aspiration/Biopsy [10]		X							(post-C3 only)			X			
EKG	X														
Symptoms/Adverse Events Assessment, Concomitant Medication Review	X	X							X			X	X	X	
Research Blood/Tissue Samples[11]		X	X	X	X	X	X		X		X	X	X	X	
Survival Status															X

NOTE: Any other tests should be performed as clinically indicated. See Section **3.4** for drug administration information. See Section **5** for information on research blood samples/correlative studies to be collected.

---

[1] Screening and Baseline evaluations should be performed within 28 days prior to enrollment and dosing, respectively, unless otherwise noted and with the following exceptions: Confirmation of diagnosis (no time limit); HIV antibody (at any time, or within 3 months in patients with high risk or clinical suspicion for HIV as determined by PI; Hepatitis B and C, karyotype, EKG, PB interphase FISH, and bone marrow aspiration/biopsy (all within 3 months) **NOTE:** Any screening tests performed within the specified time frame for baseline do not need to be repeated.

[2] Within 14 days prior to dosing on C1D1, with the following exceptions: Pregnancy test (within 3 days of dosing; must be negative).

[3] To be done at end of treatment (3-5 weeks after last dose of study treatment; may be combined with 30 day safety follow-up, if timing coincides). If subject to initiate new anti-cancer therapy assessments should occur before the first dose of the new therapy.

[4] Follow-up to occur about every 3 months (±2 weeks) for first 12 months, every 6 months for years 2-5 (±4 weeks), and then annually (±6 weeks) until disease progression or initiation of new anti-cancer therapy.

[5] After disease progression or initiation of new anti-cancer therapy, contact for survival about every 3 to 6 months (±4 weeks).

[6] Physical exams to include medical history (i.e., complete at Screening/Baseline; interim on study and in follow-up), vitals, weight, and height (screening only). ECOG PS to be documented at Screening/Baseline and Treatment Discontinuation/PD only.

[7] Chemistry panels include: Acute care, Hepatic, and Mineral.

[8] There is no time limit on IGVH mutation analysis at baseline (i.e., any time post-diagnosis and prior to treatment). Probes for PB interphase FISH panel include: ATM 11q22.3), D12Z3 (12 cen), D13S319 (13q14.3), LAMP1 (13q34) and TP53 (17p13.1); FISH at disease progression is optional.

[9] CT scans of neck, chest, abdomen, and pelvis (CT should be performed with IV and PO contrast, unless patient is allergic or has renal insufficiency; other imaging may be substituted at the discretion of the investigator) at baseline and after cycle 6 of treatment. Other body areas may be imaged if clinically indicated. The same imaging done at baseline should be done after treatment to assess for response. In patients without clinical evidence of progression, follow-up imaging may be done at 6 months after treatment, then annually, at the discretion of the clinical team. MRI of brain only required in patients with known suspected involvement of CNS.

[10] Peripheral blood flow cytometry for diagnostic and staging purposes for CLL at baseline and after cycles 3 and 6 for response assessment. Bone marrow aspiration/biopsy (within 3 months prior to starting treatment) and optional at baseline and after cycle 3 and 6; if clinically indicated. During post-treatment follow-up, samples may be done on blood, bone marrow aspirate and/or lymph node biopsy as clinically indicated.

[11] Samples for correlative research are to be collected as indicated in Section **5**

3.10 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from study, effort must be made to have all patients complete a safety visit approximately 30 days following the last dose of study therapy. The reason for removal from protocol therapy and off study will be clearly documented in the medical record. Additional safety visits and follow-up will continue as per Section **3.8**.

3.10.1 Criteria for Removal from Protocol Therapy

- Completed planned treatment regimen/duration (i.e., up to 6 cycles)
- Confirmed hematologic or radiographic disease progression
- Unacceptable toxicity occuring at any time during treatment as listed in Section **3.2** or those toxicities listed in Section **3.5** that require treatment to be stopped.
- Intercurrent illness that prevents further administration of treatment
- Requirement for use of prohibited therapies as listed in Section **4.2**
- Pregnancy
- Subject's requests to be withdrawn from protocol therapy
- Noncompliance with trial treatment or procedure requirements that requires removal in the opinion of the PI
- Investigator's decision to withdraw the subject
- Study is cancelled for any reason

3.10.2 Off-Study Criteria

- Subject requests to be withdrawn from study
- Subject is lost to follow-up
- Death
- Study is cancelled for any reason

3.11 COST AND COMPENSATION

3.11.1 Costs

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures performed outside the NIH Clinical Center, participants may have to pay for these costs if they are not covered by insurance company. Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.

3.11.2 Compensation

Participants will not be compensated on this study.

3.11.3 Reimbursement

The NCI will cover the costs of some expenses associated with protocol participation. Some of these costs may be paid directly by the NIH and some may be reimbursed to the participant/guardian as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy.

4 CONCOMITANT MEDICATIONS/MEASURES

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required.

4.1 ACCEPTABLE MEDICATIONS

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded.

4.2 PROHIBITED MEDICATIONS

Patients are prohibited from receiving the following therapies during treatment on this trial:

- Other therapy for the disease under study not specified in this protocol, unless specifically noted as permitted
- Investigational agents other than rhIL-15 and obinutuzumab
- Radiation therapy

  NOTE: Radiation therapy to a symptomatic solitary lesion may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.

Patients who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from study treatment. Patients may receive other medications that the investigator deems to be medically necessary.

5 CORRELATIVE STUDIES FOR RESEARCH

5.1 BIOSPECIMEN COLLECTION

This study will attempt to use rhIL-15 to increase NK cell number and activity, thereby enhancing the ADCC of obinutuzumab in treatment of patients with relapsed and refractory CLL. ADCC capacity of *ex vivo* PBMCs will be tested on CD20-expressing cell lines before, during and after protocol treatment. Differences in immune cell subsets associated with administration will be followed throughout treatment to both study the effects of combined rhIL-15/obinutuzumab therapy on the immune system, and to identify potential biomarkers that would be predictive of response.

Sample	**Collection Details***	**Time Points**								**Supervising Laboratory/ Investigator**
		Baseline	C1 D4	C1 D5	C1 D8	C1 D11	C2-6 D1	C2-6 D8	Follow up[#]	
Blood Samples										
Lymphocyte subset testing	• 2 x 10mL K_2EDTA tubes (lavender top)	X	(X)		X	(X)	(X)	(X)	(X)[1]	Immunology section, NIH CC
ADCC of obinutuzumab	• 3 x 10mL NaHep tubes (green top)	(X)[2]	(X)[2]	(X)[2]	(X)[2]			(X)[2]		Waldmann
Tissue immune cell subsets (comparison)	• 1 x 5mL green-top tube	(X)			(X)				(X)	Waldmann
Circulating tumor DNA, plasma banking	• 1 x 10mL K_2EDTA tube • 1 x 10mL Streck/BCT tube	X	(X)		(X)			(X)	X[3]	Waldmann (Leidos CSL)
Anti-IL-15 antibodies	• 1 x 4mL SST tube	X					X		X[1]	
Tissue Samples										
Tissue immune cell subsets	• Two core biopsy samples in RPMI 1640 with 10% human serum and antibiotics • One core biopsy sample in formalin NOTE: Samples may be tumor tissue or bone marrow aspirate/biopsy	(X)			(X)				(X)	Waldmann/ (RPMI 1640) and DLM/ NCI LP (formalin)
Other Samples										
Germline DNA	• Blood, Buccal Swab, or Saliva (preferred)	X								Waldmann

Sample	Collection Details*	Time Points								Supervising Laboratory/ Investigator
		Baseline	C1 D4	C1 D5	C1 D8	C1 D11	C2-6 D1	C2-6 D8	Follow up[#]	
(X) = Optional; samples will be collected if adequate time/staff available for processing. If an optional sample is not collected at baseline, it would also not be collected in follow-up unless specifically requested by the PI. *Tubes/media may be adjusted at the time of collection based upon materials available or to ensure the best samples are collected for planned analyses. [#]Subjects who discontinue treatment for a reason other than disease progression and who do not start new treatment should continue to have study bloods collected at the scheduled time points. [1] At the end of treatment only. [2] For ADCC of obinutuzumab, Baseline, C1D4, C1D5 and C1D8 samples should be collected for at least one patient per dose level, and for at least three patients at the MTD; C2-6 samples may be collected at the discretion of the PI, but are not required. [3] At each follow-up visit prior to disease progression, as specified in Section **3.8.2**.										

5.2 SAMPLE COLLECTION AND PROCESSING

5.2.1 Summary

The planned analyses described below may be done on leftover and/or shared sample portions from the respective laboratories, as needed. In addition to the prospectively collected samples below, leftover portions of samples sent for routine laboratory testing (e.g., plasma from CBC/hematologies) may also be retrieved for research tests prior to being discarded. The planned prospective analyses are identified below; laboratories may share resources or collaborate on analyses, if appropriate.

Portions of all samples may be banked for future research analyses; prospective consent will be obtained during the informed consent process.

The blood drawing limits for research purposes are as follows:

- For adult subjects: The amount of blood that may be drawn from adult patients for research purposes shall not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight-week period.

All samples will be delivered to the laboratory of Dr. Thomas Waldmann, Lymphoid Malignancies Branch. The laboratory staff will handle processing or delivery/shipping of associated labs, if applicable. To arrange for sample processing, contact: Bonnita Bryant, Lymphoid Malignancies Branch (Building 10, Room 3B35; phone: 240-858-3479), Mike Petrus, Lymphoid Malignancies Branch (Building 10, Room 4B40; phone:240-858-3485) or Sigrid Dubois, Ph.D., Lymphoid Malignancies Branch (Building 10, Room 4B47; phone: 301-435-4441). Tissue samples will also be sent to the Hematopathology Section of Laboratory of Pathology, NIH Clinical Center, by courier service.

5.2.2 Blood Samples

All blood samples will be drawn by NIH Clinical Center phlebotomy, outpatient clinic, or day hospital staff.

5.2.2.1 Lymphocyte subset testing by flow cytometry (FACS)

- Collect blood in EDTA tubes; gently invert tubes 8-10 times immediately after collection.

- Labels listing the patient's name, date of birth, date and time of the blood draw will be affixed to all the tubes by the staff person who obtained the samples.
- Lymphoid Malignancies Branch Clinical Research personnel will arrange for these samples to be delivered to: Immunology Lab, NIH Clinical Center Bldg. 10/ Room 2C410. If the Immunology Section Laboratory is unable to perform this analysis on the specified days, this assessment maybe omitted or replaced with standard TBNK panel.

