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Title: A Phase I Study of Moxetumomab Pasudotox-tdfk (Lumoxiti™) and either Rituximab (Rituxan®) or Ruxience for Relapsed Hairy Cell Leukemia

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Drug Name:	Moxetumomab pasudotox-tdfk; CAT-8015; HA22	Rituximab (Rituxan®)	Ruxience
IND Number:	140552	140552	140552
Sponsor:	Center for Cancer Research	Center for Cancer Research	Center for Cancer Research
Manufacturer:	AstraZeneca	Genentech	Pfizer
Supplier	AstraZeneca	CC Pharmacy	CC Pharmacy

Commercial Agents: None

PRÉCIS

Background:

- Hairy cell leukemia (HCL) is an indolent CD22+ B-cell leukemia comprising 2% of all leukemias, or approximately 1200 of the 62,130 new cases of leukemia/year in the US. HCL variant (HCLv), also CD22+, is 10-20% as common as HCL, but more common in the relapsed/refractory population due to its poor prognosis and response to standard purine analog chemotherapy. HCLv cells are CD25-negative and wild type for BRAF, so HCLv patients are not candidates for BRAF inhibitors. CD25+ classic-appearing HCL-cells that express unmutated IGHV4-34 are wild-type for BRAF, remain brightly CD22 positive, and confer a poor prognosis when treated with chemotherapy.
- Moxetumomab pasudotox-tdfk is a recombinant immunotoxin containing a variable domain (Fv) fragment of an anti-CD22 monoclonal antibody and truncated Pseudomonas exotoxin, which kills CD22+ cells by binding to CD22 via the Fv fragment, and induction of apoptotic cell death catalytic inhibition of protein synthesis in the cytosol.
- Moxetumomab pasudotox-tdfk in phase 1 testing demonstrated a high complete response (CR) rate in patients with chemoresistant HCL, without dose-limiting toxicity (DLT), but with reversible grade 2 hemolytic uremic syndrome (HUS) not requiring plasmapheresis.
- Moxetumomab pasudotox-tdfk completed multicenter phase 3 testing in 80 patients, meeting its CR endpoint, with 8.8% incidence each of capillary leak syndrome (CLS, grade 3-4 2.5%), and HUS (grade 3-4 6.3%), both reversible.
- Moxetumomab pasudotox-tdfk is the only known non-chemotherapy-containing regimen for HCL which can consistently eradicate minimal residual disease (MRD), and this is associated with prolonged CR durations. Recently, US Food and Drug Administration (FDA) has accepted the Biologics License Application (BLA) for moxetumomab pasudotox-tdfk as the treatment of adult patients with HCL.
- Patients who did not achieve CR, or CR with MRD, often made neutralizing antibodies to the bacterial-based toxin, and/or had collections of HCL cells not completely eradicated by moxetumomab pasudotox-tdfk. Both issues may be addressed by the addition of anti-CD20 monoclonal antibody (Mab) rituximab or Ruxience to Moxetumomab pasudotox-tdfk.

Objective:

- To determine the safety and toxicity of Moxetumomab pasudotox-tdfk and rituximab/Ruxience used at the planned dose level, in participants with HCL and HCLv.

Eligibility:

- HCL or HCLv with at least 1 prior purine analog, and, for HCL participants with ≥2-years 1 month response, at least 1 other therapy.
- Need for treatment, either 1) ANC <1/nL, 2) Hgb <10g/dL, 3) Plt <100/nL, 4) symptomatic splenomegaly, or enlarging HCL mass > 2cm in short axis
- Serum creatinine < 1.5 mg/dL, or creatinine clearance ≥ 60 mL/min by Cockcroft-Gault equation, where creatinine clearance = (140-age)(kg weight)/(72 x Creatinine).
- No uncontrolled infection or cardiopulmonary dysfunction

Design:

- Phase I trial, two arm, non-randomized, dose escalation
- Administration:
  - Participants 1-13: Moxetumomab pasudotox-tdfk 30-40 mcg/kg intravenous (iv) over 30 min, rituximab 375 mg/m^2 iv, 50-400 mg/hr.
  - Participants 14-26: Moxetumomab pasudotox-tdfk 40 mcg/kg intravenous (iv) over 30 min, Ruxience 375 mg/m^2 iv, 50-400 mg/hr
  - Rituximab or Ruxience day 1 (begin day -2 on cycle 1), Moxetumomab pasudotox-tdfk days 1, 3, and 5.
  - Participants will receive up to 4 cycles past documentation of CR without MRD, maximum 8.
  - To prevent renal toxicity and hypovolemia, participants will be encouraged to drink water gradually, approximately 1 cup/hour or 6L/day, not going >3 hours without drinking from days 1 to 8 and to keep a hydration diary to record daily fluid consumption.
  - To prevent rituximab/Ruxience toxicity, participants will receive prophylactic dexamethasone orally 0.5-2 hours before the 1st dose of rituximab/Ruxience, and before subsequent doses until rituximab/Ruxience infusion reactions are not seen. Participants will also receive diphenhydramine, famotidine and acetaminophen.
  - Dexamethasone 4 mg orally (maximum 2 doses/day) will be given as needed to treat nausea or fever associated with Moxetumomab pasudotox-tdfk, which might prevent adequate water intake
- Statistical design:
  - Up to 26 participants are intended to be treated in the trial. While a total of 26 evaluable participants will be enrolled, the accrual ceiling will be set at 30 to include screen failures and inevaluable participants.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council for 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 Objective

To determine the safety and toxicity of moxetumomab pasudotox-tdfk and rituximab/Ruxience treated at the planned dose level, in participants with HCL and HCLv.

1.1.2 Secondary Objectives

- To determine the minimal residual disease (MRD)-free CR rate of the study drug combination is higher than that achieved with 40-50 mcg/kg dose levels of Moxetumomab pasudotox-tdfk alone.
- To determine response rates and duration of response.

1.1.3 Exploratory Objectives

- To determine the incidence of anti-moxetumomab antibodies after combined treatment.
- To determine the plasma levels of moxetumomab pasudotox-tdfk with combined treatment.
- To determine the effects of combined therapy on normal B and T-cells.

1.2 BACKGROUND AND RATIONALE

1.2.1 Background

Hairy cell leukemia (HCL) is an indolent CD22+ B-cell leukemia comprising 2% of all leukemias [1, 2], or approximately 1200 of the 62,130 new cases of leukemia/year in the US [3]. HCL variant (HCLv), also CD22+, is 10-20% as common as HCL, but more common in the relapsed/refractory

population due to its poor prognosis and response to standard purine analog chemotherapy [4, 5]. HCLv cells are CD25-negative and wild type for BRAF, so HCLv patients are not candidates for BRAF inhibitors [6]. CD25+ classic-appearing HCL-cells that express unmutated IGHV4-34 are wild-type for BRAF, remain brightly CD22 positive, and confer a poor prognosis when treated with chemotherapy [7].

Moxetumomab pasudotox-tdfk is an anti-CD22 recombinant immunotoxin reported in the dose-escalation part of a phase I trial to achieve 46% complete remission (CR) and 86% overall response (ORR) rates, without dose-limiting toxicity (DLT) [8]. Two patients had completely reversible grade 2 hemolytic uremic syndrome (HUS), but no chemotherapy-type myelosuppressive or cumulative toxicities were observed.

Long-term follow-up of these 28 patients, including 12 who received the upper dose 50 mcg/kg every other day for 3 doses (QODx3), and an extension cohort of 21 patients receiving this dose, documented a CR rate of 64% in the 33 patients receiving 50 mcg/kg QODx3. Moreover, of 32 patients evaluated for minimal residual disease (MRD) with bone marrow biopsy (BMBx) immunohistochemistry (IHC) and flow cytometry of blood and bone marrow aspirate (BMA), 11 (34%) were MRD-negative. Median CR duration was not reached (up to 72 months) in those MRD-negative vs 13.5 months in those MRD+ ($p<0.0001$). Of the 3 tests for MRD, the most sensitive by far was BMA flow cytometry, and patients MRD+ by this study were sometimes positive by blood flow cytometry, IHC, or both [9]. Multicolor high sensitivity flow cytometry was used for both blood and BMA, and results read as suspicious are considered negative. MRD+ by IHC of BMBx requires at least as many B as T-cells, and for most of the B-cells to be consistent with HCL [10]. As exploratory endpoints, MRD is also determined by PCR, using consensus primers to a variable framework domain (FR1, FR2 or FR3), and a junctional or constant domain (J_H or C_H) of the immunoglobulin heavy chain rearrangement (IgH) [11, 12]. This assay, performed in the Molecular Pathology Section of the Laboratory of Pathology, NCI, is considered positive if the band corresponding to the HCL IgH can be recognized over a background of IgH bands from normal B-cells. Lack of normal B-cells, either due to HCL, chemotherapy or rituximab, may allow the HCL IgH band to more easily be seen. A research PCR assay is also done in the Kreitman Lab using patient- specific primers with a probe [11]. This patient- or clone-specific assay can detect 1 HCL in 10^6 normal cells but requires a different PCR assay for each patient.

Of 32 patients at 50 mcg/kg QOD x3 evaluated for neutralizing (antidrug) antibodies, 24 (75%) had >50% neutralization of 200 ng/ml, and 17 (53%) had >75% neutralization of 1000 ng/ml of moxetumomab pasudotox-tdfk. Since CR duration was higher with compared to without consolidation cycles of moxetumomab pasudotox-tdfk ($p=0.0004$), and since early immunogenicity prevented consolidation cycles, prevention of immunogenicity is an important goal in immunotoxin treatment of HCL [9]. Further analysis of response vs immunogenicity, reported in the supplemental section of phase I report [9], showed trends for higher MRD-negative CR rate (8 of 15 vs. 3 of 17; $P = .06$) and longer CR duration (median undefined vs. 19.1 months, $P = .05$) in patients without vs. with antibodies neutralizing more than 75% of the activity of 1000 ng/ml of moxetumomab pasudotox-tdfk. Pharmacokinetic analysis in this report showed that despite early neutralizing antibodies which made patients ineligible for future cycles (>50% neutralization of 200 ng/ml), we could observe increases in peak level and area under curve (AUC), and decreases in volume of distribution and clearance, from the 1st dose to the 3rd dose of the last cycle. This indicated that even secondary immunogenicity with moxetumomab pasudotox-tdfk in

HCL was too weak to prevent titration of antidrug antibodies by repeated dosing. This make it possible that an agent like rituximab, which could not prevent immunogenicity in solid tumors [13] receiving a large immunotoxin chemical conjugate, may prevent it in HCL patients with impaired immune system receiving a smaller recombinant immunotoxin.

A phase 3 pivotal multicenter single-arm trial (NCT01829711) was designed for relapsed/refractory HCL patients with ≥2 prior systemic therapies including ≥1 prior purine analog. Patients received moxetumomab pasudotox-tdfk 40 mcg/kg intravenously on days 1, 3, and 5 of each 28-day cycle for 6 cycles, or until MRD-negative CR, disease progression, initiation of alternate therapy, or unacceptable toxicity. Disease response and immunohistochemistry MRD status were determined by blinded independent central review. The primary endpoint was durable CR, which required achieving CR and maintaining hematologic remission (HR) for >180 days). HR was defined as hemoglobin ≥11.0 g/dL, absolute neutrophil count ≥1.5/nL, and platelet count ≥100/nL without transfusions or growth factors within the preceding 4 weeks of assessments. Eighty patients (63 males, 17 females; median age 60 years (range 34–84) were enrolled. The median number of previous systemic therapies was 3 (2–11); 48.8% of patients were purine analog refractory and 37.5% were unfit for purine analog retreatment. The median number of treatment cycles administered was 6 (1–7). As of May 24, 2017, the durable CR rate was 30.0%, 24/80 patients; 95% confidence interval (CI): 20.3, 41.3). CR rate was 41.3% (33/80 patients; 95% CI: 30.4, 52.8), and ORR was 75% (95% CI: 64.1, 84.0). Among 33 patients who achieved a CR, 27 (81.8%) also achieved MRD negativity. Median time to OR was 5.7 months (95% CI: 5.7, 5.9). Sixty-four patients (80%) achieved hematologic remission. The median duration of hematologic remission from CR, median duration of response, and PFS were not reached.

Of 64 patients treated on the phase 1 (NCT01087333) and 3 (NCT01829711) trials at NIH with 40-50 mcg/kg dose levels of moxetumomab pasudotox-tdfk and evaluated for MRD by bone marrow aspirate flow cytometry, the 30 (47%) of 64 achieved MRD-free CR.

The most frequently reported adverse events (AEs) occurring in >40% of subjects overall were hypoalbuminemia (71.4%), increased ALT (67.3%); increased AST (63.3%), lymphopenia (59.2%), myalgia (57.1%); decreased white blood cell count (51.0%); pyrexia (49.0%); peripheral edema (44.9%); and hypertriglyceridemia (40.8%).

A total of 48 phase I subjects (98%) had AEs that were assessed by the investigator as related (possibly, probably, or definitely) to investigational product. The most frequent treatment-related AEs occurring in > 20% of subjects were hypoalbuminemia (69.4%), increased ALT (63.3%), increased AST (61.2%), peripheral edema (42.9%), pyrexia (42.9%), myalgia (40.8%), headache (36.7%), nausea (32.7%), fatigue (28.6%), edema (24.5%), hypotension (24.5%), and chills (22.4%). Treatment-related grade 3/4 AEs were reported in 30.0% of patients. Three deaths were reported (due to pneumonia, sepsis, and sepsis syndrome); none were considered treatment-related by the investigators. Treatment-related AEs that most frequently led to permanent discontinuation were hemolytic uremic syndrome (HUS), capillary leak syndrome (CLS), and blood creatinine increased, reported in 4 (5.0%), 2 (2.5%), and 2 (2.5%) patients, respectively. Seven patients (8.8%) had CLS (grade 2: n=5; grade 4: n=2), 7 patients (8.8%) had HUS (grade 2: n=2; grade 3: n=3; grade 4: n=2), and 4 patients (5.0%) had both CLS and HUS. In general, CLS and HUS events were manageable and reversible with appropriate supportive care, monitoring, and, in severe events, treatment discontinuation. Grade 3-4 AEs, regardless of attribution, occurring in at least 2.5% of patients included lymphopenia (20%), hypophosphatemia or anemia (10%), leukopenia

(8.8%), hypertension, (7.5%), thrombocytopenia or neutropenia (6.3%), HUS, febrile neutropenia, or neutropenia (5%), and nausea, hypokalemia, hyponatremia, CLS, upper respiratory infection, hypoxia, lung infection, acute kidney injury, or erysipelas (2.5%). A number of eye changes have been reported in studies with moxetumomab pasudotox-tdfk; serious events including inflammation of the nerve for sight and retinal detachment have occurred in the acute lymphoblastic leukemia [14].

In this study, anti-drug antibodies were detected at baseline in 45/76 evaluable patients (59.2%). The frequency of neutralizing antibodies and anti-drug antibody titer increased with repeated cycles of treatment; reduced drug exposure was observed in patients with high-titer (>10,000) anti-drug antibodies. Patients who achieved complete or partial response typically maintained antibody titers below 10,000 and therefore maintained drug exposure for more treatment cycles than patients with stable or progressive disease, suggesting that approaches to reduce the immunogenicity of moxetumomab pasudotox-tdfk might further improve response.