5.2.2.2 Antibody-dependent cell cytotoxicity (ADCC) of obinutuzumab

- Collect blood in sodium heparin tubes; gently invert tubes 8-10 times immediately after collection.
- Samples will be processed per established laboratory techniques.

5.2.2.3 Cell-free DNA (cfDNA)/circulating tumor DNA (ctDNA) and plasma banking

- Collect blood in EDTA and cell-free DNA (i.e., Streck BCT) tubes; gently invert tubes 8-10 times immediately after collection.
- Lymphoid Malignancies Branch Research personnel will arrange for these samples to be delivered to Clinical Support Laboratory, Leidos Biomedical Research, Inc.in Frederick, MD, for sample processing per established techniques.

5.2.2.4 Anti-IL-15 antibody testing

- Collect blood in a 4mL SST tube; gently invert tubes 8-10 times immediately after collection.
- Lymphoid Malignancies Branch Research personnel will arrange for these samples to be delivered to Clinical Support Laboratory, Leidos Biomedical Research, Inc.in Frederick, MD, for storage and further analysis.
- Samples will be batch processed and analyzed per the procedure outlined in Appendix B after the last patient has been enrolled and completed treatment, or sooner if there is clinical suspicion for anti-IL-15 antibody formation.

5.2.3 Tissue Samples

Potential site(s) of biopsy include, but are not limited to: bone marrow, extramedullary disease/masses, and lymph nodes. The type of procedure to be done and manner in which it will proceed (e.g., excision/core, single vs. multiple sites of biopsy) will be discussed with the patient prior to the biopsy procedure.

The patient will be reminded that all sampling for research is voluntary. In the case of lymph node excision or core needle biopsy, these will be performed per routine standard of care by Surgery Consultants or Interventional Radiology, as appropriate; and, a procedure-specific consent form will be signed by the patient prior to the procedure. Conscious sedation may be used, if warranted, and the use and risks are acceptable to the patient. Skin biopsies may be performed by qualified clinical staff. The use of image-guidance other than ultrasound for collection of research samples is not expected (i.e., radiation exposure for research purposes is not expected).

Core tumor tissue (or bone marrow aspirate/biopsy) samples will be collected and placed in appropriate media (e.g., RPMI 1640 with 10% human serum and antibiotics, and formalin) and processed per established techniques. As indicated (Sections **5.1** and **5.2**), samples will be sent to the Department of Laboratory Medicine (DLM)/ NCI Laboratory of Pathology (LP) for concurrent routine analysis and reporting in addition to research testing (i.e., Waldmann Lab).

5.2.4 Other Samples

5.2.4.1 Germline DNA

Germline DNA will be collected by blood, buccal swab, and/or saliva samples (preferred). These will ideally be collected at baseline; however, may be collected at any point on study based on supplies. Standardized, commercial collection kits or tubes will be used (e.g., 1, 5-10 mL K_2EDTA tube for blood; Isohelix SK-1 for buccal swabs; Salviette/Oragene® for saliva). In the case of buccal swabs, two (2) samples may be collected in order to ensure adequate DNA collection.

The samples will be processed and DNA extracted/isolated per kit instructions and established techniques.

5.3 BIOMARKER AND RESEARCH METHODS

The technology platforms that are able to interrogate genomic structure and function are constantly in flux; therefore, the exact nature of the methodologies that will be employed will be assessed at the time that the samples are ready for analysis. The protocol will be amended at that time, if needed, to described the intended techniques prior to initiating the analyses.

The following are technologies that are currently in use for each planned analysis:

5.3.1 Molecular Profiling

Immunohistochemical (IHC) analyses, including FISH and/or PCR testing, will take part in tumor tissue samples, including but not necessarily limited to CD3, CD4, CD5, CD8, CD14, CD16, CD19, CD20, CD22, CD23, CD25, CD38, CD45RA, CD45RO, CD56, CD62L, CD69, CD79a/CD79b, CD122, and NKG2D.

5.3.2 Immune Subset Analysis

Peripheral blood mononuclear cells (PBMC) will be assessed using multiparameter flow cytometry for immune subsets including but not necessarily limited to CD8+ T-cells, CD4+Foxp3- T-cells, Tregs, T_{ex}, Th1, Th2 and Th17+ CD4+ T-cells, NK cells and subsets, monocyte subsets, MDSC subsets. Assessment may include functional markers, i.e. PD-1, Tim-3, CTLA-4, PD-L1, HLA-DR, Ki67 and/or CD40.

5.3.3 ADCC Analysis

Peripheral blood mononuclear cells (PBMCs) should be isolated by Ficoll-Hypaque Density Gradient Centrifugation. The viable cells should be viably frozen and stored in liquid nitrogen. The ADCC assay will be performed on the same occasion for all samples of a given patient. Vials of frozen cells will be thawed using standard procedures 18 hours before the assay in accord with our experience with normal donors. 1.5 million of patient's PBMCs obtained before and on day 15 following IL-15 injection will be tested in aliquots as follows:

- Tested alone
- Tested with untreated Raji cells and with Raji cells coated with an antibody to CD20 for 5 hours.
- In addition, we may utilize an ATL cell line in addition to Raji cells. These cell populations will be stained with CD107, CD3, CD56, and CD94.

5.3.4 cfDNA/ctDNA

Since the methods of molecular monitoring in the peripheral blood is an emerging field with numerous technologies under development, the storage of peripheral blood mononuclear cells (PBMC), serum, and plasma will all be performed allowing for future comparison of the different

compartments for analytes that include cell-free circulating tumor DNA (ctDNA), and RNA sequencing of circulating tumor cells. Studies to be performed on these samples include: cfDNA/ctDNA for liquid genotyping as a non-invasive dynamic monitoring of disease as well as monitoring for individual molecular aberrations that herald progression or disease transformation; specifically, amplification and sequencing of the VDJ segment of the immunoglobulin receptor is planned. Germline DNA obtained from saliva, blood, or buccal mucosa will be used to discriminate somatic from germline mutations during cfDNA and ctDNA analyses.

5.3.5 DNA/RNA Sequencing

Genomic DNA and total RNA will be extracted from tumor samples using a Qiagen All-prep kit. For individual target genes that are recurrently mutated in CLL, classical Sanger sequencing will be performed on PCR amplicons, using primers surrounding the known sites of mutation. To broadly assess mutations, next generation sequencing (e.g., on an Illumina HiSeq 2000 platform) will be employed, using a paired end sequencing strategy of libraries constructed from tumor DNA. DNA will either be sequenced in its entirety from a whole genome library or will be first enriched for exonic sequences using the Agilent Sure Select system, aiming for 30X or 100X average coverage per base, respectively. The sequence fragments will be mapped back to the genome using the BWA algorithm. Of sequences overlapping a particular base pair in the genome, the percent mutant calls greater that 20% with a minimum of 25X coverage will be considered as an arbitrary threshold for single nucleotide variants (SNVs). SNVs that are not present in the matched normal sample will be considered candidate somatic mutations.

A related technology, RNA-Seq, utilizes RNA from the tumor specimen to create a cDNA library for high-throughput sequencing. RNA-seq will be performed using Illumina kits followed by high-throughput sequencing on an Illumina HighSeq 2000 machine. The cutoffs for coverage and percent mutant calls mentioned above will also be used to identify putative SNVs. RNA sequencing will also be used to read out digital gene expression across the genome as described.

Recent advances in genomic technologies enable GEP at the single cell level, a distinct advantage over conventional GEP which cannot always distinguish tumor vs non-tumor gene expression. Single-cell approaches allow identification of the evolution of rare populations of resistant tumor cells, as well as identification of TME cells critical for the survival of the tumor. The Center for Cancer Research (CCR) has recently opened a single cell analysis core facility with expert staff headed by Dr. Michael Kelly within the CCR Genomics Core. This facility has the ability to take purified viably frozen cells banked from patient biopsies and prepare them, using well-validated 10X Genomics technology, for single-cell RNA sequencing. This core is directly integrated with the NCI Sequencing core facility to provide high-quality, deep-sequencing of the single cell RNA-SEQ samples, as well as ‘first-pass’ data processing and analysis. Data will then be transferred to lymphoma researchers and bio-informaticians in the Staudt lab for further analysis of gene expression patterns and cellular population dynamics.

5.3.6 Other Analyses

Other analyses include the following:

- Cell analysis and histological (e.g., H&E), immunohistochemical review and analysis per standard and established research techniques (e.g., PD-1/PD-L1 expression [Dako], FISH for del(17p), and other IHC analyses in blood and tissue).
- Cytokine analysis (e.g., IL-6, IL-10, interferon beta, TNF-alpha)

5.3.7 Future Use

Any blood, tissue, or other products or portions leftover from other analyses will be stored for future research.

5.4 SAMPLE STORAGE, TRACKING AND DISPOSITION

5.4.1 General

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without appropriate approvals and/ or agreements, if required.

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described below. The study will remain open so long as sample or data analysis continues. Samples from consenting patients will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed.

If the patient withdraws consent his/her data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements in section **7.2.1**.

5.4.2 Lymphoid Malignancies Branch – Waldmann Laboratory

Under the direction of Dr. Waldmann, all samples processed by the laboratory will be uniquely barcoded, with data entered using a secure computerized database and backup hardcopy process per standard laboratory practice.

Samples are stored in labeled boxes in secured freezers (i.e., -20ºC to -80ºC, or other, as appropriate) according to stability requirements; these freezers are located onsite. Access to stored clinical samples is restricted and limited to research personnel for approved analyses only (as per the IRB approved protocol).

Upon completion of planned analyses by the Waldmann lab, leftover samples may be stored for future analyses at the Clinical Support Laboratory, Leidos Biomedical Research, Inc.in Frederick, MD (see below).

5.4.3 Clinical Support Laboratory, Leidos Biomedical Research, Inc.in Frederick, MD

The Clinical Support Laboratory, Leidos Biomedical Research, Inc. processes and cryopreserves samples in support of IRB-approved, NCI clinical trials. The laboratory is CLIA certified for anti-IL15 and certain cytokine measurements, and all laboratory areas operate under a Quality Assurance Plan with documented Standard Operating Procedures that are reviewed annually. Laboratory personnel are assessed for competency prior to being permitted to work with patient samples. Efforts to ensure protection of patient information include:

- The laboratory is located in a controlled-access building and laboratory doors are kept locked at all times. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.
- Hard copy records or electronic copies of documents containing patient information are kept in the locked laboratory or other controlled access locations.
- An electronic database is used to store information related to patient samples processed by the laboratory.

- The database resides on a dedicated program server that is kept in a central, locked computer facility.
- The facility is supported by two IT specialists who maintain up to date security features including virus and firewall protection.
- Program access is limited to specified computers as designated by the laboratory director. Each of these computers has a password restricted login screen.
- The database sample entry program itself is accessed through a password protected entry screen.
- The database program has different levels of access approval to limit unauthorized changes to specimen records and the program maintains a sample history.
- Upon specimen receipt, each sample is assigned a unique, sequential laboratory accession ID number. All products generated by the laboratory that will be stored either in the laboratory freezers or at a central repository facility are identified by this accession ID.
- Inventory information will be stored at the vial level and each vial will be labeled with both a sample ID and a vial sequence number.
- Vial labels do not contain any personal identifier information.
- Samples are stored inventoried in locked laboratory freezers and are routinely transferred to the NCI-Frederick repository facilities for long-term storage.
- Access to stored clinical samples is restricted. Investigators establish sample collections under "Source Codes" and the investigator responsible for the collections, the protocol Principal Investigator, specifies who has access to the collection.
- Specific permissions will be required to view, input or withdraw samples from a collection. Sample withdrawal requests submitted to approved laboratory staff by anyone other than the repository source code owner are submitted to the source code owner for approval. The repository facility will also notify the Source Code holder of any submitted requests for sample withdrawal.
- It is the responsibility of the Source Code holder (the NCI Principal Investigator) to ensure that samples requested and approved for withdrawal are being used in a manner consistent with IRB approval.
- The Clinical Support Laboratory in Frederick does perform testing services that may be requested by clinical investigators including, but not limited to, immunophenotyping by flow cytometry and cytokine testing using ELISA or multiplex platforms.
- When requests are submitted by the NCI investigator for shipment of samples outside of the NIH it is the policy of the laboratory to request documentation that a Material Transfer Agreement is in place that covers the specimen transfer. The laboratory does not provide patient identifier information as part of the transfer process but may, at the discretion of the NCI investigator, group samples from individual patients when that is critical to the testing process.
- The NCI investigator responsible for the sample collection is responsible for ensuring appropriate approvals and/ or agreements are in place, if required, prior to requesting the laboratory to ship samples outside of the NIH.

5.4.4 Hematopathology Section of Laboratory of Pathology (Tissue samples)

Archival and/or freshly collected and processed tumor tissue remaining after any routine analysis and reporting may be stored in the Hematopathology Section of Laboratory of Pathology until request by the investigators for planned and/or future research assays if the patient has agreed to

allowing specimens to be used in future research studies. IRB approval will be obtained before using any samples to conduct studies that are not described within this protocol. Samples will be stored under conditions appropriate to the type of sample and processing (e.g., ambient or frozen).

Tissue that is given to the technician will be assigned an accession number (HP#) in the HP Case Log book; sample tracking also takes place with a FileMaker Pro data base called HP Patient Information and Specimen Inventory. A Patient background sheet may be filled out and filed with any accompanying paperwork, with final reports and any supplemental reports that follow added as completed.

5.5 SAMPLES FOR GENETIC/GENOMIC ANALYSIS

5.5.1 Description of the scope of genetic/genomic analysis

The research correlates for this study are expected to include DNA/RNA sequencing of tumors, including circulating tumor (ct) DNA. In addition, whole exome sequencing may include evaluation for known lymphoma mutations. For any genetic studies performed, the results will be deposited in a database such as dbGaP per NIH requirements. Although there is controlled access to such a database, such a submission carries theoretical risks of revealing the identity of the subject. This is discussed in the consent.

5.5.2 Description of how privacy and confidentiality of medical information/biological specimens will be maximized

Confidentiality for genetic samples will be maintained as described (Section **5.4.2**). In addition, a Certificate of Confidentiality has been obtained for this study.

5.5.3 Management of Results

Subjects will be contacted if a clinically actionable gene variant is discovered. Clinically actionable findings for this study are defined as disorders appearing in the American College of Medical Genetics and Genomics recommendations for the return of incidental findings that is current at the time of primary analysis. (A list of current guidelines is maintained on the CCR intranet: https://ccrod.cancer.gov/confluence/display/CCRCRO/Incidental+Findings+Lists).

5.5.4 Genetic Counseling

Subjects will be contacted with a request to provide a blood sample to be sent to a CLIA certified laboratory. If the research findings are verified in the CLIA certified lab, the subject will be offered the opportunity to come to NIH to have genetic education and counseling to explain this result; at the time of any such event(s), these activities will be funded by the NCI/CCR in consideration of the specific circumstances. If the subject does not want to come to NIH, a referral to a local genetic healthcare provider will be provided (at their expense).

This is the only time during the course of the study that incidental findings will be returned. No interrogations regarding clinically actionable findings will be made after the primary analysis.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

6.1.1 Summary

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system (C3D) and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist

with the data management efforts. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

Document AEs from the first study intervention through 30 days after the last study intervention was administered. Beyond 30 days after the last intervention, only adverse events which are serious and related to the study intervention need to be recorded.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirments in section **7.2.1**.

6.1.2 Data Collection/Recording Exceptions

6.1.2.1 Abnormal Laboratory Values

An abnormal laboratory value will be recorded in the database as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

6.1.2.2 Hospitalizations

Any cases of planned or prolonged hospitalization are not considered serious adverse events if for the following reasons:

- Technical, practical, or social reasons, in absence of an AE
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition, including scheduled therapy or standard procedure for the target disease of the study, and those required to allow efficacy measurement for the study
- Diagnostic or elective surgical procedures for preexisting conditions or a procedure that is planned (e.g., planned prior to starting of treatment on study)
- Closer monitoring and/or prophylaxis of TLS at any cycle
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

What data will be shared?
I will share human data generated in this research for future research as follows:

_X_ Coded, linked data in an NIH-funded or approved public repository.

_X_ Coded, linked data in another public repository

_X_ Coded, linked data in BTRIS (automatic for activities in the Clinical Center)

How and where will the data be shared?
Data will be shared through:

_X_ An NIH-funded or approved public repository. Insert name or names: ClinicalTrials.gov, dbGaP.

_X_ BTRIS (automatic for activities in the Clinical Center)

_X_ Publication and/or public presentations.

When will the data be shared?
_X_ At the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

6.3 RESPONSE CRITERIA

Responses for spleen and lymphadenopathy will be assessed using CT scan measurements and not physical exam. Response assessments will be made by IWCLL 2018 guidelines(9). Response includes complete response (CR), and partial response (PR).

Criteria of response				
Response	**CR**	**PR**	**PD**	**SD**
Group A[A]				
Lymphadenopathy[B]	None >1.5cm	Decrease ≥50%	Increase ≥50% or any new lesion > 1.5cm	Change of -49% to +49%
Liver and/or spleen size	Spleen size <13cm; liver size normal	Decrease ≥50% (from baseline)	Increase ≥50% from baseline or from response	Change of -49% to +49%
Constitutional symptoms	None	Any	Any	Any
Circulating lymphocyte count	Normal	Decrease ≥50% from baseline	Increase ≥50% over baseline[D]	Change of -49% to +49%
Group B[A]				
Platelet count	>100,000/ μL	>100,000/ μL or increase ≥50% over baseline	Decrease ≥50% from baseline secondary to CLL	Change of -49% to +49%

Criteria of response				
Response	**CR**	**PR**	**PD**	**SD**
Hemoglobin	>11.0 g/dL (untransfused and without erythropoietin)	>11.0 g/dL or increase ≥50% over baseline	Decrease ≥50% from baseline secondary to CLL	Increased but <11.0 g/dL or <50% over baseline, or decrease <2 g/dL
Bone marrow[C]	Normocellular, no CLL cells, no B-lymphoid nodules.	Presence of CLL cells, or of B-lymphoid nodules, or not done	Increase of CLL cells by ≥50% on successive biopsies	No change in marrow infiltrate

Footnotes:
[A] Group A criteria define the tumor load. Group B criteria define the function of the hematopoietic system or marrow. For CR, all of the criteria have to be met.
[B] Sum of the product (SPDs) of up to 6 lymph nodes as evaluated by CT scans. If CT is unavailable, the absence of enlarged lymph nodes (> 1.5cm) documented by physical exam is acceptable. For progression, SPDs should increase by >50% and at least one of the target lesions should be pathologically enlarged (> 1.5cm).
[C] Complete response requires confirmation with bone marrow biopsy.
[D] For progression, absolute lymphocyte count should increase ≥ 50% from nadir confirmed with two consecutive assessments within 3 months. CD19 B cell count should be >5,000/μL in at least one of the two assessments.
Abbreviations and definitions:
CR (complete response): Disease-related constitutional symptoms resolved and all above criteria met, includes bone marrow biopsy
CRi (complete response with incomplete marrow recovery): CR with incomplete hematopoietic recovery
PR (partial response): Two criteria from Group A if abnormal at baseline plus one of the criteria from Group B must be met, requires the absence of growth factor or transfusion support
SD (stable disease): Defined as not achieving CR, or PR, but not fulfilling the criteria for PD will be considered to have stable disease (which is equivalent to no response)
PD (progressive disease): One criteria from Group A or B are met or development of transformation to a more aggressive histology

6.3.1 Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

6.3.2 Duration of Response

The duration of response (DOR) is measured from the time measurement criteria are met for CR, CRi, or PR (whichever is recorded first) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started), death, or, in the absence of PD, date of last assessment.

6.3.3 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from the date of study enrollment until time of disease relapse, disease progression, or death, whichever occurs first.

6.3.4 Event-Free Survival

Event-free survival (EFS) is defined as the duration of time from the date of study enrollment until time of disease relapse, disease progression, alternative therapy for lymphoma given (such as radiation), or death, whichever occurs first.