In the phase 3 trial, 70 (87.5%) patients received prior rituximab, and although we do not have extramural data regarding whether rituximab was used close to the time prior to enrollment, we do know that 2 of our patients received rituximab within 6 months prior to enrollment and therefore likely had positive rituximab levels during administration of moxetumomab pasudotox-tdfk. One patient had a transient HUS-like event, and one did not, both patients achieving MRD-negative CR.

In summary, moxetumomab pasudotox-tdfk achieved a high rate of independently assessed, deep, and durable response, with ability to eradicate bone marrow MRD in heavily pretreated patients with HCL, and had a favorable safety profile, manageable and reversible CLS/HUS, and no associated myelo/immunosuppression. Both phase 1 and 3 data suggest its efficacy could be improved with addition of rituximab. Recently, US Food and Drug Administration (FDA) has accepted the Biologics License Application (BLA) for moxetumomab pasudotox-tdfk as the treatment of adult patients with HCL.

Rituximab is a genetically engineered chimeric mouse/human IgG1 anti-CD20 monoclonal antibody (mAb) approved for the treatment of non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and moderate-to-severe rheumatoid arthritis [15]. Rituximab binds to CD20 on the surface of B cells and elicits a signaling cascade resulting in cell death. It also enhances antibody dependent and complement dependent cellular toxicity. Treatment with rituximab causes depletion of CD20+ B cells in peripheral blood and tissues, thereby reducing antigen presentation and activation of T cells, autoantibody production, and cytokine production [16, 17]. Rituximab has modest single-agent activity in relapsed HCL requiring treatment due to cytopenias, with CR rate 13% and ORR 25% [18]. Rituximab has been used extensively at NCI for the treatment of HCL on two investigator sponsored trials (IST), either concurrently with the purine analogs cladribine, pentostatin or bendamustine, or in delayed fashion as a single agent for MRD clearance after cladribine. Rituximab reliably decreases circulating normal B-cells to undetectable levels for at least 6 months after the last dose. This decrease was not sufficient to block the immunogenicity of the highly immunogenic immunotoxin chemical conjugate LMB-1 in patients with solid tumors [13], but may be sufficient to block immunogenicity of the smaller recombinant immunotoxin moxetumomab pasudotox-tdfk in patients with HCL who have already compromised B-cell function and numbers.

However, access to rituximab is limited by factors such as availability, reimbursement, and

insurance coverage. Moreover, patent portfolios for rituximab have expired or are nearing the end of term, which, in turn, has prompted the development of biosimilars [19]. Rituximab biosimilars are approved by the US Food and Drug Administration (FDA) (https://www.fda.gov/drugs/fda-approves-truxima-biosimilar-rituxan-non-hodgkins-lymphoma). Ruxience was recently approved by the FDA for the treatment of non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), and granulomatosis with polyangiitis and microscopic polyangiitis (https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761103s000lbl.pdf). Ruxience has the same primary amino acid sequence as rituximab reference products [20]. Moreover, comparative studies have shown similar structural, functional, and animal toxicity profiles of Ruxience and rituximab [20]. Pharmacokinetic (PK) bioequivalence between Ruxience and rituximab-US has been demonstrated in subjects with rheumatoid arthritis [21].

Ruxience has been shown in several clinical trials to be equivalent to rituximab, including in a recent trial for follicular lymphoma in which similar CD19-positive B-cell depletion, safety, and immunogenicity between all treatment groups was demonstrated [22].

1.2.2 Rationale

Moxetumomab pasudotox-tdfk is the only known non-chemotherapy agent capable of eliminating HCL MRD in a high percentage of patients with relapse HCL, and in this patient population, elimination of MRD significantly prolongs CR duration. Of 11 participants on the phase I trial without MRD after 50 mcg/kg QODx3 of moxetumomab pasudotox-tdfk, 9 remained without MRD at 24-69 (median 42) months, suggesting that cure of this disease may be possible without chemotherapy.

Optimization of the effectiveness of moxetumomab pasudotox-tdfk, through combination with rituximab/Ruxience, may lead to more rapid and complete removal of tumor bulk and more effective tumor cell targeting of the immunotoxin, and at the same time, a decrease in immunogenicity through the action of both agents on normal B-cells.

Avoidance of chemotherapy in the treatment of HCL may prevent long term and permanent damage to stem cells and CD4+ T-cell numbers, which might, to some extent, prevent opportunistic infections and secondary malignancies. In addition, purine analog chemotherapy is associated with cumulative neurotoxicity and myelodysplastic syndrome. Except in extremely rare cases, toxicity due to rituximab/Ruxience is limited to infusion reactions which can be mostly prevented by steroids and generally resolve after the 1st or 2nd of 8 weekly doses. Our experience with the cladribine-rituximab trial is that patients with significant HCL tumor burden cannot be safely initiated with rituximab without prophylactic steroid.

If successful, this trial could potentially be used in newly diagnosed participants, since the standard of care is single-agent cladribine, which is associated with high CR rate but MRD in 76% of participants, and frequent late relapses. A chemo-free regimen capable of eliminating MRD would be a valuable goal for these participants.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Diagnosis of HCL or HCLv.

2.1.1.2 Treatment required for either 1) Absolute neutrophil count (ANC) <1/nL, 2) Hemoglobin <10g/dL, 3) Platelets<100/nL, 4) symptomatic splenomegaly, or 5) enlarging HCL mass > 2cm in short axis. Participants who have eligible blood counts within 4 weeks from the initiation of study will not be considered ineligible if subsequent blood counts prior to enrollment fluctuate and become ineligible up until the time of enrollment.

2.1.1.3 Participants must be Pseudomonas-immunotoxin naïve.

2.1.1.4 HCL or HCLv with at least 1 prior purine analog, and, for HCL participants with ≥2-years 1 month response, at least 1 other therapy.

2.1.1.5 Age ≥18 years as the disease under study, HCL/HCLv, has not been reported in children < age 18.

2.1.1.6 ECOG performance status ≤2 (Karnofsky ≥60%, see **Appendix A: Performance Status Criteria**).

2.1.1.7 Participants must have adequate organ and marrow function as defined below:

- Total bilirubin ≤ 1.5 mg/dL, unless consistent with Gilbert's (ratio between total and direct bilirubin > 5)
- AST and ALT ≤ 3x upper limit of normal (ULN)
- Alkaline phosphatase < 2.5 ULN
- Serum creatinine ≤ 1.5 mg/dL or creatinine clearance ≥ 60 mL/min by Cockcroft-Gault equation, where creatinine clearance = (140-age)(kg weight)/(72 x Creatinine)
- Serum albumin ≥ 2 g/dL
- Partial thromboplastin time (PTT) or Prothrombin time (PT)/International Normalized Ratio < 2.5x ULN (If on warfarin, PT/INR < 3.5x ULN; If on any other anticoagulation, Prothrombin time (PT) < 2.5x baseline)
- Fibrinogen ≥ 0.5 lower limit of normal

2.1.1.8 The effects of moxetumomab pasudotox-tdfk and rituximab/Ruxience on the developing human fetus are unknown therefore participants must use effective methods of contraception as directed below.

2.1.1.8.1 Females of childbearing potential (< 50 years) who are sexually active with a non-sterilized male partner must use a highly effective method of contraception prior to study entry and or the duration of study participation and must agree to continue using such precautions for 12 months after completion of rituximab/Ruxience administration. Contraception after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or those who are premenarchal or

postmenopausal (defined as 12 months with no menses without an alternative medical cause). A highly effective method of contraception is defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. Not all methods of contraception are highly effective. 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.

2.1.1.8.2 Non-sterilized males who are sexually active with a female partner of childbearing potential must use an effective method of contraception from Day 1 until 90 days after receipt of the final dose of investigational product. It is required that a female partner of a male subject also use an effective method of contraception throughout this period.

2.1.1.9 Ability of subject to understand and the willingness to sign a written informed consent document.

2.1.1.10 Participants must be willing to co-enroll in the investigator's companion protocol 10-C-0066 titled "Collection of Human Samples to Study Hairy Cell and other Leukemias, and to Develop Recombinant Immunotoxins for Cancer Treatment."

2.1.2 Exclusion Criteria

2.1.2.1 Participants who have had chemotherapy, immunotherapy or radiotherapy within 4 weeks or treatment with rituximab/Ruxience within last 3 months prior to initiation of treatment.

2.1.2.2 Participants who are receiving any other investigational agents.

2.1.2.3 Breastfeeding within the projected duration of the study, starting with the screening visit through 6 months after the last dose of rituximab/Ruxience. Pregnant women are excluded from this study because moxetumomab pasudotox-tdfk and rituximab/Ruxience are agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with moxetumomab pasudotox-tdfk and rituximab/Ruxience, breastfeeding should be discontinued if the mother is treated with moxetumomab pasudotox-tdfk and rituximab/Ruxience.

2.1.2.4 Participants with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

2.1.2.5 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, uncontrolled hypertension, uncontrolled pulmonary infection, pulmonary edema or psychiatric illness/social situations that would limit compliance with study requirements.

2.1.2.6 Participants with retinal or choroidal detachment.

2.1.2.7 Positive for Hepatitis B core antibody or surface antigen unless the participant is on Tenofovir or Entecavir and Hepatitis B Viral deoxyribonucleic acid (DNA) load is <2000 IU/mL

2.1.2.8 Active second malignancy requiring treatment other than minor resection of indolent

cancers like basal cell and squamous skin cancers.

2.1.2.9 Human immunodeficiency virus (HIV)-positive participants unless taking appropriate anti-HIV medications with a CD4 count of > 200. Otherwise, there may be an increased risk of lethal infections when temporarily suppressing normal B-cells.

2.1.2.10 History of an allogeneic bone marrow transplant.

2.1.2.11 Participants with a history of both thromboembolism and known congenital hypercoagulable conditions.

2.1.2.12 Radioimmunotherapy within 2 years prior to enrollment in the study.

2.1.2.13 Participants with history of thrombotic microangiopathy or thrombotic microangiopathy/HUS.

2.1.2.14 Participants with corrected QT interval (Frederica) elevation > 500 msec (manually over-read by medically qualified person) based on at least two separate 12-lead ECGs.

2.1.2.15 Participants on high dose estrogen (defined as > 0.625 mg/day of an estrogen compound).

2.1.2.16 Oxygen saturation at rest < 88% measured by pulse oximetry or PaO2 ≤ 55 mm Hg.

2.1.2.17 Participants with life expectancy of less than 6 months.

2.1.2.18 Participants with clinical evidence of disseminated intravascular coagulation (Grade 3-4).

2.1.2.19 Participants with < 50% of predicted forced expiratory volume (FEV1) or < 50% of predicted diffusing capacity for carbon monoxide, corrected for hemoglobin concentration and alveolar volume (DLCO). Note: Participants with no prior history of pulmonary illness are not required to have pulmonary function testing (PFT). Forced expiratory volume will be assessed after bronchodilator therapy.

2.1.3 Recruitment Strategies

Recruitment of participants from outside NIH is facilitated by multiple ongoing trials at NIH. Many participants find about NIH trials from NIH websites, such as https://clinicaltrials.gov/ or NIH social media, or from other participants through social media, and neither the PI nor the research staff interacts with these sites. The Hairy Cell Leukemia Foundation, which refers HCL and HCLv participants to trials, has an active website and is a significant source of recruitment. Finally, participants who are relapsing from NIH protocols for early HCL/HCLv may be eligible for NIH trials for relapsed HCL/HCLv.

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). See also Study Calendar in Section **3.4**.

2.2.1.1 Laboratory evaluation (needed for eligibility)

2.2.1.1.1 Within 6 months before starting drug, provided >4 weeks after chemotherapy, immunotherapy or radiotherapy prior to entering the study:

- Bone marrow biopsy (BMBx) with IHC for CD20 and CD3.

- BMBx is not needed if participants can provide test slides to be read at the Clinical Center along with reports. In case slides and reports are not available, fresh biopsy will be done.

2.2.1.1.2 Within 6 months before starting drug

- Hepatitis B (HBcAB and HBsAg), and HIV test
- CD4/CD8 (only in HIV participants)

2.2.1.1.3 Within 4 weeks before starting drug

- CBC with differential
- Chemistries including acute care panel (sodium, potassium, chloride, CO2, glucose, creatinine, and BUN), mineral panel (calcium, magnesium, phosphorus and albumin), hepatic panel (AST, ALT, total and direct bilirubin, alkaline phosphatase), total protein, creatine kinase (CK), uric acid, LDH, urinalysis, D-Dimer, Ferritin, Fibrinogen, PT/INR, PTT, amylase, lipase, GGT, IgA, IgG, IGM, CRP, TBNK, haptoglobin, Lipid panel (cholesterol, triglycerides, HDL, LDL), TSH, FT4, FT3, T4, T3,IFE.
- Flow cytometry of blood
- EKG
- History & Physical with documented performance status
- Vital signs including ambulatory oxygen saturation by pulse oximetry. Pulmonary function test (PFTs) if measuring PaO_2

2.2.1.1.4 Within 3 days before starting drug

Pregnancy test (urine or serum). Women of childbearing potential must have a negative pregnancy test

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 at: https://nih.sharepoint.com/sites/NCI-CCR-OCD-Communications/SitePages/OEC-Administrative---Clinical-Research-(ADCR).aspx?Mode=Edit.

2.3.1 Treatment Assignment Procedures

Cohort

Number	Name	Description
1	HCL/HCLv	Participants with HCL and HCLv

Arm

Number	Name	Description
1	Arm 1 – Dose escalation	Treatment with moxetumomab pasudotox-tdfk and rituximab (participants 1-13)
2	Arm 2 – Dose expansion	Treatment with moxetumomab pasudotox-tdfk and Ruxience (participants 14-26)

Arm Assignment

Participants in cohort 1 will be directly assigned to arm 1 or 2 in sequential fashion.

2.4 BASELINE EVALUATION

See also Section **3.4**, Study Calendar and Section **2.2**, Screening Evaluation

2.4.1 Within 6 months before drug

- MRI Cervical and Thoracic (C- and T-) Spine to correlate the status of the BMBx with the vertebral bone marrow aspiration (BMA) signal by MRI. May be cancelled at the discretion of the PI, including if participant unable to get MRI at NIH and not covered by insurance outside NIH.
- CT Neck-pelvis or MRI
- Abdominal Ultrasound (U/S) will be done to exclude lymph nodes potentially impacting the biliary tree
- Echo, PFTs, stress test
- BMA for FACS and PCR (if evaluable). Blood PCR should be done at the same time as BMA PCR in the CLIA certified laboratory at the Laboratory of Pathology, CCR/NCI. HLA test (May be done any time before initiation of study therapy)

2.4.2 Within 4 weeks before drug

- PaxGene RNA & DNA
- 24 hour urine for protein and creatinine clearance
- Serum tube for tumor markers and antibodies
- Peripheral blood mononuclear cells (PBMCs) in Sodium heparin tubes

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is a Phase 1 trial, two-arm, non-randomized trial involving the administration of moxetumomab pasudotox-tdfk 30-40 mcg/kg iv and rituximab/Ruxience 375 mg/m^2 iv, 50-400 mg/hr. The purpose of the rituximab/Ruxience is to decrease the HCL tumor burden, allowing the

63 kDa immunotoxin to reach all the malignant cells, thereby facilitating tumor eradication, and prevention of neutralization of the immunotoxin by the immune system, through the action of rituximab/Ruxience on normal B-cells. To allow sufficient time for the rituximab/Ruxience to act prior to moxetumomab pasudotox-tdfk, in the first cycle, rituximab/Ruxience will be given on day -2 followed by moxetumomab pasudotox-tdfk on days 1, 3 and 5. Thus on cycle 1 only, moxetumomab pasudotox-tdfk will begin on the 3rd day after rituximab/Ruxience. On subsequent cycles, spaced ~ 4 weeks (as few as 25 days) apart, rituximab/Ruxience will begin on day 1 and moxetumomab pasudotox-tdfk on days 1, 3 and 5. Participants will receive up to 4 cycles past documentation of CR without MRD, up to a maximum of 8 cycles which means, no participant in this trial will receive more than 8 cycles.