6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. For **non-hematologic toxicities**, the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

For **hematologic** toxicities, the updated IWCLL guidelines will be used(10):

Grade[1]	Decrease in platelets[2] or Hb[3] (nadir) from baseline value (%)	Absolute neutrophil count/ µL[4] (nadir)
0	No change – 10%	≥2,000
1	11%-24%	≥1,500 and <2,000
2	25%-49%	≥1,000 and <1,500
3	50%-74%	≥500 and <1,000
4	≥75%	<500

Footnotes:
[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 baseline will be recorded as grade 5.
[2] Platelet counts must be below normal levels for grades 1-4. If, at any level of decrease the platelet count is <20.000/µL, this will be considered grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (e.g., 20.000/µL) was present at baseline, in which case the patient is not evaluable for toxicity referable to platelet counts.
[3] Hb levels must be below normal levels for grades 1-4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity, but should be documented.
[4] If the absolute neutrophil count (ANC) reaches < 1.000/µL, 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, since 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 < 1.000/µL prior to 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.

7 NIH REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found **here**.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING/ IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found **here**. Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to definitions provided in Policy 801: Reporting Research Events found **here**.

7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reported to the OHSRP in iRIS will also be reported to the NCI Clinical Director. A separate submission is not necessary as reports in iRIS will be available to the Clinical Director.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email to the Clinical Director unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to Dr. Dahut at NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.4 NIH REQUIRED DATA AND SAFETY MONITORING PLAN

7.4.1 Principal Investigator/Research Team

The clinical research team will meet at least weekly when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in section **7.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 SPONSOR SAFETY REPORTING

8.1 DEFINITIONS

8.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2)).

8.1.2 Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following

- Death
- A life-threatening adverse event (see **8.1.3**)
- Inpatient hospitalization or prolongation of existing hospitalization
    - A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), a planned hospitalization for pre-existing

condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.
    - A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for patient convenience) is not considered a serious adverse event.
    - Emergency room visits or stays in observation units that do not result in admission to the hospital would not be considered a serious adverse event. The reason for seeking medical care should be evaluated for meeting one of the other serious criteria.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.3 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. (21CFR312.32).

8.1.4 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 5.

8.1.5 Relationship to Study Product

All AEs will have their relationship to study product assessed using the terms: related or not related.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.2 ASSESSMENT OF SAFETY EVENTS

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution of the event, seriousness and outcome. The assessment of severity and relationship to the study product will be done only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

SAE's will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

- Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

For timeframe of recording adverse events, please refer to section **6.1**. All serious adverse events recorded from the time of first investigational product administration must be reported to the sponsor with the exception of any listed in section **8.4**.

8.3 Reporting of Serious Adverse Events

Any AE that meets protocol-defined serious criteria or meets the definition of Adverse Event of Special Interest that require expedited reporting must be submitted immediately (within 24 hours of awareness) to OSRO Safety using the CCR SAE report form. Any exceptions to the expedited reporting requirements are found in section **8.4**.

All SAE reporting must include the elements described in section **8.2**.

SAE reports will be submitted to the Center for Cancer Research (CCR) at: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. CCR SAE report form and instructions can be found at:

https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions

Following the assessment of the SAE by OSRO, other supporting documentation of the event may be requested by the OSRO Safety and should be provided as soon as possible.

8.4 Waiver of Expedited Reporting to CCR

As death due to disease progression is part of the study objectives, and captured as an endpoint in this study, it will not be reported in expedited manner to the sponsor. However, if there is evidence suggesting a causal relationship between the study drug and the event, report the event in an expedited manner according to section **8.3**.

8.5 Safety/Other Reporting Criteria to the Pharmaceutical Manufacturer (CTEP)

The NCI Cancer Therapy Evaluation Program (CTEP) is providing clinical grade recombinant human IL-15 for this study. Because the CTEP is responsible for the Clinical Material and Confidential Information which it develops, CTEP must ensure that the Clinical Material and Confidential Information are used, communicated and reproduced appropriately and completely. The PI agrees to use the Clinical Material in accordance with all Federal laws and regulations that govern the use of investigational agents in clinical trials.

The following will be provided to CTEP during the course of the clinical study:

1. Initial FDA submission/approval, including: FDA-submitted protocol document; any FDA comments regarding the protocol and IND submission, including correspondence regarding the IND submission safe-to-proceed notice; and, a copy of the FDA acknowledgement of the IND submission(s) stating the IND number, sponsor, title and date of submission.
2. Documentation of initial IRB approval of the FDA-submitted protocol document and annual continuing IRB review approvals.
3. All significant protocol amendments, including changes in study size, eligibility criteria, study design and end points.

4. Notification of any changes in protocol status or other significant events related to the Protocol.
5. Notification of any changes in IND status.
6. Copies of any FDA communications.
7. Copies of IND Annual Reports.
8. All IND Safety Reports submitted to the FDA per 21 CFR 312.32. Copies of all IND Safety Reports submitted to the FDA should be forwarded electronically to CTEPSupportAE@tech-res.com (please provide protocol number in subject line).
9. Any abstracts, manuscripts, and publications.

Additional safety and efficacy data may also be requested by CTEP to facilitate the development of the Clinical Material across CTEP supported trials.

8.6 REPORTING PREGNANCY

All required pregnancy reports/follow-up to OSRO will be submitted to: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. Forms and instructions can be found here: https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions

8.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the study treatment should be discontinued immediately and the pregnancy reported to the Sponsor no later than 24 hours of when the Investigator becomes aware of it. The Investigator should notify the Sponsor no later than 24 hours of when the outcome of the Pregnancy becomes known.

Pregnancy itself is not regarded as an SAE. However,congenital abnormalities or birth defects and spontaneous miscarriages that meet serious criteria (section **8.1.2**) should be reported as SAEs.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented.

8.6.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 90 days after the last dose of study drug.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the first date of the first dose until 90 days after the last dose should, if possible, be followed up and documented.

8.7 REGULATORY REPORTING FOR STUDIES CONDUCTED UNDER CCR-SPONSORED IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

All serious events will be reported to the FDA at least annually in a summary format.

9 CLINICAL MONITORING

As a sponsor for clinical trials, FDA regulations require the CCR to maintain a monitoring program. The CCR's program allows for confirmation of: study data, specifically data that could affect the interpretation of primary and secondary study endpoints; adherence to the protocol, regulations, ICH E6 and SOPs; and human subjects protection. This is done through independent verification of study data with source documentation focusing on:

- Informed consent process
- Eligibility confirmation
- Drug administration and accountability
- Adverse events monitoring
- Response assessment.

The monitoring program also extends to multi-site research when the CCR is the coordinating center.

This trial will be monitored by personnel employed by a CCR contractor. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL HYPOTHESIS

- Primary Endpoints:
    - Maximum tolerated dose (MTD) of rhIL-15 administered intravenously for 5 days in combination with obinutuzumab
    - Frequency (number and percentage) of treatment-emergent AEs
- Secondary Endpoints:
    - Overall response rate (including CR, CRi, and PR)
    - Proportion of patients who are MRD-negative
    - Duration of response (for patients who do and do not achieve MRD-negativity)
    - Progression-free, event-free, and overall survival

10.2 SAMPLE SIZE DETERMINATION

The MTD will be based on the assessment of DLT during the first cycle of treatment and will be defined as the dose level at which less than one-third of patients (0 of 3 or 0-1/6 patients) treated experience a DLT, with the next higher dose level demonstrating one-third or a greater number of patients ($\geq$ 2-3 or $\geq$ 2-6 patients) having a DLT. If a subject did not experience a DLT and did not finish one cycle of treatment (28 days) he or she will not be evaluable for determination of the MTD and would be replaced in the dose level. An additional 3 to 6 patients will be enrolled at the MTD, so that a total of 9 patients will be treated at this dose.

Using this dose-escalation scheme the probability of escalating to the next dose level will be based on the true rate of DLT at the current doses given by the following table (each group will be

considered independently of the other); Thus, if the true underlying proportion of DLTs is 50% at the current dose there is a 17% probability of escalating to the next dose.

True toxicity at a given dose	10%	20%	30%	40%	50%	60%
Probability of escalating	0.91	0.71	0.49	0.31	0.17	0.08

If all three dose levels are evaluated with 6 patients per dose level and 9 total patients at the MTD, a maximum of 21 evaluable patients will be enrolled. To account for non-evaluable patients, accrual ceiling will be set at 24 patients. Similarly, if all dose levels are evaluated with 3 patients per dose level and 9 total patients at the MTD, the minimum number of evaluable patients required will be 12. It is expected that the accrual can be completed in 24 months.

10.3 POPULATIONS FOR ANALYSES

10.3.1 Evaluable for toxicity:
All patients will be evaluable for toxicity from the time of their first treatment with rhIL-15.

10.3.2 Evaluable for objective response:
Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (NOTE: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

10.3.3 Evaluable Non-Target Disease Response:
Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

10.4 STATISTICAL ANALYSES

10.4.1 General Approach
The response rate will be determined and reported along with a 95% confidence interval. Other time-to-event outcomes will be reported using Kaplan-Meier curves.

10.4.2 Analysis of the Primary Endpoints
Safety summaries will include summaries in the form of tables and listings. Reports will include the frequency (number and percentage) of treatment emergent AEs grouped by severity of the AE (per CTCAE, v5.0) and by relationship to study drug (e.g., either rhIL-15, obinutuzumab, or both).

Laboratory shift tables containing counts and percentages will be prepared by treatment assignment, laboratory parameter, and time. Summary tables will be prepared for each laboratory parameter. Figures of changes in laboratory parameters over time will be generated.

Results of vital sign assessments, ECGs, and physical exams will be tabulated and summarized.

10.4.3 Analysis of the Secondary Endpoints
The duration of response (DOR; beginning at the date clinical response is first identified), overall survival (OS), event free survival (EFS), and progression free survival (PFS) will be estimated using Kaplan-Meier curves with appropriate confidence intervals reported.

Every report of response rates and time to progression should contain all patients included in the study. For the response calculation, the report should contain at least a section with all eligible patients. Another section of the report may detail the response rate for evaluable patients only. However, a response rate analysis based on a subset of patients must explain which patients were excluded and for which reasons. 95% confidence limits will be given.

10.4.4 Safety Analyses
The type, grade and frequency of toxicities will be reported.

10.4.5 Baseline Descriptive Statistics
Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions and CIs for discrete variables) will be used to summarize data as appropriate.

10.4.6 Planned Interim Analyses
No interim analyses are planned because of the single stage design of the trial.

10.4.7 Sub-Group Analyses
All secondary endpoints will be analyzed and reported separately for:

- patients with and without presence of del(17p)
- patients who do and do not have minimal residual disease (MRD)

10.4.8 Tabulation of Individual Participant Data
None.

10.4.9 Exploratory Analyses
The exploratory objectives such as seeking to identify potential biomarkers or T-cell and B-cell clones in peripheral blood which are associated with response, will be assessed using descriptive statistics as well as non-parametric methods such as exact Wilcoxon rank sum tests. The analyses will be done without formal adjustment for multiple comparisons, but in the context of the number of tests performed.