3.1.1 Schema

Cycle 1:

DAY -2	Day -1	Day 0	**DAY 1**	Day 2	**DAY 3**	Day 4	**DAY 5**	Day ≥26
Rituximab /Ruxience			**Moxetumomab pasudotox-tdfk**		**Moxetumomab pasudotox-tdfk**		**Moxetumomab pasudotox-tdfk**	(next cycle)

Cycles 2-8:

Day -2	Day -1	Day 0	**DAY 1**	Day 2	**DAY 3**	Day 4	**DAY 5**	Day ≥26
			Rituximab/Ruxience					(next cycle)
			Moxetumomab pasudotox-tdfk		**Moxetumomab pasudotox-tdfk**		**Moxetumomab pasudotox-tdfk**	

3.1.2 Dose Limiting Toxicity

Dose limiting toxicity (DLT) is defined as all treatment related Grade 3 and greater AEs occurring from the initiation of moxetumomab pasudotox-tdfk therapy to within 30 days after the last dose of moxetumomab pasudotox-tdfk treatment. For example, grade >3 cytokine release syndrome, and failure to complete cycle 1 due to toxicity is considered DLT.

Exceptions to DLT include:

- Hematologic toxicity grade 3, or grade 4 resolving within 4 weeks.
- Hematologic toxicity managed with transfusion and/or other support would not constitute DLT.
- Grade 3-4 lymphopenia, leukopenia, or CD4 reductions.
- Grade 3 gastrointestinal toxicity resolving within 72 hours.

- Transaminase and alkaline phosphates elevations grade 3 resolving within 4 weeks.
- Bilirubin elevations associated with Gilbert's syndrome, i.e. total/direct bilirubin ratio ≥4.
- Electrolyte or mineral abnormalities which are grade 3-4, resolving within 4 weeks.
- Grade 3 proteinuria, and fever
- Lipid elevations grade 3 or grade 4 resolving within 4 weeks
- Grade 3 HUS, including HUS-related grade 1-2 creatinine, will not be considered DLT if it resolves within 2 weeks to grade 0-1 creatinine, and is not associated with significant complications including bleeding or need for dialysis or plasmapheresis.
- Allergic reactions to rituximab/Ruxience prevented by desensitization.
- Dosing of both agents must be delayed for any grade 3-4 infection at least possibly related to either drug, and if not resolved despite a 4-week delay will be considered DLT requiring removal from treatment.
- Other isolated grade 3 laboratory abnormalities (not related to CLS or HUS) without clinical signs or symptoms and not associated with clinical sequalae requiring therapeutic intervention.

3.1.3 Dose Escalation

The original plan was to treat up to 10 participants at the 40 mcg/kg dose level, up to 16 total participants could have been required (including up to 10 participants at the 30 mcg/kg dose level) if there were 2 DLTs within the first 6 participants treated at the 40 mcg/kg dose. The accrual ceiling was set at 20 participants considering screen failures and/or inevaluable participants. Please refer to Section **10.2** for dose-escalation rules and below.

Initially, 3 participants were to be treated with moxetumomab pasudotox-tdfk 30 mcg/kg and rituximab 375 mg/m^2. If 0/3 had a DLT, then the next 3 participants would be treated with moxetumomab pasudotox-tdfk 40 mg/kg and rituximab 375 mg/m^2.

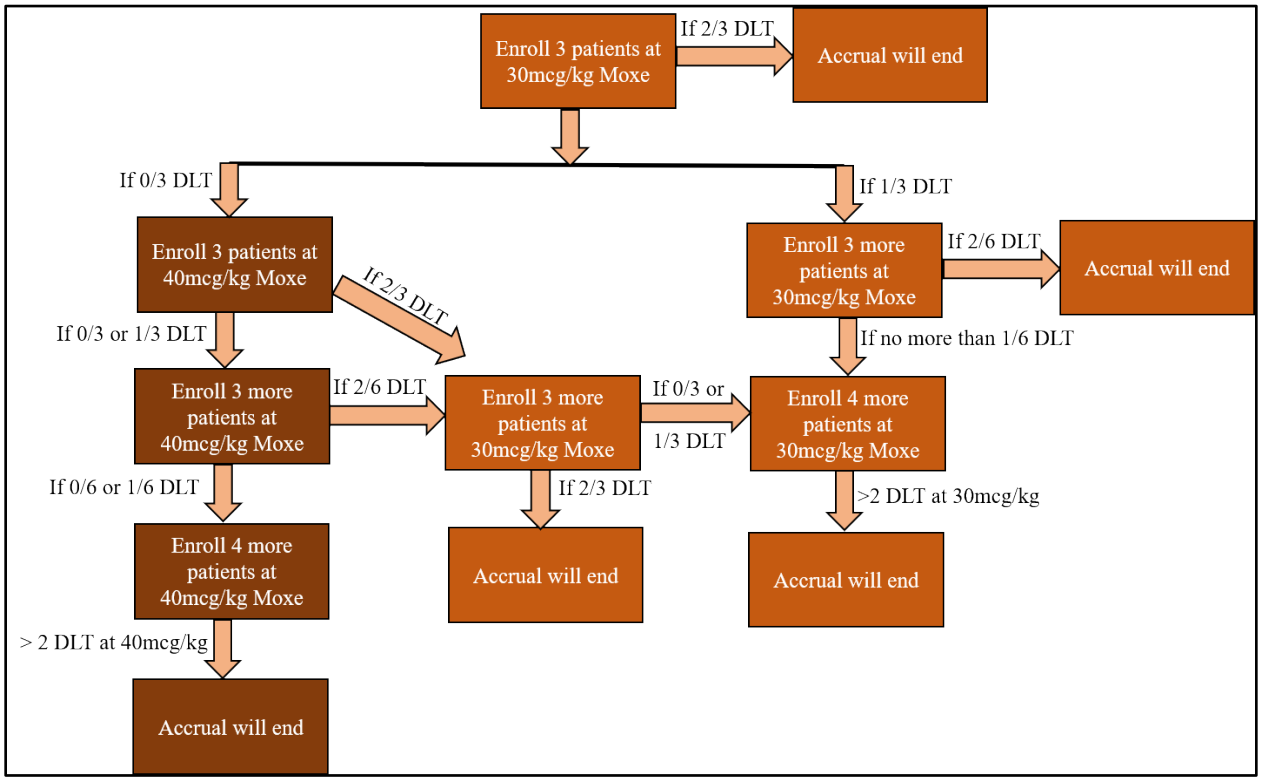
If 1/3 initial participants treated with 30 mcg/kg had a DLT, then 3 more would have been treated at 30 mcg/kg. If no more than 1 of the first 6 had a DLT, then 4 more participants were to have been enrolled at 30 mcg/kg provided that no more than a total of 2 of the 10 at the 30 mcg/kg level would have a DLT.

If participants were accrued to the 40mcg/kg level, if 0/3 or 1/3 had a DLT, then 3 more were to be treated using those dose levels. If no more than 1 of the first 6 had a DLT, then 4 more participants were to be enrolled provided that no more than 2 total of the 10 at the 40 mcg/kg level had a DLT with the exception of the types noted. If a 3rd participant had a DLT, accrual would end as soon as this is noted.

If 2 of the first 3 participants, or 2 of the first 6 participants, treated with moxetumomab pasudotox-tdfk 40 mcg/kg and rituximab 375 mg/m^2 had a DLT, then 3 additional participants were to be treated with moxetumomab pasudotox-tdfk 30 mcg/kg and rituximab 375 mg/m^2. If 0/3 or 1/3 of these next 3 had a DLT with these dose levels, then 4 more participants were to be enrolled at the 30 mcg/kg level provided that no more than 2 total of the 10 at the 30 mcg/kg level had a DLT. If 2 participants in the first 6 had a DLT at this level, then the trial would have ended accrual.

Furthermore, at any time in the 10 participants, if a 3rd participant had a DLT, accrual will also end as soon as that was noted.

3.1.3.1 Dose Escalation Schema



Though DLT will be evaluated for the duration of study therapy, the 4th and 7th evaluable participants could be enrolled after a minimum of 30 days after the previous participant received the last dose of cycle 2 or last dose of cycle 1 if the participant was not to receive a 2nd cycle.

Dose Escalation Schedule	
Dose Level	Dose of IND Agent *
Level 1	Moxetumomab pasudotox-tdfk 30 mcg/kg
Level 2	Moxetumomab pasudotox-tdfk 40 mcg/kg

3.1.4 Dose Expansion

As of 9/24/21, 12 participants were enrolled, 3 that received moxetumomab pasudotox-tdfk at 30 mcg/Kg and 9 at 40 mcg/Kg. All participants were without DLT, therefore per protocol only 1 additional eligible participant treated with moxetumomab pasudotox-tdfk at 40 mcg/Kg could be enrolled, making a total of 13 eligible participants. After these participants, to better determine safety and efficacy, an additional 13 eligible participants will be enrolled and treated with moxetumomab pasudotox-tdfk at 40 mcg/Kg in combination with Ruxience instead of rituximab.

3.2 DRUG ADMINISTRATION

3.2.1 Moxetumomab pasudotox-tdfk

Moxetumomab pasudotox-tdfk is administered at 30-40 mcg/kg intravenous (IV) over 30 min using early call back/reverse flow method (intended dose level 1). Moxetumomab pasudotox-tdfk is given on days 1, 3, and 5 of each cycle. When given on the same day as a rituximab/Ruxience infusion, the rituximab/Ruxience will be given first followed by Moxetumomab pasudotox-tdfk. Participants will receive up to 4 cycles past documentation of CR without MRD, maximum 8. To prevent renal toxicity and hypovolemia, participants will be encouraged to drink water gradually, approximately 1 cup/hour or 6L/day, and to avoid going >3 hours without drinking from days 1 to 8. To prevent rituximab/Ruxience toxicity, participants will receive prophylactic dexamethasone as indicated in Section **3.2.3**, before the 1st dose of rituximab/Ruxience, and before subsequent doses until rituximab/Ruxience infusion reactions are not seen. Diphenhydramine, famotidine, and acetaminophen may be used as needed. Dexamethasone 4 mg orally (maximum 2 doses/24 hours) will be given to treat nausea or fever associated with moxetumomab pasudotox-tdfk, which otherwise might prevent adequate water intake.

Please refer to **Appendix C** for information related to moxetumomab pasudotox-tdfk administration and preparation. Handle moxetumomab pasudotox-tdfk with caution to avoid skin and mucus membrane contact, aerosol formation, or ingestion. Monitor participants for infusion reactions, CLS, TLS, and thrombotic microangiopathy/HUS. To monitor for HUS, before every infusion, hemoglobin levels, platelet count, and serum creatinine will be checked. If HUS is suspected, blood LDH, indirect bilirubin, blood smear schistocytes for evidence of hemolysis will be promptly checked. Appropriate supportive measures will be taken, including fluid repletion and hemodynamic monitoring. Hospitalization should be considered if clinically indicated. If participants develop HUS, moxetumomab pasudotox-tdfk will be discontinued. To monitor for CLS, it is recommended that before every infusion, participants' weight and blood pressure are checked. CLS will be considered if participant's weight has increased by 5.5 pounds (2.5 kg) or ≥5% from day 1 of each cycle and the participant is hypotensive. Peripheral edema, hypoalbuminemia, and respiratory symptoms, including shortness of breath and cough, will be checked. If CLS is suspected, decrease in oxygen saturation, evidence of pulmonary edema, and/or serosal effusions will be checked. Appropriate supportive measures, including administration of concomitant corticosteroids PO or IV, will be used. Hospitalization will be considered if clinically indicated.

Vital signs will be obtained every 15 (± 10) minutes during the moxetumomab pasudotox-tdfk infusion, then every hour (±30 minutes) for an additional 4 hours during Cycle 1. During subsequent cycles, vital signs will be obtained as indicated in the **Study Calendar**. Weight, CBC + Diff, chemistries and urinalysis will be assessed prior to each infusion of moxetumomab pasudotox-tdfk.

To mitigate risk for allergic reaction and fever, participants will be premedicated with acetaminophen and famotidine, as indicated in Section **3.2.3**. Substitutions of cimetidine for famotidine is permitted. In participants experiencing infusion-related reactions, including, but not limited to pyrexia, nausea, or dyspnea, premedication with dexamethasone and/or diphenhydramine intravenous (IV) or oral may be administered at the investigator's discretion as secondary prophylaxis.

In an attempt to prevent renal insufficiency, participants will receive fluid and aspirin prophylaxis. Participants will receive low-dose aspirin orally (81 mg daily or local standard dose) on Days 1-8 of those cycles with platelet counts ≥ 100 x 10^9/L. Aspirin will be held on days where the platelet count is below 75 x 10^9/L. Participants will be hydrated (recommended over 2-4 hours) prior to the beginning of each moxetumomab pasudotox-tdfk infusion, as indicated in Section **3.2.3**. Diuresis should be considered for a > 10% increase in weight above baseline and may be most safely given during the pre-hydration liter of fluid. Participants will be encouraged to measure and record their weight daily, as well as their fluid intake during days 1-8. Participants will be provided with a hydration diary (see **Appendix D: Participant Hydration Diary**), instructed in its use, and asked to bring the diary with them at each appointment. Participants with hyperuricemia of > 10 mg/dL (> 0.59 mmol/L) prior to administration of moxetumomab pasudotox-tdfk will receive allopurinol 300 mg once daily for tumor lysis syndrome (TLS) prophylaxis. Treatment of TLS will be based on institutional guidelines. Adequate Pneumocystis carinii pneumonia (PCP) prophylaxis will be considered for participants receiving > 1 week of corticosteroids ≥ 10 mg of prednisone daily or equivalent and CD4 lymphocyte count < 0.2 x 10^9/L, or at the discretion of the investigator. Viral prophylaxis will be also considered for participants receiving chronic corticosteroids or with lymphopenia. Participants should not receive non-steroidal anti-inflammatory medications (NSAIDS), other than aspirin for prophylaxis of renal insufficiency, during the course of the study through 7 days after the last dose of moxetumomab pasudotox-tdfk. An event of ≥ Grade 2 hypercalcemia with calcium level corrected for serum albumin will require a delay in dosing until resolution to < Grade 2. If visual symptoms ≥ Grade 2 are reported, an ophthalmologic examination including slitlamp and fundoscopic evaluation is required. If a ≥ 10% increase in body weight due to fluid overload occurs, it is recommended that imaging of the chest is obtained for any evidence of pulmonary edema so appropriate treatment may be instituted promptly.
Please refer to the proper prescribing information for full details regarding toxicity as this agent has recently been FDA approved.

3.2.2 Rituximab and Ruxience

See **APPENDIX B** for Guidelines for Rituximab and Ruxience Preparation and Administration for infusion times. Briefly, rituximab/Ruxience will be given on day -2 (2 days before day 1) of Cycle 1 and on day 1 of all subsequent cycles. Rituximab/Ruxience are given at 50-400 mg/hr for the 1st dose and may be escalated to 100-400 mg/hr for subsequent doses. Premedication consisting of acetaminophen, famotidine, and diphenhydramine should be considered before each infusion of rituximab/Ruxience (see Section **3.2.3**). Since transient hypotension may occur during rituximab/Ruxience infusion, consideration should be given to withholding antihypertensive medications 12 hours before rituximab/Ruxience infusion. If a hypersensitivity (non-IgE-mediated) or an infusion reaction develops, the infusion rate should be reduced to half that rate, i.e. from 100 mg/h to 50 mg/h. Participants who experience a moderate to severe infusion related reaction (fever, chills, or hypotension) should have their infusion interrupted immediately and should receive aggressive symptomatic treatment. The infusion should not be restarted before all the symptoms have disappeared and then the infusion can continue at one-half the previous rate. Dexamethasone 12 mg PO should be given prior to rituximab/Ruxience infusions until moderate-severe infusion reactions are no longer observed.

3.2.3 Drug administration scheme

	Cycle 1 only								
Time point	**d-2**	**d1**	**d2**	**d3**	**d4**	**d5**	**d6**	**d7**	**d8**
Treatments									
Rituximab/Ruxience 375 mg/m^2	X								
Moxetumomab pasudotox-tdfk 30-40 mcg/kg		X		X		X			
Hydration									
H_2O (6 L)		X	X	X	X	X	X	X	X
Pre-hydration-5% Dextrose 0.45% NaCl (1 L)[2]		X		X		X			
Post-hydration-5% Dextrose 0.45% NaCl (1 L)[2]		X		X		X			
Premedications									
Dexamethasone (12 mg)	X								
Acetaminophen (650 mg)	X[1]	X[1]		X[1]		X[1]			
Diphenhydramine (25-50 mg)[7]	X								
Famotidine (20-40 mg)	X	X[6]		X[6]		X[6]			
Daily medication									
Aspirin (81 mg)[3]		X	X	X	X	X	X	X	X

	Cycles 2-8							
Time point	**d1**	**d2**	**d3**	**d4**	**d5**	**d6**	**d7**	**d8**
Rituximab/Ruxience	X							
Moxetumomab pasudotox-tdfk	X		X		X			
Hydration								
H_2O (6 L)	X	X	X	X	X	X	X	X
Pre-hydration-5% Dextrose 0.45% NaCl (1 L)[2]	X		X		X			
Post-hydration-5% Dextrose 0.45% NaCl (1 L)[2]	X		X		X			
Premedications								
Dexamethasone (12 mg)	X[4,5]							
Acetaminophen (650 mg)	X[1,5]		X[1]		X[1]			
Diphenhydramine (25-50 mg)[7]	X[5]							
Famotidine (20 – 40 mg)	X[6,5]		X[6]		X[6]			
Daily medication								
Aspirin (81 mg)[3]	X	X	X	X	X	X	X	X

[1] *To be given 30-90 minutes prior to every moxetumomab pasudotox-tdfk infusion and recommended every 6 hours x 4 after the end of infusion.*
[2] *0.9% Sodium Chloride Injection may be substituted for 5% Dextrose 0.45%NaCl.*
[3] *Only if platelet counts ≥ 100 x 10^9/L*
[4] *Administer 0.5-2 hours before rituximab/Ruxience. If participant has previous reaction to rituximab/Ruxience, give 12mg. If participant tolerates rituximab/Ruxience without problems, may hold at discretion of provider.*
[5] *Premedications are given prior to rituximab/Ruxience on day 1.*
[6] *Famotidine 20 – 40 mg to be given 30-90 minutes prior to every moxetumomab pasudotox-tdfk infusion and is recommended every 12 hours x 2 after the end of infusion*
[7] *May be given prior to moxetumomab pasudotox-tdfk at discretion of PI*

3.3 DOSE MODIFICATIONS

Dosing may be delayed up to 4 months for toxicity or logistical reasons, including the inability of the participant to get to the clinic. Treatment cycles need not be delayed for cytopenias but must be delayed for participants in CR presenting grade 3 cytopenia, for grade 3-4 infections and for grade 3-4 neutropenia combined with fever. Any grade >3 infection not resolving within the 4 week delay will be considered DLT.

If participants develop grade 2 CLS, dosing will be delayed until recovery of symptoms; if CLS grade ≥3 develops, moxetumomab pasudotox-tdfk will be discontinued.

Any occurrence of DLT as defined in Section **3.1.2** will result in removal from study therapy.

3.4 STUDY CALENDAR

					All cycles[22] (1 cycle=28 days)						
Procedure	**Screen/ Baseline**	**Pre-Cycle[23,32]**	**Cycle 1 Day -2[34]**	**Cycle 1 Day -1[35]**	**Days 1-5**	**Day 8**	**Day 15±3**	**EOT[1]**	**EOT + 6m[10]**	**F/U[5]**	**Restage[6]**
History & PE	X[3]	X[20]						X	X		X
Vital signs including pulse oximetry[19]	X[3]	X[20]			X[19,24]	X		X			
Performance Score	X[3]	X[20]									
CBC + Diff	X[3]	X[21]	X	X	X	X	X	X	X	X[4]	X
Weight	X	X				X					
Chemistries[11], urinalysis	X[3]	X[21]	X[36]	X[36]	X	X	X	X	X	X[12]	X
D-Dimer, Fibrinogen, Ferritin, PT/INR, PTT, amylase, lipase, GGT, IgA, IgG, IgM, CRP, haptoglobin	X[3]	X[20]	X[37]	X[37]		X[13]		X	X		X
Reticulocyte count, VWF antigen, VWF activity, PAI-1, FDP, p-selectin, thrombomodulin			X	X							
Cytokine panel 13 [33]			X	X							
Immunofixation electrophoresis (IFE) and TBNK	X	X[31]				X		X	X		X
Flow cytometry	X[3]	X[20]						X	X	X	X
EKG	X[3]	X[20]						X	X		X
Lipid panel, TSH, FT4, FT3, T4, T3, SPEP	X[3]							X	X		X
HBcAB, HBsAg, HIV test	X[7]										
Pregnancy test (females < 50 years)	X[15]										
24hr urine protein and creatinine	X[16]					X[25]					
NIH Advance Directives Form[2]	X										
CT Neck-pelvis or MRI[9]	X[7]	X						X	X		X
MRI C & T-spine[14]	X[7]	X						X	X		X

Echo, PFTs, stress test, abdominal U/S, HLA	X[7]										
Adverse Events[17]	X	X						X			
Concomitant Medications[17]	X[3]	X						X	X		
Correlative Studies[18]	(Please refer to Section **Error! Reference source not found.**)										
BMBx & BMA w/flow and PCR	X[7]	X[27]						X	X		X
Blood PCR	X	X						X[38]	X[38]		X[38]
PaxGene RNA & DNA	X[3]	X						X	X	X	X
Biomarker	X[3]	X				X		X	X	X	X
ADAs[30]	X				X[28]			X	X[29]		
PBMCs	X[3]										
Urine (renal proximal tubule cell damage)		X			X[26]	X					
PK and PK bioassay[30]					X[8]						

1. End of treatment visit will occur 28-42 days after 1st dose of last cycle.
2. All participants will be offered the opportunity to complete an NIH advance directives form (Section **12.3**). This should be done preferably at baseline but can be done at any time during the study. The completion of the form is strongly recommended but not required.
3. Within 4 weeks prior to enrollment, could be combined with pre cycle 1. Only anti-moxetumomab pasudotox-tdfk antibodies will be assessed.
4. CBC + Diff should be done every 3 months until 2.5y after EOT, then every 6 months.
5. Follow-up time points not requiring restaging are 1, 2 and 3.5 years after EOT, then every 2 years
6. Restaging requiring imaging, labs (and bone marrow if CR suspected) is 1.5 and 2.5 years after EOT, then every 2 years.
7. Within 6 months of initiation of study therapy provided within 4 weeks after last therapy. Baseline HLA may be done anytime.
8. PK and PK bioassay Time points: On days 1 and 5 of cycles 1,2,3,5,7. For cycles 1 and 2: pre, and immediately post, +/- 8 min, then 30+/-10, 60+/-15, 180+/-20,, and 360+/-50 minutes after moxetumomab pasudotox-tdfk end of infusion; On cycles 3, 5, and 7: pre and post infusion, 1-8 min; on cycles 4, 6, and 8 no PK will be drawn. Each ~6cc in K2EDTA tubes.
9. CT Neck-Pelvis is done at baseline to identify sites of disease, including spleen, and at EOT and restaging points MRI of these sites may be substituted. In asplenic participants without baseline sites of disease, MRI of the abdomen may be done at restaging time points. The entire neck to pelvis CT need not be repeated if the disease (splenomegaly) was contained within just the abdominal or abdominal-pelvis levels of the CT. Pre-cycle scans will only be performed if participant is being restaged.
10. Deviations on post-EOT time points may be +/- 2 months until 2.5 years and +/- 4 months thereafter.
11. Chemistries includes sodium, potassium, chloride, bicarbonate, creatinine, glucose, blood urea nitrogen (BUN), albumin, calcium, magnesium, phosphorus, AST (SGPT), ALT (SGOT), total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), total protein, alkaline phosphatase, creatine kinase (CK or CPK), and uric acid. Except on day 15. Day 15 only acute care panel along with CBC with c diff and urine analysis will be required.
12. Optional when not performed at NIH
13. +/- 1 day,

14. To be done at bone marrow time points, to correlate the status of the BMBx with the vertebral BMA signal by MRI. May be cancelled at the discretion of the PI, including if participant unable to get MRI at NIH and not covered by insurance outside NIH.
15. This test will be conducted within 3 days prior to enrollment
16. Performed within 4 weeks before initiation of study therapy.
17. Adverse events and concomitant medications will be monitored continuously in every visit.
18. Samples collected during the course of this study will be stored, tracked, and disposed of as specified in investigator's companion protocol, 10C0066, on which all participants will be co-enrolled.
19. During the moxetumomab pasudotox-tdfk infusion, vital signs will be obtained every 15 (±10) minutes, then every hour (±30 minutes) for an additional 4 hours during Cycle 1. During subsequent cycles, vital signs will be obtained every 15 (±5) minutes during the moxetumomab pasudotox-tdfk infusion, then every hour (±30 minutes) for an additional 2 hours. Vital signs will also be obtained on Day 8 ± 1 day for the first 3 dosing cycles.
20. May be done up to 3 days prior to day 1 of cycle.
21. Must be done on day 1 of cycle 1 prior to treatment.
22. Cycle interval may be shortened to 25-27 days due to logistical reasons.
23. Pre-cycle tests may be done 0 to 2 days before and maybe combined with either baseline for cycle 1 or day 1 or both.
24. During rituximab/Ruxience infusion on cycle 1 day -2 vital signs will be obtained with every dose change and as needed.
25. Must be completed on day 8 but may be cancelled at PI discretion.
26. Pre-cycle and pretreatment on days 3, 5, and 8.
27. Pre-cycle bone marrow and scans to be done at the discretion of the PI based on the participants HR status.
28. Sampling pre-dose before cycles 1,2,3,5, and 7.
29. Sampling at 3 and 6 months after the end of treatment evaluation.
30. Sampling in case HUS or CLS are observed.
31. Cycle 1 IFE to be done pre cycle may be combined with baseline labs +/- 1-4 days and again pre moxetumomab pasudotox-tdfk on Cycle 1 day1.
32. Screening labs can be combined with pre cycle 1 labs if done within 5 days of day -2 with the exception of the labs listed as day -2 labs
33. Pre-rituximab/Ruxience and 6-8 hours post-rituximab/Ruxience. It includes: Tumor Necrosis Factor-alpha, interleukin 2, interleukin 2 receptor soluble, interleukin 12, interferon gamma, interleukin 4, interleukin 5, interleukin 10, interleukin 13, interleukin 17, interleukin 1 beta, interleukin 6, and interleukin 8.
34. Day -2 pre Rituxan and 6-8 hours after the start of Rituxan.
35. AM of day -1
36. LDH only
37. D-dimer and haptoglobin only
38. Optional

3.5 COST AND COMPENSATION

3.5.1 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 are performed outside the NIH Clinical Center, participants may have to pay for these costs.

3.5.2 Compensation

Participants will not be compensated on this study.

3.5.3 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.

3.6 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from the study, effort must be made to have all participants complete a safety visit approximately 28-42 days following the last dose of study therapy.

3.6.1 Criteria for removal from protocol therapy

- Completion of study therapy
- Progressive disease or DLT
- HUS
- Unacceptable toxicities as described on Sections **3.1.2** and **3.3**.
- Intercurrent illness or medical circumstances, including uncontrolled infection at the discretion of the primary investigator
- Radiation therapy or other treatment for HCL other than splenectomy
- Voluntary withdrawal from the treatment regimen
- PI determines further treatment on this study is not in participant's best interest
- Participants who are off-treatment but still on-study will be followed as per the schedule in Section **3.4**, until they begin alternative therapy or voluntarily withdrawal from follow-up testing. Thereafter, they may be followed on-study for survival and other secondary endpoints.
- Positive pregnancy test

3.6.2 Off-Study Criteria

- Voluntary participant withdrawal from the study
- Death

- Non-compliance with study treatment and/or testing, or lost to follow-up, at discretion of PI.

The reason for removing participants from study will be documented in the medical record.

4 CONCOMITANT MEDICATIONS/MEASURES

- Prophylactic measures for renal toxicity, hypvolemia, rituximab/Ruxience toxicity and nausea and vomiting will be administered as described in Section **3.1.4**.
- Febrile Neutropenia, which is common in participants before responding to treatment, may require empiric antibiotics, either as an inpatient or outpatient. Hematopoietic growth factors may be used if clinically indicated, for example, if grade 3-4 neutropenia is associated with suspected infection. Fever is also common with rituximab/Ruxience and may be treated symptomatically and with interrupting or with decreasing the infusion rate.
- Symptomatic anemia should be treated with appropriate red blood cell support. Transfusion is generally recommended if the hemoglobin falls below 7g/dL. Platelets are generally given when the platelet count is < 8,000/mm^3 or when there is bleeding.
- Participants receiving rituximab/Ruxience, particularly those with high concentrations of circulating malignant cells, commonly have infusional toxicities including fever, chills, nausea and vomiting, dyspnea, hypotension, and palpitations. Infusional reactions with rituximab/Ruxience have been observed in HCL as well as other malignancies and are best managed by slowing or interrupting the rate of infusion.
- Additional toxicities that may arise will be managed per current evidence-based practice guidelines in consultation with a medically responsible investigator if available.
- Concurrent chemotherapy, radiotherapy, immunotherapy, and biologic therapies for treatment of HCL during the study are not permitted.
- Use of steroids is not routinely recommended to prevent CLS or fever from moxetumomab pasudotox-tdfk; however, secondary prophylaxis for infusion-related reactions with dexamethasone IV or oral may be administered at the investigator's discretion.
- Participants will be informed that NSAIDs (except aspirin) should not be taken from the first dose of the cycle through 7 days after the last dose of the cycle.