11 COLLABORATIVE AGREEMENTS

11.1 AGREEMENT TYPE
An MTA with Division of Cancer Treatment and Diagnosis (DCTD) for the IL-15 was executed on June 8, 2018.

12 HUMAN SUBJECTS PROTECTIONS

12.1 RATIONALE FOR SUBJECT SELECTION
CLL is a rare neoplasm that comprises a substantial proportion of all leukemia in middle-aged persons and is the most common type among elderly persons in western populations. Epidemiologic studies suggest that distribution by gender will be 66% males and 33% females(55). CLL is more common in Caucasian and African-American but rare in Hispanics and very rare in the Asian population. This study will be open to all patients who fit the inclusion criteria and

provide informed consent to protocol participation. We would predict that distribution should be comparable to that seen on the NCI screening protocol as follows:

- by gender: 33% women; 66% men
- by age: ages 23-79, median 60
- by race: 2% Asian, 11% Black, 8% Hispanic, 79% White

Subjects with HIV infection will be excluded due to potential toxicity and unknown effects of rhIL-15 and obinutuzumab on the underlying HIV infection and interference with ART. Because there is no significant preclinical information regarding the risks to a fetus or a newborn infant, all pregnant or breastfeeding woman will be excluded from participation in this trial.

12.2 Participation of Children

CLL is uncommon in patients under 45 years of age and is virtually unheard of in patients under 20 years of age. At the time of diagnosis, more than 95% of patients are 45 years old and above (1, 56). CLL may also be, biologically, a different disease in children. rhIL-15 has not been studied in human subjects under 18 years of age. For these reasons, individuals < 18 years old have been excluded from protocol participation.

12.3 Participation of Subjects Unable to Give Consent

Adults who are unable to consent are excluded from enrolling in this protocol. However, re-consent on this protocol may be necessary and there is a possibility that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (Section **12.5**), all subjects ≥ age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study.

Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation as needed for the following: an independent assessment of whether an individual has the capacity to provide consent; assistance in identifying and assessing an appropriate surrogate when indicated; and/or an assessment of the capacity to appoint a surrogate. The PI or AI will obtain permission for decisionally-impaired adults via their appointed surrogate decision-maker or another legally authorized representative (such as legal guardian or holder of the durable power of attorney; i.e., DPA).. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in NIH HRPP SOP 14E for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

12.4 Evaluation of Benefits and Risks/Discomforts

For patients with relapsed/refractory CLL, complete response rates for the six drug and drug combinations approved are no greater than 30%. Obinutuzumab, a humanized type 2 anti-CD20, is approved in combination with chlorambucil for CLL, and is thought to directly activated ADCC. Agents that may enhance ADCC, such as rhIL15, could improve efficacy of obinutuzumab. Although the clinical benefit of these drug(s) has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability.

Since fevers, rigors, lymphopenia, LFT elevations, and thrombocytopenia occurred during IL-15 infusion in the continuous IV trial, and since obinutuzumab will be given concomitantly, these toxicities may overlap. However, all IL-15-related reactions were transient and resolved by Day 8 of each cycle (third post-infusion day). Obinutuzumab manufacturer recommendations for IRR and TLS prophylaxis and criteria for discontinuing therapy in the event of either will be followed.

12.5 RISKS/BENEFITS ANALYSIS

The currently approved regimens for relapsed/refractory CLL are not adequate, and the proposed drug combination of IL-15 and obinutuzumab has the prospect of benefitting this patient population.

There have been no studies of IL-15 in patients with HIV on or off ART. Two non-human primates with SIV who were not on ART and received rhIL-15 on Study 2078-10804 both died, while subsequent animals who received viral suppression were seemingly unaffected. rhIL-15 may therefore contribute to morbidity/mortality in patients with a detectable viral load. Since potential toxicity of IL-15 and obinutzumab may interfere with ART adherence and optimal viral suppression, patients with HIV may be exposed to additional toxicity for unknown potential benefit of IL-15 and should therefore be excluded from participating in this study.

12.5.1 Risks related to CT scans

CT scans often use a contrast agent. There is a small risk of having a reaction to the contrast and most often include nausea, pain in the vein where the contrast is given, headache, metallic and/ or bitter taste in the mouth and a warm, flushing feeling. Rarely, some people have more severe allergic reactions to the contrast which may include skins rashes, shortness of breath, wheezing or low blood pressure.

12.5.2 Risks related to MRI scans

During part of the MRI participants may receive gadolinium, a contrast agent, through an intravenous (iv) catheter. The risks of an IV catheter include bleeding, infection, or inflammation of the skin and vein with pain and swelling.

Mild symptoms from gadolinium infusion occur in fewer than 1% of those who receive it and usually go away quickly. Mild symptoms may include coldness in the arm during the injection, a metallic taste, headache, and nausea. In an extremely small number, fewer than one in 300,000 people, more severe symptoms have been reported including shortness of breath, wheezing, hives, and lowering of blood pressure.

Participants with kidney disease are at risk for a serious reaction to gadolinium contrast called “nephrogenic systemic fibrosis” which has resulted in a very small number of deaths.

The FDA recently issued a safety alert that indicates small amounts of gadolinium may remain in the body for months to years. The effects of the retained gadolinium are not clear. At this time, retained gadolinium has not been linked to health risks in people whose kidneys work well.

12.5.3 Risks from Radiation Exposure

The procedures for performing the CT scans will follow clinical policies, no special procedures apply to these additional assessments for research purposes. In summary, subjects may receive additional radiation exposure from up to four (4) additional CT scans of the neck, chest, abdomen, and pelvis.

The total additional radiation dose for research purposes will be approximately 5.2 rem.

12.5.4 Risks from Blood Draws
The possible side effects of drawing blood include pain, bleeding, bruising, dizziness, light-headedness, fainting, and rarely a local blood clot formation or infection with redness and irritation of the vein.

12.5.5 Risks from EKG
Skin irritation can occur where the EKG electrodes are placed.

12.5.6 Risks from Bone Marrow Biopsy

The possible side effects associated with a bone marrow biopsy include pain, bleeding, bruising, and infection, as well as a reaction to the numbing agent.

12.5.7 Risks from Tumor Biopsy
The likely side effects include: discomfort or pain, redness, swelling, and/or bruising at the site of the needle insertion. Bleeding from the site of the needle insertion is a less likely risk. Rarely, significant infection or bleeding from this procedure, allergic reaction to the anesthetic, or formation of a scar at the site of needle entry occurs.

12.5.8 Psychological or Social Risks Associated with Loss of Privacy
Learning of genetic risks for another disease or disability may be upsetting and cause distress.

12.5.9 Privacy Risks Associated with Return of Incidental or Secondary Findings
It may be possible that genetic information could be used to help identify the participant and/or participant's relatives.

12.6 CONSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided as a physical or electronic document to the participant or consent designee(s) as applicable for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the participant/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant/consent designee, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to participant) or as described below, with a manual (non-electronic) signature on the electronic document. When required, witness signature will be obtained similarly as described for the investigator and participant.

<u>Manual (non-electronic) signature on electronic document</u>:

When a manual signature on an electronic document is used for the documentation of consent at the NIH Clinical Center, this study will use the following to obtain the required signatures:

- Adobe platform (which is not 21 CFR Part 11 compliant); or,
- iMedConsent platform (which is 21 CFR Part 11 compliant)

During the consent process, participants and investigators will view individual copies of the approved consent document on screens at their respective locations (if remote consent); the same screen may be used when in the same location, but is not required.

Both the investigator and the participant will sign the document using a finger, stylus or mouse.

Note: Refer to the CCR SOP PM-2, Obtaining and Documenting the Informed Consent Process for additional information (e.g., verification of participant identity when obtaining consent remotely) found here.

12.6.1 Consent Process for Adults Who Lack Capacity to Consent to Research Participation
For participants addressed in section **12.3**, a LAR will be identified consistent with Policy 403 and informed consent obtained from the LAR, as described in Section **12.6**.

13 REGULATORY AND OPERATIONAL CONSIDERATIONS

13.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and as applicable, Food and Drug Administration (FDA).

13.2 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented

(recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13.3 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the National Cancer Institute has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

13.4 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the/each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site(s) and NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NIH.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or

local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

14 PHARMACEUTICAL INFORMATION

This study is being conducted under a CCR-held IND: IND #140549.

14.1 rhIL-15 (NSC# 745101)

14.1.1 Source
rhIL-15 is an investigational agent supplied to the investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

14.1.2 Drug Summary Information

14.1.2.1 Chemical Name or Amino Acid Sequence
The 115 amino acid coding sequence of the pET28b/IL-15 cistron is as follows:

MNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASI
HDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS

14.1.2.2 Other Names
Recombinant Human Interleukin -15; Recombinant Human IL-15; rhIL-15

14.1.2.3 Classification
Recombinant human interleukin-15 (rhIL-15) is a cytokine of the 4-alpha helix bundle family of cytokines whose mature form consists of 115 amino acids. It has two cystine disulfide cross linkages at positions Cys 42-Cys 88 and Cys 35-Cys 85.

14.1.2.4 Molecular Weight (M.W.)
12,898.8 Daltons

14.1.2.5 Mode of Action
IL-15 interacts with a private receptor subunit IL- 15R alpha as well as the IL-2/IL-15R beta chain shared with IL-2 and the common gamma chain shared with IL-2, IL-4, IL-7, IL-9 and IL-21. IL-15 shares a number of biological activities with IL-2, including stimulation of the proliferation of activated CD4+, CD8+ as well as gamma-delta subsets of T cells. IL-15 also stimulates the proliferation of NK cells and acts as a co-stimulator with IL-12 to facilitate the production of Interferon-gamma and TNF-alpha.

14.1.3 How Supplied
IL-15 is manufactured by the Biopharmaceutical Development Program (BDP) and distributed by the Pharmaceutical Management Branch (PMB) ant CTEP. IL-15 is supplied as a sterile, frozen liquid product in single use vials containing no preservatives. Currently, IL-15 is supplied as 147 mcg / 0.3 mL (490 mcg/mL) in a 3 mL glass vial. The IL-15 is formulated in 25 mM sodium phosphate containing 0.5 M sodium chloride at a pH of 7.4.