5 CORRELATIVE STUDIES FOR RESEARCH

5.1 BIOSPECIMEN COLLECTION

5.1.1 Sample Collection Table

Test/assay	Vol	Tube[a] & Storage	Timing	Location of specimen analysis[b]
Blood Flow cytometry using TBNK assay	18 cc	3 Na-heparin Room temp	Per **Study Calendar**	Flow Lab B1B58
BMA flow cytometry	2-5 cc	2 Na-heparin Room temp		Flow Lab B1B58 & Kreitman Lab
Blood PaxGene	2-3 cc	RNA & DNA tubes, Room temp		Biospecimen Processing Core (BPC)
Serum for biomarkers	2-3 cc	1 SST (red top) -20°C or colder		Kreitman Lab
Anti-drug antibodies (ADAs)	2 cc	Na-heparin (green top) -20°C or colder		BPC
Urine to test for renal proximal tubule cell damage	2 cc	1 Urine yellow conical 8ml 4°C		
PK	2 cc	1 K_2-EDTA (lavender top) -20°C or colder		
PK bioassay	4 cc	Na-heparin (green top) -20°C or colder		
Blood PBMC	25 cc	5 Na-heparin Room temp	Baseline	

a. Tubes and media may be substituted based on availability with the permission of the PI or laboratory investigator
b. The location of specimen analysis may be adjusted at the time the analyses are performed with the permission of the PI or laboratory investigator

Note: *Samples collected during the course of this study will be stored, tracked, and disposed of as specified in investigator's companion protocol, 10-C-0066, on which all participants will be co-enrolled.*

5.1.2 Biospecimen Sharing on Protocol

We may review the participant's NIH medical records to obtain results of procedures conducted under another protocol in order to minimize repeating procedures/tests.

We may obtain existing identifiable research data and/or biospecimens collected under protocol # 10-C-0066 titled "*Collection of Human Samples to Study Hairy Cell and other Leukemias, and to*

Develop Recombinant Immunotoxins for Cancer Treatment" to minimize repeating procedures/tests.

We may share identifiable research data and/or biospecimens with protocol # 10-C-0066 titled "*Collection of Human Samples to Study Hairy Cell and other Leukemias, and to Develop Recombinant Immunotoxins for Cancer Treatment*" to which participants are co-enrolled, in order to minimize repeating procedures/tests.

5.2 PLANNED ANALYSES

Note: Platforms and procedures may be adjusted based upon current technology and/or collaborations in place at the time of actual analyses.

5.2.1 PK of Moxetumomab Pasudotox-tdfk

Concentrations of moxetumomab pasudotox-tdfk will be measured using a validated assay. The PK assay is a sandwich ELISA, where moxetumomab pasudotox-tdfk present in K2EDTA plasma is captured on ELISA plates coated with anti-idiotypic mAb against the CD22-binding domain of moxetumomab pasudotox-tdfk (clone G09.4) and detected with biotinylated monoclonal antibody that binds to the PE38 portion of moxetumomab pasudotox-tdfk (IP-49), followed by addition of streptavidin HRP conjugate and TMB substrate. The color intensity (absorbance measured at 450 nm with wavelength correction set to 650 nm) is proportional to the quantity of moxetumomab pasudotox-tdfk) is measured using the Spectramax plate reader (Molecular Devices, Sunnyvale, CA, US). Concentrations of moxetumomab pasudotox-tdfk in controls and clinical samples are interpolated from the standard curve constructed from moxetumomab pasudotox-tdfk spiked into K2EDTA plasma. If a participant develops any grade of HUS or CLS, or has an ocular event with new abnormality by ophthalmologic examination during study treatment, samples for immunogenicity evaluation will be collected within 24 hours of diagnosis, during the event as clinically indicated (e.g., in order to capture peak intensity of the event, as well as at least one timepoint during the period of improvement), and after resolution of the event.

Draw maximum volume of blood into 2.0 mL of potassium (K2) EDTA (lavender-top-tube) from a separate in-dwelling line that is not used for drug administration.

Tubes will be gently inverted 8-10 times to assure adequate mixing with the anticoagulant within 2 hours after collection. Centrifuge within 2 hours of collection for 10 min at 1100-1300 x g to generate plasma. Transfer plasma into the cryovials and immediately freeze the cryovials upright at -20°C or colder. The procedures for the handling of PK samples will be further detailed in a separate Lab Manual.

5.2.2 Evaluation of Immunogenicity

Presence of antidrug antibodies (ADA) against moxetumomab pasudotox-tdfk will be assessed in samples taken from all participants prior to the start of Cycles 1, 2, 3, 5and 7 and at the end of treatment and 3 and 6 months after the last dose. A validated moxetumomab pasudotox-tdfk specific bridging immunoassay using the Meso Scale Discovery platform will be employed to detect anti-drug antibodies. Positive-negative cut points will be used for detecting the presence of ADA. The cut points will be established by statistical evaluation of drug naive validation samples. Due to pre-existing antibodies, cross-reactive with PE38 domain of moxetumomab pasudotox-tdfk, in drug naïve human samples, cut point establishment will be done using pseudo-negative

samples where pre-existing signals will be inhibited by drug. Samples determined positive in the ADA bridging assay will subsequently be evaluated in a cell-based neutralization assay. This assay identifies neutralizing ADA (NAb), which has the ability to block moxetumomab pasudotox-tdfk-induced cytotoxicity of the B-cell lymphoma line Raji (ATCC, Manassas, VA) as assessed by adenosine triphosphate production in the cells. Titer levels and the domain specificity of ADAs (anti-CD22-binding domain or anti-PE38 domain) will be determined for participants with positive neutralizing anti-drug antibodies (NAb) and may be determined in participants with negative NAb.

If a participant develops any grade of HUS or CLS, or has an ocular event with new abnormality by ophthalmologic examination during study treatment, samples for immunogenicity evaluation will be collected within 24 hours of diagnosis, during the event as clinically indicated (eg, in order to capture peak intensity of the event, as well as at least one timepoint during the period of improvement), and after resolution of the event.

At each sample collection time, draw maximum volume of blood (4.0 mL) in sodium heparin tube. Immediately after collection, the tube will be gently inverted 8 to 10 times to mix the anticoagulant with the blood sample collected. Centrifuge blood within 2 hours of collection. Centrifuge for 10 min at 1100-1300 x g. Transfer plasma into cryovials and immediately freeze the cryovials upright at -20°C or colder. The procedures for the handling of immunogenicity samples will be further detailed in a separate Lab Manual.

5.3 Storage, Use, and Sharing of Specimens and Data (Including for Secondary Research)

5.3.1 Sample Tracking and Processing

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.

5.3.1.1 Biospecimen Processing Core (BPC)

Please email NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main BPC number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact NCIBloodcore@mail.nih.gov.

5.3.2 Sample Storage and Disposition

Barcoded samples are stored in barcoded boxes according to stability requirements. Access to stored clinical samples is restricted. Unless other permission obtained, samples are only to be used for research purposes associated with this trial (as per the IRB-approved protocol) by investigators named on the protocol. It is the responsibility of the Principal Investigator to ensure that samples are being used in a manner consistent with IRB approval.

Sample barcodes are linked to participant demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of a

sample tracking database (e.g., Labmatrix). It is critical that the sample remains linked to participant information such as race, age, dates of diagnosis and death, and histological information about the tumor, to correlate results with sample characteristics.

5.3.3 Protocol Completion/Secondary Use/Sample Destruction

Any specimens remaining at the completion of the protocol will be stored indefinitely in the conditions described above. The study will remain open so long as sample or data analysis continues. All samples and data from consenting participants will be stored in identifiable format until they are no longer of scientific value or if a participant withdraws consent for their continued use, at which time they will be destroyed.

If, at any time, a participant withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed or returned to the participant, if so requested. The participant's samples and data will be excluded from future distributions, but those which 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 of Section **7.2**.

With the permission of the participant, specimens and data collected on this study, identifiable through a code available to the study team, will be stored indefinitely and used for secondary research, including genetic research. Furthermore, the data and/or specimens, may be shared with other investigators in identifiable or coded (code key not available to recipient) format for secondary research. Any investigator conducting secondary research in human subjects will seek either additional regulatory approval or exemption for research as appropriate.

Data will also be shared in public database per the study's data sharing plan in compliance with NIH policies.

In addition, specimens/data may be anonymized and further research, including genetic research, conducted at the site or other institutions without participant consent. Participants will be informed that the possibility for this type of research exists.

5.4 SAMPLES FOR GENETIC/GENOMIC ANALYSIS

5.4.1 Description of the scope of genetic/genomic analysis

Identification and prioritization of specific metastatic sites for further analysis will be made by the investigator after taking into account various factors including the prior rate of growth of disease, response to treatment and tumor fraction in the available sample. DNA and RNA will be extracted from tumor samples and germ line DNA and RNA will be extracted from PBMCs from whole blood for molecular genetic testing using Pax-gene as specified in investigator's companion protocol, 10-C-0066.

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

- As part of study efforts to provide confidentiality of participant information, this study will obtain a Certificate of Confidentiality which helps to protect personally identifiable research information. The Certificate of Confidentiality allows investigators on this trial to refuse to disclose identifying information related to the research participants, should such disclosure have adverse consequences for participants or damage their financial standing, employability, insurability or reputation. The informed consent includes the appropriate coverage and restrictions of the Certificate of Confidentiality.
- Tissue and blood samples collected will be coded. DNA, RNA and protein isolated from these tissues and cell lines and xenografts generated will all be similarly coded. Only personnel involved in this study will have access to both the code and the name of the participant as specified in investigator's companion protocol, 10C0066.
- To help protect the privacy, investigators will obtain a Certificate of Confidentiality from the National Institute of Health. With this certificate, investigators cannot be forced to disclose information that may identify the participant or immediate family members, even by a court subpoena, in any federal, state, or local civil, criminal administrative, legislative or other proceedings. The researchers will use this Certificate of Confidentiality to resist any demands for information that would identify the participant or immediate family members. However, the Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the Food and Drug Administration (FDA).
- To facilitate genetic research, and for the purpose of publication of research work, data from genomic and proteomic studies may be deposited in appropriate public databases. Coded data will be deposited in a manner that the participant's identity cannot be traced.

5.4.3 Management of Results

Subjects will be contacted if a clinically actionable gene variant is discovered. Clinically actionable findings for the purpose of 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.

Subjects will be contacted at this time 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 (at our expense) to have genetic education and counseling to explain this result. 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.

5.4.4 Genetic Counseling

The costs of CLIA testing will be paid for by the Center for Cancer Research, the Branch, or the Principal Investigator. If the health history, family history, or tumor diagnosis from the Laboratory of Pathology at the NIH Clinical Center suggests that the participant might benefit from genetic testing, we will discuss this with him/her.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data a 21 CFR Part 11-compliant data capture system provided by the NCI CCR 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, Study Day 1, through the end of treatment. After 30 days, only adverse events which are serious and related to the study intervention need to be recorded.

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 participant's outcome.

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

6.2 DATA ELEMENTS

6.2.1 Human Data Sharing Plan

- Documentation of dosage and timing of drug administration
- Outside laboratory, radiologic, and pathology results will be sent to the PI and entered into NCI C3D at NIH
- NIH labs and tests will be downloaded into C3D

- A pre-existing (baseline) laboratory abnormality will be considered the last one obtained prior to the first dose of drug, unless the PI considers an abnormality of higher grade occurring within 100 days prior to the first dose to be a truer baseline.

6.3 DATA SHARING PLANS

6.3.1 Human Data Sharing Plan

What data will be shared?

Human data generated in this research will be shared for future research as follows:

- Coded, linked data in an NIH-funded or approved public repository.
- Coded, linked data in BTRIS (automatic for activities in the Clinical Center)
- Identified or coded, linked with approved outside collaborators under appropriate agreements.

How and where will the data be shared?

Data will be shared through:

- An NIH-funded or approved public repository: clinicaltrials.gov, and dbGaP
- BTRIS (automatic for activities in the Clinical Center)
- Approved outside collaborators under appropriate individual agreements.
- Publication and/or public presentations.

When will the data be shared?

- Before publication.
- At the time of publication or shortly thereafter.

6.3.2 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.

6.4 RESPONSE CRITERIA

6.4.1 Rules for response assessment

- No G-CSF or GM-CSF at least 4 weeks before major response (i.e. partial response or complete response).
- No transfusions at least 4 weeks before major response.
- Hgb requirement for major response may be dropped if iron stores (ferritin or iron saturation) are low

6.4.2 Complete remission (CR)

All of the following:

- Absolute neutrophil count (ANC) $\geq 1500/mm^3$
- Platelets $\geq 100{,}000/mm^3$

- Hgb ≥ 11 g/dL
- Regression of splenomegaly on physical exam or by imaging studies.
- Lymph nodes ≤ 2 cm by short axis, unless larger lymph nodes not due to HCL
- Absence of hairy cells on BM aspirate smears and H/E stain of the BM biopsy negative for HCL. If the negative BM is before 4 weeks off of growth factors or transfusions, the CR will begin after the 4 week time point once the normal blood counts are consistent with CR.
- CR with MRD in the BMBx by IHC is defined as CR and a ratio of CD20+ cells to T cells of at least 1, and most of the CD20+ cells consistent with HCL.
- CR with MRD in the peripheral blood is defined as CR and a positive peripheral blood FACS or PCR. Suspicious flow is considered positive per protocol.
- Participants meeting all criteria for CR except minimum levels of ANC, platelets and Hgb will be considered CR if MRD is absent by BMBx IHC and by flow cytometry of blood and bone marrow.

6.4.3 Partial Response (PR)

All of the following for at least 4 weeks

- Normal blood counts consistent with CR
- ≥ 50% reduction in sum of products of perpendicular diameters or decrease to ≤ 2 cm in evaluable (> 2cm) lymphadenopathy
- ≥ 50% reduction in extent of spleen below costal margin by imaging or physical exam, if abnormal at baseline
- ≥50% reduction in BM infiltration on biopsy

6.4.4 Progressive disease (PD)

Any of the following

- An increase in symptoms or ≥25% decline in hematologic parameters related to disease, based on the judgement of the PI
- ≥50% increase in sum of products of perpendicular diameters of evaluable (> 2cm) lymphadenopathy or appearance of new evaluable lymph nodes > 2 cm short axis
- ≥50% increase in extent of spleen below costal margin by imaging or physical exam

6.4.5 Stable disease (SD)

None of the above

6.5 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each participant while on the study. 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).

7 NIH REPORTING REQUIREMENTS / DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

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 found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements. Note: Only IND Safety Reports that meet the definition of an unanticipated problem or present new information that might affect the willingness of participants to enroll or remain on the study will need to be reported per these policies.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reviewed by the OHSRP in the NIH eIRB system will also be reported to the NCI Clinical Director/designee; therefore, a separate submission for these reports is not necessary.

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

To report these deaths, please send an email describing the circumstances of the death to 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 on a weekly basis when participants are being actively treated on the trial to discuss each participant. Decisions about dose level enrollment and dose de-escalation if applicable will be made based on the toxicity data from prior participants.

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 participant 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.

7.4.2 Safety Monitoring Committee (SMC) - CCR

This protocol will require oversight from the Safety Monitoring Committee (SMC). Initial review will occur as soon as possible after the annual NIH Intramural IRB continuing review date. Subsequently, each protocol will be reviewed as close to annually as the quarterly meeting schedule permits or more frequently as may be required by the SMC. For initial and subsequent reviews, protocols will not be reviewed if there is no accrual within the review period.

The SMC will operate under the rules of an approved charter that will be written and reviewed at the organization meeting of the SMC. Each review will focus on unexpected protocol-specific safety issues that are identified during the conduct of the clinical trial.

Written outcome letters will be generated in response to the monitoring activities and submitted to the Principal Investigator and Clinical Director or Deputy Clinical Director, CCR, NCI.

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 (SAE)

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 Section **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 or subject 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 (see Section **8.4.4**) 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 (return to baseline or stabilization) 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.

SAEs 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.

8.3 REPORTING OF SERIOUS ADVERSE EVENTS

Any AE that meets a protocol-defined serious criteria that require expedited reporting must be submitted immediately (within 24 hours of awareness) to OSRO Safety using the CCR SAE report form.

All SAE reporting must include the elements described in Section **8.4.4**.

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://nih.sharepoint.com/:u:/r/sites/NCI-CCR-OCD-Communications/SitePages/Forms-and-Instructions.aspx?csf=1&web=1&e=uWBXtI.

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 SAFETY REPORTING CRITERIA TO ASTRAZENECA(AZ)

8.4.1 Reporting to AZ by CCR Safety

8.4.1.1 Serious Adverse Events

All SAEs have to be reported to AZ, whether or not considered causally related to the investigational product. All SAEs will be documented. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

A copy of the MedWatch/AdEERs report must be faxed or emailed to AZ within 1 business day of PI awareness of the event. It is the responsibility of the investigator to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AZ at the same time.

8.4.1.2 Deaths

Deaths that occur during the study, or within the protocol defined 30day poststudy followup period after the administration of the last dose of study treatment, must be reported to AZ as follows:

- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the study monitor as a SAE within **24 hours of** PI awareness of the event. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. This information can be captured in the ‘‘SAE report”.

- Deaths with an unknown cause should always be reported as a SAE. A post mortem maybe helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be forwarded to AZ within one business day of learning of the death.

8.4.1.3 Details for expedited reporting to AZ

***** A **cover page** should accompany the **MedWatch/AdEERs** form indicating the following:

- External Scientific Research (ESR)
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and protocol reference number

***** Investigative site must also indicate, either in the SAE report or the cover page, the **causality** of events **in relation to all study medications** and if the SAE is **related to disease progression**, as determined by the principal investigator.

*** Send SAE report and accompanying cover page by way of Email to:**
AEMailboxClinicalTrialTCS@astrazeneca.com

8.4.2 Reporting to AZ by the Study Team

8.4.2.1 Overdose

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an AE unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the appropriate CRF.

All AEs associated with an overdose or incorrect administration of study drug should be recorded on the CRF. If the associated AE fulfills serious criteria, the event should be reported to AZ per contractual guidelines. The Sponsor should report any SAEs to the IRB and Regulatory Authorities per institutional and/or regulatory guidelines, and to AZ per the CRADA.

For other overdoses, reporting should be done within 30 days.

In the event of administration of more than the recommended dosage, observation for any symptomatic side effects should be instituted, and vital signs, biochemical and hematologic parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated.

8.4.3 Aggregated Reporting

All aggregated reporting will be done by study team/investigator on a monthly basis and under no circumstance less frequently than quarterly.

8.4.3.1 Reporting of Adverse Events (AEs) after the 30-day follow up period

At any time after a patient has completed the study therapy, if an Investigator learns of any SAE including sudden death of unknown cause, and he/she considers there is a reasonable possibility that the event is causally related to the investigational product, the investigator should notify AZ.

If patients who are gaining clinical benefit are allowed to continue study treatment post data cut off and/or post study completion, then all SAEs must continue to be collected and reported to Patient Safety within the usual timeframe.

Otherwise, after study treatment completion (i.e., after any scheduled post treatment follow-up period has ended) there is no obligation to actively report information on new AEs or SAEs occurring in former study patients. This includes new AEs/SAEs in patients still being followed up for survival but who have completed the post treatment follow up period (30 days).

8.4.3.2 Reporting of Adverse events (AEs)

AEs for new primary malignant tumors reported during a study should generally be assessed as serious AEs. If no other seriousness criteria apply, the 'important medical event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the primary malignant tumor event should be assessed and reported as a non-serious AE. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples include Stage I basal cell carcinoma and Stage IA1 cervical cancer removed via cone biopsy.

Non-serious adverse events and SAEs will be collected from the time consent is given, throughout the treatment period and up to and including the *30-day follow-up* period. After withdrawal from treatment, subjects must be followed up for all existing and new AEs for *30 calendar days after the last dose of trial drug and/or until event resolution.* All new AEs occurring during that period must be recorded (if SAEs, then they must be reported as indicated in Sections **8.3** and **8.4.1**). All study-related toxicities/ SAEs must be followed until resolution, unless in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease.

8.4.4 Requirements of adverse events (AEs) reporting

The following variables will be collected for each AE:

AE (verbatim)

- The date and time when the AE started and stopped
- Select the appropriate if needed: maximum intensity or intensity or changes in intensity
- Changes in NCI CTCAE grade and the maximum CTC grade attained
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no) comparator/combination drug (yes/no)
- Action taken with regard to investigational product/comparator/combination agent
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE

- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Description of AE
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to other medication
- Causality assessment in relation to Additional Study Drug

Send reports and accompanying cover page by way of Email to:

AEMailboxClinicalTrialTCS@astrazeneca.com

8.5 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://nih.sharepoint.com/:u:/r/sites/NCI-CCR-OCD-Communications/SitePages/Forms-and-Instructions.aspx?csf=1&web=1&e=uWBXtI.

8.5.1 Maternal Exposure

If a participant becomes pregnant during the course of the study or until 12 months after the last dose of Moxetumomab pasudotox-tdfk and rituximab/Ruxience, 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 (see Section **8.1.2**) should be reported as SAEs.

The outcome of all pregnancies from the date of the first dose of study therapy until 12 months after the last dose of study therapy should be followed up and documented.

8.5.2 Paternal Exposure

Male participants should refrain from fathering a child or donating sperm during the study and for 90 days after the last dose of Moxetumomab pasudotox-tdfk and rituximab/Ruxience.

Pregnancy of the participant's partner is not considered to be an AE. The outcome of all pregnancies occurring from the date of the first dose until 90 days after the last dose should, if possible, be followed up and documented. Pregnant partners may be offered the opportunity to participate in an institutional pregnancy registry protocol (e.g., the NIH IRP pregnancy registry study) to provide data about the outcome of the pregnancy for safety reporting purposes.

8.6 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.

8.7 Sponsor Protocol Deviation Reporting

A Protocol Deviation is defined as any non-compliance with the clinical trial Protocol, Manual of Operational Procedures (MOP) and other Sponsor approved study related documents, GCP, or protocol-specific procedural requirements on the part of the participant, the Investigator, or the study site staff inclusive of site personnel performing procedures or providing services in support of the clinical trial.

It is the responsibility of the study Staff to document any protocol deviation identified by the Staff or the site Monitor in the CCR Protocol Deviation Tracking System (PDTS) online application. The entries into the PDTS online application should be timely, complete, and maintained per CCR PDTS user requirements.

In addition, any deviation to the protocol should be documented in the participant's source records and reported to the reviewing IRB per their guidelines. OSRO required protocol deviation reporting is consistent with E6(R2) GCP: Integrated Addendum to ICH E6(R1): 4.5 Compliance with Protocol; 5.18.3 (a), and 5.20 Noncompliance; and ICH E3 16.2.2 Protocol deviations.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure:

- that the rights of the participants are protected;
- that the study is implemented per the approved protocol, Good Clinical Practice and standard operating procedures; and,
- the quality and integrity of study data and data collection methods are maintained.

Monitoring for this study will be performed by NCI CCR Office of Sponsor and Regulatory Oversight (OSRO) Sponsor and Regulatory Oversight Support (SROS) Services contractor. Clinical site monitoring activities will be based on OSRO standards, FDA Guidance E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) March 2018, and applicable regulatory requirements.

Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP) developed by OSRO. CMPs will be protocol-specific, risk-based and tailored to address human subject protections and integrity of the study data. OSRO will determine the intensity and frequency of monitoring based on several factors, including study type, phase, risk, complexity, expected enrollment rate, and any unique attributes of the study and the site. The Sponsor will conduct a periodic review of the CMP to confirm the plan's continued appropriateness. A change

to the protocol, significant or pervasive non-compliance with GCP, or the protocol may trigger CMP updates.

OSRO SROS Monitoring visits and related activities will be conducted throughout the life cycle of each protocol. The first activity is before the study starts to conduct a Site Assessment Visit (SAV) (as warranted), followed by a Site Initiation Visit (SIV), Interim Monitoring Visit(s) (IMVs), and a study Close-Out Visit (COV).

Some monitoring activities may be performed remotely, while others will occur at the study site(s). Monitoring visit reports will describe visit activities, observations, and associated action items or follow-up required for resolution of any issues, discrepancies, or deviations. Monitoring reports will be distributed to the study PI, NCI CCR QA, CCR Protocol Support Office, coordinating center (if applicable), and the Sponsor regulatory file.

The site Monitor will inform the study team of any deviations observed during monitoring visits. If unresolved, the Monitor will request that the site Staff enter the deviations in the CCR Protocol Deviation Tracking System (PDTS) for deviation reporting to the Sponsor and as applicable per institutional and IRB guidance.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL HYPOTHESIS

Moxetumomab pasudotox-tdfk may be combined with rituximab/Ruxience safely in participants with relapsed/refractory HCL.

- Primary Endpoint(s): To determine the safety and toxicity of moxetumomab pasudotox-tdfk and rituximab/Ruxience treated at the planned dose level, in participants with HCL and HCLv.
- Secondary Endpoints:
    - To determine the minimal residual disease (MRD)-free CR rate of the study drug combination is higher than that achieved with 40-50 mcg/kg dose levels of Moxetumomab pasudotox-tdfk alone.
    - To determine response rate and duration of response.

10.2 SAMPLE SIZE DETERMINATION

- The initial sample size determination: Up to 10 participants are intended to be treated in the trial using the following plan; if a different dose of moxetumomab pasudotox-tdfk is required, up to 16 participants will be needed to be enrolled.

  Initially, 3 participants will be treated with moxetumomab pasudotox-tdfk 30 mcg/kg and rituximab 375 mg/m^2. If 0/3 have a DLT, then the next 3 participants will be treated with moxetumomab pasudotox-tdfk 40 mg/kg and rituximab 375 mg/m^2.

  If 1/3 initial participants treated with 30 mcg/kg have a DLT, then 3 more will be treated at 30 mcg/kg. If no more than 1 of the first 6 have a DLT, then 4 more participants will be enrolled at 30 mcg/kg provided that no more than a total of 2 of the 10 have a DLT with the exception

of the types noted. The upper one-sided 90% confidence bound on 2/10 is 45.0%. if a 3rd participant has a DLT, accrual will end as soon as this is noted.

If participants are accrued to the 40mcg/kg level, if 0/3 or 1/3 have a DLT (with the exception of the types noted), then 3 more will be treated using those dose levels. If no more than 1 of the first 6 have a DLT, then 4 more participants will be enrolled provided that no more than 2 total of the 10 have a DLT. The upper one-sided 90% confidence bound on 2/10 is 45.0%. if a 3rd participant has a DLT, accrual will end as soon as this is noted.

If 2 of the first 3 participants, or 2 of the first 6 participants, treated with moxetumomab pasudotox-tdfk 40 mcg/kg and rituximab 375 mg/m^2 have a DLT, then 3 additional participants will be treated with moxetumomab pasudotox-tdfk 30 mcg/kg and rituximab 375 mg/m^2. If 0/3 or 1/3 of these next 3 have a DLT with these dose levels, then 4 more participants will be enrolled at the 30 mcg/kg level provided that no more than 2 total of the 10 have a DLT with the exception of the types noted. If 2 participants in the first 6 have a DLT at this level, then the trial will end accrual. Furthermore, at any time in the 10 participants, if a 3rd participant has a DLT, accrual will also end as soon as this is noted. The upper one-sided 90% confidence bound on 2/10 is 45.0%.

- Sample size determination for amendment dated 9/21/2021: As of July 2021, a total of 12 participants were enrolled without DLT up to that point, making it likely that 3 participants will be enrolled with moxetumomab pasudotox-tdfk 30 mcg/kg and rituximab 375 mg/m^2, and 10 with moxetumomab pasudotox-tdfk 40 mcg/kg and rituximab 375 mg/m^2. Of the first 9 participants so far evaluated for response, 7 (78%) achieved CR, all MRD-free.

  Given the encouraging safety and efficacy data from the phase 1 trial, it is desirable to increase the number of participants to gain more experience with moxetumomab pasudotox-tdfkand rituximab and be able to determine whether the efficacy of the combination at 30-40 mcg/kg of moxetumomab pasudotox-tdfk is better than our historical experience of 40-50 mcg/kg of moxetumomab pasudotox-tdfk alone tested for MRD at NIH. Historically, 30 of 64 evaluable phase 1-3 participants treated with moxetumomab pasudotox-tdfk alone achieved MRD-free CR assessed by bone marrow aspirate flow.

  To enable additional participants to be enrolled affordably, starting with participant 14, participants will receive the biosimilar Ruxience instead of rituximab. Moxe-R thus represents the combination of moxetumomab pasudotox-tdfk with either rituximab or Ruxience.

  If we are being conservative, the 7 of 9 participants who achieved MRD-free CR to date on Moxe-R would need to be considered an interim evaluation and its successful result would be the basis for deciding to add more participants. As such, it would be statistically appropriate to aim for a 0.025 one-sided test between 30/64 and the participants on the current trial. With a total of 26 evaluable participants on Moxe-R and 64 prior participants, a Fisher's exact test with a one sided 2.5% significance level will have 79.8% power to detect a difference between 80% MRD-free CR rate on the present trial and 47% from the 30/64 participants in the prior trials.

  While a total of 26 evaluable participants will be enrolled, the accrual ceiling will be set at 30 to include screen failures and inevaluable participants.

10.3 POPULATIONS FOR ANALYSES

10.3.1 Evaluable for toxicity

All participants will be evaluable for toxicity from the time of their first treatment

10.3.2 Evaluable for objective response:

Only those participants 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 participants will have their response classified according to the definitions stated below. (Note: Participants 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:

Participants 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

10.4.2 Safety data will be evaluated, as well as the MRD-free CR rate, in comparison to results from prior trials. Analysis of the Primary Endpoints

Meeting the primary safety endpoint will require treatment of 10 participants with no more than 2 DLT.