NOTE: IL-15 vial content may vary between lots and protocols. Use caution and consult the protocol document for specific preparation instructions when preparing each dose.

14.1.4 Preparation
Vials of frozen IL-15 should be thawed at ambient room temperature. Upon thawing, the solution should be clear and colorless with no evidence of particulates or foreign matter. The infusion solutions should be mixed in a PVC bag.

14.1.5 Storage
IL-15 vials should be stores at or below (-70°C).

14.1.6 Stability

14.1.6.1 Vials
Stability studies of the intact vials are ongoing.

14.1.6.2 Prepared Infusion
The rhIL-15 infusion solution is stable at a concentration of 1 mcg/mL with 0.1% HSA for 4 hours at controlled room temperature (15°C–30°C) prior to initiation of the 24-hour infusion or 24 hours at 2-8°C prior to initiation of the 24-hour infusion. This stability information was previously documented by the Biopharmaceutical Development Program (BDP) of Leidos Biomedical Research, Inc., the drug manufacturer.

14.1.7 Administration
For all dose levels, the dose of rhIL-15 will be diluted in the appropriate volume of 0.1% human serum albumin (HSA) in 5% dextrose in water, USP (D5W) to reach a final rhIL-15 concentration of 1 mcg/mL. The rhIL-15 infusion will be administered to the patient by continuous intravenous infusion (civ) at a dose in mcg/kg/day determined by the dose level at which the patient is enrolled over 24 hours using a portable ambulatory pump on the inpatient unit (cycle 1) or in the outpatient setting (cycles 2-6, if deemed appropriate by the PI) for a total of 120 hours. Bags must be changed every 24 hours. Treatment with rhIL-15 will begin within 4 hours of preparation of the infusion bag and the infusion must be completed within 24 hours from the time drug administration begins. Otherwise a new infusion bag must be prepared to complete administration of the remaining dose.

As noted in Section 3.4, on days that both rhIL-15 and obinutuzumab are given together (i.e., Day 4 and 5 of Cycle 1 and Day 4 of each subsequent Cycle), rhIL-15 infusion will be held up to two hours prior to, and up to two hours following the obinutuzumab infusion.

Additional diliution information and calculations can be found in **APPENDIX C: IL-15 Dilution Instructions**.

14.1.8 Toxicity
The Comprehensive Adverse Event and Potential Risks List (CAEPRs) for Recombinant Human IL-15 provides a single list of reported and/or potential adverse events (AE) associated with the agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. The CAEPR does not provide frequency data; refer to the Investigator's Brochure for this information. Below is the CAEPR for Recombinant Human IL-15.

Version 1.3, January 2, 2019*

Adverse Events with Possible Relationship to Recombinant Human IL-15 (CTCAE 5.0 Term)	**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Anemia	***Anemia (Gr 2)***
Bone marrow hypocellular	
CARDIAC DISORDERS	
Sinus tachycardia	***Sinus tachycardia (Gr 2)***
GASTROINTESTINAL DISORDERS	
Abdominal pain	
Diarrhea	
Nausea	***Nausea (Gr 2)***
Vomiting	***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Chills	***Chills (Gr 2)***
Edema limbs	
Fatigue	***Fatigue (Gr 2)***
Fever	***Fever (Gr 2)***
Injection site reaction	
INFECTIONS AND INFESTATIONS	
Sepsis	
INVESTIGATIONS	
Alanine aminotransferase increased	
Aspartate aminotransferase increased	
Blood bilirubin increased	
Creatinine increased	
Lymphocyte count decreased	***Lymphocyte count decreased (Gr 2)***
Lymphocyte count increased	
Neutrophil count decreased	
Platelet count decreased	
White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS	
Hypoalbuminemia	
Hypophosphatemia	***Hypophosphatemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
Generalized muscle weakness	
NERVOUS SYSTEM DISORDERS	
Dizziness	
Headache	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
Dyspnea	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
Dry skin	
Erythema multiforme	***Erythema multiforme (Gr 2)***
Skin and subcutaneous tissue disorders - Other (rash)	
VASCULAR DISORDERS	
Capillary leak syndrome	
Hypertension	***Hypertension (Gr 2)***

Adverse Events with Possible Relationship to Recombinant Human IL-15 (CTCAE 5.0 Term)	Specific Protocol Exceptions to Expedited Reporting (SPEER)
Hypotension	***Hypotension (Gr 2)***

*This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail

Adverse events reported on Recombinant Human IL-15 trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Recombinant Human IL-15 caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia

CARDIAC DISORDERS - Atrial fibrillation; Chest pain - cardiac; Palpitations; Pericardial effusion; Pericardial tamponade; Sinus bradycardia; Ventricular tachycardia

GASTROINTESTINAL DISORDERS - Ascites; Constipation; Duodenal hemorrhage; Gastritis; Gastrointestinal disorders - Other (increased appetite); Ileus; Mucositis oral; Pancreatitis; Visceral arterial ischemia

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Infusion site extravasation; Multi-organ failure; Pain

IMMUNE SYSTEM DISORDERS - Autoimmune disorder

INFECTIONS AND INFESTATIONS - Tooth infection; Upper respiratory infection; Urinary tract infection

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Infusion related reaction

INVESTIGATIONS - Alkaline phosphatase increased; Cardiac troponin I increased; Electrocardiogram QT corrected interval prolonged; GGT increased; INR increased; Lipase increased; Serum amylase increased; Weight gain; Weight loss

METABOLISM AND NUTRITION DISORDERS - Anorexia; Dehydration; Hyperkalemia; Hypocalcemia; Hypokalemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Bone pain; Muscle weakness upper limb; Myalgia; Pain in extremity

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain

NERVOUS SYSTEM DISORDERS - Dysgeusia; Peripheral sensory neuropathy; Presyncope; Vasovagal reaction

PSYCHIATRIC DISORDERS - Anxiety; Psychosis

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Genital edema

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Bronchopulmonary hemorrhage; Cough; Hypoxia; Laryngeal inflammation; Pleural effusion; Pneumonitis; Pulmonary edema; Wheezing

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythroderma; Palmar-plantar erythrodysesthesia syndrome; Pruritus; Rash acneiform; Skin and subcutaneous tissue disorders - Other (skin plaques)

VASCULAR DISORDERS - Hot flashes

NOTE: Recombinant Human IL-15 in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

14.1.9 CTEP Information

14.1.9.1 Agent Ordering and Agent Accountability

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

The CTEP Pharmaceutical Management Branch (PMB) will provide direction as to when sites can order PMB-supplied agents.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

14.1.9.1.1 Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

14.1.9.2 Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

14.1.9.3 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov

- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

14.2 OBINUTUZUMAB (NSC# 793436)

14.2.1 Source

Obinutuzumab (Gazyva®) is commercially available and will be purchased by the CCR and supplied to the patients enrolled on the study by the NIH Clinical Center Pharmacy Department.

14.2.2 Toxicity

The Comprehensive Adverse Event and Potential Risks List (CAEPRs) for obinutuzumab provides a single list of reported and/or potential adverse events (AE) associated with the agent using a uniform presentation of events by body system.

Version 2.3, May 14, 2020[1]

Adverse Events with Possible Relationship to Obinutuzumab (Gazyva) (CTCAE 5.0 Term) [n= 524]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
		Febrile neutropenia
Blood and lymphatics system disorders - Other (B-cell depletion)[2]		
CARDIAC DISORDERS		
		Chest pain - cardiac [3]
		Heart failure[3]
		Supraventricular tachycardia[3]
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Colitis	
	Diarrhea	
	Gastrointestinal perforation[4]	
Nausea		
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Chills[5]	
Fatigue		
Fever[5]		
	Non-cardiac chest pain	
IMMUNE SYSTEM DISORDERS		
		Anaphylaxis[6]
		Serum sickness[6]
INFECTIONS AND INFESTATIONS		
		Hepatitis B reactivation[7]
	Infection[7]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Infusion related reaction[5]		
INVESTIGATIONS		

Adverse Events with Possible Relationship to Obinutuzumab (Gazyva) (CTCAE 5.0 Term) [n= 524]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Alanine aminotransferase increased	
	Alkaline phosphatase increased	
	Aspartate aminotransferase increased	
	Lymphocyte count decreased	
	Neutrophil count decreased[8]	
	Platelet count decreased	
	White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS		
	Hyperuricemia	
		Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
	Back pain	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
		Neoplasms benign, malignant and unspecified (incl cysts and polyps - Other (basal cell carcinoma)
		Neoplasms benign, malignant and unspecified (incl cysts and polyps - Other (squamous cell carcinoma of skin)
NERVOUS SYSTEM DISORDERS		
	Dizziness	
	Headache	
		Nervous system disorders - Other (progressive multifocal leukoencephalopathy [PML])
RENAL AND URINARY DISORDERS		
	Dysuria	
	Urinary incontinence	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	
	Dyspnea[5]	
	Rhinorrhea	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Alopecia	
	Pruritus	
	Rash maculo-papular	
	Urticaria	
VASCULAR DISORDERS		
	Flushing[5]	
	Hypertension[5]	
Hypotension[5]		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]B-cell lysis and depletion are considered to be the primary mechanism of action of obinutuzumab.

[3]These events are considered expected in the context of worsening an already existing cardiac condition, such as heart failure, cardiac ischemia and arrhythmia (atrial fibrillation or atrial flutter).

[4]Gastrointestinal perforation may occur in Gastrointestinal lymphomas and may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

[5]Infusion related reactions, including high-grade hypersensitivity reactions, may occur during or immediately after administration of obinutuzumab; clinical manifestations may include as, fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing (dyspnea), bronchospasm and hypoxia.

[6]Anaphylaxis (immediate-onset hypersensitivity) with symptoms including dyspnea, bronchospasm, hypotension, urticaria, and tachycardia as well as late-onset hypersensitivity (serum sickness) with symptoms including chest pain, diffuse arthralgia, and fever, which may be life-threatening have been observed in obinutuzumab trials.

[7]Infection may include viral, bacterial and fungal infections in any organ system under the INFECTIONS AND INFESTATIONS SOC.

[8]Neutrophil count decreased (neutropenia) may be of late onset, prolonged, and in rare cases, life threatening or fatal.