10.4.3 Analysis of the Secondary Endpoint(s)

- Response rates, MRD-free rates, and response durations will be reported descriptively, and the latter will be determined using Kaplan Meier Analyses.
- The MRD-free CR rates will be compared between evaluable participants on this trial and the 30 of 64 evaluable phase 1-3 participants who achieved MRD-free CR from moxetumomab pasudotox-tdfk using a Fisher's exact test, taking the interim results from this trial into consideration.
- The change from rituximab to Ruxience is not expected to result in a change to the CD20 Mab, and the comparison between participants 1-13 treated with moxetumomab pasudotox-tdfk - rituximab and participants 14-26 treated with moxetumomab pasudotox-tdfk - Ruxience will have limited power to detect a difference between rituximab and Ruxience in HCL. After enrollment of 26 participants, if the difference in MRD-free CR rate from moxetumomab pasudotox-tdfk - rituximab vs moxetumomab pasudotox-tdfk - Ruxience results is $p>0.30$ or higher, the results from the 2 groups will be considered close enough to be pooled and the full 26 participants could be compared against the 64 from the moxetumomab pasudotox-tdfk monotherapy studies.

10.4.4 Safety Analyses

Safety analysis will focus on presence and absence of DLT, and incidence of lesser toxicities to each agent or both.

10.4.5 Sub-Group Analyses

Not Applicable.

10.4.6 Exploratory Analyses

Results of exploratory analyses will be descriptive.

11 COLLABORATIVE AGREEMENTS

11.1 CRADA

Conduct of this study and supply of moxetumomab pasudotox-tdfk and rituximab/Ruxience will be addressed by amendment (#13) to existing NCI CRADA (#1975) with AZ.

12 HUMAN SUBJECTS PROTECTIONS

12.1 Rationale For Subject Selection

Participants eligible will be relapsed. Defining the safety of moxetumomab pasudotox-tdfk in participants with relapsed HCL will be needed before considering extending this regimen to participants after only 1 or no prior therapy.

12.2 Participation of Children

HCL has not been reported in individuals < 18 therefore children will not participate in this study.

12.3 Participation of Subjects Unable to Give Consent

Adults unable to give consent are excluded from enrolling in the protocol. However, it is possible that subjects enrolled in the protocol may permanently lose the capacity to consent for themselves during the course of this study. In the event this occurs, the subjects will remain in the study because there is a prospect of direct benefit from research participation (Section **12.5.1**). ,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 to assess ongoing capacity of the subjects and to identify an LAR, as needed.

Please see Section **12.5.1** for consent procedure.

12.4 Evaluation of Benefits and Risks/Discomforts

Participants will receive evaluation of their disease at the National Cancer Institute's Clinical Center. This protocol may or may not benefit an individual, but the results may help the

investigators learn more about the disease and develop new treatments for participants with this disease.

Potential adverse reactions attributable to the administration of the drugs utilized in this trial are discussed in Sections **14.1.2** and **14.2.2**. All care will be taken to minimize side effects, but they can be unpredictable in nature and severity. Participants will be examined and evaluated prior to enrollment. All evaluations to monitor the treatment of participants will be recorded in the participant chart. If participants suffer any physical injury as a result of the participation in this study, immediate medical treatment is available at the Clinical Center, National Cancer Institute, Bethesda, Maryland.

Although no compensation is available, any injury will be evaluated and treated in keeping with the benefits or care to which participants are entitled under applicable regulations. In all publications and presentations resulting from this trial, participants' anonymity will be protected to the maximum extent possible. Authorized personnel from the National Cancer Institute (NCI) and Food and Drug Administration (FDA) or other regulatory authorities may have access to research files in order to verify that participants' rights have been safeguarded. In addition, participant names will be given to the Central Registration to register and verify participants' eligibility.

12.4.1 Potential Risks Associated with Administration of Moxetumomab pasudotox-tdfk

The primary risks of participation in this study include the possible occurrence of any of a range of side effects from moxetumomab pasudotox-tdfk are described in Sections **1.2.1**, **14.1.2** and in the consent document. Frequent monitoring for adverse effects and exclusion of subjects at risk for these adverse effects will help to minimize the risks associated with administration. Moxetumomab pasudotox-tdfk is administered intravenously. Possible risks associated with IV administration of moxetumomab pasudotox-tdfk are infection, redness, swelling, pain, and induration at the administration site.

12.4.2 Potential Risks Associated with Administration of Rituxan

Refer to Section **14.2.2** for details.

12.4.3 Potential Risks Associated with Administration of Ruxience

Refer to Section **14.3** for details.

12.4.4 Identified Risks to Study Procedures

12.4.4.1 Blood Sampling

Side effects of blood draws include pain and bruising, lightheadedness, and rarely, fainting. Up to 123 mL of research blood may be collected at any visit but no more than 315 ml in an 8 week period. Refer to study calendar (Section **3.4**) for frequency of blood draws.

12.4.4.2 Urine Collection

There is no physical risk involved with urine collection.

12.4.4.3 Bone marrow aspirate and/or biopsy

Bone marrow biopsy is minimally invasive and is typically a very safe procedure. Usually, hipbone is numbed with anesthesia. Using a needle, the solid and liquid portion of bone marrow is taken out. This procedure causes some pain. Very rarely, infection or bleeding may occur at the needle site.

12.4.4.4 Electrocardiogram

Some skin irritation can occur where the ECG/EKG electrodes are placed. The test is completely painless and generally takes less than a minute to perform.

12.4.4.5 Stress test

A stress test is generally safe, and complications are rare. Risks include hypotension, arrhythmias, or myocardial infarction.

12.4.4.6 Pulmonary function tests (PFTs)

PFTs are usually safe for most people. Risks include dizziness, asthma attack, or collapsed lung.

12.4.4.7 Abdominal ultrasounds and echocardiogram

There is no physical risk involved with abdominal ultrasounds or echo.

12.4.4.8 Imaging

In addition to the radiation risks discussed below, CT scans may include the risks of an allergic reaction to the contrast. Participants might experience hives, itching, headache, difficulty breathing, increased heartrate and swelling.

The risks of MR imaging are relatively small.

The US Food and Drug Administration has issued warnings that administration of gadolinium (updated September 9, 2010), the MRI contrast imaging agent used in this protocol, has been associated with development of a disease called **nephrogenic systemic fibrosis (NSF)**. The syndrome is rare (approximately 600 cases reported worldwide as of September 2010, out of several million administrations of gadolinium), but disabling and in some cases, fatal. All cases to date have occurred in participants with severe renal disease, including participants on dialysis. NSF has been nearly eradicated secondary to careful screening of renal function and avoiding use of gadolinium in participants with eGFR <30 ml/min/1.73 BSA. Even in participants with end stage renal disease, there have been only rare occurrences of NSF because of precautions taken to use more stable contrast agents at lower doses. This protocol excludes participants with severe renal insufficiency (eGFR <30 ml/min/1.73 BSA). The FDA has issued warnings in 2017 and 2018 that some gadolinium may be retained in the brain, bone and skin although health risks of accumulation have not been reported to date. In accordance with the FDA Drug Safety Communication of 05/16/2018, the Medication Guide for gadobutrol (or other macrocyclic gadolinium contrast agent if applicable) will be made available to all participants with scans that will involve gadolinium-based contrast agent administration.

12.4.5 Risks from Radiation Exposure

On this study, participants will receive up to 3 CT scans/year (excluding screening as these are performed on another study). The total radiation dose for research purposes will be approximately 3.9 rem. An increased risk of cancer is associated with this exposure.

12.4.6 Non-Physical Risks of Genetic Research

12.4.6.1 Risk of receiving unwanted information

Anxiety and stress may arise as a result of the anticipation that unwanted information regarding disease related genetic analysis. Patients will be clearly informed that the data related to genetic analysis is coded, investigational and will not be shared with patients, family members or health care providers.

12.4.6.2 Risk related to possibility that information may be released

This includes the risk that data related to genotype or risk for disease tendency or trait can be released to members of the public, insurers, employers, or law enforcement agencies. Although there are no plans to release results to the patients, family members or health care providers, this risk will be included in the informed consent document.

12.4.6.3 Risk to family or relatives

Family members or relatives may or may not want to be aware of familial tendencies or genetic risks of disease which may cause anxiety about possible future health problems. As previously noted, patients will be notified of any medically significant and actionable incidental findings. Study results will not be shared with patients.

12.5 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 local 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 participant 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.

Manual (non-electronic) signature on electronic document:

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 https://nih.sharepoint.com/sites/NCI-CCR-OCD-Communications/SitePages/OEC-Administrative---Clinical-Research-(ADCR).aspx?Mode=Edit.

12.5.1 Consent Process for Adults Who Lack Capacity to Consent to Research Participation

For participants addressed in Section **12.3**, an LAR will be identified consistent with Policy 403 and informed consent obtained from the LAR, as described in Section **12.5**.

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 Council for 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 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 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 and by 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

14.1 MOXETUMOMAB PASUDOTOX-TDFK (LUMOXITI™) IND # 140552

Note: The oversight and future plans for Moxetumomab pasudotox-tdfk is conducted by AZ. The manufacturer and supplier for the Moxetumomab pasudotox-tdfk used in this study is AZ.

14.1.1 Source

Moxetumomab pasudotox-tdfk (other names: CAT-8015, HA22, LUMOXITI™) is an investigational agent supplied to investigator by AZ. It is a recombinant anti-CD22 MAb conjugated immunotoxin (MW=63.5kda) composed of a disulfide-stabilized anti-CD22 Ig Fv genetically fused to a truncated form of Pseudomonas exotoxin, PE38. Moxetumomab pasudotox-tdfk specifically binds to CD22 on the cell surface of B cells. Following binding, the complex is endocytosed and then processed to release the exotoxin. The exotoxin domain is translocated to the cytosol, where it catalyzes the adenosine diphosphate ribosylation of elongation factor 2, causing inhibition of protein translation and subsequent cell death.

14.1.2 Toxicity

Please refer to background Section **1.2.1** and FDA-approved prescribing information for complete list of side effects.

14.1.3 Formulation and preparation

Please refer to **Appendix C** (FDA-approved prescribing information) for details.

14.1.4 Stability and Storage

Please refer to **Appendix C** (FDA-approved prescribing information) for details.

14.1.5 Administration procedures

Please refer to **Appendix C** (FDA-approved prescribing information) for details.

14.1.6 Incompatibilities

None known

14.2 RITUXIMAB (RITUXAN®)

14.2.1 Source

The finished injectable dosage form is jointly marketed by Biogen Idec, Inc. and Genentech, Inc. under the trade name Rituxan®. Rituximab is a highly purified, 1328-amino acid antibody with an approximate molecular mass of 145 kD. The chimeric mouse/human anti-CD20 antibody is a glycosylated IgG_1 κ immunoglobulin containing murine light and heavy chain variable regions and human γ_1 heavy chain and κ light chain constant regions. Rituximab induces apoptosis and either complement or antibody dependent cytotoxicity (ADCC or CDC).

NIH CC pharmacy will dispense commercial supplies of Rituxan.

14.2.2 Toxicity

Toxicities (% grade 3, grade 4) in non-Hodgkin's lymphoma:

- Body as a Whole: fever (53, 1%), chills (33, 3%), infection (31, 4%), asthenia (26, 1%), headache (19, 1%), abdominal Pain (14, 1%), pain (12, 1%), back Pain (10, 1%), throat Irritation (9, 0%), flushing (5, 0%)
- Cardiovascular System: Hypotension (10, 1%), hypertension (6, 1%)
- Digestive System: Nausea (23, 1%), diarrhea (10, 1%), vomiting (10, 1%)
- Hematologic and Lymphatic: Lymphopenia (48, 40%), leukopenia (14, 4%), neutropenia (14, 6%), thrombocytopenia (12, 2%), anemia (8, 3%)
- Metabolic and Nutritional: Angioedema (11, 1%), hyperglycemia (9, 1%), peripheral edema (8, 0%), LDH increase (7, 0%)
- Musculoskeletal System: Myalgia (10, 1%), arthralgia (10, 1%)
- Nervous System: Dizziness (10, 1%), anxiety (5, 1%)
- Respiratory System: Increased cough (13, 1%), rhinitis (12, 1%), bronchospasm (8, 1%), dyspnea (7, 1%), sinusitis (6, 0%)
- Skin and Appendages: Night sweats (15, 1%), rash (15, 1%), pruritis (14, 1%), urticaria (8, 1%)
- Infusion reaction: In rituximab rheumatoid arthritis placebo-controlled studies, 32% of rituximab-treated patients experienced an adverse event during or within 24 hours following their first infusion, compared to 23% of placebo-treated patients receiving their first infusion. The incidence of adverse events during the 24-hour period following the second infusion, rituximab or placebo, decreased to 11% and 13%, respectively. Acute infusion reactions

(manifested by fever, chills, rigors, pruritis, urticaria/rash, angioedema, sneezing, throat irritation, cough, and/or bronchospasm, with or without associated hypotension or hypertension) were experienced by 27% of rituximab-treated patients following their first infusion, compared to 19% of placebo-treated patients receiving their first placebo infusion. The incidence of these acute infusion reactions following the second infusion of rituximab or placebo decreased to 9% and 11%, respectively. Serious acute infusion reactions were experienced by <1% of patients in either treatment group. Acute infusion reactions required dose modification (stopping, slowing or interruption of the infusion) in 10% and 2% of patients receiving rituximab or placebo, respectively, after the first course. The proportion of patients experiencing acute infusion reactions decreased with subsequent courses of rituximab. The administration of IV glucocorticoids prior to rituximab infusions reduced the incidence and severity of such reactions, however, there was no clear benefit from the administration of oral glucocorticoids for the prevention of acute infusion reactions. Patients in clinical studies also received antihistamines and acetaminophen prior to rituximab infusions.

- Hematologic Events: In clinical trials, Grade 3 and 4 cytopenias [23] were reported in 48% of patients treated with rituximab; these include: lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1 to 588 days) and of neutropenia was 13 days (range, 2 to 116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following rituximab therapy were reported. In addition, there have been a limited number of post-marketing reports of prolonged pancytopenia, marrow hypoplasia, and late onset neutropenia (defined as occurring 40 days after the last dose of rituximab) in patients with hematologic malignancies. In reported cases of late onset neutropenia (NCI-CTC Grade 3 and 4), the median duration of neutropenia was 10 days (range 3 to 148 days). Documented resolution of the neutropenia was described in approximately one-half of the reported cases; of those with documented recovery, approximately half received growth factor support. In the remaining cases, information on resolution was not provided. More than half of the reported cases of delayed onset neutropenia occurred in patients who had undergone a prior autologous bone marrow transplantation. In an adequately designed, controlled, clinical trial, the reported incidence of NCI-CTC Grade 3 and 4 neutropenia was higher in patients receiving rituximab in combination with fludarabine as compared to those receiving fludarabine alone, 39/51 (76%) vs. 21/51 (39%) [24]

14.2.3 Formulation and preparation

Please refer to **APPENDIX B** for details.

14.2.4 Stability and Storage

Please refer to **APPENDIX B** for details.

14.2.5 Administration Procedures

Please refer to **APPENDIX B** for details.

14.2.6 Incompatibilities

None known.

14.3 RUXIENCE

Please see FDA-approved packet insert for Ruxience for complete agent information. Manufacturer: Pfizer.

14.3.1 Source

Ruxience will be obtained from commercial sources and dispensed by the NIH CC pharmacy.

14.3.2 Administration

Please refer to **APPENDIX B** for details.