Adverse events reported on Obinutuzumab (Gazyva) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Obinutuzumab (Gazyva) caused the adverse event:

CARDIAC DISORDERS - Atrial flutter; Myocardial infarction[3]
GASTROINTESTINAL DISORDERS - Constipation; Dyspepsia
METABOLISM AND NUTRITION DISORDERS - Hypokalemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Myalgia
PSYCHIATRIC DISORDERS - Insomnia
SKIN AND SUBCUTANEOUS TISSUE DISORDERS – Hyperhidrosis

NOTE: Obinutuzumab (Gazyva) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

14.2.3 Formulation and Preparation

Obinutuzumab is provided as a single 1000-mg dose liquid concentrate with a strength of 25 mg/mL. It is supplied in 50-mL glass vials containing 40 mL of the 25-mg/mL liquid concentrate. In addition to the antibody, the liquid also contains histidine/histidine-HCl, trehalose, poloxamer 188, and highly purified water (HPW). HPW meets the specified limits of HPW according to Pharm. Eur. and for water for injections (WFI) according to USP.

14.2.4 Stability and Storage

The recommended storage conditions for obinutuzumab drug product are between 2°C and 8°C, protected from light. For further instructions, as well as information on in-use stability, see the packaging label.

14.2.5 Administration procedures

Obinutuzumab will be administered by IV infusion on Days 4, 5, 11, and 18 of Cycle 1, and Day 4 of Cycles 2-6. Premedication will be used to reduce the risk of IRRs as outlined in Section **3.4.2**, prior to the obinutuzumab infusion. Not to be mixed with other drugs.

14.2.6 Incompatibilities

No incompatibilities between obinutuzumab and polyvinylchloride (PVC) or non-PVC polyolefin bags and administration sets have been observed. No formal drug interaction studies have been performed with obinutuzumab. Please refer to the package insert and PDR for full drug interactions and toxicities.

15 REFERENCES

1. Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. The Lancet Oncology. 2016;17(8):e328-e46.
2. Molica S. Sex differences in incidence and outcome of chronic lymphocytic leukemia patients. Leukemia & Lymphoma. 2006;47(8):1477-80.
3. Puente XS, Beà S, Valdés-Mas R, Villamor N, Gutiérrez-Abril J, Martín-Subero JI, et al. Non-coding recurrent mutations in chronic lymphocytic leukaemia. Nature. 2015;526:519.
4. Puente XS, Pinyol M, Quesada V, Conde L, Ordóñez GR, Villamor N, et al. Whole-genome sequencing identifies recurrent mutations in chronic lymphocytic leukaemia. Nature. 2011;475:101.
5. Parikh SA, Strati P, Tsang M, West CP, Shanafelt TD. Should IGHV status and FISH testing be performed in all CLL patients at diagnosis? A systematic review and meta-analysis. Blood. 2016;127(14):1752-60.
6. Wiestner A. Emerging role of kinase-targeted strategies in chronic lymphocytic leukemia. ASH Education Program Book. 2012;2012(1):88-96.
7. Wiestner A, Rosenwald A, Barry TS, Wright G, Davis RE, Henrickson SE, et al. ZAP-70 expression identifies a chronic lymphocytic leukemia subtype with unmutated immunoglobulin genes, inferior clinical outcome, and distinct gene expression profile. Blood. 2003;101(12):4944-51.
8. Orchard JA, Ibbotson RE, Davis Z, Wiestner A, Rosenwald A, Thomas PW, et al. ZAP-70 expression and prognosis in chronic lymphocytic leukaemia. The Lancet. 2004;363(9403):105-11.
9. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–Working Group 1996 guidelines. Blood. 2008;111(12):5446-56.
10. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. Guidelines for diagnosis, indications for treatment, response assessment and supportive management of chronic lymphocytic leukemia. Blood. 2018.
11. Rai K, Sawitsky A, Cronkite E, Chanana A, Levy R, Pasternack B. Clinical staging of chronic lymphocytic leukemia. Blood. 1975;46(2):219-34.
12. Binet JL, Auquier A, Dighiero G, Chastang C, Piguet H, Goasguen J, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer. 1981;48(1):198-206.
13. Pratt G, Thomas P, Marden N, Alexander D, Davis Z, Hussey D, et al. Evaluation of serum markers in the LRF CLL4 trial: β2-microglobulin but not serum free light chains, is an independent marker of overall survival. Leukemia & Lymphoma. 2016;57(10):2342-50.
14. Hallek M, Fischer K, Fingerle-Rowson G, Fink AM, Busch R, Mayer J, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. The Lancet. 2010;376(9747):1164-74.
15. Fischer K, Bahlo J, Fink AM, Goede V, Herling CD, Cramer P, et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. Blood. 2016;127(2):208-15.
16. Eichhorst B, Fink A-M, Bahlo J, Busch R, Kovacs G, Maurer C, 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. The Lancet Oncology. 2016;17(7):928-42.
17. Millennium and ILEX Partners L. Alemtuzumab Product Label [cited 2018 6/6/18]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2001/alemmil050701LB.htm.
18. Hillmen P, Skotnicki AB, Robak T, Jaksic B, Dmoszynska A, Wu J, et al. Alemtuzumab Compared With Chlorambucil As First-Line Therapy for Chronic Lymphocytic Leukemia. Journal of Clinical Oncology. 2007;25(35):5616-23.
19. Thompson PA, Tam CS, O'Brien SM, Wierda WG, Stingo F, Plunkett W, et al. Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term disease-free survival in IGHV-mutated chronic lymphocytic leukemia. Blood. 2016;127(3):303-9.
20. Byrd JC, Murphy T, Howard RS, Lucas MS, Goodrich A, Park K, et al. Rituximab Using A Thrice Weekly Dosing Schedule in B-Cell Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma Demonstrates Clinical Activity and Acceptable Toxicity. Journal of Clinical Oncology. 2001;19(8):2153-64.
21. Badoux XC, Keating MJ, Wang X, O'Brien SM, Ferrajoli A, Faderl S, et al. Fludarabine, cyclophosphamide, and rituximab chemoimmunotherapy is highly effective treatment for relapsed patients with CLL. Blood. 2011;117(11):3016-24.
22. Fischer K, Cramer P, Busch R, Stilgenbauer S, Bahlo J, Schweighofer CD, et al. Bendamustine Combined With Rituximab in Patients With Relapsed and/or Refractory Chronic Lymphocytic Leukemia: A Multicenter Phase II Trial of the German Chronic Lymphocytic Leukemia Study Group. Journal of Clinical Oncology. 2011;29(26):3559-66.
23. O'Brien S, Jones JA, Coutre SE, Mato AR, Hillmen P, Tam C, et al. Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): a phase 2, open-label, multicentre study. The Lancet Oncology. 2016;17(10):1409-18.
24. Furman RR, Sharman JP, Coutre SE, Cheson BD, Pagel JM, Hillmen P, et al. Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia. New England Journal of Medicine. 2014;370(11):997-1007.
25. Stilgenbauer S, Eichhorst B, Schetelig J, Coutre S, Seymour JF, Munir T, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. The Lancet Oncology. 2016;17(6):768-78.
26. Seymour JF, Kipps TJ, Eichhorst B, Hillmen P, D'Rozario J, Assouline S, et al. Venetoclax-Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. New England Journal of Medicine. 2018;378(12):1107-20.
27. Byrd JC, Furman RR, Coutre SE, Flinn IW, Burger JA, Blum KA, et al. Targeting BTK with Ibrutinib in Relapsed Chronic Lymphocytic Leukemia. New England Journal of Medicine. 2013;369(1):32-42.
28. Coiffier B, Lepretre S, Pedersen LM, Gadeberg O, Fredriksen H, van Oers MHJ, et al. Safety and efficacy of ofatumumab, a fully human monoclonal anti-CD20 antibody, in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: a phase 1-2 study. Blood. 2008;111(3):1094-100.
29. Al-Sawaf O, Fischer K, Engelke A, Pflug N, Hallek M, Goede V. Obinutuzumab in chronic lymphocytic leukemia: design, development and place in therapy. Drug Design, Development and Therapy. 2017;11:295-304.

30. Cragg MS, Walshe CA, Ivanov AO, Glennie MJ. The biology of CD20 and its potential as a target for mAb therapy. Current directions in autoimmunity. 2005;8:140-74.
31. Woyach JA, Johnson AJ, Byrd JC. The B-cell receptor signaling pathway as a therapeutic target in CLL. Blood. 2012;120(6):1175-84.
32. Chan HTC, Hughes D, French RR, Tutt AL, Walshe CA, Teeling JL, et al. CD20-induced Lymphoma Cell Death Is Independent of Both Caspases and Its Redistribution into Triton X-100 Insoluble Membrane Rafts. Cancer Research. 2003;63(17):5480-9.
33. Cragg MS, Morgan SM, Chan HTC, Morgan BP, Filatov AV, Johnson PWM, et al. Complement-mediated lysis by anti-CD20 mAb correlates with segregation into lipid rafts. Blood. 2003;101(3):1045-52.
34. Herter S, Herting F, Mundigl O, Waldhauer I, Weinzierl T, Fauti T, et al. Preclinical Activity of the Type II CD20 Antibody GA101 (Obinutuzumab) Compared with Rituximab and Ofatumumab In Vitro and in Xenograft Models. Molecular Cancer Therapeutics. 2013;12(10):2031-42.
35. Kern DJ, James BR, Blackwell S, Gassner C, Klein C, Weiner GJ. GA101 induces NK-cell activation and antibody-dependent cellular cytotoxicity more effectively than rituximab when complement is present. Leukemia & Lymphoma. 2013;54(11):2500-5.
36. Lim SH, Vaughan AT, Ashton-Key M, Williams EL, Dixon SV, Chan HTC, et al. Fc gamma receptor IIb on target B cells promotes rituximab internalization and reduces clinical efficacy. Blood. 2011;118(9):2530-40.
37. Mössner E, Brünker P, Moser S, Püntener U, Schmidt C, Herter S, et al. Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell–mediated B-cell cytotoxicity. Blood. 2010;115(22):4393-402.
38. Ferrara C, Grau S, Jäger C, Sondermann P, Brünker P, Waldhauer I, et al. Unique carbohydrate–carbohydrate interactions are required for high affinity binding between FcγRIII and antibodies lacking core fucose. Proceedings of the National Academy of Sciences. 2011;108(31):12669-74.
39. Ferrara C, Stuart F, Sondermann P, Brünker P, Umaña P. The Carbohydrate at FcγRIIIa Asn-162: AN ELEMENT REQUIRED FOR HIGH AFFINITY BINDING TO NON-FUCOSYLATED IgG GLYCOFORMS. Journal of Biological Chemistry. 2006;281(8):5032-6.
40. Golay J, Da Roit F, Bologna L, Ferrara C, Leusen JH, Rambaldi A, et al. Glycoengineered CD20 antibody obinutuzumab activates neutrophils and mediates phagocytosis through CD16B more efficiently than rituximab. Blood. 2013;122(20):3482-91.
41. Ferrara C, Brünker P, Suter T, Moser S, Püntener U, Umaña P. Modulation of therapeutic antibody effector functions by glycosylation engineering: Influence of Golgi enzyme localization domain and co-expression of heterologous β1, 4-N-acetylglucosaminyltransferase III and Golgi α-mannosidase II. Biotechnology and Bioengineering. 2006;93(5):851-61.
42. Cartron G, de Guibert S, Dilhuydy M-S, Morschhauser F, Leblond V, Dupuis J, et al. Obinutuzumab (GA101) in relapsed/refractory chronic lymphocytic leukemia: final data from the phase 1/2 GAUGUIN study. Blood. 2014;124(14):2196-202.
43. Sehn LH, Assouline SE, Stewart DA, Mangel J, Gascoyne RD, Fine G, et al. A phase 1 study of obinutuzumab induction followed by 2 years of maintenance in patients with relapsed CD20-positive B-cell malignancies. Blood. 2012;119(22):5118-25.