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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: RITUXIMAB (RITUXAN®) AND RUXIENCE PREPARATION AND ADMINISTRATION

How Supplied

Rituximab (Rituxan®) and Ruxience will be supplied in 50-mL vials containing 500 mg of antibody (50 mL of solution) at a concentration of 10 mg/mL and 10-mL vials containing 100 mg of antibody (10 mL of solution) at a concentration of 10mg/ML. Rituximab vials are sterile, preservative-free, and intended for single use only.

Stability and Storage

Rituximab and Ruxience are biologically and chemically stable at 2°C to 8°C (36°F to 46°F) and has a proposed shelf-life stability of 30 months. Once reconstituted into IV bags, rituximab and Ruxience are chemically stable for up to 24 hours at 2°C to 8°C (36°F to 46°F), followed by up to 24 hours at room temperature (23°C). However, since rituximab solutions do not contain preservative, diluted solutions should be stored refrigerated (2°C to 8°C). No incompatibilities between rituximab and Ruxience and polyvinylchloride or polyethylene bags have been observed. Rituximab vials should be protected from direct sunlight. Rituximab vials are intended for single use only. Do not use beyond the expiration date stamped on the carton.

Dose Calculation

1. Before the first infusion only, calculate the participant's body surface area (BSA). Actual body weight measured within 4 weeks prior to initial treatment with rituximab will be used for calculation of body surface area.
2. Calculate the dose to be administered. The formula for the dose calculation is as follows:

$$\frac{U(\text{Subject BSA in } mUP^2PU)\ (375mg/mUP^2P)}{10\ mg/mL} = \_\_\_mL \text{ (volume of rituximab/Ruxience for reconstitution)}$$

3. The same volume of rituximab for reconstitution will be used for each subsequent infusion.

Preparation of Rituximab or Ruxience for Intravenous Administration (First Infusion)

1. Using aseptic technique, withdraw the necessary amount of rituximab and dilute to a final concentration of 1 to 4 mg/mL into an infusion bag containing either 0.9% Sodium Chloride, USP, or 5% Dextrose in Water, USP. It is recommended that a dilution of 2 mg/mL be used for ease in calculating dose. Gently invert the bag to mix the solution. Discard any unused portion left in the vial. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.
2. **DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.** Rituximab and Ruxience can be diluted with 5% dextrose or normal saline. In general they should not be infused with other fluids or medications, but nurses may consult with a pharmacist to check for y-site compatibility with other medications if needed.
3. The first infusion of rituximab or Ruxience should be administered IV at an initial rate of 50 mg/hr. If hypersensitivity or infusion-related reactions **do not** occur, the infusion rate

can be escalated in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. Such an infusion schedule is listed below for a 1000 mg total dose:

Time (Minutes)	Infusion Rate (mg/h)	Dose in 30 minutes (mg)	Cumulative Dose (mg)
0-30	50	25	25
31-60	100	50	75
61-90	150	75	150
91-120	200	100	250
121-150	250	125	375
151-180	300	150	525
181-210	350	175	700
212-240	400	200	900
241-255*	400	200	1000

*Should complete at 255 minutes (4h 15min) to complete a 1000mg total dose.

4. Infusion and hypersensitivity reactions may occur. Premedication consisting of acetaminophen and diphenhydramine should be considered before each infusion of rituximab. Premedication may attenuate infusion reactions. Since transient hypotension may occur during rituximab infusion, consideration should be given to withholding antihypertensive medications 12 hours before rituximab infusion.

5. If a hypersensitivity (non-IgE-mediated) or an infusion reaction develops, the infusion rate should be reduced to half that rate, i.e. from 100 mg/h to 50 mg/h. Participants who experience a moderate to severe infusion related reaction (fever, chills, or hypotension) should have their infusion interrupted immediately and should receive aggressive symptomatic treatment. The infusion should not be restarted before all the symptoms have disappeared and then the infusion can continue at one-half the previous rate. Dexamethasone PO should be given prior to rituximab or Ruxience infusions until moderate-severe infusion reactions are no longer observed.

6. After the end of infusion, the intravenous line should remain in situ for at least 1 hour in order to be able to administer drugs intravenously if necessary. If there are no adverse events during this period of time, the intravenous line may be removed.

Preparation of Rituximab or Ruxience for Subsequent Intravenous Infusions

1. Using aseptic technique, withdraw the necessary amount of rituximab or Ruxience and dilute to a final concentration of 1 to 4 mg/mL into an infusion bag containing either 0.9% Sodium Chloride, USP, or 5% Dextrose in Water, USP. It is recommended that a dilution of 2 mg/mL be used for ease in calculating dose. Gently invert the bag to mix the solution. Discard any unused portion left in the vial. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

2. **DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.** Rituximab or Ruxience can be diluted with 5% dextrose or normal saline. In general they should not be infused with other fluids or medications, but nurses may consult with a pharmacist to check for y-site compatibility with other medications if needed.

3. If the participant tolerated the first infusion well, subsequent study drug infusions can be administered at an initial rate of 100 mg/hr and increased by 100 mg/hr increments at 30-minute intervals to a maximum of 400 mg/hr as tolerated. Such an infusion schedule is listed below. If the participant did not tolerate the first infusion well, the above guidelines for the first infusion should be followed for subsequent infusions.

Time (Minutes)	**Infusion Rate (mg/h)**	**Dose in 30 minutes (mg)**	**Cumulative Dose (mg)**
0-30	100	50	50
31-60	200	100	150
61-90	300	150	300
91-120	400	200	500
121-150	400	200	700
151-180	400	200	900
181-195*	400	200	1000

Should complete at 195 minutes (3h 15 min) to complete a 1000mg total dose

4. Infusion and hypersensitivity reactions may occur. Premedication consisting of acetaminophen and diphenhydramine will be required before each infusion of rituximab or Ruxience. Premedication may attenuate infusion reactions. Since transient hypotension may occur during rituximab or Ruxience infusion, consideration should be given to withholding antihypertensive medications 12 hours before rituximab or Ruxience infusion.

5. If a hypersensitivity (non-IgE-mediated) or an infusion reaction develops, the infusion rate should be reduced to half that rate, i.e. from 100 mg/h to 50 mg/h. Participants who experience a moderate to severe infusion related reaction (fever, chills, or hypotension) should have their infusion interrupted immediately and should receive aggressive symptomatic treatment. The infusion should not be restarted before all the symptoms have disappeared and then the infusion can continue at one-half the previous rate.

6. After the end of infusion, the intravenous line should remain in situ for at least 1 hour in order to be able to administer drugs intravenously if necessary. If there are no adverse events during this period of time, the intravenous line may be removed.

16.3 APPENDIX C: MOXETUMOMAB PASUDOTOX-TDFK (LUMOXITI™) PREPARATION AND ADMINISTRATION

How Supplied

- LUMOXITI and IV Solution Stabilizer are packaged separately.
- Prior to preparation, LUMOXITI and IV Solution Stabilizer should be stored at 2°C to 8°C (36°F to 46°F) in original cartons to protect from light.

LUMOXITI (moxetumomab pasudotox-tdfk)

- Each single-dose vial supplies LUMOXITI 1 mg/vial (moxetumomab pasudotox-tdfk) for injection as a lyophilized cake or powder for reconstitution and dilution prior to intravenous infusion.
- Multiple vials of LUMOXITI may be required to administer a single dose (See Step 1: Calculate Dose on next page).
- Reconstitute LUMOXITI vials with Sterile Water for Injection, USP only (not supplied).

Solution Stabilizer

- Each single-dose vial contains 1 mL IV Solution Stabilizer.
- Only one vial of IV Solution Stabilizer is needed per administration of LUMOXITI, regardless of the number of vials of LUMOXITI used to prepare the infusion.
- Do not use IV Solution Stabilizer to reconstitute LUMOXITI.
- **Do not flush IV lines with IV Solution Stabilizer.**

Storage and Handling of Reconstituted and Diluted LUMOXITI

Table 1. Storage Times and Conditions for Reconstituted and Diluted LUMOXITI Solution

Reconstituted Solution	Diluted LUMOXITI Solution in Infusion Bag	
	After Dilution	Administration
LUMOXITI does not contain bacteriostatic preservatives. Use reconstituted solution immediately. DO NOT STORE reconstituted LUMOXITI vials.	Use diluted solution immediately or after storage at room temperature (20°C to 25°C; 68°F to 77°F) for up to 4 hours or store refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours. PROTECT FROM LIGHT. DO NOT FREEZE. DO NOT SHAKE.	If the diluted solution is refrigerated (2°C to 8°C; 36°F to 46°F), allow it to equilibrate at room temperature (20°C to 25°C; 68°F to 77°F) for no more than 4 hours prior to administration. Administer diluted solution within 24 hours of reconstitution as a 30-minute infusion. PROTECT FROM LIGHT.

- Calculate the dose (mg) and the number of LUMOXITI vials (1 mg/vial) to be reconstituted. The final concentration of the reconstituted LUMOXITI solution is 1 mg/mL.
- Individualize dosing based on the participant's **actual body weight** prior to the first dose of the first treatment cycle.
- A change in dose should only be made between cycles when a change in weight of greater than 10% is observed from the weight used to calculate the first dose of the first treatment cycle. No change in dose should be made during a particular cycle.
- **Do not** round down the dose for partial vials.

Step 2: Gather Supplies

- LUMOXITI 1 mg/vial (number of vials to be reconstituted are based on Step 1)
- 1 vial of IV Solution Stabilizer (packaged separately)
- Alcohol swabs
- 1 infusion bag containing 50 mL or 100 mL 0.9% Sodium Chloride Injection, USP
- Sterile Water for Injection, USP
- Syringes and needles

Step 3: Reconstitution

- Reconstitute each LUMOXITI vial with **1.1 mL** Sterile Water for Injection, USP using aseptic technique.
- Direct the Sterile Water for Injection, USP slowly **along the walls** of the LUMOXITI vial and not directly at the lyophilized cake or powder.
- **Do not** reconstitute LUMOXITI vials with the IV Solution Stabilizer.
- **Gently** swirl the vial until completely dissolved. Invert the vial to ensure all cake or powder in the vial is dissolved. **Do not shake.**
- Visually inspect that the reconstituted solution is clear to slightly opalescent, colorless to slightly yellow, and free from visible particles.
- **Do not** use if solution is cloudy, discolored, or contains any particles.
- The resulting 1 mg/mL solution allows a withdrawal volume of 1 mL.

Note: Use reconstituted solution immediately. Do not store reconstituted LUMOXITI vials. See Table 1 for storage times and conditions for the reconstituted solution.

Step 4: Preparation of Infusion Bag with IV solution Stabilizer

- Obtain a 50 mL 0.9% Sodium Chloride Injection, USP infusion bag.
- Only one vial of IV Solution Stabilizer is needed per administration of LUMOXITI, regardless of the number of vials of LUMOXITI used to prepare the infusion.
- Add 1 mL IV Solution Stabilizer to the infusion bag containing 50 mL 0.9% Sodium Chloride Injection, USP.
- Gently invert the bag to mix the solution. **Do not shake.**

Step 5: Dilution

- Slowly withdraw the required volume of reconstituted LUMOXITI solution needed from each vial, per the calculated dose based on the participant's actual body weight (kg).
- Inject LUMOXITI into the infusion bag containing 50 mL 0.9% Sodium Chloride Injection, USP and 1 mL IV Solution Stabilizer.
- **Gently** invert the bag to mix the solution. **Do not shake.**

- Discard any partially used or empty vials of LUMOXITI and IV Solution Stabilizer.
- See **Table 1** for storage times and conditions for the diluted solution.

Step 6: Intravenous Hydration and Pre-Infusion Medications:

- Administer intravenous hydration and premedication to the participant.
- Intravenously administer 1 L of isotonic solution (e.g. 5% Dextrose Injection, USP and 0.45% or 0.9% Sodium Chloride Injection, USP) over 2 to 4 hours before each LUMOXITI infusion. Administer 0.5 L to participants under 50 kg. On day 1 of cycles 2-8, pre-hydration may be started during the rituximab infusion provided it is completed no earlier than 2 hours prior to the LUMOXITI infusion.
- Premedicate 30 to 90 minutes prior to each LUMOXITI infusion with an antihistamine (e.g. diphenhydramine), acetaminophen, and a histamine-2 receptor antagonist (e.g. famotidine, or cimetidine), with the exception of day 1 of cycles 2-8, when premedications are to be given prior to Rituxan.

Step 7: Administration

- Infuse the diluted LUMOXITI solution intravenously using early call back/reverse flow method over 30 +/- 5 minutes.
- **Do not** mix LUMOXITI, or administer as an infusion with other medicinal products.
- After the infusion, flush the intravenous administration line with of 0.9% Sodium Chloride Injection, USP at the same rate as the infusion. This ensures that the full LUMOXITI dose is delivered.

Step 8: Post-infusion Medications

- Administer post-infusion medications.
- Intravenously administer 1 L of isotonic solution (e.g. 5% Dextrose Injection, USP and 0.45% or 0.9% Sodium Chloride Injection, USP) over 2 to 4 hours after each LUMOXITI infusion. Administer 0.5 L to participants under 50 kg.
- Consider oral antihistamines and acetaminophen for up to 24 hours following LUMOXITI infusions.
- Consider oral corticosteroid (e.g. 4 mg dexamethasone) to manage nausea and vomiting.
- Maintain adequate oral fluid intake.
- Advise all participants to adequately hydrate with up to 6 L (twelve 8-oz glasses) of oral fluids (e.g. water, milk, or juice) per 24 hours on Days 1 through 8 of each 28-day treatment cycle. In participants under 50 kg, up to 2 L (eight 8-oz glasses) per 24-hour period is recommended.
- Consider low-dose aspirin on Days 1 through 8 of each 28-day treatment cycle.

Note: This Healthcare Provider Instructions for Use has been approved by the U.S. Food and Drug Administration.

16.4 APPENDIX D: PARTICIPANT HYDRATION DIARY

19C0042 - Moxe-R in HCL

Cycle #_____

Participant Name_____ Participant Study ID _____

INSTRUCTIONS TO THE PARTICIPANT:

1. Complete one form for each Cycle.
2. You will drink at least **24** cups of fluid each day (1 cup/hour; 1 cup = 8 oz; total of 1.5 gal). **Do not go more than 3 hours without drinking**.
3. Record the date, number of cups of fluid that you drank, and the time you took them.
4. Please bring this form to your physician when you go for your next appointment.

DAY 1 **Date:**																								
CUPS (#)																								
Time																								
DAY 2 **Date:**																								
CUPS (#)																								
Time																								

19C0042 - Moxe-R in HCL

Cycle #_____

Participant Name_____ Participant Study ID _____

DAY 3 **Date:**																							
CUPS (#)																							
Time																							
DAY 4 **Date:**																							
CUPS (#)																							
Time																							
DAY 5 **Date:**																							
CUPS (#)																							
Time																							

19C0042 - Moxe-R in HCL

Cycle #_____

Participant Name_____ Participant Study ID _____

DAY 6 **Date:**																							
CUPS (#)																							
Time																							
DAY 7 **Date:**																							
CUPS (#)																							
Time																							
DAY 8 **Date:**																							
CUPS (#)																							
Time																							

19C0042 - Moxe-R in HCL Cycle #_____ Participant Name_____ Participant Study ID _____
Participant's Signature: _____ Date: _____ Staff Signature: _____ Date: _____