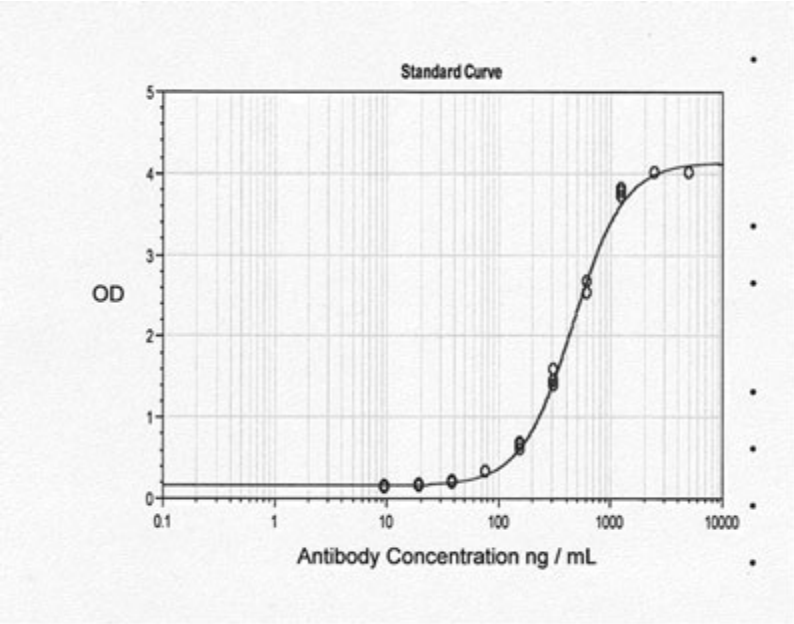
44. Byrd JC, Flynn JM, Kipps TJ, Boxer M, Kolibaba KS, Carlile DJ, et al. Randomized phase 2 study of obinutuzumab monotherapy in symptomatic, previously untreated chronic lymphocytic leukemia. Blood. 2016;127(1):79-86.
45. Goede V, Fischer K, Engelke A, Schlag R, Lepretre S, Montero LFC, et al. Obinutuzumab as frontline treatment of chronic lymphocytic leukemia: updated results of the CLL11 study. Leukemia. 2015;29:1602.
46. Genentech. Obinutuzumab product label 2016 [cited 2018 6/8/18]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125486s013lbl.pdf.
47. Waldmann TA. The biology of interleukin-2 and interleukin-15: implications for cancer therapy and vaccine design. Nature reviews Immunology. 2006;6(8):595-601.
48. Waldmann TA. The biology of IL-15: implications for cancer therapy and the treatment of autoimmune disorders. The journal of investigative dermatology Symposium proceedings. 2013;16(1):S28-30.
49. Lugli E, Goldman CK, Perera LP, Smedley J, Pung R, Yovandich JL, et al. Transient and persistent effects of IL-15 on lymphocyte homeostasis in nonhuman primates. Blood. 2010;116(17):3238-48.
50. Waldmann TA, Lugli E, Roederer M, Perera LP, Smedley JV, Macallister RP, et al. Safety (toxicity), pharmacokinetics, immunogenicity, and impact on elements of the normal immune system of recombinant human IL-15 in rhesus macaques. Blood. 2011;117(18):4787-95.
51. Conlon KC, Lugli E, Welles HC, Rosenberg SA, Fojo AT, Morris JC, et al. Redistribution, hyperproliferation, activation of natural killer cells and CD8 T cells, and cytokine production during first-in-human clinical trial of recombinant human interleukin-15 in patients with cancer. J Clin Oncol. 2015;33(1):74-82.
52. Dubois S, Conlon KC, Müller JR, Hsu-Albert J, Beltran N, Bryant BR, et al. IL15 Infusion of Cancer Patients Expands the Subpopulation of Cytotoxic CD56^{bright} NK Cells and Increases NK-Cell Cytokine Release Capabilities. Cancer Immunology Research. 2017;5(10):929-38.
53. MacFarlane AWt, Jillab M, Smith MR, Alpaugh RK, Cole ME, Litwin S, et al. NK cell dysfunction in chronic lymphocytic leukemia is associated with loss of the mature cells expressing inhibitory killer cell Ig-like receptors. Oncoimmunology. 2017;6(7):e1330235.
54. Laprevotte E, Voisin G, Ysebaert L, Klein C, Daugrois C, Laurent G, et al. Recombinant Human IL-15 Trans-Presentation by B Leukemic Cells from Chronic Lymphocytic Leukemia Induces Autologous NK Cell Proliferation Leading to Improved Anti-CD20 Immunotherapy. The Journal of Immunology. 2013;191(7):3634.
55. Hallek M. Chronic lymphocytic leukemia: 2017 update on diagnosis, risk stratification, and treatment. American Journal of Hematology. 2017;92(9):946-65.
56. Stauder R, Eichhorst B, Hamaker ME, Kaplanov K, Morrison VA, Österborg A, et al. Management of chronic lymphocytic leukemia (CLL) in the elderly: a position paper from an international Society of Geriatric Oncology (SIOG) Task Force. Annals of Oncology. 2017;28(2):218-27.

16 APPENDICES

16.1 APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

16.2 APPENDIX B: ASSAY FOR ANTIBODIES TO RHIL-15



- Plates are coated with human IL-15 for 3 hours at 37°C, washed, blocked with 3% FBS and washed again.
- A standard curve for assay quantitation and quality control is constructed using serial dilutions of a commercial affinity purified goat anti-human IL-15 that is diluted in heat-inactivated normal human serum. The standard curve samples are incubated for 2 hours at 37°C and washed.
- Biotin conjugated IL-15 is added to each well, incubated 2 hours at 37°C, and the plates are washed.
- Alkaline phosphatase–conjugated streptavidin is added to each well for 2 hours at 37°C and then washed.
- The assay is developed with the addition of diethanolamine buffer with p-Nitrophenyl Phosphatase for 1 hour at 37°C and then immediately read at 405 nm.
- To detect antibodies to human IL-15 in test samples, serum from the test subject will be assayed in duplicate at dilutions of 1/3 and 1/9 concomitantly with the standard curve samples as above and the resultant OD obtained used to quantitate the level of antibody present.

16.3 APPENDIX C: IL-15 DILUTION INSTRUCTIONS

All dose preparations will be performed in a laminar flow hood in compliance with all legal requirements and in accordance with guidelines of recognized organizations.

0.1% human serum albumin (HSA) in 5% dextrose in water, USP (D5W), will be used for the dilutions listed below.

Please note: The dosing examples listed below are for the 147 mcg/0.3 mL in a 3mL vial size and dilution ONLY. The following dosing chart may be used as a reference, but doses should always be re-calculated at the time of preparation. In the future, different concentrations of IL-15 may be available and doses and dilutions will need to be recalculated.

Dose Level 1 (0.5 mcg/kg), Dose Level 2 (1 mcg/kg), and Dose Level 3 (2 mcg/kg)

To prepare an IL-15 dose for Cohort 1 (0.5 mcg/kg):

1. Thaw vial(s) of IL-15, **147 mcg/0.3 mL (490 mcg/mL)** at room temperature.
2. Using a 27-gauge needle, slowly draw up the required dose in a 1 mL syringe. Doses should be rounded to the nearest 0.01 mL.
3. Add the calculated volume of IL-15 to 0.1% HSA in D5W in a PVC or polyolefin bag.
4. Label the bag with a 4-hour beyond-use date. The infusion may be started within 4 hours at room temperature, or within 24 hours if bag was kept at 2-8°C. The infusion must be completed within 24 hours of initiation.

Administered dose = _____ kg (Patient's weight) X _____ mcg/kg (DL) = _____ **mcg**

Prepared dose = _____ mcg (Administered dose) + 10 mcg (Overfill dose) **=** _____ **mcg**

IL-15 volume = _____ mcg (Prepared dose) ÷ 490 mcg/mL (vial concentration) = _____ **mL**

Total infusion volume =

_____ mcg (Prepared dose) ÷ 1 mcg/mL (final infusion concentration) = _____ **mL**

Diluent volume =

_____ **mL (Total infusion volume) -** _____ **mL (IL-15 volume) =** _____ **mL**

Patient weight	IL-15 volume (490 mcg/ml)			Diluent volume			Total infusion volume (1 mcg/ml)		
	DL1	DL2	DL3	DL1	DL2	DL3	DL1	DL2	DL3
60 kg	0.08	0.14	0.27	39.92	69.86	129.73	40 ml	70 ml	130 ml
75 kg	0.10	0.17	0.33	47.40	84.83	159.67	47.5 ml	85 ml	160 ml
90 kg	0.11	0.20	0.39	54.89	99.80	189.61	55 ml	100 ml	190 ml
105 kg	0.13	0.23	0.45	62.37	114.77	219.55	62.5 ml	115 ml	220 ml

Dose calculation for obese patients:
For patients whose body mass index (BMI) is >30 kg/m2, the factor for body weight used in calculating IL-15 doses will be determined as follows:

Corrected body weight (kg) = 30 x (height [m])^2